ANNEXE STATINISATION
[**Statinization Appendix**]

Complément de l'**alter dictionnaire médico-pharmaceutique bilingue**
[Supplement to the **Alternative Bilingual Medico-Pharmaceutical Dictionary**]

Mise à jour récente
30.12.2019

< Presented as a systematic alphabetical primer, without a trace of complacency towards the lipid (cholesterolist) hypothesis nor towards its proponents >

> À parcourir comme un abécédaire méthodique, sans complaisance aucune envers l'hypothèse lipidique (cholestéroliste) ni envers ses tenants <

ADR = adverse drug reaction / EIM = effet indésirable médicamenteux
AMI = acute myocardial infarction / IAM = infarctus aigu du myocarde
ACS = acute coronary syndrome / SCA = syndrome coronarien aigu
RRA = réduction du risque absolu
NS = statistically insignificant
MI = myocardial infarction / IDM = infarctus du myocarde
TC = total cholesterol / CT = cholestérol total
TG = triglycerides / triglycérides
CHD = coronary heart disease
LDL-C = LDL cholesterol

[569 entrées]

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On trouvera les occurrences d'un terme/locution/titre anglais/français par le raccourci Recherche (Ctl-F/Cmd-F)
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A DAILY PILL TO LENGHTEN LIFE : WHICH UTILITY REQUIRED ? *Pharmacoéconomie – Espérance de vie*
« A 2014 study performed in London, UK, attempted to determine the *utility* of taking a pill daily by interviewing 360 people in public streets in North West London.[1] Participants answered a questionnaire to determine the amount of life they would need to gain to take a preventive pill *for the rest of their life*...

The median increase required was 6 months, with an interquartile range from 1 to 36 months; 12% had extreme disutility (requiring more than a 10-year increase in life expectancy), whereas 34% required less than a month increase »[2]…

* If the interviewed were aged 50, it would mean taking a preventive pill daily for 30 years if their life expectancy was 80 years. If a daily statin prolongs life by 1 day for every year of treatment, after 30 years the life gain will be of 30 days or 1 month, 5 months short of the median increase of 6 months found in the aforementioned utility survey in London…

The problem is that *statins* have never been credibly and convincingly demonstrated to postpone death at all, whether in primary prevention, in women, in the aged or in coronary patients of both sexes...

[1] Fontana et al. Circulation 2014; 129: 2539 – doi: 10.1161/ CIRCULATIONAHA.113.007595
[2] Hutchins et al. Circ Cardiovasc Qual Outcomes. 2015; 8:00-00 - DOI: 10.1161/CIRCOUTCOMES.114.001240

Even in 'midlife coronary male patients', the death postponement observed in experimental conditions is *unconvincing* and *minimal* even if statistical gains in survival have been presented in some company-sponsored trials; at best, if data were not manipulated nor truncated, life would be extended by a few hours, a few days, a few weeks, but never by 6 months
un pilule par jour pour prolonger la vie : quelle utilité requise ?
Voir aussi THE EFFECT OF STATINS ON AVERAGE SURVIVAL dans la présente annexe

A TO Z, THE TRIAL *Prévention secondaire après syndrome coronarien aigu – Comparaison de doses - Simvastatine d'emblée 40-80 mg c. simvastatine différée 20 mg*

Aggrastat to Zocor (phase Z)
* Princeps publication : De Lemos/*JAMA*/2004[3]
* Funding : private, Merck

METHODOLOGY
* Randomized; double blind ; size > 1000 participants ; duration > 1 year ; no placebo ; dose comparison ; secondary prevention in unstable CHD (Acute Coronary Syndrome or MI) ; high risk of bias (NICE 2014)
* Participants demography: 4,497 randomized ; median age 61 years ; 24.5% women

* Participants health : non-ST-segment elevation acute coronary syndrome (60%) or ST-elevation MI (40%) ; hypertension 50% ; diabetes 23.5%
* Baseline lipids : TC 4.78 mM and LDL-C 2.88 mM
* Duration : 2 years (24 months)

* Comparison groups: simvastatin medium dose (40 mg) first month, high dose (80 mg) afterwards, vs. placebo first 4 months, then simvastatin medium dose (20 mg)
* Control group : simvastatin 20 mg

* Main composite endpoint = [CV mortality (MI and stroke) + non fatal MI + readmission for ACS / stroke] - Weak internal and external validity since it mixes fatal and non fatal events (weights differ), objectivity is uneven (medical decision to readmit is exposed to unblinding), and baseline frequencies and treament effects differ for each component

* Positive compliance (active group adherence) : 66%, a low figure leading to risk of bias of internal validity
* Negative compliance (control group adherence) : 68%, a low figure leading to risk of bias of internal validity

RESULTS
Surrogate
* LDL-C relative risk reduction of -19%

Clinical benefits
CV mortality relative risk reduction of -24%, NS
« No difference was evident during the first 4 months (simvastatin vs. placebo) between the groups for the primary end point… The trial did not achieve the prespecified end point »

Clinical harms
* Health related quality of life *not reported*
* New onset diabetes *not reported* in princeps publication, but a RR increase of +37% was revealed by meta-analyst Preiss

* Symptomatic myopathy as a stand-alone ADR was *not measured* or *not reported*, since the required trial definition [symptoms + creatine kinase level > 10x the upper limit or normal] missed every case with only a 9-fold increase in CK, a deceiving and low powered method aimed at minimising reports of ADRs, a frequent occurrence in sponsored RCTs of statins

* Myopathy (CK > 10x ULN associated with muscle symptoms) occurred in 9 patients (0.4% or 1/150) receiving simvastatin 80 mg/d for 2 years and in 0 patients receiving lower doses of simvastatin. Muscular symptoms without such CK elevations were not measured or reported

Transparency
The BMJ has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they

[3] De Lemos et al. JAMA 2004 ; 292(11) : 1307 - http://www.ncbi.nlm.nih.gov/pubmed/15337732

have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit *A à Z*
* Conclusion : essai négatif cliniquement chez des *coronariens instables*, avec confirmation de la dose-dépendance de l'effet hyperglycémiant (divulgué, heureusement, par un méta-analyste externe) et avec omission déplorable des myopathies symptomatiques non sévères et des effets sur la glycémie et la qualité de vie

ABSTRUSE SURROGATE OUTCOME MEASURE *Critère de substitution – Hypolipidémiant – Présentation incompréhensible – Cholestérolisme – Essai GLAGOV – PCSK9*

« The primary efficacy measure, percent atheroma volume (PAV), was calculated using the following equation: $PAV = \Sigma(EEM_{area} - Lumen_{area})/\Sigma EEM_{area} \times 100$, where EEM_{area} is the cross-sectional area of the external elastic membrane and $Lumen_{area}$ is the cross-sectional area of the lumen. The change in PAV was calculated as the PAV at 78 weeks minus the PAV at baseline. A secondary measure of efficacy, normalized total atheroma volume (TAV), was calculated using the following equation: $TAV_{normalized} = (EEM_{area} - Lumen_{area})/Number\ of\ Images\ in\ Pullback \times Median\ Number\ of\ Images\ in\ Cohort$, where the average plaque area in each image was multiplied by the median number of images analyzed in the entire cohort to compensate for differences in segment length between patients. Change in normalized TAV was calculated as the TAV at 78 weeks minus the TAV at baseline. Regression was defined as any decrease in PAV or TAV from baseline[4] »

* In less inintelligible terms, this is the atheroma volume in coronary arteries approximated by serial intravascular ultrasonography imaging as a marker for plaque size…

* One wonders if any of the 'volunteer' trial participants or even any of the cardiologists too busy to read more than the abstract, understood that this was a marketing-driven trial presented as a proof-of-concept one, but insidiously conflated as a pragmatic trial, confusing 'coronary disease' with a minute change in a 'sybilline endpoint calculated from an ultrasound image' whose validity is uncertain and providing no evaluation of any clinically relevant criteria ...

The association between coronary disease course and the absolute changes in the ad hoc morphometric values, and the thresholds for clinical relevance of experimental changes observed, are still up for debate. Industry likes to use ignorance to advocate the use of their products
critère substitutif d'évaluation abscons

ACAPS, THE TRIAL *Prévention primaire avec athéromatose – Critères angiomorphologiques et cliniques*
Asymptomatic Carotid Artery Progression Study
* Princeps publications : Furberg/*Circ*/1994[5]

METHODOLOGY
* Publication : ACAPS/*CCT*/1992[6]
* Design: randomized, placebo, duration > 1 year ; sample size < 1000 ; surrogate and clinical endpoints

* Demography of participants: 919 randomized ; aged 40-79 years - 445 or 48 % women aged around 61 years
* Health of participants : without established CHD but with carotid atheromatosis
* Funding : public, NHLBI (USA)

* Comparison: lovastatin 10 to 40 mg versus placebo
* Mean duration : 2.8 years
* Main outcome measure : ultrasonographic intimal-medial arterial wall thickening
*Secondary outcomes : total mortality, CHD mortalilty, non fatal MI

RESULTS
Harms
* Health related quality of life (QALY) *not reported*

Benefits
* Arterial wall thickness by ultrasonography, a rather imprecise method, was very slightly reduced under lovastatin but clinical

[4] Nicholls SJ et al. GLAGOV Trial. JAMA 15.11.2016 - doi:10.1001/jama.2016.16951
[5] Furberg C et al. Circulation 1994; 90: 1679 – abstract on http://www.ncbi.nlm.nih.gov/pubmed/7734010
[6] ACAPS. Control Clin Trials 1992; 13: 293

significance of results remains uncertain

Secondary benefits
a) TOTAL MORTALITY : relative risk reduction = -12%, NS – NNT annualisé : 195 patients-année
b) CHD mortality : relative risk reduction = -65% (sic), NS
c) non fatal MI : relative risk reduction = -65 % (sic), NS
l'essai dit Acaps
* Conclusion : essai négatif cliniquement et statistiquement ; réduction minimale de l'athéromatose carotidienne

ACCELERATE, THE TRIAL *Réfutation de l'hypothèse lipidique – Prévention secondaire – Essai négatif – Inhibiteur CETP*
« CETP inhibitor evacetrapib relatively reduced LDL-C by -37% and relatively raised HDL-C by +130%, but produced no discernible reduction in CV events or mortality in 12,092 high-risk patients. Evacetrapib 130 mg/day was compared to placebo for 30 months, without any clinical benefit[7] »

« After a median of 26 months of evacetrapib or placebo, a primary end-point event occurred in 12.9% of the patients in the evacetrapib group and in 12.8% of those in the placebo group. Although evacetrapib had favorable effects on established lipid biomarkers, treatment with evacetrapib did not result in a lower rate of CV events than placebo among patients with high-risk vascular disease[8] »
l'essai dit Accelerate

ACCESS TO DATA *Transparence – Essais – Oxford – CTSU - CTT*
« If you're a doctor and accept not being given access to the data – such as all doctors and statins – that's quackery not evidence based medicine »[9]

« Currently only the drug companies, the trialists, and the Cholesterol Treatment Trialists (CTT) collaboration in Oxford have access to individual patient data from the statin trials. As I understand it, even CTT does not have the data on adverse events, which were specifically excluded when the collaboration was established...

Nor does CTT have the right to share data with third parties. The 2013 Cochrane review group did not have access to the individual patient data. It based its analysis on the published information, including the published CTT analysis »[10]

« They hold all the trial data on statins including ADRs and will not allow anyone else to see it. They have signed confidentialy agreements with the companies, these data are kept secret and have never been seen by any other independent researchers » bemoans Malcolm Kendrick[11]
accès aux données
« Si vous êtes médecin et acceptez de ne pas avoir accès aux données – comme c'est le cas en statinologie – c'est du charlatanisme et non de la médecine factuelle » déplore David Healy

ACCORD, THE TRIAL *Prévention primaire chez diabétiques – Fénofibrate c. placebo chez patients sous simvastatine – Comparaison au su*
Action to Control Cardiovascular Risk in Diabetes
* Princeps publication : Accord/NEJM/2010[12]

* Participants : 5518 randomized
* Primary composite outcome : nonfatal MI/nonfatal stroke/CV mortality
* Follow-up : mean 4.7 years

RESULTS
* Health related quality of life *not reported*

Numerical results :

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[7] Nicholls et al. 2016
[8] Lincoff et al. N Engl J Med 2017;376:1933-42 DOI: 10.1056/NEJMoa1609581
[9] David Healy, 15.6.2014 -
[10] Godlee F. BMJ 2014; 349: g5038 - doi: 10.1136/bmj.g5038
[11] drmalcolmkendrick.org 2014.12.1
[12] N Engl J Med 2010; 362(17): 1563 - doi:10.1056/NEJMoa1001282 - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879499/ and http://www.nejm.org/doi/full/10.1056/NEJMoa1001282#t=articleTop

* Primary composite outcome relative risk reduction -12%, NS – absolute risk reduction = 0.2% over 4.7 years for an absolute risk reduction of 0.04% per year and an NNT of 2500 patient-years
* Total mortality relative risk reduction of -9%, NS – absolute risk reduction = 0.1% over 4.7 years for an absolute risk reduction of 0.02% per year and an NNT of 5000 patient-years

« We know after ACCORD that the combination of statin + fenofibrate does not reduce the risk as compared with statin alone. Thus aggressive cholesterol-lowering is not effective in type 2 diabetics to reduce the risk of CV complications and mortality »[13]

« Overall, the results of the ACCORD lipid trial do not support the use of combination therapy with a fibrate and a statin to reduce CV disease in most high-risk adults with type 2 diabetes. Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P=0.01 for interaction) »[14]

« ACCORD is the first large clinical trial to compare the CV effects of a statin + placebo with combination therapy of a statin + fibrate, in high-risk adults with type 2 diabetes. Researchers found that, overall, the combination therapy was safe, but it did not lower the risk of heart attack, stroke, or death from CV disease more than statins alone… Women on combination therapy appeared to have more CV problems than those on statins alone »[15]
l'essai dit Accord
* En assumant qu'un NNT doive être inférieur à 100 patients-année pour être considéré cliniquement signifiant, la réduction d'un critère combinant divers événements CV n'est pas au rendez-vous malgré une réduction tangible de la cholestérolémie par l'association simvastatine + fénofibrate, ce qui contredit l'hypothèse lipidique. Chez les femmes cette association fut néfaste

* Conclusion : résultats négatifs cliniquement pour une association fixe de 2 hypolipidémiants

ACUTE CORONARY SYNDROME (ACS) AND STATINS
« The time period shortly after an ACS is critical for patients with CHD. Pathophysiologically, endothelial dysfunction of arteries, platelet aggregability, thrombus formation and vascular inflammation increase the risk for recurrent events and death due to vessel occlusion from vulnerable coronary plaques. Thanks to their pleiotropic effects, statins may improve these unfavourable pathophysiological mechanisms and hereby reduce the risk of further ischaemic cardiovascular events..

A recent Cochrane systematic review assessed the effects of early administered statins on mortality, CV morbidity and adverse events such as myopathy of patients with ACS. The review included 18 controlled trials that randomised >14 000 patients to early statin treatment (initiation within 14 days of ACS onset) or placebo/usual care. The overall quality of the evidence was moderate because of concerns about risk of bias and imprecision of summary estimates...

Early statin therapy did not significantly reduce the risk for the combined primary outcome of death, non-fatal myocardial infarction and stroke at 1 month nor at 4 months of follow-up »[16]

ACUTE MEMORY LOSS IN FIRST MONTH OF LIPID LOWERING *Épidémiologie – Statinovigilance - Mémoire*
« Using The Health Improvement Network database 1987-2013, a retrospective cohort study compared 482 543 statin users with 2 control groups: 482 543 matched nonusers of any Lipid Lowering Drugs (LLD) and all 26 484 users of nonstatin LLDs. A case-crossover study of 68 028 patients with incident acute memory loss evaluated exposure to statins during the period immediately before the outcome vs 3 earlier periods…

When compared with matched nonusers of any LLDs, a strong association was present between first exposure to statins and incident acute memory loss diagnosed within 30 days immediately following exposure (fully adjusted OR, 4.40). This association was not reproduced in the comparison of statins vs nonstatin LLDs but was also present when comparing nonstatin LLDs with matched nonuser controls (adjusted HR 3.60)...

Both statin and nonstatin LLDs were strongly associated with acute memory loss in the first 30 days following exposure in users compared with nonusers but not when compared with each other »[17]
pertes de mémoire subites le premier mois d'une réduction lipidique
* une étude de cohorte rétrospective sur données secondaires informatisées montre que le rapport de cotes de souffrir de pertes subites de mémoire dans le mois qui suit le début d'un traitement statinique est de 4,4 fois, et de 3,6 fois pour les autres

[13] de Lorgeril et al. RRCT 2012 ; 7(2) : 1
[14] N Engl J Med 2010; 362(17): 1563 - doi:10.1056/NEJMoa1001282 - http://www.nejm.org/doi/full/10.1056/NEJMoa1001282#t=articleTop
[15] http://www.nih.gov/news/health/mar2010/nhlbi-15.htm
[16] Nordmann et al. Heart 2016;102: 653-654 - doi:10.1136/heartjnl-2015-307781
[17] Strom et al. JAMA Intern Med 2015; 175(8): 1399 - doi:10.1001/jamainternmed.2015.2092

hypolipidémiants… pas surprenant puisque le cerveau a bien besoin du cholestérol

ACUTE MYOCARDIAL INFARCTION AND EXPOSURE TO STATINS (SW) *Épidémiologie*
* No connection is found between the level of exposure to statins in the population and the incidence or mortality of acute MI in an ecological study based on Sweden's municipalities. Though a widespread and increasing utilisation of statins, no correlation with AMI incidence/AMI mortality in a general Swedish population, independent of age and gender, could be detected in this explorative study...

The benefits claimed in clinical trials could not be confirmed, despite the fact that a high fraction of the population studied used statins[18]
infarctus aigu du myocarde et exposition aux statines
* argument épidémiologique suédois qui contredit l'hypothèse statinique

ACUTE RENAL FAILURE AND ROSUVASTATIN *Statinovigilance – Néphrovigilance*
* In the JUPITER trial, an average dose (20 mg) of rosuvastatin was compared with placebo in almost 18 000 patients. Data subsequently reported to the FDA showed a non-significant RRI of **+19 %** in acute renal failure (RR = 1.19). The non-significant risk increased further to **+35%** (RR = 1.35) when the endpoint also included doubling of serum creatinine[19]

« In the ARDS trial, rosuvastatin did result in fewer days free of renal failure to day 14 (10.1 versus 11.0, P=0.01) and fewer days free of hepatic failure to day 14 (10.8 versus 11.8, P=0.003) »[20] thereby confirming the deleterious effects on kidney and liver functions
insuffisance rénale aiguë et rosuvastatine

ADR REPORTED IN NON-INDUSTRY SPONSORED STUDIES
Statinovigilance expérimentale

« A double blind RCT that compared 1016 low risk patients receiving simvastatin 20 mg or pravastatin 40 mg with placebo showed that both drugs had an adverse effect on energy/fatigue exercise score with 40% of women reporting reduced energy or fatigue with exertion (Golomb 2012, Arch Intern Med 172(15): 1180)...

Reducing exercise capacity in a healthy group when physical inactivity is a major contributor to the development of CV disease is extremely counterproductive…

A large observational study involving 153,840 postmenopausal women aged 50 to 80 years enrolled in the Women's Health Initiative study found that statins were associated with a 48% increased risk of developing diabetes (Culver 2012, Arch Intern Med 2012; 172: 144). Potential psychiatric symptoms including depression, memory loss, confusion, and aggressive reactions have also been associated with statin use (Tatley 2007, Drug Safety 30: 195) …

Erectile dysfunction, to take another adverse effect, is not mentioned in the statin trials. Yet, when it was specifically looked for, around 20% of men appeared to be affected (Solomon 2006, *Int J Clin Pract* 60(2):141) »[21]
EIM rapportés dans les études au financement hors-fabricant

ADR UNDERESTIMATION IN STATIN TRIALS
Essais – Puissance de détection faible - Statinovigilance expérimentale

« The low rate of reporting of adverse events is based on multiple factors we have reviewed here, including the routine inclusion of an initial run-in phase in which statin-intolerant individuals are removed from a study before formal initiation. Moreover, subdividing adverse events into many different categories, as in the reports for myopathy and cerebral disorders, can make it more difficult to identify subtle, but consistent, statin-related pathologies »[22]

« One must ask the question to get the answer. Most RCTs have not systematically elicited information on many potential AEs –

[18] Nilsson et al. Journal of Negative Results in BioMedicine 2011 ; 10(6) – DOI 10.1186/1477-5751-10-6
[19] Roberts MD. Drugs Advisory Committe Meeting 15.12.2009 NDA 21-366 JUPITER - www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm194918.pdf
[20] ARDS. N Engl J Med 5.6.2014 ; 370: 2191 -- DOI: 10.1056/NEJMoa1401520 - http://www.nejm.org/doi/full/10.1056/NEJMoa1401520
[21] Thompson et al. 2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf
[22] Diamond & Ravnskov, op. cit.

like fatigue, even though fatigue is among the most commonly reported statin problems by patients. Our study which was double-blinded, randomized, placebo-controlled did ask this question, and showed average harm[23] …

Our study also provided evidence to suggest that the glucose rise on statins is likely adaptive, protecting cell energy, and glucose rise on statins in the elderly related inversely to the development of fatigue on statins[24] »[25]

« Some of the factors that can lead to side-effects being under estimated:
a) they are virtually all paid for by the drug companies which have little interest in checking carefully for possible side effects. For instance diabetes is now recognised as a risk but just 2 / 29 statin trials reported on new cases of diabetes

b) many trials don't give any details about how side-effect reports were actually collected or how often
c) some trials exclude patients with disorder such as severe diabetes, kidney failure or hypertension, many of who would be likely to be given statins in the real world

d) people who volunteer for trials are often chosen because they are enthusiastic and so may be less likely to report side effects and less likely to stop taking the statins than real world patients
e) many trials start with a period when all subjects get the drug. Those that show a reaction to the drug can be excluded »[26]

« RCTs have historically been poor at statin adverse effects identification. Clinical trials often have low sensitivity for adverse events. Self-selection, human subject protections, research design *desiderata* (such as compliance run-ins) and cost efficiency conspire to produce enrollment of persons at lower risk of harm – lower comorbidities, polypharmacy, not frail or oldest elderly »[27]
sous-estimation des EIM dans les essais statiniques
« Comme beaucoup de médecins le constatent, les statines ont bien plus d'effets secondaires sérieux que ce que les fabricants avaient avancé »[28]

ADVERSE REACTIONS PROFILE OF FIBRATES
Pharmacovigilance
profil d'effets indésirables des fibrates
* Le profil d'effets indésirables des fibrates (gemfibrozil, fénofibrate, etc.) est surtout constitué de :[29]

a) troubles digestifs fréquents ;
b) céphalées, sensations vertigineuses, fatigues, visions troubles, insomnies, impuissances, dysgueusies ; éruptions cutanées, prurits, photosensibilisations, alopécies

c) thrombopénies, anémies, leucopénies ; hypoglycémies ; augmentations des transaminases ; lithiases biliaires ; insuffisances rénales aiguës et chroniques ; myopathies et rhabdomyolyses
d) Un essai à long terme a montré une surmortalité sous clofibrate, liée à plusieurs pathologies dont des cancers

ADVERSE REACTIONS PROFILE OF STATINS
Statinovigilance
profil d'effets indésirables des statines
* Le profil d'effets indésirables des statines (simvastatine, pravastatine, etc.) est surtout constitué, selon Prescrire en 2011[30], de :
« a) troubles digestifs fréquents
b) céphalées, sensations vertigineuses, insomnies, visions troubles, dysgueusies
c) atteintes musculaires, rhabdomyolyses, tendinites

d) augmentations des transaminases, justifiant un bilan hépatique avant traitement et une surveillance pendant le traitement

[23] Golomb et al. Arch Intern Med 2012; 172: 1180 – at: http://archinte.jamanetwork. com/article.aspx?articleid=1183454
[24] Golomb et al. Circulation 2013; 127: AP041 - at: http://circ.ahajournals.org/ cgi/content/meeting_abstract/127/12_MeetingAbstracts/ AP041
[25] Beatrice Golomb. European Journal of Preventive Cardiology 25.4.2014 - DOI: 10.1177/2047487314533085 – On line 25.4.2014 at http://cpr.sagepub.com/content/early/2014/04/24/2047487314533085
[26] Jerome Bern. http://healthinsightuk.org/2014/05/22/eminence-based-medicine-defends-the-status-quo-on-statins/#more-1157
[27] Beatrice Golomb. Clin Invest 2013 ; 3(10) : 913
[28] Martin Juneau, cardiologue
[29] Rev Pescrire 2011 ; 31(338 suppl. interactions) : 60-76 et 82-129
[30] Rev Pescrire 2011 ; 31(338 suppl. interactions) : 60-76 et 82-129

jusqu'à 1 an après la dernière augmentation de dose ; rares hépatites
e) éruptions cutanées
f) diabètes avec la rosuvastatine

g) rares pancréatites, polyneuropathies périphériques, pneumopathies interstitielles et fibroses pulmonaires
h) réactions d'hypersensibilité
i) Il existe un doute sur un surcroît d'insuffisances rénales avec la rosuvastatine »

AFCAPS/TexCAPS, THE TRIAL *Prévention primaire – Lovastatine 20-40 mg c. placebo – Arrêt prématuré*
= Air Force / Texas Coronary Atherosclerosis Prevention Study
* Princeps publication : Downs/*JAMA*/1998[31]

METHODOLOGY
* Participants' demography : 6605 randomized; 85% men; average age 58 years (all > 45 years); 997 women or 15% (all aged > 55 years)
* Participants' health : healthy Air Force staff
* Comparison : lovastatin 20-40 mg targeted to lower LDL-C below 1.10 g/L

* Followup : 5.16 years (62 months), prematurely stopped as planned when first CHD event relative risk reduction reached -36%
* Funding : « This study was funded by Merck & Co. Inc. The opinions stated in this study are the authors' (sic) and do not represent those of the Department of Defense or the US Air Force »[32]

* Primary endpoint : fatal MI, nonfatal MI, unstable angina, sudden cardiac death – Biased by heterogeneity of (a) relative frequencies of individual endpoints, (b) uneven patient-valued seriousness of components (two are fatal, two are not), (c) risk of subjectivity in diagnosing unstable angina

* Positive compliance (active group adherence) : 71%
* Negative compliance (control group adherence) : 63%

RESULTS
Overall relative risk reduction, absolute risk reduction (RRR) or increase (ARI) by 100 patient-years :
a) TOTAL MORTALITY: RRI of +4%, NS, from an excess of 3 more deaths overall on lovastatin (80 deaths / 3304 on statin and 77 deaths / 3301 on placebo), annual NNH = 5725 patient-years, annual inefficacy rate = 100%
b) CHD deaths : absolute risk reduction of -0.3 per 100 patient-years, NNT = 3333 patient-years, annual inefficacy rate = 99.7%

c) fatal or nonfatal MI : relative risk reduction of -40% and absolute risk reduction of 0.23 per 100 patient-years, NNT = 435 patient-years, annual inefficacy rate = 99.72%
d) fatal CV events : ARI of +0.4 per 100 patient-years, NNH = 2500 patients-years

Unreported effects :
* New onset diabetes not reported in princeps publication ; obtained later by meta-analyst Sattar, no increase
* Health related quality of life *not reported*

Numerical results in women :
a) RRI of +53 %, NS, for total mortality (4 more dead women on lovastatin certainly excludes any mortality benefit)
b) RRI of +199 %, NS, for CHD mortality (2-fold increase in CHD mortality certainly excludes any benefit)
c) relative risk reduction of -31 %, NS, for nonfatal MI
d) relative risk reduction of -46.3 %, NS, for CHD events (primary endpoint)

« If 1000 men and women (only 15% were women, normal, this is the Air Force) were treated with lovastatin for 5 years [5000 patient-years], approximately 19 acute major coronary events (12 MI and 7 unstable anginas) and 17 coronary revascularizations could be prevented »[33] …

for an annual NNT of 263 patient-years for postponing these events, or an average delay of 33 hours for these events to occur when benefit is spread over everyone of the 263 statinized patients, and an annual inefficacy rate of 99.6%... Note that

[31] Downs et al. JAMA 1998 ; 279 :1615 – Full article on http://courses.ahc.umn.edu/pharmacy/5822/Lectures/AFCAPSTEXCAPSTrial.pdf
[32] Downs et al. Am J Cardiol 1997; 80: 287 at http://www.apebm.com/workshop-materials/articles/AFCAPS%20Design_Tx_EBD_2006.pdf
[33] Downs et al. JAMA 1998; 279(20): 1615 - doi: 10.1001/jama.279.20.1615 - http://jama.jamanetwork.com/article.aspx?articleid=187569

'presentations of unstable angina' and 'decisions to revascularize' are 'soft, subjective' endpoints and highly sensitive to inadvertent unblinding through peeking at the lipid levels in the statin arm in an emergency room setting

« The total mortality rate was similar in each group, with 80 deaths among participants treated with lovastatin and 77 deaths among participants treated with placebo (0.46 and 0.44 per 100 patient-years in participants treated with lovastatin and placebo, respectively) »[34] or 3 more deaths overall on lovastatin

« Lovastatin's final mega-trial AFCAPS/TexCAPS ended with 3 fewer deaths on placebo »[35] but 4 more deaths in the subgroup of women on lovastatin

* The absolute risk reduction in the primary composite endpoint was 0.41 per 100 patient-years (despite a RR of 0.63 and a relative risk reduction of -37%) for an NNT of 244 patient-years, an annual failure rate of 99.6% and an average delay of 36 hours per year of treatment[36]. Significance threshold was arbitrary and unadjusted for multiple comparisons

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : Yes, we have access to basic data, are willing to share and have already made baseline data available to CTT

l'essai dit Afcaps/Texcaps

* Publication princeps : Downs/JAMA/1998
* Comparaison : lovastatine c. placebo
* Suivi moyen : 5,2 ans
* Critère principal combiné : mortalité totale; mortalité coronarienne; IM non fatal avec revascularization (un critère 'mou')

* Démographie des participants : 6605 - âge moyen 58 ans; 85% hommes >45 ans - 997 femmes ou 15%, toutes > 55 ans, moyenne 62 ans - 89% de blancs
* Santé des participants : IMC moyen 27 - 35% sédentaires - 0% coronariens - 16% antécédents familiaux; 6% diabétiques; 22% hypertendus; 12% fumeurs

* Dans le groupe statinisé le RR de premier événement coronarien aigu grave (critère combiné principal) fut de 0,63 (relative risk reduction de -37%, p<0,001), celui de mortalité totale fut de 1,045 (+ 4.5%, NS), celui de décès coronariens de 0,67 (- 33%, NS), et celui d'événements coronariens de 0,60 (- 40%)... Les infarctus, mortels ou non, sont réduits de 35 % (p=0,014), les gestes de revascularisation de 33 % (p=0,004), les événements CV, mortels ou non, de 24 % (p=0,006)...

Le RR de décès CV fut de 0,71 (- 27%, NS), le faible nombre survenus dans les deux groupes (20 vs 16) ne permet pas de mettre en évidence un bénéfice significatif…

La mortalité non CV et l'incidence des cancers sont identiques dans les deux groupes. La réduction absolue – même celle du critère principal combiné – ne fut que de 0,41 par 100 patients-année, d'où un NNT de 244 patients-année et un taux annualisé d'échec de 99,6%. Le seuil de signification arbitrairement fixé à 5% n'est pas ajusté pour les comparaisons multiples (multiples critères individuels), il aurait dû être au moins de 1%...

* Conclusion avec conflation (with spin) : leurs conclusions vont dans le sens de leurs intérêts. Ils se rangent derrière les recommandations de l'establishment statinique. Bel exemple de conflation intéressée qui inclue les femmes dans la conclusion, ce qui est trompeur, parce ce qu'elles ne constituaient que 15% des effectifs et virent augmenter leur risque de mortalité totale et coronarienne

* Conclusion factuelle (no spin): Aucune réduction absolue parmi les nombreux critères d'évaluation ne fut cliniquement pertinente; en assumant qu'un NNT doive être inférieur à 100 patients-année pour être considéré cliniquement signifiant dans ce contexte

AGEING PROCESS SPEEDED UP BY STATINS

Statinovigilance - Pharmacopathologie

« Statin side effects include memory loss, myopathy, cataract formation, and increased risk of diabetes. We have previously shown that aging and chronic metabolic diseases such as *diabetes* reduce the differentiation and proliferation potential of

[34] Ibidem
[35] Vos E. Nutr Metab Cardiovas Dis 2007 ; 17 : e19
[36] Ibidem, table 3

mesenchymal stem cells (MSCs)...

The novel results of this study indicate that statins impair the differentiation potential of MSCs in a similar fashion to the process of *aging* and *diabetes*. Long-term use of statins has been associated with adverse effects including myopathy, neurological side effects, and an increased risk of diabete...

Statins impaired the osteogenic and chondrogenic differentiation potential of MSCs and *increased cell senescence and apoptosis*, as indicated by upregulation of p16, p53 and Caspase 3, 8, and 9. Statins also *impaired the expression of DNA repair genes*, including XRCC4, XRCC6, and Apex1. While the effect on macrophage differentiation explains the (pleiotropic) beneficial side of statins, their impact on other biologic properties of stem cells provides a novel explanation for their adverse clinical effects…

Our study shows statins may *speed up* the *ageing process*. People who use statins as a preventative medicine should think again as our research shows they may have general unwanted effects on the body which could include muscle pain, nerve problems and joint problems »[37]
accélération statinique du processus de vieillissement

AIM-HIGH, THE TRIAL *Niacine c. placebo – Arrêt prématuré pour inefficacité – Prévention secondaire chez patients déjà sous simvastatine*

Aim for High HDL Cholesterol

« 3414 patients were randomly assigned to receive niacin or placebo over simvastatin. The trial was *stopped* after a mean follow-up period of 3 years owing to a *lack of efficacy*. At 2 years, niacin therapy had:

a) increased the median HDL-C level from 0.91 mM per liter to 1.08
b) lowered the TG level from 1.85 mM per liter to 1.38 mM
c) lowered the LDL-C level from 1.91 mM per liter to 1.60 mM, a -16% relative reduction…

The primary end point occurred in 16.4% in the niacin group and in 16.2% in the placebo group (HR = 1.02, NS)… Among patients with atherosclerotic CV disease and LDL-C levels < 1.81 mmol/l, there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite improvements in HDL cholesterol and triglyceride levels »[38]

* Health related quality of life *not reported*

* Conclusion factuelle : clinically negative trial. In contradiction with the lipid hypothesis
l'essai dit Aim-High
« La niacine va élever les HDL mais sans avoir aucun impact sur les fréquence des accidents cardiaques »[39], contredisant l'hypothèse lipidique
« A ce jour, la baisse des TG ou l'augmentation du HDL-Cholestérol par des moyens pharmacologiques n'a pas été associée à une prévention de la survenue d'évènements CV ni à une diminution de la mortalité totale »[40]

ALERT, THE TRIAL
Prévention chez transplantés rénaux – Essai cliniquement négatif – Réfutation de l'hypothèse lipidique

Princeps : Holdaas H et al. *Lancet* 2003 ; 14; 361(9374): 2024-31[41]
« 2102 patients randomised to fluvastatin 40 mg/day or placebo ; after 5.1 years, LDL-C fell -32% without CVD event reduction[42] »
l'essai dit Alert

ALLHAT-LLT, THE TRIAL
Financement majoritairement public – Pravastatine 40 mg c. soins usuels – Prévention primaire chez hypertendus – Sans double

[37] Reza Izadpanah et al. American Journal of Physiology - Cell Physiology – 2015; 309(8): C522-C531 - DOI: 10.1152/ajpcell.00406.2014 - http://ajpcell.physiology.org/content/309/8/C522
[38] AIM-HIGH. NEJM 2011 ; 365 : 2255 - http://www.nejm.org/doi/full/10.1056/NEJMoa1107579
[39] Even, page 85
[40] BIP 2014 no 2 page 5
[41] Abstract on https://www.ncbi.nlm.nih.gov/pubmed/12814712
[42] DuBroff, 2016, op. cit.

insu avec placebo

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
* Princeps Publication : Anon/*JAMA*/2002[43]
* Funding : mainly *National Institutes of Health* (USA)

METHODOLOGY
* Participants demography : 10 355 hypertensives aged > 55 years ; average age 66.4 and 55% > 65 years; 5051 women or 48.8%
* Participants health : 100% with hypertension; 14.2 % with CHD; 35% with diabetes; baseline TC 5.8 mM (120-189 mg/dL); baseline LDL-C 2.6 to 4.9 mM (100-189 mg/dL), average 3.8 mM

* Follow-up : mean 4.8 years (58 months)
* Funding : mainly public, NHLBI (USA); some support by Pfizer; pills by BMS
* Comparison : pravastatin low dose 40 mg versus usual care
* Methodology at high risk of bias (NICE 2014); randomized, open (no blinding), no placebo; sample size > 10K, duration >1 year

* Positive compliance (active group adherence) : 80%
* Negative compliance (control group adherence) : 83%

RESULTS
Surrogate lipid reduction :
a) relative risk reduction of TC
b) relative risk reduction for LDL-C : -28% at 4.8 years and -9.75 % at 6 years – Absolute levels were 4.77 mM under statin and 5.32 mM under usual care (from NICE 2014)

Clinical data:
a) TOTAL MORTALITY : Relative Risk Increase is 1% and NS (521 deaths / 4465 in treated arm - 513 deaths / 4405 in placebo arm) – 6 year mortality rate is 14.9% in treated group and 15.3% in control usual care group - Rate difference is 0.4%, NNH = 250 over 6 years, and 1500 per treatment-year
b) CHD events relative risk reduction = -9%, NS

* Health related quality of life *not reported*
* New onset diabetes not reported in princeps publication ; obtained later by meta-analyst Sattar, a +15% RRI. And also by NICE 2014, calculated for 6 years : 238 cases/3017 (7.9%) under statin, 212 cases/3070 under usual care (6.9%), a +1% ARI
* Total serious adverse events *not reported*

« Afer 4.8 years, no benefit was observed on the primary endpoint of :
a) total mortality with pravastatin (14.9% vs. 15.3% for usual care), or on the secondary endpoints of
b) CHD events (nonfatal MI or CHD death) : 9.3% with pravastatin vs. 10.4% with usual care, or on

c) cause-specific mortality,
d) cancer (9.6% vs. 9.3%), or
e) stroke incidence, which was similar between treatment groups (5.3% vs. 5.8%) »

Numerical results in women :
a) RRI of total mortality: +2%, NS
b) RRI of CHD events : +2 %, NS

« The reduction in the primary CV outcomes did not reach a statistical significance »[44] - « Only one major non-industry funded study on statins has been done, ALLHAT-LLT. The main findings were summarised: 'Although pravastatin has been shown in multiple large clinical trials to reduce CHD morbidity and CHD mortality (sic), no benefit was demonstrated in ALLHAT-LLT, the largest clinical event trial of pravastatin published to date'»[45]

« The only major non pharmaceutical funded study on statins vs placebo was ALLHAT-LLP. Which was run by the National Institutes for Health (NIH). It was reported thus:

[43] JAMA 2002 ; 288 : 2998 - summary at http://www.ncbi.nlm.nih.gov/pubmed/12479764
[44] Zhou et al. Am Heart J 2006 ; 151(2) : 273
[45] Thompson et al. 2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf

'Washington, DC – Surprising results of an unblinded but randomized comparison of pravastatin (Pravachol® – Bristol-Myers Squibb) vs "usual care" in patients with hypertension and moderate hypercholesterolemia enrolled in ALLHAT-LLT show that pravastatin did not significantly reduce either all-cause mortality or fatal or nonfatal CHD in these patients.' »[46]

Diabetic subgroup : no benefit[47]

Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE

Factual conclusion : Results are negative clinically, even if trial was not double-blinded or placebo-controlled
l'essai dit Allhat-Llt
« Il s'agissait en 2002 de l'essai le plus large jamais réalisé en utilisant la pravastatine, 10 000 participants au LDL-C élevé, divisés en deux groupes. Un sous pravastatine, l'autre avec des conseils sur le mode de vie. Pour les décès dus à des IDM, aucune différence entre les deux groupes. La statine avait bien baissé la cholestérolémie de 28% des sujets parmi ceux qui la prenaient, mais pas une seule vie n'avait été sauvée...

La pravastatine n'avais pas significativement réduit la mortalité toutes causes confondues, pas plus que les maladies coronarienne fatales ou non fatales »[48]

ALLIANCE OF CHOLESTEROLISTS
Persuation clandestine
= AHA + ACC + NCEP (USA), 'The Alliance'
l'Alliance des hypercholestérolistes
NdT : terme proposé par Jean-Marie Therrien pour désigner les principales institutions qui utilisent avec une efficacité redoutable la *persuasion clandestine* pour désinformer les médias, les prescripteurs et la population[49]

ALLIANCE, THE TRIAL *Atorvastatine dosée sur cible c. atorvastatine en dosage usuel – Essai au su – Prévention secondaire chez coronariens*
Aggressive Lipid-Lowering Initiation Abates New Cardiac Events[50]
Princeps publication : Koren/*JACC*/2004

METHODOLOGY
* Randomised : 2442 patients
* Comparison : atorvastatin 80 mg vs. usual care by family doctors using as statin at standard dosages; unblinded
* Duration : 54 months

RESULTS
* Lipid reduction : relative risk reduction of -25% under atorvastatin and relative risk reduction of -15% under usual care (normal doses of statins by primary care physicians)

* TOTAL MORTALITY : relative risk reduction = -4%, NS – 121 deaths / 1217 patients on targeted dose and 127 / 1225 patients on usual dose, over 54 months
* Kaplan-Meier plot on all-cause mortality was not published
Commentary : « Hardly surprising, corroborating the result of IDEAL and TNT »[51]

* Non-fatal MI : 52 under atorvastatin and 94 under 'usual care', a relative risk reduction of -45%
Commentary : « Totally unverifiable… How could a relative reduction in non-fatal MI approaching 50% be without any impact on

[46] Kendrick M. http://drmalcolmkendrick.org/2015/09/07/the-augean-stables-part-ii/
[47] Dubroff, QJM 2.11.2017 - https://academic.oup.com/qjmed/advance-article-abstract/doi/10.1093/qjmed/hcx213/4587483?redirectedFrom=fulltext
[48] Sinatra & Bowden, 2014, page 179
[49] Une histoire inventée : Essai sur le cholestérol. Montréal : Carte Blanche ; 2014
[50] Koren & Huninghake. J Am Coll Cardiol 2004; 44(9): 1772 - doi:10.1016/j.jacc.2004.07.053 - http://content.onlinejacc.org/article.aspx?articleid=1136072
[51] de Lorgeril 2014, Cholesterol and statins : Sham science and bad medicine (Kindle)

mortality … unless the figures were tampered with ? »[52] or maybe unblinding led to biased diagnoses of non-fatal MI

« The ALLIANCE study[53] was a 4-year, population-based, open-label, randomized study that compared aggressive lipid-lowering with atorvastatin to usual medical care in a managed healthcare environment. The primary objective was to test the hypothesis that lowering LDL-C to levels lower than current NCEP guidelines would provide an incremental reduction in major CV events compared to standard clinical practice in patients with CHD »[54]

« 1,217 patients were randomized to the atorvastatin group and 1,225 to the usual care group. Followed for 53 months. The absolute risk reduction attributable to aggressive lipid therapy compared to usual care was 4% for a NNT of 25 patients treated to be spared 1 primary endpoint »[55] but the annualized NNT (the only method of fair comparisons across trials) is 110 patient-years…

LDL-C dropped 16% from 2.9 to 2.5 mM. The results do not support the hypothesis that LDL-C reduction reduces cardiac death…

The primary composite endpoint is heterogenous, associating : cardiac death, non-fatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization. In a trial without blinding, diagnoses of non-fatal MI and unstable angina are more subject to the attitude of carers, and opting for revascularization is influenced by availability of cat lab facilities of local hospitals and by their cardiologists' attitude...

The only endpoint reaching significance is non-fatal MI but the absolute risk reduction is clinically negligible since 3.4% less over 4.4 years amounts to 0.77% per year and annualized NNT = 129 patient-years (the only method of fair comparisons across trials) in trial conditions
* Health related quality of life *not reported*

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE. What does the manufacture have to hide ?
l'essai dit Alliance

AMI INCIDENCE AND MORTALITY UNRELATED TO STATINIZATION (SW) *Épidémiologie*
« In Sweden, the utilisation rate of statins increased almost 3 times for both men and women between 1998 and 2002. During 1998-2000 the incidence of acute myocardial infarctions (AMI) decreased clearly for men but only slightly for women. Mortality decreased from 1998 to 2002. The change in statin utilisation from 1998 to 2000 showed no correlation to the change in AMI mortality from 2000 to 2002...

Statin utilisation and AMI-incidence or mortality showed no correlations when adjusting for socio-economic deprivation, antidiabetic drugs and geographic coordinates. Despite a widespread and increasing utilisation of statins, no correlation to the incidence or mortality of AMI could be detected »[56]
incidence et mortalité de l'IAM non reliées à la statinisation

AMYOTROPHIC LATERAL SCLEROSIS or ALS ; UPPER MOTOR NEURONE DISEASE *Statinovigilance*
* Golomb et al. 2018 examined US FDA Adverse Event Reporting System (FAERS) data to compare reporting odds ratios (RORs) of ALS and ALS-like conditions between statins and other drugs, for each statin agent. They were elevated for all statins : 9.90 for rosuvastatin, 16.2 for pravastatin, both hydrophilic ; 17 for atorvastatin, 23 for simvastatin and 107 for lovastastin, all lipophilic ; 57.1 for simvastatin[57].

« The WHO Foundation Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre or UMC) has received many individual case safety reports (ICSRs) associating statin use with the occurrence of muscle damage, including

[52] de Lorgeril 2014, op. cit.
[53] Koren & Huninghake. J Am Coll Cardiol 2004; 44(9): 1772 - doi:10.1016/j.jacc.2004.07.053 - http://content.onlinejacc.org/article.aspx?articleid=1136072
[54] http://www.cardiologyupdate.ca/crus/202-047_English.pdf
[55] Koren & Huninghake. J Am Coll Cardiol 2004; 44(9): 1772 - doi:10.1016/j.jacc.2004.07.053 http://content.onlinejacc.org/article.aspx?articleid=1136072
[56] Nilsson et al. Journal of Negative Results in BioMedicine 2011; 10: 6 - doi:10.1186/1477-5751-10-6
[57] Golomb et al. *Drug Saf* 2018 Apr;41(4):403-413 - https://doi.org/10.1007/s40264-017-0620-4 - https://www.ncbi.nlm.nih.gov/pubmed/29427042

rhabdomyolysis, and also peripheral neuropathy. A *new signal* has now appeared of disproportionally high reporting of upper motor neurone lesions (amyotrophic lateral sclerosis (ALS)-like syndrome)...

Upper motor neurone lesion is a rare adverse event reported in relationship to drugs in Vigibase (a database containing nearly 4 million case reports in 2007). Of the total of 172 ICSRs on this reported term, 43 were related to statins, of which 40 were considered further: all but one case was reported as ALS. In 34/40 reports a statin was the *sole reported suspected drug*. The diagnostic criteria were variable, and 7 of the statin cases also had features of peripheral neuropathy...

Of a total of 5534 case reports of *peripheral neuro*pathy related to any drug in Vigibase, 547 were on statins. The disproportional reporting of statins and upper motor neurone lesion persisted after age stratification, and such disproportionality was not seen for statins and Parkinson's disease, Alzheimer's disease, extrapyramidal disorders, or multiple sclerosis-like syndromes[58]
maladie du neurone moteur / du motoneurone ; sclérose latérale amyotrophique
* pour des raisons intriguantes, ce signal émis en 2017 par le directeur de la pharmacovigilance mondiale (Prof. Edwards) n'a pas été l'objet d'une enquête de pharmacovigilance en bonne et due forme. S'agit-il d'autocensure ? de pression des fabricants ? Par contre, Golomb et coll. ont fouillé dans la base étatsunienne de pharmacovigilance et ont publié en 2018 des taux disproportionnels de signalement troublants pour toutes les statines

« Sclérose latérale amyotrophique et statines ? - La sclérose latérale amyotrophique (SLA) est une maladie neurodégénérative caractérisée par une paralysie musculaire progressive due à une dégénérescence des motoneurones du cortex moteur primaire, de la voie corticospinale, du tronc cérébral et de la moelle épinière. Les mécanismes suggérés sont une dysfonction mitochondriale et un stress oxydatif, des mutations génétiques étant aussi identifiées.

Concernant les statines pour lesquelles les effets musculaires divers sont pharmacologiquement « attendus » et bien décrits (rhabdomyolyse, faiblesse ou douleur musculaire, myopathie autoimmune,...), des analyses antérieures de la base mondiale de Pharmacovigilance (Vigibase) et celle de la FDA (Adverse Event Reporting System) avaient identifié des cas de notification spontanée de SLA sous statines. Récemment, des auteurs (*Drug Saf* 2018;41:403) ont réalisé une étude de disproportionnalité (cas-non cas) pour mesurer l'association SLA-Statines dans le FAERS en calculant le ROR (Reporting Odds ratio).

Les données montrent un ROR plus élevé pour les statines lipophiles : ROR de 9,1 pour la rosuvastatine et 16,2 pour la pravastatine, statines hydrophiles et ROR de 17,0 pour l'atorvastatine, 23,0 pour la simvastatine et de 107,0 pour la lovastatine non commercialisée en France. Les limites de l'étude concernent essentiellement la réelle identification des SLA dans une base de données avec des erreurs de codage ou de diagnostic et l'absence de dénominateur par rapport au nombre de sujets exposés.

Néanmoins, au niveau animal, une étude a mis en évidence une accélération de la progression de la maladie et une réduction de survie chez les souris SOD1 (mimant la SLA) dans *Muscle Nerve* 2016;54:284. Enfin, les auteurs discutent l'association entre la réduction de survie des patients atteints par la SLA et l'exposition aux statines et l'accélération d'un processus existant. Les données restent controversées. Malgré l'existence de nombreux points d'interrogations, le sujet de SLA d'origine médicamenteuse mérite attention dans les années à venir.[59] »

AN APPLE A DAY KEEPS THE STATIN AWAY *Proverbe*
* inspired by a humorous *BMJ* paper, « A statin a day keeps the doctor away »[60]
Une pomme par jour dispense d'une statine par jour – (Traduction libre)
* Noter que les couts directs (achat en épicerie) sont parfois identiques en achetant générique ! Mais les coûts indirects de la statinothérapie sont considérables

ANTIHYPERLIPIDEMIC AGENTS OVERUSE (USA) *Revue d'utilisation*
* Estimated prevalence (1 prescription in last 30 days) in the period 2007-2010[61] :

a) 44.3 % in women aged 75+
b) 55.1 % in men aged 75+

c) 39.6 % in women aged 65-74
d) 51.5 % in men aged 65-74

[58] Edwards IR et al. *Drug Saf* 2007; 30(6): 515 - https://www.ncbi.nlm.nih.gov/pubmed/17536877
[59] Haleh Bagheri (CRPV de Toulouse)
[60] Briggs & Mizdrak. http://www.bmj.com/content/347/bmj.f7267
[61] http://www.cdc.gov/nchs/data/hus/2013/093.pdf

d) 19.2 % in women aged 45-64
e) 24.7 % in men aged 45-64

f) 11.6 % of women of all ages
g) 13.5 % of men of all ages
surutilisation des agents antihyperlipidémiants (ÉU)
* Cette revue d'utilisation de médicaments vient des *Centers for Disease Control* états-uniens et porte sur la population civile non institutionnalisée

APPROVAL BY SURROGATE ENDPOINTS LOWERING (FDA)
"Knowing what [drugs] do to LDL and HDL doesn't tell you what they'll do to people[62][treated for their cholesterol levels] »
« In 1992, the FDA initiated an accelerated-approval pathway (Subpart H) to allow approval on the basis of surrogate end points that were seen as reasonably likely to predict patient benefit. Subpart H shortened the clinical-investigation process by permitting trials to end before the occurrence of hard clinical end points (e.g., hospitalization, MI, and death) »[63]
approbation sur la base d'une réduction de critères de substitution
* Cette permissivité réglementaire protège les promoteurs mais compromet la santé et les budgets associés

ARBITRARY LDL-C DIAGNOSTIC THRESHOLDS
« Current clinical evidence does not demonstrate that titrating lipid therapy to achieve proposed low LDL cholesterol levels is beneficial or safe… No high-quality evidence could be found that suggests that titrating lipid therapy to recommended low-density lipoprotein (LDL) cholesterol targets is superior to empirically prescribing doses of statins used in clinical trials for all patients at high cardiovascular risk...

Studies addressing benefits of achieving LDL cholesterol goals have had avoidable problems, such as reliance on ecological (aggregate) analyses, ignoring statins' other proposed mechanisms of action, and not accounting for known confounders (especially healthy volunteer effects). Much more reliable evidence on currently proposed LDL cholesterol goals could be expeditiously produced by conducting cohort analyses of past statin trials that control for statin dose and pill adherence...

Dichotomous comparisons (such as comparing those who reach goal vs. those who do not) can mistakenly suggest that not achieving the treatment goal results in moderate risk when in fact almost all of the risk is caused by large deviations from the ideal goal. Proposals for treatment goals should also consider the risks, patient burden, and societal costs of the treatments that may be needed to reach those goals »[64]

« In 1988, the LDL level of 160 mg/dL (4.14 mM) was selected as abnormal in part because it was a value above which the risk of CHD was said to increase 'steeply' and in part because it corresponded 'approximately to the 75th percentile for the adult US population' »[65]

* In 2013 the ACC/AHA controversial guidelines[66] still use diagnostic LDL levels : diabetics aged 40-75 with between 70 and 189 mg/dL (1.83 mM and 4.89 mM), adults with 190 mg/dL (4.9 mM)[67] but in the same document the LDL treatment targets are abandoned !

« The assumption that reducing LDL and raising HDL would lower the risk of heart attack and stroke is now being rejected [at last !]. There is no need to routinely monitor blood cholesterol any more, according to the new 2013 ACC/AHA guidelines. Why? Because the arbitrary cholesterol targets are not supported by scientific evidence. Let's not forget that about three-quarters of people have normal cholesterol levels when they have heart attacks...

That hasn't changed during the great statins experiment of the past decade. Logically, that means physicians should be prescribing fewer statins, not more...

But the new guidelines are being sold as a leap of faith, a belief that statins can prevent heart attacks and strokes, even if that potential benefit doesn't seem to come from controlling cholesterol... They are not effective in women. And they don't provide

[62] Harlan Krumholz
[63] Darrow et al. http://www.nejm.org/doi/full/10.1056/NEJMhle1311493
[64] Rodney Hayward et al. Ann Intern Med 2006; 145: 520
[65] Psaty & Weiss. 21.11.2013. doi:10.1001/jama.2013.28420
[66] Stone et al. Circulation - doi:10.1161/01.cir.0000437738.63853.7a
[67] Psaty & Weiss. 21.11.2013. doi:10.1001/jama.2013.28420

much benefit, if any, to healthy people without a history of heart disease – regardless of their cholesterol levels »[68]

« As a consequence of PROVE IT-TIMI-22, IDEAL and other trials, the most recent update to the NCEP recommends a target level of LDL cholesterol of 1.8 mM (70 mg/dL) for high-risk patients »[69] is a patent example of biased recommendations ; PROVE IT-TIMI-22 should not be cited as evidence and deserves retraction (from the NEJM) for having 'forgotten' to analyze and publish their full data[70]

seuils diagnostiques arbitraires du LDL-C

ASCOT-LLA, THE TRIAL *Atorvastatine 10 mg c. placebo - Prévention primaire chez hypertendus – Arrêt prématuré injustifié*
Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
* Princeps publication : Sever/*Lancet*/2003[71]

METHODOLOGY
* Comparison : atorvastatin 10 mg vs. placebo
* Primary composite endpoint contains 3 components: [CHD death + non fatal overt MI + silent non fatal MI]
and is biased by the heterogeneity/incoherence of individual outcomes :

(a) uneven patient-valued *seriousness* (one fatal, two non fatal),
(b) uneven baseline *frequencies* of individual events
(c) uneven between-treatment observed *differences*,
(d) subjectivity in *diagnosing* silent MI

* Participants demography : 10 305 randomized ; 1942 women (18,8 %); 81.2% men; mean age 63 years (64% > 65 years, inclusion range 40-79 years)
* Participants health : 100 % hypertensive with 160/100 mmHg untreated or 140/90 treated; TC < 6,5 mM, mean 5.5 mM ; mean LDL-C of 3.4 mM (132 mg/dl), 80% > 2,6 mM (100mg/dl); 25% diabetics; 33% smokers; ?% with TIA ; ?% with peripheral arteriopathy; ?% with LVH ; 0% prior CHD ; at least one CV risk factor

* Follow-up and early stopping:

Planned for 5 years but stopped at 3.3 years (40 months) when there were 100 primary CHD events in the statin group (1.9 %) and 154 CV events in the placebo group (3.0 %), a relative risk reduction of -36 % with a P = 0.0005 and an absolute risk reduction of 54 events and an annual absolute risk reduction of only 0.34 per 100 patient-years equivalent to an annualized NNT_{exp} of 294 and presumably higher NNT_{clin}. The *stopping boundary* was a P value of 0.001 for the relative risk reduction of the primary CHD events... CV mortality reduction from 1.6% in placebo to 1.4% in statin group was NS. All cause mortality reduction from 4.1% down to 3.6% was NS.

Early stopping was justified by authors « on the grounds that atorvastatin had resulted in a highly significant statistical reduction in the primary endpoint of CHD events compared with placebo and a significant statistical reduction in the incidence of stroke »…

but those reductions were presented as RR, as if the trial was only aimed at efficacy, the proper outcome for *internal* validity, whereas the trial was *pragmatic*, aimed at decision making, and should have used a clinically significant absolute risk reduction, the proper outcome for *external* validity...

Premature termination at 3.3 years was not based on reaching a clinically relevant annualized absolute risk reduction of a totally valid outcome (such as CV or all cause death) and therefore was not justified as a pragmatic trial intended to serve as an aid to clinical decision taking

* Positive compliance (active group adherence) : 87% during 3.3 years, but 0% for the next 1.7 years since 5 years were planned
* Negative compliance (control group adherence) : 91% for 3.3 years, but 0% during next 1.7 years since 5 years were planned

RESULTS
* Health related quality of life *not reported*

[68] André Picard 2013, http://www.theglobeandmail.com/authors/andre-picard
[69] Steven E Nissen. J Am Coll Cardiol 2009 ; 54(25) : 2363
[70] Paul v Nguyen
[71] Sever P et al. Lancet 2003 ; 361 : 1149 – Summary at http://www.ncbi.nlm.nih.gov/pubmed/12686036

Numerical results
* Lipid reduction, a surrogate outcome : relative risk reduction of LDL-C of -44%, a surrogate outcome, showing drug efficacy and satisfactory compliance

* Primary composite endpoint (fatal and nonfatal MI) : relative risk reduction of -36 % (HR = 0.64) but absolute risk reduction of only 0.34 events per 100 patient-years corresponding to an annual NNT = 294 patient-years (the only method for fair comparisons across trials), for a virtual average delay of only 30 hours per year of treatment when spread over everyone of the 294 participants…

With 293 patient-years not benefiting, hardly a motive for premature stopping of the trial at 3.3 years ; the 'clinical setting NNT' is presumably much higher

« In the placebo group, 3% suffered a heart attack vs 1.9% in the atorvastatin group. Thus, the absolute risk reduction was only 1.1 percentage points, which is 36% of 3 and 3 minus 1.9 = 1.1 [And the annual absolute risk reduction was 0.34 percentage point since 1.1 / 3.3 = 0.34] »[72]

« Moreover, there was no significant benefit in subgroups of patients at high risk of CHD, including those with diabetes, left-ventricular hypertrophy and previous vascular disease or for patients aged 60 years or younger, for those without renal dysfunction and for individuals with metabolic syndrome. For *women* there were *no benefits* at all. Indeed, there was a trend for worse, albeit non-significant, effects. Finally, there was no effect on either CV or non cardiovascular mortality »[73] - Diabetic subgroup : no benefit in primary endpoint (non-fatal MI + fat CHD) reported in princeps 2003 report, although a relative risk reduction in total CV events and procedures was added in a 2005 report…[74]

* Coronary events : relative risk reduction of -29 % (HR = 0.71) but absolute risk reduction of 0.44 events per 100 patient-years equivalent to an annual NNT of 230 patient-years for a secondary endpoint

* Composite secondary endpoint of CV events + procedures : relative risk reduction of 21 % (HR 0.79); but absolute risk reduction of only 0.65 per 100 patient-years equivalent to an annual NNT of 154 patient-years (the only method of fair comparisons across trials). Heterogeneity and softness of criteria within the composite endpoint makes it unreliable

Planned for 5 years but stopped at 3.3 years (40 months) when there were 100 primary CHD events in the statin group and 154 CHD events in the placebo group, a relative risk reduction of -36 % with a P = 0.0005 and an absolute risk reduction of 54 events (among 10 305 patients) and an annual absolute risk reduction of only 0.34 per 100 patient-years equivalent to an annualized NNT_{exp} of 294 and safely assumed higher NNT_{clin}. The *stopping boundary* was a P value of 0.001 for the relative risk reduction of the primary CHD events...

* Total mortality :
Internal validity : relative risk reduction of -13 % (HR = 0.87), NS
External validity : absolute risk reduction of only 0.17 per 100 patient-years equivalent to an annual NNT = 588 patient-years, corresponding to a virtual average life extension of 15 hours per year of treatment in trial-controlled conditions and presumably much less in clinical settings

* CV mortality :
Internal validity : relative risk reduction of -10 % (HR = 0.90), NS -
External validity : NONE, with an absolute risk reduction of only 0.05 per 100 patient-years, annual NNT_{exp} = 2000 patient-years

* Stroke, fatal or not : relative risk reduction of -27%, NS and absolute risk reduction of only 0.2 per 100 patient-years, annual NNT = 500 patient-years
* Serious adverse events : no reduction[75]

« The ASCOT study found angina relatively reduced by -41%, likely by the NO/eNOS nitroglycerin mimicking action that all statins

[72] Diamond & Ravnskov, op. cit.
[73] Diamond & Ravnskov, op. cit.
[74] Dubroff, QJM 2.11.2017 - https://academic.oup.com/qjmed/advance-article-abstract/doi/10.1093/qjmed/hcx213/4587483?redirectedFrom=fulltext
[75] Abramson et al. BMJ 2013;347:f6123 - doi: 10.1136/bmj.f6123

share »[76] a subjective symptom and a subjective diagnostic decision

* New onset diabetes reported in princeps publication, RR increase = +15%, NS

* ASCOT-LLA addressed the benefit of atorvastatin 10 mg (a cholesterol-lowering drug) in patients with hypertension (high blood pressure) but no previous CV disease (primary prevention). The trial was stopped at 3.3 years, and during this period the relative risk of a 'primary event' (heart attack, fatal or not) was reduced relatively by -36%...

The absolute risk reduction, however, was much smaller because the study group did not have a very high rate of CV events over the study period: 2.67% in the control group, compared to 1.65% in the treatment group...

Taking atorvastatin for 3.3 years, therefore, would lead to an absolute risk reduction of only 1.02% (2.67% minus 1.65%). The NNT to prevent 1 CV event would then be 98 over 3.3 years or 322 patient-years of exposure for 1 person to benefit, 321 patients being treated a whole year without benefit, representing a waste in health resources. The rate of inefficacy per year of treatment is 99.7%, thus there is no clinically meaningful benefit, but the authors conclude otherwise

« A meta-analysis[77] noted the weakness of the total mortality data in ASCOT-LLA. This study ended with 2 more undefined 'events' in women on atorvastatin than on placebo. During the study, the population assigned to the placebo did numerically better at a mean study duration of 1.7 years, whereas at 3.3 years the mortality curves did not differentiate »[78]

« In the placebo group, 3% suffered a heart attack vs 1.9% in the atorvastatin group. Thus, the absolute risk reduction was only 1.1 percentage points, which is 36% of 3. Moreover, there was no significant benefit in subgroups of patients at high risk of CHD, including those with diabetes, left-ventricular hypertrophy and previous vascular disease or for patients aged 60 years or younger, for those without renal dysfunction and for individuals with metabolic syndrome...

For women there were no benefits at all. Indeed, there was a trend for worse, albeit non-significant, effects. Finally, there was no effect on either CV or non-CV mortality »[79]

« ASCOT reported data on serious adverse events (SAE) but did not find a reduction associated with statins »[80]
« Why did ASCOT not detect significant adverse effects of statins? Simply because neither in its protocol, its performance, its analysis or its publication, was it able to do so :

a) Concomitant drugs (including some lipid-lowering treatments) were not controlled for
b) The investigators did not treat blindly the included patients, which deprived of any significance the way they managed, recorded or reported adverse effects (be they afterwards reviewed by an ad hoc committee 'unaware of treatment assignment')…

c) Those responsible for the study focused their analysis on statistical differences in 'serious' adverse events between both treatment groups, which left an impressive room for non-serious events of medical significance (e.g. myalgias...) as well as for differences of great epidemiological impact (e.g. rhabdomyolyses) even without reaching statistical significance (especially in a trial failing to identify any statistical benefit in term of total mortality…

and in a general context where the obvious aim is to treat, under the pretext of prevention, the maximum of subjects in perfect health)…

d) This is a worrying indicator of the current state of the art in clinical research to find, as illustrated by the letter of Peter Sever[81], a study such as ASCOT presented as a model of safety assessment when, after 3.3 years of treatment of more than 19K patients, the authors of the final publication did not need more than a 5-line paragraph to present the safety results »[82]..

e) Transparency
« Until we have completed and published our findings, we would be *reluctant* to hand over the database for pooled analyses »

[76] Eddie Vos. J Am Coll Cardiol 2009; 54: 2353
[77] Kostis et al. J Am Coll Cardiol 2012; 59(6): 572 – doi: 10.1016/j.jacc.2011.09.067
[78] Vos, Rose & Biron. J Clin Lipidol 2013 ; 7(3) : 222 & 228
[79] Diamond & Ravnosk, 2015, op. cit.
[80] Abramson et al 2012, op. cit.
[81] http://www.bmj.com/content/348/bmj.g4030
[82] Marc Girard, 27.6.2014 - http://www.bmj.com/content/348/bmj.g4030/rr/703689

answers co-chief investigator Peter S Sever to the *BMJ* in 2015 who had asked him in 2014 whether they have the patient level data and under what circumstances they would be willing to share them[83]…

The BMJ has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 is a record of the status and nature of response : « Yes, we have access to data. Once completed own data collection would be willing to share for purposes of meta-analysis »[84]

l'essai dit Ascot-Lla

* Publication princeps : Sever/*Lancet*/2003
* Comparaison : atorvastatine 10 mg c. placebo
* Démographie des participants : 10 305 ; 18,8 % de femmes ou 1 942 ; âge moyen 63 ans et 64% > 60 ans

* Santé des participants : 100 % hypertendus ; 25 % diabétiques ; cholestérol total < 6,5 mM, moyenne 5.5 mM ; LDL-C moyen de 3.4 mM
* Durée prévue : 5 ans ; *arrêt prématuré* après 3,3 ans (médiane) / 3,5 ans (moyenne) de suivi
* Critère principal : IM fatal ou non

Résultats numériques:
* Cholestérol total : réduction absolue de 1,3 mmol/L et relative de 10 %
* LDL-Cholestérol : réduction absolue de 1,1 mmol/L et relative de -9 %,

* Mortalité totale :
Validité interne : relative risk reduction -13 %, NS, soit 185 décès sous atorvastatine, 212 sous placebo ; une différence absolue de 27 morts

Validité n : Le taux de mortalité est après 3,5 ans de suivi de 3,6% sous statine et 4,1% sous placebo, pour une réduction statistique NS et une réduction absolue de 0,14% (4,1 - 3,6 = 1,1 / 3,5 = 0,14%, NNT annualisé = 714), non signifiante. Le retard de mortalité est de 13,6 heures par année de traitement (selon Kristensen et coll. qui se basent sur l'aire sous la courbe de survie pour le calcul) et de 12,3 heures si on utilise la méthode arithmétique et un NNT de 714 patients-année, d'où 713 patients sans bénéfice sur 714.

* La réduction absolue des AVC est de seulement 0,63% (NNT = 159)[85]

* Décès coronariens : relative risk reduction -10 %, NS
* Critère primaire (mortalité coronaire ou IDM non fatal) : relative risk reduction de -36%, soit 100 sous atorvastatine et 154 sous polacebo

* Événements coronariens : réduction relative du risque de -29 %, soit 178 sous atorvastatine, 247 sous placebo. Le NNT est de 322 années-patients pour retarder 1 événement coronarien (de 26 heures en moyenne si on répartit ce bénéfice parmi les 322 patients): bénéfice cliniquement insignifiant

* AVC fatal ou non : réduction relative du risque de - 27 %, NS ; 89 sous atorvastatine, 121 sous placebo
* Évènements CV : réduction relative du risque de - 21 %; 389 sous atorvastatine, 486 sous placebo
* Événements coronariens chez les femmes : augmentation relative du risque de +10%, mais NS
* Augmentation relative de +15 % de nouveau diabète mais NS

« On ne lit nulle part 'double insu' que ce soit dans le résumé, ou dans la section méthodes, ou dans la discussion. On ne trouve ensuite aucune description :

a) du dispositif pour assurer l'insu ;
b) de celui pour le maintenir ;
c) de la procédure pour lever l'insu en cas d'urgence

Enfin, si l'essai s'était effectivement déroulé en double aveugle, il n'y aurait aucune nécessité de préciser que le comité d'évaluation des effets indésirables était 'unaware of treatment assignment' : cela irait de soi, la levée de l'insu n'intervenant

[83] http://www.bmj.com/campaign/statins-open-data, 2015
[84] http://www.bmj.com/campaign/statins-open-data
[85] BIT (Espagne) Janvier 2007 ; 15(1) :1

d'habitude qu'en toute fin d'analyse »[86] - Cette remarque s'applique d'ailleurs à un grand nombre d'essais statiniques, et l'usage croissant de dossiers médicaux informatisés ne fait qu'augmenter le risque chez les soignants de découvrir la cholestérolémie[87]

ASPEN, THE TRIAL *Prévention primaire et secondaire chez diabétiques – Atorvastatine 10 mg c. placebo*
Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus

* Funding : private, Merck
* Princeps publication : Knopp/Diabetes Care/2006[88]
http://care.diabetesjournals.org/content/29/7/1478

* Median (50th percentile) duration : 4 years
* Comparison : atorvastatin 10 mg (medium dose) vs. placebo
* Methodology : randomized ; double-blind ; size > 1000 ; duration > 1 year

* Composite primary end point :
(a) objective events: CV death, nonfatal MI, nonfatal stroke, resuscitated cardiac arrest ; and
(b) subjective decisions: hospitalization for unstable angina, recanalization, bypass surgery

The endpoint validity is weakened by heterogeneity of outcomes concerning frequencies, differences under treatment, and relevance to patients' value, and by risk of unblinding before taking decisions. It cannot validly be used to estimate efficacy.

* Participants demography : 2,410 randomized diabetics ; 34 % women ; mean age 61 years (range 40-75)
* Participants health : 100 % diabetics ; 45% with CHD history (MI/revascularization/angina) and 23 % with other CV disease ; low LDL-C ; 58% hypertensive ; 1905 without (79 %) and 505 (21 %) with MI or intervention – (NB : No patients in renal failure such as in 4D trial in diabetics)

RESULTS
Surrogate
* Lipid reduction : LDL-Cholesterol relative risk reduction of -29%, from 2.93 mM (113 mg/dL) to 2.18 mM (84 mg/dL)

Clinical
* TOTAL MORTALITY RRI of +1%, NS – 70 deaths/1211 or 5.78% on atorvastatin and 68/1199 or 5.67% on placebo in 4 years ; 2 more deaths on statin (Kaplan-Meier plot on all-cause mortality was not published)
* CV mortality relative risk reduction of -2.6%, NS – 38 CV deaths/1211 on atorvastatin, 37/1199 on placebo, only 1 more on placebo

* Primary endpoint :
a) relative risk reduction of -10%, NS – 166 composite events on atorvastatin, 180 under placebo
b) absolute risk reduction of -1.3% (from 15% to 13.7%) over 4 years, or -0.325 % per year for a NNT of 308 patient-years in trial conditions, presumably larger in clinical setting, therefore clinically futile

c) in primary prevention subgroup of 1905 without MI or intervention : relative risk reduction of -3 %, NS (10.4% on atorvastatin, 10.8% on placebo)
d) in *secondary prevention* subgroup of 505 with MI or intervention : relative risk reduction of -18 %, NS (26.2% on atorvastatin, 30.8% on placebo)

* Myocardial infarction relative risk reduction of -27%, NS
* Myocardial infarction in primary prevention subgroup relative risk reduction of -19%, NS
* Myocardial infarction in *secondary prevention* subgroup relative risk reduction of -36%, NS
* Fatal and non fatal stroke relative risk reduction -2.8%, NS, 34 in treatment, 37 in control

HARMS
* Rhabdomyolysis (CK>10 x ULN) : RR = 1.0, one case in the statin group and 1 in the placebo group over 4 years – This result implies that no more severe myopathies developed over a period of 4,824 patient-years of atorvastatin exposure than under placebo, difficult to believe

[86] Marc Girard, 2014
[87] Nguyen, BMJ, 2014
[88] Knopp RH et al. Diabetes Care 2006 ; 29: 1478 – abstract on http://www.ncbi.nlm.nih.gov/pubmed/16801565

* Myalgia : RRI of +89 %, 36 cases on atorvastatin and 19 on placebo – ARI of +0.35 per 100 patient-years and NNH of 288 patient-years – This experimental NNH is much higher than NNHs nearing 5 patient-years reported by several observational studies non funded by promoters

* Liver transaminase elevation (> 3 x ULN) : RRI = +21%, NS - 17 under statin, 14 under placebo – ARI of 0.06% patient-years and NNH of 1667 patient-years – Such virtual absence of liver injury is incompatible with the known hepatovigilance profile of statins

* Health related quality of life *not reported*

* Authors' incoherent and spinned conclusions: « Results of the ASPEN trial did not confirm the benefit of therapy. Composite end point reductions were NS, but do not detract from the imperative that the majority of diabetic patients are at risk of coronary heart disease and deserve LDL-C lowering to the currently recommended targets (sic) »[89] - « The conclusions claimed were the exact opposite of what had been found ! »[90]

* Factual conclusion without spin:
a) The clinically negative trial results, despite a marked reduction of LDL-C, contradict the lipid hypothesis.

b) The discrepancy (aka conflation) between the results and the conclusion is striking and results from the ideology prevailing among the 'alliance of hypercholesterolists'[91] aka the 'ayatollahs of the lipid hypothesis'.
c) Reported frequencies of harms (myopathy, myalgia, liver injury) are either too low to inspire credibility, or outright unreported (hyperglycemic effect)

d) « In the ASPEN trial, 2410 people with type 2 diabetes were randomised to either atorvastatin 10 mg/day or placebo and no benefit in total mortality or combined clinical end points was seen after 4 years »[92]

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : Yes, clarification pending

L'essai dit Aspen

* Résultats négatifs cliniquement malgré une baisse du cholestérol
* Commentaire: malgré l'admission de l'échec de l'étude, les auteurs concluent en promouvant la statinisation des diabétiques et à l'abaissement du LDL-C à des niveaux cibles – Pourtant, comme le rappellent de Lorgeril et coll., les 4 essais d'hypocholestérolémiants chez des diabétiques ont été négatifs (Cards, 4D, Aspen, Field)[93] : L'étude ASPEN de 2010 a randomisé 2410 patients pour tester 10 mg d'atorvastatine contre placebo. Malgré une réduction moyenne de -29% de LDL-CHO l'essai fut absolument négatif et nous valut une des conclusions qui restera la plus représentative de la difficulté qu'il y a à devoir avaler des couleuvres quand on est statisticien, lisez plutôt la conclusion incohérente (en traduction) :

« Les réductions des critères composites finaux ne furent *pas statistiquement significatifs*. Ce résultat peut être lié à la conception globale de l'étude, aux types de sujets recrutés, à la nature du critère d'évaluation principal et aux modifications de protocoles requis en raison de la modification des traitements. Pour ces raisons, les résultats de l'étude Aspen sur la prévention des effets coronariens dans le diabète sucré non insulino-dépendant n'ont *pas confirmé l'avantage* du traitement, mais n'empiètent pas sur la nécessité pour la majorité des diabétiques à risque de maladie coronarienne de mériter un abaissement du cholestérol LDL conformément aux objectifs actuellement recommandés (sic)[94] »

astatin in diabetes) – similar to JUPITER
c) PROVE IT : 2.7% (pravastatin < 11 days after an acute coronary syndrome) – 1.03 times lower than in Jupiter
d) ALLHAT-LLT : 2.2% (atorvastatin in hypertension) – 1.3 times lower than in Jupiter

e) ASPEN : 1.9% (atorvastatin in diabetes) – 2.2 times lower than in JUPITER
f) ASCOT : 1.6% (atorvastatin in hypertension) – 1.8 times lower than in JUPITER

[89] Knopp et al. Op. cit.
[90] Michel de Lorgeril, 2014. Cholesterol and statins : Sham science and bad medicine (Kindle)
[91] Therrien, op. cit.
[92] DuBroff RJ. Evid Based Med 2015 ; 20(4) : 1 – DOI: 10.1136/ebmed-2015-110236
[93] Reviews on Recent Clinical Trials, 2012, 7(2):1
[94] AIMSIB 22 Avr 2019

g) PREVEND IT : 1.2% (pravastatin in albuminuria) – 2.3 times lower than in JUPITER

h) HYRIM: 0.9% (fluvastatin in hypertension) – 3.1 times lower than in JUPITER
i) WOSCOPS : 0.9% (pravastatin in healthy) – 3.1 times lower than in JUPITER
j) AFCAPS : 0.8% (pravastatin in healthy) – 3.5 times lower than in JUPITER
h) MEGA : 0.5% (pravastatin in healthy) – 5.6 times lower than in JUPITER
mortalité de toute cause à 21 mois chez les témoins sous placebo : Jupiter se démarque

EXTREME ALL-CAUSE MORTALITY IN JUPITER REQUIRES REEXAMINATION OF VITAL RECORDS – (Article)
Victor L SEREBRUANY. *Cardiology* 2011; 120(2): 84-8 (Editorial) - DOI:10.1159/000330507

« Despite enrolling apparently healthy subjects and early trial termination at 21 months of mean follow-up, JUPITER revealed very high total mortality in both the placebo (2.8%) and rosuvastatin (2.2%) arms. The total mortality in JUPITER was more than twice that of the average of primary prevention studies...

Since the 'play of chance' is unlikely to explain these discrepancies due to excellent baseline match, excess total mortality rates in both JUPITER arms must be questioned. Excess total mortality rates in the apparently relatively healthy JUPITER population are alarming and require independent verification. If, indeed, the surprising outcomes in JUPITER are successfully challenged, millions of patients may find better and safer options for primary prevention of vascular events…

Trial integrity has been overlooked… Patient enrollment was monitored by the same study sponsor (AstraZeneca) as SPORTIF-III (ximelagatran) and PLATO (ticagrelor), who experienced similar controversies such as disproportional benefit, exaggerated benefits from Eastern Europe, very high rate of fatalities and remarkable mortality reduction… »
See also TOTAL MORTALITY IN PLACEBO-CONTROLS AT 21-MONTHS ACROSS TRIALS
L'extrême mortalité de toute cause impose un réexamen des relevés de décès dans Jupiter (Traduction libre)
* L'auteur a comparé la mortalité totale à 21 mois dans Jupiter avec celle de 9 autres essais statine-contre-placebo en prévention primaire à faible et à haut risque (diabète, hypertension, dialyse) et contre un essai de prévention secondaire à haut risque (après épisode coronarien aigu)…

Avec un taux de mortalité de 2,8% à 21 mois dans son groupe placebo, Jupiter dépasse les autres essais comparés, constat peu crédible qui fait soupçonner des erreurs (involontaires bien évidemment…) dans le relevé des décès de toute cause et pourrait à lui seul invalider les conclusions des auteurs (en sous-main) des innombrables republications d'un essai qui a été le moteur des ventes mirobolantes de Crestor™

TOTAL ANNUALIZED MORTALITY DIFFERENCES AT 21 MONTHS ACROSS TRIALS
* Presented as annual (12 months) absolute risks of death between placebo control groups and statin groups, and corresponding NNT/NNHs[95]:

a) WOSCOPS : absolute risk reduction -0.17%, NNT = 588 patient-years
b) AFCAPS : 0% - infinite NNT
c) ALLHAT : ARI +0.057%, NNH = 1754 patient-years
d) MEGA : -0.057%, NNT = 1754 patient-years

e) ASPEN : 0%- infinite NNT
f) CARDS : -0.457%, NNT = 219 patient-years
g) PREVEND : -0.11%, NNT = 909 patient-years
h) ASCOT : 0%, - infinite NNT

i) HYRIM : 0%, - infinite NNT
j) JUPITER : -0.34%, NNT = 294 patient-years
k) PROVE-IT : -0.286%, NNT = 350 patient-years

In none of these 11 trials does annual absolute risk reduction even approaches 1% (NNT = 100) at 21 weeks in trial controlled conditions. Anyone who claims that statins save lives should take the time to read the reports of those trials one by one instead of relying on meta-analyses biased by the COI of their authors
différences à 21 mois dans la mortalité totale annualisée entre groupes témoin et expérimental selon les essais

[95] Victor L Serebruany. Op. cit.

ASTRONOMER, THE TRIAL
Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin

ATORVASTATIN LABELED ADRs *Statinovigilance*
« The patient leaflet for Lipitor™ – the most lucrative statin - indeed the most lucrative drug ever - state the following: 'Common side effects (which may affect up to 1/10 people) include:

a) inflammation of the nasal passages, pain in the throat, nose bleed
b) allergic reactions
c) increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels)
d) increase in blood creatine kinase (CK)

e) headache
f) nausea, constipation, wind, indigestion, diarrhoea
g) joint pain, muscle pain and back pain
h) blood test results that show your liver function can become abnormal' »[96]
EIM libellés de l'atorvastatine

ATORVASTATIN TRIALS
* ASCOT-LLA, CARDS, SPARCL, ASPEN, 4D, GREACE, IDEAL, TNT, ILLUMINATE, MIRACLE, PROVE-IT-TIMI 22…
essais de l'atorvastatine

ATORVASTATIN VS PLACEBO : NO LIVES SAVED
« Atorvastatin (Lipitor) is a statin that in all placebo controlled trials showed no longevity benefit, for example, SPARCL [Medline 16899775] and ASCOT [Medline 12686036]. The latter trial, as of 13 years after study end, has failed to report on women's deaths, arguably the easiest to count endpoint »[97]
atorvastatine contre placébo : pas de vies sauvées

AURORA, THE TRIAL
Prévention primaire et secondaire chez diabétiques en insuffisance rénale terminale et sous dialyse – Rosuvastatine 10 mg c. placebo
* Princeps publication : Fellström/*NEJM*/2009[98]
http://www.nejm.org/doi/full/10.1056/NEJMoa0810177 - t=article

METHODOLOGY
* Comparison : rosuvastatine (Crestor™) 10 mg vs. placebo
* Mean duration : 3.2 years (38 months)
* Sample size : 2776 randomized
* Design : double-blind, parallel

* Primary endpoint : [CVD death + nonfatal MI + nonfatal stroke] : Biased composite endpoint because of heterogeneity of :
(a) relative frequencies of individual outcomes,
(b) uneven patient-valued seriousness of endpoints (1 fatal, 2 non fatal),
(c) possible subjectivity in diagnoses of MI and strokes unless criteria are well defined and adjucators remain blinded despite risk of uncovering serum lipid levels

* Positive compliance (active adherence) : 91.7%
* Negative compliance (control group adherence) : 89.5%

RESULTS
* Health related quality of life *not reported*
* Kaplan-Meier plot on all-cause mortality was *not published*
* relative risk reduction of primary endpoint = -4%, NS
* relative risk reduction of total mortality = -4%, NS

[96] Zoe Harcombe. 22.5.2014 - http://www.bmj.com/content/348/bmj.g3306?page=1&tab=responses
[97] Eddie Vos. http://www.bmj.com/content/352/bmj.i1395/rapid-responses
[98] Fellstrom et al. NEJM 2009; 360: 1395-407 - doi: 10.1056/NEJMoa0810177

« More than 50% of the patients had some CV diseases in the AURORA trial,[99] in addition to their kidney problem, and were, therefore, also in secondary prevention. However, despite striking reduction of cholesterol and CRP, rosuvastatin (Crestor™) failed to show any protection »[100]

« In dialysis patients, Aurora found no benefit in any department after 5 years. 35% of patients in either group suffered cardiac problems anyhow »[101]

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Aurora
* Santé des participants : insuffisants rénaux en phase terminale et hémodialysés
* Aucun bénéfice en terme de mortalité totale (relative risk reduction de -4%, NS), tout comme dans Jupiter, Prosper, Corona et Giffi-HF
* Aucun bénéfice pour le critère primaire combiné (relative risk reduction -4%, NS)
* Pour rappel, l'essai dit 4D de l'atorvastatine chez des diabétiques insuffisants rénaux sous hémodialyse n'a pas fait mieux

AUTHORITY AS ARGUMENT (QC)
argument d'autorité
« En 2009, forte du *support unanime* de ses 402 membres, l'*Association des cardiologues du Québec* reste convaincue de l'utilité de la réduction du taux de cholestérol sanguin en prévention des maladies cardio-vasculaires; est convaincue de l'utilité de la prise de médicaments hypolipémiants, *statines* ou autres, particulièrement en présence d'une maladie cardio-vasculaire établie, de diabète ou d'hypercholestérolémie marquée; … et incite les patients actuellement sous traitement avec une statine à ne pas l'interrompre sans en avoir discuté au préalable avec leur médecin traitant[102]

AVERAGE CHOLESTEROL REDUCTION AND STATIN DOSAGE
* An average 22% relative reduction in TC is achieved by daily doses of fluvastatin 40 mg, pravastatin 20 mg, lovastatin 20 mg, simvastatin 10 mg, atorvastatin 5 mg or rosuvastatin 2.5 mg[103]
réduction moyenne du cholestérol et posologie statinique

BASELINE RISK MEANS IN PLACEBO GROUPS
risques de base moyens dans les groupes sous placebo
= risque situé entre 2 et 2,9 événements par 100 patients-année (fourchette proposée dans le présent ouvrage pour décrire un 'risque moyen')

a) Dans AFCAPS-TexCAPS sur la lovastatine, le risque sous placebo était de 2,1 événements principaux par 100 AP (risque moyen)
b) Dans l'essai CARDS de l'atorvastatine chez des diabétiques, le risque sous placebo était de 2,5 événements principaux par 100 AP (risque moyen)

c) Dans l'essai ASPEN de l'atorvastatine chez les diabétiques, dans le sous-groupe sans antécédents vasculaires le risque de base était de 2,7 événements principaux par 100 AP (risque moyen)
d) Dans l'essai HPS (Heart Protection Study) de la simvastatine, le sous-groupe sans antécédents vasculaires présentait un risque sous placebo de 2,7 événements principaux par 100 AP (risque moyen)

BASELINE RISK QUANTIFICATION
« There's now a movement to give these cholesterol-lowering tablets to everyone. But I wouldn't take one unless I had proof I was at significant risk. Whenever you're taking a drug, you've got to think about the risks and the benefits. Statins reduce your chance of heart attack or stroke by about 30 %, so, yes, there's a benefit. But in real terms it's very small. As a 60-year-old, healthy, non-smoking man, statistically my annual risk of a stroke or heart attack is about 1% - very low...

Taking a statin would take it down to 0.7 % - still very low. And I've spent my professional life prescribing statins, so I know about the side-effects: muscle aches, general debility and stomach upsets. Some say statins should be given when the risk is

[99] Fellstrom et al. N. Engl. J. Med 2009 ; 360 (14): 1395 - doi:10.1056/NEJMoa0810177
[100] Michel de Lorgeril et al. BMC Medicine 2013 ; 11 : 5
[101] Eddie Vos
[102] http://www.lapresse.ca/le-soleil/opinions/points-de-vue/200901/22/01-820013-cholesterol-au-dela-de-la-medecine-spectacle.php
[103] Wright J et al. Therapeutics Newsletter # 49 and Marron et al. Circ 2000 : 101 : 207

1.5 %, but I personally wouldn't consider taking the drug unless my risk was 3 %...

Anyone who's had a stroke or heart attack has a risk of about 3 % and for them the pain is definitely worth the gain »[104] - This cardiologist assumes that he requires an absolute risk reduction of at least 1 % to compensate for statin adverse effects but does not mention a time course

quantification du risque de base / des témoins

* Dans le présent ouvrage, les risques CV sont quantifiés (arbitrairement mais logiquement) pour éviter la confusion provenant des divergences rencontrées dans la documentation du risque dans les groupes témoins (placebo) des essais statiniques et dans la définition de la prévention primaire et secondaire selon les auteurs. Voici les catégories proposées en fourchettes :

a) risque très faible : < 1 événement cardiovasculaire par 100 années-patients (AP)
b) risque faible : 1 à 1,9 événements CV par 100 AP
c) risque moyen : 2 à 2,9 événements CV par 100 AP
d) risque élevé : 3 à 3,9 événements CV par 100 AP
e) risque très élevé : ≥ 4 événements CV par 100 AP

* Quand une statine induit une relative risk reduction de -15% (RR = 0,85) pour la mortalité totale (comme calculé par Zhou en 2006)[105], le risque (très élevé) chez les témoins devrait atteindre 6,6% par an pour diminuer à 5,6% par an, d'où une réduction annuelle de 1%, seuil que nous concédons généreusement – dans la présente discussion – comme étant cliniquement signifiant, même si cette réduction n'équivaut qu'à une prolongation moyenne de la vie de 3,65 jours…

Si une statine cause une réduction relative de -18% (RR = 0,82) pour la mortalité coronaire et cérébrovasculaire (Zhou, 2006), le risque chez les témoins devrait être de 5,5 % par an pour diminuer à 4,5 par 100 patients-année, atteignant ainsi une réduction absolue de 1% par année de traitement

Si une statine cause une réduction relative de -20% (RR = 0,80), le risque très élevé chez les témoins doit atteindre 5% par an pour réaliser une réduction absolue de 1% par an, ramenant le risque à 4 événements par 100 patients-année.

Si une statine réduit le risque relatif de 25% (RR = 0,75) des infarctus fatals et non fatals (Zhou, 2006) , le risque des témoins doit être très élevé, 4% par an pour descendre à 3 par années-patients, d'où une réduction absolue de 1% AP qui seule peut parvenir à un NNT de 100 années-patient. C'est justement -25% (RR = 0,75) qu'observent Zhou et coll. 2006 dans leur synthèse sélective de 8 essais permettant une comparaison inter-statines indirecte et ajustée[106]

Si enfin une statine provoquait par miracle une réduction relative de 33% (RR = 0,67), le risque des témoins devrait être élevé, 3% par an, pour descendre à 2%, entrainant une réduction absolue de 1% par an

BELLES, THE TRIAL *Ciblé sur la calcification des coronaires – Résultats négatifs cliniquement*
« In postmenopausal women, intensive statin therapy for 1 year caused a greater LDL reduction than moderate therapy but did not result in less progression of coronary calcification »
l'essai dit Belles[107]

BEYOND CONFUSION AND CONTROVERSY, CAN WE EVALUATE THE REAL EFFICACY AND SAFETY OF CHOLESTEROL-LOWERING WITH STATINS? – (Article) *Synthèse méthodique*
De LORGERIL M, RABAEUS M. *Journal of Controversies in Biomedical Research* 2015; 1(1): 67-92[108]
http://dx.doi.org/10.15586/jcbmr.2015.11

« Rosuvastatin is not effective in secondary prevention, while the results are highly debatable in primary prevention...Recent RCTs clearly indicate that intense cholesterol-lowering (including those with statins) does not protect high-risk patients any better than less-intense statin regimens… Once secondary analyses and subgroup analyses are excluded, statins do not appear to protect diabetics…

The studies published before 2005/2006 were probably flawed, and this concerned in particular the safety issue. A complete reassessment is mandatory. Until then, physicians should be aware that the present claims about the efficacy and safety of

[104] Kevin Channer, 2014 - Cardiologist, Sheffield, UK
[105] Zhou et al. Am Heart J 2006 ; 151(2) : 273
[106] Zhou et al. Am Heart J 2006 ; 151(2) : 273 – Figure 1, page 275
[107] Raggi et al. Circulation 2005; 112: 563 - doi: 10.1161/CIRCULATIONAHA.104.512681 - http://circ.ahajournals.org/content/112/4/563
[108] http://jcbmr.com/index.php/jcbmr/article/view/11/24

statins are not evidence based »
Au delà de la confusion et de la controverse, peut-on évaluer l'efficacité et la sécurité réelles de la réduction du cholestérol par les statines ? – (Traduction libre)

BIASED NICE 2014 GUIDELINES (UK)
Directives biaisées – Résistance des soignants

« In 2014, NICE decided (super short summary) that everyone with a risk of a cardiovascular event greater than 10%, over the next ten years, should be put on a statin. There was much debate, and the BMA (British Medical Association) voted – unanimously – that these guidelines should not be followed. Did this make any difference? No. Did it make any difference that the Local Medical Committees (that represent all GPs) at their annual conference voted unanimously against these guideline?...

No. What are NICE doing about the fact that, at least, two thirds of GPs are completely ignoring these guidelines. Nothing…yet. No debate, no discussion. Nothing. They know that, over time, their guidelines will solidify into something that becomes, effectively, mandatory »[109]

« A leading US academic has praised UK GPs for their 'widespread resistance' to the unquestioned adoption of the new NICE guidelines [on statins] leading to the over-prescribing of statins. In a column in the Pharmaceutical Journal,[110] Dr John Abramson, a Harvard University healthcare policy lecturer, said GPs should be congratulated for not routinely adopting NICE guidance from last year (2014) that lowered the threshold of CV disease risk for statin therapy from 20% to a 10% ten-year risk...

Two-thirds of GPs are disregarding NICE's advice to offer statins to more patients. In 2013, he and colleagues re-evaluated a 2012 meta-analysis by the *Cholesterol Treatment Trialists* (CTT) Collaboration and concluded that taking statins brought no significant reduction in mortality for people with a 10% 5-year CV disease risk [2% annually]... 'It is just the example du jour of the extent to which the primary function of medical information has become tipped toward serving commercial rather than public interest »
directives biaisées du Nice en 2014 (RU)
* le *National Institute for Clinical Excellence* agit comme un *Conseil du médicament* britannique, et est de plus en plus soumis aux pressions des lobbys industriels

* si les statines abaissaient le risque *relatif* de mortalité générale de 25%, ce qu'elles ne font pas, il faudrait que le risque initial soit d'au moins 4% par an si on convient que le risque *absolu* doit être abaissé d'au moins 1% par an en situation expérimentale pour justifier l'indication

BIASED PRIMARY PREVENTION TRIALS
ASCOT-LLA, CARDS, JUPITER and MEGA[111]
essais biaisés en prévention primaire

BIG PHARMAS' DIRTY LITTLE SECRET ABOUT CHOLESTEROL LOWERING DRUGS – (Blogue sur la finance)
Mark Chapman. *Seeking Alpha* 15.4.2015
http://seekingalpha.com/article/3072186-big-pharmas-dirty-little-secret-about-cholesterol-lowering-drugs

« Cholesterol lowering drugs bring in billions to the pharmaceutical industry, despite questionable benefits… The book *Grain Brain* by Dr. David Perlmutter, neurologist and nutritionist, is an absolutely astonishing read, and while focused on brain health, goes into great detail on how our diet controls our whole autoimmune system and general health. It also explains how many diseases can be controlled by simply *changing our diets* and avoiding the pitfalls of Big Pharmas' latest "wonder drug"…

There is plenty of research readily available as to how and why cholesterol was *originally believed* to increase CV risk, and why the pharmaceutical industry developed drugs to lower cholesterol. Statins are the best-selling (and most lucrative) drugs in the history of mankind. Perlmutter writes :

'Part of the reason I am focusing on fats, and cholesterol in particular, is not only because these ingredients have everything to do with brain health, but also because we live in a society that continues to demonize them, and the huge pharmaceutical industry *preys on the public's misinformation* and *perpetuates falsehoods*, many of which could physically destroy us'

[109] http://drmalcolmkendrick.org/2015/03/13/nice/
[110] http://www.pharmaceutical-journal.com/opinion/comment/prescribing-statins-time-to-rein-it-in/20068145.fullarticle?adfesuccess=1#fn_7
[111] Therapeutics Initiative March-April 2010

Once the person starts taking the statin, a nasty cycle of events often leads to *weight gain*, *memory loss*, *muscle soreness* and other serious ailments. Dr. Perlmutter details the copious amount of research to explain the memory loss (in addition to *dementia, Alzheimer's, ALS*, and a variety of other diseases...

The investment implications ? With the advice from the *Dietary Guidelines for Americans Committee* to finally remove dietary cholesterol limits from the 2015 update of the US government's *Dietary Guidelines,* the stage appears to be set for the beginning of a major dietary shift that could have a wide ranging effect on stocks from protein producers, farming, grain processors, and of course, the pharmaceutical industry…

There is exuberance over the next round of cholesterol lowering drugs due to hit the market this 2015 summer (PCSK9 inhibitors). Although I doubt that the FDA will do an about-face and eliminate high cholesterol (and in particular LDL) as a biomarker in cardiovascular risk right now, I believe we're in the first inning for that to happen...

When the 2015 Dietary Guidelines are finalized and published, the removal of a dietary cholesterol limit will send far reaching shock waves through our society. The FDA will likely need to perform extra scrutiny on the risk-benefit analysis of any cholesterol lowering drug »
Le vilain secret bien gardé des mondiales du médicaments sur les réducteurs du cholestérol (Traduction libre du titre du blogue)

BIP, THE TRIAL *Fibrate*
Bezafibrate Infarction Prevention Study[112]
* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Bip

BRAIN-WASHING BY THE CHOLESTEROL ESTABLISHMENT
Meneurs d'opinion – FMC trompeuse
bourrage de crâne par l'establishment du cholestérol[113]

BRANDED OR GENERIC STATINS ? *Pharmacoéconomie*
« Kale et al[114] reported in 2011 that US primary care physicians' use of branded statins results in $5.8 billion excess annual health care spending »[115]
statines brevetées ou génériquées ?
* il n'y a aucune justification médicale validée pour préférer une statine brevetée à sa forme générique en prévention primaire, ni en prévention secondaire, même dans les hyperlipidémies familiales et dans des hypercholestérolémies polygéniques à très haut risque. La prescription des versions originales de statines en médecine générale génère un surplus dans les dépenses à hauteur de 5,8 G$ aux É-U dans la seule année 2011

BREAST CANCER IN STATINISED WOMEN *Pharmacovigilance – Essais – Épidémiologie (cas-témoin) – Signal faible*
« Among patients with average cholesterol levels, women randomized to pravastatin therapy exhibited a huge and unexplained increase in *breast cancer* incidence (p=0.002), some of which were recurrences. Subsequently, cancer was an exclusion criterion in randomized statin trials »[116]

« The controversy began in 1996 with the publication of the CARE trial. It was a double-blind randomized trial comparing the effects (versus placebo) of the cholesterol-lowering pravastatin against coronary event after myocardial infarction in 3,583 men and 576 women. 12 / 286 women in the statin group but only 1 / 290 in the placebo group had breast cancer at follow-up…

After that, most statin investigators took care not to include high-risk women in their trials and carefully monitored them through repeated interim analyses for early detection of inter-group difference trends in cancer incidence. To further confuse the data, many statin trials were prematurely terminated - and it is likely that not all have been published - without valid scientific justification…

[112] BIP. Circulation 2000 ; 102 : 21 – Tenenbaum et al. Arch Intern Med 2005 ; 165 : 1154
[113] Sinatra & Bowden, 2014, page 37
[114] Larkin C. at http://www.bloomberg.com/news /2011-02-10/lipitor-topped-worldwide-drug -sales-in-2010-crestor-gains-most.html.
[115] Green et al. JAMA Intern Med 2013 - doi:10.1001/jamainternmed.2013.1529
[116] Rosenberg et al. Int J Cardiol 2009 : 145 - doi:10.1016/j.ijcard.2008.12.122

A meta-analysis of clinical trials published in 2006 (Dale 2006, JAMA 295:74) found a 33% increase in *breast cancer* incidence with statins compared with a placebo… The recent demonstration that long-term (10-year) statin use was associated with a 2-fold increase in breast cancer risk among contemporary postmenopausal women (McDougall 2013, *Cancer Epidemiol Biomarkers Prev* 22: 1529 »[117]

« Hypercholesterolemia is inherently associated with lower risk of breast cancer recurrence »[118], a reason to avoid statins in women where evidence for cardiac protection and life extension is inexistent

« Among patients with average cholesterol levels [in the CARE trial], women randomized to pravastatin therapy exhibited a huge and unexplained increase in breast cancer incidence (p=0.002), some of which were recurrences. Subsequently, cancer was an exclusion criterion in randomized statin trials »[119]

« In the Seattle-Puget Sound region (USA) contemporary population-based case–control study, current users of statins for 10 years or longer had a 1.83-fold increased risk of invasive ductal carcinoma and a 1.97-fold increased risk of invasive lobular carcinoma compared with never users of statins. Among women diagnosed with hypercholesterolemia, current users of statins for 10 years or longer had more than double the risk of both ductal (OR: 2.04) and lobular (OR: 2.43) invasive carcinoma compared with never users »[120]

cancer du sein chez les femmes statinisées

* Une étude cas-témoin (MacDougall et coll, 2013[121]) révèle une augmentation relative de 83% de cancers canalaires envahissants chez les consommatrices de statines et une augmentation relative de 97% de cancers lobulaires invahissants, ce qui constitue un signal sérieux à ne pas négliger, notamment quand une femme est particulièrement à risque de cancer du sein

BRIEL 2009, THE META-ANALYSIS[122]

* Other interventions inspired by the lipid / cholesterol hypothesis were reviewed : Fibrates (9 trials); resins (3 trials); niacin combinations with a statin, fibrate, or resin (6 trials); n-3 fatty acids (9 trials); acyl-CoA:cholesterol acyltransferase inhibitors (2 trials); probucol (2 trials); glitazones (2 trials); hormones (9 trials); torcetrapib (2 trials); low fat diets and surgery (5 trials) - For statins, outcomes commented here are relative risk ratios for total death, CHD deaths and CHD events.

OUT OF 54 COMPARISONS OF *STATINS* AGAINST A CONTROL GROUP (52 PLACEBO / 2 USUAL CARE)

a) only 5 trials or 9 % (ACAPS, LIPID, GREACE, 4S and HPS) showed a numerical relative risk reduction of *total mortality*. But GREACE was not blinded when comparing usual care, leaving us with 4 blinded trials or 7 %, none of which demonstrated a clinically meaningful reduction (hereby defined as an absolute risk reduction > 1 per 100 patient-years equivalent to an NNT < 100 patient-years)

b) only 5 or 9 % of trials (GISSI-P, LIPID, GREACE, 4S and HPS) showed a numerical reduction in relative risk reduction for *CHD mortality*. But GREACE was not blinded when comparing usual care, leaving us with 4 blinded trials or 7 %, none of which demonstrated a clinically relevant reduction (defined here as an NNT < 100 patient-years)

c) 14 trials or 26 % (AFCAPS/TexCAPS, CARE, LIPID, MEGA, PLACE, PROSPER, WOSCOPS, ASCOT-LLA, CARDS, GREACE, SPARCL, FLARE, 4S and HPS) showed a numerical relative risk reduction for *CHD events* but no clinically relevant reductions

IN 8 STATIN-DOSE COMPARISONS TRIALS

a) only one or 13 % (PROVE IT) showed a relative risk reduction of total mortality, but the annualized absolute risk reduction was 0.9% for a NNT of 111 patient-years, not clinically relevant ; and the *credibility* of the results was fatally weakened by a belated (2 years) correction admitting a large number of missing data in the princeps publication, not followed by recalculation or retraction

b) only one trial (A to Z) showed a relative risk reduction for *CHD death* but not for the more sensitive composite primary endpoint

c) only one trial (TNT) showed a relative risk reduction for *CHD events*, offset by a +1% relative risk *increase* (RRI) in total mortality

[117] de Lorgeril & Salen. BMC Medicine 2014 ; 12: 94 - http://www.biomedcentral.com/1741-7015/12/94
[118] Ibidem.
[119] Rosenberg et al. Int J Cardiol 2009 : 145 - doi:10.1016/j.ijcard.2008.12.122
[120] Jean A McDougall et al. Cancer Epidemiol Biomarkers Prev; 22(9); 1529 - http://cebp.aacrjournals.org/content/22/9/1529
[121] Jean A McDougall et al. op. cit.
[122] Briel et al. BMJ 2009; 338: b92 - doi: http://dx.doi.org/10.1136/bmj.b92 - Online appendix tables

la méta-analyse de Briel en 2009

BRITISH STATINOVIGILANCE IN 2015
« In total there have been 18,928 separate reports filed to the Medicines and Healthcare Products Regulatory Agency (MHRA) where side-effects were connected to statins detailing 21,440 alleged reactions. The reports included 227 deaths linked to statins, although the MHRA points out that the fact a report of a reaction or death following drug use does not prove the drug was the cause...

Amongst the available breakdown on recorded side effects of the 3 main statin drugs prescribed were 187 cases of blood disorders, 4 of which were linked to deaths. Included among these reports to the drug watchdog were also 252 cases of eye disorders, 2,922 cases of stomach problems - 19 of which were patients who died - 3,470 patients suffered nervous system disorders, 16 of these died, and 880 cases of breathing problems, of which 16 patients died...

A separate study carried out in America shows statins were have been linked to 3039 cases of rhabdomyolysis over 12 years where the body can be poisoned by muscles breaking down leading to acute kidney failure. 240 of these patients died… The news follows a study released earlier this year by two experts claimed the benefits of taking statins had been exaggerated...

Dr David Diamond, a professor in molecular pharmacology, and Dr Uffe Ravnskov, an expert in CV disease, published their study, based on statin trials, in the *Expert Review of Clinical Pharmacology*. They concluded: "The adverse effects suffered by people taking statins are more common than reported in the media and at medical conferences. "Increased rates of cancer, cataracts, diabetes, cognitive impairments and musculoskeletal disorders more than offset the modest cardiovascular benefits of statin treatment."..

They add: "There is a great appeal to the public to take a pill that offers the promise of a longer life and to live heart attack free. "The reality, however, is that statins actually produce only small beneficial effects on CV outcomes, and their adverse effects are far more substantial than is generally known." »

A study last week showed that women who took statins became more aggressive, and that the reverse was true in men. Professor Klim McPherson, an leading expert in public health at Oxford University, who himself suffered severe muscle pains while he was prescribed statins for 4 years said he was worried about the side effects we had uncovered:

"I am concerned about these data. Some of the side effects are serious. There should be thorough review attributable to side effects of statins which there has not been." Professor McPherson, whose debilitating symptoms stopped after he ceased taking statins a year ago added: "This is evidence that the harm may outweigh the benefits of these drugs for many patients."

Dr Malcolm Kendrick, who has studied the effects of statins said: "These reports are just the tip of the iceberg as most doctors do not report side effects. The data uncovered is very alarming and shows the risks of these drugs have been downplayed. For many patients the benefits of statins may not be worth the harms." »[123]
la statinovigilance britannique en 2015

BULLSHIT
N.d.T. terme anglais à la limite de la vulgarité
connerie(s); foutaise
* peut souvent s'appliquer aux discours des publicitaires engagés par les fabricants de produits de santé, et aux institutions médicales qui trop souvent les relaient béatement aux praticiens sous l'appellation de directives cliniques, notamment en pharmaco-prévention; les directives fin 2013 de l'ACC/AHA sur la statinisation élargie sont un bel exemple[124] … C'est la honte de la profession que de participer aussi allègrement à cette abominable régression politique et sociale

BYPASS *Critère de jugement partiellement subjectif*
coronary bypass ; aorto-coronary bypass grafting or ACBG; coronary revascularization
pontage (aorto-coronarien) ; revascularisation (coronaire)
* souvent utilisé à tort comme élément dan un critère d'évaluation *combiné* car il s'agit d'une décision médicale relevant de plusieurs éléments subjectifs et contextuels

C-REACTIVE PROTEIN; CRP *Biomarqueur non pertinent*
Voir aussi HIGH SENSITIVITY-C-REACTIVE PROTEIN

[123] Lucy Johnston, 5.6.2015 - http://www.express.co.uk/news/sunday/588889/Statin-drug-linked-increasing-side-effects-deaths
[124] http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a

protéine C-réactive
* utilisée, sans fondement scientifique solide, pour sélectionner les participants au très controversé et fortement biaisé essai clinique dit Jupiter portant sur la rosuvastatine (Crestor®) chez des aînés non coronariens

C'est la recommandation dans les *Annals* par Glasziou et coll. en 2008[125] : ces auteurs déconseillent la surveillance annuelle ou plus fréquente, la considérant inutile. En suivant ces directives, on économiserait bien des dosages sanguins. Aucun COI potentiel n'est déclaré par les auteurs, des universitaires de Oxford (R.-U.) et d'AU. Cette étude a été greffée sur l'essai LIPID, conduit en AU et en NZ de 1990 à 1997 et portait sur la pravastatine

CAIUS, THE TRIAL
Carotid Atherosclerosis Italian Ultrasound Study

CALCIFICATION OF CORONARIES IN STATINISED DIABETICS *Calcification des coronaires – Étude observationnelle - Aggravation*
« Progression of coronary artery calcification (CAC) was assessed according to the frequency of statin use in 197 participants with T2DM. After adjustment for baseline CAC and other confounders, progression of CAC was higher in more frequent statin users than in less frequent users (mean 8.2 mm vs. 4.2 mm). More frequent statin use is associated with accelerated CAC in T2DM patients with advanced atherosclerosis »[126]
calcification des coronaires chez diabétiques statinisés
* On observe une augmentation relative de 95% dans la progression de la calcification des coronaires chez les diabétiques utilisateurs fréquents de statines comparés aux utilisateurs moins fréquents. Évidemment association ne veut pas dire nécessairement causalité, il y a des facteurs confondants.

CALCIFIED CORONARY ARTERIOSCLEROSIS *Calcification coronaire – Statinothérapie intensive– Inefficacité statinique*
« Over a period of 12 months, *intensive atorvastatin* therapy was unable to attenuate coronary arteriosclerosis calcification progression compared with standard atorvastatin therapy »[127] - « Atorvastatin does not slow arterial calcification, the structural declines continues unabated notwithstanding this top-selling statin, atorvastatin[128] … apart from the drug's inability to lower mortality[129]»
artériosclérose coronaire calcifiée

CALCIFIED STENOTIC AORTIC VALVE *Calcification aortique – Inefficacité statinique*
« Atorvastatin does not slow stenotic aortic valve calcification[130], the structural declines continues unabated notwithstanding this top-selling statin, atorvastatin (Lipitor™) »[131]
sténose valvulaire aortique calcifiée

CANCER MORTALITY IN STATINIZED WOMEN *Signal faible – Pharmacovigilance - Femmes*
« The secondary analysis[132] of the TNT study reported a large excess in *cancer mortality* in women. Alarmingly, annualized cancer mortality was 1 in 1000 patients in the low-dose atorvastatin group and 4 in 1000 patients in the high-dose group. Furthermore, there was a trend towards increased *total mortality* in the high-dose compared to the low-dose atorvastatin group, neutralizing any benefit in CV mortality »[133]
mortalité par cancer chez les femmes statinisées

CARDIAC MORTALITY AND CHOLESTEROL LEVELS *Hypothèse lipidique – Hypercholestérolémie polygénique*
mortalité cardiaque et niveaux de cholestérol
« Aucune étude n'a montré de lien fort entre cholestérol (total) et mortalité cardiaque, notamment en dessous de 6,7 mM (2,6 g/l) [hypercholestérolémie polygénique], et au delà il y a peut être un lien, mais ténu »[134]

CARDIOVASCULAR DEATH RATES IN BELGIAN WOMEN (BE) – (Rapport)

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[125] Glasziou et al. Ann Intern Med 2008; 148(9): 656
[126] Saremi et al. Diabetes Care 2012; 35(11): 2390
[127] Schmermund et al. Circulation 2006; 113: 427 - DOI: 10.1161/CIRCULATIONAHA.105.568147
[128] Vos E. Nutr Metab Cardiovas Dis 2007 ; 17 : e19
[129] Eddie Vos. http://www.bmj.com/content/352/bmj.i1395/rapid-responses
[130] Cowell et al. NEJM 352(23) : 2389
[131] Vos E. Nutr Metab Cardiovas Dis 2007 ; 17 : e19
[132] Wenger et al. Heart 2008 ; 94 : 434
[133] Rosenberg et al. Int J Cardiol 2009 : 145 - doi:10.1016/j.ijcard.2008.12.122
[134] Even, page 157

* Percentage of death rates from CV disease compared with total death rates in women are :[135]

a) 14% in women in their forties (2.1 CV deaths per 10 000 women-years); total death rate is 15 per 10 000 women-years
b) 16% in women in their fifties (5.9 CV deaths per 10 000 women-years); total death rate is 36.8 per 10 000 women-years
c) 20% in women in their sixties (15.1 CV deaths per 10 000 women-years); total death rate is 75.5 per 10 000 women-years
d) 27% in women in their seventies (53.9 CV deaths per 10 000 women-years); total death rate is 199.5 per 10 000 women-years
taux de mortalité cardiovasculaire chez les femmes belges
* ces taux sont à comparer avec ceux observés dans les essais de statines chez des femmes pour évaluer la représentativité des échantillons souvent hautement sélectionnés

CARDIOVASCULAR MORTALITY AND STATINS
« The four post-2007 trials of rosuvastatin vs placebo are all without a CV mortality benefit despite about 126 000 patient-years of randomization, e.g. CORONA, AURORA, JUPITER and HOPE-3 »[136]
mortalité cardiovasculaire et statines

CARDIOVASCULAR RISK THRESHOLDS FOR STATINISATION
« For some time, UK and US guidelines have recommended statins for primary prevention in patients with a 20% or greater estimated risk of CV disease over 10 years [2% per year]...

In a 2013 American College of Cardiology/American Heart Association guideline, this recommendation has changed radically to include moderate-to-high intensity statin treatment for patients aged 40-75 years with a predicted 7·5% or higher 10 year CV risk, without a requirement for monitoring of lipid concentrations »…

implying that treatment is indicated at a 0.75% annual baseline risk and implying that the cholesterol hypothesis does not hold anymore ! Even if statins were miraclously demonstrated to reduce relative risk by 33 %, the absolute risk reduction would be 0.25% (1 in 400 patient-years), for an inefficacy rate of 99.75% and an average delay of CV events of 22 hours per year of treatment offset by direct and indirect costs and adverse reactions that have been hidden or brushed a side for too long

* If we assume that NNTs for statinisation should not exceed 100 patient-years (which amounts to an annual ineffectivess rate of 99% and already a substantial burden on health resources) and that statins reduce risk by 25%, then the threshold baseline annual risk should be 4%, not 0.75%. A yearly baseline risk of 4% is found only in some men with established coronary disease and several concomitant risk factors…

If we more realistically assume that NNTs observed under experimental conditions are presumably and reasonably doubled in clinical settings – because of the numerous biases weakening the internal and external validities of sponsored statin trials – then an 'experimental' NNT of 50 patient-years should be the threshold (which, by the way, is what Nortin Hadler suggests) to predict a 'clinical' NNT of 100, and clinical setting baseline risk should reach 3-4% per year before considering statinisation, a rather rare situation...

Another reason for requiring an NNT_{exp} of 50 patient-years or less – and an optimal treatment threshold of 3-4% clincal setting annual baseline risk - is the « Accumulating and concerning information on potential harms (myopathy, diabetes and more) but less systematically collected and thus carrying more uncertainty than the benefits. The exact incidence of harms could markedly affect the optimal risk threshold for treatment »
seuils du risque cardiovasculaire justifiant la statinisation

CARDS, THE TRIAL *Prévention primaire chez diabétiques – Arrêt prématuré injustifié – Haut risque de biais*
Collaborative Atorvastatin Diabetes Study

* Princeps publication : Colhoun/Lancet/2004[137]
* Comparison : atorvastatin 10 mg vs. placebo
* Funding : private, Pfizer. The promoter did more than finance the study : « Site monitoring, data collection, and data entry was done by staff at Pfizer UK, page 688, 2nd paragraph of princeps article »[138] Ghoswriting is almost written on the wall !

* Control measures : Double blind, randomized

[135] KCE Report 216, page 45, at https://kce.fgov.be/sites/default/files/page_documents/KCE_216_breast_cancer_screening.pdf
[136] Eddie Vos, 2016, communication
[137] Colhoun et al. Lancet 2004; 364: 685
[138] Quoted by de Lorgeril et al. RRCT 2012 ; 7(2) :1

* Follow-up : 3.9 years, stopped prematurely 2 years before the anticipated end, and in the absence of significant effect on both total mortality and CV mortality, the lack of confirmation in subsequent trials also testing atorvastatin, and the absence of pertinent justification for an early termination, suggest that the trial should not have been prematurely stopped and is suspected of being flawed[139]

* Participants demography : 2838; mean age 62, 62 % > 65 years ; 32 % women
* Participants health : 100% diabetics ; 84 % hypertensive ; 0 % with CHD ; mean TC 5.4 mM ; LDL-C mean 3 mM, none > 4.1 mM
* Composite endpoint of CV morbidity : [acute CHD events + coronary revascularisation + stroke] – (Note : Revascularisation is a medical decision, not an objective outome. CV deaths and total deaths were not included as a primary endpoint)

* Health related quality of life *not reported*

RESULTS
* Relative risk for surrogate outcomes:
a) relative risk reduction of TC = -26%
b) relative risk reduction of LDL-Cholesterol = -40 %
c) relative risk reduction of TG = -19%

* Relative risk for clinical endpoints :
a) relative risk reduction of composite primary endpoint of -37%, statistically significant but made of small numbers, 83 on statin, 127 on placebo
b) relative risk reduction of total mortality of -27%, NS
c) relative risk reduction of CHD mortality, NS

Abolute risk results :

* For the composite endpoint, absolute risk reduction is based on low numbers, 83 major CV events under atorvastatin (2.46 per 100 person-years) and 127 under placebo (1.54 per 100 person-years), an absolute difference of 0.92 endpoint per 100 patient-years, an NNT of 108 patient-years under trial conditions and presumably much larger in clinical settings... ; heterogeneity of outcomes, mixing soft with hard criteria, not including mortality, is not robust enough for stopping a trial or for clinical decision making

The authors stated that 37 events would be prevented per 1000 persons treated 4 years, which corresponds exactly to an NNT of 108 patient-years. Equivalent to a virtual delay of 81 hours for first CV events per year of treatment and much fewer hours in clinical settings. This numerical benefit of the heterogenous composite endpoint is not large enough to justify stopping the trial or prescribing the study drug in this indication

* Authors' conflation :
(a) atorvastatin is « safe », although adverse events were ostensibly not sufficiently looked for ;
(b) atorvastatin is « efficacious », when the yearly rate of inefficiency is 99.8% and the NNT > 100 patient-years in experimental conditions ;
(c) all people with this disorder « warrant statin treatment », an obvious discrepancy from the data reported in this and other trials in diabetics (Aspen, 4D)

* External interpretations:
« Early termination of CARDS was a mistake :
a) absence of pertinent justification for premature termination,
b) lack of significant effect on mortality,
c) lack of confirmation in subsequent trials,
d) lack of reliability of outcome reporting … »[140]

« Curiously, the one study (CARDS) that did specifically target patients with diabetes showed a statistical benefit in the combined clinical end point but not in total mortality. This discordance between CARDS showing a clinical benefit, and ASPEN and 4D not demonstrating a clinical benefit may be related to the duration of diabetes »[141] - Also, the composite endpoint is not

[139] de Lorgeril et al, ibidem
[140] de Lorgeril et al, ibidem
[141] DuBroff RJ. Evid Based Med 2015 ; 20(4) : 1 – DOI: 10.1136/ebmed-2015-110236

valid internally or externally

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : Yes, we have access to anonymised data. Has shared data with CTT and wiling in theory to share data with others with 'governance approval'…

l'essai dit Cards

* Aucun excès d'effets indésirables ne fut observé, ce qui est non plausible considérant la documentation disponible en statinovigilance – « En 2004 il y a eu l'essai CARDS, positif s'agissant de l'utilisation de l'atorvastatine avec une réduction du taux de mortalité des diabétiques égale à -27% [NS] ... Dommage seulement que l'étude ait été prématurément interrompue, très dommage surtout que les investigateurs aient tenté longtemps et fort maladroitement de masquer leurs pauvres liens de subordinations financières avec le géant Pfizer. Encore plus dommage que cette étude n'ait plus jamais été reproductible, donc compte tenu des parts d'ombres liées à la réalisation de cette étude, celle-ci doit nous laisser franchement dubitatif quant à la réalité des résultats affichés[142] »

CARE, THE TRIAL

Prévention secondaire – Pravastatine 40 mg c. placebo

Cholesterol and Recurrent Events Trial

* Princeps publication : Sacks/NEJM/1996[143]

http://www.nejm.org/doi/full/10.1056 /NEJM199610033351401 - t=article

METHODOLOGY

* Participants' demography : 4159 randomized; average age 59 years (31 % > 65 years); 576 women or 14%
* Participants' health : 100% with prior CHD (MI) ; mean TC 5,4 mM (209 mg/dL), all < 6.2 mM ; LDL-C range 3-4.5 mM, mean 3.6 mM; 43 % hypertensive ; 14 % diabetic
* Duration : 5 years (60 months)

* Primary composite endpoint : [CHD death + nonfatal MI + CABG + PTCA]. Heterogeneity of endpoints introduces risk of bias since :

(a) individual endpoints have different values for the patient (1 fatal, 1 non fatal, 2 interventions),
(b) bypass and angioplasty are ischemia driven medical decisions subject to doctors' opinions and facilities, and
(c) frequencies of baseline endpoints and their changes under treatment are uneven

* Positive compliance (active group adherence) : 96%
* Negative compliance (control group adherence) : 92%

RESULTS

* Health related quality of life *not reported*
* Kaplan-Meier plot on all-cause mortality was *not published*

a) relative risk reduction of CHD death was -37 % (NS) ; absolute risk reduction was 0.68 percentage points over 5 years and 0.136% per treatment-years, annual NNT = 735 patient-years, for an average delay of 12 hours per year of treatment
b) relative risk reduction of TOTAL MORTALITY was -8 % (NS) ; absolute risk reduction = 0.6 % per year and NNT = 168 patient-years
c) relative risk reduction of CHD events in composite primary endpoint was -24% (p=0.003) ; NNT = 168 patient-years, delaying an event by 11 hours for each year of treatment

d) relative risk reduction of stroke was -31 % (NS)
e) relative risk reduction of TC was -20 %, from 5.4 mM
f) relative risk reduction of LDL-C was -28 %, from 3.6 mM

* Clinical importance is negligible: The absolute risk reduction was not clinically meaningful for CHD events, without a reduction in total mortality or CHD death, in addition to using a composite primary outcome with high risk of bias

Benefits as relative risks in women :

* CHD mortality relative risk reduction of -20%, NS

[142] Aimsib.org, 22 avril 2019
[143] Sacks et al. N Engl J Med 1996; 335: 1001

* Nonfatal MI relative risk reduction of -49%, NS
* CHD events relative risk reduction of -40%, NS

Harms :
Breast cancer : RRI of +1200 %, for an ARI of +34% and a NNH of 294 ; 12 / 286 women (4.2%) in the statin group but only 1 / 290 in the placebo group (0.34%) had breast cancer … « The findings of increased incidence of breast cancers is documented in earlier statin trials with a sufficient number of women included, like the CARE trial"[144] …

"The most serious adverse event was breast cancer, which occurred in 12 of the women (4.2%) in the pravastatin group but in only 1 of the women (0.34%) in the placebo group."[145]

« The treated subjects in the CARE trial can never gain [in life span]. There were other reported benefits with treatment in CARE, including their lesser need for revascularization procedures [a soft/subjective outcome, ischemia driven]. However, the average delay of revascularization was 0.09 years (33 days) over 5 years.[146] To delay that need for only 1 year would require this group to continue pravastatin for 55 years »[147]

« The CARE study found no reduction in total mortality or coronary mortality in secondary prevention »[148]
* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Care

CATARACTS AND STATINS
Statinovigilance – Épidémiologie

« We determined associations between age-related cataract, type 2 diabetes, and reported statin use in a large optometric clinic population. 6397 patient files (ages <1-93 years) were reviewed. Overall prevalence of statin use was calculated for patients with type 2 diabetes (n = 452) and without diabetes (n = 5884). Multivariable logistic regression analysis for age related cataract was performed controlling for patient sex, smoking, high blood pressure, type 2 diabetes, and statin use...

The prevalence of statin use (in patients aged >38 years) was 56% for those with type 2 diabetes and 16% for those without diabetes. Type 2 diabetes was significantly associated with nuclear sclerosis (OR = 1.62, 1.14-2.29) and cortical cataract (OR = 1.37, 1.02-1.83). Statin use was associated with nuclear sclerosis (OR = 1.48, 1.09-2.00) and posterior subcapsular cataract (OR = 1.48, 1.07-2.04)...

The 50% probability of cataract in statin users occurred at age 51.7 and 54.9 years in patients with type 2 diabetes and without diabetes, respectively. In non-statin users, it was significantly later at age 55.1 and 57.3 years for patients with type 2 diabetes and without diabetes, respectively ($p < 0.001$). In this population, statin use was substantially higher in patients with type 2 diabetes and was associated with AR cataracts »[149]

« We sought to examine the effect of statin use on the risk of cataract and need for surgical intervention in 2 North American populations. This retrospective nested case-control study derived data from the British Columbia (BC) Ministry of Health databases from 2000-2007 and the IMS LifeLink database from 2001-2011 to form 2 patient cohorts. The BC cohort was comprised of female and male patients; 162,501 patients were matched with 650,004 control subjects...

The IMS LifeLink cohort was comprised of male patients aged 40-85 years; 45,065 patients were matched with 450,650 control subjects. Patients with statin use for > 1 year before the initial ophthalmology visit were identified. Diagnosis and surgical management of cataract were followed. Conditional logistic regression models were used to analyze data...

For the BC cohort, the crude rate ratio (RR) for use of any statin was 1.30, and the adjusted RR was 1.27 (95% confidence interval, 1.24-1.30). The adjusted RRs for each individual statin were all statistically significant. For the IMS LifeLink cohort, the crude RR for use of any statin was 1.13, and the adjusted RR was 1.07 (95% confidence interval, 1.04-1.10)...

[144] Paul v Nguyen, 2014
[145] Diamond & Ravnskov, op. cit.
[146] Bassan & Panush. Am J Cardiol 1997; 79: 1001
[147] Krut LH. American Journal of Cardiology 1998, 81(8): 1045 - DOI: 10.1016/S0002-9149(98)00084-8
[148] Bassan & Panush. Am J Cardiol 1997 ;79 : 1001
[149] Machan et al. Optom Vis Sci 2012; 89(8): 1165 - doi: 10.1097/OPX.0b013e3182644cd1 - https://www.ncbi.nlm.nih.gov/pubmed/22797512

This study demonstrates that statin use is significantly associated with cataract requiring surgical intervention. This relationship was consistent in both North American cohorts »[150]

« We compared the risks for development of cataracts between 13 626 statin users and 32 623 nonusers by a propensity score–matched cohort analysis using retrospective data from October 1, 2003, to March 1, 2010. A propensity score–matched cohort of statin users and nonusers was created using 44 variables. For our primary analysis, we matched 6972 pairs of statin users and nonusers...

The risk for cataract was higher among statin users in comparison with nonusers in the propensity score–matched cohort (odds ratio, 1.09; 95% CI, 1.02-1.17). In secondary analyses, after adjusting for identified confounders, the incidence of cataract was higher in statin users in comparison with nonusers (odds ratio, 1.27; 95% CI, 1.15-1.40). Sensitivity analysis confirmed this relationship. The risk for cataract is increased among statin users as compared with nonusers »[151]

« In a prospective cohort study in a large population of primary care patients using version 24 of the General Practice Research Database, Qresearch (UK), statin use was associated with cataracts. In women the NNH for an additional case of cataract over 5 years was 33 (95% CI : 28 to 38) [and the annualized NNH was 165 women-years (95% CI : 140 to 190)]. After stopping treatment the risk of cataract returned to normal within a year in men and women [A sort of collective positive dechallenge]…

Each statin was associated with an increased risk of cataract in both men and women. There was no evidence of a dose-response relation. The time varying analysis showed the risk was significantly increased within a year of starting statins, persisted during treatment, and returned to normal within the 1st year after stopping treatment [A sort of positive collective dechallenge]…

The case series analysis confirmed the significantly increased risk of cataract during the period of use of each statin compared with the period of non-use, except for pravastatin »[152]
cataractes et statines

CATZ, THE TRIAL
Calcification des coronaires
« Simvastatin treatment does not reduce progression of coronary artery calcium or abdominal artery calcium compared with placebo »[153]
l'essai dit Catz

CENSORHIP IN LIPID LAND – (Article)
« Stories from AU and UK reveal the dangers of telling the truth about statins... Welcome to Lipid Land, ruled by our old friends Scandal, Deception and Deceit… It's time to add Censorship to the list... There are 3 generally irrefutable points you can summarize from the research on the effectiveness and safety of statins:

a) statins 'work' primarily for a small subset of men who have heart disease
b) most people currently prescribed statins are unlikely to see any net health benefit
c) all statin takers expose themselves to risks of harm

When I say 'work,' I don't mean lowering your cholesterol, I mean preventing a heart attack or stroke. The only ones who benefit from the drugs are men who have had heart disease or previously had a heart attack. They may see a 4-5% reduced risk of a heart attack or stroke over 5 years by swallowing a daily statin [NNT > 100 patient-years ; no established survival benefit ; 1/5 with ADRs]…

There is a lack of evidence showing women, the elderly and 'low risk' men (i.e. most of us) will benefit from statins… The big manufacturer-funded statin trials show a very small level of adverse effects, yet other case studies or observational studies note perhaps as many as 1/5 statin users will experience adverse effects...

I have to give the last word to French cardiologist and researcher Michel de Lorgeril. In his book, Cholesterol and Statins: Sham

[150] Wise et al. Can J Cardiol 2014 ; 30(12): 1613 - doi: 10.1016/j.cjca.2014.08.020 - https://www.ncbi.nlm.nih.gov/pubmed/25475465
[151] Leuschen et al. JAMA Ophthalmol 2013; 131(11): 1427 -doi:10.1001/jamaophthalmol.2013.4575 - http://jamanetwork.com/journals/jamaophthalmology/fullarticle/1739520?resultClick=3
[152] Julia Hippisley-Cox, & Carol Coupland. BMJ 2010; 340: c2197
[153] Terry et al. Am J Cardiol 2007; 99: 1714

Science and Bad Medicine, he asks, 'Why does challenging the cholesterol theory trigger such extreme reactions?' And further, 'Why are the media afraid of revealing the greatest medical scandal in modern time?' All I can add is 'Why indeed?' »[154]
La censure en territoire lipidique (Traduction libre du titre de l'article)

CEREBELLAR ATAXIA
Statinovigilance – Notification spontanée – Vignettes cliniques
* Four cases of progressive cerebellar gait ataxia in patients taking a statin were published from Brazil in 2016[155] :

a) In a 52 year old man, time to onset was 30 days after starting atorvastatin 10 mg, time to positive dechallenge 1 month ; after a positive rechallenge, time to second positive dechallenge was 30 days. The chronology is a compelling argument for causality and the case was previously published[156] after eliminating other causes by a thorough neurological workup up to brain MRI and magnetic resonance cervical angiography.

b) In a 68 year old woman, time to onset was 180 days after starting simvastatin 40 mg, time to positive dechallenge 30 days helped by coenzyme Q10 as corrective treatment, and after a positive rechallenge, time to second positive dechallenge was 20 days. The chronological evidence for a causal link and the exclusion of other neuropathologies by extensive laboratory investigations, are compelling

c) In a 65 year old man, time to onset was 120 days after starting simvastatin 40 mg, time to positive dechallenge 45 days aided by coenzyme Q10, and after a positive rechallenge, time to second positive dechallenge was 30 days. Again the chronology is in favor of statin neurotoxicity, especially since alternative etiologies were eliminated by the complementary investigations

d) In a 58 year old man, time to onset was 150 days after starting simvastatin 60 mg, time to positive dechallenge was 25 days with correction by coenzyme Q10, and after a positive rechallenge, time to second positive dechallenge was 30 days. The chronology and the exclusion of alternatives after a complete differential diagnosis make a *definitive* case for the statin induction of the gait ataxia

In 2000 a case of reversible atorvastatin-associated external ophthalmoplegia, anti-acetylcholine receptor antibodies, and *ataxia* was reported[157]. In 2010 two cases of *ataxia* in bipolar disorder were also published[158]
ataxie cérébelleuse
* ces 4 observations cliniques ont une excellente *informativité* – on est allé jusqu'à l'angiographie cervicale avec résonnance magnétique – et une quasi parfaite *imputabilité*...

Une telle force de preuve ne pourrait être obtenue par une étude observationnelle car cet EIM est rarissime et un résultat négatif serait à prévoir même si on utilisait les méga-données que peuvent maintenant fournir les bases administratives sanitaires qui réunissent toutes les activités médicales et pharmaceutiques en cabinet et à l'hôpital à des fins de remboursement...

De toute façon ces bases de données ne comptabilisent pas les déchallenges et les rechallenges ni l'exclusion des alternatives par les explorations cliniques appropriées pour faire un diagnostic différentiel

CEREBRAL MICROBLEEDS, LOW TOTAL CHOLESTEROL AND STATIN USE
Épidémiologie – Framingham – Prévalence – Corrélation

« Our Framingham sample comprised 1965 participants – original and offspring - who attended a baseline examination (1998-2008) and underwent a brain MRI (2000-2009) for measuring cerebral microbleeds (CMB). Odds ratios (OR) calculated by logistic regression :

a) Very low TC levels (< 10th percentile) were associated with any CMB (OR = 1.91 or +91 %) and lobar CMB (OR = 1.99 or +99 %) - Results concur with a previous report from the Rotterdam study[159]

b) Statin use was somewhat related to all CMB (odds ratio = 1.67 or +67 %), to lobar CMB (OR = 1.52 or +52%) and to any deep

[154] Alan Cassels. http://commonground.ca/2014/06/censorship-in-lipid-land/
[155] Hélio AG Teive et al. Parkinsonism and Related Disorders 2016 : 1-3
[156] H.A. Teive et al. Arq Neuropsiquiatr 2012 ; 70 : 152 (In Portuguese)
[157] Negvesky GJ et al. Arch Ophthalmol 2000 ; 118 : 427
[158] Berner JE. J Clin Psychiatry 2010 ; 71 : 359
[159] Vernooij et al. Neurology 2008 ; 70 : 1208

CMB (OR = 1.92 or +92 %) by logistic regression. We report, for the first time in a community-based study, an association of statin use with the risk of cerebral microbleeds. Statin use was independently associated with CMB risk, not affected by adjustment for cholesterol levels or concomitant medication or antithrombic use or inflammatory markers»[160]
microhémoragies cérébrales, cholestérol total bas et statinisation
* l'augmentation des microhémorragies cérébrales lobaires et profondes en présence de cholestérol total très bas contredit l'hypothèse lipidique
* l'augmentation des microhémorragies cérébrales lobaires et profondes par l'utilisation de statines contredit l'hypothèse statiniques

* l'indépendance de cet effet indésirable statinique avec les niveaux de cholestérol contredit l'hypothèse lipidique
* l'âge, le sexe masculin et l'hypertension sont associés à ces microhémorragies

CERIVASTATIN AND RHABDOMYOLYSIS
Médicament mortel – Retrait criminellement tardif
« On 9.8.2001, following the death of 52 patients, Bayer decided to withdraw its star choelsterol-lowering drug, cerivastatin »
cérivastatine et rhabdomyolyse
« L'histoire des statines a été marquée damatiquement par la cérivastatine (Staltor™, Baycol™) retirée en 2001 à cause d'un nombre de rhabdomyolyses (ruptures et hémorragies musculaires, myoglobinurie et insuffisance rénale) 60 fois plus élevé que pour les autres statines, risque certes très rare mais que Bayer connaissait et n'a reconnu qu'avec 4 ans de retard et 52 d'accidents mortels »[161]

« Sortie en 1997 et commercialisée par GSK, elle donnait 80 fois plus de rhabdomyolyses que l'atorvastatine (Lipitor™) et a été retirée en catastrophe mais seulement en 2001 alors que Bayer connaissait le risque »[162], soit 4 ans trop tard et après des centaines de décès

CERIVASTATIN MARKET WITHDRAWAL
Retrait pour motif de pharmacovigilance – Rhabdomyolyse
« Cerivastatin was withdrawn from the market in the year 2001 after a 10- to 100-fold increased risk of total mortality was observed among individuals using cerivastatin compared with those on other statin drugs »[163]
retrait du marché de la cérivastatine

CHD ACROSS EUROPE
Épidémiologie
* According to a EuroHeart mapping project update in 2009, involving 16 countries followed for 3 years, rates of death from CHD among men under the age of 65 were 17 per 100K population in France and 44 in the UK ; for women under 65, rates were 3 in France and 11 in the UK[164] … differences in blood TC or LDL-C cannot explain those marked differences
la maladie coronarienne en Europe

CHD DEATH
TN : heart death *lacks specificity*
décès coronarien
* à distinguer de décès CV qui incluent les décès par AVC ischémique et hémorragique, et autres angiopathies (anévrisme, AVC par embolie non artérielle, insuffisance cardiaque valvulaire et autre, etc.). Les auteurs spécifient parfois leur définition de décès CV, mais ils devraient toujours le faire dès la publication princeps

CHD INCIDENCE DENSITY AND TC ACROSS THREE COUNTRIES
Épidémiologie – Hypothèse du cholestérol

« Rate of CHD / 10 000 / year in 2008 was
a) 45.8 in Japan (total cholesterol 5.1 mmol/l)
b) 143.7 in the UK (TC 5.4) and
c) 150.7 in the USA (TC 5.1), showing no correlation between the two

[160] Romero et al. Stroke 2014 ; 45(5): 1492 - doi: 10.1161/STROKEAHA.114.004130 – abstract at http://stroke.ahajournals.org/content/45/5/1492.abstract
[161] Even, page 95
[162] even, page 279
[163] Bhardwaj et al. Clinical Interventions in Aging 2013; 8: 47
[164] http://www.medicalnewstoday.com/articles/163589.php

Perhaps the most important finding is that the rate of CHD in men in Japan was 62.4 (per 100,000/year) in the years 1980 – 83, when their average total cholesterol level was 4.8 mmol/l. Since then TC has risen 9% to 5.2mmol/l; meanwhile the CHD rate has fallen by 27%. In fact, this trend of rising cholesterol and falling CHD has been going on since the 1960 »[165]
densité d'incidence de la cardiopathie ischémique et cholestérol total selon les pays
* Une explication, rarement mentionnée par l'establishment, est que le cholestérol n'a rien à voir avec la cardiopathie ischémique

CHD MORTALITY UNRELATED TO STATIN USE ACROSS COUNTRIES (EU)
Épidémiologie – Étude écologique

« Among the 12 Western European countries studied, the large increase in statin utilisation between 2000 and 2012 was not associated with CHD mortality, nor with its rate of change over the years. Factors different from the individual coronary risk, such as population ageing, health authority programmes, guidelines, media attention and pharmaceutical industry marketing, may have influenced the large increase in statin utilisation…

Since CHD is largely dependent on health factors, such as diet and exercise, the apparent lack of association we observed between CHD mortality and statin utilisation supports the need for greater implementation of population life-style changes instead of additional initiatives to further enhance statin utilisation to reduce the burden of CHD »[166].
la mortalité coronarienne sans lien avec l'utilisation nationale des statines (EU)

CHOLESTEROL : LE BON, LE MAUVAIS ET LE TRUAND – (Article de site web)
Sylvain DUVAL. *Formindep* 21.2.2013 sur
http://www.formindep.org/Cholesterol-le-bon-le-mauvais-et.html
* Bon survol de la question, dans la foulée de *La vérité sur le cholestérol* par Philippe Even

« La controverse actuelle sur le cholestérol fait couler beaucoup d'encre. Pour s'y retrouver, il faut regarder les données scientifiques avec méthode. Il y a 3 aspects à passer en revue : physiologiques, épidémiologiques et cliniques. Cela permet de critiquer la notion statistique de 'bon' et de 'mauvais' cholestérol, et d'identifier les 'truands', ceux qui ont dissimulé des données pour renforcer leur théorie, créer un dogme et le maintenir en place »

CHOLESTÉROL : MENSONGES ET PROPAGANDE – Pourquoi les médicaments anticholestérol sont inutiles – Comment l'industrie manipule les médecins – Comment vraiment empêcher un infarctus
Michel DE LORGERIL. Vergèze (FR): Thierry-Souccar; 2008 – 319 pages - ISBN-13 : 978-2916878171
* Un très bon livre, à lire surtout si vous êtes déjà statinisé(e) ou risquez de l'être …

« L'origine de la théorie du cholestérol remonte à des observations faites sur des rats en 1910. Mais c'est dans les années 1950-1960, avec l'étude épidémiologique de Framingham, du nom d'une petite ville des É-U, que le cholestérol acquiert ces lettres de noblesse. Des révélations récentes montrent comment des données de cette étude ont été dissimulées car elles ne confortaient pas la théorie. A la suite de Framingham tout s'est enchaîné…

Michel de Lorgeril apporte un éclairage déterminant sur deux points majeurs. D'abord l'étude épidémiologique Monica, qui a montré que 50 % des personnes ayant eu un infarctus du myocarde décédaient à court terme. Si les statines diminuaient réellement le risque d'infarctus, une baisse de la mortalité aurait dû être observée. Ce n'était pas le cas…

De Lorgeril est un partisan de la diète méditerranéenne qui a une probable efficacité chez les patients ayant présenté un infarctus du myocarde. Inspirée de l'alimentation traditionnelle des Crétois, elle associe une alimentation peu calorique par rapport à l'activité physique, une grande consommation de fruits et légumes, d'huile d'olive, de fromages frais, de poisson, et du vin en quantité modérée »[167]

CHOLESTEROL AND STATINS: Sham Science and Bad Medicine – (Livre numérique)
Michel DE LORGERIL. France : Thierry Souccar Publishing ; 2014 (Kindle / Amazon) – DOI : 978-2-36549-080-1 (Traduction par Anne Pietrasic, enrichie par l'auteur, du livre *Cholestérol, mensonges et propagande*)

[165] Malcolm Kendrick - http://drmalcolmkendrick.org/2015/12/21/cholesterol-goes-up-heart-disease-goes-down/, quoting Ueshima H et al. in Circulation 2008; 118: 2702–09 and Sekikawa et al. at http://ije.oxfordjournals.org/content/44/5/1614.short?rss=1.
[166] Vancheri F, et al. BMJ Open 2016; 6: e010500 - doi:10.1136/bmjopen-2015-010500
[167] Philippe Nicot. Formindep sur http://www.formindep.org/Cholesterol-mensonges-et.html

« This book critically evaluated clinical papers claiming that statins are effective in lowering CHD events. The important roles of the new penal regulations on clinical trials, which came into effect in 2004 in the EU, were emphasized; dramatic decrease in effectiveness of statins in CHD was noted after the EU regulations »[168]

« Dr. de Lorgeril, the architect of the famous secondary prevention trial of the Mediterranean Diet has written a *game-changing book* exposing the truth about cholesterol and statins. In short, his comprehensive assessment of pharmaceutical trials is the most *meticulous dissection* of statin clinical trials I have ever seen...

This book is a must read for anyone with clinical heart disease or anyone vulnerable to heart disease including those with positive family histories, and especially in those considering statin therapy. Highly recommended! »[169]

« With the 2013 US and 2014 UK guidelines on the prevention of CV disease, tens of millions of healthy people over the world will find themselves prescribed with statins. These tens of millions of people will be added to the tens of millions already taking this medication for high cholesterol, previous CV issues or diabetes...

However, not one of these patients will see their health improved or their lives saved by statins, and a large number of them will fall victim to their serious side effects that are often irreversible, such as diabetes, eye and neurological disorders, even cancers...

This is what Michel de Lorgeril brilliantly demonstrates with this new book. Dr. de Lorgeril is a medical doctor and scientist, internationally renowned for his research into the Mediterranean Diet, omega-3 fatty acids and polyphenols. He speaks out against this *collective regulatory insanity*, based on biased, truncated and often falsified studies…

The theory that cholesterol 'blocks arteries', that it causes heart attacks and strokes is an illusion that does not stand up to any physiological, experimental, epidemiological or clinical argument...

Contrary to current dogma, statins do not reduce total mortality, and this book provides irrefutable proof of this. These drugs, which can lead to diabetes and cancers, can also cause severe muscle damage, cognitive impairment and sexual dysfunction. Doctors and patients need good quality scientific evidence in order to make informed decisions...

But for decades now they have been misled by directives based on corrupt clinical studies, which have been knowingly altered to exaggerate the benefits of their molecules and to minimise their secondary effects...

When their findings are carefully analyzed, nothing remains of their claims. By far the most serious side effect, says de Lorgeril, is that these prescriptions convey a false sense of security and prevent the population from adopting healthier lifestyle measures. Measures whose efficacy in the prevention of heart attacks and CV disease has been proven - and which are presented in this book…

Michel de Lorgeril is a cardiologist, nutritionist and researcher at France's National Center for Scientific Research (CNRS) and a member of the European Society of Cardiology, internationally renowned for his research into the Mediterranean diet, omega-3 fatty acids and polyphenols. In recent years, he has published numerous articles in the medical and scientific press denouncing the systematic disinformation around cholesterol and statins »

« In his book, de Lorgeril asks, 'Why does challenging the cholesterol theory trigger such extreme reactions?' And further, 'Why are the media afraid of revealing the greatest medical scandal in modern time?' All I can add is 'Why indeed? »[170]
Cholestérol et statines : pseudo-science et mauvaise médecine (Traduction libre du titre du livre)

CHOLESTEROL DECEPTION
cholesterol hypothesis deception
la supercherie du cholestérol / de l'hypothèse du cholestérol

CHOLESTEROL EVANGELISTS
évangélistes du cholestérol
* certains sont sincères (mais ignares et sans financement industriel), certains sont sincères mais vénaux sans trop se l'avouer (ignares et financés par l'industrie), d'autres savent ce qu'ils font mais ferment les yeux sur les conflits d'intérêts et ouvrent toute grande la porte de leur compte de banque et la voie vers le succès professionnel (carriérisme)

[168] Okuyama et al. Expert Rev Clin Pharmacol, 2015 ; 1
[169] Stephen T. Sinatra
[170] Alan Cassel, 2014 - http://commonground.ca/2014/06/censorship-in-lipid-land/

CHOLESTEROL GUIDELINES : SO-CALLED NATIONAL (USA)
Recommandations – Sponsoring corporatif – Liens d'intérêts des panélistes

« The panels issuing the 2001 and 2004 guideline and update for the National Cholesterol Education Project of the National Heart, Lung and Blood Institute - which greatly expanded the number of people for whom cholesterol lowering drugs were recommended - were profoundly compromised by financial conflicts »[171]

« In 2004 the U.S. National Cholesterol Education Program (NCEP) updated its guidelines… It was subsequently disclosed that most of the committee members had extensive financial connections to the manufacturers of statins, which stood to gain from increased use of these drugs »
* One wonders if *National* is not sometimes - if not often - a substitute for *Corporate*…
directives lipidiques soi-disant nationales
* l'adjectif national implique trompeusement une reconnaissance gouvernementale objective et indépendante. On se demande si *National* n'est pas parfois - sinon souvent - un substitut à *Corporatif*

CHOLESTEROL HYPOTHESIS
See LIPID HYPOTHESIS

CHOLESTEROL HYPOTHESIS : TIME FOR THE OBITUARY ? – (Article)
Hypothèse lipidique
Tore Scherstén et al. *Scandinavian Cardiovascular Journal* 2011; 45: 322
« The cholesterol hypothesis links cholesterol intake and blood levels to CV disease. It has had enormous impact on health care and society during decades, but has little or no scientific backing that is relevant for the human species. Apparently, the hypothesis is false and should be buried » écrivent des universitaires scandinaves en 2011…

* In 1856 Virchow describes cholesterol deposits in atheromatous plaques
* In 1913 Anitchkov feed rabbits with egg yokes and provoques atheromatous plaques but when he tried with other animals, crnivores, he *cannot* reproduce the results

* In 1953 Keys (*J Mt Sinai Hosp* 20 : 118) reports that dietary intake of fat is significantly correlated to cholesterolemia and to CV deaths in 6 countries, except that those 6 were *selected* from 22 countries and there was no correlation when all countries were included « The study was obviously a falsification »

* In 1986 Keys publishes the *Seven Countries* study and, with statistical maneuvers, he 'showed' that saturated fat is the culprit after recording diet and cholesterol in 12 000 middle-aged men (*Am J Epidemiol* 124 :903) - He chose the data to fit his hypothesis (it was initially a 23 countries study). Not only defective but fraudulous

* The idea that cholesterol is dangerous took root in the Framingham study claiming that hypercholesterolemia was a risk factor for MI, but when the 30-year follow-up was published in 1987 (Andersson. *JAMA* 257: 2176) it turned out that :

a) hypercholesterolemia was not a risk factor for men > 47 years, and
b) not a risk at all for women, and
c) more men died of MI when their cholesterol had *decreased* over the years ;

d) the authors even wrote « For every milligram percent cholesterol had *decreased*, CV mortality and total mortality *increased* by 14% and 17% respectively »

* Sachdeva in 2009 found that cholesterolemia in patients with AMI was substantially *lower* than in normal controls at the same age (*Am Heart J* 157 :111)
* Al-Mallah in 2009 found *lower* LDL-C values in patients with AMI, and the mortality rate twice as high in patients with the *lowest* LDL-C (*Cardiol J* 16 :227)

* In an excellent and unmasking article, De Lorgeril wrote in 2010 that following the stricter regulations implemented after 2005 (post-Vioxx scandal), most studies of statins had been either negative or obviously biased (*J Lipid Nutr* 19 :65)

* A Swedish ecological study by Nilsson in 2011, including 2 M men and 2 M women, found that despite increasing use of statins

[171] Lenzer et al. BMJ 2013; 347: f5535 - doi: 10.1136/bmj.f5535

between 1998 and 2002 there was no correlation with MI incidence or CHD mortality (*JNR BioMed* 10.1186/1477-5751)
* The meta-analysis of Ray in 2010 showed no life prolongation by statins in 11 randomized trials involving 65 229 participants (*Arch Intern Med* 170 :1074)

« These studies showed clearly that there is no causal relationship between the cholesterol level in blood and the risk of dying from a MI, but the so-called *cholesterol hypothesis* is still alive… It has become a *modus operandi* for statin manufacturers to plan, carry out and analyze the results of clinical trials and then use professionnals (aka ghostwriters) to write the articles under the name of well-known academics (aka KOLs)… It is time to say goodbye to this old, ill-founded and fallacious *lipid hypothesis* »
L'hypothèse du cholestérol : Est-ce temps d'en écrire la nécrologie? (Traduction libre du titre de l'article)

CHOLESTEROL IS NOT THE CULPRIT : A Guide to Preventing Heart Disease – (Livre imprimé et numérique)
Fred A KUMMEROW. Jean M KUMMOROW, Editor : 14.2.2014

« You will find a lot in this book related to diet and heart disease; it is the No 1 cause of death in the U.S. and throughout much of the world and also the focus of the majority of my career. To me, researching diet and heart disease is like being the detective in a good mystery book who follows clue after clue and finally comes up with an unexpected answer. The detective is always trying to find out who and what killed the person...

Some detectives view *cholesterol* as the killer in heart disease, but I show you why that's not so. I hope in reading this book, you'll not only learn what is healthy to eat, but also why it is healthy to do so. How the body uses food to make what we need to keep going is an incredible, almost magical, process. We, as well as all animals and plants, are not programmed to live forever, but we can certainly increase the number of high quality years of life »
Le cholestérol n'est pas le coupable : Un guide de prévention de la maladie coronaire – (Traduction libre du titre du livre)

CHOLESTEROL IS NOT THE CULPRIT : A Special Interview With Fred Kummerow[172]
Hypothèse lipidique
Joseph Mercola :
« Heart disease is one of the leading causes of death, and cholesterol is frequently given the blame. But is that even justified? Dr. Fred Kummerow is one of the leading pioneers in this area. For nearly 8 decades – yes, you heard me right – he has been researching the science of lipids, cholesterol, heart disease, and nutrition. Since the late '70s, he's also studied the imbalance of nutrients in the American diet that lead to obesity....

He was the first researcher to identify the fact that *trans* fat was a major cause of heart disease… His new book, *Cholesterol Is Not the Culprit*, focuses on the basic chemistry of food, how your body works, and how food fits into the whole equation »

Fred Kummerow :
« In 1957, I had shown that people who eat partially hydrogenated fat and people who had been autopsied at that time contained *trans* fatty acids in their artery cells and in their other body tissue, too. It was published in *Science*. That was the first article that showed that *trans* fatty acids, which are present in hydrogenated fats, caused heart disease...

Ancel Keys just confused the physicians because he said, at the beginning, that *cholesterol* was the cause of heart disease, and then he later *retracted* that… This one man had such a profound influence on the whole strategy and position of the healthcare system, pretty much on a global basis, in vilifying cholesterol and saturated fat and not understanding the true causes, trans fats…Processed food is where all this *trans* fat lies. There are 37,000 products with it in the American diet, which is incredible...

In 1975, when I acted as an expert witness at the *Federal Trade Commission* hearing, I was in opposition to what all cardiologists at that time were saying. I never got another cent from the NIH because I differed with the cardiologists on what they were saying… If you can eliminate *trans* from your diet, put in fresh, locally grown vegetables, healthy fats, and animal proteins in appropriate amounts, you're going to be healthy. These *trans* fats are going to be removed from your system within 30 days...

For breakfast, you should eat an egg; cooked oatmeal or wheat; a tablespoon of yogurt, of nuts, crushed nuts like almonds and walnuts; some fruit, 2 to 3 different kinds of fruit ; 2 or 3 kinds of vegetables; a meat source (beef, pork, chicken, fish, seafood like crab or shrimp); and also cheese as a source of protein…

For dinner, I would say, as I explained, eat vegetables either raw or cooked, fruits either raw or cooked, meats, and milk products »

[172] Joseph Mercola, 20.4.2014 - http://mercola.fileburst.com/PDF/ExpertInterviewTranscripts/Fred%20Kummerow_cholesterol_April%202014_transcript2.pdf

Le cholestérol n'est pas le coupable : Interview particulière avec le Dr Fred Kummerow – (Traduction libre du titre de l'interview)

CHOLESTEROL LOWERING, CARDIOVASCULAR DISEASES, AND THE ROSUVASTATIN-JUPITER CONTROVERSY : A Critical Reappraisal. – (Article)
Michel de Lorgeril et al. *Arch Intern Med* 2010; 170(12): 1032 - doi:10.1001/archinternmed.2010.184[173]
Réduction du cholestérol, maladies cardiovasculaires et la controverse Rosuvastatine-Jupiter : Réévaluation critique
(Traduction libre du titre de l'article)

CHOLESTEROL PARADOX : A Correlate Does Not A Surrogate Make – (Article)
DUBROFF, ROBERT. *Evid Based Med* 20.12.2016 – DOI : 10.1136/ebmed-2016-110602
Synthèse méthodique réfutant 'hypothèse lipidique

« The global campaign to lower cholesterol by diet and drugs has failed to thwart the developing pandemic of coronary heart disease around the world. Some experts believe this failure is due to the explosive rise in obesity and diabetes, but it is equally plausible that the cholesterol hypothesis, which posits that lowering cholesterol prevents cardiovascular disease, is incorrect.

The recently presented ACCELERATE trial dumbfounded many experts by failing to demonstrate any CV benefit of *evacetrapib* despite dramatically lowering low-density lipoprotein cholesterol and raising highdensity lipoprotein cholesterol in high-risk patients with coronary disease.

This clinical trial adds to a growing volume of knowledge that *challenges the validity of the cholesterol hypothesis* and the utility of cholesterol as a surrogate end point. Inadvertently, the cholesterol hypothesis may have even contributed to this pandemic. This perspective critically reviews this evidence and our reluctance to acknowledge contradictory information »

* 44 randomized controlled trials in cholesterol reduction are reviewed for a statistical relative risk reduction of CVD events. The interventions included cholesterol-reducing diets, statins, estrogens, a fibrate, niacin, ezetimibe, cholestyramine and evacetrapid.

* Of 10 studies with more than 10,000 participants, 5 (50%) showed a statistical reduction, the regulatory objective of sponsors who can afford such mega-trials, knowing that a statistically significant reduction of a major outcome is sufficient to gain marketing approval unless a major safety issue emerges, without taking into

* 9/44 studies (20%) showed *paradoxical* results in the form of an *excess* of a CVD events or in total mortality or in morbidity ; these 9 studies are seldom cited in the literature ; in 5 of the 9 (56%) the trial was terminated prematurely for safety reasons;

* 44/44 (100%) studies *failed* to show a reduction in total mortality, the most clinically relevant and valid outcome measure

* 14/44 (32%) studies reported a statistical reduction in one or more CVD event, but none obtained a large enough absolute risk reduction of a clinically relevant valid endpoint

* For example, the ACCELERATE trial enrolled 12 092 participants at high risk to compare ECTP inhibitor *evacetrapib* 130 mg/day with placebo, lasted 30 months, reduced LDL-C by -37% and raised HDL-C by +130% in relative terms but achieved *no discernible CVC event or mortality reduction*.

« The trial adds to the chorus that cholesterol is not a valid surrogate end point for CVD events and dumbfounded many experts by failing to demonstrate any CV benefit despite dramatically lowering LDL-C and raising HDL-C in secondary prevention »

CHOLESTEROL SCREENING
"For primary prevention, whatever the level of LDL cholesterol, men > 65 years and women of any age who take statins receive no benefit",[174] a good reason to stop repeatedly screening healthy people for cholesterol levels. So why screen those who dont' benefit from statins ?

« After age 50 years there is no increased *total mortality* with either high or low serum cholesterol levels. After age 50 years the association of total mortality with cholesterol values is confounded by people whose cholesterol levels are falling »,[175] in a 30-

[173] Free on line at http://archinte.jamanetwork.com/article.aspx?articleid=416101
[174] James Wright. Protégez-Vous, Feb 2010, interview translated by Carol Kuschner
[175] Anderson et al. JAMA 1987; 257: 2176

year Framingham follow-up. So why screen after age 50 ?
dépistage du cholestérol ; cholestérolémie de dépistage
* Le temps ne serait-il pas venu pour un moratoire sur les cholestérolémies de dépistage ? Du moins pour leur remboursement par les régimes publics de soins ? Puisque la seule utilité est de mener à une statinisation à vie, qui réduit à divers degrés la qualité de vie, ne prolonge pas l'espérance de vie, ne retarde pas de façon cliniquement tangible la survenue d'accidents artériels thrombotiques, en plus d'être pharmaco-économiquement indéfendable et à l'origine de nombreux EIM

* Vu 'l'innocuité du cholestérol, l'inefficacité des statines et le gaspilage qu'elles entraînent'[176]… 'un seul dosage dans votre vie montrant qu'il est inférieur à 7,7 mmol/l (3 g/L) suffit,[177] question de diagnostiquer une très rare hypercholestérolémie familiale

« Tous les jours je dis à des patients que je ne connais pas mon taux de cholestérol et que ça ne m'intéresse pas de le connaître », confie un urgentologue qui pratique dans un établissement unversitaire de cardiologie renommé[178]

CHOLESTEROL SCREENING : SOME PREDICTED NNSs AND NNTs *Dépistage futile et inefficient - Épidémiologie*
dépistage du cholestérol : quelques prévisions du nombre de sujets à dépister et à traiter un an
* L'épidémiologiste Geoffrey Rose a fait quelques calculs du nombre à dépister et à statiniser une année pour éviter un seul décès coronarien cette année là quand la cholestérolémie dépasse 6,5 mmol/l (2.5 g/L):[179]

a) de 55 à 64 ans, il faut dépister 1 150 hommes ou 2 250 femmes, et statiniser 500 hommes ou 1 600 femmes pendant un an
b) entre 45 et 54 ans, il faudrait dépister 3 000 hommes ou 1 100 femmes, et statiniser 1 150 hommes ou 5 500 femmes durant 12 mois
c) de 35 à 44 ans, il faut dépister 12 500 hommes ou 116 000 femmes, et statiniser 4 300 hommes ou 22 800 femmes pendant une année
d) entre 25-34 ans, il faudrait dépister 105 500 hommes ou 685 000 femmes (dont le taux de mortalité coronarienne est de 1 sur 1000 femmes-année), et statiniser 21 000 hommes ou 103 000 femmes pendant 12 mois

* Et pourtant, et pourtant… la cholestérolémie fait partie de pratiquement tous les bilans médicaux périodiques dans les pays développés, et une fois débutés chez un bien portant, ils sont répétés périodiquement 'pour la vie'. Pourtant les preuves sont là, la prévention primaire est futile, inutile, couteuse psychologiquement (effet d'étiquetage), économiquement (gaspillage des ressources, couts directs et indirects), médicalement (effets indésirables). À quand un moratoire sur le dépistage du cholestérol ?

CHOLESTEROL SCREENING IN ADULTS
Remboursement – Dépistage - Lipidologie
« The co-pay for cholesterol screening as primary prevention should be 100%, as would the cost of pharmaceutically altering serum cholesterol as primary prevention… [There should be] no coverage in the absence of quantification of effectiveness »[180] writes Nortin Hadler
Time for a moratorium on cholesterol screening ?
dépistage du cholestérol chez l'adulte
= mesure de la cholestérolémie dans le cadre d'un dépistage chez des bien-portants

* les régimes publics (et privés) n'ont pas de justification pour rembourser les cholestérolémies de dépistage et la statinothérapie en prévention primaire, vu l'absence ou la futilité des bénéfices connus, exprimés en Nombre de sujets à dépister – qu'on ne connaît pas - ou en NNT – quand ils dépassent un seuil raisonnable de $NNT_{expérimental}$ comme celui de 50 années-personnes tel que proposé par Hadler[181]

« Le temps ne serait-il pas venu pour un moratoire sur les cholestérolémies de dépistage ? Du moins pour leur remboursement par les régimes publics de soins? » - « Un seul dosage dans votre vie montrant que votre cholestérol est au-dessous de 7,7 mmol/l (3 g/L) suffit. N'y revenez plus… si vous n'avez pas d'hypercholestérolémie familiale »[182]

« Je suis un médecin sceptique et opposé à la mesure de mon cholestérol tant qu'on ne m'aura pas montré des données

[176] Even, page 10
[177] Apfelbaum 1997 cité par Even, page 15
[178] Georges Lévesque, 2013, de l'Institut de cardiologie de Montréal
[179] Joseph Dumit. Drugs for life, page 152-3
[180] Nortin Hadler. Worried Sick, page 224
[181] Op. cit.
[182] Marian Apfelbaum, 1997. Cité par Even, La vérité sur le cholestérol, page 15

établissant que la consommation de statines me procurera un avantage significatif »[183]

CHOLESTEROL SCREENING IN PEDIATRICS
Dépistage injustifié – Lipidologie – Directives suspectes
cholestérolémies de dépistage en pédatrie
« Les nouvelles lignes directrices américaines de dépistage des dyslipidémies prônent l'analyse de sang systématique et universelle de tous les enfants âgés de 9 à 11 ans et un dépistage ciblé de 30 à 40% des enfants âgés de 2 à 8 ans et de 12 à 16 ans, pour certains profils lipidiques...

Rédigées par un groupe d'experts du National Heart, Lung and Blood Institute, une filiale des National Institutes of Health américains, ces nouvelles recommandations ont également été approuvées par l'American Academy of Pediatrics

'Vous n'avez pas besoin d'un test sanguin pour savoir si un enfant a besoin de perdre du poids!', écrivent des chercheurs de l'Université de Californie San Francisco (UCSF) dans l'édition du 23.7.2012 de la revue *Pediatrics* et notent que le président du comité et tous les membres du Comité d'experts présentent 'Un large assortiment de relations financières avec les laboratoires fabricants d'hypocholestérolémiants' »[184]

« Les statines ne devraient jamais être prescrites aux enfants » car le cholestérol est important dans le cerveau et celui-ici est en plein développement

CHOLESTEROL SCREENING IN THE ELDERLY
Surdiagnostic – Dépistage inutile – Prévention quaternaire

« Many studies have shown that people with high cholesterol live the longest. Supporters of the cholesterol campaign have explained this fact away by claiming that serious diseases, for instance cancer and infections, lower cholesterol. But as I have shown as well, it is just the opposite; low cholesterol predisposes to cancer and it also predisposes to infectious diseases...

With 16 experienced colleagues from various countries, we searched the medical literature after all studies, where the authors had analysed LDL-cholesterol in elderly people representing the general population and followed them for several years. We identified 19 such studies including 30 cohorts with a total of 68 094 individuals age 60 or older. We have now published our result in the medical journal BMJ Open[185]…

What we found was that in 16 of the cohorts including 92% of the total number of individuals, those with high LDL-C lived the longest; in the rest (14 cohorts), no difference as regards longevity was found. Thus, we didn´t find any study having shown that high LDL-cholesterol is a risk factor for elderly people …

It is correct that statin treatment is able to prolong your life with a few days on average, as documented recently in BMJ Open[186] by Danish researchers, but it is most likely due to their other effects, not by cholesterol lowering. If elderly people with high LDL-cholesterol live longer than people with low, how could its lowering be beneficial?[187] »…

Therefore cholesterolemia screening after 60 is definitely useless (in addition to being useless in anyone but those with familial hyperlipidemia or relatives with premature coronary disease, and even then only midlife men may prolong their lives by a few days per treatment-year with statinization).

« Cholesterol reduction has been found to reduce CHD morbidity and CHD mortality in middle-aged men, but it did not improve overall survival during the study periods of the randomized trials (usually less than 10 years). Consequently, data about existing treatments do not provide convincing evidence that cholesterol reduction would increase life expectancy among the *elderly* …

Because no study has documented the survival or morbidity benefits of cholesterol reduction in the asymptomatic *elderly*, a precise estimate of the costs and effectiveness of cholesterol screening is impossible…

Cholesterol is not as powerful a risk factor for CHD in the *elderly* as it is in the middle-aged. Furthermore, epidemiologic studies have found that the cholesterol level is either not associated with total mortality rates or is inversely associated with it. In

[183] Hadler NM. Patient et Citoyen Québec : PUL ; 2014, page 42
[184] Profession Santé / L'Actualité médicale (Montréal) 25.7.2012
[185] http://bmjopen.bmj.com/content/6/6/e010401.full.pdf+html
[186] http://bmjopen.bmj.com/content/5/9/e007118.full.pdf+html
[187] Uffe Ravnskov. June 2016 Newsletter

addition, randomized controlled trials of the health effects of cholesterol reduction have not included *elderly* participants...

It would be difficult to infer from available evidence that *elderly* individuals with an elevated blood cholesterol level would benefit from cholesterol reduction, even if the cholesterol could be lowered without side effects from medication or dietary change »[188]

« The strongest argument against cholesterol-lowering treatment of old people is that more than 20 studies have shown that old people with high cholesterol live the longest »[189]
dépistage du cholestérol chez les gens âgés
« L étude Framingham ainsi que beaucoup d'autres ont démontré que si le cholesterol total (et le LDL-C) *diminue* pendant une longue période, il y a *augmentation* de la mortalité »[190], enlevant la pertinence des cholestérolémies de dépistage ou de contrôle en gériatrie

CHOLESTEROL SURVEYS
enquêtes sur le cholestérol
« Les 4 plus grandes, dont aucune ne démontre de lien entre mortalité cardiaque et cholestérol jusqu'à 7 mM (2,7 g/l) ; au delà, la mortalité augmente faiblement avec le cholestérol mais corrélation n'est pas causalité:[191]

a) l'américaine Framingham
b) la britannique Wolfson, plus étendue, dite 'Des 13 Pays', 1986
c) l'américaine MRFIT, 1986, dont l'ampleur n'a jamais été dépassée
d) la méta-analyse PSC, 2007 »

CHOLESTEROL TARGETS
« Treating to LDL cholesterol targets is no longer recommended », arbitrarily decide AHA/ACC guidelines committees in 2013 faced with compelling evidence that low targets do not improve outcomes, thus contradicting the lipid hypothesis
cibles cholestérolémiques; objectifs de cholestérol(émie); cholestérolémies ciblées

CHOLESTEROL TESTING
Dépistage – Prévention primaire - Lipidologie
« In 2009, there were 4.7 M physician visits related to cholesterol in Canada[192], at $50 per visit and for blood lipids, that's $235 M out of the people's pocket; if three-fourth are for primary prevention, that's $176 250 000 of wasted money and diversion of medical resources"

"I am the skeptical physician who is unwilling to let anyone test my cholesterol until I see unequivocal data that taking a statin yields meaningful benefit for me[193]"

"I tell patients to ignore cholesterol because it's a highly inadequate bio-marker, more suited to sales promotion and physician innumeracy than to rational clinical behavior. I focus instead on their daily choices for food, physical activity, stress management and social networking. And tell them the world is changing, and encourage them to be part of that change[194]"
mesure de la cholestérolémie / du cholestérol

CHOLESTEROL, THE MYTH
* If the myth is only a myth, is it not time to consider a moratorium on cholesterol screening in the healthy, and on repeated testing over their lifetime in patients with overt coronary disease, whether they are statinised or not ?
le mythe du cholestérol
« Un étrange mélange fait d'informations erronées, d'études scientifiques dont la fiabilité est sujette à caution, de cupidité d'entreprises et de marketing trompeur a conspiré afin de créer un des mythes les plus indestructibles mais les plus dommageables de l'histoire de la médecine : le cholestérol provoquerait les maladies CV »[195]

[188] http://www.princeton.edu/~ota/disk1/1989/8911/891108.PDF
[189] http://www.ravnskov.nu/myth9.htm
[190] Anderson KM. JAMA 1987; 257(16): 2176
[191] Even, pages 141-2
[192] Alan Cassels. Vancouver Sun.
[193] Nortin Hadler. Communication, 2008
[194] Warren Bell. Communication
[195] Sinatra & Bowden, 2014, page 23

CHOLESTEROL, THE SAGA
la saga du cholestérol
« La bataille du cholestérol a commencé au milieu du XXe siècle, elle va de 'l'hypothèse lipidique' à la 'guerre des statines', c'est une bataille sans merci entre les prohibitionnistes du cholestérol et les cholestérolo-sceptiques. Ces derniers pourraient bien finir par la gagner »[196]

CHOLESTEROL: THE HYPOTHESIS
Lipidologie – Épidémiologie

« Dutch cardiologist Paul de Groot expessed his doubts about cholesterol as a causal factor and postulated that statins sometimes do more harm than good especially in primary prevention. Dr Uffe Ravnskov, who won the prestigious Leo Prize for independent science, pointed out the many flaws in the cholesterol hypothesis. Interviewed people had experienced devastating side effects from statins, which quickly disappeared upon discontinuation »[197]

« In a large cohort of patients hospitalized with coronary artery disease, almost half have admission LDL-C < 100 mg/dL or <2.6 mM. In 136,905 patients admittted for CHD, mean LDL-C levels were 104.9 mg/dl or 2.7 mM, and LDL cholesterol <70 mg/dL or 1.8 mM were observed in 17.6% »[198]

« Two thirds of people admitted to hospital with a diagnosis of acute myocardial infarction really have metabolic syndrome—but 75% of these patients have completely normal TC concentrations. Maybe this is because TC isn't really the problem »[199]

« One difficult piece of research to explain [by hypercholesterolists], published in the *American Heart Journal* in 2009, showed 75% of patients admitted to hospital with a heart attack had cholesterol levels within the safe range; 50% had optimal levels of cholesterol. Furthermore, your cholesterol falls naturally with age, particularly in older people with chronic health problems...

And it may be *unhealthy to have low levels*. A 20-year study published in the *Lancet* in 2001 showed long-term low cholesterol increases the risk of premature death — 'and the earlier that patients start to have lower cholesterol, the greater the risk' »[200]

"Though LDL cholesterol is hypothesised to have a causal role in the atherosclerotic disease process, it has not been conclusively proven[201]" - "There is no question that blood cholesterol is a risk factor. But it's not much of a risk factor[202]"
« People with xanthelasmata and relatively low lipid concentrations are at an increased risk of myocardial infarction, ischaemic heart disease, and early death, independent of their lipid profiles[203]»

« Contrary to popular belief, more than half of patients who have heart attacks have normal cholesterol levels[204] » - « We already know that half of all heart attacks occur in those with normal cholesterol. Cholesterol deposits in blood vessels are not a direct outcome of high blood cholesterol levels »[205]" - « More than half of the population who suffer heart attacks has normal cholesterol »[206]

"After a myocardial infarction, a Mediterranean-type diet compared to a usual low fat diet, is associated with a 50% relative reduction in total mortality. This is independent of any change in serum cholesterol[207]»

"Heart disease risk does not correlate with fat intake within nations in contrast to between nations. Also development of CHD involves inter alia arterial spasm, cardiac rhythm, metabolism of connective tissue, glucose and homocysteine, plus para-oxonase activity and thrombus formation which generally are unaffected by dietary fat[208]"

"Although Americans take billions of dollars worth of statins per year, their average life expectancy is less than Cubans who take

[196] Dominique Dupagne. Médecine 2013 ; 9(6) : 267 sur http://www.jle.com/fr/revues/medecine/med/e-docs/00/04/88/ED/article.phtml
[197] Doctoring Data, quoting Melchior Meijer on a Dutch discussion forum
[198] Sachdeva et al. AHJ 2009 ; 157(1) : 111-117.e2 at http://www.ahjonline.com/article/S0002-8703(08)00717-5/abstract
[199] Aseem Malhotra. BMJ 2013;347:f6340 - doi: 10.1136/bmj.f6340
[200] Feinman et al. DailyMail.co.uk, 19.4.2015
[201] Micheel CM, Ball JR, eds. Institute of Medicine. National Academies Press, 2010, cité par Ray Moynihan 2011
[202] Nortin Hadler. Worried Sick, p 33
[203] Mette Christoffersen et al. BMJ 2011; 343: d5497
[204] Ray Strand. Opus cité, page 94
[205] Arndt von Hippel, cardiac surgeon
[206] Joseph Dumit. Drugs for life, page 161
[207] David Colquhoun. www.australianprescriber.com 2008; 31(5): 119
[208] LM Klevay. Cellular and Molecular Biology 2004; 50(8):877

none[209]" - « The failure of torcetrapib has not ended the development of new cholesterol medications—the potential market is simply too huge »[210], even if its development came to a halt in 2006 after phase III studies showed more total mortality in the treatment group receiving a combination of atorvastatin (Lipitor™) and torcetrapib

« Despite how slowly the narrative is changing I'm still feeling pretty sure that when the history of statins is written, they will go down in the history books as one of the most unmitigated disasters of our time »[211] - « The strongest argument against cholesterol-lowering treatment of old people is that more than 20 studies have shown that old people with high cholesterol live the longest »[212]

« Shirasaki published a Japanese paper about the relationship between TC levels and total mortality in Fukui City, JA. In the present study, we re-calculated his data for meta-analysis. The relative risk (RR) of total mortality adjusted for age and sex showed a decreasing trend with TC levels (p for trend <0.0001)… His meta-analysis revealed that :

a) RR of death in the low TC (<160 mg/dL or <4.14 mM) group was 1.71, or 71% higher than in the reference group, 160-199 mg/dL (4.14-5.17 mM)]
b) RR in the 200-239 mg/dL (5.18-6.21 mM) group was 0.83, or 17% lower
c) RR in the high TC (≥240 mg/dL or ≥6.22 mM) group was 0.78, or 22% lower …

We suggest that subjects with cholesterol levels ≥240 mg/dL or ≥6.22 mM should not be regarded as hypercholesterolemic or dyslipidemic (except when having familial hypercholesterolemia) because they are in the safest ranges in terms of all-cause mortality »[213]

« In 85-year-old Japanese population, decreased TC was associated with an increased mortality, after adjustment for various confounding factors, suggesting that low TC concentration may be an independent predictor of shorter survival periods among the very elderly… Adjusted mortality decreased 0.9% with each 1 mg/dL (0.026 mM) increase in the serum TC concentration and decreased 0.8% with each 1 mg/dL (0.026 mM) increase in the LDL-C concentration »[214]

cholestérol : l'hypothèse

« Il n'y a aucun lien de causalité démontré entre mortalité coronaire et taux de cholestérol, comme le montrent de nombreuses études épidémiologiques malgré que deux d'entre elles soient toujours citées par les cardiologues, mais complètement falsifiées, comme l'ont montré de multiples analyses...

Rappelons d'ailleurs que la fréquence de l'athérome est en France presqu'aussi basse qu'au Japon, 1,5 fois inférieure à celle de l'Italie et de l'Espagne, 2 à 3 fois inférieure à celle du nord de l'Europe et des ÉU, alors que les taux de cholestérol y sont aussi élevés que dans ces pays. Ajoutons encore que les patients qui souffrent d'infarctus du myocarde n'ont pas un cholestérol plus élevé que ceux qui n'en souffrent pas »[215]

« Il y a deux sources de cholestérol : le cholestérol de l'alimentation – qui ne joue aucun rôle sur le niveau de cholestérol dans le sang – et le cholestérol que nos cellules fabriquent elles-mêmes en fonction de leurs besoins »[216]

* Le pactimibe n'a pas réussi à faire régresser les plaques intracoronaires évaluées par ultrasonie intracoronaire; une tendance contraire a même été décelée. Le promoteur japonais annonçait le 26.10.2005 la fin de la mise au point clinique à l'échelle mondiale...

Il s'agissait pourtant d'une innovation technologique car en inhibant la acyl-Coenzyme A: cholestérol O-acyltransferase qui promeut l'accumulation de cholestérol estérifié dans les macrophages vasculaires, on souhaitait réduire ainsi le volume des athéromes qui mènent aux infarctus[217]

« En 2006, la firme Pfizer a arrêté un essai clinique avec 15.000 participants portant sur le torcetrapib, un anti-cholestérol qui a

[209] Colin Rose, communication
[210] Jonah Lehrer. Site http://www.wired.com/magazine/2011/12/ff_causation/4/
[211] Alan Cassells, 2013
[212] http://www.ravnskov.nu/myth9.htm
[213] Kirihara et al. Journal of Lipid Nutrition 2008; 17(1): 67
[214] Takata Y et al. Clinical Interventions in Aging 2014 ; 9 : 293 – doi: 10.2147/CIA.S53754 - full paper on http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928456/
[215] Philippe Even. http://www.lanutrition.fr/bien-dans-sa-sante/les-maladies/le-cholesterol/polemique-sur-l-arret-des-statines.-le-commentaire-du-pr-even.html
[216] Michel de Lorgeril. http://michel.delorgeril.info/index.php/2009/06/21/44-statines-et-cholesterol-illusions-scientifiques-et-medicales
[217] Nissen. http://www.medscape.com/viewarticle/518572, consulté 18 février 2006

provoqué des crises cardiaques et des accidents vasculaires cérébraux… tout en baissant le 'mauvais' cholestérol et en augmentant le 'bon'. Heureusement, l'essai clinique a été mené – pour une fois – avant que l'agence du médicament l'autorise »[218]

« Warren Sperry qui avait inventé la technique de dosage du cholestérol sanguin dès 1936, disait que ni l'incidence ni la gravité de l'athérome ne sont liés au cholestérol sanguin tandis que le grand chirurgien cardiaque DeBakey conclut lui aussi en 1987 à l'absence de tout lien entre le cholestérol et les maladies CV »[219]

« Chez mes propres patients, certains qui présentaient un taux bas de cholestérol total (parfois 3,9mM) développaient une maladie cardiaque »[220]

CHOLESTEROLEMIA CONVERSION
* For TC or LDL cholesterol: 100 mg/dL (or 1 g/L) = 2.6 mM – Also, 1 mM = 39 mg/dL (or 0.39 g/L)
conversion de la cholestérolémie

CHOLESTEROLEMIAS INTERVALS IN STATINIZED PATIENTS
Cholestérolémies
intervalles des cholestérolémies de suivi chez les patients statinisés
* Le cholestérol augmente d'environ 2% par année durant la vie, sous pravastastine ou non. Il varie à plus court terme, c'est le 'bruit de fond' (7% de coefficient de variabilité dans les dosages annuels), et il varie aussi à long terme (coefficient de variation de 11%); il faut environ 4 ans pour que la variation à long terme dépasse celle à court terme. Ce qui veut dire qu'il faudrait attendre 4 ans pour déceler avec confiance un vrai changement chez des patients observants sous statine...

* si vous ou vos clients / patients – encore peu familiers avec la documentation savante impartiale sur ce sujet - insistez pour un suivi du cholestérol, attendez 4 ans entre chaque contrôle

CHOLESTEROLIST'S BELATED CONVERSION TO THE VIRTUES OF A MEDITERRANEAN DIET
Hypothèse lipidique

« When he ended his career, after 50 years of anti-cholesterol activism, Ancel Keys admitted modestly but officiously, that he had slightly erred and that the most importing thing to prevent heart attacks was not to eat less fat (saturated fats and cholesterol, as he had proclaimed, but to adopt an entire dieteru pattern. After being one of the most ardent defenders of cholesterol toxicity, Keys 'invented' the concept of the Meditterranean diet pattern »[221]
conversion tardive d'un 'cholestéroliste' aux vertus d'un régime Méditerranéen

CITATION BIAS IN CHOLESTEROL LOWERING TRIALS
« Trials considered by their directors as supportive of the contention were cited almost 6 times more often than others, according to Science Citation Index. Unsupportive trials were not cited after 1970, although their number almost equalled the number considered supportive »[222]
biais de citation des essais de réduction du cholestérol
« Les défenseurs de l'hypothèse du cholestérol citent toujours les mêmes études et oublient toujours de citer les études - contraires à leur hypothèse - qui ne trouvent pas de liens entre maladie CV et LDL-cholestérol »

CLINICAL GUIDELINES OUT OF CONTROL
Conflits d'intérêts des panels de directives

« When the last guidelines were issued by the NHLBI in 2001, they nearly tripled the number of Americans for whom cholesterol-lowering drug therapy was recommended — from 13 M to 36 M. These guidelines were reportedly based strictly on results from clinical trials. But this was contradicted by the data described in the document itself…

For example, even though the guidelines recommended that women between the ages of 45 and 75 at increased risk of heart disease and with relatively high LDL levels take statins, the fine print in the 284-page document admitted, 'Clinical trials of LDL lowering generally are lacking for this risk category.' The general lack of evidence for LDL level targets is why they have been

[218] Eelna Pasca. pharmacritique.20minutes-blogs.fr/
[219] Even, page 144, citant de Lorgeril
[220] Sinatra & Bowden, 2014, page 33
[221] de Lorgeril, 2014, Cholesterol and statins : Sham science and bad medicine (Kindle)
[222] Ravnskov U. BMJ 1992; 305(6844): 15

dropped from the current guidelines »[223]

* In 2004 newley issued cholesterol guidelines greatly expanded the number of people for whom treatment is recommended. A firestorm broke out when it was learnt that all but one of the guideline authors had ties to the manufacturers of cholesterol lowering drugs

« In November 2013, the American Heart Association and the American College of Cardiology issued new cholesterol guidelines that essentially declared that millions of healthy Americans should immediately start taking pills — namely statins — for undefined health 'benefits'…

This announcement is not a result of a sudden epidemic of heart disease, nor is it based on new data showing the benefits of lower cholesterol. Instead, it is a consequence of simply expanding the definition of who should take the drugs — a decision that will benefit the pharmaceutical industry more than anyone else...

The new guidelines now recommend statins for people with a lower risk of heart disease (a 7.5 percent risk over the next 10 years, compared with the previous guidelines' 10 to 20 percent risk), and for people with a risk of stroke. They eliminate the earlier criteria that a patient's 'bad cholesterol' or LDL, be at or above a certain level...

Although statins are no longer recommended for the small group of patients who were on the drugs only to lower their bad cholesterol, eliminating the LDL criteria will mean a vast increase in prescriptions over all. According to our calculations, it will increase the number of healthy people for whom statins are recommended by nearly 70 %...

This may sound like good news for patients, and it would be — if statins actually offered meaningful protection from our No. 1 killer, heart disease; if they helped people live longer or better; and if they had minimal adverse side effects. However, none of these are the case. Statins are effective for people with known heart disease. But for people who have < 20% risk of getting heart disease in the next 10 years, statins not only fail to reduce the risk of death, but also fail even to reduce the risk of serious.

We have shown that, based on the same data the new guidelines rely on, 140 people in this risk group would need to be treated with statins in order to prevent a single heart attack or stroke, without any overall reduction in death or serious illness. At the same time, 18 % or more of this group would experience side effects, including muscle pain or weakness, decreased cognitive function, increased risk of diabetes (especially for women), cataracts or sexual dysfunction...

Perhaps more dangerous, statins provide false reassurances that may discourage patients from taking the steps that actually reduce CV disease…

According to the WHO, 80% of CV disease is caused by smoking, lack of exercise, an unhealthy diet, and other lifestyle factors. Statins give the illusion of protection to many people, who would be much better served, for example, by simply walking an extra 10 minutes per day. Aside from these concerns, we have more reasons to be wary about the data behind this expansion of drug therapy…

In fact, committee members noted that cholesterol lowered by drugs may not have the same effect as cholesterol lowered by nondrug methods, such as diet, exercise and being lucky enough to have good genes. The process by which these latest guidelines were developed gives rise to further skepticism...

The group that wrote the recommendations was not sufficiently free of COIs; several of the experts on the panel have recent or current financial ties to drug makers. In addition, both the AHA and the ACC, while nonprofit entities, are heavily supported by drug companies...

The new 2013 guidelines are not adequately supported by objective data, statins should not be recommended for this vastly expanded class of healthy Americans. Instead of converting millions of people into statin customers, we should be focusing on healthy diets, exercise and avoiding smoking. Patients should be skeptical about the guidelines, and have a meaningful dialogue with their doctors about statins, including what the evidence does and does not show, before deciding what is best for them »[224]

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[223] John D. Abramson & Rita F. Redberg. at http://www.nytimes.com/2013/11/14/opinion/dont-give-more-patients-statins.html?emc=edit_tnt_20131113&tntemail0=y&_r=0

[224] John D. Abramson & Rita F. Redberg. at http://www.nytimes.com/2013/11/14/opinion/dont-give-more-patients-statins.html?emc=edit_tnt_20131113&tntemail0=y&_r=0

« Increasingly that GPs are being asked to prescribe statins despite feeling it is inappropriate »[225]
directives cliniques à la dérive
« C'est la première fois en novembre 2013 que l'American Heart Association admet la supériorité de la diète méditerranéenne ; et nous sommes presque en 2014 ; nous avons publié notre premier rapport sur la Lyon Diet Heart Study (analyse intermédiaire) en 1994. Comptons ensemble : il aura donc fallu 20 ans pour leur ouvrir les yeux … en l'absence de conflit d'intérêt ou autre effet de compétition. Il leur faudra sans doute le double pour admettre que le cholestérol est innocent »[226]

CLINICAL HERMENEUTICS
Pratique

= listening to, believing, recording and interpreting commentaries of patients, especially those under pharmacotherapy
« The patient may seem peculiar, but he may be telling you something that is revolutionary. We ignore such things that do not fit into the standard view at our peril »[227]

* In pharmacovigilance, it means listening to, believing, recording and interpreting complaints of adverse reactions of patients on pharmacotherapy, such as a *statinized* woman complaining of muscle pain or weakness, especially when proximal (arm, thigh) and bilateral
herméneutique clinique
= écouter, croire, noter et interpréter les commentaires des patients, notamment ceux en pharmacothérapie; par exemple quand une femme statinisée se plaint de malaises ou de faiblesses musculaires…

CLINICAL INSIGNIFICANCE
clinical futility

« The argument for the use of statin in secondary prevention comes from industry funded clinical trials with a statistically significant difference in favor of the experimental statin groups. If we look at the details of the CARE and LIPID studies for instance (secondary prevention) the reduction in fatal and nonfatal heart attacks in the people treated with Pravachol™ (pravastatin) was 0.6 % each year which means that 166 people need to be treated for a full year to delay 1 heart attack[228]…

Aren't we rolling from a statistical significance to a *clinical insignificance* situation here ? »[229]
insignificance / futilité clinique

CLINICAL TRIAL SERVICE UNIT;[230] **CTSU (UK)** *Centre de recherche sponsorisé – PPP universitaire camouflé*
* *Service* is a well chosen term, at the service of the industry…

« They hold all the trial data on statins including ADRs and will not allow anyone else to see it. They have signed confidentialy agreements with the companies, these data are kept secret and have never been seen by any other independent researchers » bemoans Malcolm Kendrick[231]
Unité de prestation de recherche clinique (Traduction libre du nom de l'organisation)
« Le Clinical Trial Services Unit (CTSU) d'Oxford est le groupe de statisticiens de loin le plus favorable aux statines et pour cause, car, malgré ses apparences officielles et publiques, le CTSU est une officine privée, certes liée par contrat à la Radcliffe Infirmery d'Oxford, qui lui confère son apparence publique, mais il est pour la plus grande part, et de loin, financé statutairement par MSD et au cas par cas, par les firmes GSK, Astra-Zeneca et BMS, fabricants des statines…

Le CTSU a été fondé par Sir Richard Doll, lourdement condamné peu avant sa mort pour malversations et falsifications graves »[232] - « Une officine déguisée, une société-écran, au service de l'industrie, sous couleur de l'être à l'Université d'Oxford (RU), et qui a promu l'idée qu'il fallait traiter, quel que soit le taux de cholestérol, multipliant les ventes par quatre »[233]

[225] Sir Richard Thompson et al. 2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf
[226] http://michel.delorgeril.info/non-classe/nouvelles-recommandations-aux-usa-attention-danger/comment-page-1#comment-14313
[227] Iona Heath. CMAJ 2011, 183(7): 776
[228] John Abramson. Overdosed America. Harper 2005 p. 143
[229] Jacques Thivierge, 2013, communication
[230] http://www.ctsu.ox.ac.uk/
[231] drmalcolmkendrick.org 2014.12.1
[232] Philippe Even. http://www.lanutrition.fr/bien-dans-sa-sante/les-maladies/le-cholesterol/polemique-sur-l-arret-des-statines.-le-commentaire-du-pr-even.html
[233] Even 2013, page 36

COGNITIVE DECLINE AND STATINS

« Investigators from Queens University, Belfast, has used standard Cochrane methodology to evaluate the efficacy and safety of statins for the prevention of dementia in people at risk for dementia owing to their age. This third Cochrane review[234] of the topic included two new trials with 26,340 participants aged 40 to 82 years of whom 11,610 were aged 70 or older...

The researchers found that there is good evidence that statins do not prevent cognitive decline or dementia when given to people in late life who are at risk for vascular diseaseFrom a clinical perspective, many *physicians themselves*—because of the widespread belief that logically, they should be effective—used to take statins in part to possibly delay cognitive decline. We can now (2016) unequivocally advise our patients, and *our colleagues*, that statins are not effective in preventing dementia… »[235]

déclin cognitif et statines

* un autre mythe qui tombe

COLESTIPOL STUDY *Prévention surtout primaire – Séquestrant des acides biliaires c. placebo -*

l'Étude du colestipol

* Année de publication : Dorr/JCD/1978[236]
* Effectif : 2278
* Démographie: 1094 hommes et 1184 femmes ou 52% ; age moyen des femmes, 57 ans
* Santé des participantes : 20% de coronariennes

* Critère principal : mortalité totale ou coronarienne
* Suivi : 3 ans
* Comparaison : colestipol (séquestrant des acides biliaires, comme la cholestyramine) contre placebo

* Résultats chez les femmes:

a) réduction relative de -8 % pour la mortalité totale, NS

b) augmentation du risque relatif de +8 % pour la mortalité coronarienne, NS

* Conclusion : essai négatif cliniquement chez les femmes malgré une chute de la lipidémie, contredisant l'hypothèse lipidique

COLLINS vs BMJ (UK)

Intimidation de chercheurs – Intimidation de revue savante

« Rory Collins, head of the Cholesterol Treatment Trialists' Collaboration (Oxford), had demanded that the BMJ retract two articles that were highly critical of statins. Although the journal issued a correction for both papers for inaccurately citing an earlier publication and therefore overstating the incidence of adverse effects of statins, this response did not satisfy Collins...

He repeatedly requested that the journal issue a retraction, prompting the BMJ's editor-in-chief to convene an outside panel of experts. The panel's report exonerates the journal from wrongdoing and said the controversial articles should not be retracted. In fact, the panel was *critical of Collins* for refusing to submit a published response »[237]

« In 2016 there has been no progress that I am aware of on the availability of the trial data on statins for independent scrutiny doi:10.1136/bmj.h3908 »[238]

Collins c. BMJ

* Rory Collins est un meneur d'opinion influent responsable de recherches généreusement financées par les firmes. Sa tentative d'intimidation de chercheurs (John Abramson et Aseem Malhotra) ayant publié chacun un article peu flatteur pour les statines, et de la revue savante (BMJ) qui avait publié ces articles, a échoué

COMBINING HARD ENDPOINTS WITH REVASCULARISATION, A SOFTER OUTCOME

Critères d'évaluation combinés – Critères cardiovasculaires cliniques

« Some studies, including CTT publications, have increased statistical power by including 'softer' outcomes such as coronary revascularisation procedures. However, rates of revascularisation are less precise because of geographical variations in thresholds for intervention and because treatment allocation is largely unblinded, made apparent by the lower total and LDL

[234] Cochrane Database Syst Rev 2016; 1: CD003160 - doi: 10.1002/14651858.CD003160.pub3 - http://www.ncbi.nlm.nih.gov/pubmed/26727124
[235] Peter Yellowlees, 2016
[236] Dorr et al. J Chronic Dis 1978; 31: 5
[237] Larry Husten, Physician's First Watch, 4.8.2014
[238] Fiona Godlee. BMJ 2016; 352: i1261- doi: http://dx.doi.org/10.1136/bmj.i1261

cholesterol levels in people assigned to the statin arms of the clinical trials...

Bias resulting from unblinding has been documented[239] for all outcomes except total mortality, particularly subjectively determined outcomes »[240] - « Researchers often use composite outcomes in an attempt to boost statistical power but the components might be subject to clinically subjective decisions, eg, the composite of death, myocardial infarction, or repeat revascularisation »[241]

* Combining a softer, more subjective outcome (like revascularisation) with hard endpoints such as total mortality or myocardial infarction, into composite endpoints, in order to more easily reach statistical significance, is downrightly misleading and has almost become a trademark of statinator trialists
combinaison de critères solides avec la revascularisation, un critère plus flou / mou

COMPELLING
Imputabilité – Mémoire - Statinovigilance
« FDA has received MedWatch reports of memory loss and *compelling* anecdotal reports with statin use »
convaincant ; probant ; incontestable ; persuasif
* Si la justification médicale de la statinisation est très discutable et proche de zéro, ses risques sont, eux, incontestables

COMPLAINT BY MANUFACTURER AGAINST HEALTH INSURER (FR) *Harcèlement juridique*
« According to the French news service Agence France-Presse in 2010, a French appeals court has dismissed a complaint by European pharmaceutical firm AstraZeneca against French health insurers, who advised doctors to be sparing when prescribing one of the company's top drugs, rosuvastatin. The pharmaceutical giant had brought a complaint against a local arm of the the primary health insurance fund of France because of comments the insurer had made about AstraZeneca's star cholesterol drug, Crestor, in a guideline for doctors published in 2006. The insurer had said that a 5-milligram dose of rosuvastatin "does not provide any significant added benefit" compared to other medicines and recommended that doctors only prescribe it in serious cases.[242] »
plainte d'un fabricant contre une caisse d'assurance maladie (FR)
* Il s'agit de la Caisse primaire d'assurance maladie de l'Aude. Le fabricant a tenté devant les tribunaux de censurer une directive clinique décourageant l'usage de la dose de 5 mg

COMPOSITE ENDPOINTS RAISE PROBLEMS OF CONFIDENCE
« Confident interpretation of composite end point results requires relatively small gradients of importance to patients and similar relative risk reductions across components. Our findings suggest that most composite end points used in CV randomised controlled trials have substantial gradients in both *importance to patients* and *treatment effects* across component end points...

Furthermore, less important outcomes provide larger contributions to the composite end point event rate and show larger treatment effects. In particular, mortality outcomes, present in almost all CV composite end points, provide the lowest event rate and show the smallest treatment effects...

Thus, an important and plausible risk of misleading conclusions associated with the use of composite endpoints is to attribute reductions in total mortality to interventions that do not, in fact, reduce death rates… Components of greater importance to patients were associated with smaller treatment effects than less important ones (relative risk reduction of 8% for death but of 33% for components of minor importance to patients) »[243]
les critères combinés soulèvent des problèmes de confiance
* la majorité des critères combinés utilisés en recherche CVmanquent de validité à cause de l'hétérogénéité :
a) de la gravité des composants aux yeux des patients (e.g. hospitalisation pour ischémie coronaire contre décès de toute cause, angioplastie contre infarctus fatal)

b) de leur fréquence relative des composants (de 3.3-3.7% pour les critères fatals/critiques/majeurs à 12.3% pour les critères modérés et 8% pour les critères mineurs) ; et, enfin
b) des réductions relatives de ces risques par statines : par exemple -8% pour la mort mais -33% pour des composants d'importance clinique moindre

[239] Wood et al. BMJ 2008 ; 336 : 601
[240] Abramson et al. BMJ 2013; 347: f6123 - doi: 10.1136/bmj.f6123 – 22.10.2013 - available at http://www.abc.net.au/catalyst/heartofthematter/download/StatinsshouldNOTbebroadedtowiderpopulation.pdf
[241] Ioannidis JPA et al. Lancet 2014 ; 383(9912): 166 - doi:10.1016/S0140-6736(13)62227-8
[242] Worst Pills Best Pills Newsletter (USA) article, September, 2010
[243] Ferreira-Gonzales et al. BMJ 2007 ; 334 : 786 - http://www.bmj.com/content/334/7597/786

COMPOSITE ENDPOINTS WITH SOFTER OUTCOMES
Critères d'évaluation combinés

« Some studies, including CTT publications, have increased statistical power by including 'softer' outcomes such as coronary revascularisation procedures. However, rates of revascularisation are less precise because of geographical variations in thresholds for intervention and because treatment allocation is largely unblinded, made apparent by the lower total and LDL cholesterol levels in people assigned to the statin arms of the clinical trials...

Bias resulting from unblinding has been documented[244] for all outcomes except total mortality, particularly subjectively determined outcomes »[245]

* Combining softer, more subjective endpoints with hard endpoints such as total mortality or death from myocardial infarction into composite endpoints, in order to more easily reach statistical significance, is downright misleading and has almost become a trademark of statinator trialists

« The 'statin success' story is largely from non-fatal endpoint studies that may well derive much of such benefit from reduced angina and thus hospital visits and resulting interventions »[246] and even though they are statistically significant in some trials, they are not clinically significant
critères combinés contenant des variables plus floues / molles

CONFIRM, THE REGISTRY
Calcifications coronaires – Statinovigilance - Pharmacoépidémiologie
« Statin use is associated with an increased prevalence and extent of coronary plaques possessing calcium »[247]

« From 6673 consecutive individuals - 2413 on statin therapy and 4260 not on statin therapy - with no known coronary heart disease and available statin use status, we studied the relationship between statin use and the presence and extent of specific plaque composition types. Statin use is associated with an increased prevalence and extent of coronary plaques possessing calcium »[248]
le registre dit Confirm
* Ce genre de publication est ignoré des statinistes quand il écrivent des synthèses, des articles, des commentaires

CONTROLLED TRIALS AND STATIN ADVERSE EFFECTS *Validité externe – Déni des EIM – Sélection biaisée des participants – Dénigrement de la statinovigilance*

« In a BMJ blog Richard Lehman says that adverse effects are much more common than the trials suggest (blogs.bmj.com/ bmj). "*Muscle pain* and *fatigability* are not a figment of misattribution and public misinformation," he says. "They are too prevalent and recurrent in people who desperately want to stay on statins...

Rather than *discount* a widely observed phenomenon, we should ask why there is such a mismatch with reporting in the trials." Could this mismatch be due to exclusion of people who experienced side effects during "run-in periods" before randomisation? »[249] writes BMJ Editor in chief in 2016
essais contrôlés et effets indésirables statiniques
* la rédactrice en chef a bien raison d'appuyer l'interprétation de Lehman, à savoir que des éléments d'information tirés d'observations cliniques de pharmacovigilance peuvent être aussi probants que ceux obtenus par des essais cliniques dont la validité externe est volontairement compromise par une sélection préliminaire excluant les patients atteints d'effets indésirables

CONTROVERSIAL 2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines – (Rapport)

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[244] Wood et al. BMJ 2008 ; 336 : 601
[245] Abramson et al. BMJ 2013; 347: f6123 - doi: 10.1136/bmj.f6123 – 22.10.2013 - available at http://www.abc.net.au/catalyst/heartofthematter/download/StatinsshouldNOTbebroadedtowiderpopulation.pdf
[246] Vos E. Nutr Metab Cardiovas Dis 2997 ; 17 : e19
[247] Nakazato et al. Atherosclerosis 2012 ; 225 : 148 - http://dx.doi.org/10.1016/j.atherosclerosis.2012.08.002
[248] Nakasato et al. Atherosclerosis 2012 ; 225 : 148 - http://dx.doi.org/10.1016/j.atherosclerosis.2012.08.002
[249] Fiona Godlee. BMJ 2016;354:i4992 - doi: 10.1136/bmj.i4992

STONE NJ et al. *Circulation* 2013 - Print ISSN: 0009-7322 - Online ISSN: 1524-4539

1) Those controversial guidelines recommend initiating moderate- or high-intensity statin monotherapy as the first-line strategy for ASCVD risk reduction among patients with estimated 10-year ASCVD risk of 7.5% or greater, which amounts to an annual risk of 0.75% or 1 event per 133 patient-years. Why controversial ?...

Well, if statinisation reduces relative risk by 25%, the annual absolute risk reduction to be expected will be a mere 0.1875%, benefiting only 1 patient per 533 patients-years of statinisation (annualized NNT = 533), which is like delaying a major cardiac event by 0.68 day (16 hours) in each patient treated for 1 year, which is frankly futile considering costs, burden and ADRs...

If statinisation was to reduce relative risk by 33%, the annual absolute risk reduction would be 0.2475%, leading to a NNT of 404 patient-years, which amonts to delaying an event by only 0.9 day (22 hours), just as futile, and representing a substantial burden on health resources

2) Those controversial guidelines recommend initiating moderate- or high-intensity statin monotherapy as the first-line strategy for ASCVD risk reduction among patients with preexisting diabetes mellitus (DM), irrespective of overt ASCVD or cholesterol level. Why controversial ? Because :

a) new onset diabetes is itself an adverse reaction to statins, as shown in several clinical trials
b) if cholesterol level is not important, then the cholesterol hypothesis does not hold
c) several trials have shown that statinisation of diabetics does not prevent the micro- and macro-CV complications

* Those controversial guidelines recommend initiating moderate- or high-intensity statin monotherapy as the first-line strategy for ASCVD risk reduction among patients with LDL cholesterol levels of 4.91 mM or greater (≥190 mg/dL). Why controversial ? Because :

a) low cholesterol is almost as much at risk marker of early death as high cholesterol, discrediting the cholesterol hypothesis
b) the trials showing risk reductions that are statistically significant do not show a large enough correlation between cholesterol reduction and clinical benefit

c) no statin trials have demonstrated a clinically significant reduction in total mortality by statinizing people with hypercholesterolemias except maybe in severe familial hyperlipidemias
d) it has never been statistically demontrated that cholesterol screening save lives among healthy populations, or reduce non-fatal CV events in a clinically significant fashion

e) it has never been demonstrated that intense statinization and frequent testing saves lives in a clinically significant fashion in secondary prevention by reducing cholesterolemia, especially in women (with or without coronary disease), and in elderly men (with or without coronary disease)

DEMENTIA AND STATINS

« It has been established from RCTs and a Cochrane review that statins do not prevent dementia. The claims that they do are unfounded. The link between statins and memory loss are based on case reports, some of which were validated by rechallenge »[250]

démence et statines

CONTROVERSIAL COCHRANE 2013 REVIEW: STATINS FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE – (Méta-analyse en 2013) – *Conflation – Controverse - Collusion*

« Of 1 000 people treated with a statin for 5 years, 18 would avoid a major CVD event which compares well with other treatments used for preventing CV disease »,[251] is stated in the summary of the 2013 Cochrane meta-analysis by Taylor et al. even if it amounts to a mere 18 fewer events per 5 000 person-years of statinisation and…

a NNT of 278 person-years, a yearly absolute risk reduction of 0.36%, a yearly rate of inefficacy of 99.64%, 277 person-years of useless treatment still exposed to the direct and indirect costs plus the risk of adverse reactions, and a mere 32 hours virtual delay of the occurrence of a CV event per year of treatment. Furthermore NNTs obtained in experimental conditions would sensibly be larger under usual care conditions...

[250] Jim Wright 2014
[251] Taylor F et al. (2013) Statins for the primary prevention of CV disease. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD004816 - DOI: 10.1002/14651858.CD004816.pub5 - http://summaries.cochrane.org/CD004816/statins-for-the-primary-prevention-of-CV-disease

Taylor et al. should instead have concluded that this is a *negligible, futile, clinically insignificant* benefit. Their conclusion is unexplainably exagerated: « Statins are likely to be cost-effective in primary prevention »,[252] is stated without considering the direct and indirect burden on medical resources and health expenditures besides pill costs, the underestimated frequency of myopathy symptoms and other ADRs and the conversion of well-being persons into patients

* 43% of major vascular events are coronary revascularizations, an ischemia driven outcome that is highly subject to subjective assessments and decisions, and to loss of blinding ; thus the benefit observed could partially or completely be a measure of bias. Loss of blinding is likely to occur in statin trials because the drugs are so good at lowering cholesterol that cardiologists know who is receiving the drug before deciding on revascularization

« A Cochrane review of Statins that focusing exclusively on their lipid lowering effects, neglecting their effects on muscle, endocrine and cognitive function, concluded that the evidence supports their use (Cochrane Library 2013, Issue 1). Only time will tell which of the current blockbuster drugs will in the longer run take the title for the drug group that has caused the most damage but the statins are worth betting on »[253]
Synthèse Cochrane 2013 controversée: Statines en prévention primaire de la maladie cardiovasculaire (Traduction libre du titre de la méta-analyse)

COCHRANE 2013 AND DR BRIFFA[254]
« In 2011, Cochrane researchers assessed the evidence relating to statin use in individuals at low risk of CV disease (defined as <2% per year) and concluded that there was limited evidence of overall benefit.[255] …

Then in 2013,[256] the same Cochrane group updated (sic) their data and concluded that overall risk of death and CV events (e.g. heart attack or stroke) were reduced by statins in low risk individuals, without increasing the risk of adverse events including muscle, liver and kidney damage (sic)…

Three New Zealand doctors reacted as follows:

« More recent American guidelines now recognise the absence of evidence to support any particular arbitrary LDL target in primary prevention… There is no evidence that ezetimibe improves meaningful clinical outcomes either with or without statins in any population… For a patient who develops muscle pain whilst taking a statin, whether their CK is raised beyond an arbitrary threshold is unimportant, the question is whether or not the pain is linked to their medication …

There is ample evidence from cohort, adverse events report data, and case reports, to suggest myalgia without enzyme alteration is a problem, and is not rare… Given that the overwhelming majority of those who take statins for primary prevention will not derive any benefit from them, it is crucial that decisions to initiate lifetime therapy are informed by a clear presentation and discussion of the best available evidence »[257]

A paper published in the BMJ in October 2013 by Abramson et al.[258] questions the evidence on which this U-turn appeared to have been made

COCHRANE 2013 and ABRAMSON
« Although the results of 4 additional clinical trials were included in the 2013 review, these did not substantially alter the previously documented effect of statin therapy. Instead, the change in advice was based on a meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration published in 2012[259]…

The 2012 CTT authors calculated that in low risk patients, statins prevented 11 major vascular events per 1000 people treated for 5 years for each 1.0 mM reduction in LDL cholesterol [absolute risk reduction = 0.22% per year ; NNT = 455 person-years]. Our calculations show that statins do not have a significant effect on total mortality in this group of patients (RR = 0.95, NS)

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[252] Op. cit.
[253] David Healy, 14.5.2015 - http://davidhealy.org/marilyns-curse/
[254] http://www.drbriffa.com/2014/02/07/is-the-editor-of-the-bmj-suffering-from-statin-induced-amnesia/
[255] Taylor F, et al. Statins for the primary prevention of CV disease. Cochrane Database Syst Rev 2011;1:CD004816.
[256] Taylor F, et al. Statins for the primary prevention of CV disease. Cochrane Database Syst Rev 2013;1:CD004816.
[257] Hudson B et al. BMJ Rapid response 30.1.2014
[258] Abramson JD et al. BMJ 2013; 347: f6123 - doi: 10.1136/bmj.f6123
[259] CTT (Cholesterol Treatment Trialists' Collaboration) - www.ctsu.ox.ac.uk/research/meta-trials/ctt/ctt-website

Our calculations using data presented in the 2012 CTT patient level meta-analysis show that statin therapy prevents 1 serious CV event per 140 low risk (< 2% per year) people treated for 5 years [NNT = 700 person-years] for each 1 mM reduction in LDL cholesterol. Statin therapy in low risk people does not reduce total mortality or serious illness and has about an 18% risk of causing side effects that range from minor and reversible to serious and irreversible »[260]
Cochrane 2013 et Abramson

COCHRANE 2013 and FIONA GODLEE of THE BMJ
« Currently only the drug companies, the trialists, and the Cholesterol Treatment Trialists (CTT) collaboration in Oxford have access to individual patient data from the *statin* trials. As I understand it, even CTT does not have the data on adverse events, which were specifically excluded when the collaboration was established. Nor does CTT have the right to share data with third parties...

The Cochrane review group did not have access to the individual patient data. It based its analysis on the published information, including the published CTT analysis »[261]

CORONA, THE TRIAL *Rosuvastasine 10 mg c. placebo – Chez aînés avec insuffisance cardiaque d'origine coronarienne – Prévention secondaire – Cliniquement négatif – Réfutation de l'hypothèse lipidique*
Controlled Rosuvastatin Multinational Trial in Heart Failure

* Princeps publication : Kjekshus/*NEJM*/2007[262]
http://www.nejm.org/doi/full/10.1056/NEJMoa0706201#t=article
* Funding : private, AstraZeneca. Every co-author has financial links with the sponsor

« A total of 5011 patients at least 60 years of age with NYHA class II, III, or IV ischemic, systolic heart failure were randomly assigned to receive 10 mg of rosuvastatin (Crestor™) or placebo per day. The primary composite outcome was :[death from CV causes, nonfatal myocardial infarction, or nonfatal stroke]. As compared with the placebo group, patients in the rosuvastatin group had decreased levels of LDL cholesterol (-45%) and of high-sensitivity CRP (-37%)…

During a median follow-up of 32.8 months, the primary outcome occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (HR = 0.92, NS ; relative risk reduction = -8%) ; 728 rosuvastatin patients and 759 placebo patients died (HR = 0.95, relative risk reduction = -5%, NS). There were no differences between the two groups in the coronary outcome or death from CV causes »[263]

« Rosuvastastin failed despite a striking reduction of cholesterol levels as well as of the inflammatory marker CRP … 100% of the recruited patients were survivors of a previous myocardial infarctions … A total lack of effect of the statin regarding the ischemic events expected to be prevented…

The overall clinical data regarding rosuvastatin consists in 3 totally negative RCTs in high-risk patients mainly in secondary prevention – CORONA, GIFFI-HF, AURORA - and one highly questionable trial in primary prevention – JUPITER »[264]
« The results showed a lack of significant improvements in CV outcomes despite a lowering of LDL-C of -45% with rosuvastatin »[265]

METHODOLOGY
* Participants demography : 14% women ; average age 73 years
* Participants' health : 29.5% had diabetes ; 100% were post-MI survivors
* Followup median : 2.7 years (32.8 months)

* Composite primary endpoint : [CV death (fatal MI and fatal stroke) + nonfatal MI + nonfatal stroke]. Biased by the heterogeneity of outcomes :
a) mixing fatal with non fatal events ;
b) uneven frequencies of the four outcomes, for example recurrent AMIs explained most deaths ;
c) possible subjectivity in the adjucation of non fatal events

[260] Abramson JD et al. BMJ 2013; 347: f6123 - doi: 10.1136/bmj.f6123
[261] Godlee F. BMJ 2014; 349: g5038 - doi: 10.1136/bmj.g5038
[262] Kjekshus J et al. CORONA Group. Rosuvastatin in Older Patients with Systolic Heart Failure. NEJM 2007 ; 357 : 2248-61
[263] Kjekshus et al. NEJM 2007 ; 357 : 2248 for the CORONA Group – Summary at http://www.nejm.org/doi/full/10.1056/NEJMoa0706201
[264] de Lorgeril et al. BMC Medicine 2013 ; 11 : 5 available at http://www.biomedcentral.com/1741-7015/11/5
[265] Kaul et al. op. cit.

* Positive compliance (active group adherence) : 97.3%
* Negative compliance (control group adherence) : 95.2%

RESULTS
Surrogate endpoint :
* A -45% relative risk reduction in LDL-cholesterol

Clinical outcomes :
* Health related quality of life *not reported*

* A -5% relative risk reduction in TOTAL MORTALITY (NS)
* An -8 % relative risk reduction in the primary composite endpoint (NS) ; even if the RRT had been high enough and the absolute risk reduction had been clinically important, its heterogeneity precludes its use as evidence to support the use of rosuvastatin in its labeled indications

* A -17% relative risk reduction in AMI (NS)
* relative risk reduction of CV death is NS

* recurrent AMI explained most deaths, neither were reduced; age at baseline was not a predictor of efficacy, nor the degree of cardiac dysfunction[266]
« Failed to show a reduction in major vascular events with the use of rosuvastatin in older patients with systolic heart failure »[267]

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
L'essai dit Corona
* Une comparaison rosuvastatine (Crestor™) contre placebo chez 5 011 insuffisants cardiaques (d'origine coronarienne) âgés de > 60 ans a été incapable de démontrer une réduction du critère principal d'efficacité combiné de : 'IDM non fatal ou AVC non fatal ou mortalité CV (par IDM ou AVC)'[268]

* Cet essai contrôlé, le premier à évaluer cette statine dans l'insuffisance cardiaque chronique, n'a pas démontré de bénéfice sur la mortalité totale, pas plus que Gissi-HF, Aurora, Jupiter ou Prosper

* CORONA est l'un des 4 essais contrôlés de la rosuvastatine contre placebo, exécutés depuis la nouvelle réglementation des essais cliniques (2005-2007). Les 3 en prévention secondaire furent négatifs (CORONA, GIFFI-HF et AURORA) et celui en prévention primaire (JUPITER) fut suffisamment défectueux pour que son interprétation soit mise en doute[269]

* Un autre essai de la rosuvastatine dans l'insuffisance cardiaque fut négatif (GISSI-HF) et de plus, un cholestérol bas est associé à une plus grande morbi-mortalité par insuffisance cardiaque sévère dans une étude d'observation[270]
« La rosuvastatine, pas plus que les autres statines, n'a d'intérêt prouvé en termes de morbimortalité des patients insuffisants cardiaques »[271]

* Conclusion : l'essai dit CORONA fut négatif cliniquement, contredisant l'hypothèse lipidique et l'hypothèse statinique

***CORONARY DRUG PROJECT, THE TRIAL ;* CDP**
Clofibrate, thyroxine, niacine, estrogènes c. placebo – Prévention secondaire – Échec de tous les traitements – Réfutation de l'hypothèse lipidique
CANNER et al. *JACC* 1986 ; 8(6) : 1245
https://www.ncbi.nlm.nih.gov/pubmed/3782631

[266] Michel de Lorgeril, 2014, Cholesterol and statins : Sham science and bad medicine (Kindle)
[267] Florkowski et al. N Engl J Med 2008; 358:1301 - DOI: 10.1056/NEJMc073536
[268] Kjekshus et al. NEJM 2007 ; 357 : 2248 for the CORONA Group
[269] de Lorgeril, Cholesterol and statins : Sham science and bad medicine (Kindle)
[270] Horwich et al. Journal of Cardiac Failure 2002 ; 8(4) : 216 - doi: 10.1054/jcaf.2002.126519 - http://www.ncbi.nlm.nih.gov/pubmed/12397569
[271] Rev Prescrire 2008 ; 28(300) : 770

Comment
« 8,341 men randomized to dextrothyroxine (stopped at 3 years for excess mortality), clofibrate (5 years), niacin (5 years), estrogen 2,5 mg (stopped at 56 months for excess thromboembolism and cancer), estrogen 5 mg (stopped at 18 months for excess non-fatal MI) or placebo. No CVD event reduction in any treatment arm despite reductions in total cholesterol[272] »

« After 30 years of basic and clinical research and a great deal of work, it became apparent in about 1978 that *clofibrate* was not an appropriate drug to use to reduce raised plasma cholesterol and LDL, and morbidity and mortality from CHD. The positive effects were small and the adverse effects unacceptably large. Yet, it was the only lipid-lowering drug available in the early 1960s »[273]

« The CDP reported Serious Adverse Events, and the percentage of patients ever hospitalized at 5 years was 55.1% for clofibrate and 52.4% for placebo »[274], a 5 % relative increase and a +2.7% absolute increase, translated into a 0.54% annual increase, NNH = 185 patient-years
* Health related quality of life *not reported*

* Healthier good adherers, an unintended finding: « The 5-year mortality in 1103 men treated with clofibrate was 20.0 %, as compared with 20.9 % in 2789 men given placebo (NS). *Good adherers* to clofibrate, i.e., patients who took 80 % or more of the protocol prescription during the 5-year follow-up period, had a substantially lower 5-year mortality than did *poor adherers* to clofibrate (15.0 vs. 24.6 %, a 9.4% absolute difference)...

However, similar findings were noted in the placebo group (15.1 % mortality for good adherers and 28.3 % for poor adherers, a 13.2% absolute difference. These findings show the serious difficulty, if not impossibility, of evaluating treatment efficacy in subgroups determined by patient responses (e.g., adherence or cholesterol change) to the treatment protocol after randomization[275] »
l'essai dit CDP
* Un des premiers grands essais de contrôle pharmacologique des lipides en prévention secondaire[276]
* Le risque de mortalité toute cause était de 4,18 par 100 patients-année dans le groupe placebo (risque très élevé) et de 4,0 par 100 patients-année sous clofibrate, une réduction absolue de 0,18 par 100 patients-année, pour un NNT annualisé de 555 et un taux annuel d'inefficacité de 99,82%

* Il y eut plus d'évènements indésirables graves sous clofibrate que sous placebo au bout de 5 ans, dont une augmentation absolue de 2,7% des hospitalisations
* Démonstration frappante de la meilleure santé des plus observants : la mortalité est plus basse chez les plus adhérents tant dans le groupe placébo que dans le groupe clofibrate

CORONARY HEART DISEASE; CHD
cardiopathie ischémique; maladie coronarienne

CORONARY MORTALITY ACROSS COUNTRIES IN EUROPE
Épidémiologie – Hypothèse lipidique contredite

* Age-standardized CHD disease mortality rates in men aged < 65 years in diffferent European countries and regions according to WHO data demonstrate that lifestyle, markedly influenced by social-economical-educational-environmental-status (SEEES), is several times (7x) a more powerful determinant of male CHD mortality than conventional medicalized risk factors or even from treatments. The rates per 100 000 person-years varied in 2005 as follows:[277]

Russia 250/100 000, Lithuania 145, Eastern Europe 80, Poland 55, Scandinavia and Southern Europe 35/100 000. The ratio between Russia and Mediterrannean countries is 7-fold or 700%. Cholesterolemia is not 700% higher in Russia than in Southern Europe !
mortalité coronarienne selon les pays en Europe
* La vraie prévention, à la lumière de ces données épidémiologiques, ne peut pas reposer sur la médicalisation des facteurs de

[272] Robert DuBroff, 2016, op. cit.
[273] Michael Oliver. Br J Clin Pharmacol 2012; 74(6): 907 - doi: 10.1111/j.1365-2125.2012.04282.x
[274] http://drmalcolmkendrick.org/2014/05/20/catalyst-crushed/
[275] Canner et al. N Engl J Med 1980; 303: 1038
[276] Canner et coll. N Engl J Med. 1980; 303(18): 1038-41
[277] Graham & Cooney. Eur Heart J – 2013; 35: 537 - DOI: http://dx.doi.org/10.1093/eurheartj/eht286 - http://eurheartj.oxfordjournals.org/content/early/2013/11/07/eurheartj.eht286 - Voir la figure 1

risque comme la cholestérolémie, la glycémie, la tension artérielle

CORONARY MORTALITY IN EUROPE IN 2000
Hypothèse du cholestérol infirmée - Épidémiologie
mortalité coronarienne en Europe en 2000
* Les 5 taux les plus bas, standardisés pour l'âge, en taux annuel par 100 000 habitants de 45 à 74 ans, furent de 65 en France, 87 au Portugal, 91 en Italie, 92 en Espagne et 97 en Suisse. Les 5 taux les plus élevés furent de 461 en Latvie, 446 en Estonie, 369 en Slovakie, 357 en Lithuanie et 343 en Hongrie. Le rapport de 5,3 fois entre la France et la Latvie ne s'explique pas par le cholestérol, tout comme le gradient orienté du sud-ouest au nord-est dans toute l'Europe[278]

CORONARY REVASCULARIZATION REDUCTION ACROSS STATIN TRIALS *Critère 'mou' – Essais positifs quant à la réduction relative*
a) « In AFCAPS/TexCAPS, treatment with lovastatin 20-40 mg daily reduced the [relative] rate of coronary revascularisation by -33% (RR 0.67) »[279]

b) « The MEGA trial showed that after an average follow-up of 5.3 years pravastatin 10-20 mg daily reduced the relative risk of coronary revascularisation by -40% (HR 0.60) »[280]

c) In JUPITER revascularization was decided by attending physicians at a rate of 0.71 per 100 person-years in the placebo group and of 0.38 in the rosuvastatin group, for a relative risk reduction of -46% (HR 0.54)...

However, the absolute risk reduction was 0.33 per 100 person-years, giving a NNT of 303 person-years, for an inefficacy rate of 99.67% per year of treatment, 110 595 pills being needed for a 1 year virtual delay in revascularisation in 1 patient, which may be expressed as an average delay of only 29 hours when this benefit is spread across 303 persons - « And costing over 20 times more to prevent one procedure than to perform one[281] »
réduction de la revascularisation coronarienne selon les essais statiniques
* la décision clinique de faire une angioplastie ou un pontage chez les participants est partiellement subjective car elle dépend du seuil de douleur du patient, de l'attitude des urgentologues et cardiologues, des équipement hospitaliers en cardiologie d'intervention, et de la levée de l'insu quand des soignants découvrent la cholestérolémie avant de prendre leur décision

CREATINE PHOSPHOKINASE; CPK *EIM biologique*
* Muscle lesions can occur without symptoms and pain and weakness can occur without a 10-fold CPK elevation
créatine phosphokinase
* son augmentation dans la sang est un EIM statinique et témoigne d'une atteinte moléculaire dans la musculature squelettique

Dal-OUTCOME, THE TRIAL *Dalcetrapib c. placebo – Critères cliniques – Prévention secondaire après syndrome coronarien aigu – Échec clinique – Interruption prématurée pour inefficacité – HDL*

« Patients were followed for a median of 31 months. At a prespecified interim analysis that included 1135 primary end-point events (71% of the projected total number), the independent data and safety monitoring board recommended termination of the trial for futility…

As compared with placebo, dalcetrapib did not alter the risk of the primary end point (cumulative event rate, 8.0% and 8.3%, respectively (HR = 1.04, NS) and did not have a significant effect on any component of the primary end point or total mortality. In patients who had had a recent acute coronary syndrome, dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent CV events »[282]
l'essai dit Outcome
« Faut l'interrompre tant les résultats sont négatifs »[283] - « A ce jour, la baisse des TG ou l'augmentation du HDL-C par des moyens pharmacologiques n'a pas été associée à une prévention de la survenue d'évènements CV voire à une diminution de la mortalité totale »[284]

[278] Müller-Nordhorn et al. Eur Heart J 2008 ; 29(10) : 1316 - http://eurheartj.oxfordjournals.org/content/29/10/1316 - DOI: http://dx.doi.org/10.1093/eurheartj/ehm604
[279] Davis & Dietrich. BMJ 2014; 348: g1795 - doi: 10.1136/bmj.g1795 (26.2.2014)
[280] Davis & Dietrich. BMJ 2014; 348: g1795 - doi: 10.1136/bmj.g1795 (26.2.2014)
[281] Eddie Vos, communication
[282] Schwartz et al. N Engl J Med 2012; 367(22): 2089 - doi: 10.1056/NEJMoa1206797
[283] Even, page 86
[284] BIP 2014 no 2 page 5

DANGEROUS ME-TOO *Mises au point*
« The manufacturer Bayer faced possibly bankruptcy because so many lawsuits claimed that cerivastatin (Baycol™) had an unusually high fatality rate from muscle breakdown, a me-too statin they developed and promoted when half-a-dozen other cholesterol-reducing statin drugs were already on the market »[285]
facsimilé dangereux ; moi-aussi dangereux *emprunt*; quasi-copie / fausse nouveauté dangereuse

DATA MINING IN STATINOVIGILANCE
Pharmacoépidémiologie
« Data mining of the FDA's adverse event reporting system, the Adverse Event Reporting System (AERS), is useful for examining statin-associated muscular and renal adverse events. The data strongly suggest the necessity of well-organized clinical studies with respect to statin-associated adverse events...

Based on 1,644,220 AERS reports from 2004 to 2009, signals were detected for 4 statins with respect to myalgia, rhabdomyolysis, and an increase in creatine phosphokinase (CK alias CPK) level, but these signals were stronger for rosuvastatin (Crestor™) than pravastatin and atorvastatin »[286]
exploration de données en statinovigilance
* C'est la recherche des signaux en exploitant une base de notifications spontanées (safety database) provenant des fabricants, des professionnels et parfois des victimes elles-mêmes

* On peut aussi explorer une base administrative de données médicales, hospitalières et pharmaceutiques (health database), constituées majoritairement de réclamations pour remboursement (claims database). Cette approche relativement peu couteuse s'est historiquement avérée moins souvent utile, pour découvrir les premiers signaux, qu'un programme bien organisé de notification spontanée appuyé par une communication empressée aux prescripteurs quand un signal important est détecté

DAVID PURKISS' MYOPATHY : VIGNETTE (UK)
« When David Purkiss was told he was at risk of a heart attack, and taking a cholesterol-lowering statin could protect him, it seemed the sensible thing to do. The carpenter, then 44, was in hospital for a routine varicose vein operation when he was told his condition was linked to furring of the arteries (sic), and he was advised to take statins. David says he noticed dramatic changes *within we*eks of taking pravastatin. I developed terrible muscle pains,' says David, now 70. 'My strength started to go...

My GP didn't know what was causing it, but *didn't thi*nk it was the statins, and was convinced the benefit was so huge it was worth putting up with the pain. It was so bad I would hang on to a kitchen work surface and weep while I tried to stay upright. 'I got more and more disabled and had to give up work. I was going upstairs on my backside and could hardly walk from the front door to the garden gate.'..

David's doctor *refused to listen* to any suggestion that statins might be to blame but in 2008, switched him to a different version, simvastatin. This did nothing to improve David's health and within months he was in a *wheelchair*. He went to see an orthopaedic surgeon, depressed, desperate and in a *wheelchair*,' says David. 'I told him it had taken me three-quarters-of-an-hour to get from the car park…

'He asked me what I thought was wrong and I said: "Statins." He said I could stop taking them to see what would happen.' David says he started to *feel better* almost straight away. Within a few weeks he was able to walk, and 6 months later he was as fit as he had been before starting the drugs. 'I went for a check-up with the orthopaedic surgeon, marched into his office, spun round in a pirouette, and said: "What do you think about that, then?" He couldn't believe the change.'…

Since he took his last statin on November 6, 2008, David has regained his health, strength and mobility and is a competitive weightlifter. He has a gym in his house and thinks nothing of heaving weights of eight stone »[287]
la myopathie de David Purkis, vignette clinique (R-U)
* tout y est : prescription en prévention primaire, faiblesse musculaire invalidante, douleurs musculaires, refus d'un médecin de suspecter une statine, délai d'apparition de quelques semaines, déchallenge positif en quelques semaines, exclusion de causes alternatives pharmacologiques ou pathologiques

[285] Arndt von Hippel
[286] Sakaeda T et al. PLoS ONE 2011 ; 6(12): e28124 – Site http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0028124
[287] http://www.dailymail.co.uk/health/article-3300937/Crippled-statins-Cholesterol-busting-drugs-left-David-wheelchair-doctors-insisted-taking-them.html

DEADLY FIBRATES ?
« There was no total mortality benefit in a large bezafibrate trial[288] and there have now (2006) been 3 trials with different fibrates that ended with numerically more deaths in the fibrates than in the placebo groups – gemfibrozil,[289] clofibrate[290] and fenofibrate[291] … The established failure of fibrates to lower total mortality should lead to an urgent call to stop their use and to examine the clinical efficacy of the lipid guidelines[292] »
fibrates mortels ?

DECREASE, THE TRIAL
« The study with fluvastatin was done by Dr Poldermans. Most of the data were fabricated »
l'essai dit Decrease

DEFINING NORMALITY
« Defining normality is somewhat arbitrary. Lipid levels have a normal bell-shaped or n-shaped distribution. In such cases the abnormality is quantitative rather than qualitative. The point at which clinicians decide that something is abnormal and warrants treatment is an arbitrary decision usually based on population risk »[293] - Anyway, lipidemia is not a disease but a surrogate risk factor at extreme levels (very high or very low)
définir la normalité

DENIAL OF STATIN ADRs BY PRESCRIBERS *Statinovigilance - Pratique*
« Half the patients on statins who complained of muscle aches, pain, memory lapses or cognitive impairments were told by their doctors that their problems were not related to their statins »[294] - « Doctors should serve as trusted protectors of their patients, mention adverse reactions when they prescribe, and not dismiss them when they arise »[295]

« Most of the literature on statins has focused on the benefits. As a result awareness of statin harms is low, and many specialists propound that statin harms are very unusual… the reported incidence of common statin effects, such as muscle pain and weakening, is low in randomized trials but higher in studies of real world use…

To some extent this is explained by use of a 'run-in period' in some statin RCTs when all patients are exposed to the drug prior to randomization and only those tolerating the drug are randomized… warnings about statin-related harm issued by the FDA or Health Canada are slow to be released, and as with past advisories have little impact »[296]

« I find it incredible how many people are taking these drugs and have side effects, many of which are not reported to their doctors and, if they are discussed, are not reported as serious side effects to the authorities. Patients' complaints are ignored by many GPs and hospital consultants »[297]

« In a survey of 650 patients by Dr. Golomb of the UC San Diego College of Medicine statin study, 87% reported ADRs to their doctors. Patients and not the doctors initiated the discussion in 98% vs 2% for cognition, 96% vs 4% for neuropathy and 86% vs 14% for muscle. Physicians are far more likely to deny rather than affirm patient ADRs. Rejection by physicians occurred even when symptoms had strong literature based support...

Physicians are unlikely to report ADRs to FDA in these circumstances. ADR reporting by patients is likely to give major boost to credible side effect reporting. A continuing complaint from patients reporting statin side effects is lack of MD responsiveness and, sometimes, downright hostility »[298]
déni des EIM statiniques par les prescripteurs

DERMATOMYOSITIS INDUCED BY STATINS : CASE REPORTS
Statinovigilance
a) Zuech P et al. *Pravastatin*-induced dermatomyositis. *Rev Med Interne* 2005; 26: 897

[288] BIP. Circulation 2000 ; 102 : 21
[289] HHS. J Intern Med 1994 ; 235 : 31
[290] WHO. Lancet 1980 ; 2 : 379
[291] Keech et al. Lancet 2005 ; 366 : 849
[292] Vos E. CMAJ 2006 ; 175(10) : 1246
[293] Mark Greener cité par Joseph Dumit, Drugs for life, page 150
[294] Golomb B. Drug Saf 2007 ; 30 : 669 quoted by Donald Light, 2010
[295] Donald Light, 2010
[296] Therapeutics Initiative. Therapeutics Letter #89, April-May 2014– free on http://www.ti.ubc.ca/sites/ti.ubc.ca/files/89.pdf
[297] Andrew Demaine. http://www.bmj.com/content/348/bmj.g1520/rr/692195
[298] Duane Graveline. Drug Safety 2007 ; 30(8) : 669

b) Thual N et al. *Fluvastatin*-induced dermatomyositis. *Ann Dermatol Venereol* 2005; 132: 996
c) Schalke BB et al. *Pravastatin* associated inflammatory myopathy. *N Engl J Med* 1992; 327: 649

c) Khattak FH et al. *Simvastatin*-associated dermatomyositis. *Br J Rheumatol* 1994; 33: 199
d) Rodriguez-Garcia & Serrano Commino M. *Lovastatin*-associated dermatomyositis. *Postgrad Med J* 1996; 72: 694
e) Hill C et al. Dermatomyositis with lung involvement in a patient treated with *simvastatin*. *Aust N Z J Med* 1995; 25: 745
observations cliniques de dermatomyosites statiniques

DESTATINIZATION IN PRIMARY PREVENTION
« The great majority of people taking statins have no history of heart attack or stroke, and the idea of taking statins is to prevent such an occurrence – so-called 'primary prevention'. In this context, statins do not save lives. For healthy individuals, then, the evidence shows that countless individuals might stop their statins, but not one of them will lose their life as a result…

What might happen to the risk of having a nonfatal heart attack, though? Well, the data here[299] shows that in primary prevention, 300 people will need to be treated with statins for 1 year to prevent 1 heart attack. It's only by taking a cold hard look at the data and understanding it in real [absolute] terms that we can make an accurate judgment about the supposed risks of stopping statins...

I think we doctors do a huge disservice to people by either not being aware of the data or giving patients a false impression of the risks of stopping statin therapy »
déstatinisation en prévention primaire
* c'est une forme de prévention quaternaire

DIABETOGENIC EFFECT ACROSS STATINS AND STUDIES
hyperglycemic effect across statins and studies
Épidémiologie – Étude observationnelle – Étude prospective – Diabètogenèse - Statinovigilance
« Dans Vigibase (UMC/WHO, 2017[300]), un peu plus de 13 000 observations de diabète ont été rapportées avec les 8 statines commercialisées… Cet EIM est un effet de classe[301] »

« The aim of this work – also presented by Laakso et al. in *Diabetologia* 4.3.2015 - was to investigate the mechanisms underlying the risk of type 2 diabetes (T2D) associated with statin treatment in the population-based *Metabolic Syndrome in Men* cohort…

A total of 8,749 non-diabetic male participants in East Finland, aged 45–73 years, were followed up for 5.9 years. New diabetes was diagnosed in 625 men by means of an oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c) ≥6.5% (48 mM) or glucose-lowering medication started during the follow-up. Insulin sensitivity and secretion were evaluated with OGTT-derived indices. Results Participants on statin treatment (N=2,142) had a 46% increased risk of T2D (adjusted HR 1.46) ...

The risk was dose dependent for simvastatin and atorvastatin. Statin treatment significantly increased 2 h glucose and glucose AUC of an OGTT at follow-up, with a nominally significant increase in fasting plasma glucose. Insulin sensitivity was decreased by -24% and insulin secretion by -12% in individuals on statin treatment (at fasting plasma glucose and 2h plasma glucose <5.0 mM) compared with individuals without statin treatment …

Decreases in insulin sensitivity and insulin secretion were dose dependent for simvastatin and atorvastatin »[302] according to the East Finland cohort study by Cederberg et al. in 2015…

« In this study, both the relative and absolute increases in diabetes incidence among statin users were somewhat higher than previously reported. Although the results could reflect confounding (e.g., if hyperlipidemic patients had intrinsically higher risk for developing diabetes than patients with normal lipid levels), the researchers conducted additional unpublished genetic analyses whose results make that possibility unlikely (personal communication from authors)...

I am unaware of published data on whether statin-related diabetes is reversible; if it is not reversible, it should be factored into decision-making for patients with borderline indications for statin therapy », Alan Brett comments

« In a pooled analysis of data from 5 statin trials (32 752 participants), intensive-dose statin therapy was associated with an

[299] http://www.thennt.com/nnt/statins-for-heart-disease-prevention-without-prior-heart-disease
[300] François Montastruc et al. *Pharmacoepidemiol Drug Saf* 2017 DOI 10.1002/ pds.4296
[301] J-L Montastruc. *BIP31* 2017 ;31(3) : 8
[302] Cederberg et al. Diabetologia 2015 - DOI 10.1007/s00125-015-3528-5

increased risk of new-onset diabetes compared with moderate-dose statin therapy. As compared with moderate-dose statin therapy, the NNH per year for intensive-dose statin therapy was 498 for new-onset diabetes, while the NNT per year for intensive-dose statin therapy was 155 for CV events »[303], according to the Preiss/*JAMA*/2011 meta-analysis…

In other words, high-dose statins, compared with moderate dose, accelerate development of diabetes by 19 hours for each year of treatment if that harm is spread across 498 patient-years, and delay major CV events by 57 hours for each year of treatment if that benefit is spread across 155 patient-years. If ascertainment of incident diabetes had been as powerful as that for measuring reduction in CV events, the NNT would have been higher

* In a retrolective cohort study conducted in a prescription database (NZ), patients prescribed statins have the highest risk of new-onset diabetes, strengthening the recent signal from current literature. Endpoint is risk of first metformin prescription, compared to a control group. Of 12 616 statinised patients, 391 (3.1%) had a first metformin prescription over 6 years...

The hazard ratio (univariate) is 2.66 ; when adjusted for age, sex and ethnicity, the HR (multivariate) rises to 3.31. The absolute risk (incidence rate) of new diabetes under statin treatment is 0.55 per 100 patient-years, the NNH is 182 patient-years[304]…

« Recent studies suggested that statins may also increase the risk of new-onset diabetes, which in turn increases the risk of CV events. One meta-analysis reported the odds to be 9% (OR 1.09) with other studies showing the association with pravastatin and rosuvastatin (Crestor™) use. More recent data indicate that the risk of new-onset diabetes with statin use could also be dose dependent, further supporting a causal link »[305]

* In the JUPITER study, involving 17,802 participants without diabetes, the relative risk (hazard ratio 1.25) for newly diagnosed diabetes was relatively increased by +25% in the rosuvastatin group compared to the placebo group. Little to no heterogeneity in the risk of new-onset diabetes has been observed among trials...

Statins appear to have a class effect, unrelated to the individual statin, its potency, or its lipophilic or hydrophilic properties. Their effect also appears to be dose-dependent: the odds ratio for new-onset diabetes is 12% higher with intensive-dose therapy than with moderate-dose therapy[306]

* A meta-analysis of 6 statin trials that included 57,593 participants revealed a 13% increase in the relative risk of new-onset diabetes[307]. Two victims' vignettes in support :

a) « I was on Zocor™ and now on Lipitor™ for the last 3 years. I started with 40 mg and my blood sugar went to 180mg (4.6 mmol/l). The doctor recently changed me to 80mg and now my blood sugar is 250mg/dl (6.5 mmol/l)
b) « I wish to inform you that I have been on Lipitor™ for about a year. I started developing leg pains and elevated blood sugar. I discontinued the Lipitor™ and my leg pains are going away and my blood sugar levels are coming down »[308]

« We're overdosing on cholesterol-lowering statins, and the consequence could be a sharp increase in the incidence of Type 2 diabetes. In Feb. 2012, the FDA raised questions about the side effects of these drugs and developed new labels for these medications that will now warn of the risk of diabetes and memory loss. The magnitude of the problem for diabetes becomes much more apparent with careful examination of the data from large clinical trials...

Statins have been available since the 1980s but their risk of inducing diabetes did not surface for nearly 20 years. When all the data available from multiple studies was pooled in 2010 for more than 91,000 patients randomly assigned to be treated with a statin or a sugar pill (placebo), the risk of developing diabetes with any statin was 1 / 255 patients treated or NNH = 255...

But this figure is misleading since it includes weaker statins like Pravachol™ and Mevacor™ - which were introduced earlier and do not carry any clear-cut risk. It is only with the more potent statins – Zocor™ (simvastatin), Lipitor™ (atorvastatin) and Crestor™ (rosuvastatin) - particularly at higher doses, that the risk of diabetes shows up...

The cause and effect was unequivocal because the multiple large trials of the more potent statins had a consistent excess of diabetes, the higher the dose, the more diabetes. The numbers increase to 1 / 167 for patients taking 20 mg of Crestor™, and up

[303] Preiss et al. JAMA 2011; 305(24): 2556 – Full paper at http://jama.jamanetwork.com/article.aspx?articleid=646699
[304] Currie et al. BMJ Open 2013; 3: e003475 - doi:10.1136/bmjopen-2013-003475
[305] Ibidem
[306] Allison B Goldfine. NEJM 2012 sur http://www.nejm.org/doi/full/10.1056/NEJMp1203020?query=TOC
[307] Rajpathak SN et al. Diabetes Care 2009; 32: 1924
[308] http://www.peoplespharmacy.com/2010/03/01/listen-to-patients-when-it-comes-to-statin-side-effects/

to 1 / 125 for intensive statin treatments involving drug strategies to markedly lower cholesterol levels...

Let's say that 1 / 200 patients treated with any of the 3 most potent statins will get the side effect of diabetes. That's quite a conservative number because diabetes was not even being carefully looked for in most of the trials. And we have data for only 5 years of treatment; it might be worse with longer statin therapy...

In patients who have never had heart disease and are taking statins to lower their risk (so-called primary prevention), the reduction of heart attacks and other major events occurs in only 1 / 50 [even fewer when presented in patient-years]. The margin of benefit to risk is quite narrow...

The announcement, medication label change and health advisory by the F.D.A. were long overdue, and have brought this important public health issue to light. The information that we have does not support that this is a 'small' problem. The problem of statin-induced diabetes cannot be underplayed while the country is being overdosed »[309]

« In a population based cohort study with time to event analyses to estimate the relation between use of particular statins and incident diabetes, there was no significantly increased risk among people who received fluvastatin or lovastatin. The absolute risk for incident diabetes was about 3.1 / 100 person years (NNH = 32 patient-years) for atorvastatin (Lipitor™) and 3.4 per 100 person years (NNH = 29 patient-years) for rosuvastatin (Crestor™)...

There was a slightly lower absolute risk reduction with simvastatin, 2.6 / 100 person years (NNH = 38 patient-years) compared with pravastatin, 2.3 / 100 person years (NNH = 43 patient-years) »[310]

* In JUPITER, the hazard ratio for investigator reported diabetes mellitus was 1.27 (a 27% increase), 251 cases under rosuvastatin (2.8%) and 205 under placebo (2.3%). The rate of newly diagnosed diabetes was 2.4 cases per 100 person-years in the placebo group and 3 cases in the rosuvastatin group, for a relative risk increase of +27% (p= 0.01) and an absolute rate increase of +0.6 cases per 100 person-years, yielding a NNH of 167 person-years

« A retrolective cohort study was performed using the Irish Health Services Executive Primary Care Reimbursement Services national pharmacy claims database. Statin use was associated with an increased risk of new onset treated diabetes (HR = 1.18, an 18% increase). Increased risk of new onset treated diabetes was found with Crestor™ / rosuvastatin (HR = 1.41, a 41% increase, with Lipitor™ / atorvastatin (HR = 1.23, a 23% increase) and with simvastatin (HR = 1.15, a 15% increase)...

There were overall dose and duration effects for all statins, excepting fluvastatin, which only demonstrated a duration effect »[311]

« In the Women's Health Initiative (WHI) Study, statin medication use in postmenopausal women is associated with an increased risk for diabetes mellitus. Statin use at baseline was associated with an increased risk, a hazard ratio (HR) of 1.71 (+ 71%); this association remained after adjusting for other potential confounders, multivariate-adjusted HR was 1.48 (or + 48%) and observed for all types of statin medications...

Subset analyses evaluating the association of self-reported diabetes mellitus with longitudinal measures of statin use confirmed these findings[312]»

* In the NAVIGATOR trial,[313] during the median 5 years of follow-up, statins were started in 22.0% of patients. After adjusting for baseline characteristics and time varying confounders, statins were associated with an increased relative risk of 14% for new onset diabetes (hazard ratio 1.14)[314]

« In the Dormuth 2014 study,[315] investigators used data from 8 population-based Canadian, U.S., and U.K. cohort studies to evaluate risk for developing diabetes in 137,000 patients (age, ≥40) who were hospitalized for major adverse CV events and who received new prescriptions for high-potency or low-potency statins...

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[309] Eric J Topol. NY Times, March 4, 2012
[310] Carter et al. http://www.bmj.com/content/346/bmj.f2610 - doi: http://dx.doi.org/10.1136/bmj.f2610
[311] Zaharan et al. Brit J Clin Pharmacology 2013 ; 75(4) : 1118 - DOI: 10.1111/j.1365-2125.2012.04403.x
[312] Culver et al. Arch Intern Med 2012; 172(2): 144 - doi:10.1001/archinternmed.2011.625 - http://www.ncbi.nlm.nih.gov/pubmed/22231607
[313] McMrray et al. N Engl J Med 2010; 362: 1477
[314] Shen et al. BMJ 2013; 347: f6745 - http://www.bmj.com/content/347/bmj.f6745
[315] Dormuth CR et al, BMJ 2014; 348: g3244

Diabetes incidence in new users of high-potency statins (rosuvastatin [Crestor] ≥10 mg, atorvastatin ≥20 mg, or simvastatin ≥40 mg) was compared with incidence in new users of low-potency statins (all other statins). Within the first 2 years of statin use, new-onset diabetes was significantly more common with high-potency stains than with low-potency statins (rate ratio, 1.2). Risk was highest during the first 4 months of use (RR, 1.3)...

In this study, which involved patients with established CV disease, high-potency statins were associated with excess risk for diabetes compared with low-potency statins. However, the absolute risk was small: The authors estimate that 342 secondary-prevention patients would need to be treated with a high-potency statin instead of a low-potency statin for 2 years to cause 1 additional case of diabetes »[316] but the dose-relatedness of diabetogeny is thereby confirmed for statins

« A meta-analysis by Sattar et al. - *Lancet* 2010; 375(9716): 735 - which included 13 statin trials with 91,140 participants, reported that statin therapy was associated with a +9% increased risk for incident diabetes (odds ratio 1.09), with little heterogeneity between trials...

A meta-analysis by Rajpathak et al. - *Diabetes Care* 2009; 32(10): 1924 - which included 6 statin trials with 57,593 participants, also reported a small increase in diabetes risk (relative risk 1.13 or +13%), with no evidence of heterogeneity across trials...

A recent study by Culver et al. - *Arch Intern Med* 2012; 172(2): 144 - using data from the *Women's Health Initiative*, reported that statin use conveys an increased risk of new-onset diabetes in postmenopausal women, and noted that the effect appears to be a medication class effect, unrelated to potency or to individual statin »[317]

« One study reported a RRI of diabetes of +363% after 15-20 years of statin treatment, another one reported a RI of +46% after 5.9 years of therapy »[318]

effet diabétogène selon les statines et les études

NDT : on devrait dire 'effet hyperglycémiant' car le diagnostic du diabète (variable dichotomique) est posé arbitrairement par un niveau de glycémie à jeun ou d'hémoglobine glycquée et ces niveaux (variable continue) varient d'une étude à l'autre

* Une étude populationnelle cas-témoin intra-cohorte dans des bases administratives de 8 cohortes de patients traités en prévention secondaire en pratique courante[319] a révélé une augmentation relative de +15% du risque de nouveau diabète (hospitalisation, insuline, hypoglycémiant oral) dans les 2 ans suivant le début du traitement en prévention secondaire par des fortes doses de statines (rosuvastatine 20mg+, atorvastatine 40 mg+, simvastatine 80 mg+) comparées à de faibles doses

* Pour chaque année de statinisation avec Lipitor™ (atorvastatine), 1 / 32 deviendra diabétique, tandis que 1 / 29 le deviendra sous Crestor™ (rosuvastastine), 1 / 38 sous simvastatine et 1 / 43 sous pravastatine, selon une étude observationnelle de cohorte. Même si les taux sont moindres durant les essais cliniques, le dépistage périodique du diabète chez les statinisés augmente les couts indirects de la statinisation et s'impose maintenant devant l'accumulation des preuves de la diabétogénicité

« Dans l'essai de prévention primaire Jupiter,[320] les sujets traités par 20 mg de rosuvastatine (Crestor™) étaient à risque accru de diabète (RR 1,28 ou +28%) s'ils avaient au moins un facteur de risque de diabète »[321]

* Durant l'essai de la WHI sur l'hormonothérapie de substitution, une évaluation épidémiologique fut faite du risque de diabète chez les femmes statinisées. Les résultats montent une augmentation relative du risque de +71%. Même après ajustement pour des facteurs de confusion, l'augmentation persiste, est de +48% et fut observée sous toutes les statines

« Nous savions que les statines augmentent le risque d'avoir un diabète, nous le disions dans notre premier livre sur ce sujet en 2006. Ce ne fut pourtant admis (après de lourdes hésitations) par les experts qu'en 2012 alors que ces médicaments sont commercialisés depuis les années 1990s. Il aura fallu plus de 20 ans pour que l'évidence soit démasquée … presque par hasard »[322]

DIABETOGENIC EFFECT IN A RETROSPECTIVE COHORT STUDY *Statinovigilance – Diabète – Obésité - Épidémiologie*

« 25,970 patients (3982 statin users and 21,988 nonusers) were identified as healthy adults at baseline. Of these, 3351 statins

[316] NEJM Journal Watch
[317] http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm
[318] DuBroff, *QMJ*, 1.11.2017
[319] Dormuth et al. BMJ 29.5.2014 - http://www.bmj.com/content/348/bmj.g3244
[320] Ridker et al. Lancet 2012; 380: 565
[321] Michel Gerson. Médecine 2013; 9(6) : 255 sur http://www.jle.com/fr/revues/medecine/med/e-docs/00/04/88/EA/article.phtml
[322] http://michel.delorgeril.info/

users and 3351 nonusers were propensity score-matched. Statin users had higher odds of :

a) new-onset diabetes, odds ratio 1.87 or +87%
b) diabetes with complications, odds ratio 2.50 or +150%
c) overweight/obesity, odds ratio 1.14 or +14% »[323]
effet diabétogène dans une étude de cohorte rétrospective

DIABETOGENIC EFFECT OF LIPITOR™ LEADS TO LEGAL PROCEEDINGS
« Court records indicate that the litigation surrounding Lipitor™ and diabetes began to grow in the wake of a U.S. Food & Drug Administration (FDA) alert in 2012 regarding a possible association between the use of cholesterol-lowering statins and Type 2 diabetes. At the time, the agency said the labels for Lipitor™ and other statins would be updated to include new information about their potential association with Type 2 diabetes...

The FDA was prompted to act by the publication of a study in *JAMA Internal Medicine* the previous month (in 2012) which suggested that post-menopausal women treated with statins faced an increased risk of developing new-onset Type 2 diabetes. Since then, court records indicate that more than 1,600 Lipitor™ diabetes claims have been filed in state and federal courts around the country, the majority of which are pending in the federal proceeding underway in South Carolina...

Among other things, the lawsuits assert the modifications made to the Lipitor™ label to comply with the FDA's 2012 mandate still do not sufficiently inform patients about Lipitor's association with Type 2 diabetes. The drug's manufacturer, Pfizer, Inc., is also accused of *concealing information* about diabetes in order to protect sales of Lipitor »[324]
l'effet diabétogène du Lipitor™ mène à des procédures judiciaires

DIET-HEART : END OF AN ERA – (Article)
MANN GV. (Editorial) *NEJM* 1977; 297(12) : 644
« This call for a paradigm change appeared years before statins put the cholesterol-as-cause hypothesis on costly life support only to have it, again, shown a failure in women and in most men at the age when vascular disease causes most deaths »[325]
L'hypothèse diète et cœur, la fin d'une ère (Traduction libre du titre de l'article)

DIET-HEART HYPOTHESIS
TN : aka the *lipid hypothesis*, although the latter encompasses dieting *and* pharmacotherapy
See also LIPID HYPOTHESIS
hypothèse de la cardioprotection alimentaire

DIETARY FATTY ACIDS AND CORONARY DISEASE : A META-ANALYSIS
« Current evidence does not clearly support CV guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats »[326]
acides gras alimentaires et coronaropathies : une méta-analyse

DIFFERENT TIME TRENDS OF CALORIC AND FAT INTAKE BETWEEN STATIN USERS AND NONUSERS AMONG US ADULTS: Gluttony In The Time Of Statins? **(USA) -** (Article)
Épidémiologie – EIM – Enquête prospective - Nutrition
Sugiyama et al. online 24.4.2014 *JAMA Intern Med*[327] - Full paper at :
http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1861769

* A repeated cross-sectional study in a nationally representative sample of 7 886 US adults, 20+ years, from the National Health and Nutrition Examination Survey (NHANES), 1999-2010. Caloric and fat intake measured through 24-hour dietary recall and body mass index from weight/height. Time trends in these 3 variables were compared between statin users and nonusers.

« Among statin users, caloric intake in the 2009-2010 period was 9.6% higher than that in the 1999-2000 period. In contrast, no significant change was observed among nonusers during the same study period. Fat intake increased 14.4% among statin users while not changing significantly among nonusers...

[323] Mansi et al. J Gen Intern Med SEP 23.4.2015 - DOI: 10.1007/s11606-015-3335-1
[324] Bernstein Liebhard, 7.2.2015 - http://www.prweb.com/releases/lipitor-lawsuit/lipitor-diabetes/prweb12501498.htm
[325] Vos E. Nutr Metab Cardiovas Dis 2007 ; 17 : e19
[326] Chowdhury et al. Ann Intern Med 2014; 160(6): 398 - doi: 10.7326/M13-1788http://annals.org/article.aspx?articleid=1846638
[327] doi: 10.1001/jamainternmed.2014.1927 - http://archinte.jamanetwork.com/article.aspx?articleid=1861769

Also, BMI increased more among statin users (+1.3) than among nonusers (+0.4), a 0.9 [absolute difference ; for example, 7 pounds for a 6-footer]. Efforts aimed at dietary control among statin users may be becoming less intensive »

* On a person-year basis, statinization is associated with a 0.96% relative increase in caloric intake each year, a 1.44% relative increase in fat intake and a 0.09 absolute increase in BMI. Since these variables are continuous, NNH calculations are not applicable

« They found that statin users significantly inceased their fat intake and calorie consumption, along with their BMI, in the last decade. This article raises concerns of a potential moral hazard of statin use, in addition to the already known adverse effects : besides muscle aches, diabetes, cognitive dysfunction, focusing on cholesterol levels can be distracting from the more benefical focus on healty lifestyle »[328]

See also WEIGHT GAIN…
Évolution dans le temps de l'ingestion en calories et graisses chez l'adulte étastunien statinisé et non-statinisé (Traduction libre du titre de l'article)
« Une grande étude américaine sur près de 28,000 adultes (20+ ans) suivis sur 10 ans et comparant des personnes sous statines à d'autres sans statines nous annonce que les statines entrainent une prise de poids [IMC augmenté de 0,9]. C'est dans JAMA Intern Med et publié le 24 Avril 2014 en ligne »[329] - De Lorgeril propose deux explications au gain pondéral statinique:

a) les statinisés mangent plus et plus gras
b) la myotoxicité statinique diminue l'activité physique

DILAPIDATION OF PUBLIC FUNDS
dilapidation des fonds publics
« Les praticiens dilapident les fonds publics en prescrivant des statines [en prévention primaire] »[330]

DILAPIDATION OF PUBLIC FUNDS (FR)
Pharmacoéconomie - Gaspillage
dilapidation des fonds publics
« Les praticiens dilapident les fonds publics en prescrivant des statines [en prévention primaire] »[331] - « Aussi lentement que le discours soit en train de changer, je demeure pas mal convaincu que lorsque l'histoire des statines sera écrite, ce sera celle de l'un des plus purs désastres [pharmacoéconomiques] de notre époque »[332]

« Ce marché est le premier marché de médicaments du monde et, en France, loin devant les antibiotiques, les antidépresseurs et la plupart des antihypertenseurs et des chimiothérapies anticancéreuses. Il a rapporté en 20 ans, 300 milliards de $ aux firmes pharmaceutiques et coûte chaque année 2 milliards d'€ à la Caisse nationale d'assurance-maladie française (l'équivalent par exemple du salaire brut de 35.000 infirmières) …

Beaucoup de cardiologues en vivent, car 6 M de consommateurs de statines, c'est au bas mot 12 M de consultations et d'examens biologiques par an »[333] - « La population française jouit d'un risque CV comparable à celui des japonais, coréens et suisses, avec la plus faible incidence au monde des décès par cardiopathie ischémique »[334], le gaspillage y est encore plus inacceptable qu'ailleurs dans le monde

DIRECT TO CONSUMER ADVERTISING OF STATINS *Promotion – Gaspillage – Pharmacoéconomie*
DTCA of statins

« Exposure to statin TV ads increased the odds of being diagnosed with high cholesterol by 16 to 20 %, and increased statin use by 16 to 22 %, among both men and women. These associations were driven almost exclusively by men and women at low risk for future cardiac events. There was also evidence of a negative association between direct to consumer advertisement (DTCA) exposure and statin use among high-risk women...

[328] Rita Redberg
[329] http://michel.delorgeril.info/
[330] Marc Girard, cité sur http://www.centpapiers.com/medicaments-dangereux-a-qui-la-faute/67105
[331] Marc Girard, cité sur http://www.centpapiers.com/medicaments-dangereux-a-qui-la-faute/67105
[332] Alan Cassells, 2013
[333] Philippe Even. http://www.lanutrition.fr/bien-dans-sa-sante/les-maladies/le-cholesterol/polemique-sur-l-arret-des-statines.-le-commentaire-du-pr-even.html
[334] François Pesty 2013

This study provides new evidence that DTCA may promote over-diagnosis of high cholesterol and over-treatment for populations where risks of statin use may outweigh potential benefit »[335]
publicité directe des statines

DISCONTINUATION OF STATINS IN END-OF-LIFE PATIENTS *Déprescription en gériatrie*
* Kutner et al.[336] (*JAMA Intern Med*, 2015) presented their results of this randomized trial comparing statin discontinuation vs. continuation in 381 patients (mean age 74 years) with advanced life-limiting illness on statin therapy for ≥ 3 months. All patients included in this trial had an estimated life expectancy of 1 month to 1 year and recent functional status deterioration (unrelated to CV health/status)...

Most patients (69%) had been taking statins for > 5 years and nearly half of patients (48.8%) had a primary diagnosis of cancer. Although this trial was originally designed to determine the effect of statin discontinuation on survival, this primary outcome was modified to *death within 60 days* after a prespecified interim analysis observed a longer median survival than initially projected. Median duration of follow-up was 18 weeks and overall mean survival was 213 days...

Comparing statin discontinuation vs. continuation, death within 60 days occurred in 23.8% vs. 20.3% (not significant) and median time to death was 229 days vs. 190 days (not significant). There were also no significant differences in CV-related events, physical symptoms, statin-specific symptoms, or performance status. Statin discontinuation tended to increase total McGill Quality of Life score compared to statin continuation (7.11 vs. 6.85, p = 0.04), a 3.8% absolute increase...

* Comment : « Kutner and her colleagues with the *Palliative Care Research Cooperative Group*, which includes more than 20 US member institutions, reported in 2014 having enrolled 381 patients whose estimated life expectancy was 7 months. About half had cancer and all had taken a statin for at least 3 months. Half of the patients were randomized to continue the drug, and the other half to stop taking it. Patients were monitored for up to a year to track CV events, changes in quality of life, and survival...

Rates of CV events were approximately 6% in each group. Median survival was 190 days among patients who continued taking a statin compared with 229 days among those who stopped the drug [a gain of 39 days or 20%]. Patients who quit statins had significant improvements in quality of life, especially in feelings of well-being and support. Stopping the drug also saves money….

Whether or when to stop preventive medications is an important issue in end-of-life care, the investigators noted. Some patients may start anticancer drugs or opioids for pain, increasing the risk of drug interaction. Medications to prevent *osteoporosis, anticoagulants, high blood pressure,* and *diabetes* are candidates for future studies[337] »…
cessation des statines chez des patients en fin de vie
« Cette réflexion sur la déprescription de statine peut être étendue à d'autres classes de médicaments, particulièrement chez les personnes âgées[338] »

* voilà une situation clinique où l'on vient de démontrer par essai contrôlé que cesser une statinisation en fin de vie améliore la qualité de vie et l'espérance de vie, ce qui revient à dire que les statines diminuent ces deux indices de santé. Qu'attend-on pour cesser toute statinisation en prévention primaire, celle en prévention secondaire chez les femmes ainsi que chez les hommes de plus de 75 ans ?

* sans oublier les anti-ostéoporose et les compléments alimentaires, les anticoagulants et les antiplaquettaires, les antihypertenseurs et les hypoglycémiants, dont les indications – qui ne sont que des promesses au long cours - perdent leur sens en fin de vie

DISMISSIVENESS
brushing aside
« Doctors are dismissive of patients' reports or complaints of statin ADRs like cognitive or muscular problems »
indifférence
« Les médecins sont *indifférents* aux / font peu de cas des / balaient du revers de la main les signalements d'EIM statiniques, comme les troubles cognitifs ou musculaires, par leurs patients

[335] Niederdeppe J et al. Journal of General Internal Medicine 2013 ; 28(7) : 886 – http://link.springer.com/article/10.1007/s11606-013-2379-3?no-access=true
[336] JAMA Intern Med 2015 Mar 23 - doi: 10.1001/jamainternmed.2015.0289 – abstract http://www.ncbi.nlm.nih.gov/pubmed/25798575?dopt=Abstract
[337] Rebecca Voelker, 20.5.2014 - http://newsatjama.jama.com/2014/05/30/statin-use-can-stop-when-illness-is-terminal-study-reports/
[338] Prescrire 2017 ; 37(399) : 73

DITES À VOTRE MÉDECIN QUE LE CHOLESTÉROL EST INNOCENT, IL VOUS SOIGNERA SANS MÉDICAMENT – (Livre pour public averti)
Michel DE LORGERIL. Vergèze (FR): Thierry-Souccar; 2007 – 318 pages
Voir l'annexe DOCUMENTATION pour la présentation

DO STATINS HAVE A ROLE IN PRIMARY PREVENTION? An update – (Synthèse indépendante)
WRIGHT JM. *Ther Lett* 2010;77:1-2
« A well-done meta-analysis of statins for primary prevention, showing no mortality benefit » writes *Archives of Internal Medicine* editor[339]

DR CHOLESTEROL
Sir Rory Collins (UK)[340]
* The most renown, if not infamous, among British hypercholesterolists, an influential KOL for industry – He holds 'confidential data' on statins and up to 2016 - « There has been no progress on the availability of the trial data on statins for independent scrutiny, doi:10.1136/bmj.h3908 » according to the BMJ Editor[341]

« This is also how Sir Rory Collins works : He runs the Clinical Trial Service Unit (CTSU) in Oxford. It runs trials that are almost entirely funded by the pharmaceutical industry. Nearly 300 M pounds sterling ($500 M at the time) over the last 10 years or so. He states he receives no money from the pharmaceutical industry (sic), and therefore is not biased in any way. Once again…Industry pays CTSU and CTSU pays Sir Rory Collins = no payment from industry and no COI !»[342]
le Docteur Cholestérol
* on pourrait en dire autant d'autres meneurs d'opinion sponsorisés du cholestérol :
a) Jane Armitage, Colin Baigent, George Davey Smith, Liam Smeeth, etc. au R-U ;
b) Ancel Keys, Jeremy Stamler, Eugene Braunwald, Paul Ridker, Ken Williams, Kathleen Kimler Altobelli, Michael J Pencina, Christopher P Cannon, etc. aux É-U.
c) Jean-Michel Lecerf, Bruno Vergès, etc. en FR

DRUG INDUCED REDUCTION OF TRIGLYCERIDES OR INCREASE IN HDL-C (USA) *Retrait du marché – Hypothèse lipidique désavouée*

« In April 2016, FDA withdraws approvals for 2 medications that had been used with statins to treat high levels of cholesterol. The affected therapies are *niacin* extended release (Niaspan), *fenofibric acid* (Tripilix), Advicor™, which combines niacin with *lovastatin*, and Simcor™, which combines niacin with *simvastatin*…

The evidence from ACCORD, AIM-HIGH, and HPS2-THRIVE Collaboration Group "no longer supports the conclusion that a drug-induced *reduction in triglyceride* leels and/or *increase in HDL-cholesterol* levels in statin-treated patients results in a reduction in the risk of cardiovascular events »[343]
réduction médicamenteuse des triglycérides et augmentation médicamenteuse du HDL-C
« Maintenant que les brevets sont échus, les autorités de réglementation se comportent tout à coup de façon rationnelle ! »[344]

EFFECT OF STATIN THERAPY ON MORTALITY IN OLDER ADULTS HOSPITALIZED WITH CORONARY ARTERY DISEASE : A Propensity-Adjusted Analysis – (Article)
Daniel P. ROTHSCHILD et al. *J Am Geriatr Soc* 2016; 64(7): 1475-1479 - DOI: 10.1111/jgs.14207
Gériatrie – Prévention secondaire – Étude observationnelle – Cohorte prospective – Statistiquement négative

« Individuals aged 80+ hospitalized from January 2006 to December 2010 with acute myocardial infarction (AMI), unstable angina pectoris, or chronic CAD and discharged alive (N = 1,262) were divided into those who did (n = 913) and did not (n = 349) receive a discharge prescription for a statin...

Outcome measured was all-cause mortality over a median follow-up of 3.1 years. In a cohort of older adults hospitalized with CAD, statin therapy had no statistically significant effect on long-term survival after adjustment for between-group differences.

[339] Rita Redberg, 2012, Editor of Archives of Internal Medicine - http://www.nejm.org/doi/full/10.1056/NEJMc1207079
[340] http://www.nogracias.eu/2014/08/07/dr-cholesterol-british-medical-journal/
[341] Fiona Godlee. BMJ 2016; 352: i1261- doi: http://dx.doi.org/10.1136/bmj.i1261
[342] http://drmalcolmkendrick.org/2015/10/13/the-longest-journey/
[343] http://www.ajmc.com/newsroom/fda-to-pull-approval-of-2-drugs-used-in-combo-with-statins
[344] Paul v Nguyen

These findings call into question the benefit of statin therapy for secondary prevention in a real-world population of adults aged 80+ »
Effet de la statinothérapie sur la mortalité d'adultes plus âgés ayant été hospitalisés pour coronaropathie : Une analyse ajustée en fonction de la prédisposition – (Traduction libre)

EFFECTS OF STATIN ON ENERGY AND FATIGUE WITH EXERTION : RESULTS FROM A RANDOMIZED CONTROLLED TRIAL –
(Article) *Statinovigilance expérimentale – Fatigue - Énergie*
GOLOMB BA et al. *Arch Intern Med* 2012: 172(15): 1180-82 - doi :10.1001/archinternmed.2012.2171- free on http://archinte.jamanetwork.com/article.aspx?articleid=1183454

« The RCT shows that simvastatin and pravastatin significantly decrease energy and increase fatigue after exertion compared with placebo »[345]

« Golomb et al. performed a RCT that included 1016 healthy men and women with high LDL- C. Here, the participants were divided into 3 groups that were given 20 mg simvastatin, 40 mg pravastatin or placebo. After 6 months of treatment, 40% of the women on statin treatment experienced adverse effects on energy or *exertional fatigue* »

EFFICACY AND SAFETY OF LDL-LOWERING THERAPY AMONG MEN AND WOMEN: Meta-Analysis Of Individual Data From 174 000 Participants In 27 Randomised Trials – (Méta-analyse controversée)
CTT Collaboration. *Lancet* 2015; 385 : 1397-1405

* all-cause mortality relative risk reduction per 1 mmol/L reduction in LDL-C is -9% in women and -10% in men; this reporting format does not allow the calculation of the absolute risk reduction per year of statinisation. In a person with a baseline total mortality risk of 1% per year, the annual reduction of absolute risk by a statinisation achieving a 1 mmol/L reduction in LDL-C would only be of -0.1%, for an annual NNT of 1 000 patient-years

* among low risk people (absolute risk of any CV event < 2% per year), absolute risk reduction of major vascular events per 1 mmol/L in men is -12/ 5 000 patient-years for an annual NNT of 417 and -9/5 000 patient-years in women for an annual NNT of 556; this reporting format does not allow the calculation of the absolute risk reduction per year of statinisation

* the CTT is an industry friendly group driven by Sir Rory Collins, a powerful KOL in the heartland of statinology but the declaration of interests omits his name although he partly 'conceived and designed' the study:

« The CTT Collaboration is funded by the UK Medical Research Council, British Heart Foundation, Cancer Research UK, and the Australian National Health and Medical Research Council, and not by the pharmaceutical industry (sic). Most of the trials in this report were supported (at least in part) by research *grants* from the pharmaceutical industry...

Representatives of the pharmaceutical companies funding trials included in the CTT are *invited* to *attend* meetings and to *comment* on draft papers, but the final content of publications is determined by members of the writing committee...

JF reports personal fees from AstraZeneca and Pfizer outside the submitted work.
RS reports grants from Merck Sharp & Dohme, AstraZeneca, and Pfizer during the conduct of the study and grants from Merck Sharp & Dohme, AstraZeneca, and Pfizer outside the submitted work.

HC reports personal fees from Pfizer and Eli Lilly; grants from Boehringer Ingelheim and AstraZeneca; institutional consultancy fees from and shares held in Roche Pharmaceuticals; and institutional consultancy fees from Novartis Pharmaceuticals, Sanofi-Aventis, and Eli Lilly outside the submitted work.

EB reports grants to institutions, uncompensated consultancies and lecture fees from Merck Sharpe & Dohme during the conduct of the study; grants to institutions from AstraZeneca, Johnson & Johnson, SanofiAventis, Daiichi Sankyo, GlaxoSmithKline, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics, Pfizer, and Duke University outside the submitted work;

and personal fees from Genzyme, Amorcyte, Medicines Co, CardioRentis, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, Menarini International, Medscape, and Bayer outside the submitted work.

JLR reports personal fees and honoraria from Pfizer during the conduct of the study and personal fees from Pfizer and Amgen

[345] TI/Therapeutics Letter # 89, 2014

outside the submitted work.

TP reports grants, personal fees and non-financial support from Merck Sharpe & Dohme, Pfizer, and Amgen and personal fees and non-financial support from AstraZeneca during the conduct of the study.

CB reports grants from Merck Sharp & Dohme during the conduct of the study and grants from Novartis and Pfizer outside the submitted work.
AK reports personal fees from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Pfizer and honararia for lectures or advisory committees from Abbott and Bristol-Myers Squibb outside the submitted work »

ENFORCED SUSPICION
Cholestérolémies de dépistage

« The *National Cholesterol Education Guidelines* of 2001 insisted that doctors start screening everyone at age 20 rather than the 1993 recommendation of 40, and every 5 years thereafter, even if they show no signs of the disease… *Enforced suspicion* was now becoming the norm »[346]
suspicion (rendue) obligatoire

ENHANCE, THE TRIAL *Essai négatif – Hyperlipidémie familiale hétérozygote – Critère de substitution – Simvastatine c. ezetimibe + simvastatine*

« In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima–media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein »[347]

« The FDA approved ezetimibe in 2002 for use in the US primarily because it lowered LDL-C levels, a surrogate marker for prevention of CV disease. Whether ezetimibe improved clinically meaningful outcomes remained a question...

That question was somewhat answered in January 2008, with the announcement that the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, sponsored and conducted by industry, found that the addition of ezetimibe failed to reduce atherosclerosis progression compared with simvastatin alone, despite lowering LDL-C levels...

Atherosclerosis progression was determined by a change in the intima-media thickness of the walls of the carotid and femoral arteries—yet another surrogate end point »[348]

« In a study[349] published in the *American Heart Journal*, researchers looked at ezetimibe prescription trends before and after ENHANCE, using data collected from CompuScript in Canada and IMS Health in the USA from 1.1.2002 to 31.12.2009. The researchers found the monthly number of ezetimibe prescriptions per 100 000 population rose from 6 to 1082 in the USA from November 2002 to January 2008 and then declined to 572 per 100 000 population by December 2009, a decrease of 47.1%...

In Canada, however, use continuously increased from 2 to 495 per 100 000 from June 2003 (when the drug was approved in Canada) to December 2009 »[350]
l'essai dit Enhance
* le critère substitutif était l'épaisseur ultrasonographique de l'intima-media carotidienne et fémorale
* Une AMM sur critère de substitution ne doit pas suffire pour valider une recommandation clinique
* Une importante baisse de cholestérolémie est sans impact sur l'athérogénèse
* Il révèle un retard indû de publication par le promoteur

« En 2008, les résultats de l'essai testant une double thérapie anti-cholestérol permettant une réduction de 50% du cholestérol chez des personnes avec hyperlipidémie familiale, ont été publiés. L'essai est totalement négatif. Je ne rentrerai pas dans les détails techniques de l'essai mais les faits sont là : 50% de réduction du cholestérol n'a eu aucun bénéfice pour les patients avec

[346] Joseph Dumit. Drugs for life, page 125
[347] Kastelein et al. NEJM 2008 ; 358 : 1431 - http://www.nejm.org/doi/full/10.1056/NEJMoa0800742
[348] Mitka M. JAMA 19.3.2014 - doi:10.1001/jama.2014.2896
[349] Lu L et al. Am Heart J 27.2.2014 - doi:10.1016/j.ahj.2014.01.014
[350] Mitka M. JAMA 2014; 311(13): 11279 - doi:10.1001/jama.2014.2896

hyperlipidémie familiale traités ! »[351]

« Cet essai Enhance avait donné lieu en 2008 à l'intervention du Sénat étatsunien pour obtenir la publication des résultats que l'industriel essayait de cacher »[352]

ERASE, THE TRIAL
l'essai dit Erase

ERECTILE DYSFUNCTION
Statinovigilance – Déchallenge positif – Rechallenge positif
trouble de l'érection
* En France, sur 40 observations signalées, 31 de 36 cas avec déchallenge furent positifs (De+, érection améliorée dans 86%). Un rechallenge fut positif dans 6 cas avec la même statine et dans 5 cas avec une autre statine. En Espagne, sur 34 observations notifiées, 84% des déchallenges furent positifs...

On ne peut exclure le rôle d'un effet nocebo et de médicaments concomitants, mais la plainte d'un trouble de l'érection mérite un arrêt et s'il y a amélioration, réintroduire une autre statine est peu prometteur car il semble y avoir EIM dit de classe[353]

ESPLANADE, THE TRIAL
European Study for Preventing by Lipid-lowering Agents and ACE-inhibition Dialysis Endpoints

EVERGREENING MANOEUVERS
Pharmacoéconomie
« The drug company Pfizer is adding yet another twist to its efforts to delay generic competitors. As The New York Times reports (12.11.2011), the company seems to have struck a deal with certain pharmacy benefit managers — the middlemen in the pharmaceutical industry — to block generic versions of Lipitor™»[354]
manoeuvres anti-copie / obstructionnistes

EVIDENCE OR BETTING : WHICH BASIS FOR TREATMENT DECISIONS?
* when the NNT is low, the treatment decision is more evidence based, whereas when the NNT is high, the treatment decision is more like betting in a lottery. Which is what happens in most industry-driven pharmaco-prevention endeavors, as evidenced by statins occupying the Top Ten sales figures in developed countries year after year
comment fonder les décisions thérapeutiques : sur des preuves ou sur le hasard ?
* des NNT expérimentaux et annualisés élevés (50, 100 et plus) assimilent la décision thérapeutique à une loterie, un casino, alors que des NNT bas (5 à 20 par exemple) procurent un fondement scientifique plus solide, d'autant plus que les NNT transposés en clinique sont immanquablement plus élevés

* En France l'assureur maladie obligatoire recommande en 2011 de statiniser les diabétiques en prévention secondaire (ceux atteint d'artériopathie clinique) dont la LDL dépasse 2,4 mmol/l (0,9 g/l) parce que le NNT expérimental serait d'environ 50 par patients-année[355] (et le nombre de sujets à traiter en clinique est possiblement de 75 à 100 patients-année)

Les taux annuels d'échecs de la statinisation se situent donc entre 98% et 99%… On est à la limite du raisonnable, médicalement et économiquement… Quant à la prévention primaire, on recommande de statiniser les gens de 40 ans et plus parce que le NNT expérimental serait d'environ 100 patients-année (et le NNT clinique probablement de 150 à 200 patients-année)…

Ici on dépasse le raisonnable. Cette recommandation d'une pharmacothérapie dont le taux annuel d'échec varie de 99% à 99,5% ne devrait pas être endossée par les assureurs et encore moins imposée par la 'rémunération sur résultats'

EVIDENCE OR BETTING ? WHICH BASIS FOR SCREENING DECISIONS ?
comment fonder les décisions de dépistage : sur des preuves ou sur le hasard ?
* la question se pose notamment au sujet du dépistage des cancers du sein et de la prostate à cause des effets pervers de ces dépistages, mais aussi au sujet d'autres dépistages comme la cholestérolémie périodique, l'ostéodensitométrie ménopausale, les tests de mémoire, les cliniques du sommeil, la glycémie de dépistage des 'pré-diabétiques', la tension de dépistage des 'pré-

[351] Michel de Lorgeril. http://michel.delorgeril.info/index.php/2009/06/21/44-statines-et-cholesterol-illusions-scientifiques-et-medicales
[352] Michel de Lorgeril. ''infarctus et l'accident vasculaire cérébral. Vergèze (FR) :Thierry Souccar ; 2011 – page 192
[353] Prescrire 2005 ; 25(265) : 672
[354] http://www.propublica.org/article/pfizers-latest-twist-on-pay-for-delay, 14.11.2011
[355] Prescrire 2013 ; 33(353) : 223

hypertendus'…

Il faut déterminer le Nombre nécessaire de dépister (Number Needed to Screen or NNS) pour prévenir une complication grave, et décider en conséquence

EXCEL, THE TRIAL *Lovastatine c. placebo – Prévention primaire*
Expanded Clinical Evaluation of Lovastatin
* Princeps publication : Bradford/*Arch Intern Med*/1991[356]

METHODOLOGY
* Participants demography : 8 245 randomized (twice more than in the 4S trial !); 6 582 to four lovastatin dosages, 1 663 to placebo ; mean age 56
* Participants health : no CHD, moderately elevated TC (average 6.7 mmol/L) ; 33% with prior MI or CHD
* Trial metrics: size > 1000 ; duration < 1 year ; very high risk of bias

* Duration : 48 weeks (0.9 year); early termination (because of catastrophic results)
* Comparison : 4 doses of lovastatin vs. placebo ; 20 mg ; 40 mg; 20 mg bid (total 40 mg) ; 80 mg
* Double blind, placebo controlled

RESULTS
* TOTAL MORTALITY : 0.501 % in treatment groups and 0.180 % in control group – The RRI is +2.78% and the ARI is +0.32% for an NNH of 313 patient-years, a paradoxical effect

« Data on all cause mortality from the first year of follow up of the ECXEL trial are not encouraging as 33 / 6582 (0.5%) patients treated with drugs died compared with only 3 / 1663 (0.18%) patients taking the placebo »[357]

CHD deaths numbered 28 / 6582 (0.425 %) under lovastatin and 3 / 1663 under placebo (0.180 %) for a RRI of +2.36% and an ARI of +2.45 %[358]

* Health related quality of life *not reported*
* Myopathy with CK elevation < 10 ULN *not reported.*
« Myopathy, defined as muscle symptoms with a creatine kinase elevation > 10 x the ULN, was found in only one patient (0.1%) receiving 40 mg once daily and 4 patients (0.2%) receiving 80 mg/d of lovastatin »[359]

* Authors' conflation : « Lovastatin, when added after an adequate trial of a prudent diet, is a highly effective (sic) and generally well-tolerated treatment for patients with moderate hypercholesterolemia » [360]
* Factual conclusion : at any dose in primary or secondary prevention, exposure to lovastatin in 4 different dosages for almost 1 year nominally increased total mortality and coronary mortality
l'essai dit Excel
« Le premier essai sur les statines fut un échec. Nul n'en parle, il était mal fait, pas assez marketing et dérangeant »[361]

EXERCISE LEVEL IN STATINIZED > 55-YEAR OLD
Statinovigilance - Myopathie
« We have observed a reduction in spontaneous physical activity levels in individuals over age 55 years treated with atorvastatin »[362]
niveau d'exercice chez les statinisés de 55 ans et plus
* pourtant l'exercice et une saine alimentation sont de meilleurs déterminants de la santé cardiaque que les pilules dites préventives, quel que soit le niveau de risque (i.e. en prévention primaire ou secondaire)
* les statines *nuisent* à l'activité physique chez les aînés sédentaires, les privant d'un comportement sanitaire qui améliore la qualité de vie reliée à la santé en agissant positivement sur plusieurs fonctions de l'organisme

[356] Bradford et al. Arch Intern Med 1991 ; 151(1) : 43
[357] Davey Smith G, Pekkanen J. BMJ 1992; 304: 431 - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1881265/pdf/bmj00060-0042.pdf
[358] http://www.trialresultscenter.org/ultimate3/ficheEssai/TrialSynopsis.asp?IdEssai=6983
[359] Bradford et al. 1991 - http://www.ncbi.nlm.nih.gov/pubmed/1985608?dopt=Abstract
[360] Bradford et al. 1991 - http://www.ncbi.nlm.nih.gov/pubmed/1985608?dopt=Abstract
[361] http://cholesterol-verite.blogspot.fr/2013/04/excel-le-premier-essai-sur-les-statines.html
[362] Parker et al. Circulation. 2013; 127: 96-103

EXERCISE VERSUS STATINISATION
Santé publique
« The maintenance of Regent's Park in London, to allow outdoor recreation and activity on an ongoing basis (it is heavily used), was far more cost-effective than putting all hyperlipidemic members of the population served by the park on statins or other lipid-lowering therapy ! »[363]
exercice contre statinisation

EXERTIONAL FATIGUE AND STATINIZATION
Statinovigilance

« Decreases in energy and increases in exertional fatigue on statins represent important findings which should be taken into account in risk-benefit determinations for statins. This is particularly true for groups for whom evidence does not support total mortality benefit on statins – such as most patients without heart disease, and women, and those over 70 or 75 even if heart disease is present[364] …

A publicly-funded randomised trial[365] from 2012 that studied the impact of statins on energy and exertional fatigue got results that could be interpreted as 20% of the men and 40% of the women experiencing a worsening in either energy or exertional fatigue[366] »

« Physically active individuals might have the best CV risk profile, but they might be more vulnerable to the skeletal muscle side-effects of statins. Sinzinger and O'Grady reported statin intolerance in elite soccer players, and the PRIMO study reported a higher incidence of statin induced myalgia in subjects performing intense sports. We have reported previously that statins magnify the increase in serum creatine kinase produced by exercise »[367]

« In 37 participants, overweight or obese at risk of the metabolic syndrome, randomized to 12 weeks of aerobic exercise – with or without a statin : cardiorespiratory fitness increased by +10% in response to exercise training alone, but was blunted by the addition of simvastatin resulting in only a +1.5% increase...

EXPERIMENTAL STATINOVIGILANCE
= detection and measurement of adverse reactions in the treated groups during controlled trials, in opposition to spontaneous reporting after marketing and phase IV pharmacoepidemiological structured observational studies
* the track record is very poor and meta-analysts should take that into account, and avoid committing the stupidity of including drug safety results of trials reporting an incidence of around 1% for muscular symptoms in the treated groups…
statinovigilance expérimentale

EXPLAINING-AWAY AN ADR
expliquer / justifier / minimiser / ignorer / balayer du revers de la main un EIM

EZETIMIBE REPORTING DELAYED
Éthique d'entreprise

« An example of the marketing consequences of selective suppression of data can be seen in the handling of the drug Zetia™ (ezetimibe). Currently (2009), this drug is earning about $4 billion a year. It was approved by the FDA in 2002, and the manufacturer (Merck/Schering-Plough) began an events-and-outcome type of trial in 2004. This trial was completed in 2006, but the data did not surface...

Eventually, the cardiologists involved in the study demanded to see the data, which the company, under pressure, presented at a professional meeting in 2008. That data showed there was no benefit in outcome with Zetia™, compared with other comparable anticholesterol drugs. In the meantime, Zetia™ had claimed 20% of the statin market and huge earnings, which more than offset the bad publicity »[368]
retard de présentation des résultats sur l'ezetimibe

[363] Warren Bell 2013
[364] Golomb BA. http://archinte.jamanetwork.com/article.aspx?articleid=1182551
[365] Golomb et al. Arch Intern Med 2012 ; 172 : 1180
[366] Gotzsche 2014 at http://www.bmj.com/content/348/bmj.g3306?tab=responses
[367] Thijs M H Eijsvogels et al. The Lancet 2013 ;381(9878) : 1621 - doi:10.1016/S0140-6736(13)61015-6
[368] http://www.jfponline.com/fileadmin/content_pdf/cpn/archive_pdf/vol37iss4/70103_main.pdf

FAMILIAL HYPERCHOLESTEROLEMIA CANADA , THE SPONSORS (CA)
* Sanofi, Amgen, Pfizer, Aegerion, Valeant, Merck. In case that is not enough, in 2016 FH Canada sends the message to other companies 'Get involved, to become a FH Canada partner, please contact us'
Hypercholestérolémie familiale Canada, les commanditaires

FAMILIAL HYPERLIPIDEMIA
Lipidologie
= monogenic disorder caracterized by high lipid levels and associated with a greatly increased risk of coronary heart disease[369]
* by contrast, non-familial hypercholesterolemia may be called polygenic hypercholesterolemia[370]
hyperlipidémie familiale
* Dans la cohorte hollandaise d'hyperlipidémie familiale publiée en 2009[371], le risque avant de commencer une statine était de 11,0 événements coronariens par 100 patients-année (risque extrême). Bien que la prévention par statine soit impérative, elle n'est pas 'secondaire' au sens strict du terme (tant qu'il n'y a pas de coronaropathie clinique, mais le risque pourrait être qualifié de 'extrême' sans abus de langage. On est ici en prévention primaire à risque extrême

FAT AND CHOLESTEROL DON'T CAUSE HEART ATTACKS : And Statins Are Not The Solution – (Livre)
KENDRICK, Malcolm , Uffe Ravnskov, Zoë Harcombe, Fred A. Kummerow, Harumi Okuyama, Niamh Hynes, Peter H. Langsjoen, Duane Graveline, David M. Diamond & Paul Rosch.
York (UK): Columbus Publishing; 2016 – 433 pages – ISBN 978 1 907797 65 5 ver 20160912

« This book is dedicated to Uffe Ravnskov and THINCS, for his seminal and propaedeutic achievements in disputing the dogma that fat and cholesterol cause coronary heart disease, and that statins are safe and cardioprotective for everyone. As will be seen, no studies support the notion that restricting fat reduces coronary morbidity or mortality. More importantly, government recommendations mandating low fat diets are likely the cause of the escalating epidemic of obesity and type 2 diabetes...

Several chapters detail the panoply of significant adverse health effects of statins that have been ignored or suppressed in reports of drug company sponsored trials. These include promoting the development of coronary atherosclerosis and congestive failure. In addition, the putative benefits of statins are clearly unrelated to lowering LDL or cholesterol, but rather anti-inflammatory and especially anticoagulant activities...

THINCS members discuss the numerous ways data are doctored to hype the benefits and minimize the dangers of statins. All of these contributions expose the fallacies of the lipid hypothesis, which was called "the greatest scientific deception of this century, perhaps of any century" by the distinguished nutritionist George Mann, former Co-Director of the Framingham Study »
Les gras et le cholestérol ne sont pas responsables des crises cardiaques et les statines ne sont pas la solution (Traduction libre)
* ce livre écrit par un collectif de critiques de l'hypothèse lipidique et de la statinisation – les sceptiques du cholestérol - est porteur des mêmes messages que ceux que Michel de Lorgeril diffuse – en français - depuis des décennies

FENOFIBRATE REVISITED
Lipidologie
« Fenofibrate at a dose equivalent to 135 mg of Trilipix™ (fenofibric acid) was not shown to reduce coronary heart disease morbidity and mortality in patients in two large randomized controlled trials of patients with type 2 diabetes mellitus »[372] according to the FDA

« Clofibrate was withdrawn, bezafibrate showed no mortality benefit, and both gemfibrozil and fenofibrate – as TriCor™ in the FIELD trial - have increased mortality in trials »[373]
le fénofibrate revisité
* Le fénofibrate – qui abaisse les triglycérides - n'a pas pu ralentir l'apparition d'infarctus ni la mortalité cardiaque chez les diabétiques de l'âge mûr[374], un argument contre l'hypothèse lipidique et un autre contre la réduction pharmacologique du cholestérol des diabétiques

FIELD, THE TRIAL *Fénofibrate 200 mg vs. placebo – Diabétiques*

[369] http://www.bmj.com/content/337/bmj.a2423
[370] Coined by JM Therrien, 2013
[371] Versmissen et coll. BMJ 2009;338 :223
[372] http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm279185.htm - November 9, 2011
[373] Eddie Vos, 2012, communication
[374] Keech. Lancet 2005;366 :1849

Fenofibrate Intervention and Event Lowering in Diabetes[375]

* Princeps publication : Keech/*Lancet*/2005[376]
* Participants demography: 9 795 randomized
* Participants health : 100% diabetics T2
* Funding : private

* Followup : 5 years
* Positive compliance (active group adherence) : 92%
* Negative compliance (control group adherence) : 83%

RESULTS
Benefits as relative risks of surrogate endpoints:
* relative risk reduction of cholesterol of -11%
* relative risk reduction of triglycerides of -29%

Relative risks of clinical outcomes :
* relative risk reduction of primary endpoint = -11%, NS (256 events under fenofibrate vs. 288 under placebo)

* RR increase of total mortality = +11%, NS, a paradoxical effect (356 in treatment arm, 323 in control arm)
* Effect on CV morbidity : NS reduction
* Effect on CHD deaths : (110 in treatment arm, 93 in control arm)

* Effect on CV mortality : NS increase (140 in treatment, 127 in placebo); sudden cardiac death is not reported separately
* Effect on coronary revascularisation : statistical reduction (390 events under fenofibrate vs. 364 under placebo)
* Effect on nonfatal MI : 158 under fenofibrate vs. 207 under placebo

Absolute risk reduction converted to NNT :
* Annual NNT for CV events = 250 patient-years

HARMS
* Health related quality of life *not reported*
* Results as *absolute risks increases* converted to NNH:

* annual NNH for pancreatitis = 333 patient-years, statistically significant
* annual NNH for pulmonary embolism = 333 patient-years, NS
* annual NNH for deep vein thromboses = 250 patient-years, statistically significant
* annual composite NNH for serious ADRs = 100 patient-years, 2.5 times lower than NNT of 250 for CV events

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Field

FLAWED GUIDELINES FOR STATINIZATION (USA) *Pharma-co-dépendance à son meilleur*
« In November 2013, the nation's leading heart organizations (AHC and ACC) released a sweeping new set of guidelines for lowering cholesterol, along with an online calculator meant to help doctors assess risks and treatment options. But, in a major embarrassment to the health groups, the calculator appears to greatly overestimate risk, so much so that it could mistakenly suggest that millions more people are candidates for statin drugs »[377]

« Dr. Neil J. Stone, chair of the lipid expert panel that wrote them is coincidentally a physician also heavily supported by drug companies »[378] « Chairman Stone acknowledged to the BMJ that before being empanelled he had financial ties to Abbott, AstraZeneca, Merck, Pfizer, Sanofi-Aventis, and Schering-Plough, and he had served as a consultant to Abbott, AstraZeneca,

[375] Keech et al. Lancet 2005 ; 366 : 849 – Scott et al. Diabetes Care 2009; 32: 493
[376] Keech et al. Lancet 2005; 366: 1849 and erratum Lancet 2006 ; 368: 1415
[377] Gina Kolata 2013 at http://www.nytimes.com/2013/11/18/health/risk-calculator-for-cholesterol-appears-flawed.html?smid=tw-share&_r=1&
[378] http://ethicalnag.org/2013/11/19/statins-guidelines/

Merck, Pfizer, Reliant, Schering-Plough, and Sonaste. All 6 corporations to which Stone had financial ties make drugs to treat hyperlipidemia »[379]

directives fautives sur la statinisation

* les 'directives de novembre 2013' méritent d'être ajoutées au dossier noir de la corruption des institutions médicales
* ces fautes ont malheureusement été répétées par le NICE au R-U en 2014

FLAWED META-ANALYSIS IN PRIMARY PREVENTION *Synthèse méthodique – Prévention primaire*

TONELLI et al. *CMAJ* 2011[380]

« A *flawed* pro-industry jumbo-meta-analysis »[381] - « Tonelli et al's recent systematic review of statins for primary preventionmay *mislead* readers in a number of ways and each of these represents a serious flaw :

1) the review implies that the meta-analytic results are relevant to low-risk individuals,
2) the abstract does not present the benefits as absolute risk reductions (absolute risk reduction),
3) the interpretation and conclusions in the abstract do not reflect the authors' assessment of the risk of bias,

4) it includes a non-randomized trial in a pre-planned analysis of 'only' randomized trials and
5) the abstract and conclusions ignore the total serious adverse event (SAE) outcome data…

The most important finding in Tonelli et al's meta-analysis is that statins *do not* reduce total *serious adverse events* and thus do not provide a net health benefit in primary prevention populations. Because the authors failed to appreciate the importance of serious adverse events as an outcome, they draw the opposite conclusion that statins are beneficial and their use should be promoted in this population »[382]

méta-analyse fautive / erronée en prévention primaire

FLAWED RECOMMENDATIONS

« The statins correct plasma lipid levels optimally, yet the real magnitude of their benefits is marginal and certainly not better than attained with agents that do not affect plasma lipid levels. It is suggested that some of our recommendations and actions relating to plasma cholesterol levels and to atherosclerosis are based on concepts that are fundamentally flawed and need to be revised »[383]

recommandations fautives / défecteuses

FOURRIER, THE TRIAL

* Here is Uffe Ravnskov take in March 2017 on this infamous trial :

« *Is the drug industry honest?* You have probably heard or read about the recent trial named FOURIER where the drug company Amgen has tested a new cholesterol-lowering drug, evolocumab or Repatha (a so-called PCSK9-inhibitor and monoclonal antibody) on almost 30,000 patients with heart disease...

Half of them got the drug injected twice a month; the other half was injected with an innocent liquid (probably saline) and both groups received statin treatment as well. The "bad" LDL-C was lowered by 59%; from 92 mg/dl (2.4 mmol/l) to 30 mg/dl (0.78 mmol/l). Very few cholesterol-lowering trials have succeeded with that before. But what about the outcome? If high LDL-C the bad guy - haven´t such low values eradicated all types of CV disease?

According to the trial report published in NEJM, evolocumab was able to lower the number of various types of heart attacks by 1.5 %. As the trial went on for 26 months, it means that to prevent 1 heart attack per year it is necessary to treat 140 patients. As the costs for 1 year´s treatment is about $14,500 it means that the costs for preventing 1 heart attack per year is more than $2M

The trial was originally planned to go on for 4 years, but as the number of cardiac events was statistically lower in the treatment group already after 26 months, the authors decided to stop the trial...

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[379] Jenne Lenzer 2013. BMJ 2013; 347: f6989 - http://www.bmj.com/content/347/bmj.f6989
[380] Tonelli et al. CMAJ 2011 ; 183(6) - DOI:10.1503/cmaj.101280 – full text at http://www.cmaj.ca/content/183/16/E1189.full
[381] Harriet Rosenberg
[382] Aaron M. Tejani, Vijaya Musini, Ken Bassett, Tom Perry, Colin Dormuth, James M. Wright for Therapeutics Initiative at http://www.ecmaj.ca/content/183/16/E1189.full/reply#cmaj_el_680382
[383] Krut LH. American Journal of Cardiology 1998, 81(8): 1045 - DOI: 10.1016/S0002-9149(98)00084-8

But the number of deaths, both from heart disease and from other causes, had *increased*! Not with statistically significance, but it might have become significant if the trial had continued. A relevant question is therefore: Did they stop the trial because the total number of events had become significantly lower in the treatment group, or because the number of deaths was increasing?

How do they explain that 444 died in the treatment group, but only 426 among the untreated (+4%) ? If the "bad" high LDL-C was the cause of atherosclerosis and heart disease, then we should expect that a 59% lowering of this "poisonous" molecule should *lower* mortality, not increae it..

The reason is of course that a high level of LDL-C is not poisonous; it is beneficial, as we documented in a recent paper published in BMJ Open You can read more about our findings in my June 2016 Newsletter. One of the most interesting findings was that elderly people with the highest LDL-C levels lived longer than elderly people on statin treatment...

A reasonable question is therefore: Why should we lower the bad cholesterol if those with the highest values live the longest? But our findings haven´t made any impression on the directors of the FOURIER trial. Their conclusion is that "patients with atherosclerotic cardiovascular disease benefit from lowering of LDL-C levels below current targets"...

There are also reasons for questioning the beneficial results in the FOURIER trial. According to the paper´s disclosure form three of the main authors (Narimon Honarpour, Thomas Liu and Scott Wasserman) are employees at Amgen, the producer of the drug. All of the others have been paid by Amgen and by other drug companies as well; five of them, including the main author, by more than ten different companies...

And in a previous paper you can read that Charles H. Hennekens, head of the trial´s "Independent Data Monitoring Committee" has served on the speaker's bureaus for AstraZeneca concerning lipids and heart failure, and Bristol-Myers Squibb, Reliant, and Pfizer, concerning lipids; that he has received royalties for authorship or editorship of 3 textbooks; and that he has received royalties as co-inventor on patents concerning inflammatory markers and cardiovascular disease...

Our BMJ Open-paper did not make any impression either on other "authorities". Here is what Rory Collins, head of the Cholesterol Treatment Trialists' (CTT) Collaboration in Oxford, and the main author of the paper we criticized said to the science journalist Michael Brooks in the 11 February 2017 issue of New Scientist:

"Those who deny a link (between cholesterol and CV disease) are talking complete nonsense. The few people who have raised the question are a bit like those individuals who think homoeopathy works or think Earth is flat." And along the same line Liam Smeeth at the London School of Hygiene and Tropical Medicine agrees: "I'm all for proper debate, providing the people I'm debating with are not denying science."

But hitherto none of them have presented any study showing the opposite of our findings. Who are denying science? »

l'essai dit Fourrier

* essai interrompu sans bénéfice cliniquement signifiant, augmentation absolue de la mortalité toutes causes confondues de 4%, conflits d'intérêt manifestes des signataires de l'article, conclusions de l'article contraires aux données présentées, aucune discussion des coûts exorbitants, insultes à l'égard des commentaires critiques du Pr Ravnskov, tout y est pour qualifier cet essai d'infâme

FRAGILITY INDEX OF P VALUES

Statistiques – Analyse explicative – Validité interne

* The fragility index proposed by Walsh et al.[384] complements the P value by looking at the absolute number of primary endpoint events measured in a trial irrespective of the number of participating patients (sample size) ; when there are not enough events, the confidence expressed by the p value is weakened. The statistically significant results of many RCTs hinge on small numbers of events.

« The Fragility Index complements the P-value and helps identify less robust results. Yusuf et al.[385] suggested trials of at least 650 events were required to be sufficiently confident that true effects were identified in cardiovascular trials, and this was reinforced by simulation data by Thorlund et coll.[386] »

index de fragilité

* Combien d'essais de statines ont comporté au moins 650 événements indésirables parmi les critères primaires d'évaluation,

[384] J Clin Epidemiol 2014 ; 67 : 622-628

[385] Prog Cardiovasc Dis 1985; 27(5): 335e71.

[386] Thorlund et al. PLoS One 2011; 6(10): e25491

parmi les rares qui ont rapporté des réductions significatives de la mortalité générale ou de la mortalité CV ?

FRAMINGHAM, THE SURVEY

l'enquête dite de Framingham

« Les premiers résultats tombent au bout de 6 ans en 1964, surprenants et décevants. Il n'y a qu'un lien très faible entre cholestérol et maladies artérielles et ce lien n'existe que chez les hommes de < 50 ans. Cette constatation, en contradiction avec le dogme, sera effacée de la publication et sera selon M. de Lorgeril, exhumée des années après par le journaliste Gary Taubes »[387]

GERMAN DIABETES AND DIALYSIS STUDY; 4D, THE TRIAL *Diabétiques sous dialyse – Atorvastatine 20 mg c. placebo*

Die Deutsche Dialyse Studie (4D)[388]

* Princeps publication : Wanner/*NEJM*/2005[389]

METHODOLOGY

* Median duration (50th percentile) : 4 years
* Comparison : atorvastatin 20 mg vs. placebo

* Risks of bias : low « This trial meets major quality criteria : death's circumstances are very well described, particularly frequency of sudden deaths, which is exceptional when one looks at the statin trials of the past 10 years. No interim analyses, no premature discontinuation »[390]

* Total participants : 1255
* Participants health : 100% diabetics, in chronic renal failure, on maintenance hemodialysis
* Primary endpoint : CV death, nonfatal MI and stroke

RESULTS

Harms

* Health related quality of life *not reported*

Benefits

* TOTAL MORTALITY : relative risk reduction = -7%, NS
* Sudden deaths : 83 under placebo, 77 in statin group
* Primary endpoint : relative risk reduction = -8%, NS
* Fatal stroke : RRI = +103% « Last but not least, there were significantly more lethal strokes, twice as many, in the statin group »[391]

« Atorvastatin had no effect on the composite primary end point (CV death, nonfatal myocardial infarction and stroke) in patients with diabetes receiving hemodialysis… Fatal stroke was increased relatively by 103% (HR = 2.03)… Total mortality was lowered by -7% (NS, p= 0.33) »[392]

Factual conclusions :

* statinisation does not prevent macrovascular complications of diabetics in chronic renal failure under hemodialysis and does not prolong their lives

« The conclusions of the authors were quite clear : the statin or the cholesterol reduction did not protect these diabetic patients, the 4D trial is therefore negative »[393]

« The 4D study randomised 1255 people with type 2 diabetes on dialysis to either atorvastatin 20 mg/ day or placebo for approximately 4 years and also demonstrated no benefit in either total mortality or combined clinical end points »[394]

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[387] Even, page 143
[388] Wanner et al. NEJM 2005 ; 353 : 238 - http://www.ncbi.nlm.nih.gov/pubmed/16034009
[389] WANNER. NEJM 2005;353 :238 - http://content.nejm.org/cgi/content/short/353/3/238?query=TOC, consulté 21 juillet 2005
[390] de Lorgeril 2014, op. cit.
[391] de Lorgeril 2014, op. cit.
[392] Wanner et al. Op. cit.
[393] de Lorgeril 2014, op. cit.
[394] DuBroff RJ. Evid Based Med 2015 ; 20(4) : 1 – DOI: 10.1136/ebmed-2015-110236

* Belated conflation : a secondary publication[395] reporting results on post-hoc subgroups with LDL-C > 3.76 mM (145 mg/dl) claims that « atorvastatin significantly reduces the risk of fatal and nonfatal cardiac events and death from any cause », but they are not at the 0.01 level and, even if significant at the 0.001 level, would only have an exploratory value and would remain clinically irrevelant

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : Yes, we have access to data. Have shared data with CTT and two other bodies; in principle willing to share

l'essai dit 4D

* Effectifs : 1255 diabétiques hémodialysés
* Durée : médiane 4 ans
* Comparaison : atorvastatine 20 mg c. placebo

Réduction des lipides

* relative risk reduction de -42% du LDL-C

Résultats négatifs cliniquement :

* réduction relative de -8%, NS pour le critère d'évaluation primaire combiné (mortalité CV, IDM non fatal, AVC)
* réduction relative de -7%, NS pour la mortalité totale
* réduction relative de -15%, NS pour le taux d'infarctus du myocarde (IDM)
* Augmentation de +103% du risque relatif (RR = 2.03) pour l'AVC fatal

* Pour rappel, l'essai dit Aurora, comparant la rosuvastatine 10 mg à un placebo chez des insuffisants rénaux en phase terminale, fut négatif pour le critère primaire d'évaluation combiné (réduction relative -4%, NS) et la mortalité totale (réduction relative de -4%, NS) – « La petite étude 4D souhaitant juger de la protection supposée des statines à l'égard d'une population fragile de diabétiques type 2 dialysés fut absolument négative et les auteurs n'en font nul mystère : L'atorvastatine n'a eu *aucun effet* statistiquement significatif sur le critère d'évaluation principal composite du décès d'origine cardiovasculaire, de l'infarctus du myocarde non mortel et de l'AVC chez les patients diabétiques sous hémodialyse[396] ».

GISSI-HF, THE TRIAL

Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico - Heart Failure
Prévention chez insuffisants cardiaques – Rosuvastasine 10 mg c. placebo

* Princeps publication : Tavazzi/Lancet/2008[397]
* Participants' health : 50% with CHD ; 100 % in cardiac failure ; at high risk of CV death

« 657 (29%) patients died from any cause in the rosuvastatin group and 644 (28%) in the placebo group (adjusted HR = 1.00). 1305 (57%) patients in the rosuvastatin group and 1283 (56%) in the placebo group died or were admitted to hospital for cardiovascular reasons (adjusted HR 1.01)… Rosuvastatin 10 mg daily did not affect clinical outcomes in patients with chronic heart failure of any cause, in whom the drug was safe »[398]

« 33% of the patients were survivors of a previous infarction… A total lack of effect of rosuvastatin regarding the ischemic events expected to be prevented was observed… Strikingly, there was no protection in GISSI-HF testing of rosuvastatin »[399]

* New onset diabetes not reported in princeps publication ; obtained later by meta-analyst Sattar, RRI = +10%, NS
* Health related quality of life *not reported*

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE

l'essai dit Gissi-HF

* Aucun bénéfice en terme de mortalité toute cause avec la rosuvastatine (Crestor™). Il en fut fut de même pour *Jupiter, Prosper,*

[395] März et al. Clin J Am Soc Nephrol 2011; 6: 1316 - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109927/
[396] aimsib.org, 22 Avril 2019
[397] Tavazzi et al. Lancet 2008; 372(9645): 1231 - DOI: 10.1016/S0140-6736(08)61240-4
[398] Gissi-HF. Lancet 2008; 372: 1231 - DOI:10.1016/S0140- 6736(08)61240-4
[399] Michel de Lorgeril et al. BMC Medicine 2013 ; 11 : 5

Corona et *Aurora*

GISSI-PREVENZIONE, THE TRIAL ; GISSI-P *Prévention secondaire – Pravastatine 20 mg c. soins usuels – Non contrôlé par double-insu et placebo – Échec clinique*
* Princeps publication : GISSI/*Ital Heart J*/2000[400]

METHODOLOGY
* Duration : median (50th percentile) of 1.9 year (23 months), stopped prematurely late 1996 for futility after publication of CARE
* Design : open label, randomized, no placebo
* Participants demography : 4271 randomized; 13.7% women ; 86.3% men ; mean age 59.3 years

* Participants health : recent (< 6 months) acute MI; 13.6 % diabetics ; 36.5% hypertensive ; TC > 5.2 mM (200 mg/dL), mean 5.9 mmol/L (229 mg/dL)
* Comparison : low dose pravastatin 20 mg vs. usual care
* Control group : usual care
* Composite primary endpoint : [total mortality + non fatal stroke + non fatal MI]

* Positive compliance (active group adherence): 86.2%, since 13.8% in treatment group (statin) stopped taking pravastatin
* Negative compliance (control group adherence) : 81.2%, since 18.8% in control group (usual care) started taking a cholesterol lowering treatment

* New onset diabetes : not reported in princeps publication ; data obtained later by meta-analyst Sattar
* Serious adverse events : not reported
* Health related quality of life *not reported*

RESULTS
a) TOTAL MORTALITY relative risk reduction = -16%, NS ; annual absolute risk reduction of -0.38 %, annual NNT = 263 patient-years – 72 deaths /2138 treated patients and 88 / 2133 under usual care
b) composite primary endpoint relative risk reduction = -10%, NS – annual NNT = 266 patient-years

c) CHD mortality relative risk reduction = -40%, NS either by per-protocole analysis (internal validity) or by intention to treat analysis (external validity)
d) stroke RRI of + 5%, NS ; fatal stroke relative risk reduction = 0%

* Summary: weak methodology ; clinically negative results

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Gissi-Prevenzione

GLYCATED HEMOGLOBIN ; Hb1ac
Diabète - Statinovigilance
hémoglobine glyquée ; Hb1ac
* sa mesure est un meilleur critère que la glycémie à jeun pour évaluer l'effet diabétogène d'une statine car il témoigne de l'équilibre glycémique des 2-3 derniers mois ; et n'exige pas d'être à jeun

GOOD CALORIES, BAD CALORIES : Fats, Carbs And The Controversial Science Of Diet And Health – (Livre) *Hypothèse lipidique*
Gary TAUBES, 2008

« For decades we have been taught that fat is bad for us, carbohydrates better, and that the key to a healthy weight is eating less and exercising more. Yet despite this advice, we have seen unprecedented epidemics of obesity and diabetes...

Taubes argues that the problem lies in refined carbohydrates, like white flour, easily digested starches, and sugars, and that the key to good health is the kind of calories we take in, not the number. In this groundbreaking book, award-winning science writer Gary Taubes shows us that almost everything we believe about the nature of a healthy diet is wrong »

[400] GISSI. Ital Heart J 2000 ; 1 : 810 – abstract on http://www.ncbi.nlm.nih.gov/pubmed/11302109

Bonnes calories, mauvaises calories : Les graisses, les sucres et les liens controversés entre l'alimentation et la santé
(Traduction libre du titre du livre)

* Les graisses alimentaires, saturées ou non, ne sont pas la cause des maladies cardiaques
* L'apparente 'épidémie' de coronaropathies aux É-U après la 2e Guerre mondiale résultait de meilleures techniques diagnostiques, du vieillissement de la population, et non d'une modification alimentaire ni du cholestérol ; les américains ont toujours été de grands mangeurs de viande et celle-ci ne peut expliquer cette 'épidémie' décelée au milieu du 20e siècle

* C'est après la 2e Guerre mondiale que le cholestérol a commencé à être blâmé, pour le motif simpliste que les plaques athéromateuses en contiennent beaucoup. Sans toutefois prouver la causalité. Surtout que plusieurs coronariens ont un cholestérol normal ou bas et plusieurs hypercholestérolémiques ne deviennent pas coronariens.

* C'est Ancel Keys qui fut le grand promoteur de l'hypothèse lipidique : les graisses alimentaires augmentent le cholestérol plasmatique et ceci cause la coronaropathie. Mais les faits ne confortaient pas l'hypothèse, y compris ceux révélés par l'enquête dite de Framingham, que les sponsors pourtant gouvernementaux, les NIH, refusèrent de divulguer

* L'étude épidémiologique *Seven Countries* de Keys, pour relier l'alimentation en gras et la maladie CV, fut proclamée être en faveur des cholestérolistes, mais elle était fondamentalement défectueuse car l'auteur sélectionna 7 pays conformes à son hypothèse sans mentionner l'absence de relation dans 14 autres pays étudiés

* De nombreux essais ne purent démontrer qu'un régime faible en graisses, surtout saturées, prévient tangiblement la coronaropathie ; certains ne furent pas publiés, comme celui de Ivan Frantz au Minnesota

* L'essai MRFIT par Jeremie Stamler fut de grande ampleur : le groupe expérimental devait cesser de fumer, prendre des anti-hyeprtenseurs au besoin et manger une diète faible en graisses et en cholestérol. Résultat : ce groupe connut un plus haut taux de mortalité totale ! Conflation oblige, on ne cessa de subventionner les recherches sur le cholestérol

* Le LRC CPPT par Rifkind, un essai clinique de réducteurs du cholestérol sur la maladie cardiaque, donna des résultats positifs, mais trop minimes pour justifier une directive clinique ; hélas la conflation fut évidente dans leur présentation
* L'hypothèse lipidique a été un mélimélo de mauvaise science et de faits contradictoires (qu'on préférait taire). On a imposé le concept que la *totalité des preuves* doit s'assimiler à l'*hypothèse de recherche*

GREACE, THE TRIAL *Prévention secondaire – Posologie ajustée – Atorvastatin c. soins usuels – Non contrôlé par double insu et placebo*
Greek Atorvastatin and Coronary-heart-disease Evaluation Study[401]
* Princeps publication : Athyros/*Curr Med Res Opin*/ 2002 - Has not been published in a *high impact* journal ; has not been *confirmed*

METHODOLOGY
* Participants demography: 1600 patients ; 22 % women ; 59 years average, 50% > 65 year
* Participants health : 100% with CHD history, 81% with prior MI (recent MI or > 70% stenosis of at least 1 coronary artery); 43 % hypertensive ; 19.5% diabetics ; 0% smokers ; TC average of 6.6 mM ; LDL-Cholesterol > 2.6 mM, average 4.6 mM (179 mg/dl)

* Comparison : atorvastatin titrated 10 mg to 80 mg vs usual care ; dose adjusted to target : LDL < 2.6 mM
* Duration : 3 years (36 months)
* Design: randomized ; no blinding of patients or caregivers ; only assessors were blinded ; no placebo

* Primary composite endpoint : [total mortality + nonfatal MI + stroke + unstable angina + angioplasty + coronary bypass + CHF]. Invalidated by mixing :
a) differing frequencies of 7 outcomes and differing responses to treatment,
b) fatal and nonfatal events of uneven seriousness and values to the patient,
c) hard and softer subjective endpoints such as deciding to revascularize or adjucating unstable angina

* Positive compliance (active group adherence) : 98.8%
* Negative compliance (control group adherence) : 74%

RESULTS

[401] Athyros et al. Curr Med Res Opin 2002 ; 18(4): 220 and 499

* Health related quality of life *not reported*
* Total serious events : not reported

Lipid reduction :
a) relative risk reduction of -36 % for TC
b) relative risk reduction of -46% for LDL-C

* Results are unusual by their amplitude and raise doubts about their credibility:

a) relative risk reduction of -42 % for TOTAL MORTALITY, NS at the 0.005 level ; absolute risk reduction = 2.1% and NNT = 48 for 3 years [annual NNT = 144 patient-years]. Life extension would be 2.5 days per year of statinization in trial conditions if the data were internally valid, if the design had included a placebo under blinded conditions, etc. Trials conducted before 2004 are known for their numerous biases
b) relative risk reduction of -47 % for CHD mortality

c) relative risk reduction of -56 % for any CHD events ; the annual NNT of 48 patient-years under experimental conditions is an outlier that has never been confirmed in any other statin trials, raising doubts about its validity
d) relative risk reduction of -54% for fatal CHD and non fatal MI

e) relative risk reduction of -47% for fatal and non fatal stroke, NS
f) relative risk reduction of -53% for total MI or stroke (composite) - absolute risk reduction = 7.0% and NNT of 14 for 3 years or annual NNT = 42 patient-years

* Comments : This study should not be included in meta-analyses of trials controlled with double-blinding and placebo. It is strange that the NICE 2014 guidelines document considers GREACE as placebo controlled
l'essai dit Greace
* Conclusion factuelle : L'absence de double-insu et de placebo affaiblit considérablement la validité interne – Ces résultats n'ont pas été confirmés ni publiés dans des revues à fort impact

GUIDELINE PANELS MEMBERSHIP : REFORM NEEDED
Recommandations - Directives
« The debate over the 2013 ACC/ AHA guidelines offers an opportunity to rethink the membership of these influential panels. As articulated by the American Cancer Society and as recommended by the Institute of Medicine, the American Cancer Society will separate the processes of specialty input and evidence synthesis from writing of the actual guideline...

Perhaps these panels should include knowledgeable patients who are well versed in understanding the scientific background (eg, predictive models), many methodologists (ideally working in different applied fields), and excellent clinicians/scientists from other specialties whose practice volume is not at stake. Content experts [cardiologists] could serve as nonvoting members or advisors to such panels »[402]
une réforme s'impose dans la composition des panels de directives / des comités de recommandations

GUIDELINES : SO-CALLED NATIONAL
Recommandations
« In 2004 the *National Cholesterol Education Program* (NCEP) updated its guidelines… It was subsequently disclosed that most of the committee members had extensive financial connections to the manufacturers of statins, which stood to gain from increased use of these drugs »
directives cliniques soi-disant nationales
* l'adjectif *national* implique trompeusement une reconnaissance gouvernementale objective et indépendante

HALF OF OVER 75 YEARS IN USA ARE TAKING CHOLESTEROL LOWERING DRUGS, REPORT SAYS – (Bref commentaire) *Gériatrie – Revue d'utilisation – Indication injustifiée*
Jeanne LENZER. *BMJ* 2014; 349: g7820 - doi: http://dx.doi.org/10.1136/bmj.g7820

* Selon le Centre étatsunien de veille sanitaire, plus de la moitié des plus de 75 ans sont sous réducteurs du cholestérol [403]; c'est une indication injustifiée, couteuse, sans bénéfices et dont les effets indésirables sont plus nuisibles dans cette population

[402] Ioannidis JPA. - doi:10.1001/jama.2013.284657 - http://www.cardiovalens.com/featuredarticle/featured-article-for-cv-dec07-v2.pdf
[403] Gu Q et al. NCHS data brief, No 177. National Center for Health Statistics. 2014

HARMS OF STATINS, A SYSTEMATIC REVIEW *Statinovigilance – Fortes doses*
* In April-May 2014 the ISDB-member Therapeutics Letter, produced by Vancouver-based Therapeutics Initiative, reviewed proven and associated harms contained in meta-analyses, single randomized clinical trials and population observational studies.

« From this analysis it is clear that the magnitude of statin harms is greater with high doses than with low doses and that the added benefits of high doses is unlikely to exceed the magnitude of the harms in most if not all clinical settings »[404]

* From the TI data, the 10-year absolute risk increases (ARI) and corresponding Numbers Needed to Harm (NNH) over 10 years of treatment, were calculated for comparison of high over low doses, or statin versus placebo, assuming constancy of effect size over those years :

1. Based on meta-analyses of RCTs :

a) Withdrawal due to ADRs, high versus low dose : ARI is 6% over 10 years and NNH is 17 patients (Silva et al. 2007)
b) Hepatic enzyme elevation, high vs. low dose : ARI is 3.5% and NNH is 29 patients (Silva et al. 2007)
c) New diabetes, high vs. low dose: ARI is 2.5% and NNH is 40 patients (Preiss et al.)
d) New diabetes, statin vs. placebo : ARI is 1% and NNH is 100 patients (et al.)

e) Myopathy (CK > 10x), high vs. low dose : ARI is 0.07% and NNH is 500 patients (Silva et al. 2007). Of course things are different in the real world since muscle problems of all sorts are reported in up to 17.4% of patients in clinical settings. But a meta-analysis of trials underpowered for detecting all forms of myopathy simply expands misleading results. Muscle lesions can occur without symptoms and pain and weakness can occur without a 10-fold CK elevation

2. Based on single RCTs

a) New diabetes, high dose vs. placebo : ARI is 3.2% and NNH is 32 patients (Ridker et al. 2008)
b) Hemorrhagic stroke, high dose vs. placebo : ARI is 1.8% and NNH is 55 patients (Amarenco et al. 2006)

3. Based on population observational studies, providing a lower level of proof :

a) Any musculosquetelal conditions : ARI is 4.8 % and NNH is 21 patients (Mansi et al. 2013)
b) Cataracts : any dose against placebo : ARI is 4 % and NNH is 25 patients (Hippisley-Cox & Coupland. 2010)
c) Moderate/serious myopathy : ARI is 1.4 % and NNH is 75 patients (Hippisley-Cox & Coupland. 2010)
d) Acute renal failure : ARI is **+0.4 %** and NNH is 250 patients (Hippisley-Cox & Coupland. 2010)

4. Based on case series and reports :

« The growing list of harms now includes peripheral neuropathy, sexual dysfunction, gynecomastia, irritability, aggression, behaviour change, memory loss, depression, psychosis, interstitial lung disease, heart failure, Parkinson syndrome, lupus-like syndrome, dermatomyositis, other auto-immune syndromes, pancreatitis and others (Golomb and Evans, 2009) » as well as BMI, caloric and fat intake, and sedentarism (from exertional fatigue), risk factors for CV and many other diseases
méfaits des statines, une synthèse méthodique
* Ces chiffres de statinovigilance ne sont pas exhaustifs. On sait que la statinisation fait grossir, elle augmente l'IMC, l'ingestion calorique et graisseuse. Elle sédentarise, ce qui nuit au bénéfice CV de l'exercice, et contribue indirectement à faire grossir

HDL CHOLESTEROL AND ATHEROMATOSIS
Hypothèse lipidique contredite – Échecs cliniques – Interruptions prématurées - Aggravation

« Nearly two decades ago, the discovery that persons in Japan had extremely high levels of HDL cholesterol because of a genetic deficiency involving the cholesteryl ester transfer protein (CETP) led to the concept that pharmacologic inhibition of CETP could raise HDL cholesterol levels »[405]

* The hypothesis that raising HDL cholesterol level will slow down atherogenesis and reduce thrombogenesis is unsupported by the negative AIM-HIGH (niacin), dal-OUTCOME (dalcetrapib) and ILLUMINATE (torcetrapib) trials, the two first ones interrupted for futility and the last one stopped for aggravation

[404] Jim Wright et al. Therapeutics Letter 89, April/May 2014 - http://www.ti.ubc.ca/letter89
[405] Daniel Rader. N Engl J Med 2007; 357:2180 - DOI: 10.1056/NEJMe0707210

See also AIM-HIGH, dal-OUTCOME and ILLUMINATE

HDL cholestérol et athéromatose

« L'hypothèse d'une protection contre l'athérome par les HDL, basée sur des données épidémiologiques contestables et quelques données animales, est maintenant réfutée sans ambiguïté »[406]

HDL-C AND CORONARY HEART DISEASE *Épidémiologie – Hypothèse lipidique*

« In 5 populations with 6859 men and women, mean levels of HDL cholesterol were lower in persons with CHD than in those without the disease. The average difference was small – typically 3 to 4 mg/dl (0.08 to 0.10 mM) »[407]…

This was considered a 'landmark' paper in 1997 implying that the pharmacological or dietary elevation of HDL would prevent CHD. Unfortunately the hypothesis was not evidence based, as numerous trials have subsequently shown

« High density lipoprotein cholesterol was selected [2013 ACC/AHA] even though it is clearly noncausally related to coronary artery disease »[408] declares one of the most respected and influential methodologist in 2014

HDL-cholestérol et maladie coronarienne

« A ce jour, la baisse des TG ou l'augmentation du HDL-C par des moyens pharmacologiques n'a pas été associée à une prévention d'évènements CV et encore moins à une diminution de la mortalité totale »[409]

HEALTHY ADHERER EFFECT

Facteur de confusion – Essais - Statines

« Bias in studies of preventive medications can occur when healthier patients are more likely to initiate and adhere to therapy than less healthy patients. We sought evidence of this bias by examining associations between statin exposure and various outcomes that should not be causally affected by statin exposure, such as workplace and motor vehicle accidents. The results showed that more adherent patients were less likely to have accidents than less adherent patients…

More adherent patients had a greater likelihood of using screening services and a lower likelihood of developing other diseases likely to be unrelated to a biological affect of a statin. Our study contributes compelling evidence that patients who adhere to statins are systematically more health seeking than comparable patients who do not remain adherent. Caution is warranted when interpreting analyses that attribute surprising protective effects to preventive medications »[410]

effet de l'utilisateur sain

HEALTHY MEN IN PRIMARY PREVENTION

« Healthy Men Should Not Take Statins … Statin therapy whould not be recommended for men with elevated cholesterol who are otherwise healthy »[411]

hommes bien-portants en prévention primaire

* et encore moins les femmes

HEALTHY USER EFFECT AND STATIN COMPLIANCE *Épidémiologie*

« Early statin discontinuation may be a marker of a 'healthy adherer effect'; a confounding behavioural char- acteristic of the individual impacting both statin adherence, but also on risk of MI and death by CV disease beyond the effect of early statin discontinuation alone, as illustrated by a tendency towards increased risk of death by traffic-related causes[412] »[413]

effet de l'utilisateur sain et observance statinique

HEART ATTACK

= acute myocardial infarction ; AMI

crise cardiaque *langage courant*

= infarctus (aigu) du myocarde ; IDM

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[406] DJ Rader & AR Tall. Nat Med 2012 ; 18 : 1344 - doi:10.1038/nm.2937 - cité par Even, page 86

[407] Castelli et al. Circulation 1977 ; 55(5) : 767 - doi: 10.1161/01.CIR.55.5.767

[408] Ioannidis JPA. JAMA 2014 ; 311(5): 463 - doi: 10.1001/jama.2013.284657

[409] BIP 2014 no 2 page 5

[410] Dormuth et al. Circulation 2009; 119(15): 2051 - doi: 10.1161/CIRCULATIONAHA.108.824151

[411] Redberg & Katz. JAMA 2012; 307(14): 1491 - doi:10.1001/jama.2012.423

[412] Dormuth et al. Circulation 2009;119:2051

[413] http://eurheartj.oxfordjournals.org/content/ehj/37/11/908.full.pdf?etoc=

HEART FAILURE : A Critical Inquiry into American Medicine and the Revolution in Heart Care - (Livre) *Hypothèse lipidique*
Thomas J MOORE. New York : Random House ; 1989 – 308 pages
Voir aussi THE CHOLESTEROL MYTH

« Moore's book has all the intrigue of a good thriller: a conspiracy theory, dangerous drugs, forced behavior modification and the threat of death. There's no spy in his work, a nonfictional investigation of heart care. But its lengthy section on a national obsession—cholesterol—has become more controversial than any international whodunit...

Armed with 4 years of research, he challenges conventional medical thinking by claiming that reducing cholesterol levels is difficult with diet, risky with drugs—and may not even do much to lower the risk of a heart attack… The anticholesterol movement, he further charges, is mainly the result of a coalition between an elite group of doctors, government health officials and the drug companies that contribute to cholesterol research...

'They've oversold the role of cholesterol as if it were the only cause of heart attacks,' he insists. The heart of the cholesterol controversy lies in how you crunch the numbers. When Moore, who has training in statistical analysis, looks at the figures from the major cholesterol studies, he sees 'millions of dollars spent putting thousands of people on special diets and drugs, but with little significant reduction in cholesterol levels—or deaths from heart attacks'…

What makes Moore's blood boil are two fundamental National Cholesterol Education Program recommendations, affecting about a third of the adult population. First, that everyone with serum-cholesterol levels of 240 milligrams or more be treated with a restricted diet or cholesterol-lowering drugs or both. Second, that people with cholesterol counts between 200 and 239 milligrams be considered for treatment if two other risk factors (including smoking, obesity, diabetes, hypertension or a family history of heart disease) exist.

Casting the net so wide, Moore says, 'results in the treatment of millions of people who will show little gain from it.' He is particularly concerned about the side effects of cholesterol-lowering drugs »[414]
La dérive des soins cardiaques : Une enquête critique de la médecine américaine et de la révolution des soins cardiaques
(Traduction libre du titre du livre)

HHS, THE TRIAL *Prévention primaire – Prévention secondaire - Fibrate*
Helsinki Heart Study[415]

« This fenofibrate study in secondary prevention was published 6 years after the initial primary prevention study, in an obscure journal. Why ? Maybe because there were *more deaths* in the treated group »[416]
l'essai dit HHS

HIGH AND LOW DOSES[417]
a) Rosuvastatin : 5 mg is low, 10 mg is high
b) Atorvastatin : 10 mg is low, 20 mg is high
c) Simvastatin : 20 mg is low, 40 mg is high
doses fortes et faibles

HIGH AND MODERATE DOSES
high and moderate intensity
« High-intensity statin therapies are atorvastatin (40–80 mg) or rosuvastatin (Crestor; 20–40 mg)...

Moderate-intensity statin therapies include atorvastatin (10–20 mg), rosuvastatin (5–10 mg), simvastatin (20–40 mg), pravastatin (40–80 mg) »
posologie forte et moyenne

HIGH BASELINE RISK *Définition maison*
risque de base élevé
* Dans le présent ouvrage, risque élevé désigne un risque CV absolu de ≥ 4 par 100 années-patients en conditions expérimentales. On ne rencontre généralement ce niveau de risque que chez les hommes coronariens et dans l'hyperlipidémie

[414] Farrell & Castelli. 1989 ; 32(20) - Site http://www.people.com/people/archive/article/0,,20115928,00.html
[415] Frick et al. NEJM 1987 ; 317 : 1237 - HHS. J Intern Med 1994 ; 235 : 31 – Manninen et al. Circulation 1992; 85: 37
[416] Paul v Nguyen, 2014
[417] Dormuth et al. BMJ 2013; 346: f880 - doi: http://dx.doi.org/10.1136/bmj.f880

familiale. Et nous considérons qu'une réduction du risque absolu doit atteindre 1 par 100 années-patients (d'où un NNT_{exp} annualisé de 100) pour être considéré cliniquement signifiant. Il s'ensuit que :

* Si une statine réduit relativement le risque de -25% (RR = 0,75), et que le risque des témoins sous placebo atteint 4% par an, alors on obtient une réduction absolue de 1 par cent années-patients, ramenant le risque à 3% par an
* Si une statine cause une réduction relative de -20% (RR = 0,80), le risque chez les témoins doit atteindre 5% par an pour réaliser une réduction absolue de 1% et être considéré cliniquement pertinent, le ramenant 4% par an

* Si une statine cause une réduction relative de -17% (RR = 0,83), le risque chez les témoins doit atteindre 6% par an pour réaliser une réduction absolue de 1% qui le ramènera à 5% par an

HIGH CHOLESTEROL AND LOWER RISK OF TYPE 2 DIABETES
Épidémiologie – Étude transversale

« In a cross-sectional analysis in the Netherlands, the prevalence of type 2 diabetes among patients with familial hypercholesterolemia was significantly *lower* than among unaffected relatives, with variability by mutation type. If this finding is confirmed in longitudinal analysis, it would raise the possibility of a causal relationship between LDL receptor-mediated transmembrane cholesterol transport and type 2 diabetes…

The prevalence of type 2 diabetes was 1.75% in familial hypercholesterolemia patients vs 2.93% in unaffected relatives. The adjusted prevalence of type 2 diabetes in familial hypercholesterolemia, determined using multivariable regression models, was 1.44% (difference, 1.49% - OR = 0.49) »[418]
cholestérol élevé et risque amoindri de diabète de type 2
* une autre bonne raison, à confirmer, de ne pas statiniser les diabétiques ni les prédiabétiques

HIGH CHOLESTEROL LABELING
Surdiagnostic - Lipidologie
« Nearly all who are labeled 'high cholesterol' are far from the extreme and have minimal risk… and are contending with a reduction in life expectancy of months. Do you think a reduction of months of life expectancy is meaningful, or even measurable ? »[419]
l'étiquetage de 'cholestérol élevé'

HIGH DENSITY LIPOPROTEIN-CHOLESTEROL : PHARMACOLOGIC ELEVATION *Lipidologie – Méta-analyse*
HDL-cholesterol elevation : pharmacologic elevation

« Available data suggest that simply increasing the amount of circulating HDL cholesterol does not reduce the risk of :
a) coronary heart disease events,
b) coronary heart disease deaths, or
c) total mortality »…
according to a 2009 systematic review and meta-regression analysis by Briel et al.[420]

« It is interesting how a statistical exercise (Briel et al.) financed [in part] by Pfizer about HDL-cholesterol winds up suggesting that raising HDL does not matter while lowering LDL-cholesterol does - in CV events and total deaths. This study has flaws...

a) the exclusion of positive studies not fitting limiting modeling criteria, like the Coronary Drug Project regarding niacin vs. placebo and that significantly prevented second heart attacks with a post-study total mortality benefit. No niacin-only study fits the inclusion criteria while niacin (very high dose vitamin B3) is the undisputed therapy to raise HDL-cholesterol…

b) the inclusion criteria captured most LDL-lowering controlled and dose/drug-comparison studies with the sponsor's atorvastatin (Lipitor™), a statin not raising HDL-cholesterol (ASCOT trial) and that never lowered mortality in anyone. Moreover, atorvastatin found no 'event' benefit in women as indeed no LDL-lowering study ever found a mortality benefit in women, including statins…

c) there is no biological rationale for LDL adjustment when studying HDL since HDL is a blood particle with about 80 (presumably useful) associated proteins, while 'LDL-cholesterol' represents the concentration of a single-protein lipid transport particle of

[418] Besseling et al. JAMA 2015; 313(10): 1029 - doi:10.1001/jama.2015.1206.
[419] Nortin Hadler. Worried Sick, page 34
[420] Briel et al. BMJ 2009; 338: b92 - doi:10.1136/bmj.b92

which the composition (in trans-fats, omega-3, carotenoids, homocysteine, other) varies widely depending upon food intakes…

d) analysis including 'events' are confounded by statin's well known 'nitroglycerin mimicking' effect, promoting NO/eNOS, an unadjusted confounder that may explain, for example, much of the uniquely male nonfatal event benefit in ASCOT trial »[421]

élévation pharmacologique du HDL-cholestérol

* Les essais pharmaco-thérapeutiques visant à réduire les risques cardiovasculaires en augmentant la concentration du HDL-cholestérol ont été négatifs. Peut-être tout simplement parce que l'hypothèse qui justifie ces essais est fausse

« A ce jour, la baisse des triglycerides ou l'augmentation du HDL-Cholesterol par des moyens pharmacologiques n'a pas été associée à une prévention de la survenue d'évènements cardiovasculaires voire à une diminution de la mortalité totale »[422]

« a) L'étude AMI-HIGH, qui évaluait l'impact d'un traitement par niacine, en sus d'une statine, chez des patients avec un profil lipidique athérogène et des antécédents cardiovasculaires, a été interrompue prématurément du fait d'un manque d'efficacité clinique

b) L'association acide nicotinique-inhibiteur du récepteur endothélial des prostaglandines (Tredaptive™) a été retirée du marché suite aux résultats négatifs de l'étude HPS2-THRIVE : absence d'efficacité supplémentaire sur le risque d'événements cardiovasculaires de l'adjonction de ce traitement à une statine et augmentation des effets indésirables graves…

Autre voie de recherche : l'inhibition du CETP (cholesteryl ester transfer protein), protéine qui joue un rôle dans les échanges entre lipoprotéines circulantes

c) Un essai mené avec un premier inhibiteur, le torcetrapid (laboratoire Pfizer) a été arrêté en raison d'une augmentation significative des décès

d) Le développement du dalcetrapib (laboratoire Roche) a été abandonné après les résultats négatifs de l'essai de phase 3 dal-OUTCOMES »[423]

HIGH DOSE : MORE RISKS THAN BENEFITS *Épidémiologie – Base de données administratives – Diabétogénicité – Statinovigilance*

« In the first 2 years of regular statin use, we observed a significant increase in the risk of new onset diabetes with higher potency statins compared with lower potency agents (rate ratio 1.15). The risk increase seemed to be highest in the first 4 months of use...

Head to head randomised trials of higher potency versus lower potency statins (IDEAL, TNT, SEARCH) have not shown a reduction in total mortality or serious adverse events in secondary prevention patients with stable disease »[424]

« Harms is greater with high doses than with low doses and the added benefits of high doses is unlikely to exceed the magnitude of the harms in most if not all clinical settings »[425]

forte dose : plus risquée qu'utile

HIGH DOSE : NO BETTER THAN LOW DOSE *Prévention secondaire – Synthèse méthodique - ISDB*

« In patients with stable CHD who tolerate a standard dose of a statin:

a) High dose statins *do not reduce mortality* as compared to standard dose statins, RR 0.99

b) High dose statins reduce non-fatal MI as compared to standard dose statins, RR = 0.83 (-17%), absolute risk reduction = 1.2%, but this is not reflected in a reduction in total SAEs, RR 1.00

c) In women high dose statins numerically *increased total mortality*, RR 1.32 (+ 32%) and numerically reduced non fatal MI, RR = 0.75 (- 25%) as compared to standard dose statins

d) High dose statins *increased withdrawals* due to adverse effects, RR 1.45 (+45%), absolute risk increase of +2.5%, as compared to standard dose statins [NNH = 40 patients, presumably lower in clinical settings]

e) Because of the lack of effect on mortality and total serious adverse event there is *no net health benefit* from high dose

[421] Eddie Vos. Rapid response to BMJ 2009; 338: b92
[422] BIP 2014 no 2 page 5
[423] Isabelle Hoppenot, 2013
[424] Dormuth et al. BMJ 2014; 348: g3244 - doi: http://dx.doi.org/10.1136/bmj.g3244 - http://www.bmj.com/content/348/bmj.g3244?etoc=
[425] Therapeutics Initiative. Letter #89 at http://www.ti.ubc.ca/sites/ti.ubc.ca/files/89.pdf

prescribing high dose statins »[426]

HIGH DOSE STATIN TRIALS AGAINST PLACEBO
* High statin intensity vs placebo ; with > 1000 participants and lasting > 1 year[427]
SPARCL, GREACE, ALLIANCE, JUPITER
essais de statine fortement dosée contre placebo

HIGH DOSE STATINS AND ACUTE KIDNEY INJURY *Statinovigilance –Dossiers médico-hospitaliers – Enquête cas-témoins intra-cohorte*

« A Canadian Network for Observational Drug Effect Studies study[428] found that people taking higher strength statins (drugs to lower cholesterol, like Lipitor, Crestor or Zocor) face an increased risk of kidney injury after looking at health records of 2 M patients in CA, the USA and the UK. High potency statin treatment was defined as ≥10 mg rosuvastatin, ≥20 mg atorvastatin, and ≥40 mg simvastatin; all other statin treatments were defined as low potency...

The absolute risk of kidney injury seemed small (about one in 275 high-dose statin patients were hospitalized for acute kidney injury, versus one in 375 for those on low-dose statins)…

In patients with non-chronic kidney disease, current users of high potency statins were 34% more likely to be hospitalized with acute kidney injury within 120 days after starting treatment (rate ratio 1.34). Use of high potency statins is associated with an increased rate of diagnosis for acute kidney injury in hospital admissions compared with low potency statins. The effect seems to be strongest in the first 120 days after initiation of statin treatment »[429]

« A large, population based cohort study of over 2 M patients also reported that statin use was associated with a **>50%** increase in risk of acute renal failure, with evidence of raised risk within the first year of statin use, and a dose-response effect »[430]
« In 2003 the *Lancet* editor and *WorstPillsBestPills* thought Crestor™ should be taken off the market »[431]
statines fortement dosées et atteintes rénales aiguës

HIGH SENSITIVITY C-REACTIVE PROTEIN; hs-CRP
Critère de sélection - Essais
* used as a debatable selection criterion in the infamous JUPITER trial of rosuvastatin (Crestor™) in primary prevention
protéine C-réactive à mesure sensible / à dosage ultrasensible; PCRms
N.d.T. protéine C-réactive ultrasensible est un anglicisme sémantique car ce n'est pas la protéine qui est sensible, mais sa méthode de mesure, son dosage

* Utilisée, sans réel fondement scientifique, pour sélectionner les participants au controversé et fortement biaisé essai clinique Jupiter portant sur la rosuvastatine (Crestor™) chez des aînés non coronariens sans hypercholestérolémie polygénique; les résultats sont très beaux mais sont-ils véridiques? Peu de scientifiques impartiaux le croient, sinon aucun

HOMO STATINISUS, A SHORT ESSAY
l'homme statinisé, un bref essai
Un moratoire sur les cholestérolémies *de dépistage* (systématiquement incluses dans les bilans annuels de santé) chez les clients et sur celles *de suivi* sur les patients, serait un cadeau, une gracieuseté de la rigueur scientifique envers la santé publique et les budgets de santé.

COMMENT LES CANADIENS GASPILLENT LEUR ARGENT EN RÉDUCTION DU CHOLESTÉROL
En 2012-2013 le marché des réducteurs de cholestérol vendus au détail en pharmacies communautaires s'élevait à 1.643 M $CA, soit 7,2% du budget global, pour une dépense annuelle de 47 $ par habitant, surpassé seulement par l'ensemble des anti-hypertenseurs. Même s'il est bien démontré que les statines ne réduisent pas la mortalité chez les femmes, elles forment 43% des consommatrices, pour une dépense de 40 $ par canadienne. La part des dépenses attribuable aux honoraires des pharmaciens est estimée à 26%, soit 427 M $. Les deux plus populaires statines expliquent 70,1% des dépenses (l'ezetimibe

[426] Wright J et al. http://www.ti.ubc.ca/sites/ti.ubc.ca/files/87.pdf
[427] NICE 2014
[428] Dormuth et al. BMJ 2013; 346: f880 - doi: http://dx.doi.org/10.1136/bmj.f880
[429] Alan Cassels. http://www.evidencenetwork.ca/FINAL_EBOOK2.pdf
[430] Hippisley-Cox & Coupland. BMJ 2010; 340: c2197, cité par Dormuth et al. 2013
[431] H Rosenberg, 2015

12,7 % et le fénofibrate 3,2%)[432] et pourtant il est bien démontré que les statines brevetées ne sont pas supérieures à celles déjà génériquées.

CHOLESTÉROLÉMIES DE DÉPISTAGE ET CHOLESTÉROLÉMIES DE SUIVI, UNE FORME D'ASSERVISSEMENT
J'aimerais soumettre l'idée que le dépistage du cholestérol mène à une perte de liberté individuelle des bien-portants qui risquent d'être statinisés pour la vie, dépendants de la médecine, de la pharmacie et du laboratoire pour le reste de leur jours, sans pourtant être malades, étiquetés 'malades de leur cholestérol', libellés personnes 'à risque', exposés aux interactions médicamenteuses, victimes d'effets indésirables de plus en plus divulgués, et vecteurs involontaires de substantielles dépenses personnelles et collectives. C'est une forme d'esclavage où l'on enchaîne les patients par une laisse pharmacologique.

L'homme sain, *Homo Vivens*, est un homme libre sanitairement parlant; c'est « cet être vivant, incarné, mortel, imparfait, limité[433] ». *Homo Statinisus* n'est plus libre, ses niveaux lipidiques le placent sous surveillance rapprochée. « Mesurer la condition humaine à l'échelle du cholestérol est une absurdité » nous rappelle Peter Skarabek[434].

HOPE-3, THE TRIAL
* L'ajout de la rosuvastatine (Crestor) comparé à l'ajout d'un placebo chez un peu plus de 3000 patients en prévention primaire durant 5,6 ans (médiane) n'a pas réduit statistiquement la mortalité CV ni la mortalité totale, et n'a pas réduit les accidents CV (critère combiné) de façon cliniquement signifiante car le NNT annualisé est 510 années-patients (186 150 comprimés pour retarder un seul événement cardiovasculaire) en conditions expérimentales, et raisonnablement plus élevé en situation clinique courante vu les biais décelés dans l'analyse pragmatique de l'essai.
l'essai dit Hope-3

HOW STATIN DRUGS REALLY LOWER CHOLESTEROL: And Kill You One Cell at a Time **-** (Livre)
James B YOSEPH & Hannah YOSEPH. Self-published : 2012 - ISBN : 0615618170 – EAN13 : 9780615618173 – 358 pages

« The Yosephs have written the most stunning exposé. In simple language they reveal the science, the corruption and the enormous conspiracy it took to bring statins to market. As fast paced as a Mickey Spillane novel they report the research, the fraud and the facts like a detective in hot pursuit of a Nazi war criminal. Once picked up it cannot be put down until the reading is done. It is riveting…

They have accomplished the impossible: they have made both complex science and medical history fascinating to read. What could not be done in an exposé they accomplished with almost unbelievable ease. It will change your paradigms about medicine forever as will the sequel "Poisoned! (Recovery From Statin Side Effects)" »
Comment les statines abaissent vraiment le cholestérol : Et vous tuent une cellule à la fois (Traduction libre du titre du livre)

HOW STATISTICAL DECEPTION CREATED THE APPEARANCE THAT STATINS ARE SAFE AND EFFECTIVE IN PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE – (Article) *Tromperies statistiques*
Diamond DM & Ravnskov U. *Expert Rev Clin Pharmacol* 2005: 1-10[435]

« We have provided a critical assessment of research on the reduction of cholesterol levels by statin treatment to reduce CV disease. Our opinion is that although statins are effective at reducing cholesterol levels, they have failed to substantially improve CV outcomes...

We have described the deceptive approach statin advocates have deployed to create the appearance that cholesterol reduction results in an impressive reduction in CV disease outcomes through their use of a statistical tool called relative risk reduction (relative risk reduction), a method which amplifies the trivial beneficial effects of statins. We have also described how the directors of the clinical trials have succeeded in minimizing the significance of the numerous adverse effects of statin treatment »
Comment la tromperie statistique a donné l'impression que les statines sont sécuritaires et efficaces en prévention primaire et secondaire de la maladie cardiovasculaire
* Les auteurs démontrent comment les principaux essais ont été volontairement l'objet de conflation impardonnable en substituant les réduction relatives aux réductions absolues qui seules sont valides quand on présente les résultats à visée pragmatique et quand on prépare des directives cliniques

[432] Steve Morgan et coll. UBC Centre for Health Services and Policy Research. *The Canadian Rx Atlas,* 3rd Edition, December 2013 – Libre accès sur http://www.chspr.ubc.ca/sites/default/files/file_upload/publications/2013/RxAtlas/canadianrxatlas2013.pdf
[433] Biron P. http://agora.qc.ca/fr/homo_vivens_le_manifeste
[434] La fin de la médecine à visage humain. Paris : Odile Jacob ; 1995, page 108
[435] abstract on http://www.ncbi.nlm.nih.gov/pubmed/25672965

HPS, THE TRIAL *Simvastatine 40 mg c. placebo – Prévention primaire à haut risque et secondaire*
Heart Protection Study; British HPS
* Princeps publication : HPS/*Lancet*/2002[436]; see also Meade/*EHJ*/1999[437]

* Private funding of HPS 1993-2002 : Merck: £5.5M plus drug supply - Roche: £5.5M plus drug supply - Funding of follow-up studies 2003-ongoing : Merck: £1.2M - GSK: $400K - Liposcience: £50K – « The connection between Merck and the University of Oxford provides an excellent example of partnership with the industry. They jointly conducted several trials, the most famous being the HPS trial »[438]

METHODOLOGY
* Comparison : simvastatin 40 mg vs. placebo
* Mean follow-up : 5 years (60 months)

* Participants demography: total of 20 536 (10 269 under statin and 10 267 under placebo); mean age 64 years, range 40-80 years ; 24.8% women; 75.2% men
* Run-in period : 32,145 recruited patients were first 'tested' for 4-6 weeks with the active ingredient (40 mg), and 11,609 or 36% were dropped from inclusion

* Participants health :
a) 5963 or 29% in high risk primary prevention and 14 573 in secondary prevention
b) 1816 women or 30% in primary prevention without CHD, and 3266 women or 22% in secondary prevention with CHD, other angiopathies or diabetes

c) TC > 3.5 mM (135 mg/dL), mean 5.9 mM; 80% had an LDL-C > 2.6 mM (100 mg/dL)
d) hypertension in 41%
e) 19% diabetics : 2912 diabetics without angiopathies (high risk primary prevention) and 3051 with (secondary prevention)
f) 14 573 with prior coronary/cerebral/peripheral angiopathies (70%); 65% of participants had known CHD

* Positive compliance (active group adherence) : 85% according to protocol
* Negative compliance (control group adherence) : 83% according to protocol

* Primary composite outcome has 5 components : [total mortality + nonfatal MI + nonfatal stroke + coronary revascularization + noncoronary revascularization]; heterogeneity/incoherence invalidates the outcome as a basis for establishing the benefit-risk balance : 3 components are clinical outcomes and 2 are subjective medical decisions (objectivity is uneven); 1 component is fatal and 4 are not (seriousness is unequal); baseline values and treatment differences are heterogenous (sizes are variable)

Unreported outcomes :
* Serious adverse events (SAE) *not reported*, as a composite outcome
* Quality of life *not measured* or reported
* Kaplan-Meier plot on all-cause mortality was *not published*

Methodology at high risk of bias, such as *unblinding* :

« On page 375 under the paragraph: 'Effects of study treatments on blood lipids and vitamins', it is clearly written: 'Each year, therefore, about 1300 of the randomized patients are selected (irrespective of whether or not they are continuing to take the study treatments or to attend the follow-up clinics) for extensive analysis of their nonfasting blood samples, with storage of aliquots of plasma in liquid nitrogen for any subsequent analyses required...

Compared with those allocated placebo tablets, allocation to 40 mg daily simvastatin is producing reductions of about 1.5–1.6 mM in blood TC, 1.1-1.2 mM in LDL-C, and 0.4-0.5 mM in triglycerides, but an increase of only about 0.04 mM in HDL (Fig. 2). Comparable changes in the levels of apolipoproteins B and A1 are also seen, and these differences are maintained during, at least, the first 2 years of follow-up'. Consequently the investigators were *clearly aware* of at least 10% or more of patients' allocation yearly »[439]

[436] HPS Collaborative Group. Lancet 2002; 360(9326): 7 - doi:10.1016/S0140-6736(02)09327-3
[437] Meade et al. Eur Heart J 1999 ; 20(10) : 725
[438] de Lorgeril 2014, op. cit.
[439] Paul v Nguyen, 2014

Methodology at high risk of bias, such as a biased *selection* leading to poor external validity for benefit, and low power to detect ADRs :

« It is essential to remember that the HPS was in people with existing CV disease (secondary prevention) and that all patients were treated with simvastatin 40 mg daily for 4 to 6 weeks and only those did well during that period were randomised to simvastatin or placebo. I have pasted the information from the *Therapeutics Letter* about this :

"HPS was unusual in having a pre-randomization period in which 32,145 recruited patients were treated with simvastatin 40 mg for 4 to 6 weeks and 36% (11,609) of these patients were dropped from the study for various reasons: *poor compliance, patient choice, side effects*, etc. Because large numbers of problematic patients were excluded, the HPS results cannot be used to predict the safety and tolerance of simvastatin in the general population"[440]

« A largely undiscussed feature of the study, which is common to statin trials, in general, was that 36% of all eligible subjects withdrew from the study after being on simvastatin for 1 month before the formal initiation of the study (the run-in period). The reason for their withdrawal was not provided, but a likely explanation may be that they did not tolerate the adverse effects of the drug...

Thus, any study that has a period in which subjects with adverse events may withdraw before formal study initiation has an inherent bias against providing a representation of the actual rate of adverse events. Hence, the rate of statin adverse effects cannot be determined from such studies[441]»

« One major statin trial, the HPS, headed by Professor Sir Rory Collins, employed a run-in period which subjected all potential participants to the active drug. Individuals with evidence of adverse events were excluded, which obviously means a higher percentage of 'statin tolerant' individuals made it into the study proper »[442], a major flaw in external validity and a form of cheating in a pragmatic trial

RESULTS
Surrogate outcomes (lipid reduction) :
a) relative risk reduction of -20 % for TC, from 5,9 mM
b) relative risk reduction of -29% for LDL-C; absolute risk reduction of 1 mmol/L, from 3,35 mM

« The proportional reduction in the event rate was similar in each subcategory of participant studied, even those who presented with LDL cholesterol < 3·0 mM (116 mg/dL) or TC < 5·0 mM (193 mg/dL) »,[443]

Clinical benefits in relative risk reduction (relative risk reduction is relevant only to an *explanatory* interpretation) :

* TOTAL MORTALITY : relative risk reduction of -12%; such an effect has never been obtained elsewhere and remains unconfirmed
* CHD MORTALITY : relative risk reduction of -18%

* First nonfatal MI : relative risk reduction of -38%
* Fatal and nonfatal MI : relative risk reduction of -27%

« In the largest statin trial, the patient group achieving the most reduction in LDL-C had the same relative benefit (relative risk reduction -21%) as the group with the least reduction (relative risk reduction -22%) »[444], in contradiction to the lipid hypothesis

Clinical benefits in absolute risk reduction (absolute risk reduction is relevant to a *pragmatic* interpretation):

* TOTAL MORTALITY : absolute risk reduction of -1.8% over 5 years (1328 deaths in 10 269 treated patients, and 1507 in 10 267 placebo controls) - absolute risk reduction of -0.36 per 100 patient-years –- NNT = 278 patient-years, for an annualized inefficacy rate of 99.64% and a life extension of 32 hours per treatment-year when spread across 278 patients, and reasonably less in a clinical setting (24 hours ? 16 hours ?). To gain one more year in life expectancy, a theoretical patient should have to take 101,

[440] James Wright, 2011, Editor in Chief, Therapeutics Initiative
[441] Diamond & Ravnskov, op. cit.
[442] John Briffa, 20.5.2014 - http://www.bmj.com/content/348/bmj.g3306?page=1&tab=responses
[443] HPS 2002, op. cit.
[444] http://www.ti.ubc.ca/letter92

470 tablets of simvastatin over 278 years in experimental conditions, and presumably even more in a usual care setting…

* CHD MORTALITY : absolute risk reduction of -1.5% over 5 years - 781 coronary deaths (7.6%) under simvastatin and 937 (9.1%) under placebo – absolute risk reduction of -0.3 per 100 patient-years, annualized NNT = 333 patient-years, for an annualized inefficacy rate of 99,7% and a life extension of 26 hours per treatment-year when spread acoss 333 patients, and reasonably less in a clinical setting (19 hours ? 13 hours ?)…

Results in diabetics :
* In diabetics without prior angiopathy (occlusive arterial disease), absolute risk reduction of 0.9 major CV events per 100 patient-years, or annual NNT of 111, or annual inefficacy rate of 99.1%, equivalent to postponing such event by 3.39 days (79 hours) per year of treatment if benefit is spread across 111 statinated patients, and most likely fewer hours in a clinical setting. Furthermore, this outcome is a composite made of heterogenous components and unreliable in itself for supporting clinical guidelines

* In diabetic women in 'high risk' primary prevention : relative risk reduction of -24 % for CHD events but NS as required by multiple comparisons
* In diabetic women with CHD in secondary prevention : relative risk reduction of -15 % for CHD events but NS at the level required by multiple comparisons

Results concerning women :
« Absence of event or total mortality benefit in women in combined primary and secondary prevention trials (HPS, PROSPER, MEGA) »[445] was found in the sensitivity analysis of Petretta et al. in 2010 - « Another 'successful' study, HPS in 2005 (*BMC Med* 3 : 6) found no significant mortality benefit in women »

Harms : results in relative risk increase :
* New onset diabetes RRI of +15%, NS
* Myopathy ARI of +0.01 per 100 patient-years with an annual NNH of 8557 patient-years[446]; this is about 1711 times lower than the observational rate of almost 20% and the NNH of almost 5. The low reported rate of myopathy is therefore implausible, suggesting that myopathy was not looked for or, better said, not listened to and not recorded...

There were 10 cases under simvastatin and 4 cases under placebo, a difference of only 6 cases after 51 340 patient-years of observation. Clearly, HPS is underpowered to detect symptomatic myopathy and its reporting is at high risk of bias
* Health related quality of life *not reported*

Conflated authors recommendation : « Statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events »[447]

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Hps
* Seul essai contrôlé, avec 4S, à avoir observé une réduction de la mortalité générale, limitée toutefois aux hommes, mais les données brutes demeurent cachées. Aucun parmi une trentaine d'autres essais ne l'ont confirmé. Les auteurs de la HPS entretiennent des liens importants avec l'industrie. En 2014, l'auteur principal harcelait le BMJ au sujet de la fréquence des effets indésirables des statines qui aurait été exagérée, mais un comité indépendant donna raison au BMJ...

En 2015 ce même dealeur d'opinion admet enfin que la recherche des effets indésirables a été insuffisante !

HPS2-THRIVE, THE TRIAL *Niacine*
Anderson TJ et al., *N Engl J Med* 2014; 371: 288
* Comparison : niacin/laropiprant (2005-ongoing)
* Funding : Merck: £53M plus drug supply
l'essai dit Hps2-Thrive

[445] Eisenberg et al
[446] Table 4, HPS, quoted by Dr Briffa at http://www.drbriffa.com/2014/08/22/how-accurate-are-professor-collins-claims-about-the-rates-of-muscle-problems-with-statins/
[447] HPS Collaborative Group. Lancet 2005 ; 361(9374) : 2005 - doi:10.1016/S0140-6736(03)13636-7- http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(03)13636-7/abstract

HPS3/TIMI55-REVEAL, THE TRIAL
* Comparison : anacetrapib (2010-ongoing)
* Funding : Merck: £96M plus drug supply
l'essai dit Hps3 / Timi55-Reveal

HUMAN ATHEROSCLEROSIS IN RELATION TO CHOLESTEROL CONTENT OF BLOOD SERUM – (Article) *Hypothèse lipidique*
Lande KE & Sperry WM. *Arch Pathol* 1936 ; 22 : 301
« An absence of an association between cholesterol levels and the degree of atherosclerosis in unselected people was originally described in 1936 »[448]
* bel exemple pour expliquer pourquoi on n'enseigne pas l'histoire du médicament et de la médecine

HYPERCHOLESTEROLISM
hypercholestérolisme
* néologisme proposé par Jean-Marie Therrien[449]

= doctrine créée à propos du cholestérol et qui utilise la persuasion clandestine et exerce le musellement des opposants; elle s'acharne sur les formes alimentaire et sanguine du cholestérol en les accusant d'être la cause de la maladie coronarienne. Elle veut que le taux de cholestérol soit vérifié réglièrement dans la population et a consacré le taux de cholestérol élevé au titre de maladie[450]

HYPERCHOLESTEROLIST
hypercholestéroliste
* on doit le terme à Jean-Marie Therrien[451]
= professionnel de santé qui pratique l'hypercholestérolisme (en prescrivant des statines; en participant aux essais sponsorisés) ou en fait la promotion (en devenant meneur d'opinion)

HYPERLIPIDAEMIA IN WOMEN
« For women without CV disease, lipid lowering does not affect total or CHD mortality. Lipid lowering may reduce CHD (non fatal) events, but current evidence is insufficient to determine this conclusively. For women with known CV disease, treatment of hyperlipidemia is effective in reducing CHD events, CHD mortality, nonfatal myocardial infarction, and revascularization, but it does not affect total mortality »[452]
hyperlipidémie chez la femme
* les réductions dans la prévention secondaire ne sont pas cliniquement pertinentes

HYPOCHOLESTEROLEMIA AS A RISK FACTOR
* it can be drug induced (statins) or natural (polygenic) or disease-related (wasting diseases)
hypocholestérolémie comme facteur de risque
Voir aussi les entrées LOW CHOLESTEROL

HYPOLIPIDEMIC'S BURDEN OF HOSPITAL CARE *Pharmacovigilance - Pharmacoéconomie*
"Antilipemics account for 0,6% (n = 12 600) of ADR diagnoses made in inpatients stays and 0,8% (n = 8 100) of those made in emergency visits, in US hospitals in 2008[453]"
fardeau hospitalier des hypolipidémiants
* on peut raisonnablement extrapoler que la même année au Canada, 10 fois moins peuplé, il y aurait eu 1 260 hospitalisations et 810 visites aux urgences menant au diagnostic d'EIM par hypolipidémiant

HYRIM, THE TRIAL
Hypertension High-Risk Management Trial

I think we doctors do a huge disservice to people by either not being aware of the data or giving patients a false impression of

[448] Diamond & Ravnskov, op. cit.
[449] Une histoire inventée : Essai sur le cholestérol. Montréal : Carte Blanche ; 2014
[450] Une histoire inventée : Essai sur le cholestérol. Montréal : Carte Blanche ; 2014
[451] Une histoire inventée : Essai sur le cholestérol. Montréal : Carte Blanche ; 2014
[452] Walsh & Pignone. JAMA 2004; 291: 2243
[453] H-CUP, http://www.hcup-us.ahrq.gov/reports/statbriefs/sb109.pdf

the risks of stopping statin therapy »[454]
déstatinisation en prévention secondaire

IDEAL, THE TRIAL *Prévention secondaire chez coronariens stable – Atorvastatine 80 mg c. simvastatine 20-40 mg – Pas de placebo – Comparaison de deux statines à doses différents*
Incremental Decrease in End Points Through Aggressive Lipid Lowering

* Financing : private, Pfizer – « A trial without any scientific interest whatsoever given that its sole objective was to try to impose Tahor™ instead of Zocor™, year 2005 was right in the middle of the transition phase from the pre-Vioxx™ to the post-Vioxx™ era »[455]

* Princeps publication : Pedersen/JAMA/2005[456] - An exploratory re-analysis was published later[457]
* Comparison : 80-mg of atorvastatin (strong dose) vs. 20 to 40 mg of simvastatin (standard/titrated doses)
* Duration : median (50th percentile) 4.8 years
* Participants' health : prior MI

* Participants demography : 8888 stable CHD patients
* Primary endpoint : nonfatal MI + cardiac mortality
* No reduction in total mortality or serious adverse events in high-dose group

RESULTS

Benefits
* TOTAL MORTALITY : 374 under atorvastatin ; 366 under simvastatin ; NS
* Cardiac mortality : 178 under atorvastatin ; 175 under simvastatin ; NS
* Primary endpoint : absolute risk reduction of 1.1% in 4.8 y, NS, in major coronary events, primarily nonfatal acute MI, which is equivalent to an absolute risk reduction of 0.23 % per year (NNT = 435 patient-years)
* CV mortality RRI of +3% (NNH = 33), NS, in favor of lower dosed simvastatin

« Differences in the primary outcome of major coronary events were not demonstrated »[458] when comparing high-dose with low dose statinization in secondary prevention

Harms :
* New onset diabetes *not reported* in princeps publication but retrieved by meta-analyst Preiss, RRI = +15%, NS
* Health related quality of life *not reported*

Comments about pharmacoeconomy and lack of NNTs :
« High-dose statin, not so IDEAL? Tikkanen et al. present an interesting post-hoc analysis of the IDEAL study with a novel statistical method using all vascular rather than just the first CV events recorded, and they propose highly significant p-values in support of using top-dose atorvastatin (80 mg/d) versus 'standard' dose (20 mg/d or uptirated) simvastatin…

The authors propose that such statistical approach is of value because of the health economic importance of subsequent events and that their results "suggest that clinicians should not hesitate to prescribe high-dose statin therapy for patients experiencing multiple recurrent CV events."

The background: IDEAL was an apparently well run open-label drug comparison trial in all post myocardial infarct (MI) patients of whom about 40% had already experienced revascularization and an 8.3% mortality (+/-0.1% between groups) during the mean 4.8 years of follow-up...

The lack of mortality benefit is in-line with atorvastatin's well known *inability to lower mortality*, with the notable findings of the TNT and SPARCL trials that ending with numerically more deaths on top-dose atorvastatin than on low-dose and placebo, respectively

[454] John Briffa at http://www.drbriffa.com/2013/12/12/what-are-the-risks-of-coming-off-statins/
[455] de Lorgeril 2014, op. cit.
[456] Pedersen et al. JAMA 2005; 294(19): 2437 - doi:10.1001/jama.294.19.243 – complet sur http://jama.jamanetwork.com/article.aspx?articleid=201883
[457] Tikkanen MJ et al. J Am Coll Cardiol 2009; 54: 2353
[458] Green et al. JAMA Intern Med on line 7.1.2013 - doi:10.1001/jamainternmed.2013.1529

Since mortality is not reduced, we have to ask about the nature of events prevented. The authors report that the 1st, 2nd and 3rd events recorded were 46%, 51% and 43% based on decisions to hospitalize or to revascularize, while non-fatal MIs represented only 18%, 15% and 15%, respectively. The ASCOT study found angina reduced by 41%, likely by the NO/eNOS nitroglycerin mimicking action that all statins share...

The amount of angina experienced is a factor potentially affecting the above mentioned medical decisions and the number of MIs recorded in a trial…

We thus have to be careful including these softer endpoints and since the authors bring up health-economics, we should be aware that at the current (Vermont) retail prices of $5/pill for "high dose-statin" (Lipitor 80 mg and Crestor 40 mg), it would cost, as an example, from $560,000 to $1,160,000 to prevent either a revascularization, stroke or MI, based on the recent JUPITER primary prevention study (rosuvastatin 20 mg vs. placebo), slightly less in men, more in women...

Even at the current Vermont price for generic lovastatin ($0.78/20 mg), such costs, likely even in secondary prevention, may be many times those of an angioplasty, a hospitalization for angina or the cost of a peripheral vascular disease event. These drug costs calls into question the benefit of statin including high-dose statin regarding health economic benefits...

Therefore, could the authors comment on the health economic effects of their expanded endpoint analysis and provide NNTs for individual endpoints, with confidence intervals »[459]

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE

l'essai dit Ideal

* Publication princeps : Pedersen/*JAMA*/2005
* Effectifs randomisés : 8888
* Suivi médian (50^{e} percentile) : 4,8 ans

* Groupe expérimental : atorvastatine 80 mg
* Groupe témoin: simvastatine 20-40 mg
* Âge moyen : 62 ans (tous < 80 ans)

ILLUMINATE, THE TRIAL *Atorvastatine + placebo c. torcetrapid + atorvastatine – Prévention secondaire – Arrêt prématuré pour aggravation des critères d'évaluation*

« Randomized, double-blind study involving 15,067 patients at high CV risk. The patients received either torcetrapib plus atorvastatin or atorvastatin alone. At 12 months in patients who received torcetrapib, there was an increase of 72.1% in HDL cholesterol and a decrease of 24.9% in LDL cholesterol, as compared with baseline, in addition to an increase of 5.4 mm Hg in SBP, a decrease in serum K, and increases in serum Na, bicarbonate, and aldosterone...

There was also an increased risk of CV events (HR = 1.25, P=0.001) and death from any cause (HR 1.58, P=0.006) at study termination when the median follow-up in each group was 550 days. Earlier discontinuation of treatment had occurred in 831 patients in the atorvastatin-only group (11.0%) and in 1008 patients in the torcetrapib group (13.4%) »[460]

« Torcetrapib substantially reduced LDL-C and substantially increased HDL-C, yet it increased mortality and CV morbidity »[461] - « Undesirable effects were reported by 83.3% of patients taking atorvastatin alone. Severe adverse events were reported by 15% taking the statin. This amazingly high figure has little to do with the 1/10 000 claimed by the Oxford CTSU… Sponsor is omnipresent and overlooked such blunders as the lack of equivalence of the randomised groups »[462]

l'essai dit Illuminate

* Financement : entreprises

« Un jackpot se prépare. Les HDL augmentent bien de façon vertigineuse de 72%, l'essai - 15 000 patients recrutés en 15 mois dans 260 centres – qui devait éclairer l'univers tout entier, démarre pour 4 ans et demi. Il faudra le stopper en catastrophe 550

[459] Eddie Vos. J Am Coll Cardiol, 2009; 54: 2353 - doi:10.1016/j.jacc.2009.08.035 (Letter re: http://content.onlinejacc.org/cgi/content/full/54/25/2353)
[460] Barter et al. N Engl J Med 2007; 357:2109 - DOI: 10.1056/NEJMoa0706628http://www.nejm.org/doi/full/10.1056/NEJMoa0706628
[461] http://www.ti.ubc.ca/letter92
[462] de Lorgeril 2014, op. cit

jours après, le 2.12.2006, comme un coup d'État. Un désastre…

Les complications cardiaques ne sont pas réduites mais au contraire dramatiquement plus fréquentes : 93 morts sur 15 000 patients, 1,6 fois plus que dans le groupe témoin, par les pathologies mêmes qu'on voulait éviter, infarctus, AVC, hypertension artérielle sévère (1 400 cas, 9%), mort subite, etc., sans compter 1,7 fois plus de cancer. Le président de Pfizer, Kindler, doit démissionner »[463]

IMPROVE-IT, THE TRIAL *Ezetimibe + simvastatine c. simvastatine – Conflation – Essai cliniquement négatif – Sans groupe placebo*

Numerical results presented at AHA meeting in November 2014 :
* TOTAL MORTALITY: 15.3% over 7 years on statin alone, 15.4% on statin + ezetimibe, NS – Amounting to an absolute risk *increase* of +0.1 per hundred patients over 7 years or +0.014 per hundred patient years (NNH = 7143 patient-years). Despite following 18 144 patients for 7 years (127 008 patient-years), the study is totally negative for the outcome most valuable to patients…

* Composite endpoint (CV death, MI, unstable angina requiring hospitalisation, revascularization, stroke) : 34.7% over 7 years on statin alone, 32.7% on statin + ezetimibe[464]... But the primary composite endpoint is invalidated by mixing heterogenous outcomes:
a) different patient-valued *seriousnesses* such as dying versus being hospitalized
b) uneven *baseline* values and treatment effects, such as an increase in mortality (sic) and a decrease in other endpoints
c) different degrees of *objectivity* since both hospitalisation and revascularization are medical decisions and prone to unblinding

* Non fatal MI : absolute reduction of 1.5% over 7 years, or 0,2% per annum in ezetimibe group, for an annualized experimental NNT of 500 patient-years in patients already on a statin

Amounting to an absolute risk reduction of -2.0% in 7 years or -0.29 per 100 patient-years, NNT = 350 patient-years, virtually equivalent to an average delay of 25 hours per year of treatment under experimental conditions, and presumably less in clinical settings (17 hours ? 12 hours and 39 minutes ? Nobody knows). Even if the composite endpoint was valid, there is no clinical importance whatsoever …

* Differences for stroke, unstable angina requiring hospitalisation and coronary revascularization were neglible and even plagued statistically by multiple comparisons
* The trial was unblinded after one year under the pretext of demonstrating the absence of a cancerogenic adverse reaction

* Duration was *prolonged* over 5 years in the false hope of proving that the primary hypothesis was true and of finding at least some statistical significance by multiplying comparisons of secondary endpoints

Commentary by independent source :
* Dr Sanjay Kaul questions the clinical significance of the findings, noting the overall treatment effect was 'modest'. He also points out that the difference in the composite primary end point "was elevated to the lofty pedestal of statistical significance simply due to the large sample size, a classic example of a disconnect between statistical significance and clinical importance"

« For the *Lown Institute* in June 2015, industry funded trials like IMPROVE-IT sometimes alter research designs to show statistically significant benefits, but those alterations undermine the ability to interpret or trust their findings »

Commentary by sponsored KOLs :
« At the AHA meeting in Chicago in November 2014 results were presented of the IMPROVE-IT trial; the addition of ezetimibe to background simvastatin therapy was studied in 18 144 patients stabilized following an acute coronary syndrome; 5314 primary composite endpoint events were observed over a 5.68 years period; LDL-C was reduced to a median time average of 69.5 and 53.7 mg/dL, in respectively, the simvastatin and the simvastatine/ ezetimibe group...

The primary composite endpoint was reached in 34.7% of the simvastatin group and in 32.7% of the simvastatin/ezetimibe group resulting in a HR of 0.936, NNT = 50 »[465], amounting to annualized NNT of 184 patient-years, which is devoid of external

[463] Even, pages 86-87
[464] David Colquhoun. R. Soc. open sci. 2014 ; 1: 140216 - http://dx.doi.org/10.1098/rsos.140216
[465] de Baker et al. European Heart Journal 2015; 36 : 214 – doi:10.1093/eurheartj/ehu482
http://eurheartj.oxfordjournals.org/content/ehj/36/4/214.full.pdf?etoc=

validity, even if the methodology was internally valid

* A slide summary of the trial is available, prepared by promoters for journalists, where reporting *total deaths* is carefully avoided; there were about *10 more* in the EZ+S group and the study had to be stopped…[466]

* In 2016 the FDA did not recommend approval of an expanded indication for eztimibe + simvastatin in secondary prevention after reviewing the trial[467]

l'essai dit Improve-It

* un exercice couteux, aux résultats futiles, mais qui sera présenté comme un 'succès incrémental', bel exemple de conflation à son meilleur à la recherche de chiffres de vente faramineux. L'ezetimibe n'a jamais été démontré capable contre placebo de prolonger la vie ni de réduire la mortalité CV

« Quoiqu'il faille faire attention, en l'absence de données publiées dans un vrai article, de sur-réagir aux résultats et commentaires "visibles" sur Internet ; et sachant que pour le moment, seuls les "experts patentés" ont droit à la parole via les agences commerciales subventionnées, on ne peut qu'être désolés du spectacle offert par les experts US à l'AHA à propos de IMPROVE-IT ! …

On connaissait le biais par arrêt prématuré, ceux-là inventent le biais par *arrêt retardé* ; dans les deux cas, on casse le code, on désaveugle et le bricolage commence. Seul le respect strict du protocole (durée fixée à l'avance du suivi et de la taille de l'échantillon, glaciation de la base de données avant de désaveugler) permet un minimum de crédibilité; …

car dire qu'on le fait ne veut pas dire qu'on le fasse vraiment ; les enjeux financiers sont énormes et un petit mensonge ou une petite entorse à la règle de ci de là pour fluidifier le parcours (l'air de rien ...) ...

Ceci dit, seuls les niais peuvent se laisser prendre : ils n'osent pas trop bricoler les données de mortalité car c'est ça qui sera le plus facilement vérifiable le jour où une Autorité libérée du business exigera de voir les données brutes ... Et effectivement les données de mortalité semblent être absolument identiques dans les deux groupes ! …

Toutefois, la suite sera intéressante à suivre car ceux qui s'expriment ainsi (y compris les investigateurs de l'essai) confirment, s'il était besoin, qu'ils ne valent pas plus chers que nos "chers amis" d'Oxford (Collins, Peto and Cie.) puisqu'ils nous refont le "coup" de SHARP ; peut-être en plus grossier encore (mais il faudrait qu'on ait l'article in extenso ou au moins ce qu'ils veulent bien dire) …

Tout ça est assez réjouissant car nous voyons que la grosse dispute à propos des nouvelles recommandations de l'AHA de décembre 2013 n'était finalement que le cache-sexe d'une autre grosse (et grossière) dispute à propos de qui s'octroiera les "petits" profits générés par les nouveaux anticholestérol injectables »[468]

« Ils ont procédé à une douzaine d'analyses intérimaires pour finalement arrêter un essai qui depuis 2008 n'était plus conduit en double aveugle… Le résultat final et calamiteux est simple : il n'y a pas de différence entre les deux groupes sur la mortalité totale et la mortalité cardiovasculaire, les seuls critères de jugement recevables (et encore…) vu les défauts de l'essai »[469]

INDEPENDENT STATINS REVIEW PANEL REPORT (UK) *Arbitrage du harcèlement d'une revue savante - BMJ*
http://www.bmj.com/content/independent-statins-review-panel-report-0

« The independent panel of internationally renowned experts asked by The BMJ to review its handling of two articles that contained the same error has reported its findings, and were unanimous in their decision that the two papers do not meet any of the criteria for retraction, endorsing The BMJ approach. After a two-month review, the panel has advised The BMJ that its handling of the two articles was appropriate and that its processes were timely and reasonable…

They have also called for the the individual patient data to be made available for independent scrutiny. Patients and their doctors need access to all relevant information to make informed decisions about their health »[470]

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[466] http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469669.pdf
[467] Dubroff, QMJ 2.11.2017 - https://academic.oup.com/qjmed/advance-article-abstract/doi/10.1093/qjmed/hcx213/4587483?redirectedFrom=fulltext
[468] Michel de Lorgeril, 2014
[469] De Lorgeril M, 22.6.2015 - http://michel.delorgeril.info/non-classe/lessai-improve-it-un-coup-pour-rien-revelateur-de-lepoque-quand-meme
[470] Heath et al. http:// journals.bmj.com/site/bmj/statins/Final%20report%20of%20the%20independent%20panel% 20310714.pdf.

* The two articles are Abramson JD, Rosenberg HG, Jewell N, Wright JM. *Should people at low risk of cardiovascular disease take a statin? BMJ* 2013; 347: f6123 and Malhotra A. *Saturated fat is not the major issue*. *BMJ* 2013; 347: f6340

INFORMED CONSENT BEFORE BEING PRESCRIBED LIFELONG STATINIZATION
* Before being statinized, middle aged male patients with a coronary condition should share the decision and be informed of the nature and magnitude of risks. The more relevant outcome is the absolute risk of CV mortality and, more importantly, total mortality - with and without statinisation for life.

Number needed to treat (annualised NNT) for one year to avoid these two outcomes is the best format for insuring comprehension. Women, and elderlies of both sexes, should be told that statinization has no benefits on these two outcomes whether or not they have a coronary condition.
consentement informé avant de recevoir une ordonnance de statinisation à vie

INTENSIVE LIPID LOWERING TRIALS *Comparaison de doses – Prévention secondaire*
A to Z, IDEAL, Post-CABG, PROVE-IT TIMI 22, TNT, SEARCH

* Only one (PROVE-IT in 2004) had a significant relative risk reduction of total mortality but not for CV mortality, which is strange; one had a relative risk reduction for CHD death (A to Z, in 2004) or of CHD events (TNT, in 2005), but none at the 1% level required by multiple comparisons
* Two (IDEAL and Post-CABG) were unblinded for patients and caregivers
* A meta-analysis by Krumholz (brother-in-law of statin-KOL Paul Ridker) shows that the combined relative risk reduction for CV deaths was NS (-4%)
essais de la réduction lipidique intensive

INTENSIVE STATINISATION : A META-ANALYSIS OF FIVE TRIALS
* The Preiss/*JAMA*/2005 meta-analysis[471] of 5 trials comparing intensive-dose statinisation with moderate-dose (PROVE IT-TIMI 22, A to Z, TNT, IDEAL and SEARCH) showed pooled odds ratios of :

a) 1.12 (or +12%) for new-onset diabetes and
b) 0.84 (or -16%) for the composite endpoint of major CV events, « too modest in the context of multiple statistical tests », not significant at the 0.005 level. For individual components :

c) 0.94 (NS) for CV death
d) 0.87 (or -13 %) for nonfatal MI; annual NNT_{exp} of 578 patient-years
e) 0.90 (NS) for nonfatal stroke
f) 0.80 for coronary revascularization, a subjective/soft outcome since it is a medical decision ; annual NNT of 171 patient-years
statinisation intensive : une méta-analyse de cinq essais

INTERACTIONS WITH PROTEASE INHIBITORS *Interactions dangereuses*
* The FDA published in March 2012 a list of 7 statins to be avoided or whose dosing levels should be limited when coadministered with protease inhibitors. Atorvastatin (Lipitor™), lovastatin, rosuvastatin, and simvastatin are either listed as contraindicated or have had limits put on dosages.

In particular, lovastatin and simvastatin blood levels can increase beyond 10-fold when used with protease inhibitors, and rosuvastatin (Crestor™) exposure can increase up to 3-fold, risking rhabdomyolysis[472]
interactions avec les inhibiteurs de la protéase / de protéases
* ces inhibiteurs sont utilisés contre le VIH et l'hépatite C

INTERNATIONAL COST DIFFERENCES
« While Ontario (CA) pays 62.5 cents for one 20mg tablet of simvastatin, New Zealand pays 2.4 cents. In fact, the price in NZ dropped to 1.8 cents after the research was completed, while Ontario's stayed the same. That means Ontarians now (2102) pay 36 times more than New Zealanders for the same drug »[473]
différences internationales des coûts

INTERSTITIAL LUNG DISEASE *Statinovigilance - Vignette*

[471] Preiss et al. JAMA 2011; 305(24): 2556 – Full paper at http://jama.jamanetwork.com/article.aspx?articleid=646699
[472] http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm
[473] http://umanitoba.ca/outreach/evidencenetwork/wp-content/uploads/2012/12/Canadian-Health-Policy-in-the-News_DEC-10_12.pdf

pneumopathie interstitielle
* Une femme de 69 ans sous pravastatine présente une toux sèche, avec images bilatérales de pneumopathie interstitielle, hypoxémie et 15% d'éosinophiles dans le lavage bronchoalvéolaire. Déchallenge positif (De+): franche amélioration clinique et radiologique[474]

INTOLERANCE RATE ESTIMATION
« Statin intolerance, predominantly due to muscle-related side effects, is reported in up to 10%-20% of patients[475] »
estimation du taux d'intolérance

IRRESPONSIBLE STATINIZATION *Vignette*
« About 9 years ago, my sister (who was in her mid-30s) had a routine physical that revealed elevated cholesterol. Her (highly-rated) doctor immediately suggested statins, without even discussing other possible approaches (she was overweight and sedentary at the time). Fortunately, she was resistant enough to meds as a first resort to ignore his advice -- he didn't even consider that she was breastfeeding at the time, nor did he warn her that statins were contraindicated in that situation...

(It was not a secret; she told him during her appointment that breastfeeding made fasting for the blood exam particularly difficult.) She started eating better and exercising and lost weight, and today her numbers are normal. She also immediately found a new doctor because she no longer trusted the one who was insane (or negligent) enough to suggest pills right off the bat, without even considering all the relevant factors[476] »
statinisation irresponsable
* et en plus, un cholestérol même modérément élevé, surtout chez une femme, n'a pas à être abaissé, puisque l'hypothèse lipidique ne tient pas la route. Tant mieux si cette dame a amélioré sa diète et son activité physique, mais ce n'était pas nécessaire de 'normaliser ses chiffres'

IS THE USE OF CHOLESTEROL-LOWERING DRUGS FOR THE PREVENTION OF CARDIOVASCULAR COMPLICATIONS IN TYPE 2 DIABETICS EVIDENCE-BASED? A Systematic Review – (Article de synthèse) *Statines chez diabétiques*
Michel de LORGERIL et al. *Reviews on Recent Clinical Trials*, 2012, 7(2):1

« In summary, the 4D and ASPEN trials showed that statins do not provide any benefit in diabetics in terms of both CV complications and overall mortality. The two trials complement each other: in 4D (diabetics with end-stage kidney failure), patients were at very high risk while in ASPEN patients were at rather low risk. Furthermore, FIELD showed that cholesterol-lowering through the use of a non statin drug also had no benefit »
L'utilisation des réducteurs de cholestérol pour prévenir les complications cardiovasculaires dans le diabète de type 2 est-elle factuelle ? Une synthèse méthodique (Traduction libre du titre de l'article)
* Les hypocholestérolémiants ne préviennent pas les complications CV chez les diabétiques, selon 4 essais contrôlés (atorvastatine dans Cards, 4D et Aspen ; fénofibrate dans Field). Ajoutés à l'effet diabétogène des statines, ces faits rendent douteuse leur indication chez tous les diabétiques, pourtant promue par les meneurs d'opinion, les organismes émetteurs de directives et les institutions universitaires et professionnelles

ISCHEMIC HEART DISEASE ; IHD
cardiopathie ischémie ou CI ; coronaropathie ; angiopathie coronaire / coronarienne

Isolated cases of statin-associated neuropathy have been reported since 1994. Epidemiological and case-control studies from the U.K. and Denmark suggest elevated odds ratios (ORs) of 2.5 (95% CI 0.3–14.2) to 3.7 (1.8–7.6), respectively, for the development of neuropathy while on statin therapy. The OR jumped to 26.4 (7.8−45.4) in patients with confirmed neuropathy taking statins for >2 years[477] »

« Peripheral nerves may be targets of statin-induced pathology, as well. This issue was addressed by Gaist et al. (*Neurology* 2002; 58: 1333) in a study of 465,000 people in Denmark. The authors asked all patients who had polyneuropathy of unknown cause how many were on statin treatment compared with the general population in the county... They calculated that the risk for definite polyneuropathy was 16.1-times higher for current statin users than for non-users and 26.4-times higher for those who had used statins for more than 2 years »[478]
polyneuropathie statinique

[474] Prescrire 2005 ; 25(265) : 672
[475] Stroes et al. J Am Coll Cardiol 2014 - doi:10.1016/j.jacc.2014.03.019
[476] Sam Raider. http://well.blogs.nytimes.com/2014/05/05/a-new-womens-issue-statins/?_php=true&_type=blogs&_r=0
[477] Diabetes Care 2005 Aug; 28(8): 2082-2082 - http://care.diabetesjournals.org/content/28/8/2082.1
[478] Okuyama et al. Expert Rev Clin Pharmacol 2015 : 1 - doi: 10.1586/17512433.2015.1012494

* elle peut être sensitive, sensitivo-motrice, ou une aréflexie achilléenne; rarissime, le NNH annualisé est estimé à 10 000 mais les études sponsorisées sous-estiment systématiquement et intentionnellement ces risques... Le lien de causalité est cependant conforté par plusieurs cas de déchallenge positif (De+) et même de rechallenge positif (Re+) [479], démontrant que l'imputabilité (i.e. confiance dans le lien causal) n'attend pas après les fréquences 'statistiquement significatives' qui seules sont reconnues par les promoteurs craignant pour leurs chiffres de ventes…

J-LIT, THE TRIAL (JA)[480] *Prévention primaire – Essai cliniquement négatif – Arrêt prématuré injustifié – Rosuvastatine* -
l'essai dit J-Lit

JAPAN LIPID INTERVENTION TRIAL - (Article) *Épidémiologie – Cohorte sous statine*
Matsuzaki et al. *Circ J* 2002 ; 66(12) : 1087-95

« A cohort study of 47,294 Japanese patients treated for 6 years with open-labeled simvastatin (5-10 mg/day) and monitored by physicians under standard clinical conditions, aimed at studying the relationship between the occurrence of CHD and the serum lipid concentrations during low-dose simvastatin treatment »[481]

« Patients wih TC levels above 5.7 mM (220 mg/dl) were treated with low-dose simvastatin with *no control group*. Mortality rates for CV disease, stroke, cancer and all causes were *elevated* with *decreasing* TC levels from 5.7 mM [unsupportive of cholesterol hypothesis]. Results are inconsistent with the authors' cholesterol guidelines aiming to lower TC levels below 5.7 mM »[482]

JUPITER : INCREDIBLE RELATIVE RISK REDUCTION OF CORONARY EVENTS *Plausibilité factuelle douteuse*
« The relative risk reduction of -44% was much higher than in previous trials »[483]
réduction non crédible du risque relatif dans l'essai dit Jupiter
* Si une statine réduit relativement de -25% (RR = 0,75) le risque d'événements coronariens et que le risque des témoins sous placebo atteint 4% par an, comme chez certains hommes d'âge mûr et coronariens, alors on obtient une réduction absolue de 1% par année-patient, ramenant le risque à 3% par an, et l'on pourrait alors – et seulement alors - considérer qu'il s'agit d'un effet cliniquement non négligable...

Une méta-analyse de Baigent et coll., effectuée par un groupe notoirement pro-industrie (Cholesterol Clinical Trialists), rapporte une réduction relative de -23% du risque coronarien dans une population moitié primaire (53%) moitié secondaire (47%) et une réduction du risque absolu de seulement -0,48% par année-patient, pour un NNT_{exp} de 208 patients-année, un taux annuel d'inefficacité de 99,52%, un délai moyen d'événement coronarien de 1,75 jour ou 42 heures si on répartit le bénéfice sur l'ensemble de 208 patients traités un an et 75 920 comprimés ...

La réduction relative de -54% rapportée dans JUPITER pour les événements coronariens manque de crédibilité car tout nouvel essai doit être évalué dans le contexte de tous les précédents essais et quand une discordance est observée, il faut l'expliquer

JUPITER : *BY JOVE! WHAT IS A CLINICIAN TO MAKE OF JUPITER?* – (Article)
Kaul S et al. *Arch Intern Med* 2010; 28; 170(12):1073 - doi: 10.1001/archinternmed.2010.189[484]

« Treatment benefit is likely to be overestimated and risk underestimated by early stopping of the trial… Do not stratify treatment decisions by hsCRP level… Do not expect 50% relative risk reduction in outcomes… Do not forget diet and exercise since lifestyle modification trumps pharmacologic interventions for primary prevention »

JUPITER : CONFLICTS OF INTEREST SITUATIONS *Méga-essai - Liens d'intérêts – Leaders d'opinion*
* The highly controversial megatrial of rosuvastatin in primary cardiovascular prevention was supported by Astra-Zeneca. Here follow the stated pharmaceutical industry COI situations of the stated authors :

« Lead author Dr. Ridker reports receiving grant support from AstraZeneca, Novartis, Merck, Abbott, Roche, and Sanofi-Aventis; consulting fees or lecture fees or both from AstraZeneca, Novartis, Merck, Merck–Schering-Plough, Sanofi-Aventis, Isis, Dade Behring, and Vascular Biogenics; and is listed as a *coinventor on patents* held by Brigham and Women's Hospital that relate to

[479] Prescrire 2007;27(282) :269
[480] Matsuzaki et al. Circ J 002 ; 66(12) : 1087
[481] http://www.ncbi.nlm.nih.gov/pubmed/12499611
[482] Okuyama et al. Expert Rev Clin Pharmacol 2015 : 1 - doi: 10.1586/17512433.2015.1012494
[483] Donner-Banzhoff & Andreas Sönnichsen. BMJ 2008 ; 337 : a2576
[484] Abstract at http://www.ncbi.nlm.nih.gov/pubmed/20585074

the use of inflammatory biomarkers in cardiovascular disease, including the use of high-sensitivity C-reactive protein in the evaluation of patients' risk of cardiovascular disease. These patents have been *licensed* to Dade Behring and AstraZeneca.

Dr. Fonseca reports receiving research grants, lecture fees, and consulting fees from AstraZeneca, Pfizer, Schering-Plough, Sanofi-Aventis, and Merck; and

Dr. Genest (Montreal), lecture fees from AstraZeneca, Schering-Plough, Merck–Schering-Plough, Pfizer, Novartis, and Sanofi-Aventis and consulting fees from AstraZeneca, Merck, Merck Frosst, Schering-Plough, Pfizer, Novartis, Resverlogix, and Sanofi-Aventis.

Dr. Gotto reports receiving consulting fees from Dupont, Novartis, Aegerion, Arisaph, Kowa, Merck, Merck–Schering-Plough, Pfizer, Genentech, Martek, and Reliant; serving as an expert witness; and receiving publication royalties.

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Dr. Koenig reports receiving grant support from AstraZeneca, Roche, Anthera, Dade Behring and GlaxoSmithKline; lecture fees from AstraZeneca, Pfizer, Novartis, GlaxoSmithKline, DiaDexus, Roche, and Boehringer Ingelheim; and consulting fees from GlaxoSmithKline, Medlogix, Anthera, and Roche.

Dr. Libby reports receiving lecture fees from Pfizer and lecture or consulting fees from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, Sanofi-Aventis, VIA Pharmaceuticals, Interleukin Genetics, Kowa Research Institute, Novartis, and Merck–Schering-Plough.

Dr. Lorenzatti reports receiving grant support, lecture fees, and consulting fees from AstraZeneca, Takeda, and Novartis; Dr. Nordestgaard, lecture fees from AstraZeneca, Sanofi-Aventis, Pfizer, Boehringer Ingelheim, and Merck and consulting fees from AstraZeneca and BG Medicine;

Dr. Shepherd, lecture fees from AstraZeneca, Pfizer, and Merck and consulting fees from AstraZeneca, Merck, Roche, GlaxoSmithKline, Pfizer, Nicox, and Oxford Biosciences; and

Dr. Glynn, grant support from AstraZeneca and Bristol-Myers Squibb. No other (sic) potential conflict of interest relevant to this article was reported »[485]

situations de conflits d'intérêts dans l'essai Jupiter

JUPITER : MISREPORTING OF CHD DEATHS AND ABUSE OF RELATIVE RISKS

« The trial was stopped after a median follow-up of 1.9 years. The number of subjects with a primary endpoint was 251 (2.8%) in the control group and 142 (1.6%) in the rosuvastatin group. The difference in endpoint rate of 2.8% vs 1.6% yields an absolute risk reduction of 1.2 percentage points and an NNT of 83 [over 1.9 year; but an annual NNT of 158 patient-years]. The benefit with regards to the number of fatal and nonfatal heart attacks was even smaller...

There were only 68 (0.76%) vs 31 (0.35%) events, respectively, resulting in an absolute risk reduction of 0.41 percentage points and an NNT of 244 [over 1.9 year ; but an annual NNT_{exp} of 464 patient-years]. This means that regarding fatal and nonfatal CHD, less than one-half of 1% of the treated population (0.41%) benefited from rosuvastatin treatment, and 244 people needed to be treated to prevent a single fatal or nonfatal heart attack…

Despite this meager effect, in the media the benefit was stated as 'more than 50% avoided a fatal heart attack'...

Thus, the public and healthcare workers were informed of a 54% reduction of heart attacks when the actual effect in the treated population was a reduction of less than 1 percentage point. Moreover, the absolute risk reduction of 0.41 percentage points – and its corresponding NNT_{exp} of 464 patient-years] was the combination of fatal and nonfatal heart attacks. There was little attention paid to the fact that more people had died from a heart attack in the treatment group...

Even experienced researchers may have overlooked this finding because the figures were not explicitly stated in the report. One

[485] Ridker et al. N Engl J Med 2008; 359:2195-2207 November 20, 2008 – Site http://www.nejm.org/doi/full/10.1056/NEJMoa0807646#t=articleTop

needs to subtract the number of nonfatal CHD from the number of 'any MI' to see that there were 11 fatal heart attacks in the treatment group, but only 6 in the control group »[486]
Jupiter : fausse représentation des décès coronariens et abus des risques relatifs

JUPITER : NO HEAD-TO-HEAD COMPARISON
« Because rosuvastatin was not compared directly with simvastatin and other statins, we do not know whether it is really better. Established and cheaper statins should be preferred »[487] by good-faith prescribers who still believe in statins
Jupiter : pas de comparaison face-à-face
* de voir le Crestor™ figurer en haut du palmarès des produits les plus prescrits au monde année après année dans les pays développés, y prenant le relais du Lipitor™ en fin d'exclusivité, est un scandale pharmaco-économique qui montre l'influence de la promotion et les faiblessese de la FMC

JUPITER : NONFATAL MI REDUCTION
* In JUPITER, in primary prevention, the rate was 0.33% per person-years in the placebo group and 0.12% in the rosuvastatin arm. Relative risk reduction was -65% (HR 0.35, 95% CI 0.22 to 0.58) and absolute risk reduction was 0.21 per 100 person-years, yielding a NNT of 476 person-years and a rate of inefficacy of 99.79% per treatment-years. The perfect example of negligible clinical relevance. « At a retail cost of 5 US$ for daily Crestor™, the cost per event prevented would be US$ 868 700, much higher than treating a non fatal MI
réduction de l'IDM non fatal dans Jupiter

JUPITER : NONFATAL STROKE REDUCTION
* In JUPITER, the reduction of nonfatal stroke risk is clinically futile. The annual NNT for nonfatal stroke reduction was 667 since the annual rate was 0.31 per 100 persons in the placebo group and 0.16 in the Crestor™ arm for a relative risk reduction of 48% (hazard ratio 0.54) and an absolute risk reduction of 0.15 per 100 person-years, a yearly inefficacy rate of 99.85% (100 - 0.15 = 0.9985), not to mention adverse reactions and costs…

« At $5.10 retail per pill (USA, 2009, one drugstore) the cost per event prevented is over $1.2 M, not to mention other related costs »[488], which is of course ridiculous
réduction des AVC non fatals dans Jupiter

JUPITER : RUN-IN PHASE TO SELECT THE MORE COMPLIANT *Validité externe biaisée et trompeuse*
« A 4-week placebo run-in phase allowed Jupiter investigators to select highly compliant patients, limiting the external validity of the trial »[489]
Jupiter : phase de qualification permettant de choisir les plus-observants
* bel exemple de 'tricherie organisée'…

JUPITER : THE CRITICISM *Statines – Prévention primaire*
« The results[490] of the trial do not support the use of statin treatment for primary prevention of CV diseases and raise troubling questions concerning the role of commercial sponsors - The trial was flawed. It was discontinued (according to prespecified rules) after fewer than 2 years of follow-up, with no differences between the 2 groups on the most objective criteria...

Clinical data showed a major discrepancy between significant reduction of nonfatal stroke and myocardial infarction but no effect on mortality from stroke and myocardial infarction…

CV mortality was surprisingly low compared with total mortality—between 5% and 18%—whereas the expected rate would have been close to 40%. Finally, there was a very low case-fatality rate of myocardial infarction, far from the expected number of close to 50%. The possibility that bias entered the trial is particularly concerning because of the strong commercial interest in the study »[491]

"In the JUPITER trial the NNT's are massive and women have double the NNT for 'MI + stroke + death', a composite endpoint not reported separately for women, which adds to the fact that statins don't affect female mortality in any study ever published - The FDA is clear that CV mortality was not reduced [in JUPITER] while the other two rosuvastatin studies, CORONA and AURORA,

[486] Diamond & Ravnosk, Expert Rev Clin Pharmacol 2015 ; 1 – DOI : 10.1586/17512433.2015.1012494
[487] Donner-Banzhoff & Andreas Sönnichsen. BMJ 2008 ; 337 : a2576
[488] Eddie Vos, 2009
[489] Donner-Banzhoff & Andreas Sönnichsen. BMJ 2008 ; 337 : a2576
[490] Ridker et al. NEJM 2008 ; 359 : 2195
[491] Michel de Lorgeril et al. Arch Intern Med 2010; 170(12): 1032

were resounding failures in any aspect"[492]

"In the JUPITER trial there were about 3,400 women in each group and there were 21 fewer revascularizations under rosuvastatin (Crestor™), amounting to a NNT of 307 women-years to avoid a single revascularization, in other words an unjustified treatment in 306 women-years, notwithstanding the adverse reactions. At an average purchasing cost of $5.53 per day of Crestor™, it amounts to $625,660 per procedure avoided[493]"

"JUPITER should simply be discarded as irrelevant and at best doubtful in its conclusions[494]"
« JUPITER was stopped early as benefit was shown, such terminations tend to introduce biases that oversate benefits while underestimating long-term harms »[495]
* The quality and credibility of JUPITER are too low to take its results seriously and make its recommendations valid

"The rate of heart attacks was 0.37%, or 68 patients out of 8,901 who took a sugar pill. Among the Crestor™ patients it was 0.17%, or 31 patients. That 55% relative difference between the two groups translates to only 0.2 percentage points in absolute terms — or 2 people out of 1000. Stated another way, 500 people would need to be treated with Crestor™ for a year to avoid one usually survivable heart attack…

Stroke numbers were similar. That's not clinically significant, said cardiologist Steven W. Seiden. At $3.50 a pill, the cost of prescribing Crestor™ to 500 people for a year would be $638,000 to delay 1 heart attack[496]"

"A recent clinical study so totally out of this world it bore the name of a distant planet. Whatever you might conclude about the jaw-dropping JUPITER trial (take home message: regardless of your cholesterol level, get your CRP checked and eat statins every day), you can't deny it was seriously red-lining on the gullibility tachometer...

Because the reports of the study openly disclosed that the co-inventor on the patent for the C-reactive protein test headed up the study, we ordinary rubes, no doubt fortified by such disclosure, lined up to whip out our checkbooks and invest in this tidy little bit of pharma ingenuity"[497]
* Serious adverse events were reported but not reduced in the treatment arm[498]

« The Baycol™ story has been a masterpiece of diverting attention away from harm as evidenced by the triumph of Crestor™ (still a 'do no use drug' at WorstPillsBestPills), Crestor™ emerged in triumph after the 'statin wars' in Lancet 2003-2004 or so when Horton called for it to be pulled off the market. Poster child for one of the worst conflicted and manipulated trials »[499]
« JUPITER reported data on serious adverse events but did not find a reduction associated with statins »[500]

« Five different versions of CV mortality were (unaceptably) reported »[501], an example of data manipulation
« The small difference in overall mortality was not validated by FDA statisticians… CV mortality was ultimately not judged different »[502]
Jupiter : la critique
« Le plan d'analyse initial de Jupiter était que les patients soient suivis au moins 4 ans pour espérer voir un effet bénéfique du traitement. Mais au bout de < 2 ans, Jupiter a été arrêté sous prétexte que les effets bénéfiques étaient extraordinaires (sic), un peu comme si dans une course de chevaux prévue sur 4 tours d'hippodrome, les organisateurs - qui avaient eux-mêmes engagé un cheval et parié très gros sur lui - décident d'arrêter la course après moins de 2 tours sous prétexte que leur favori a une si grande avance qu'il ne peut plus être rattrapé ! »[503]

JUPITER : THE TRIAL VENUES *Délocalisation des essais*
les lieux de l'essai
« L'appendice de la publication princeps dans le *NEJM* donne le nombre de patients inclus par pays… *Argentine*, Belgique, *Brésil*,

[492] Eddie Vos. Communication, 2009
[493] Eddie Vos. Communication, 2010
[494] Mikael Rabaeus. BMJ 2008; 337 :1368 and 337: a7921 – Rabaeus is a Swiss cardiologist
[495] Mike Mika. JAMA 2011; 306(19): 2077
[496] Duff Wilson. New York Times 30.3.2010, on http://www.nytimes.com/2010/03/31/business/31statins.html?pagewanted=1&emc=eta1
[497] Alan Cassels. http://www.cmaj.ca/cgi/content/full/181/1-2/112?etoc
[498] http://www.bmj.com/content/347/bmj.f6123
[499] Harriet Rosenberg, 2013
[500] Abramson et al, 2012, op. cit.
[501] Michel de Lorgeril, AHA, Los Angeles, 2012
[502] de Lorgeril et al. Arch Intern Med 2010 ; 170 : 1032 – de Lorgeril et al. BMC Med 2013 ; 11 : 5
[503] Michel de Lorgeril. http://michel.delorgeril.info/index.php/2009/06/21/44-statines-et-cholesterol-illusions-scientifiques-et-medicales

Bulgarie, Canada, Chili, *Colombie*, *Costa-Rica*, Danemark, *El Salvador*, Estonie, Allemagne, Israel, *Mexique*, Hollande, Norvège, *Panama*, Pologne, É.-U., R.-U. - Plusieurs (cités en *italique*) n'ont pas de tradition suffisante en science et en éthique cliniques pour inspirer confiance et la FDA n'a pas les ressources ni la volonté politique pour y effectuer les contrôles nécessaires

JUPITER : THE WOMEN

« In JUPITER, the only benefit in women in any of the 5 primary endpoint components was the 73% relative reduction in revascularizations… translated in absolute terms in only 21 fewer revascularizations after 6 500 women-on-statin years, or one event avoided per 303 women-years of treatment... Mora et al.[504] admit that 'statins had not been found to reduce total or coronary mortality in women, men, or combined for primary prevention' »[505]

« In JUPITER women, there was a reduction in revascularization/unstable angina and reductions in other components of the primary end point »[506] - "In the JUPITER trial the NNT's are massive and women have double the NNT for 'MI + stroke + death', a composite endpoint not reported separately for women, which adds to the fact that statins don't affect female mortality in any study ever published"[507]

« The JUPITER trial, which included 6,801 women age 60 and older, found a lower risk of so-called soft endpoints, like hospitalization for unstable angina, among healthy women taking statins. But the absolute number of these health setbacks was small, and there was no reduction in heart attacks, strokes and deaths among these women »[508]

les femmes de Jupiter

* Dans une republication bien orchestrée[509] pour augmenter la visiblité du Crestor™ ou encore pour se défendre contre les critiques, on concède qu'il faille 303 femmes-années sous rosuvastatine (Crestor™) pour éviter une seule revascularisation coronaire, et ce, en situation expérimentale chez des patientes hautement sélectionnées et encadrées…

Il s'ensuit que 302 femmes sur 303, prétendues à haut risque par un taux élevé de protéine C-réactive (PCR), seront exposées au Crestor™ durant toute une année sans service médical rendu tout en les exposant aux effets indésirables directs (myopathie, diabète et autres) et indirects (interactions médicamenteuses), aux effets psychologiques (le fait d'être considérée 'malade du cholestérol' et suivie par un médecin et médicamentée), en plus de coûter cher à l'achat durant la durée du brevet...

Rien ne nous dit que le NNT annualisé expérimental corresponde à celui de la pratique courante, où les patientes ne sont pas hautement sélectionnées comme elles le furent dans Jupiter; le NNT clinique est toujours plus élevé qu'en situation expérimentale, c'est raisonnable et réaliste de l'affirmer. Le NNT clinique est peut-être de 400, 500 voire 600 femmes-année...

De plus, ce critère est dit 'mou' parce que lié au seuil de douleur angineuse de la patiente, à l'attitude des urgentologues et au seuil utilisé par les cardiologues, à la proximité d'un hôpital équipé d'une salle de cathétérisme…

Dans cet essai, rappelons que chez les femmes ni la mortalité générale, ni la mortalité CV, ni les infarctus non fatals (NNT = 470 années patientes), ni les AVC (NNT = 660 années-patientes), n'ont été réduits dans le groupe exposé au Crestor™. En résumé : Un NNT de 303 femmes années, et un coût de 553 000$ pour éviter une angioplastie. Le Crestor™ coutait environ 5 US$ par jour en 2009 au Vermont au moment de faire le calcul…[510]

Si on ajoute les frais indirects (visites au médecin, mesures répétées du cholestérol, diagnostic et traitement d'une éventuelle myopathie ou d'un nouveau diabète), le coût pour reporter d'une année une angioplastie pourrait facilement être supérieur voire doublé. Sans compter les effets psychologiques de la médicalisation et de la médicamentation, en plus du détournement des ressources, tous des éléments qui ont un coût sociétal

La statinisation des femmes ménopausées et non coronariennes, comme celles recrutées dans Jupiter, est injustifiable médicalement et économiquement, même si la FDA et l'EMA ont reconnu en 2010 cette indication sur la base d'un seul essai, de grande envergure certes, mais criblé de biais, porteur de données douteuses et débordant de conflits d'intérêts

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[504] Circulation 2010; 121: 1069
[505] Vos, Rose & Biron. Circulation 7.12.2010 (Correspondence)
[506] Circulation 2010; 121: 1069
[507] Eddie Vos. Communication, 2009
[508] Roni Caryn Robin. http://well.blogs.nytimes.com/2014/05/05
[509] Mora S et coll. Circulation 2010;121(9) :1069
[510] Vos E, Rose C & Biron P. Statins don't extend lives in high risk women. Letter, Circulation 2010;122(23) :e577 on line 8.12.2010, site http://circ.ahajournals.org/cgi/content/extract/122/23/e576

JUPITER : UNJUSTIFIED PREMATURE INTERRUPTION

« Stopping the trial prematurely may have introduced biases, potentially resulting in an overestimate of benefit and an underestimate of harm (Vaccarino et al. *CCQO* 2009; 2(3) : 286 - Yusuf et al. *Lancet* 2009; 373(9670) : 1152) … Prematurely truncated trials are notorious for being vulnerable to implausibly large ("too good to be true") estimates of treatment benefits that later exhibit "regression to the mean" on longer follow-up »[511]

« JUPITER was an event-driven trial designed to detect a 25% reduction in risk of a major cardiac event. Two interim analyses were prespecified, the first after 3/8th of the projected 520 outcome events occurred (195 events), and the second after 3/4th of the outcome events occurred (390 events). The 2nd analysis was actually conducted after only 5/8th of the events occurred (328 instead of the planned 390 events)...

Based on this 2nd analysis, the *Independent Data Monitoring Board* recommended early termination of the study after a median follow-up of only 1.9 years instead of the projected 4 years. The details of the stopping rules on which this decision was based were not published in the primary report »[512], making this a breach in the protocol that is not only controversial, but outright fraudulous intellectualy

« Trials stopped early pose interpretive challenges for estimating benefit-risk balance. Results tend to fluctuate in the early stages of trials, until sufficient events occur to stabilize the rates, and interim analyses can truncate trials at a random high (or low) point, producing misleading estimates of treatment benefits (or harm)…

A recently published systematic review of 515 trials reported that most truncated trials overestimate benefits compared with their matched completed trials (Bassler D et al. *JAMA* 2010; 303(12) : 1180). On average, the ratio of RRs in the truncated and matching completed trials was 0.71 »[513] … If one applies this ratio to Jupiter, its results were conflated by +29%
interruption prématurée de Jupiter injustifiée

JUPITER STANDS OUT IN TOTAL MORTALITY IN PLACEBO-CONTROLS AT 21-MONTHS *Crédibilité des données cliniques*

* Jupiter was stopped prematurely (and without sound medical or ethical reasons) at around 21 months. Being a primary prevention trial with low risk patients (no hypercholesterolemia, no previous CV disease, no diabetics, no hypertensives, only 16% smokers), the 21-month total mortality rate in the placebo group should have been :

a) equal to other primary prevention trials with healthy patients (< 1%)
b) slightly lower than in primary prevention trials with higher risk patients (diabetes, hypertension, renal failure)
c) much lower than in a secondary prevention trial (shortly after an acute coronary syndrome, 2.7%)...

But it was almost twice as high, does not make sense, and raises suspicion of errors warranting an independant re-examination of vital records gathered by the promoter :[514]

a) JUPITER : (rosuvastatin in healthy) the rate is 2.8% in the placebo group, instead of an expected < 1%
b) CARDS : 2.8% (

JUPITER, THE TRIAL

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
* Princeps publication : Ridker, *NEJM*, 2008[515]

METHODOLOGY
* Participants demography : 38% women
* Duration : median of 1.9 year (22.8 months), stopped prematurely without valid justification
* Primary composite outcome made of major CV events : [non fatal MI + non fatal stroke + arterial revascularization + hospitalized unstable angina + CV death] – Too *heterogenous* for both internal and external validities
* Positive compliance (active group adherence) : 75% - Note that 0% were in-trial after premature termination and their course remains unkown, thus reducing internal validity
* Negative compliance (control group adherence) : 75% - Note that 0% were in-trial after premature termination and their

[511] Kaul et al. Arch Intern Med 2010; 170 (12) : 1073 - http://www.courses.ahc.umn.edu/pharmacy/5822/Kaul_by%20Jove%20-%20What%20is%20a%20clinician%20to%20make%20of%20JUPITER_ARch%20Int%20Med%202010.pdf
[512] Kaul et al. op. cit.
[513] Kaul et al. op.. cit.
[514] Victor L Serebruany. Cardiology 2011; 120(2): 84-8 (Editorial) - DOI:10.1159/000330507
[515] Ridker et al. NEJM 2008 ; 359 : 2195

course remains unknown, thus reducing internal validity.

NOTE : From the Jupiter publication in the NEJM, the trial was conducted at 1315 sites in 26 countries. It is well known that the Department of Justice (US) is particularly interested in corrupt payments that may have influenced the reliability or integrity of data in any clinical trials performed outside the US" but this aspect of the Jupiter trial has never been investigated or reported on.

RESULTS
* Primary endpoint : « 251 (2.8%) in the control group and 142 (1.6%) in the rosuvastatin group. The difference in endpoint rate of 2.8% vs 1.6% yields an absolute risk reduction of 1.2 percentage points and an NNT of 83 »[516], amounting to an absolute risk reduction of 0.63 percentage points per treatment-years, a too minuscule benefit to justify premature termination, equivalent to an annual NNT of 158 patient-years under trial conditions, and possibly ranging from 237 to 316 patient-years in a clinical setting

* Fatal and non fatal MI : « The benefit with regards to the number of fatal and nonfatal heart attacks was even smaller. There were only 68 (0.76%) vs 31 (0.35%) events, respectively, resulting in, an absolute risk reduction of 0.41 percentage points and an NNT of 244 »[517], equivalent to an annual NNT of 464 patient-years in experimental conditions
* Fatal MI : a NS absolute increase of 5 cases, not properly explicited (i.e. hidden) by the princeps authors :

« There was little attention paid to the fact that more people had died from a heart attack in the treatment group. Even experienced researchers may have overlooked this finding because the figures were not explicitly stated in the report. One needs to subtract the number of 'nonfatal CHD' from the number of 'any MI' to see that there were 11 fatal heart attacks in the treatment group, but only 6 in the control group »[518]

* Health related quality of life *not reported*
* New onset diabetes : « In the rosuvastatin group there were 270 new cases of diabetes, but only 216 in the control group (3% vs 2.4%). Unlike beneficial effects, which the authors amplified in the magnitude of its appearance using relative risk reduction, the significant effect of *new onset diabetes* by Crestor™ treatment was expressed only in the absolute risk reduction form »[519] - Presenting ADRs in absolute risk increases (ARI) is a statistical manipulation typical of ghostwritten sponsored trials

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : Yes, we have access to data, shared with CTT
l'essai dit Jupiter
Chercher JUPITER avec la fonction Ctl-F ou Cmd-F dans la présente annexe

KAPS, THE TRIAL
Kuopio Atherosclerosis Prevention Study

KEY OPINION LEADERS IN CANADA
TN : Number of titles after their names ranges from 2 to 8, which increases the potential to influence colleagues

a) Interested in PCSK9 inhibitors : Lawrence A. Leiter, Robert Dufour, Gordon A. Francis, Jacques Genest Jr, Shaun Goodman, Jean C. Grégoire, Milan Gupta, Robert A Hegele, John Mancini, James A. Stone, Peter Lin, Gorge Honos, Nabil Seidah, Subodh Verma, Jean-François Tanguay...

b) Interested in bringing LDL-cholesterol below 2.6 mmol/L or below 3.0 mmol/L in already statinized patients : David Bewick, Daniel Gaudet, Jacques Genest Jr, Robert Hegele, Eva Lonn, Daniel Ngui, Milan Gupta, Narendra Singh

c) Promoting use of statins in younger people : George Thanassoulis ; Allan D Sniderman
meneurs d'opinion canadiens influents
* ceux-là – il y en a d'autres - figurent sur la liste des membres de comités scientifiques de conférences visant la promotion de la réduction du LDL-C par la nouvelle classe des inhibiteurs de la PCSK9, même si des chercheurs indépendants ont déjà

[516] Diamond & Ravnskov, op. cit.
[517] Diamond & Ravnskov, op. cit.
[518] Diamond & Ravnskov, op. cit.
[519] Diamond & Ravnskov, op. cit.

démontré l'inutilité des cibles chiffrées, et l'existence d'une association épidémiologique entre un bas cholestérol et un surcroit de mortalité dans plusieurs pays et dans la majorité des situations cliniques...

Les inhibiteurs de la PCSK9 sont autorisés dans les pays riches, avec un empressement incompréhensible malgré l'absence de démonstration d'une réduction de la mortalité toute cause ou coronarienne ou d'une amélioration de la qualité de vie, ce qui soulève d'importantes questions ...

Sans compter que des troubles cognitifs[520] ont été associés à ces produits, et que la pharmacovigilance des anticorps monoclonaux doit toujours être poursuivie avec rigueur et transparence. Ce sont des protéines, des réactions immuno-allergiques sont possibles et peuvent être graves

KIDNEY DISEASES AND LONG-TERM STATINIZATION
Néphrovigilance – Épidémiologie - Statinovigilance
« In this retrospective cohort study, we analyzed data from the San Antonio area military health care system from 10.2003 through 3.2012 (8.4 years). Statin users were propensity score matched to nonusers. Outcomes were acute kidney injury, chronic kidney disease, and nephritis/nephrosis/renal sclerosis...

Of the 43,438 subjects included, we propensity score matched 6,342 statin users with 6,342 nonusers. Statin users had greater odds ratios of acute kidney injury (1.30), chronic kidney disease (1.36) and nephritis/nephrosis/renal sclerosis (1.35). In a subset of patients without co-morbidities, the association of statin use with chronic kidney disease remained significant (OR 1.53)...

In conclusion, statin use is associated with increased incidence of acute and chronic kidney disease. These findings are cautionary and suggest that long-term effects of statins in real-life patients may differ from shorter term effects in selected clinical trial populations »[521]
maladies rénales et statinisation au long cours
* Dans une étude d'observation de cohorte rétrolective durant 8,4 ans, 12 684 employés de l'armée sous statines furent comparés aux non statinisés, avec ajustement sur les scores de propension. Les critères évalués furent les atteintes rénales aigues, la maladie rénale chronique et différentes néphroses.

Le risque relatif (estimé par le rapport de cote) des statinisés fut de +30% pour les atteintes aigues, de +36% pour les atteintes chroniques et de +35% pour différentes néphroses. Même chez un sous-groupe sans comorbidités, le rapport de cotes demeure significatif et est plus élevé à 1,53 ou +53%

KLIS, THE TRIAL
Kyushu Lipid Intervention Study

KRAUS CRITICISM OF WORLD-LEADING RCTs INCLUDING 4S AND WOSCOPS
* World-leading RCTs that have influenced policy have also produce biased results :
a) participants' background traits affect outcomes (external validity of included population)
b) factors influencing treatment response are often poorly distributed between trial groups (internal validity);
c) alternative factors contributing to main reported outcome are neglected (internal validity : co-treatments not comparable);
d) trials are often only partially blinded or unblinded (internal validity : co-treatments and outcome evaluations not comparable)[522]
les critiques de Kraus à l'égard des ECC mondialement reconnus, incluant 4S et Woscops

l'essai dit Excel

***L'HORRIBLE VÉRITÉ SUR LES MÉDICAMENTS ANTICHOLESTÉROL : Comment les statines empoisonnent en silence* (FR)** – (Livre numérique et broché)
Michel DE LORGERIL. Vergèze (FR): Thierry-Souccard ; 2015 – 256 pages - ISBN 978-2-36549-156-3

« L'auteur a été le premier à montrer que les études 'miraculeuses' sur les médicaments contre le cholestérol sont, comme le dit le Dr Horton, biaisées. En réalité, les statines n'empêchent ni les infarctus ni les AVC. Avec ce nouveau livre, il révèle que ces médicaments pris par des millions de personnes, sont terriblement toxiques. Cette toxicité peut rester silencieuse pendant des

[520] http://www.acc.org/latest-in-cardiology/articles/2015/06/01/12/36/early-evidence-linking-pcsk9-inhibitors-to-neurocognitive-adverse-events
[521] Acharya et al. http://www.ajconline.org/article/S0002-9149(15)02315-2/pdf - DOI: http://dx.doi.org/10.1016/j.amjcard.2015.11.031
[522] Krauss, op. cit.

années mais hélas, elle est réelle...

Elle est d'autant plus 'silencieuse' qu'une corruption généralisée touche les sciences biomédicales. Les données publiées sont modelées pour servir les intérêts de l'industrie pharmaceutique. Les autres, les gênantes, restent dans l'ombre sous le sceau du secret industriel. Il aura fallu toute l'expérience du Dr de Lorgeril, médecin et scientifique de renommée internationale, pour arriver à cette conclusion implacable :

Tous les médicaments anticholestérol, les anciens comme les nouveaux, sont toxiques du fait de leur mode d'action et aussi parce qu'ils privent le corps d'un facteur protecteur : le cholestérol ! Cette *horrible vérité* appelle trois mesures d'urgence : l'information immédiate des patients, le retrait des statines du marché et un moratoire sur la commercialisation des anti-PCSK9, la nouvelle génération d'anticholestérol »

La femme bien-portante et statinisée à vie est une femme stigmatisée, marquée pour la vie sans la prolonger ni en augmenter la qualité. Pire, c'est aussi le cas de la coronarienne statinisée. Quant au septuagénaire coronarien, il ne prolongera pas sa vie lui non plus.

À quand un moratoire sur la cholestérolémie de dépistage des bien-portants? Et sur la répétition « à vie » d'innombrables cholestérolémies de suivi ? Pourquoi pas, puisque les quelques heures ou jours de vie gagnés par année de statinisation de rares hommes coronariens pas trop âgés ne résultent probablement pas - et même les ayatollahs du cholestérol l'admettent enfin - de l'abaissement de la cholestérolémie.

Un cholestérol très bas ou très haut n'est pas un gage de longue vie, alors laissons le tranquille car rien ne sert de l'altérer artificiellement par nos poisons à petite dose. Si on expliquait impartialement la situation aux patients, question de partager la décision, on peut se demander combien s'engageraient dans une statinisation à vie en pleine connaissance de cause.

Même chez les diabétiques, chez qui les quatre essais d'hypocholestérolémiants ont été négatifs (*Cards, 4D, Aspen, Field*), à quoi servent les cholestérolémies à vie ? Sans oublier que l'effet diabétogénique des statines est maintenant reconnu et libellé dans la documentation officielle.

Même en utilisant les statines à forte dose chez des coronariens avérés, quatre essais publiés (*TNT, Ideal, Search, A to Z*) ne purent démontrer leur supériorité aux doses habituelles en termes de survie ; un cinquième qui fut positif statistiquement seulement, *Prove-It Timi-2*, se disqualia deux ans plus tard quand ses auteurs, sans refaire leurs calculs ni se rétracter, avouèrent avoir oublié (sic) une partie des résultats. Et nous passons sous silence les essais négatifs qui seraient demeurés enfouis dans les voutes des promoteurs.

Quand on analyse de façon critique la méthodologie et tous les résultats de tous les essais cliniques sponsorisés publiés, en écartant la conflation - l'inflation des conclusions -, on ne trouve pas de fondement scientifique solide à la statinisation en général. Ce qui n'empêche pas leurs auteurs (authentiques ou prête noms), les relationnistes, ainsi que plusieurs éditorialistes, méta-analystes, rédacteurs de directives cliniques, ou meneurs d'opinions cooptés en formation médicale sponsorisée, de dire, d'écrire, d'enseigner ou de recommander présomptueusement le contraire. *Homo Statinisus* est victime de *Homo Economicus.*

On exclue ici les rares hyperlipidémies familiales. Mais ce ne sont pas ces victimes génétiques qui grugent nos budgets pharmaceutiques. On les dépiste de toute façon par leur histoire personnelle et familiale et l'examen.

HUIT PROFESSIONNELS QUÉBÉCOIS TÉMOIGNENT

Martin Juneau, cardiologue (Institut de cardiologie de Montréal et Centre Épic), déplore que les statines engendrent 6,8 % des coûts en médicaments de la *Régie de l'assurance médicament du Québec* (214 M$ sur 3.126 G$ en 2012), alors que la prévention authentique par l'amélioration du mode de vie (sédentarité, malbouffe, stress) et des conditions de vie (statut socio-économique) n'est guère financée. - Robert Béliveau, généraliste qui se consacre à déstresser les coronariens (Centre Épic, Montréal), croit que l'hypothèse du cholestérol engendre une perte de liberté et de jouissance, une culpabilisation inutile, une tentative vaine, vouée à l'échec, à vouloir naïvement endiguer tous les risques et prolonger indéfiniment la vie. - Colin Rose, cardiologue (Centre universitaire de santé de l'Université McGill), a cru durant toute sa carrière rendre un service médical en sortant ses patients des griffes de la statinisation à vie, et en dénonçant la malbouffe dans son site web iconoclaste. - Paul van Nguyen, interniste (Centre hospitalier de l'Université de Montréal), témoin privilégié des effets indésirables graves voire fatals des statines, est aussi un 'déprescripteur' convaincu et conférencier sur le sujet. - Marc Zaffran, généraliste, écrivain, alias Martin Winkler, français mais québécois d'adoption, trouve que considérer le cholestérol, composant normal de notre physiologie, en poison lent, qu'il faut réduire à tout prix dans les deux sens de l'expression, par des médicaments inutiles et dangereux, représente une escroquerie planétaire. - Jean-Marie Therrien, généraliste en région estrienne, a suivi la scène du

cholestérol pendant 30 ans avant de conclure dans un livre[523] que les hypocholestérolémiants représentaient une grande supercherie. - Eddie Vos, chercheur indépendant en Estrie, dénonce ces vaines et ruineuses dépenses de la Ramq, dans un breffage qu'il a cosigné et soumis à l'*INESSS* le 25.2.2014. - Paul Poirier, cardiologue au Centre hospitalier de l'Université Laval de Québec[524], en a contre l'impression trompeuse des messages des pharmaceutiques sur les avantages des pilules contre le cholestérol et contre leurs lobbyistes qui disent que ça va sauver la vie; les pilules contre le cholestérol sont une fausse sécurité, mieux vaut prendre des marches et mieux manger.

LA SAGA DU CHOLESTÉROL – (Article en ligne)
DUPAGNE, Dominique.
http://www.atoute.org/n/La-saga-du-cholesterol.html
* Une très courte synthèse, bien ficelée, pour s'introduire à la plus grande supercherie intellectuelle - doublée d'escroquerie pharmacoéconomique - des dernières décennies

LA VÉRITÉ SUR LE CHOLESTÉROL - (Livre)
Philippe EVEN. Paris : Cherche-Midi; 2013 -378 pages – ISBN 978-2-7491-3013-2 – Préface Bernard Debré
« Les statines ne devaient être prescrites (au bénéfice du doute) qu'aux sujets à très haut risque cardiaque »

« Les 3/4 du cholestérol sont fabriqués dans le foie et seulement un 1/4 vient de l'alimentation. Il n'y a pas de valeur normale du cholestérol, mais seulement une valeur moyenne (environ 5,2 mmol/l ou 2 g/l), qui varie d'un individu à l'autre, exactement comme la taille ou le taux des globules blancs, etc. Contrairement à ce qu'on avait cru dans les années 1970, le cholestérol ne joue aucun rôle dans les maladies artérielles, l'infarctus du myocarde et les AVC...

Il n'est, avec les autres graisses (acides gras, triglycérides, etc.) qu'un simple tatouage sans conséquence sur les lésions de fibrose artérielle. Les régimes restreignant le cholestérol alimentaire ne changent rien à la fréquence des IDM ou des AVC. 30 études financées par les grandes firmes ont tenté de démontrer l'utilité des statines pour faire baisser le cholestérol et réduire les complications CV...

Aucune n'a montré la moindre diminution de la mortalité cardiaque par infarctus (sauf la 1re en 1994, l'étude 4S) contredite par toutes les autres). En revanche, les statines, qui inhibent la synthèse du cholestérol par le foie, sont capables d'en réduire le taux de 20 à 50% selon la dose, mais cette réduction ne modifie en rien la mortalité cardiaque ou cérébrale. Ces molécules biologiquement efficaces sont cliniquement sans bénéfice pour les malades...

En revanche, elles entraînent de multiples complications, souvent modérées, mais parfois très sévères : douleurs et ruptures musculaires, faiblesses musculaires entravant l'activité et l'exercice, maladies cutanées parfois très graves, fibroses pulmonaires, accentuation de l'ostéoporose, hépatites, troubles de l'attention et de la mémoire, troubles de l'érection et de la vie sexuelle. Les statines ont donc un rapport bénéfice/risque négatif...

Elles ne sont (peut-être) indiquées que dans les très rares cas d'hypercholestérolémies familiales génétiques...

Sur la base d'idées périmées impliquant le cholestérol dans les maladies cardiaques et sous la pression du marketing et de la désinformation de l'industrie pharmaceutique, les cardiologues se sont mis à prescrire les statines au robinet (quel que soit le niveau du cholestérol) et à doses de plus en plus élevées, à près d'un sur deux des plus de 50 ans (7 M de personnes en France, 2 fois plus que partout ailleurs), soit une dépense annuelle de plus d'un milliard d'euros pour rien…

Pire, le cholestérol est devenu le fond de commerce de beaucoup de cardiologues et de médecins généralistes. La surveillance du cholestérol 3 à 4 fois par an de millions de gens parfaitement sains représente aujourd'hui 10 à 30% de leur clientèle, à quoi s'ajoutent à chaque consultation dosages du cholestérol et des lipides, électrocardiogramme, échographie, etc., soit une dépense d'un autre milliard d'euros chaque année...

Parallèlement, les statines sont devenues le plus gros marché pharmaceutique mondial ($ 25 Mds en 2009) pour le plus grand bénéfice des firmes qui les produisent, essentiellement Pfizer, Merck et Astra-Zeneca. Les statines doivent être impérativement déremboursées »

LaROSA et al, THE META-ANALYSIS
Synthèse suspecte

[523] Une histoire inventée : Essai sur le cholestérol. Montréal : Carte Blanche ; 2014
[524] Interviewé le 18.1.2015 par *Le Soleil* à Québec

LaRosa JC, He J, Vupputuri S. *JAMA* 1999[525]

« Data from the 5 trials, with 30 817 participants, were included in this meta-analysis. The mean duration of treatment was 5.4 years. Statin drug treatment was associated with a 20% relative reduction in total cholesterol, 28% reduction in LDL-C, 13% reduction in triglycerides, and 5% increase in high-density lipoprotein cholesterol. Overall, statin drug treatment reduced relative risk by 31 % in major coronary events and by 21 % in all-cause mortality…

The relative risk reduction in major coronary events was similar between women (-29%) and men (-31 %), and between persons aged > 65 years (-32%) and persons < 65 years (-31 %). Our meta-analysis indicates that reduction in LDL-C associated with statin drug treatment decreases the risk of CHD and all-cause mortality. The risk reduction was similar for men and women and for elderly and middle-aged persons »
la méta-analyse de LaRosa et coll.
* Les 5 essais choisis furent: 4S, CARE, LIPID, WOSCOPS et AFCAPS/TexCAPS
* Une méta-analyse *sélective* a plus de chances d'être biaisée, car les analystes choisissent bien ce qu'ils veulent…

LDL CHOLESTEROL AND HEART DISEASE
« Researchers using the NHANES (USA) data looked at the change in the prevalence of elevated LDL cholesterol and found that it fell substantially from 1999-2000 to 2005-2006.[526] In a period of about 6 years the prevalence of high LDL cholesterol dropped by a third, which is a lot of drop in a fairly short period of time. And the prevalence of heart disease actually increased… »[527]
LDL cholestérol et maladie cardiaque

LDL CHOLESTEROL IN PATIENTS ADMITTED WITH CORONARY ARTERY DISEASE (CAD)
Épidémiologie – Coronaropathies sans LDL augmentées – Hypothèse lipidique infirmée
* Admission lipid levels were documented in 136,905 hospitalized CHD patients (59.0%)[528]:

a) Mean lipid levels were TC 4.5 mM (174.4 mg/dl), LDL 2.7 mM (104.9 mg/dL), HDL 1 mM (39.7 mg/dL) and triglyceride 1.8 mM (161 mg/dL)
b) LDL cholesterol <1.8 mM (<70 mg/dL) was observed in 17.6% - less than 25% had an LDL-C > 3.36 mM (130 mg/dL)
c) ideal levels [LDL <1.8 mM with HDL ≥1.5 mM] - in only 1.4%

Before admission, only 21.1% patients were receiving lipid-lowering medications and their LDL-C was 2.44 mM (94.3 mg/dL), only modestly lower than the hospitalization average of 2.7 mM.

In conclusion, in a large cohort of patients hospitalized with CAD, almost half have admission normal LDL cholesterol levels <2.6 mM (100 mg/dL) and normal TC 4,5 mM (174 mg/dL)
LDL-cholestérol chez les patients admis pour cardiopathie ischémique / coronaropathie

LDL TARGETING UNRELATED TO PREVENTION
Acharnement préventif – Ciblage posologique

"For those with LDL cholesterol levels < 3.36 mM (130 mg/dL), the authors found no clinical trial subgroup analyses or valid cohort or case–control analyses suggesting that the degree to which LDL cholesterol responds to a statin independently predicts the degree of CV risk reduction. Current clinical evidence does not demonstrate that titrating lipid therapy to achieve proposed low LDL cholesterol levels is beneficial or safe[529]"
ciblage du LDL-cholestérol non associé à la prévention

LDL-C DOES NOT CAUSE CARDIOVASCULAR DISEASE: A COMPREHENSIVE REVIEW OF THE CURRENT LITERATURE.
Ravnskov U, de Lorgeril M, Diamond DM4, Hama R, Hamazaki T, Hammarskjöld B, Hynes N, Kendrick M, Langsjoen PH, Mascitelli L, McCully KS, Okuyama H, Rosch PJ, Schersten T, Sultan S, Sundberg R.
Expert Rev Clin Pharmacol. 2018 Oct;11(10):959-970 - doi: 10.1080/17512433.2018.1519391

« For half a century, a high level of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) has been considered to be the major cause of atherosclerosis and cardiovascular disease (CVD), and statin treatment has been widely promoted for CV

[525] LaRosa et al. JAMA 1999; 282(24): 2340 - doi:10.1001/jama.282.24.2340 - http://jama.jamanetwork.com/article.aspx?articleid=192226
[526] Kuklina et al. JAMA 2009; 302(19): 2104 - doi:10.1001/jama.2009.1672
[527] http://www.proteinpower.com/drmike/CV-disease/the-statinator-paradox/
[528] Sachdeva et al. Am Heart J 2009 ; 157(1) : 111-117.e2 - http://www.ahjonline.com/article/S0002-8703(08)00717-5/abstract
[529] Rodney Hayward. Ann Int Med 2006;145(7):520

prevention. However, there is an increasing understanding that the mechanisms are more complicated and that statin treatment, in particular when used as primary prevention, is of doubtful benefit.

Areas covered: The authors of three large reviews recently published by statin advocates have attempted to validate the current dogma. This article delineates the serious errors in these three reviews as well as other obvious falsifications of the cholesterol hypothesis.

Expert commentary: Our search for falsifications of the cholesterol hypothesis confirms that it is unable to satisfy any of the Bradford Hill criteria for causality and that the conclusions of the authors of the three reviews are based on misleading statistics, exclusion of unsuccessful trials and by ignoring numerous contradictory observations.[530] »

LDL-C TARGETS' OBSOLETENESS

« This study - JUPITER - in which almost half of the subjects were below the target level for LDL-C lowering in ischaemic heart disease - makes the whole concept of lipid lowering to a specific LDL-C target look more obsolete than before »[531]

Jupiter rend obsolètes les cibles de LDL-C

* Ridker, probablement intéressé à vendre des dosages de protéine C-réactive à mesure sensible, sur lesquels il détient un brevet, dénigre implicitement l'hypothèse cholestéroliste, laquelle prétend que 'abaisser les LDL réduit le risque coronarien' et 'viser une cible de LDL est un objectif à poursuivre'

LE GRAND BLUFF DU CHOLESTÉROL (Documentaire exceptionnel à visionner absolument)
https://www.youtube.com/watch?v=txJnD60BcGM

* Vous y voyez et entendez entre autres De Lorgeril (cardiologue, nutritioniste, chercheur), Rabaeus (cardiologue), Le Grand (biochimiste), Toussaint (revue Prescrire), Bégaud (pharmaco-épidémiologiste),

« Je suis entièrement d'accord avec Michel de Lorgeril quant à l'absence de preuves convaincantes de l'effet des statines en prévention secondaire. Nous avons d'ailleurs publié un article dans ce sens : la rosuvastatine - qui est la seule statine testée depuis 2005 quand les règles de conduite des études sont devenues plus sévères - a été utilisée dans trois études de prévention secondaire. Dans les trois études, elle n'a montré aucun effet favorable sur le pronostic...

Les études de prévention secondaire qui semblent montrer un effet sont les études précoces, faites à une époque où la manipulation était encore très facile. Et rappelons le : nous ne disposons toujours pas des données brutes de toutes ces études. Dès lors qu'on refuse de nous les procurer, on est en droit d'exprimer des doutes très sérieux sur la valeur des études, compte tenu de toutes les questions qui sont soulevées[532]»

LEAP OF FAITH

leap of trust

« The new statin guidelines – AHH/ACC 2013 - are being sold as a *leap of faith* » [533]

acte de foi

« Les nouvelles directives – de l'AHA et de l'ACC en 2013 – sont promues comme un *acte de foi*, une croyance dans la capacité des statines de prévenir crises cardiaques et AVC, même si ce bienfait ne provient pas du contrôle du cholestérol »

LEG WEAKNESSES AND STATINS : VIGNETTES

« I wish to inform you that I have been on Lipitor™ for about a year. I started developing *leg pains* and elevated *blood sugar*. I discontinued the Lipitor™ and my leg pains are going away and my blood sugar levels are coming down »[534]

« My GP advised me to go onto simvastatin. I was quite active, could walk well and tended my garden without difficulty. Within a day of starting the treatment I experienced muscle pains which I had not experienced before. From the explanatory leaflet I gathered that this was a common initial response, and would quickly go away. I continued the prescribed treatment and my condition deteriorated so that by the 5th day I was incapacitated to the extent that I could not leave the house...

I had difficulty getting up and down stairs , and in rising from a chair. I gathered that such side effects were reversible if the treatment was not prolonged and so I stopped. Within 48 hours the side effects subsided and I returned to the condition I had

[530] https://www.ncbi.nlm.nih.gov/pubmed/30198808
[531] Donner-Banzhoff & Andreas Sönnichsen. BMJ 2008 ; 337 : a2576
[532] Mikael Rabaeus. 14.10.2016 - http://www.atoute.org/n/spip.php?page=forum&id_article=348&id_forum=10984
[533] André Picard 2013, http://www.theglobeandmail.com/authors/andre-picard
[534] http://www.peoplespharmacy.com/2010/03/01/listen-to-patients-when-it-comes-to-statin-side-effects/

previously enjoyed. I declined my GP's suggestion to try a different statin because the experience, to me, had been so adverse, even frightening », writes a healthy woman aged 83[535]

« Fellow members of a golf club, golfers who had played for years but who now, after going onto statins, could no longer complete even a few holes »[536] - « I am a woman over 65. I was put on statins and for the first 3 months I was fine. Then I experience total muscle collapse when I tried to step up on a chair to reach something »[537]

« 67-year-old Eva Kelly felt abandoned when they he develop side-effects. Eva, a retired council worker from Harringay, North-East London, says she 'went through hell on those drugs — how can anyone suggest I somehow made it all up?' She was put on statins in 2006 and all was fine for three years, but then she began to get the occasional bad cramp and pains in her left leg. Her GP said it was probably a coincidence, but switched brands of statins. But then, last August, the cramps set in 24/7...

'I couldn't leave home,' she says. 'It was unbearable, like someone was taking a hammer to my leg. 'I cried buckets in the surgery, begging the doctors to take me seriously. I'm not a hypochondriac, I said. I'm not a time-waster. But I was scared to stop taking the drugs. 'One of the doctors asked if I wanted to die prematurely from heart disease. 'Eventually I persuaded one to send me for an MRI scan; that showed I had a neurological problem...

'The consultant said it was probably caused by medical treatment. 'I was sent for physiotherapy because my leg muscles were so weak, but no one told me what to do about the statin. 'This January I decided to stop it anyway. My cramps are 50 per cent better and I can walk a bit. You don't make that kind of thing up.' »[538]

faiblesses dans les james et statines : vignettes

* statiniser une femme, une personne de > 75 ans ou une personne non coronarienne, c'est déjà de la surprescription. Quand la victime présente les trois caractéristiques, c'est une aberration résultant d'un lavage de cerveau du prescripteur

LIFE EXPECTANCY AND CARDIOVASCULAR DISEASE (CA) *Enquête épidémiologique populationnelle – Tables de survie – Statistique Canada*

« In total, 4.5 years of life expectancy and 2.8 years of healthy life expectancy were lost due to CVD. Eliminating 100% of CV disease in Canada in 2000/2001 will extend Canadian life expectancy by 3.5 years for men and 3.1 years in women, but the gains in Health Adjusted Life Expectancy (HALE) show that not all of this increase would be in a healthy state, 3.0 years for men and 2.6 years for women »[539]

espérance de vie et maladie cardiovasculaire

« Bien que la maladie CV demeure la cause principale de décès au Canada, pendant la période de 1950 à 1999 (49 ans), le taux de mortalité attribuable à la maladie CV a chuté de 702 à 288 par 100 000 hommes et de 562 à 175 par 100 000 femmes. Au total, la maladie CV diminue de 4,5 années l'espérance de vie et de 2,8 années l'espérance de vie en santé au Canada en 2000/2001 »

LIFE EXPECTANCY AND ISCHEMIC HEART DISEASE (CA)

Enquête épidémiologique populationnelle – Tables de survie – Statistique Canada

« In Canada in 1998/99, life expectancy for men and women in Canada was 76.0 and 81.5 years respectively; Health Adjusted Life Expectancy (HALE) was 67.9 years for men and 71.1 years for women »[540]

espérance de vie et cardiopathie ischémique

* Les gains en espérance de vie au Canada en 1998-99[541] par l'absence théorique de cardiopathie ischémique seraient:

a) 2,4 ans pour les hommes [Si les statines prescrites 'pour la vie' réduisaient vraiment le risque relatif de mortalité par coronaropathie de 10%, la vie serait théoriquement prolongée de 0,24 année ou 12,5 semaines; sauf que les statines n'ont pas été démontrées capables d'une réduction absolue annualisée qui soit cliniquement signifiante et les essais cliniques ne durent que quelques années]

b) 1,8 an pour les femmes [une réduction pharmacologique 'à vie' de 10% de la mortalité coronaire allongerait théoriquement la vie de 0,18 année ou 9,4 semaines; sauf que chez les femmes la statinisation ne réduit pas ce critère d'évaluation et même que

[535] BMJ 2014; 348: g3306 at http://www.bmj.com/content/348/bmj.g3306?tab=responses
[536] Ibidem
[537] Anonymous, 2014
[538] Jerome Burne, 2014. http://www.dailymail.co.uk/health/article-2582958/Statins-Millions-healthy-Britons-set-prescribed-GPs-say-wont-statins.html#ixzz3ATCZUQ9C
[539] Manuel et al. Can J Cardiol 2003 ; 19(9) : 997
[540] Manuel et al. Chronic Dis Can 2003; 24(4): 108
[541] Manuel et coll. Maladies Chroniques au Canada 2003 ; 24(4) : 121

dans de rares essais on observe le contraire, soit une tendance à augmenter cette cause de décès]

Les gains en espérance de vie *corrigée* en fonction de la santé après statinisation à vie et réduction relative de 100% du risque de cardiopathie ischémique seraient théoriquement de:
a) 2,2 ans pour les hommes [pour 10% de réduction relative, de 11,4 semaines…]
b) 1,5 an pour les femmes [pour 10% de réduction relative, de 7,8 semaines…]

LIFE EXTENSION WITH PRIMARY PREVENTION STATINIZATION *Modélisation*
« How much longer would people be living ? The *JAMA* 14.7.2015 papers[542] gives us the answer. According the authors' model, if we gave statins to everybody judged to have a risk of heart attack or stroke of at least 7.5% over the next 10 years (as the AHA currently recommends) as opposed to restricting their use to patients with pre-existing CV disease, diabetes or severely elevated LDL levels, life expectancy would increase by 43 days...

We don't know that even the meager results demonstrated in clinical trials will be forthcoming in actual clinical practice (the patients in clinical trials are in no way representative of those taking the drug in the real world). We don't know that benefits demonstrated in short-term trials can be extrapolated for the lifetime of the patient (in the absence of data, you just don't know) …

Data on the incidence of heart attacks and strokes for the *JAMA* paper were taken from a 2005 meta-analysis published by the Cholesterol Treatment Trialists' Collaboration. When Dr. John Abramson of Harvard University School of Medicine re-analyzed the CCT's 2012 data, he found that statins conferred no mortality benefits to those whose risk of heart attack or stroke was less than 20 percent over 10 years »[543]
prolongation de la vie sous statines en prévention primaire
* cette modélisation est optimiste et tendancieuse car il est bien démontré qu'en prévention primaire – surtout si le seuil de risque choisi arbitrairement est de 0,75% par année - la vie n'est pas prolongée en *situation expérimentale*. Et si l'efficacité est réduite de moitié en *situation clinique*, la prolongation vitale calculée serait réduite à 21 jours et 12 heures, mais à quel prix en termes de coûts directs et indirects, de contraintes et d'effets indésirables

LIFE-THREATENING WITHOUT SAVING LIVES
« Most of Pharma's drugs are *not even life-saving*—a lot more thyroid, *cholesterol*, ADHD and acid reflux drugs are sold than cancer drugs, their demand whipped up by direct-to-consumer drug ads. Some widely marketed drugs like *statins* have *life-threatening* side effects of their own »[544]
impliquant un risque vital sans sauver de vies

LIFESTYLE OR STATINIZATION ?
« There may be an interaction between medication and lifestyle. Namely, if statin users consume more calories, gain weight, and exercise less, it becomes easy to see why CV benefits are so small. It's been really hard to explain why the striking reductions in LDL cholesterol—up to 30% to 50%—from statins haven't translated into significant future benefit. One possibility is that cholesterol levels are a lousy surrogate for outcomes »[545] … Or because the cholesterol hypothesis is dead wrong !
hygiène ou statinisation ?
« On dépense 500 M$ (QC) pour des médicaments hypolipémiants, mais on ne donne pas un sou aux nutritionnistes kinésiologues. Il faut commencer à regarder de près le budget de la santé et voir où nous mettons nos ressources en priorité »[546] déplore un cardiologue, promoteur de prévention non-pharmacologique

LIPID HYPOTHESIS : SCIENTIFICALLY INDEFENSIBLE
diet-heart hypothesis challenged

« The cholesterol hypothesis of coronary disease is fundamentally flawed » - « Nearly 50 years ago, three Harvard researchers were paid thousands of dollars by the sugar industry to write a review in the *N Engl J Med* emphasising the importance of fat and cholesterol in CHDwhile minimising the importance of sugar[547]… A growing body of knowledge challenges the validity of the cholesterol hypothesis and the utility of cholesterol as a surrogate end point[548] »

[542] http://jama.jamanetwork.com/article.aspx?articleid=2396463
[543] Patrick D Hahn, 30.7.2015 - http://www.baltimoresun.com/news/opinion/oped/bs-ed-statin-costs-20150728-story.html
[544] http://www.alternet.org/drugs/10-worst-big-pharma-company-rip-offs-and-their-plan-keep-gravy-train-rolling
[545] John Mandrola. 16.6.2014 at http://www.drjohnm.org
[546] Martin Juneau cité par Fabienne Papin. L'Actualité médicale (Montréal) 15.12.2010 page 4
[547] Kearns et al. JAMA Intern Med 2016 ; 176 : 1680
[548] Robert Dubroff, 2016

« Using total cholesterol, despite the widespread view that elevated TC is a risk factor for death, a number of studies have found that elevated TC is either associated with decreased mortality or not associated with mortality »[549]
« A comprehensive review of the literature reveals that there is a lack of evidence of a causal link between cholesterol and CHD… Extensive research demonstrated that CHD occurs independent of cholesterol levels »[550]

« In a meta-analysis of RCTs of dietary fats, 2467 males participated in 6 dietary trials: 5 secondary prevention studies and 1 including healthy participants. There were 370 deaths from *total mortality* in the intervention and control groups. The risk ratio (RR) from meta-analysis was 0.996 (95% CI 0.865 to 1.147). There were 207 and 216 *deaths from CHD* in the intervention and control groups, respectively...

The RR was 0.989 (95% CI 0.784 to 1.247). There were no differences in all-cause mortality and non-significant differences in CHD mortality, resulting from the dietary interventions despite reductions in mean serum cholesterol levels that were significantly higher in the intervention groups. Government dietary recommendations were therefore introduced for 220 M US and 56 M UK citizens by 1983, in the absence of supporting evidence from RCTs »[551]

« Dietary total and saturated fat do not correlate with risk for CV disease. Several large and expensive clinical studies have been carried out since the so-called *diet–heart hypothesis* was framed in the middle of the 20th century [Keys]. From the original Framingham study [Anderson 1987] to the WHI [Howard 2006], as well as more than a dozen additional studies, have failed to show an association between dietary lipids and risk for CV disease…

There is now a large volume of literature of both scientific papers and popular books [Teicholz 2014 ; Kendrick 2008; Ravnskov 2000; Taubes 2007] documenting the failure of attempts to support the diet–heart hypothesis. Few rebuttals have been offered [Steinberg 2007]. The very strong recommendations from health agencies predicted that none of these trials should fail. In fact, almost all of them have failed »[552]

« We physicians with all our training, knowledge and authority often acquire a rather large ego that tends to make it difficult to admit we are wrong. So, here it is. I freely admit to being wrong. As a heart surgeon with 25 years experience and having performed over 5,000 open-heart surgeries, today is my day to right the wrong with medical and scientific fact. I trained for many years with other prominent physicians labeled 'opinion makers'…

Bombarded with scientific literature, continually attending education seminars, we opinion makers insisted heart disease resulted from the simple fact of elevated blood cholesterol. The only accepted therapy was prescribing medications to lower cholesterol and a diet that severely restricted fat intake, which we insisted would lower cholesterol and heart disease...

Deviations from these recommendations were considered heresy and could quite possibly result in malpractice. It Is Not Working These recommendations are no longer scientifically or morally defensible »[553]

« In 18 countries on 5 continents, the Prospective Urban Rural Epidemiology (PURE) study on 135 000 individuals aged 35–70 years (enrolled between 2003 and 2013) in 18 countries with a median follow-up of 7,4 years, high carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Total fat and types of fat were not associated with CV disease, myocardial infarction, or CV disease mortality[554] »
hypothèse lipidique scientifiquement indéfendable ; hypothèse des lipides / du cholestérol / **cholestéroliste** re**mise en question**
« Le médecin généraliste et biochimiste George Mann de la Vanderbilt University, qui avait participé au développeement de la trop célèbre Framingham Heart Study, devait plus tard décrire l'hypothèse du 'cholestérol-comme-indicateur-des-maladies-cardiovasculaires' comme étant la 'plus grosse arnaque jamais perpétrée sur le public américain' »[555]

« Le lien systématique entre taux de cholestérol et problèmes de cœur a été largement exagéré : abaissement du seuil de cholestérol, invention de maladie, médicalisation de gens sains… La maxime simpliste 'Plus le cholestérol est bas, plus

[549] http://www.ti.ubc.ca/letter92
[550] Diamond & Ravnskov, op. cit.
[551] Harcombe et al. Open Heart 2015; 2:e000196 - doi:10.1136/openhrt-2014- 000196 – full paper at http://openheart.bmj.com/content/2/1/e000196.full.pdf+html
[552] Feinman et al. Nutrition 2014 : 1, at http://www.nutritionjrnl.com/article/S0899-9007%2814%2900332-3/pdf
[553] Dwight Lundell, 2013
[554] Dehghan et al. 2017 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32252-3/fulltext
[555] Sinatra & Bowden, 2014, page 33

longtemps vous vivrez' a *perverti* les esprits de beaucoup trop de docteurs dans les pays développés »[556] confie un ex-directeur médical chez Merck-France

LIPID LOWERING DRUG
hypolipidemic drug
(médicament) hypolipidémiant

LIPID REGULATION *Physiologie - Métabolisme*
régulation des lipides

LIPID REGULATOR *Physiologie - Métabolisme*
régulateur des lipides

LIPID, THE TRIAL *Prévention secondaire chez coronariens stables – Pravastastine 40 mg c. placebo - Conflation*
Long-Term Intervention with Pravastatin in Ischaemic Disease

* Princeps publication: LIPID/*NEJM*/1998[557]
* Funding : private, Bristol-Myers-Squibb

METHODOLOGY
* Participants' demography : 9014 randomized ; median age 62 years, range 55-68 years (NICE) – 31-75 (LIPID); 3266 or 17% women ; 83% men
* Participants' health : prior CHD in 100% ; 38% with unstable angina ; 64% with MI ; hypertension in 42 % ; 9 % diabetics ; TC 4 to 7 mM, mean 5,7 mM ; LDL-C average 3.6 mM

* Comparison : pravastatin 40 mg vs placebo
* Duration : 6.1 years (73.2 months)
* Primary composite outcome : fatal MI + nonfatal MI

* Positive compliance (active group adherence) : 89%
* Negative compliance (control group adherence) : 91%

RESULTS
Lipid reduction :
a) TC relative risk reduction of -18 %, from 5.7 mM
b) LDL-Cholesterol relative risk reduction of -25 %, from 3,6 mM

Relative risks:
a) TOTAL MORTALITY : relative risk reduction of -22%, statistically significant; and of -18% by logrank analysis (from NICE) – 498 deaths / 4512 treated patients and 633 deaths / 4502 controls on placebo
b) CHD MORTALITY relative risk reduction of -24 %
c) CV MORTALITY (coronary + stoke) : relative risk reduction -25%, statistically significant

d) fatal and non fatal MI : relative risk reduction of -22 %, NS
e) non fatal MI : relative risk reduction of -21 %

f) fatal and non fatal stroke relative risk reduction of -17%, NS
g) hemorhagic stroke RRI of +200%, NS
h) Serious adverse events : reported and not reduced by treatment[558]

Absolute risks :
a) TOTAL MORTALITY : absolute risk reduction of 0.49 % per year; annual NNT = 204 patient-years, prolonging life by an average of 43 hours per year of treatment (or 7 minutes per tablet) under experimental conditions, most likely by about 22 hours in a clinical setting (without selection and other biases)…

[556] Bernard Dalbègue. Omerta dans les laboratoires pharmaceutiques : confessions d'un médecin. Paris : Flammarion Enquête ; 2014
[557] LIPID. N Engl J Med 1998; 339(19): 1349 - DOI: 10.1056/NEJM199811053391902 - http://www.nejm.org/doi/full/10.1056/NEJM199811053391902 - t=article
[558] Abramson et al. http://www.bmj.com/content/347/bmj.f6123

One of the rare secondary prevention trials reporting a reduction in total mortality. But the absolute risk reduction reduction is too minuscule to have any clinical significance when considering that the absolute risk reduction is presumably halved in actual practice is probably closer to 0.25 % per year for a NNT of 400 patient-years

b) CHD MORTALITY, a primary outcome: absolute risk reduction = 0.31 % per year, annual NNT = 323 patient-years, delaying this event by 26 hours per year of treatment under experimental conditions, presumably by around 13 hours in a clinical setting

c) CVD mortality annual NNT = 268 patient-years

d) CHD event annual NNT = 172 patient-years, for a yearly inefficacy rate of 99.4% and an average CHD event delay of 11.3 hours per year of treatment

Harms in absolute risks :
e) hemorrhagic stroke : annual NNH = 394 patient-years

f) New onset diabetes marginally reduced (sic), annual NNT = 1179 patient-years (high risk of bias, the opposite is demonstrated in most other trials)

Unreported protocol outcomes :
g) rhabdomyolysis, myalgia, liver enzymes elevation

Other unreported outcome :
h) Health related quality of life *not reported*

Relative risks in women :

a) TOTAL MORTALITY relative risk reduction of -5%, NS
b) CHD mortality relative risk reduction of -21%, NS
c) nonfatal MI relative risk reduction of -11%, NS
d) CHD events relative risk reduction of -12%, NS

Therefore the benefits were limited to men

Factual conclusion:
a) results may be considered clinically negative, whether a NNT exceeds 100 patients-years for total mortality reduction, used as a therapeutic benefit threshold to compensate for ADRs and costs, or whether a NNT exceeds 50 patient-years for composite outcome measures (usually a heterogenous mix of fatal and nonfatal events, of hard and soft events and of endpoints with differing frequencies)

b) although the reported trend for an increased risk of hemorrhagic stroke has exploratory value only, this ADR has been observed in other studies (Amarenco et al. 2006 for high-dose statins ; low cholesterol, in Japan…). Statins are supposed to protect, not to harm

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : Yes, clarification pending

l'essai dit Lipid

* L'essai fut réalisé avant la nouvelle règlementation régissant la façon dont les études doivent être faites et publiées, c'est-à-dire avant le scandale du Vioxx™[559]

LIPIDOLOGIST *Science appliquée - Métabolisme*

* not to be confused with the powerful brotherhood of hypercholesterolists

lipidologue

= scientifique qui étudie le rôle des lipides dans les aliments, dans la physiologie du corps humain et dans la physiopathologie de certaines maladies

[559] De Lorgeril

* ne pas confondre avec les *hypercholestérolistes*, fondus en une confrérie imitant une spécialité sans en être une[560]

LIPITOR WARNINGS
* Lipitor™ (atorvastatin), the best-selling drug in the history of pharmaceuticals, made $125 billion in 14½ years and as much as $11 billion in a single year… But in 2012—the same year its patent expired—those 29 M people (and millions taking other statins) got a surprise from the FDA. The agency made a label change warning that Lipitor™ and other statins could cause diabetes, liver injury, muscle damage and memory impairment
mises en garde au sujet du Lipitor™

LIPITOR™, THIEF OF MEMORY, STATIN DRUGS AND THE MISGUIDED WAR ON CHOLESTEROL **–** (Livre)
Duane GRAVELINE. 2006 – ISBN 13: 9781424301621

« Dr. Duane Graveline, former USA astronaut, aerospace medical research scientist, flight surgeon, and family doctor, given Lipitor™ to lower his cholesterol, loses his short-term memory for several hours. He discontinues the drug, but a year later at his annual NASA physical is urged to resume it at half the dose. Six weeks later he loses both short and retrograde memories for half a day and is diagnosed in the emergency room with transient global amnesia …

Appalled by the medical community's ignorance of the cognitive side effects of the statin drugs, he begins searching for answers to his traumatic experience. The book is the 'scary, appealingly written' account of his findings »
Le Lipitor™, ce voleur de la mémoire, les statines, et cette guerre malavisée contre le cholestérol – (Traduction libre)
* L'auteur est décédé d'un syndrome de type maladie du neurone moteur (ou SLA). Fut-ce enclenché ou favorisé par la statinisation ? La question demeure ouverte

LIPOPHILIC STATINS AND PARKINSON'S DISEASE *Statinovigilance – Syndrome de sevrage - Épidémiologie*
* In an observational study, patients who stopped lipophilic (but not hydrophilic) statins had an increased risk for incident Parkinson's disease[561]
statines lipophiles et maladie de Parkinson
* les statines lipophiles franchissent la barrière méningée et pénètrent le cerveau, où des effets indésirables peuvent alors se produire pendant le traitement et lors du sevrage

LIPOPHOBE
cholesterolophobe
lipophobe ; cholestérolophobe
= victime des campagnes de peur sur les dangers du cholestérol

LIVER INJURY AND ATORVASTATIN – *Étude observationnelle sur registres publics*
hépatotoxicité et atorvastatine (Lipitor)
* En Islande le système de santé public permet de croiser prospectivement les hépatites avec les exposition médicamenteuses. Une étude portant sur les dossiers d'un quart de million d'habitants suivis deux ans démontre que l'exposition à l'atorvastatine arrive au 7e rang et le NNH est évalué à 3 693 patients traités[562].

LORD, THE TRIAL
Lipid Lowering and Onset of Renal Disease

LOVASTATIN TRIALS
AFCAPS-TexCAPS, ACAPS, CRISP, CCAIT, MARS, CLAPT
essais de la lovastatine

LOW BASELINE RISK
« Absolute CVD rates (per 100 person-years) in JUPITER women for placebo (1.04) were lower than for men (1.54) »[563]
risque de base faible
= risque de 1 à 1,9 événements CV par 100 patients-année (risque faible selon notre définition)

* Si on applique cette définition aux participants de l'essai dit JUPITER quant au critère combiné principal (IM, AVC, décès CV,

[560] Therrien, op. cit.
[561] Lee Y-C et al., Neurology 2013 Jul 24
[562] Björnsson et al. Gastroenterology 2013 ; 144 : 1419
[563] Mora et al. Circulation 2010; 121: 1069

angioplastie/pontage, hospitalisation angine instable), on trouve sous placebo un risque d'événement principal de 1,36 par 100 AP (risque faible selon nos critères) – 1.04 chez les femmes et 1.54 chez les hommes

* Dans l'essai dit WOSCOPS le risque du groupe placebo était de 1,6 événement principal par 100 AP (risque faible selon nos critères)

LOW CHOLESTEROL : BIOMARKER FOR SEPSIS RISK FROM CARDIOPULMONARY BYPASS FOR CARDIAC SURGERY
« Low cholesterol levels before elective cardiac surgery with cardiopulmonary bypass may be a simple biomarker for the early identification of patients with a high risk of sepsis… A low preoperative cholesterol level is associated with an increased risk of sepsis and complications in patients undergoing cardiac surgery with cardiopulmonary bypass, regardless of the prebypass state of the patient »[564]
hypocholestérolémie comme biomarqueur du risque de sepsis par circulation extracorporelle en chirurgie cardiaque

LOW CHOLESTEROL AND CANCER RISK *Épidémiologie*
« At least 9 cohort studies have shown that low cholesterol measured 10-30 years previously is a risk factor for cancer later in life »[565]

« Data from the Framingham Study show elevations in cancer incidence primarily at low levels of serum cholesterol < 190 mg/dl or 4.9 mM. However, a strong impression is conveyed that the largest elevation in risk appears for those with serum cholesterol < 190 mg/dl in the Paris (FR) study, those < 193 mg/dl in the Maoris-(NZ) study, those < 195 mg/dl in the Puerto Rico (USA) study, and those < 180 mg/dl in the Hawaii (USA) study. The studies from Sweden and Whitehall (UK) show a more steady gradient of risk »[566]
cholestérol bas et risque de cancer

LOW CHOLESTEROL AND COGNITIVE FUNCTION
cholestérol bas et fonction cognitive
« Un taux de cholestérol bas est associé avec une performance plus pauvre dans les mesures cognitives, qui font appel au raisonnement abstrait, à l'attention, à la concentration, à la fluidité de langage, aux fonctions exécutives »[567]

LOW CHOLESTEROL AND IN-HOSPITAL MORTALITY FROM HEART FAILURE
Lipidologie - Épidémiologie

"A recent observational study found 2.6 times the in-hospital mortality from heart failure in those with lowest cholesterol, an effect that became highly significant among statin users[568]" – « It is well documented that low cholesterol levels are associated with poor outcomes in those with chronic heart failure, and these low total cholesterol levels are also associated with increased in-hospital mortality »[569]
cholestérol bas et mortalité hospitalière par insuffisance cardiaque

LOW CHOLESTEROL AND MORBI-MORTALITY
Épidémiologie
cholestérol bas et morbi-mortalité
« Pour rappel, chez les très âgés comme on en retrouve en CSLD, un trop bas cholestérol est biologiquement de mauvais présage car la mortalité augmente quand le cholestérol total est sous la barre de 5,5 mmol/l »[570]

« Lorsque le cholestérol est trop bas, certaines études (mais pas toutes) ont suggéré que ce taux est associé à des troubles de mémoire, à certaines maladies psychiatriques et même à des syndromes démentiels. Plusieurs patients prenant des statines se plaignent d'ailleurs de troubles de mémoire et de difficulté de concentration…

Les patients souffrant d'insuffisance cardiaque ayant des taux de cholestérol entre 190 et 200 mg/dl (4,9 à 5,2 mmol/l) ont de

[564] Lagrost et al. Crit Care Med 2014; 42:1065–1073 - DOI: 10.1097/CCM.0000000000000165
[565] Ravnskov et al. QJM 2012 ; 105 : 383
[566] Sorlie & Feinlieb. INCI 2982 ; 69(5) : 989
[567] Framingham Study, Elias et al.
[568] Eddie Vos citant http://www.neurology.org/cgi/eletters/71/5/344 - Referring to Horwich. Am Heart J 2008;156 :1170
[569] Green et al. EVEREST Trial. Am J Cardiol 2013 ; 111 : 574
[570] LK Petersen, K Christensen, J Kragstrup. Age and Ageing 14.10.2010 p.1-7. Lipid-lowering treatment to the end? - E Vos & P de Groot. Neurology 11.6.2007 Low LDL cholesterol, statins, and brain hemorrhage: Should we worry? Disponible sur http://www.neurology.org/cgi/eletters/68/10/719#7946 – Noda et al. Circulation. 2009;119:2136-2145 The Ibaraki Prefectural Health Study

1,5 à 3 fois le risque de mourir que ceux avec des niveaux plus élevés de cholestérol total.

L'équipe du docteur Harlan Krumholz a démontré que les gens de 70+ dont le cholestérol sanguin était bas mouraient 2 fois plus souvent d'infarctus que ceux avec un cholestérol plus élevé. Cette étude semble avoir été confirmée par les résultats de l'étude MONICA de l'OMS qui n'a trouvé aucun lien entre le taux moyen de mortalité cardiaque et le pourcentage de la population souffrant d'hypercholestérolémie dans chacun des pays comparés »[571]

« Pour les >50 ans, il y a une association entre une baisse du cholestérol durant les premières 14 années et la mortalité durant les 18 années subséquentes (augmentation de +11% de la mortalité totale et de +14% de la mortalité CV pour chaque baisse annuelle de 0.2 mM de cholestérol total »[572]

LOW CHOLESTEROL AND SUICIDE RISK
Risque de l'hypocholestérolémie
« In the 1970-1972 Nutrition Canada Survey, after adjusting for age and sex, we found that those in the lowest quartile of serum TC concentration (4.27 mM) had more than 6 times the risk of committing suicide as did subjects in the highest quartile (5.77 mM)…

The effect persisted after the exclusion from the analysis of the first 5 years of follow-up and after the removal of those who were unemployed or who had been treated for depression. These data indicate that low serum TC level is associated with an increased risk of suicide »[573]

« Our case-control study, comparing suicide attempts (cases) with with healthy and psychiatric controls (non-cases), somewhat limited by the small sample size, suggests that low cholesterol may be associated (OR 2.0 in men, 1.8 in women) with suicide attempts. Low cholesterol level in suicide attempters may be more important from a pathophysiologic than from a diagnostic point of view »[574]
cholestérol bas et risque de suicide

LOW CHOLESTEROL AND TOTAL MORTALITY IN OLD WOMEN
Risque de l'hypocholestérolémie - Gériatrie
« 92 women aged 60 years and over (mean 82.2) living in a nursing home and free from overt cancer were followed-up for 5 years. 53 died during this period; necropsy revealed cancer in only 1 patient. Serum TC at entry ranged from 4.0 to 8.8 mmol/l. Cox's proportional hazards analysis showed a J-shaped relation between serum cholesterol and total mortality...

Mortality was :
a) lowest at serum cholesterol 7.0 mmol/l,
b) 5.2 times higher than the minimum at serum cholesterol 4.0 mmol/l
c) only 1.8 times higher when cholesterol concentration was 8.8 mmol/l

This relation held true irrespective of age, even when blood pressure, body weight, history of myocardial infarction, creatinine clearance, and plasma proteins were taken into account. The relation between low cholesterol values and increased total mortality was independent of the incidence of cancer »[575]
bas cholestérol et mortalité toutes causes chez les femmes âgées
* dans une étude observationnelle de faible ampleur chez des femmes âgées, un bas taux de cholestérol (4 mM) est davantage associé à la mortalité totale qu'un taux élevé (8,8 mM)

LOW CHOLESTEROL ASSOCIATED WITH MORTALITY
Épidémiologie - Japon
« Low cholesterol is associated with mortality from stroke, heart disease, and cancer. As compared with a moderate cholesterol level (4.14-5.17 mM), the age-adjusted hazard ratio (HR) of low cholesterol (<4.14 mM) for mortality was 1.49 in men and 1.50 in women. High cholesterol (≥6.21 mM) was not a risk factor for mortality…

This association was unchanged in analyses that excluded deaths due to liver disease, which yielded age-adjusted HRs of 1.38 in men and 1.49 in women. The multivariate-adjusted HRs of the lowest cholesterol group for hemorrhagic stroke, heart failure

[571] François Melançon, Clinicien plus, mars 2013
[572] Framingham Study, JAMA 1987 ; 257 : 2176 - cité par Paul v Nguyen
[573] Ellison & Morrison. Epidemiology 2001; 12: 168
[574] Perez-Rodriguez et al. J Clin Psychiatry 2008: e1–e8 (pii: ej07m03866)
[575] Forette B et al. Lancet 1989; 1(8643): 868

(excluding myocardial infarction), and cancer mortality were significantly higher than those of the moderate cholesterol group, for each cause of death »
bas cholestérol associé à la mortalité

LOW CHOLESTEROL IN WOMEN AND HEMORRHAGIC STROKE
« Roughly 0.8 percent of women in the Women's Health Study (Brigham, Boston) with LDL cholesterol 70 mg/dL or lower had a bleeding stroke compared to 0.4 percent of women with levels between 100 mg/dL and 130 mg/dL. That means women with very low LDL cholesterol were more than twice as likely to have a hemorrhagic stroke. Additionally, researchers found that 0.6 percent of women with the lowest levels of had a bleeding stroke compared to 0.4 percent of women with the highest levels – meaning women with low levels had double the risk.[576] »
cholestérol bas et AVC hémorragique chez les femmes

LOW DOSE STATIN TRIALS AGAINST PLACEBO
* Low statin intensity vs placebo ; with > 1000 participants and lasting > 1 year[577]
GISSI, ALLHAT-LLT, WOSCOPS, PROSPER, LIPID, MEGA, CARE
essais de statine faiblement dosée contre placebo

LRC-CPPT, THE TRIAL
Prévention primaire – Essai négatif — Cholestyramine c. placebo
Lipid Research Clinics Coronary Primary Prevention Trial

* Asymptomatic middle-aged men with primary hypercholesterolemia, following a cholesterol-lowering diet, and followed for 7 years after randomization to cholestyramine or placebo

* There is clear evidence of conflation : « The trial was well designed and superbly carried out. However, the reported conclusions seem to go beyond what is reasonably justified… The presentation of the results did not adquately reflect the weaness of the evidence for a positive effect of cholestyramine in reducing CHD endpoint rates…

These results were used to make unwarrantd extensions to a large portion of the US population… The scientific presentations that the product of a clinical trial such as the CPPT should be free of such advocacy »[578]

« The difference in life-table event rate for the composite primary endpoint (nonfatal myocardial infarction or coronary disease death) was 1.6% at 7 years of follow-up (8.6% under placebo, 7.0% with cholestyramine), NS at the 0.01 one-sided level or two-sided 0.05 level », for an absolute risk reduction of only 0.23% per patient-year, an NNT of 435 patient-years, and a yearly inefficacy rate of 99.77%

« The designers set the significance level at one-sided 0.01 rather than the usual two-sided 0.05. However, sometime between the design and the reporting of the results, the original criteria was changed and a 0.05 one-sided test was deemed satisfactory, thus lowering the standard of evidence. Had the trialists used the usual 0.05 two-sided test they would have been unable to reject the null hypothesis...

This change was not discussed in the two publications in JAMA. The beneficial effect was reported as statistically significant at the 0.05 level and this is based on a change in the criteria that apparently took place after analyzing the data »[579], a blatant example of changing the rules post-hoc to suit the theory, aka statistical manipulations, a form of cheating leading to biased reporting, showing the way to all subsequent hypercholesterolists...

A p level < 0.001 should be used throughout since « if you use p = 0.05 to suggest that you have made a discovery, you will be wrong at least 30% of the time and if you wish to keep your false discovery rate below 5%, you need to use a three-sigma rule (99% CI), or to insist on p ≤ 0.001 [especially for multiple comparisons]. And never use the word 'significant'[580] »

* Reporting benefits in relative risk reduction (-17%) instead of absolute risk reduction (-1.6%) was also an innovative misleading trick for future statin trialists

[576] Rist et al. https://n.neurology.org/content/early/2019/04/10/WNL.0000000000007454
[577] NICE 2014
[578] Kronmal RA. JAMA 1985 ; 253(14) : 2091
[579] Kronmal RA. op. cit.
[580] David Colquhoun. R. Soc. open sci. 2014 ; 1: 140216 - http://dx.doi.org/10.1098/rsos.140216

« The 0.1% total mortality reduction over 7 years is not significant »[581], which the trialists admit : « The risk of death from all causes (total mortality) was only slightly and nonsignificantly reduced in the cholestyramine group »[582]
l'essai dit LRC-CPPT

LYON DIET HEART STUDY
Essai nutritionnel positif en prévention secondaire

« At a time when health professionals, the pharmaceutical industries, and the research funding and regulatory agencies are almost totally focused on lowering plasma cholesterol levels by drugs, it is heartening to see a well-conducted study finding that relatively simple dietary changes achieved greater reductions in risk of total and CHD mortality in a secondary prevention trial than any of the cholesterol-lowering studies to date…

The unprecedented reduction in risk of CHD was not associated with differences in TC levels between the control and experimental groups and that the survival curves showed a very early separation quite unlike what has been reported in the cholesterol reduction studies…

It is much to the credit of Dr de Lorgeril and associates that they persisted in following the original enrollees despite the official termination of the study and publication of the initial findings so that they are now able to report their more extended observations. With the mean follow-up time of 46 months per patient, the initial remarkably beneficial effects of the experimental dietary program persisted compared with the control group consuming the 'prudent Western-type diet' …

The unprecedented magnitude of the benefits achieved is especially notable because the study was undertaken in a very-low-risk population. Of the 36 selected countries listed, the American Heart Association's 1998 Heart and Stroke Statistical Update ranks France second to the lowest in CV mortality in men, with only Japan ranked lower, and France ranked the lowest in female CV mortality »[583]

« The Lyon Diet Heart Study is a randomized secondary prevention trial aimed at testing whether a Mediterranean-type diet may reduce the rate of recurrence after a first MI. An intermediate analysis showed a striking protective effect after 27 months of follow-up…

The protective effect of the Mediterranean dietary pattern was maintained up to 4 years after the first infarction, confirming previous intermediate analyses. Thus, a comprehensive strategy to decrease CV morbidity and mortality should include primarily a cardioprotective diet »[584]

« Methods and Results—Three composite outcomes (COs) combining either
a) CO1 = [cardiac death + nonfatal myocardial infarction], or
b) CO2 = the preceding + major secondary end points [unstable angina + stroke + heart failure + pulmonary or peripheral embolism] or
c) CO3 = the preceding + [minor events requiring hospital admission] were studied...

In the Mediterranean diet group, CO1 was reduced (14 events versus 44 in the prudent Western-type diet group), as were CO2 (27 events versus 90) and CO3 (95 events versus 180). Adjusted risk ratios ranged from 0.28 to 0.53…

Among the traditional risk factors, TC (1 mmol/L being associated with an increased risk of 18% to 28%), systolic blood pressure (1 mm Hg being associated with an increased risk of 1% to 2%), leukocyte count (adjusted risk ratios ranging from 1.64 to 2.86 with count .93109/L), female sex (adjusted risk ratios, 0.27 to 0.46), and aspirin use (adjusted risk ratios, 0.59 to 0.82) were each significantly and independently associated with recurrence »[585]
l'étude de Lyon
« C'est la première fois en novembre 2013 que l'*American Heart Association* admet la supériorité de la diète méditerranéenne ; et nous sommes presque en 2014 ; nous avons publié notre premier rapport sur la Lyon Diet Heart Study (analyse intermédiaire) en 1994. Comptons ensemble : il aura donc fallu 20 ans pour leur ouvrir les yeux … en l'absence de conflit d'intérêt ou autre effet de compétition. Il leur faudra sans doute le double pour admettre que le cholestérol est innocent »[586]

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[581] Kronmal RA. op.cit
[582] LRC-CPPT. JAMA 1984; 251: 351
[583] Alexander Leaf. Circulation 1999; 99: 733 - doi: 10.1161/01.CIR.99.6.733 - on line http://circ.ahajournals.org/content/99/6/733.full
[584] De Lorgeril et al. Circulation 1999; 99: 779 - doi: 10.1161/01.CIR.99.6.779 http://circ.ahajournals.org/content/99/6/779.full.pdf
[585] Axel Ellrodt, 2014
[586] http://michel.delorgeril.info/non-classe/nouvelles-recommandations-aux-usa-attention-danger/comment-page-1#comment-14313

MACROLIDE INTERACTION AND RISK OF RHABDOMYOLYSIS, RENAL FAILURE AND DEATH
Interaction médicamenteuse – Médicaments mortels – Épidémiologie - Statinovigilance

« Compared with the control group, patients co-prescribed clarithromycin and a statin not metabolized by CYP3A4 were at increased risk of hospital admission with acute kidney injury (adjusted relative risk [RR] 1.65 (95% CI 1.31 to 2.09), admission with hyperkalemia (adjusted RR 2.17, 95% CI 1.22 to 3.86) and all-cause *mortality* (adjusted RR 1.43, 95% CI 1.15 to 1.76). The adjusted RR for admission with rhabdomyolysis was 2.27 (95% CI 0.86 to 5.96) »[587]

« This population-based cohort study in hospital administrative databases showed that older people taking statins who were prescribed clarithromycin or erythromycin were hospitalized more frequently for *rhabdomyolysis* and acute *kidney* injury and had higher all-cause *mortality* than people who were prescribed azithromycin…

In older adults, coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 increases the risk for statin toxicity (atorvastatin, simvastatin, lovastatin)… The study used administrative *codes* to identify rhabdomyolysis and kidney injury, and these codes are insensitive, therefore the risks were underestimated »[588]
interaction avec macrolide et risque de rhabdomyolyse, insuffisance rénale et décès

MAGNITUDE OF BENEFITS
« The statins correct plasma lipids remarkably, and numerous benefits have statistical support, but the magnitude of the benefits disappoints … Despite outstanding plasma lipid corrections, the real benefits of the statins are marginal »[589]
ampleur des bénéfices
* la significance clinique des résultats d'un essai dépend de l'ampleur des bénéfices et celle-ci doit être comparée à l'ampleur des inconvénients, soit les EIM et les couts de tout genre. L'ampleur des bénéfices s'exprime le plus utilement en NNT annualisé (l'inverse de la réduction du risque absolu d'un événement CV signifiant). L'ampleur des EIM s'exprime en NNH (l'inverse de l'augmentation du risque d'un effet indésirable)

MAINSTREAM MEDIA AND PATENTED PRODUCTS
Statinovigilance - Diabète

« The CBS news [USA] show '60 Minutes' made waves with a story asserting that the antidepressants taken by millions of Americans daily are actually no more effective than sugar pill placebos… the national evening TV news reported on a research publication from Harvard that found a 50% increase in the chance of *diabetes* among women who took cholesterol lowering *statin* drugs…

Those are just examples of a new trend in mainstream media to expose controversies in blockbuster drugs that generate tens of billions of dollars in revenue for the drug industry… The most likely explanation is that the same drugs now being exposed as unsafe and ineffective have also lost patent protection, and therefore, are no longer generating the huge advertising revenue for the networks. A significant portion of the revenue for the broadcast networks is derived from pharmaceutical advertisements…

If the mounting evidence linking increased Type 2 diabetes risk to statin use is correct, then tens of millions of patients have developed diabetes as a result of their Lipitor™, while at the same time not benefiting from any reduction in mortality »[590]
médias traditionnels / presse dominante / médias dominants et produits brevetés

MASS SCREENINGS
Dépistages – Prévention primaire – Façonnage de maladies
= public health promotion of sreening tests in healthy people with no symtoms
« There is no better scientific support for the screening you for high cholesterol, diabetes, osteoporosis, or breast and prostate cancer, will advantage you than there is for neutraceucals, glucosamine, vitamin E and the like »[591]
dépistage systématique / de masse
* à distinguer des examens diagnostiques et des examens de suivi chez un malade

[587] Li et al. CMAJ 2014 - http://www.cmaj.ca/content/early/2014/12/22/cmaj.140950.full.pdf - DOI:10.1503 /cmaj.140950
[588] Patel et al. Ann Intern Med 2013; 158: 869
[589] Krut LH. American Journal of Cardiology 1998, 81(8): 1045 - DOI: 10.1016/S0002-9149(98)00084-8
[590] Steven Greer, 19.02.2012. Currentmedicine.tv - Site http://currentmedicine.tv/2012/specialties/psychiatry/youre-telling-me-this-now-why-the-news-is-suddenly-critical-of-statins-and-antidepressants/
[591] Nortin Hadler. Worried Sick, p 106

MEDIUM DOSE STATIN TRIALS AGAINST PLACEBO
* Medium statin intensity vs placebo ; with > 1000 participants and lasting > 1 year[592]
4S, CARDS, ASPEN, LIPS, HPS, ASCOT-LLA
essais de statine modérément dosée contre placebo

MEGA, THE TRIAL (JA)
Prévention primaire – Pravastatine 10 et 20mg + diète c. diète seule – Essai sans double insu ni placebo - Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study[593]

METHODOLOGY
* Participants demography : average age 58 years ; 31% men ; 69% women
* Participants health : 21% diabetics

* Duration : 5.3 years (63.6 months)
* Comparison : pravastatin 10 or 20 mg + diet vs. diet alone
* Control group : diet alone

* Primary composite endpoint has 6 components : [cardiac death + sudden death + fatal MI + non-fatal MI + new angina + revascularisation] - The whole endpoint is heterogenous in *seriousness* (some fatal, some not), *objectivity* (new angina and revascularisation are soft and bias is likely by risk of unblinding) and relative *frequencies* and treatment differences of individual components

* Positive compliance (active group adherence) : 90%
* Negative compliance (control group adherence) : 75%

RESULTS
* Health related quality of life *not reported*
* New onset diabetes *not reported* in princeps publication ; RRI of +7%, NS, obtained later by meta-analyst Sattar

« Calculated from the hazard ratio, the NNT to prevent 1 CHD event was 119 during the average 5·3 years follow-up » for a NNT of 631 person-years, an average postponement of 14 hours for the first CHD event to occur per year of treatment
« The mortality benefit of MEGA hazard ratio was not from fewer CV deaths, which were identical in the statin and nonstatin groups, but from the anomaly of fewer deaths from cancer »[594]

« Nakamura et al. report the efficacy of pravastatin over diet alone in the primary prevention of CV diseases in a low-risk (Japanese) population. However :

a) A revascularisation procedure is included in the primary composite endpoint. Hence, more patients assigned diet therapy than pravastatin could have been arbitrarily recommended for revascularisation because of the open-labelled nature of the trial and coronary revascularisation accounts for more than half of the primary endpoints reached

b) Because 40% of the patients in the MEGA trial had hypertension and 21% diabetes, the population does not represent the general hypercholesterolemic population in Japan
c) MEGA did not show any benefit of statins for women (primary endpoint HR = 0.71, NS) »[595]

« Absence of event or mortality benefit in women in combined primary and secondary prevention trials (HPS, PROSPER, MEGA) »[596] was found in the sensitivity analysis of Petretta et al. in 2010
« The recent MEGA study enrolled more women than men in large numbers, but the reduction in events was significant only in men »[597]

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[592] NICE 2014
[593] Nakamura et al. Lancet 2006 ; 368 : 1155 - doi:10.1016/S0140-6736(06)69472-5 – full paper at http://www.esculape.com/cardiologie/MEGA-pravastatine-fulltxt.pdf
[594] Vos, Rose & Biron. Circulation 2010 ; 122(23): e576 (Correspondence) - doi: 10.1161/ CIRCULATIONAHA.110.954016
[595] Nango et al. Lancet - http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(06)69830-9/fulltext
[596] Eisenberg et al
[597] Walsh JM, Pignone M. JAMA 2004; 291: 2243 - Petretta M et al. Int J Cardiol. 2010; 138: 25 - Thavendiranathan P et al.. Arch Intern Med. 2006; 166: 2307

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE

L'essai dit Mega

* La réduction relative du critère principal combiné fut de -33% (HR = 0,67) mais près de la moitié de cette réduction provenait de la revascularisation, un critère trop flou pour être validement combiné avec la mortalité coronaire ou toutes causes, surtout dans un essai sans double-insu ni placebo; de plus, le seuil statistique aurait du être de 0,001, entre autres pour compenser les comparaisons multiples de 14 critères d'évaluation (fig. 2 dans Kanamura 2006)

* La réduction absolue du critère combiné fut de 0,17 par 100 personnes-année selon la fig. 2 dans Kanamura 2006, pour un NNT de 588 personnes-année, un taux annuel d'inefficacité de 99,83% et un délai moyen d'événement coronarien de 15 heures si on répartit le bénéfice sur 588 personnes statinisées durant un an...

En s'inspirant du risque instantané, les auteurs ont obtenu un NNT annualisé de 631 personnes-année, supposant une réduction du risque absolu de 0,158 par 100 personnes-année, un taux annuel d'inefficacité de 99,84% et un délai moyen d'événement coronarien de 14 heures 53 minutes après consommation de 230 315 comprimés. Combien coutera cet exercice futile? S'il en coute 1000$US ou 1000 euros par année pour statiniser une personne, l'événement retardé chez un seul chanceux coutera 631 000 dollars ou euros

MEMORY AND STATINS IN GERIATRICS *Statinovigilance*

« Dr. Katherine Samaras (AU) and her associates did neuropsychometric testing on 377 subjects 70-90 years old who had been on statins for 2-22 years, and 301 controls who had not taken the drugs. They then repeated the assessments at 2 and 4 years, and calculated composite, normalized *Z* scores for various cognitive functions. The team found a greater decline in memory *Z* score from baseline among statin users at both 2 and 4 years (4-year *Z* score of –0.27 vs. –0.07, a 0.20 difference) »[598]

mémoire et statines en gériatrie

MER/29 SAGA

triparanol saga

Catastrophe de pharmacovigilance

« Before Paul Rheingold took on the Dalkon Shield™ mass tort/class action case in the 1970s he actually invented this legal form - a decade earlier in relation to MER/29 (triparanol) a cholesterol-lowering drug taken off the market in 1961 for causing blindness among other things. In those days it was rightly called a 'mass disaster' case and of course it still is a mass disaster ...

Rheingold's 1968 account in the California Law Review is called 'The Mer/29 Story: An instance in successful mass disaster litigation' »[599]

la saga du Mer 29 / du triparanol

META-ANALYSES OF STATINS IN WOMEN

a) Criqui & Golomb. *J Am Coll Cardiol* 2004; 44 : 1009
b) Walsh & Pignone. *JAMA* 2004 ; 291 : 2243
c) Abramson & Wright. *Lancet* 2007; 369 : 168
d) Eisenberg & Wells. *J Empirical Legal Stud* 2008; 5(3) : 507
e) Petretta et al. *Int J Cardiol* 2010 ; 138 : 25
f) CTT Collaboration. *Lancet* 2015 ; 385 : 1397

META-ANALYSIS OF IMPACT OF DIFFERENT TYPES AND DOSES OF STATINS ON NEW-ONSET DIABETES MELLITUS

Statinovigilance – Effet diabétogène

NAVARESE EP, Buffon A, Andreotti F, et al. *Am J Cardiol*. 2013; 111(8): 1123-1130

« A 2013 review of 17 different randomized, controlled studies, involving 113,394 patients, compared the risk of developing diabetes in patients taking statins. The studies compared either a statin versus a placebo or high-dose versus moderate-dose statin therapy.[SEP][SEP]The authors found that pravastatin was associated with the lowest risk for new-onset diabetes compared with a placebo...

[598] Frontline Cardiology News, 10.7.2014
[599] Harriet Rosenberg 2013

Conversely, rosuvastatin (Crestor™) was associated with the largest relative risk increase for diabetes (25 %) compared with a placebo. The risk of diabetes appeared to be intermediate with atorvastatin compared with a placebo. Simvastatin performed poorly in the trials (+21% RRI of diabetes). The study concluded that 'high-dose pravastatin had the highest probability to be the safest treatment in terms of new-onset [diabetes], with rosuvastatin and simvastatin performing least well' »
Méta-analyse de l'impact de différentes statines à différentes posologies sur le risque de nouveau diabète de type 2 –
(Traduction libre du titre de l'article)

METEOR, THE TRIAL *Rosuvastatine*
Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin

METHODOLOGY
* Princeps publication : Armitage/*Lancet*/2010[600]
* Duration : mean 6.7 years (80.4 months)
* Funding : private, Merck: £22.7M plus drug supply
* Participants demography : 12 064 randomized ; aged 18-80 years, mean 64 years ; 10 012 men ; 2052 women or 17%

* Participants health : previous MI as inclusion criteria
* Lipids at baseline : TC mean 4.23 mM ; LDL-C mean 2.54 mM (98 mg/dL)
* Comparison : two intensities of simvastatin, 80 vs. 20 mg
* Control group : simvastatin 20mg

* Composite endpoint : [CHD death + MI + stroke + arterial revascularization] - Of low validity because of heterogeneity of :
a) seriousness, mixing a fatal event, a non fatal event and an intervention;
b) objectivity (revascularization is a medical decision, at risk of unblinding and subject to provider opinion),
c) different frequencies of the 4 criteria. Total mortality, the most patient-relevant endpoint, is not included.

RESULTS
* Positive compliance (active group adherence) : 90% actually received intended experimental treatment with 80mg until end of trial
* Negative compliance (control group adherence) : 93% actually received intended control treatment with 80mg until end of trial
* Lipid reduction : LDL-C absolute risk reduction of -0.35 mM (-13 mg/dl)

Absolute differences in benefits : none are statistically or clinically significant
a) TOTAL MORTALITY : 6 fewer on high dose (NS) - annual NNT = 1 005 patient-years ; 964 deaths overall on 80 mg, 970 deaths on 20 mg,
b) CV mortality : 8 fewer on high dose (NS) - annual NNT = 862 patient-years ; 447 CHD deaths on 20 mg, 439 deaths under 80 mg

c) non-fatal stroke : annual NNT = 431 patient-years (NS)
d) non fatal MI : annual NNT = 91 patient-years (NS)

e) stroke :
f) primary composite endpoint : 1477 or 24.5% on 80 mg, 1553 events or 25.7% on 20 mg, absolute risk reduction of -1.2% (NS)

g) non vascular deaths : 399 or 6.6% on 80 mg, 398 or 6.6% on 20 mg (NS)
h) vascular deaths : 565 or 9.4% on 80 mg, 572 or 9.5% on 20 mg (NS)
i) total deaths : 964 deaths or 16% on 80 mg, 967 deaths or 16.1% on 20 mg (NS)

j) major vascular events : 36 fewer events - 1189 on 80 mg, 1225 on 20 mg (NS)

Absolute differences for harms:
a) rhabdomyolysis (CK > 10 times normal); annual NNH = 1005 patient-years
b) rhabdomyolysis (CK 10x to 40x ULN) : annual NNH = 183 patient-years

c) myopathy : 53 cases or 0.9% on 80 mg, 2 cases or 0.03% on 20 mg, ARI of +0.87% over 6.7 years, annual ARI of -0.13% and

[600] Armitage et al. Lancet 2010: 376(9753): 1658 - doi:10.1016/S0140-6736(10)60310-8 - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988223/

annual NNH of 769 patient-years. The low absolute increase may indicate a poor ascertainment of this ADR very well known to be dose-related. The high relative risk increase of 26.5 (53 / 2) does, however, confirm dose-dependency

d) new onset diabetes : RRI = +7%, NS ; annual NNH = 144 patient-years
e) serious adverse events : *not reported*
f) health related quality of life *not reported*

* Authors' conclusion : whether more intensive therapy safely produces extra benefits is uncertain
* Factual conclusions:
a) no clinically significant reduction of hard or soft desirable endpoints;
b) not even a reduction of composite primary endpoint ;

c) confirmation of dose dependency of rhabdomyolysis and diabetes as adverse effects ;
d) results incompatible with the lipid hypothesis since LDL cholesterol was 0.35 mM lower under the higher dose and there was no benefit whatsoever
l'essai dit Meteor

MIDDLE-AGED MEN WITH OVERT CHD
hommes d'âge moyen avec maladie coronarienne avérée
* les seuls patients où des bénéfices *numériques* sur des critères objectifs (hard endpoints), comme la mortalité toutes causes et la mortalité coronarienne, ont été observés au cours d'essais cliniques sponsorisés …

Malheureusement l'amplitude de ces bienfaits est minime et n'atteint pas la signifiance clinique. Des NNTs de 100 patients-année et plus doivent être discutés avec les patients, même si ces NNT ne font guère le poids quand on considère l'incertaine crédibilité des essais sponsorisés et tous les effets indésirables directs et indirects (et souvent non publiés) des statines sur la qualité de vie, les ressources et les budgets

MILLS et al, THE META-ANALYSIS[601]
« We included a total of 76 RCTs involving 170 255 participants »

* There are incoherent data on total mortality. In a first set of data, page 112 :
« There were a total of 14 878 deaths… In all trials combined, there were a total of 7004 (8.1%) deaths among the 86 328 patients receiving a statin and 7713 (9.5%) deaths among 80 365 patients receiving a control intervention [total deaths 14 717]. Combined, this represents a numerical 10% relative risk reduction in all-cause mortality ». The abstract repeats the 14 878 figure.

* On page 115 in Figure 2 one can read Any death as 6240 / 88 100 in treatment group and 7157 / 82 155 in control goups [total deaths 13 397]. Why such a discrepancy between text/abstract and figure 2 ?

Unreported absolute risk reduction of total mortality :

* When calculating the absolute risk reduction from the first set of figures (7004 deaths / 86 328 under a statin and 7713 deaths in 80 365 control patients) and adjusting them to a reported average trial duration of 2.7 years, it boils down to a -0.55 % annual absolute risk reduction of total mortality per year of treatment or an annual NNT of 182 patient-years, amounting to an annual inefficacy rate of 99.45% and an average survival advantage, when spread over 182 participants, of 42 days 8 minutes per treatment-year in trial conditions and much less in clinical settings...

Which consideration the authors failed to take into account when concluding that « Our analysis demonstrates that statin therapy reduces all-cause mortality ». But what is the clinical signifiance ? Not much, Much ado about nothing !…

Unreported absolute rates of ADRs. Figure 4 on page 118 only reports relative risks increases:

* Rhabdomyolysis RRI of +4%
* Creatine kinase RRI of +7 %
* New onset diabetes RRI of +9%
* ALT elevation RRI of +30 %
la méta-analyse de Mills et coll. en 2011

[601] Mills et al. Q J Med 2011; 104: 109 - 1 SEP doi:10.1093/qjmed/hcq165

MINIMISATION OF ADRs IN CLINICAL TRIALS
Pharmacovigilance – Éthique de la recherche
« Industry-driven RCTs use several tricks to minimise adverse effects of their drugs :

a) The exclusion of individuals from trials with known health issues likely to be exacerbated by statins or signal susceptibility to statin side effects (such as liver, kidney and muscle disease)
b) The use of a 'run-in' period before the study starts which detects and then excludes individuals who do not tolerate statins

c) The possibility that individuals 'drop out' from the study because of side effects, meaning that the incidence of some side effects can be 'lost' from the data
d) Failure of the study investigators to assess and monitor adverse events such as muscle damage and changes in brain function
e) Failure to properly ascertain or report adverse events »[602]
minimisation des EIM dans les essais cliniques

MIRACL, THE TRIAL *Prévention secondaire après syndrome coronarien aigü – Atorvastatin 80 mg c. placebo*
Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering

* Funding : private (Pfizer, Lipitor™) - « The trial was conducted by the sponsor's staff, the only statistician belonged to the sponsor's staff. This would not be acceptable today, with the new regulations »[603]

* Princeps publication : Schwartz/*JAMA*/2001[604]
* Methodology : > 1000 patients ; < 1 year ; prior to 2005 New Regulations ; high risk of bias
* Inclusion criteria : 2 to 4 days after an acute coronary syndrome defined as : (a) unstable angina + some objective evidence of myocardial ischemia (46% of patients) and (b) non-Q-wave acute MI (54% of patients)

* Primary composite endpoint has 4 components: [death + nonfatal acute MI + cardiac arrest with resuscitation + recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization] …

That outcome is heterogenous ; most of the apparent benefit results from the reduction of rehospitalization, a soft, subjective ischemia driven outcome, invented by the corporate sponsors, sensitive to unintended unblinding (from LDL reduction), to patient's interpretation of symptoms and to attitude of ER physicians and cardiologists

* Participants demography: 3086 randomized ; 34,8% women ; mean age 65 years
* Participants health : 15% hypertension, 23% diabetics ; 54% with MI ; 46% with unstable angina ; TC: 5,3 mM

* Comparison : atorvastatin 80 mg (high dose) vs. placebo
* Duration : 16 weeks

RESULTS
Lipid reduction
* LDL cholesterol : absolute risk reduction of -1.3 mM (52 mg/dL), from 3.2 mM (124 mg/dL) to 1.9 mM (72 mg/dL)

Benefits
* TOTAL MORTALITY : 68 or 4.4% under placebo ; 64 or 4.2% under atorvastatin, relative risk reduction = -6%, NS, absolute risk reduction = -0.2%, not clinicaly significant
* CHD mortality : NS
* Non-fatal MI : 101 under atorvastatin ; 113 under placebo
* Cardiac arrests : 8 under atorvastatin ; 10 under placebo

* Primary endpoint : 269 or 17.4% under placebo and 228 or 14.8% under atorvastatin, relative risk reduction = -16%, NS; the absolute risk reduction of the primary composite endpoint is 2,6% (NNT = 38 patients) and inefficacy rate is 97,4% …

Most of the apparent benefit results from the reduction of *emergency rehospitalization*, a soft, subjective ischemia driven outcome, « not MIs, not unstable angina, but something else, not corresponding to any known clinical category, dependent on

[602] http://www.drbriffa.com/2014/02/07/is-the-editor-of-the-bmj-suffering-from-statin-induced-amnesia/
[603] de Lorgeril 2014, op. cit.
[604] Schwartz et al. MIRACL. JAMA 2001 ; 385 : 1711 – abstract on http://www.ncbi.nlm.nih.gov/pubmed/11277825 - full paper on http://www.courses.ahc.umn.edu/pharmacy/5822/lectures/miracl.pdf

data collected field field investigators that belonged to the sponsor's staff »[605] - « No reduction of death, nonfatalMI, resuscitated cardiac arrest, which were primary outcomes »[606]

* Emergency rehospitalization : 130 or 8.4% under placebo ; 95 or 6.2% under atorvastatin, NS; this outcome is too subjective, and apparently created to reach the 'sacred but inadequate' 5% significant level, to be combined with a hard endpoint such as death, which was not reduced

* Nonfatal acute MI : 113 or 7.3% under placebo ; 101 or 6.6% under atorvastatin, relative risk reduction = -10%, NS
* Cardiac arrest : 10 or 0.6% under placebo ; 8 or 0.5% under atorvastatin, relative risk reduction = -8%, NS
* Worsening angina : 106 or 6.8% under placebo ; 91 or 5.9% under atorvastatin, relative risk reduction = -14%, NS
* Stroke : 24 or 1.6% under placebo, 12 or 0.8% under atorvastatin, relative risk reduction = -50%, NS

Harms
* Health related quality of life *not reported*
* 3 incidents of rhabdomyolysis (0.04%) under the statin

* Authors conflation : For patients with acute coronary syndrome, lipid-lowering therapy with atorvastatin, 80 mg/d, reduces recurrent ischemic events (worsening angina with objective evidence of myocardial ischemia requiring urgent rehospitalization) in the first 16 weeks[607]
* Factual interpretation: No benefit demonstrated on hard, objective endpoints in Miracl
l'essai dit Miracl[608]
* la seule réduction d'un critère d'évaluation individuel, observée durant les 16 semaines après un syndrome coronarien aigu, est celle de l'hospitalisation pour angine récidivante, critère subjectif et mou s'il en est, sensible à la moindre levée du double insu (par simple coup d'œil à la cholestérolémie), à l'interpération des symptômes par les patients et à l'attitude des urgentologues et cardiologues. De plus cette réduction n'atteint même pas le seuil de signification de 1%

* la réduction absolue du critère combiné principal prédéfini est de -2,6% et NS au seuil de 1% mais ce critère est trop hétérogène pour être valide, notamment à cause de la grande contribution à ce bénéfice du critère mou décrit ci-haut, la réhospitalisation d'urgence

MISINTERPRETATION OF TRIAL EVIDENCE ON STATIN ADVERSE EFFECTS MAY HARM PATIENTS - (Article) *Statinovigilance*
Beatrice A GOLOMB. *European Journal of Preventive Cardiology* 25.4.2014 - DOI: 10.1177/2047487314533085
http://cpr.sagepub.com/content/early/2014/04/24/2047487314533085
La mésinterprétation des données expérimentales de statinovigilance peut être préjudiciable aux patients (Traduction libre du titre de l'article)
* Golomb est une experte mondialement reconnue en statinovigilance

MISLEADING PRESENTATION OF STATIN TRIAL FINDINGS
« We have documented that the *presentation of statin trial findings* can be characterized as a *deceptive strategy* in which negligible benefits of statin treatment have been amplified with the use of *relative risk* statistics, and that serious adverse effects are either ignored or explained away as a chance occurrences. Moreover, the authors of these studies have presented the rate of adverse events in terms of *absolute risk*, which, compared to relative risk, minimizes the appearance of their magnitudes »[609]
présentation trompeuse des résultats d'essais statiniques

MISLEADING RELATIVE RISKS
risques relatifs trompeurs
* L'expression d'un résulat en risque relatif est légitime après l'analyse *explicative* d'un essai clinique de médicament, mais c'est le risque absolu qui est cliniquement pertinent dans l'analyse *pragmatique*. Les promoteurs commettent systématiquement ce mélange de genres afin de magnifier le bénéfice observé ; cette pratique trompeuse fait partie de la *conflation*.

* Dans la présentation d'un suivi de 20 ans après l'essai statinique Woscops, on rapporte une réduction de -28% dans la mortalité coronarienne, exprimée en risque relatif. Par contre la réduction du risque absolu n'est que de -0,115% par année,

[605] de Lorgeril 2014, op. cit.
[606] DuBroff, *QMJ* 1.11.2017
[607] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC59635/
[608] Schwartz et al. JAMA 2001; 285: 1711 - http://www.ncbi.nlm.nih.gov/pubmed/11277825?dopt=Abstract
[609] Diamond & Ravnskov, op. cit.

équivalent à un retard de cette mortalité par 870 patients-année[610], soit après consommation de 317 550 comprimés. L'erreur est à la limite épistémologique, elle est voulue par les promoteurs et relayée par les revues savantes, en plus d'être diffusée par l'establishment médical, par ignorance ou par pharma-co-dépendance (pour demeurer poli...)

MODELLING THE DECLINE IN CORONARY HEART DISEASE DEATHS – (Article) *Étude populationnelle – Financement public*
UNAL et al. *Brit Med J* 2005; 331 : 614 - http://www.bmj.com/content/331/7517/614.full
Modélisation du déclin de la mortalité coronarienne
« Les décès coronariens sont en baisse au R.-U., mais pourquoi ? Des chercheurs en santé publique financés par le ministère britannique de la Santé se sont penchés sur les déterminants de cette baisse au R.-U.. Unal et coll. ont effectué une enquête populationnelle sur la chute de la mortalité coronarienne sur une période de 19 ans (1981-2000). Les données portaient sur quelque 35 M d'adultes entre 25 et 84 ans…

Elles furent tirées d'enquêtes nationales, de statistiques officielles, d'audits cliniques, d'essais cliniques et de synthèses méthodiques. Les méthodes furent basées sur une modélisation épidémiologique (nommée IMPACT) préalablement validée en Écosse, en NZ et à Beijing. La mortalité coronarienne fut réduite de moitié, en termes absolus cela fait 68 230 décès coronariens en moins par année…

Cette réduction de 68 230 décès s'expliquerait par deux facteurs : de meilleurs traitements (médicaments, techniques invasives, unités coronariennes, etc.) des victimes de la maladie, entraînant 25 805 décès coronariens en moins (-42%) et des interventions préventives responsables de 45 370 décès coronariens en moins (-58%)...

La réduction préventive de 45 370 décès est attribuable à la prévention dite primaire (chez des non coronariens), responsable de 36 625 décès coronariens en moins (-81%). Et à la prévention secondaire (chez des coronariens avérés) responsables de 8 745 décès en moins (-19%). La prévention primaire serait la composante majeure de la chute des décès coronariens sur une période de 19 ans au RU avec 36 625 décès en moins (-54% des 68 230) et il convenait d'en quantifier les déterminants :

1. L'arrêt du *tabagisme* chez environ un tiers des fumeurs non coronariens, qui expliquerait une réduction absolue de 24 680 décès coronariens, soit -67% de 36 625

2. La baisse relative de -4,2% du cholestérol total, associée à 4 710 décès coronariens en moins, soit -13% de 36 625. Cette amélioration est attribuée à deux composantes :
(a) Une alimentation plus saine à laquelle on associe 4 565 décès coronariens en moins, soit 97% de 4 710
(b) La prise de statines, à laquelle on associe seulement 145 décès coronariens en moins, soit 3% de 4 710

3. La baisse relative de -7,7% de la tension artérielle diastolique, à laquelle on associe 7 235 décès coronariens en moins, soit -20% de 36 625

Les faits parlent par eux-mêmes: la prévention primaire – qui aurait évité annuellement 36 625 décès coronariens – aurait accompli cet exploit dans la population britannique par la prise de mesures d'hygiène : l'arrêt du tabac et une alimentation plus saine, auxquels on attribue 34 590 décès coronariens en moins (-94%), par opposition aux 2 035 décès coronariens en moins (-6%) attribués à la prise de pilules préventives (statines + antihypertenseurs)

Les pilules à titre préventif sont les plus grandes *perdantes* dans cette enquête populationnelle : elles se sont avérées 16 x moins utiles qu'un style de vie plus sain. Les statines en prévention primaire, avec 145 décès coronariens évités, se sont avérées 470 fois moins utiles que le régime alimentaire. Aussi bien dire qu'elles ne servent pas à grand-chose chez les non coronariens tout en coutant une fortune si l'association est causale

Il faut certes être prudent avec ce genre de calculs effectués depuis de grandes bases de données. Admettons pour un instant - parce que nous sommes loin de la valeur probante d'un essai contrôlé bien fait - que la marge d'erreur soit de 1000 % ou de 10x, on conclurait alors avec beaucoup plus de fermeté que les pilules préventives sont 1,6 fois moins utiles que le régime

On conclurait aussi que les statines chez les non coronariens sont 47 fois moins utiles qu'un régime sain, ce que clament depuis des années une poignée de 'sceptiques du cholestérol' comme de Lorgeril, Ravnskov et cie. Un nombre croissant d'études fiables convergent vers le même constat. Les statines exerceraient un rôle négligeable par rapport à un régime de vie sain dans la prévention primaire qui explique la moitié de la chute de la mortalité coronarienne observée au R-U entre 1981 et 2000 »[611]

[610] Diamond DM. BMJ 2017;358:j4171- http://www.bmj.com/content/358/bmj.j4171/rr
[611] Biron P. Médecine 2013 ; 9(6) : 244

MORATORIUM ON SCREENING CHOLESTEROLEMIAS?
un moratoire sur les cholestérolémies de dépistages?
* Le temps ne serait-il pas venu pour un moratoire sur les cholestérolémies de dépistage ? Du moins pour leur remboursement par les régimes publics de soins. Poser la question c'est y répondre. Le dépistage du cholestérol mène à une perte de liberté individuelle des bien-portants...

Celui qui deviendra statinisé pour la vie devient dépendant du médecin sans pourtant être malade, soumis à des cholestérolémies de suivi pour la vie, étiqueté 'malade de son cholestérol', libellé personne 'à risque', exposé aux interactions médicamenteuses et aux effets indésirables, à risque de surprime d'assurance santé / voyage, et source bien involontaire d'énormes dépenses à même le budget public de la santé...

À quand un moratoire sur la cholestérolémie de dépistage des bien-portants? Et sur la répétition 'à vie' d'innombrables cholestérolémies de suivi ? Pourqoi pas, puisque les quelques heures de vie gagnés par chaque année de statinisation d'hommes coronariens pas trop âgés ne résultent probablement pas - et même les ayatollahs du cholestérol l'admettent enfin - de l'abaissement de la cholestérolémie...

Un cholestérol bas ou haut est n'est pas un gage de longue vie, laissons le tranquille car rien ne sert de l'altérer artificiellement par nos poisons à petite dose

MORTALITY NEUTRALITY
« Statins are *mortality neutral* in many groups. They have *not* reduced mortality in *women* with heart disease ; nor in the high-risk *elderly* including those with heart disease ; nor in high-risk primary prevention »[612]
neutralité actuarielle / vitale

MOTOR NEURONE DISEASE FUNCTIONAL STATUS *Statinovigilance*
« To determine if statin medications affect the rate of disease progression, we conducted a prospective cohort study in patients diagnosed with ALS with statin medication as the predetermined exposure variable and the rate of decline of the ALS Functional Rating Scale-Revised (ALSFRS-R) as the primary outcome. 164 consecutive patients with laboratory supported probable, clinically probable, or clinically definite ALS were evaluated from January 2006 to September 2007...

32 patients (20%) were taking statin medications and 132 were in the control group. After adjusting for covariates, we found a highly significant increase in the rate of decline in the ALSFRS-R for the statin group (1.71 units/month) compared to the control group (1.05 units/month) representing a 63% increase in the rate of functional decline.[613] »
état fonctionnel dans la maladie du motoneurone

MUSCLE MASS AND LIFE SPAN
« In 3659 U.S. adults (age, ≥55 in men and ≥65 in women) who were not underweight, muscle mass was measured. During median follow-up of 13.2 person-years and after adjusting for confounders, total mortality was lower (relative risk reduction = 19%) among people in the highest quartile of muscle mass relative to those in the lowest quartile. In contrast, BMI was not associated with total mortality »[614]

* There is an urgent need to compare by various methodological approaches the muscle mass in older patients exposed to statins, before treatment onset and yearly thereafter, to find out whether myalgia, muscular weakness and exercise intolerance, well known statin ADRs, are associated with muscle wasting
masse musculaire et espérance de vie
* Comme la fonte musculaire est un facteur de risque de mortalité en gériatrie, et que cette fonte est accélérée par la statinisation, notamment quand celle-ci a entrainé myalgie, faiblesse musculaire et intolérance à l'exercice, on vient de trouver une autre bonne raison de protéger les gens âgés de la statinisation à vie. Les statines ne font pas maigrir par la graisse mais par les muscles.

MUSCLE PAIN FROM STATINS
Statinovigilance
« Up to 75 % of people who are prescribed statins stop taking them within 2 years, and 65% of those patients reported that they stopped because of side effects, primarily muscle pain (*Eur Heart J* 2015; 36(17): 1012-1022)...

[612] BA Golomb. Clin Invest 2013 ; 3(10): 913
[613] Zinman et al. Amyotroph Lateral Scler 2008; 9(4): 223 - doi: 10.1080/17482960802031092 -https://www.ncbi.nlm.nih.gov/pubmed/18608105
[614] Srikanthan & Karlamangla. Am J Med 2014; 127: 547 - http://dx.doi.org/10.1016/j.amjmed.2014.02.007

A study from the Cleveland Clinic showed that 42.6% of 491 patients who had previously reported muscle pain with at least 2 different statins had a recurrence of symptoms during blinded administration of Lipitor (atorvastatin) but not while taking a placebo (*J. Amer. Med. Assoc* 2016; 315(15): 1580-1590)...

There is no question that statins are very frequent causes of both muscle pain and delayed recovery from exercise. In my more than 45 years of medical practice, I saw many cases of muscle pain from statins, particularly in people who exercised regularly »[615]
myalgie statinique

MUSCLE WEAKNESS DISMISSED AS AN ADR
Déni des médecins
* too many practitioners still fail to link muscle symptoms (weakness with or without pain or wasting) with statinization
faiblesse musculaire écartée /rejetée comme étant un EIM
* trop de praticiens refusent encore de voir un lien de causalité entre la statinisation et les plaintes de symptomes musculaires (avec ou sans douleur ou fonte ou élévation de la CK)

MUSCULAR ADVERSE EVENTS IN FDA DATABASE (USA)
« Muscular adverse events : myalgia, rhabdomyolysis, increase in creatine phosphokinase level. Muscle pain and muscle tenderness are included in myalgia. Statin-associated asthenia, chest pain, pain in the extremities, muscle spasms, muscular weakness, myositis, and myopathy »[616]
évènements / effets indésirables musculaires dans la pharmacovigilance étatsunienne
N.d.T. en fait on devrait privilégier le terme *effets* plutôt que *événements*, car dès qu'on signale un évènement indésirable suspecté d'être statinique, l'événement devient par définition un effet

MUSCULAR AND NEUROLOGIC ADRs : VIGNETTE
Statinovigilance
effets indésirables musculaires et neurologiques : vignette
« On lui prescrivit une très forte dose de statine. Le patient développa des problèmes d'épaule débilitants, des douleurs musculaires et des faiblesses (ne pouvait plus ouvrir les tiroirs ou les pots de conserve), des problèmes cognifitfs et de mémoire, sans oublier une dépression nerveuse. Quand il abandonna son traitement par statine, tous ses symptômes disparurent. Inutile de préciser qu'il changea également de médecin »[617]

MUSCULO-SKELETAL ADRs
« During a cohort retrolective study in a military healthcare claims database, the odds ratios for statin users versus non users were :

a) 1.19 for all musculoskeletal diseases (+19%),
b) 1.07 for arthropathies and related diseases (+7%),
c) 1.13 for injury-related diseases (dislocation, sprain, strain) (+13%)
d) 1.09 for drug-associated musculoskeletal pain (+9%) »[618]
EIM musculo-squelettiques
* on doit retenir le chiffre de +19%, bien au delà de ce que les monographies admettent…

MYALGIA
= marked discomfort sensation originating from a muscle or group of muscles[619]
myalgie
* à rechercher chez tout consommateur de statine. On estime la fréquence jusqu'à près de 18%. Elle atteint surtout les muscles proximaux (cuisse, bras) de façon bilatérale. L'intensité et la fréquence sont souvent proportionnelles à la posologie

MYOPATHY AND STRUCTURAL MUSCLE INJURY
Statinovigilance – Lésions histologiques
« Persistent myopathy in patients taking statins reflects structural muscle damage. A lack of elevated levels of circulating

[615] http://www.drmirkin.com - 2.10.2016
[616] Sakaeda et al. PloS One 2011 - DOI: 10.1371/journal.pone.0028124
[617] Stephanie Seneff, citée par Sinatra & Bowden, 2014, page 146-7
[618] Mansi et al. JAMA Intern Med. 2013; 173(14): 1- doi:10.1001/jamainternmed.2013.6184
[619] RxISK / David Healy

creatine phosphokinase (CK, alias CPK) does not rule out structural muscle injury »[620]
myopathie et lésions musculaires structurelles
* un patient statinisé qui se plaint de faiblesse ou douleur musculaire, même sans élévation de la CK, souffre quand même de myopathie statinique. La clinique doit l'emporter sur le labo

MYOPATHY CONFUSED WITH SPINAL STENOSIS *Interférence diagnostique*
« Severe muscle symptoms with lipid-lowering agents may be confused with neurogenic claudication associated with spinal canal stenosis. Three case histories (in WHO Vigibase) recorded details suggestive of diagnostic confusion between severe and disabling muscle symptoms affecting the lower limbs attributable to a statin and symptoms of neurogenic claudication due to spinal stenosis. The reports include two safety issues, the need to :

a) consider statins as a cause of severe lower limb muscle symptoms even in the presence of spinal stenosis and normal CK levels
b) measure serum creatine kinase when these symptoms occur to detect progression of myopathy and potentially serious outcomes[621]
myopathie confondue avec une sténose spinale

MYOPATHY DEFINITIONS[622] *Statinovigilance - Myotoxicité*
a) Myopathy = any disease of muscle (according to ACC/AHA/NHLBI) – Symptoms of myalgia (pain or soreness), weakness or cramps ; plus creatine kinase > 10 times the upper limit of normal (according to NLA) – Creatine kinase > 10 x ULN (according to FDA)
b) Myalgia = muscle aches or weakness *without* CK elevation (ACC/AHA/NHLBI)
c) Myositis = Muscle symptoms *with* increased CK (ACC/AHA/NHLBI)
d) Rhabdomyolysis, graded
1. Muscle symptoms associated with marked CK elevations, typically substantially over 10 times ULN (according to ACC/AHA/NHLBI) -
2. CK > 10,000 IU/L -
3. CK > 10 times ULN plus (i) an elevation in serum creatinine or (ii) medical intervention with IV hydration (NLA definition) -
4. CK > 50 times ULN and evidence of organ damage such as renal compromise (FDA definition)
définitions des myopathies

MYOPATHY DENIALIST
= prescriber who brushes away complaints of muscle weakness or cramps of patients exposed to statins
négationniste des myopathies

MYOPATHY UNDERESTIMATION IN CLINICAL TRIALS
« How could the statin RCTs miss detecting mild statin-related muscle adverse effects such as myalgia? By not asking. A review of 44 statin RCTs reveals that only 1 directly asked about muscle-related adverse effects[623]. In the STOMP trial, investigators called patients twice monthly to ask specifically about muscle symptoms »[624]

« The 2011 Cochrane review of statins for the primary prevention of CV disease reported a risk ratio of 1.03 for muscle pain, i.e. 3% more patients developed muscle pain on drug than on placebo. However, industry-funded randomised trials are notoriously unreliable when it comes to the harms of drugs...

A publicly-funded randomised trial from 2012[625] that studied the impact of statins on energy and exertional fatigue got results that could be interpreted as 20% of the men and 40% of the women experiencing a worsening in either energy or exertional fatigue »[626]

« It is widely accepted that myopathy is the commonest adverse effect from statin treatment and it is seen most often in women and elderly people. However, in almost all reports from the statin trials it is said that muscle damage occurs in less than 1% of treated subjects. To reach that number, the authors have only recorded muscular damage in patients with high creatine

[620] Mohaupt et al. CMAJ 2009; 181(1-2): E11-E18
[621] Savage et al. IJRSM 2012 ; 24(4) at http://iospress.metapress.com/content/k2q76p65l0227t40/?id=K2Q76P65L0227T40
[622] Bhardwaj et al. Clinical Interventions in Aging 2013; 8: 47 quoting Joy & Hegele, AIM 2009
[623] Ganga et al. Am Heart J 2014; 168(1): 6-15
[624] Thompson PD. JAMA 2016; 316(19): 1969-1970 - doi:10.1001/jama.2016.16557 http://jamanetwork.com/journals/jama/fullarticle/2584061
[625] Golomb BA et al. Arch Intern Med 2012; 172: 1180
[626] Peter C Gøtzsche, 21.5.2014 - http://www.bmj.com/content/348/bmj.g3306?page=1&tab=responses

kinase (CK), and high CK is defined as a value that is 10x the upper limit of normal (ULN) at 2 successive determinations...

A relevant question is what happens after many years of statin treatment with the muscles of people whose CK is 'only' 9x higher than normal? Furthermore, people on statins may have muscular problems although their CK is normal, and even people on statins without any symptoms may have microscopic evidence of muscular damage »[627]
sous-estimation de la myopathie au cours des essais cliniques
* Si la myopathie est sous-estimée dans les essais cliniques sponsorisés, c'est en partie en jouant sur la définition, en exigeant que les symptômes soient accompagnés d'élévation de la créatine kinase à 10x la limite supérieure de la normalité, parfois à deux reprises...

Les douleurs et faiblesses musculaires qui ne sont pas accompagnées d'une telle anomalie biologique sont tout simplement ignorés. C'est une forme de tricherie intellectuelle en statinovigilance expérimentale

MYOTOXICITY OF STATINS
« Statins exert their myotoxic effect by inhibiting protein farnesylation and prenylation… ubiquinone (coenzyme Q_{10}) is one of the prenylated proteins exhibiting reduced levels as a result of statin use. The net myotoxic effect seems to be a dose-dependent and pro-apoptotic effect[628]»
myotoxicité statinique
* le symptôme le plus fréquent est la myalgie (douleur musculaire), souvent aggravée par l'activité physique; suit la faiblesse, la fatigabilité, plus proximale (plus près de l'épaule ou de la hanche) que distale, et symétrique

NAVIGATOR, THE TRIAL[629] *Étude observationnelle prospective post-hoc dans un essai clinique contrôlé – Statinovigilance - Effet diabétogène*
l'essai dit Navigator
* À l'intérieur d'un essai contrôlé sur 9306 patients prédiabétiques suivis environ 5 ans et portant sur l'effet du valsartan et du natÉglinide sur la survenue de nouveaux diabètes et d'événements CV, 1353 patients ont débuté un traitement par statine et leur risque relatif de présenter un nouveau diabète fut de +32 % par rapport aux non statinisés[630]

NECROTIZING AUTOIMMUNE MYOPATHY (NAM)
Statinovigilance
* This immune-mediated myotoxicity has been associated with statins. It is characterized by irritable myopathy on electromyography and muscle necrosis with minimal inflammation on muscle biopsy. CK elevation and weakness may persist after dechallenge

« An autoimmune necrotizing myopathy is a rare form of statin myopathy… discontinuation does not translate into recovery even after several months off the drug. Patient have a predominantly proximal, often painless weakness »[631]
myopathie nécrosante auto-immune / immuno-médiée
= aggravation lente et progressive des symptômes musculaires malgré l'arrêt des statines et la présence d'anticorps anti-HMGCoA réductase. Un effet indésirable à connaître[632]
* ce rarissime EIM est de découverte relativement récente mais d'anecdotique (niveau 2 sur 4 de documentation préalable alias imputabilité extrinsèque) il est passé en France le 12.5.2015[633] à libellé pleinement dans sa pleine expression (niveau 4 sur 4 de documentation préalable) :

« En 2012, une revue de la littérature réalisée par Padala et al.[1] rapportait 63 cas décrivant une association entre un traitement par statine et la survenue de myopathies nécrosantes. Le nom de la statine impliquée avait été identifié dans 33 cas. Depuis cette revue, d'autres publications ont porté sur l'existence de myopathie immuno-médiée au cours de traitement par statines [2,3,4,5,6,7,8,9]…

SÉMIOLOGIE
La myopathie nécrosante immuno-médiée se distingue des atteintes musculaires habituellement décrites avec les produits de

[627] Diamond & Ravnskov, op. cit.
[628] Oskarsson B
[629] Shen et al. BMJ 2013; 347: f6745 - doi: http://dx.doi.org/10.1136/bmj.f6745 - http://www.bmj.com/content/347/bmj.f6745/rr/679717
[630] Stambach, Frédérick. Thèse de doctorat, Université de Limoges, 2014 – Direction Philippe Nicot
[631] Oskarsson B
[632] Montastruc JL,. BIP 2015 Déc ; 31(4) : 7
[633] http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Statines-et-myopathie-necrosante-immuno-mediee-renforcement-des-informations-de-securite-Point-d-information

cette classe. Elle se caractérise par :

a) une atteinte musculaire *proximale*,
b) une élévation marquée du taux de *créatine phosphokinase* (CPK),
c) une aggravation lente et progressive de la symptomatologie *malgré l'arrêt* du traitement par statine [déchallenge négatif],

d) des signes de myopathie nécrosante à la *biopsie* musculaire sans autre étiologie retrouvée,
e) la présence d'un taux significatif d'*anticorps* anti-HMGCoA réductase,
f) une amélioration sous traitement *immunosuppresseur* après l'arrêt du traitement par statine

En janvier 2015, sur la base des nouvelles publications, le Comité d'évaluation des risques en pharmacovigilance (alias PRAC) de l'Ema a recommandé d'ajouter les myopathies nécrosantes dans les résumés des caractéristiques des produits (RCP) et les notices d'information destinées aux patients de l'ensemble des produits contenant une statine

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[3] Hamann PDH, Cooper R, McHugh NJ, Chinoy H. Statin-induced necrotizing myosistis. A discrete autoimmune entity within the "statin-induced myopathy spectrum". *Autoimmunity Reviews* 2013 ; 12(12): 1177-1181
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[6] Mammen AL, Pak K, Williams EK et al. Rarity of anti-3-hydroxy-3-methylglutaryl-coemzyme A reductase antibodies in statin users, including those with self-limited musculoskeletal side effects. *Arthritis Care Res* 2012 ; 64(2): 269-272

[7] Mammen A.L: Toxic myopathies. *CONTINUUM Lifelong Learning in Neurology* 2013; 19 (6): 1634-1649
[8] Mygland A and al. Persisting weakness after withdrawal of a statin. *BMJ Case Reports* 2014 - Doi: 10.1136/bcr-2013-203094
[9] Albayda J and Mammen AL. Is Statin-induced Myositis part of the polymyositis disease spectrum? *Curr Reumathol Rep* 2014 ; 16: 433 »

* Noter que le niveau de causalité implicite reconnu par l'Agence est de 4/4 (très probable, *definite*), sur la seule base de la notification spontanée, sinon l'ajout de cet EIM dans le RCP n'aurait pas été justifié. Cela réfute le discours défensif de l'industrie et de ses acolytes, qu'il soit basé sur l'ignorance ou la mauvaise foi, à l'effet que seul un essai clinique contrôlé - ou encore une enquête observationnelle structurée sur registres administratifs contenant des mégadonnées – soit requis pour confirmer la causalité d'un EIM

NEW ONSET DIABETES ; NOD *Statinovigilance*
nouveau diabète
* cet EIM est reconnu et en principe libellé pour la classe des statines, dose-dépendant, statine-dépendant et durée-dépendant ; les facteurs de risque sont le surpoids (IMC > 30), l'hyperglycémie à jeun (>5,6 mM), l'âge avancé (>70), le sexe féminin, l'ethnie asiatique, l'hypertriglycéridémie, l'hypertension artérielle[634]…

Voilè donc une autre bonne raison de ne pas statiniser - et de déstatiniser - les obèses, les diabétiques, les aînés, les femmes, les asiatiques, les hypertriglycéridémiques, les hypertendus, et de cesser de répéter les cholestérolémies périodiques qui ne mènent pas à un service médical rendu tangible

NEW ONSET DIABETES IN RELATIVE TERMS ACROSS STUDIES[635]
Statinovigilance – Effet diabétogène

1. From clinical trials of statins :

a) hazard ratio of 0.7, and odds ratio of 0.79, NS in WOSCOPS 2001 for pravastatin ; high risk of bias

[634] Stambach, Frédérick. Thèse de doctorat, Université de Limoges, 2014 – Direction Philippe Nicot
[635] Stambach, Frédérick. Thèse de doctorat, Université de Limoges, 2014 – Direction Philippe Nicot

b) odds ratio of 1.32, in PROSPER 2002 for pravastatin
c) hazard ratio of 1.34, in SPARCL 2006 for atorvastatin
d) odds ratio of 1.26, in JUPITER 2008 for rosuvastatin

2. From meta-analyses of statin studies :

a) relative risk of 1.14, in Coleman et al 2008, for statin class without WOSCOPS
b) relative risk of 1.13, in Rajpathak et al 2009, for statin class without WOSCOPS
c) odds ratios of 1.09, in Sattar et al 2010, for statin class, ; 1.14 for atorvastatin ; 0.98 for lovastatin ; 1.03 for pravastatin ; 1.18 for rosuvastatin, ; 1.11 for simvastatin

d) odds ratio of 1.09, in Mills et al 2011, for statin class
e) odds ratios of 1.09, in Alberton et al 2012, for statin class ; 1.04 for pravastatin ; 1.14 for rosuvastatin ; 1.10 for simvastatin
f) odds ratio of 1.18, in Taylor et al 2013, for statin class

g) odds ratios in Navarese et al 2013, for high doses: 1.13 for atorvastatin ; 0.98 for lovastatin ; 1.07 for pravastatin ; 1.27 for simvastatin ; dose-effect confirmed
h) odds ratio in Naci et al 2013, 1.09, for statin class

i) attributable risk in Finegold et al 2014 : 20%

3. From pharmaco-epidemiological studies :

a) hazard ratios in Culver et al 2012: 1.48 for statin class, ; 1.61 for atorvastatin, ; 1.61 for fluvastatin, ; 1.35 for fluvastatin, ; 1.63 for pravastatin, ; 1.41 for simvastatin, ; duration-effect confirmed
b) hazard ratios in Wang et al 2012 : 1.15 for statin class, ; 1.58 for atorvastatin, ; 1.26 for fluvastatin; 1.77 for fluvastatin, ; 1.69 for pravastatin, ; 1.26 for rosuvastatin ; 1.57 for simvastatin,

c) hazard ratios in Zaharan et al 2013: 1.20 for statin class, ; 1.25 for atorvastatin, ; 1.04 for fluvastatin; 1.02 for pravastatin; 1.42 for rosuvastatin, ; 1.14 for simvastatin, ; dose-effect and duration-effect both confirmed
d) hazard ratios in Carter et al 2013 : 1.22 for atorvastatin, ; 0.95 for fluvastatin ; 0.99 for lovastatin ; 1.18 for rosuvastatin, ; 1.10 for simvastatin, ; dose-effect and duration-effect both confirmed

e) odds ratios in Chen et al 2013, case-control : 2.80 for atorvastatin ; 3.41 for pravastatin ; 4.69 for rosuvastatin ; 4.09 for simvastatin ; dose-effect confirmed
f) hazard ratio in Currie al 2013 : 3.31 for statin class ; duration-effect confirmed

g) hazard ratios in Wang et al 2014 : 1.20 for statin class; 1.28 for atorvastatin; 1.13 for fluvastatin ; 1.14 for lovastatin; 1.15 for pravastatin ; 1.19 for rosuvastatin ; 1.22 for simvastatin; dose-effect and duration-effect both confirmed
h) relative risks in Preiss et al 2011, for high doses : 1.12, for statin class ; 1.19, for atorvastatin ; 1.07 and 1.37 for simvastatin ; dose-effect confirmed in dose-comparison trials
nouveau diabète en termes relatifs selon les études
* quand on connaît le risque relatif (ou son approximation statistique) pour une statine, et le pourcentage de patients consommant cette statine dans une population donnée, on peut calculer la fraction attribuable (à cette statine) de tous les nouveaux diabètes dans cette population. Mesure utile en pharmacoéconomie pour évaluer le fardeau de la statinisation sur les budgets

Voir POPULATION ETIOLOGIC FRACTION OF RISK

NICE 2014 GUIDELINES : SOME ARE SENSIBLE
* From Q31 of the Full Draft Apendices : Drug therapy for the primary prevention of cardiovascular disease[636]:

a) No to targets : « A target for total or LDL-C is not recommended for people who are treated with a statin for primary prevention of CVD »

b) No to repeat cholesterolemias : « Once a person has been started on a statin for primary prevention, repeat lipid measurement is *unnecessary* ». - It assumes that a sufficient lipid reduction is guaranteed and that it explains the effectiveness

[636] http://www.nice.org.uk/guidance/cg181/resources/lipid-modification-update-draft-full-guideline-appendices2

(the latter assumption is unproven) or that levels are unimportant (which implicitely contradicts the lipid hypothesis)

c) No to nicotinic acid : « Nicotinic acid should not be offered for the primary prevention of CVD ». NICE thereby assumes that raising HDL or lowering triglycerides is ineffective, also assuming that screening for HLD/LDL ratio and triglyceridemia is irrelevant

d) Watch for potential interactions : « If a person taking a statin starts taking additional drugs, or needs treatment for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions, consider *reducing* the dose of the statin, or temporarily or permanently *stopping* it » – This an admission that interactions may pose serious risks, that statins are 'last line' drugs, and may be stopped permanently without harm

e) Statin myalgias deserve medical attention : « People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured » - Not mentioned is that myalgias may occur without elevation of creatine kinase

f) Neuropathy is an ADR and *deserves* medical attention : « If a person develops an unexplained peripheral neuropathy, statins should be discontinued and specialist advice sought ». – Before calling on a neurologist, better *stop* the statin, wait a few weeks or months and watch for a positive dechallenge

g) No to high doses : « Higher intensity statins should not routinely be offered to people for the primary prevention of CVD » - Indeed, high daily doses increase the likelyhood of ADRs and further reduce lipid levels, but do not significantly reduce some soft and hard CV events

directives du Nice (RU) en 2014 : quelques unes sont sensées

NICE'S 2014 NNTs

Directives cliniques aberrantes – Liens d'intérêt – Dénonciation du NICE

«The new 2014 NICE guidelines on lipid modification omits the key information that clinicians will need to help inform patients' own treatment choices: the NNT for statin treatment in different risk groups, at different levels of treatment intensity. The most attentive reader might find that for every 1000 people without CV disease taking a statin, overall there would be 7 fewer 'non-fatal myocardial infarctions' [NNT = 143 persons]...

To establish the time period over which this figure applies, a table summarises data from a 2013 Cochrane review, which (arguably) relates to a 15% 10-year risk population, and reports an NNT of 88 for 'total CHD events' over 5 years [or 440 patient-years]. An attentive reader could further deduce that these events are non-fatal, since the NNT for total mortality in the same table is higher »[637]

« NICE should publish NNTs and NNHs for statins »[638]

« Two thirds of general practitioners in the UK are opposed to recent NHS guidelines saying the docs should "advise 40% of adults" to take statins, according to a survey of family doctors. Physicians claim the new guidelines are too simplistic. In July 2014, NICE wrote that statins should be prescribed to anyone with a 1/10 chance of developing heart disease in the next 10 years »[639]…

That recommandation does not make sense since if everyone with a 1 % annual risk of a CV adverse event is statinized, and even if we concede that statins can at best reduce the relative risk by 33%, the absolute risk reduction would be a mere 33% of 1% (0.33% or 0.033), leading to a NNT per annum of 333 patient years and an average delay of only 26 hours of that event per year of treatment

les NNT du NICE en 2014

* Les directives du NICE britannique en 2014 qui recommandent une statinisation élargie à tous ceux dont le risque annuel est d'au moins 1,5 % par année – et négligent de souligner qu'une telle intervention préventive n'est efficace qu'une fois par 440 patients-année sur un critère combiné hétérogène peu valide, et que l'espérance de vie n'en n'est pas prolongée - sont factuellement indéfendables et doivent être dénoncées haut et fort

NITRIC OXIDE SYNTHASE PATHWAY

[637] Goldacre B. BMJ 2014; 349: g4356 - http://www.bmj.com/content/349/bmj.g4356/rr/761330
[638] Tressider A. BMJ 2014 ; 348 : g3458
[639] http://www.mmm-online.com, 2.11.2014

NO synthase enzymatic pathway
Enzyme – Effet pléiotrope

* The cholesterol hypothesis is wrong but statins exert a minor beneficial effect on some coronary events in very high risk patients ; there has to be another mechanism than LDL-C lowering, so called pleiotropic. And that effect is, in Malcom Hendrick's opinion[640], almost entirely to do with the ability of statins to increase nitric oxide (NO) production:

« Endothelial nitric oxide (eNO) bioavailability is severely reduced after myocardial infarction (MI) and in heart failure. Statins enhance eNO availability by both increasing eNO production and reducing NO inactivation. We therefore studied the effect of statin treatment on eNO availability after MI and tested its role for endothelial progenitor cell mobilization, myocardial neovascularization, left ventricular (LV) dysfunction, remodeling, and survival after MI…

These findings suggest that increased eNO availability is required for statin-induced improvement of endothelial progenitor cell mobilization, myocardial neovascularization, LV dysfunction, interstitial fibrosis, and survival after MI. eNO bioavailability after MI likely represents an important therapeutic target in heart failure after MI and mediates beneficial effects of statin treatment after MI »[641]

* The cholesterol-independent effects of statins involve normalization of the nitric oxide NO synthase system and others[642] - The statins' well known nitric oxide synthase pathway effect is nitroglycerin mimicking and may explain such benefits as reduced angina, hospitalisations and stenting[643] – shown statistically in very high risk patients in some trials – but not clinically significant or economically sensible

« By increasing NO production, statins may interfere with atherosclerotic lesion development, stabilise plaque, inhibit platelet aggregation, improve blood flow and protect against ischaemia. Therefore, the ability of statins to improve endothelial function through the release of NO may partially account for their beneficial effects at reducing the incidence of [nonfatal] CV events »[644]
voie de l' (enzyme) oxyde nitrique

NNT AND LIFE EXTENSION *Statistiques*
NNT et espérance de vie
* Retarder la mort c'est prolonger l'espérance de vie. Or, pour rendre le NNT plus convivial, on peut extrapoler sans mentir, pour un NNT annualisé de 100, que si 1 patient en profite, les 99 autres n'en profitent pas, et que la prolongation de la vie sera de 1 an (365 jours) pour 1 personne chanceuse et de 0 jour pour les 99 autres…

On pourrait aussi intrapoler qu'en moyenne chaque patient traité 1 an verra sa vie virtuellement prolongée de 3,65 jours (365 jours / 100 patients) ou encore que les 36 135 comprimés (99 patients x 365 jours) consommés par les 99 non-répondants auront été pris en vain bien que toujours porteurs d'EIM parfois insidieux, tantôt tardifs, souvent niés par le médecin traitant, et vendus au prix fort sans garantie de service médical rendu…

Engageriez-vous un agent de sécurité qui ne ferait sa ronde qu'une journée sur 100 pour vous protéger ? Achèteriez-vous un bracelet alerteur qui ne fonctionne qu'une fois sur 100 activations ? ou un parapluie qui ne s'ouvre qu'une fois sur 100 quand il pleut ? Si oui, vous êtes mûr pour acheter des statines…

Si le NNT = 1 000 années-patients, on prolonge la vie de 0,365 jour (8 hres 46 min) après un an de statinisation, car si on répartit le gain de 365 jours (chez un seul patient) parmi les 1000 patients traités, 365 / 1000 = 0,365
Si le NNT = 500 années-patients, la statinisation ajoute 0,73 jour (18 hres) de plus pour 1 an de traitement
Si le NNT = 300 années-patients, la statinisation ajoute 1,22 jours (29 hres) de vie au patient traité un an

Si le NNT = 200 années-patients, cela ajoute 1,8 jours (43 heures) de vie au patient statinisé un an
Si le NNT = 100 années-patients, on ajoute 3,65 jours (88 heures) de vie après un an de traitement ; aucune statine n'a été démontrée capable d'un NNT si bas quand on utilise des critères vitaux (mortalité totale, coronaire, CV)

Si le NNT = 50 années-patients, le traité bénéficierait d'un délai de 7,3 jours par année de statinisation; aucune statine n'a été démontrée capable d'un NNT si bas même chez des hommes coronariens d'âge mûr

[640] http://drmalcolmkendrick.org/2016/03/10/what-causes-heart-disease-part-viii/
[641] Landmesser et al. Circulation 2004;110(14): 1933 - http://www.ncbi.nlm.nih.gov/pubmed/15466656
[642] Kumai et al. Curr Med Chem Cardiovasc Hematol Agents 2005; 3(3): 195 - http://www.ncbi.nlm.nih.gov/pubmed/15974884
[643] Eddie Vos
[644] Ulrich Laufs. Eur J Clin Pharmacol 2003; 58: 719 - DOI 10.1007/s00228-002-0556-0

À 1 000 $ par année (générique/pharmacien/laboratoire/médecin) pour retarder la mort de 1 an chez 1 parmi 100 patients, il en coute 100 000$ pour chaque année de vie sauvée, ce qui dépasse le plafond pharmacoéconomique habituel de 50 000 $ utilisé par NICE et d'autres grandes institutions qui décident des remboursements à même les budgets publics de santé

N'oublions pas que le fardeau de la preuve repose sur les épaules du promoteur, et qu'il n'est même pas tenu compte dans ces calculs de l'intervalle de confiance de ces NNT ; c'est la borne supérieure qu'il faudrait utiliser si on veut atteindre 95% de confiance dans notre interprétation. L'intervalle de confiance varie selon chaque étude car il est fonction du nombre de décès survenus dans le groupe statinisé et dans le groupe placebo …

N'oublions pas non plus que les NNT observés en conditions expérimentales reflètent l'efficacité (trial efficacy) alors que les NNT que l'on observera sur le terrain reflètent l'effectivité (field effectiveness) et seront vraisemblablement et sensément plus élevés, peut-être de 50% (1,5x), peut être de 100% (2x) car, entre autres sources de biais, la validité externe des essais sur les statines est toujours affaiblie par l'immense sélection des patients durant le recrutement et la période de qualification (run-in period)…

Rappelons-le haut et fort, les $NNT_{cliniques}$ sont toujours plus grands que les $NNT_{expérimentaux.}$ De combien on ne le sait pas .

Soulignons enfin que si la statinisation se fait après 70 ans, et que l'on prévoit statiniser durant 10 ans, l'objectif de vouloir prolonger la vie est un pari risqué, car après 80 ans la moindre prolongation de la vie pourrait bien équivaloir à déposer le patient dans les bras de la démence, du cancer, de l'invalidité locomotrice, de la dépendance, de la mise en institution et, au final, d'une qualité de vie négative…

« Et la démence avancée ça peut vouloir dire finir dans ces mouroirs de centres d'hébergement, dans des couches, dans ses défécations, alimenté à la chaîne comme des bêtes, et ne reconnaissant aucun membre de sa famille »[645]

NNTs IN PRIMARY PREVENTION
http://www.thennt.com/statins-for-heart-disease-prevention-without-prior-heart-disease/

Here's the numerical summary for those who took the statin for 5 years:
a) 98% saw no benefit at all
b) 0% were helped by being saved from death

c) 1.6% were helped by preventing a heart attack
d) 0.4% were helped by preventing a stroke
e) 1.5% were harmed by developing diabetes
f) 10% were harmed by muscle damage

In Other Words:
a) None were helped in living longer
b) 1 in 60 were helped in postponing a heart attack for 1 year, annual NNT = 300 patient years (PY)

c) 1 in 268 were helped postponing a stroke, annual NNT = 1340 PY
d)1 in 67 were harmed by hyperglycemic effect / diabetes, annual NNH = 335 PY
e) 1 in 10 were harmed by muscle damage, annual NNH = 50 PY
les NNT en prévention primaire

NNTs IN STATIN TRIALS[646]
les NNT dans les essais statiniques
* Même en prévention secondaire, les NNT annualisés en situation expérimentale sont trop élevés et présumément encore plus élevés en situation clinique. C'est une question épistémique et le faible bénéfice doit être opposé aux inconvénients directs et indirects (opportunité, achat, nocebo, EIM, labo, consultations…), et la décision partagée par le patient quand il le souhaite et peut comprendre la notion de NNT annualisé.

Les statines n'ont pas démontré un bénéfice suffisant même en prévention secondaire chez les hommes, mais je respecte ceux qui ont des conclusions différentes devant ces chiffres. Je n'engagerais pas un gardien de sécurité qui ne ferait sa tournée qu'une journée sur 50 ou sur 100 pour me protéger du risque de petits voleurs (re : IDM non fatal) ou de grands criminels (re :

[645] Paul v Nguyen, 2014
[646] http://www.thennt.com/nnt/statins-persons-low-risk-cardiovascular-disease/

mortalité).

Quant aux risques relatifs, ils n'ont leur place qu'en attitude explicative, mais pas en attitude pragmatique comme dans les essais statiniques. Et si jamais on démontrait très solidement que l'arrêt d'une statine augmente le risque CV, faudrait ajouter cet événement à la liste des EIM de cette classe. L'échec monumental des PCKS9 sur des critères cliniques ne fait qu'enfoncer un clou dans l'hypothèse cholestérolémique.

NON-STATIN CHOLESTEROL LOWERING DRUGS
« As a primary treatment for LDL cholesterol, the other drugs or classes—fibrates, niacin, bile acid sequestrants, ezetimibe, and omega-3 fatty acids—generally lack consistent or compelling evidence of health benefits necessary for major public health recommendations »[647] - The same can be said of newer lipid reducers in the pipeline, probably more dangerous
hypocholestérolémiants / réducteurs du cholestérol non statiniques

NUMBER NEEDED TO TREAT : FINDING A REASONABLE THRESHOLD
« Let's say I have to treat more than 50 people [absolute risk reduction = 2% and NNT = 50] in the hope of doing something important for one. Do you believe that's an effective treatment? Nearly all of us involved in biostatistics will tell you that such an outcome is barely measurable and not likely to reproduce. I would argue that an NNT = 50 [absolute risk reduction = 2%, failure rate 98%] is ephemeral; it is too small a health effect to measure reliably. I would countenance a debate as to setting the cutoff at less than NNT = 50 for hard outcomes…

Statin therapy to reduce cholesterol [a surrogate] and thereby save lives would not even qualify at this level of effectiveness based on scientific trials designed to test their efficacy »[648]
nombre de sujets à traiter : déterminer un seuil raisonnable

ON THE STATINS, CORRECTING PLASMA LIPID LEVELS, AND PREVENTING THE CLINICAL SEQUELAE OF ATHEROSCLEROTIC CORONARY HEART DISEASE – (Article)
Hypothèse lipidique non fondée – Hypothèse statinique non confirmée
KRUT LH. *Am J Cardiol* 1998 ; 81(8): 1045-6

« The statins correct plasma lipid levels optimally, yet the real magnitude of their benefits is marginal and certainly not better than attained with agents that do not affect plasma lipid levels. It is suggested that some of our recommendations and actions relating to plasma cholesterol levels and to atherosclerosis are based on concepts that are fundamentally flawed and need to be revised »

* Factual interpretation : « Statins had a close call with their first mega-trial ending with almost significantly more deaths on lovastatin than placebo and where, at 11 months, the drug's maker simply discontinued the placebo group »[649]
« The study was stopped early (at 48 weeks) because there were more deaths in the lovastatin group, and never incorporated in any meta-analysis »[650]

ON-STATIN PATIENT
patient statinisé

OPINION LEADERS UNDECLARED IN FRANCE
meneurs d'opinion non divulgués
« L'association anricorruption Anticor dépose plainte le 3.10.2018 contre 6 des 9 experts de la HAS pour avoir négligé de déclarer leurs COI avec des labos, concernant la prise en charge des dyslipidémies (cholestérol, triglyrédies), notamment Bruno Vergès et Jean-Michel Lecerf… Le Formindep a d'ailleurs déposé une requête au Conseil d'Etat fin août 2018, demandant le retrait de la fiche mémo produite par le groupe d'experts[651] »

* Certains passent à la télévision française (6.10.2015, France 5, émission *Enquête de santé*) sans révéler leurs liens, malgré la loi Kouchner de 2002 qui l'interdit :

[647] Psaty & Weiss. 21.11.2013. doi:10.1001/jama.2013.28420
[648] Nortin Hadler. Worried Sick, page 219
[649] Vos E. Nutr Metab Cardiovas Dis 2007 ; 17 : e19
[650] Paul v Nguyen, 2014
[651] https://www.lemonde.fr/sante/article/2018/10/21/anticor-depose-plainte-contre-des-medecins-experts-du-cholesterol_5372531_1651302.html - xtor=AL-32280270

« Philippe Giral est un médecin lipidologue de l'hôpital de la Pitié Salpêtrière à Paris. Il a déjà été invité dans l'émission Allo Docteurs des mêmes animateurs et on connait sa position sur l'intérêt de faire baisser le cholestérol. Lors de ses différentes interventions sur le sujet, il affirme que les statines sont des médicaments « efficaces » et « bien tolérés »...

Le Dr Giral affiche de nombreux liens d'intérêt avec les laboratoires pharmaceutiques qui fabriquent des médicaments à visée cardiovasculaire ou hypocholestérolémiante : Astra Zeneca*, Daiichi Sankyo*, Genzyme, Lilly, MSD*, Novartis*, Pfizer*, Roche, Sanofi*, Wyeth…

Gérard Helft exerce aussi à la Pitié-Salpêtrière et on trouve sur le site du Ministère de la Santé pas moins de 8 pages de ses liens avec l'industrie pharmaceutique (77 avantages et 22 contrats), dont les laboratoires fabriquant les anti-cholestérols : Abbott*, Astra Zeneca*, Bristol-Myers Squibb*, Daiichi Sankyo*, Merck Serono*, Novartis*, Sanofi Aventis*, Servier*...

Au premier rang de ceux-ci, AstraZeneca, fabricant du Crestor, statine la plus vendue en France, l'a ainsi invité au congrès de la société européenne de cardiologie d'Athènes et rémunéré en tant qu'orateur. Ces entreprises commercialisent des anti-cholestérolémiants ou des statines :

Abbott (Simcor° : simvastatine), Astrazeneca (Crestor° : rosuvastatine), Bristol Myers Squibb (Elisor° : pravastatine), Daiichi Sankyo (Welchol° : colesevelam), MSD ou Merck (Zocor° : simvastatine), Novartis (Lescol° : fluvastatine), Pfizer (Tahor° : atorvastatine), Sanofi Aventis (Vasten° : pravastatine, Lodales° : simvastatine). Le laboratoire SERVIER détient la filiale BIOGARAN, produisant une statine générique (simvastatine) et un fibrate (fénofibrate) »[652]

OVERDIAGNOSES
Surdiagnostic
« Evidence is mounting that medicine is harming healthy people through ever earlier detection and ever wider definition of disease. Here is an example : Estimates that up to 80% of people with near normal cholesterol treated for life may be overdiagnosed with hypercholesterolemia »[653]
surdiagnostics; diagnostics par excès

OVERPRESCRIBING OF STATINES (QC)
Pratique - Gaspillage
surprescription de statines
« Selon le cardiologue Martin Juneau (Montréal) il se prescrit pour des millions de dollars de statines en trop au Québec annuellement car seules 20% des ordonnances sont vraiment indiquées, i.e. permettraient de réduire les événements coronariens de manière cliniquement significative. Pour le reste, il s'agit de surprescription (QC)»[654]
« Il est vrai que des milliers de médecins prescrivent des statines inutiles et dangereuses (FR)»[655]

* En 2009, les médecins québécois ont prescrit 9 813 400 ordonnances de statines selon la RAMQ; en 2010 c'était 10 671 043, en 2011 on était rendu à 11 468 826, en 2012 on a atteint le chiffre de 12 207 203 et la tendance continue en 2013 avec 12 775 483 soit 7,7% de toutes les prescriptions au Québec. Si seules 20% des ordonnances sont vraiment indiquées, c'est 10 220 384 prescriptions inutiles durant l'année 2013[656]

PACT, THE TRIAL *Pravastatine 20-40 mg c. placebo – Prévention secondaire après syndrome coronarien aigu*
Pravastatin in Acute Coronary Treatment

* In 3 408 patients with ACS (unstable angina, STEMI or non-STEMI), 20 to 40 mg of pravastatin administered within 24 hours of the onset of symptoms of an acute coronary event do not reduce outcome at 30 days compared with placebo. Recruitment was stopped early because of futility, although planned for 10,000 patients with 1200 endpoints [657]
l'essai dit Pact
* Publication : 2004
* Effectif randomisé : 3 408
* Indications : angine instable, IM avec ou sans élévation du segment ST
* Début du traitement: < 24 heures après début de syndrome coronarien aigu

[652] http://www.formindep.org/Des-conflits-d-interets-caches.html - 22.10.2015
[653] Roy Monihan et al. BMJ 2012; 344: e3502
[654] Alain Vadeboncoeur. L'Actualité médicale (Montréal) 29 juilllet 2011
[655] Anonyme. Le Quotidien du médecin 20.2.2014 (FR)
[656] Héloïse Archambault, 2014
[657] Thompson PL et al. Am Heart J 2004; 148: e2 - http://www.ncbi.nlm.nih.gov/pubmed/15215811

* Durée de traitement: 1 mois
* Cholestérolémie totale avant traitement : 5,6 mM
* Critère combiné d'évaluation : mort / récidive d'infarctus / réhospitalisation pour angine instable < 30 jours après randomisation
* Cessation d'essai justifiable: après avoir recruté 3 408 au lieu de 10 000 patients, à cause de la futilité du bénéfice

* Résultats négatifs cliniquement : 11,6% présentent une complication CV sous statine et 12,4% sous placebo ; réduction relative de 6,4% (NS) et absolue de -0,8%

PARADIGM
« De Lorgeril and Salen[658] call for a new paradigm excluding cholesterol »[659]
paradigme

PARKINSON'S RISK ASSOCIATED WITH LOW LDL-C *Étude observationnelle*
« Previous findings on the association of statins, plasma lipids, and Parkinson's disease (PD) are confounded by the fact that statins also affect lipid profiles. We prospectively examined plasma lipids and statin use in relation to PD in the Atherosclerosis Risk in Communities (ARIC) Study. Statin use and plasma lipids were assessed at baseline (visit 1, 1987-89) and at three triennial visits thereafter (visits 2-4) until 1998...

The primary analysis was limited to incident PD cases diagnosed between 1998 and 2008. During this time frame, total-cholesterol (TC) levels decreased, particularly among statin users. 56 PD cases were identified after 1998. Statin use before 1998 was associated with higher PD risk after 1998 (odds ratio = 2.39, + 130%) after adjusting for TC and other confounders...

Conversely, higher TC was associated with lower risk for PD after adjustment for statin usage and confounders, odds ratio of PD in lowest tertile of average TC was 0.56 (-44%) in middle tertile and 0.43 (- 57%) in third tertile. Conclusion : Statin use may be associated with a higher PD risk, whereas higher TC may be associated with lower risk. These data are inconsistent with the hypothesis that statins are protective against Parkinson »[660]

« In this prospective study, fasting lipids were measured from 1991 to 1993 in a group of 3,233 men of Japanese ancestry who took part in a long-running study called the Honolulu-Asia Aging Study. These data were collected before statin therapy for lowering cholesterol was widely available. When followed for about 10 years, the incidence of Parkinson's disease increased with decreasing levels of LDL cholesterol…

After adjusting their statistical analysis for age, smoking, coffee intake and other factors, the researchers calculated that the relative odds of Parkinson's for men with lower LDL levels (85 milligrams per deciliter) was about twice that of those with higher LDL levels (135 milligrams per deciliter). They concluded that this study supports the hypothesis that low LDL levels are associated with an increased future risk of Parkinson's[661] »
LDL-C bas associé au risque de Parkinson

PCKS9 FAILURE ON CLINICAL ENDPOINTS
* no postponement of CV death or all-cause death
échec des Pcks9 sur des critères cliniques
« Buletins d'Informations de Pharmacologie a déjà évoqué la classe d'anticorps humanisés alirocumab Praluent® et evolucumab Repatha®, utilisés par voie parentérale et jusqu'ici commercialisés dans les hypercholestérolémies familiales. Une extension de l'AMM a porté sur la prévention secondaire en association avec les statines en cas d'échec biologique des statines seules (ou encore seuls ou avec d'autres hypolipémiants en cas d'échec).

L'essai clinique pour le second de ces médicaments, incluant plus de 27 000 patients suivis environ 2 ans montre une réduction de la fréquence des événements cardio-vasculaires par rapport au placebo (1 événement évité pour 67 patients traités pendant 2 ans, d'où NNT annualisé de 134 patients-année [en situation expérimentale, donc davantage en situation clinique]), mais, fait important, sans modification de la mortalité cardio-vasculaire ou totale. Pour la HAS, l'ASMR est à ce jour (2019) de V (« pas d'amélioration du service médical rendu ») pour un SMR insuffisant.

[658] de Lorgeril & Salen. Nutr Metab Cardiovas Dis 2006 ; 16(6) : 387
[659] Eddie Vos. Nutrition, Metabolism & Cardiovascular Diseases 2007 ; 17 : e19
[660] Huang et al. Mov Disord 2015, Jan. 4 - DOI: 10.1002/mds.26152 -
[661] Huang et al. Mov Disord 2008 ; 23(7):1013 - doi: 10.1002/mds.22013 - http://www.ncbi.nlm.nih.gov/pubmed/18381649

Un bel exemple de ce qu'évoque BIP depuis de nombreuses années : l'amélioration d'un critère intermédiaire (ici le cholestérol plasmatique qui diminue, rappelons-le, avec ces médicaments de 60 à 70 %) ne s'accompagne pas obligatoirement d'effectivité au sens pharmacoclinique du terme (ici la mortalité totale) [662]»

PERIOPERATIVE STATINS AND ACUTE KIDNEY INJURY *Néphrotoxicité statinique – Essais – Méta-analyses – Statinovigilance expérimentale*

« In a meta-analysis of perioperative statins and acute kidney injury, when including 3 trials with low risk of bias, the administration of perioperative statins was associated with increased incidence of postoperative acute kidney injury as compared with placebo (314 of 1318 patients (23.82%) in the statin group versus 262 of 1319 patients (19.86%) in the placebo group; OR 1.26 (95% CI 1.05–1.52); p = 0.01; absolute risk difference = 4, NNH = 25)...

The results are supported by the trial sequential analysis, which showed firm evidence for a 25% RRI. The overall quality of evidence was high according to GRADE[663] »

« 1922 patients in sinus rhythm who were scheduled for elective cardiac surgery were randomly assigned to receive perioperative rosuvastatin (at a dose of 20 mg daily) or placebo. Rosuvastatin did not result in beneficial effects on any of the secondary outcomes but was associated with a statistically significant absolute excess of 5.4 percentage points in the rate of postoperative acute kidney injury »[664]

rosuvastatine et atteinte rénale aigue postopératoire

* Un patient sur 25 dans une méta-analyse, un sur 19 dans un essai, est victime d'une atteinte rénale aigue si sa chirurgie cardiaque s'accompagne d'une statinothérapie périopératoire. Ce qui confirme la toxicité rénale des statines *même sans rhabdomyolyse*

PHARMACOECONOMIC ASPECTS OF STATINS

* Statin costs are a public health pharmacoeconomic scandal of contemporary medicine. Statins are not only in the Top Ten list for sales in most developed countries but very often occupy the 1st position. Not only overpriced, but overprescribed since they are prescribed without extending life, familial hyperlipidemias being believed to be a rare exception although there is no solid supporting evidence

« The (statins) debate has big financial implications. Sales of lipid regulators, which are primarily statin drugs, were $29 billion last year [2013], according to IMS Health, which tracks sales of pharmaceuticals. That number is down 11 % from the year prior, largely due to the introduction of cheaper generic alternatives. Expanding the use of the drug to healthier patients is one way to counter counter declining sales »[665]

« The claims made for statins are overblown. The pharmaceutical industry has created a monster. While statins are now (2014) almost entirely off-patent – so they make very little profit nowadays – at their peak they were a sales colossus. Trial upon trial was set up and hyped. The marketing machine was relentless. Resistance was futile »[666]

"According to the IMS Institute for Healthcare Informatics review on the use of medicines in the US, in 2011 a total of 19.8 M Americans used cholesterol-lowering medicines regularly, spending approximately $20.1 billion on these medications »[667]

"In the JUPITER trial there were about 3400 women in each group and there were 21 fewer revascularizations under rosuvastatin (Crestor™), amounting to a number needed to treat of 307 women-years to avoid a single revascularization, in other words an unjustified treatment in 306 women-years, notwithstanding the adverse reactions. At an average purchasing cost of $5.53 per day of Crestor™, it amounts to $625 660 per procedure avoided[668]"

"On January 4, 2013, Wallmart Retail Prescription Program in the USA offers generic Lovastatin™ 10 and 20mg tablets and Pravastatin™ 10, 20 and 40 mg tablets for 11 cents per tablet if you buy a 3-month supply »,[669] and still makes a profit. Showing how little it costs to manufacture, package and distribute a statin

[662] JL Montastruc, BIP Occitanie 2019; 26(4): 5
[663] Putzu et al. Critical Care 2016 ; 20: 395 - DOI 10.1186/s13054-016-1560-6
[664] Zheng et al. N Engl J Med 2016; 374: 1744 - doi: 10.1056/NEJMoa1507750
[665] http://www.businessweek.com/articles/2014-07-11/harvard-vs-dot-oxford-in-a-multibillion-dollar-cholesterol-drug-cage-match
[666] Malcom Kendrick, 2014
[667] Bhardwaj et al. Clinical Interventions in Aging 2013; 8: 47
[668] Eddie Vos. Communication, 2010
[669] http://i.walmartimages.com/i/if/hmp/fusion/customer_list.pdf

« By April 1st, 2013 the Ontario Public Drug Program will pay only 18% - $0.39 per 20mg tablet generic atorvastatin - of the brand price for Lipitor™ - $2.18 »[670]
aspects pharmacoéconomiques des statines
« En 2012 elles étaient consommées par environ 6,4 M de Français pour un coût d'environ 1,2 milliard d'euros d'après l'Assurance Maladie »[671]

« En 2006 les médicaments hypocholestérolémiants sont toujours en tête, devant les anticancéreux. L'atorvastatine (Lipitor™, Tahor™) arrive en tête du chiffre d'affaires mondial : 13,6 G de $ US au prix de vente fabricant, soit 2,2% du marché mondial du médicament »[672]

« En 2007 quelque 3 M de Canadien(ne)s prennent une statine tous les jours… Les statines comptent parmi les médicaments les plus prescrits aux femmes en prévention CV (CA) »[673]

« Crestor™ d'AstraZeneca est la statine (anticholestérol) la plus prescrite en FR, avec près de 340 M € remboursés en 2012, et plus généralement, la part de marché des marques (Tahor™ ou atorvastastine...) reste très importante alors qu'il existe de nombreux génériques »[674]
« Les couts d'achat (FR) doivent être au moins doublés par le cout des consultations et examens biologiques »[675]

* Au Canada les pharmaciens vendent en 2012-13 pour 1 643 000 000 $ d'hypolipidémiants, dont ils prennent 423 180 000 $ en profits et honoraires. La somme de 706 490 000 $ est dépensée pour des canadiennes, soit 43% du total national , même si les statines ne les protègent pas et nuisent à leur qualité de vie
* Au Québec en 2013, on a prescrit 12 775 483 fois une statine, soit 7,7% de toutes les prescriptions, au coût de 149 809 457$[676]

PHARMACOECONOMICAL SCAM
arnaque pharmacoéconomique
« Les statines, la plus rentable des erreurs qui fût jamais. Certains journalistes en viennent à parler d'arnaque commerciale »[677]
« La plus grande arnaque pharmacoéconomique et médico-scientifique des dernières décennies »[678]

PHYLLIS, THE TRIAL
Plaque Hypertension Lipid-Lowering Italian Study

PHYSICIAN INNUMERACY
FMC
"I tell patients to ignore cholesterol because it's a highly inadequate bio-marker, more suited to sales promotion and physician innumeracy than to rational clinical behavior[679]"
innuméracie médicale / des médecins

PHYSICIAN RESPONSE TO PATIENT REPORTS OF ADVERSE DRUG EFFECTS: Implications for patient-targeted adverse effect surveillance. – (Article)
GOLOMB BA, McGRAW JJ, EVANS MA, et al. *Drug Safety* 2007 ; 30: 669–675

« Patients reported that they - and not the doctor - most commonly initiated the discussion regarding the possible connection of statin to symptoms :

a) 98% vs 2% for cognitive difficulties
b) 96% vs 4% for neuropathic symptoms
c) 86% vs 14% muscle problems

[670] PDCI Market Access, Ottawa (CA), 2013
[671] Stambach, Frédérick. Thèse de doctorat, Université de Limoges, 2014 – Direction Philippe Nicot
[672] Prescrire 2008 ; 28(293) : 227
[673] H Rosenberg & AD Allard. Prudence oblige : l'emploi des statines chez les femmes. Action pour la protection de la santé des femmes, 2007
[674] Le Monde 7.1.2014
[675] Even, page 219
[676] Héloïse Archambault citant la RAMQ sur http://www.journaldemontreal.com/2014/01/31/une-majorite-de-quebecois-prend-des-pilules-contre-le-cholesterol-pour-rien-selon-des-medecins
[677] Even 2013, page 208
[678] Paul v Nguyen
[679] Warren Bell. Communication

Physicians were more likely to deny than affirm the possibility of a connection. Rejection of a possible connection was reported to occur even :

a) for symptoms with strong literature support for a drug connection, and
b) in patients for whom the symptom met presumptive literature-based criteria for probable or definite drug-adverse effect causality »[680]

réaction des médecins quand les patients se plaignent des EIM

« Selon une étude effectuée sur un panel de 650 patients sous statines, 87 % des patients ont consulté leur médecin suite à des effets secondaires, tels que des douleurs musculaires »[681]

PHYSICIAN VISITS (CA) FOR HYPERLIPIDEMIA

Revue d'utilisation

* Reasons for visits at physicians' offices in Canada in 2014 according to IMS Health Brogan : Hyperlipidemia ranks 7th of all visits ; total number was 4,911,000, 46% were men, 54% were women ; 100% left the office with a prescription[682], for a total of 4,911,000 prescriptions annually to reduce cholesterol…

Assuming a minimum of 30$ per prescription (1$ a day for 1 month supply of a generic) and 30$ per visit for the doctor, 295 M are spent on lipid control annually, mostly a waste of money and ressources, a reduction in quality of life in most, and life extension in extremely few (familial hyperlipidemias)

consultations médicales pour hyperlipidémie (CA)

* ces chiffres démontrent[683] que 2 651 940 consultations en cabinet de médecin par des femmes (0,54 x 4 911 000) et 2 651 940 ordonnances (probablement) de statines sont faites *inutilement* chaque année au pays, assumant qu'aucun bénéfice n'a été démontré chez les femmes même coronariennes et que les statines altèrent chez plusieurs la qualité de vie, sans compter les couts de tout genre...

Quant aux hommes, si on prend comme critère d'évaluation la prolongation de la vie, les mêmes commentaires s'appliquent, même s'il a été rapporté des bénéfices (pléiotropes) statistiquement significatifs – mais cliiquement minimes - sur des incidents coronariens non fatals dans quelques essais contrôlés (contrôlés par les fabricants)

PLEIOTROPIC EFFECT ON STEM CELLS

Pharmacodynamie

« Statins reduce atherosclerotic events and CV mortality. Their side effects include memory loss, myopathy, cataract formation, and increased risk of diabetes. As CV mortality relates to plaque instability, which depends on the integrity of the fibrous cap, we hypothesize that the inhibition of the potential of mesenchymal stem cells (MSCs) to differentiate into macrophages would help to explain the long known, but less understood "non-lipid-associated" or pleiotropic benefit of statins on CV mortality...

In the present investigation, MSCs were treated with atorvastatin or pravastatin at clinically relevant concentrations and their proliferation, differentiation potential, and gene expression profile were assessed. Both types of statins reduced the overall growth rate of MSCs. Especially, statins reduced the potential of MSCs to differentiate into macrophages while they exhibited no direct effect on macrophage function...

These findings suggest that the limited capacity of MSCs to differentiate into macrophages could possibly result in decreased macrophage density within the arterial plaque, reduced inflammation, and subsequently enhance plaque stability. This would explain the non-lipid-associated reduction in CV events »[684]

effet pléoiotrope sur les cellules souches

PLEIOTROPIC EFFECTS

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[680] Golomb et al. Drug Safety 2007; 30 (8): 669

[681] Jean-Marc Dupuis, citant Golomb et coll.

[682] https://www.imshealth.com/files/imshealth/Global/North%20America/Canada/Home%20Page%20Content/Pharma%20Trends/Top10Reasons_EN_14.pdf

[683] https://www.imshealth.com/files/imshealth/Global/North%20America/Canada/Home%20Page%20Content/Pharma%20Trends/Top10Reasons_FR_14.pdf

[684] Reza Izadpanah et al. American Journal of Physiology - Cell Physiology – 2015; 309(8): C522-C531 - DOI: 10.1152/ajpcell.00406.2014 - http://ajpcell.physiology.org/content/309/8/C522

= effects others than the main effect
* in the case of statins, it could be 'anti-inflammatory', vasodilating through the NO pathway, or other
effets pléiotropes

POINT : WHY STATINS HAVE FAILED TO REDUCE MORTALITY IN JUST ABOUT ANYBODY – (Article)
VOS E, ROSE CP, BIRON P. *J Clin Lipidol* 2013 ; 7(3) : 222
« There are no individual placebo-controlled statin trials ever reporting a mortality benefit in women and other groups. There has never been a placebo-controlled trial using atorvastatin, lovastatin, fluvastatin, cerivastatin or pitavastatin that lowered mortality[685] »
Pourquoi les statines n'ont réduit la mortalité chez à peu près personne – (Traduction libre)

POLYGENIC HYPERCHOLESTEROLEMIA
hypercholesterolemia
hypercholestérolémie polygénique; HP
N.d.T. terme mis de l'avant par Therrien[686]
* par opposition à l'hyperlipidémie familiale qui est une vraie maladie
« Un seul dosage dans votre vie montrant que votre cholestérol est au-dessous de 7,7 mmol/l (3 g/L) suffit. N'y revenez plus… si vous n'avez pas d'hypercholestérolémie familiale »[687]

POPULATION ETIOLOGIC FRACTION OF RISK
population attributable fraction of risk
Épidémiologie - Statistique
fraction étiologique / attribuable du risque dans la population
* si l'on connaît le taux d'exposition aux statines dans une population donnée et si l'on connaît le risque relatif de nouveau diabète sous statine, on calcule ainsi la fraction étiologique populationnelle :

$$\frac{\text{Taux d'exposition} \times [RR - 1]}{1 + \text{Taux d'exposition} \times [RR - 1]}$$

Par exemple si 25% ou 0,25 des personnes âgées dans une région sont statinisées, et que le risque relatif dans cette catégorie de sujets est de 110% ou 1,1, la fraction étiologique du diabète d'origine statinique parmi les statinisés est :

$$\frac{0{,}25 \times [1{,}1 - 1]}{1 + 0{,}25 \times [1{,}1 - 1]} = 0{,}025 / 1{,}025 = 0{,}024 \text{ ou } 2{,}4\%$$

Il s'ensuit que 1 diabète sur 42 dans cette population est d'origine statinique. Il s'ensuit aussi que si on cessait les statines dans cette population, le RR de diabète diminuerait de 2,4%

POTENTIAL LIVES SAVED FROM EIGHT PREVENTIVE MEASURES *Pharmaco-prévention – Étude observationnelle – Santé publique - Modélisation*
* The potential maximum lives saved per 100,000 per year from 8 preventive measures in the National Health System (UK),[688] using the McColl[689] performance indicators:

a) 308 lives saved, for angiotensin converting enzyme inhibitors in heart failure ; annual NNT = 325
b) 146, for influenza immunization in over 65, annual NNT = 685
c) 120, for advice to stop moking + nicotine replacement, annual NNT = 833
d) 71, for screening + treatment of hypertension, annual NNT = 1,408

e) 48, for aspirin in ischaemic heart disease (secondary prevention), annual NNT = 2,083
f) 33, for warfarin in atrial fibrillation (tertiary prevention), annual NNT = 3,030
g) 13.8, for statins in ischaemic heart disease (secondary prevention), annual NNT = 7,246 patient-years
h) 2.8, lives saved for statins in primary prevention, annual NNT = 35,714 patient-years

[685] Eddie Vos, communication
[686] Une histoire inventée : Essai sur le cholestérol. Montréal : Carte Blanche ; 2014
[687] Marian Apfelbaum, 1997. Cité par Even, La vérité sur le cholestérol, page 15
[688] Fleetcrock & Cookson. Journal of Health Services Research & Policy 2006 ; 11(1) : 27
[689] McColl et al. BMJ 1998; 317: 1354

The total is 742,6 potential lives saved per 100,000 patient-years if patients in an average UK practice were to be exposed to those 8 preventive measures combined, for an annual NNT of 135, an inefficacy rate of 99.2% per year of medically prescribed preventive measures
décès potentiellement évités par huit interventions préventives
* Noter que les statines arrivent au bas du tableau et que la prévention primaire est 5 fois moins 'efficace' que la prévention secondaire. De toute évidence, la prescription de statines pour 'sauver des vies' n'est ni fondée ni sensée

PRAVASTATIN TRIALS
WOSCOPS, PREVEND IT, CARE, LIPID, PACT, PROSPER, MEGA, PMSG, ALLHAT-LLT, GISSI-PREVENZIONE, ATHEROMA, REGRESS
essais de la pravastatine

PRE-2002 TRIALS
essais antérieurs à 2002
« Les 4 essais positifs datent de 1994 à 2002, aucun depuis ne les a jamais confirmés, peut-être parce que les essais après 2003 (affaire du Vioxx™) sont un peu plus contrôlés qu'avant »[690]

PREHYPERLIPIDEMIA
Maladie inventée
proto-hyperlipidemia ; latent hyperlipidemia
« Until mid 1950s there was no one being treated for raised lipids »[691]
préhyperlipidémie

PREVEND IT, THE TRIAL
Résultats négatifs – Prévention secondaire ciblée (micro-albuminurie)
Prevention of Renal and Vascular Endstage Disease Intervention Trial

* Pravastatin reduced the incidence of myocardial ischemia, but had no effect on the incidence of mortality or stroke compared with placebo during 46 months

« Mean age was 51; 65% male, only 3.4% had a previous CV event, mean cholesterol 5.8 mM, mean blood pressure 130/76 mm Hg, and median urinary albumin excretion was 22.8 mg/24 hours. 864 were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo...

Treatment with pravastatin had no effect on the primary end point in despite a reduction in TC and LDL cholesterol concentrations. On the basis of cholesterol lowering, a reduction in clinical events on the order of 25% could have been expected (sic) »[692] …

But the expected reduction did not occur, evidence that lowering both total and LDL-cholesterol by 0.8 mM over 4 years with a statin does not prevent stroke, CV death or total mortality
l'essai dit Prevend It

PRÉVENIR L'INFARCTUS ET L'ACCIDENT VASCULAIRE CÉRÉBRAL : Ce livre peut vous sauver la vie et vous épargner de lourds handicaps
Michel De LORGERIL & Patrician SALEN. Vergèze (FR) : Thierry Souccar Editions ; 2011 – 416 pages - ISBN 978-2-916878-88-1

« Les statines peuvent ruiner la vie sexuelle des individus traités, considérablement diminuer leurs capacités cognitives, augmenter le risque de troubles de la vision, augmenter ou aggraver le risque de dépression et augmenter le risque de cancer »[693]

***PRÉVENIR L'INFARCTUS ET L'ACCIDENT VASCULAIRE CÉRÉBRAL* (FR)** – (Livre)
DE LORGERIL, Michel. Vergèze (FR) : Thierry Souccar Éditions; 2011 – 415 pages - Avec la participation de Patricia Salen

* Destiné à un grand public avisé… La nutrition et le mode de vie protègent votre cœur et vos artères… 30 ans de recherche traduits en recommandations pratiques… Les médicaments utiles et ceux à éviter… L'efficacité et l'utilité de la plupart des

[690] Philippe Even 2013
[691] Pharmageddon, page 46
[692] Asselbergs et al. Circulation 2004; 110: 2809 - http://circ.ahajournals.org/content/110/18/2809.full
[693] p 198

traitements conventionnels sont remises en cause aujourd'hui… Vous pouvez réduire considérablement votre risque en adoptant une nutrition et un mode de vie protecteurs[694]

PRICE DIFFERENCES ACROSS COUNTRIES
Pharmacoéconomie
« Take, for instance, 20 mg of the cholesterol-lowering drug simvastatin. Albertans (CA) pay 90 cents for each tablet. In NZ the government drug plan buys the same drug for 1.8 cents, or 50 times cheaper »[695]
* The average monthly refill of Lipitor™ (atorvastatin) is $123 in the USA (private health care) and $6 in NZ (universal health care)[696]
écarts de prix entre pays

PRIMARY PREVENTION ANNUALIZED NNTs *Inefficacité – Synthèse méthodique*
« According to my systematic review, in each year of treatment, 99.6% saw no benefit, 0% were helped by being saved from death, 0.32% were helped by preventing a heart attack, 0.07% were helped by preventing a stroke ; 0.3% were harmed by developing diabetes and 2% were harmed by muscle damage. The effectiveness of the statins appears to be reproducible across studies in this group—they do lower cholesterol in most people who took them...

But very few people will avoid a heart attack or stroke by virtue of this change. Most disappointing, statins seem unable to prevent death in this group. And most concerning, the drugs may increase diabetes, a serious and life-altering disease »[697]

* The annualized NNTs of the 2013 controversial and unconscionable ACC/AHA guidelines for statinisation for life in primary prevention, calculated under experimental conditions, are as follows[698] :

a) 690 person-years for total mortality, giving a yearly rate of inefficacy of 99.86%
b) 245 person-years for fatal and non fatal CV disease, yielding a yearly rate of inefficacy of 99.59%
c) 440 person-years for fatal and nonfatal coronary heart disease, or a yearly rate of inefficacy of 99.78%
d) 775 person-years for total and non fatal stroke, or a yearly rate of inefficacy of 99.87%
NNT et NNH annualisés en prévention primaire
* Selon une synthèse méthodique, le NNT est de 312 patients-année pour retarder d'un an une crise cardiaque, de 1 340 pour retarder un AVC; le NNH est de 135 patients-année pour devenir diabétique, de 50 pour devenir myopathique; aucune statine n'a prolongé la vie, et ce, en situation expérimentale forcément artificielle…

Les chiffres sont encore plus décevants – mais non documentés faute (intentionnelle assurément) de subventions - en contexte clinique où les NNT sont vraisemblablement plus élevés et les NNH sensément moindres, à cause des faibles validités interne et externe des méga-essais sponsorisés de statines contre placebo

PRIMARY PREVENTION IN STATINOLOGY
prévention primaire en statinologie
= celle chez des sujets à risque allant de très faible à moyen, sans antécédent vasculaire personnel et sans hyperlipidémie familiale. La statino-thérapie vise alors le retard du premier événement CV, surtout coronarien. Elle serait justifiée si elle retardait de façon tangible, avec des coûts directs et indirects acceptables et des effets indésirables psychologiques et physiques tolérables, l'apparition d'un premier événement CV athéro-thrombotique robuste et grave (hard and serious) tels que :

a) angine instable,
b) IM non fatal, asystolie réanimée, AVC non fatal,
c) décès coronarien par arythmie, défaillance congestive ou IDM;
d) AVC fatal

« Notre analyse suggère que les statines ne devraient pas être prescrites en prévention primaire aux femmes, quel que soit leur âge, ou aux hommes de plus de 69 ans »[699]

[694] Michel de Lorgeril. Prévenir l'infarctus. Vergèze (FR) : Thierry Souccar Éditions ; 2011 – 415 pages
[695] Law & Kratzer. http://www.evidencenetwork.ca/FINAL_EBOOK2.pdf
[696] http://www.nytimes.com/2013/06/02/health/colonoscopies-explain-why-us-leads-the-world-in-health-expenditures.html?_r=1&
[697] David Newman 2010 at http://www.thennt.com/nnt/statins-for-heart-disease-prevention-without-prior-heart-disease/
[698] Ibidem
[699] Cité par Sinatra & Bowden, 2014, page 194

PRIMARY PREVENTION IN WOMEN *Synthèse méthodique*
« Before 2003 there were 10,990 women in the primary prevention trials (28% of the total). Only coronary events were reported for women, but when these were pooled they were not reduced by statin therapy, RR 0.98, NS. Thus the coronary benefit in primary prevention trials appears to be limited to men, RR 0.74, absolute risk reduction 2.0%, NNT 50 for 3 to 5 years [annual NNTs 150 to 250]»[700]
prévention primaire chez les femmes

PRIMARY PREVENTION OF CARDIOVASCULAR DISEASES WITH STATIN THERAPY: A meta-analysis of randomized controlled trials – (Article)
Statinisation – Prévention primaire – Méta-analyse
THAVENDIRANATHAN P et al : *Arch Intern Med* 2006 ; 166: 2307–2313
* Authors' conclusion : « Statin therapy does not decrease the incidence coronary heart disease or overall mortality »

PRIMARY PREVENTION TRIALS OF STATINS AGAINST PLACEBO
* With > 1000 participants and lasting > 1 year, on adults without established CV disease[701]
ALLHAT-LLT, MEGA, ASCOT-LLA, WOSCOPS, JUPITER
essais statiniques en prévention primaire contre placebo

PRIMO, THE STUDY *Myotoxicité – Étude observationnelle – Statinovigilance structurée*
« The PRIMO study, an observational study of muscular symptoms in an unselected population of about 8 000 hyperlipidemic patients receiving high doses of statins, indicated that the symptoms were reported by 10.5% of patients. In a recently published review,[702] it was suggested that the muscular symptoms occurred in 'up to 20%' of patients in observational studies. Dirks and Jones[703] indicated that as many as 25% of statin users who exercise may experience muscular symptoms »[704]

« An observational study of muscular symptoms in an unselected population of 7 924 hyperlipidemic patients receiving high-dosage statin therapy in a usual care, outpatient setting in France. Muscular symptoms were reported by 10.5% of patients, with a median time of onset of 1 month following initiation of statin therapy...

Muscular pain prevented even moderate exertion during everyday activities in 38% (of the 10.5%, or 4% or 1/15 exposed patients), while 4% (of the 10.5%, or 0.4% or 1/125 statinised patients) were confined to bed or unable to work. Fluvastatin XL™ was associated with the lowest rate (5.1%) of muscular symptoms among individual statins »[705]
l'étude dite Primo
* Quelque 8000 Français fortement statinisés furent suivis pour estimer les EIM de nature musculaire
* La fréquence de symptômes musculaires fut de 10,5%, le délai d'apparition médian de 1 mois
* Une myalgie empêche 4% (1/25) des statinisés de s'adonner à des activités physique d'intensité même modérée
* Une faiblesse musculaire rend 0,4% (1/250) des statinisés incapables de travailler et même parfois de marcher

PRO-TARGETS AND NO-TARGETS *Cholestérolémie – Objectifs thérapeutiques*
pro-cibles et sans-cibles
* les deux sont dans l'erreur mais les premiers sont plus dangereux

PROGRESSIVE WASTING VIGNETTE
Statinovigilance – Fonte musculaire – Amaigrissement inexpliqué - Myopathie

« As a clinician, I encountered many patients whose doctors had failed to recognize, or had dismissed, a possible statin connection to their problem, to their grave detriment. One man had been hospitalized for months for undiagnosed progressive wasting (losing >70 lbs), and remained on 80 mg simvastatin when I arrived on the inpatient service – by then he was in intensive care requiring ventilator support with no apparent prospects for recovery...

I stopped his statin and he was off ventilator support, sitting up, no longer ptotic, in just days. Recovery to discharge took longer,

[700] Wright et al. TI 49 - http://www.ti.ubc.ca/PDF/49.pdf
[701] NICE 2014
[702] Fernandez et al. Cleveland Clinic Journal of Medicine 2011 ; 78 (6) : 393 - doi: 10.3949/ccjm.78a.10073
[703] Am J Physiol - Cell Physiology 2006 ; 291(C1208-C1212) - DOI: 10.1152/ajpcell.00226.2006
[704] Sakaeda et al. PLoS ONE 2011 ; 6(12): e28124 – Site http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0028124
[705] Bruckert et al. (2005) Cardiovasc Drugs Ther 2005 ; 19: 403

but occurred… The death would not have even been recognized as statin-related »[706]
amaigrissement progressif : vignette clinique
* le déchallenge positif en quelques jours représente un argument fort en faveur du lien de causalité
* l'amaigrissement progressif inexpliqué doit maintenant inclure la statinisation fortement dosée parmi les étiologies à rechercher

PROPONENT OF THE CHOLESTEROL HYPOTHESIS
« The pharmaceutical industry has invested heavily in convincing medical scientists, patient groups and our prescribing doctors to think about cholesterol as a *nasty foreign enemy* which needs to be brought down at all costs instead of a substance essential for life that actually resents being chemically tinkered with »[707]
défenseur / promoteur / partisan de l'hypothèse du cholestérol
« L'industrie pharmaceutique a investi massivement de manière à convaincre les scientifiques médicaux, les groupes de patients et nos médecins prescripteurs de considérer le cholestérol comme un *perfide ennemi* étranger qu'il faut réduire à tout prix plutôt qu'une substance essentielle à la vie qui ne supporte pas qu'on la soumette à des manipulations chimiques »

PROPORTION OF SPONSORED TRIALS
Financement
* Only 8.7 % of controlled trials of statins are publicly financed, 42 out of 46 are financed by the statin manufacturer, an open field for manipulation of design, conduct, analysis, reporting, intepretations and publications of results
proportion d'essais sponsorisés
« Sur 46 essais cliniques contrôlés, seuls 4 sont sponsorisés par un organisme public. Aucun des essais sponsorisés par l'industrie (42 sur 46) n'apparaît comme indépendant ; à la limite, tous se résument à ce qu'il faut bien appeler publicité rédactionnelle »[708]

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) INHIBITORS *Anticorps monoclonaux inhibiteurs enzymatiques*
« The FDA informed Amgen and Regeneron on 18.12.2015 that there have been a number of post marketing reports of *serious brain infection* following the administration of PCSK9 agents. While they have not indicated any causal effect they have asked both manufacturers to prepare to attend a briefing at FDA after the new year...

The agency has not indicated if they will issue any warnings or updates to the prescribing community as yet, there are 7 reports for Repatha™ (*evolocumab*) and 5 for Pralulent™ (*alirocumab*). Amgen R&D is working thru the weekend to prepare for the meeting. It's not clear if the company will be sharing this with the field (the reps) at this point »[709]

* According to Prescrire (FR), Worst Pills Best Pills (USA) and Arznei-Telegramm (DE) in 2016, no clinical benefit – like a reduction in mortality or CHD events - has been demonstrated, and long term adverse reactions are still unknown ; clinicians should be cautious and wait the years needed to ascertain the benefit-risk ratio in clinical settings
inhibiteurs de la proprotéine convertase subtilisine/kexine de type 9 ; PCSK9
a) des anticorps monoclonaux – évolocumab (Repatha™) et alirocumab (Praluent™) par exemple – inhibent cette enzyme
b) cette enzyme dégrade des récepteurs situés à la surface des cellules hépatiques et capables de fixer les LDL circulantes
c) la captation hépatique du LDL-C réduit son taux plasmatiques

d) ces anticorps monoclonaux augmentent ainsi le nombre de récepteurs hépatiques capteurs du LDL-C et abaissent dramatiquement son taux plasmatique

PROSPER, THE TRIAL
Pravastatine 40 mg c. placebo - Prévention primaire et secondaire en gériatrie

Prospective Study of Pravastatin in the Elderly at Risk
* Princeps publication: Shepherd/*Lancet*/2002[710]
* Funding : private, Bristol Myers Squibb

METHODOLOGY

[706] Beatrice Golomb. European Journal of Preventive Cardiology 25.4.2014 - DOI: 10.1177/2047487314533085 - http://cpr.sagepub.com/content/early/2014/04/24/2047487314533085
[707] http://umanitoba.ca/outreach/evidencenetwork/wp-content/uploads/2012/12/Canadian-Health-Policy-in-the-News_DEC-10_12.pdf
[708] Even 2013, page 195
[709] http://cafepharma.com/boards/threads/fda-and-pcsk9.589499/
[710] Shepherd J et al. Lancet 2002 ; 360 : 1623

* Participants' demography : geriatric : 5804 randomized, mean age 75 years (range 70-82), 100 % > 65 years; 3000 or 52 % women
* Participants health : 2565 or 44% in secondary prevention, of which 13% with prior MI; 3235 or 56% in primary prevention; 62% hypertensive; 11% diabetics; TC 4-9 mM, average 5,7 mM; LDL-C average 3.8 mM; TG < 6 mM

* Comparison : pravastatin 40 mg vs placebo
* Follow-up : 3.2 years (38.4 months)

* Primary composite endpoint : [CHD mortality + nonfatal MI + fatal stroke + nonfatal stroke]
Although MI and stroke are hard endpoints, the fatal versions do not have the same value for the patient. Specific outcomes occurred at uneven frequencies within the composite endpoint. Total mortality not included. Therefore not externally valid.

* Positive compliance (adherence to statin exposure according to protocol in active group) : 86%
* Negative compliance (adherence to nocontrol group adherence) : 86%

RESULTS
* Lipid reduction : relative risk reduction for LDL-cholesterol of -34 % and relative risk reduction for TC of -23%

Benefits as relative risk, the proper statistic contributing to internal validity (confidence in causality):
a) relative risk reduction of -19 % for CHD events; in women the relative risk reduction is -3%, NS
b) RRI for serious adverse events = +1 %, NS
c) relative risk reduction for CHD death = -24%, NS

d) relative risk reduction for total mortality = -2%, NS
e) relative risk reduction of composite endpoint = -15% for [total MI or total stroke] in primary prevention (-6% in primary prevention and -20% in secondary prevention)

f) relative risk reduction of total MI = -19%
g) Fatal and nonfatal stroke : no difference

Benefits as absolute risk reductions, the proper statistic contributing to external validity and underlying clinical significance:
* TOTAL MORTALITY : annual NNT = 1088 patient-years (298 deaths in 2891 elderlies under statin, and 306 deaths in 2913 under placebo over 3.2 years, a difference of 8 deaths)
* Kaplan-Meier plot on all-cause mortality was not reported

* CHD mortality : absolute risk reduction of -0.9% over 3.2 years or -0.28% annually, for an annual NNT of 356 patient-years (3.3% CHD deaths under pravastatin, 4.2% under placebo, over 3.2 years). Not clinicaly relevant
* CHD events : annual NNT = 145 patient-years. Not clinicaly relevant

* Diabetic subgroup : no benefit[711]

* Composite endpoint (total MI or total stroke) in secondary prevention :
absolute risk reduction = -4.3%, NNT = 23 over 3.2 years, annual NNT = 74 patient-years, a life extension average of 4,9 days per treatment-year; and the NNT_{clin} is safely assumed to exceed 100 in a usual care setting... Not clinically relevant. Furthermore the composite outcome is heterogenous in seriousness and frequency of components and cannot be used by itself to determine the risk-benefit balance and support a clinical recommendation, even if specified as primary in the protocol.

Results for harms :
h) New onset diabetes unreported in princeps publication but RRI of +32%, found later by meta-analyst Sattar
i) Myalgia : « The incidences of myalgia and rhabdomyolysis were comparable between the 2 groups »[712] - which is not plausible
j) Cognition : no effect reported. Was it even measured?

k) Disability : none reported
l) Health related quality of life : *not reported*
m) New cancers : RRI = +25%, 46 more cases (245 under statin and 199 under placebo) over 3.2 years

[711] Dubroff, QJM 2.11.2017 - https://academic.oup.com/qjmed/advance-article-abstract/doi/10.1093/qjmed/hcx213/4587483?redirectedFrom=fulltext
[712] Luis Gruberg/Shepherd J. http://www.medscape.com/viewarticle/444971#3

Comments :
« PROSPER studied the effect of pravastatin compared to placebo in two older populations of patients: 56% primary prevention (no past or symptomatic CV disease) and 44% secondary prevention (past or symptomatic CV disease)... Measures of overall health impact in the combined populations, total mortality (RR 0.98, relative risk reduction of 2%) and total serious adverse events (RR 1.01, RRI of 1%), were *unchanged* by pravastatin as compared to placebo »[713]

« PROSPER ended with *identical total mortality* between groups and more new cancers on statin »[714]
« *Absence of* event or total mortality *benefit in women* in combined primary and secondary prevention trials (HPS, PROSPER, MEGA) »[715] was found in the sensitivity analysis of Petretta et al. in 2010

« In a high risk population, the placebo controlled PROSPER study found absolutely *no mortality benefit* but increased cancer in a statin group with fewer smokers »[716] - « In PROSPER, the only trial that included old people only, lowering of heart mortality was smaller than the increase of cancer mortality »[717] - « Pravastatin Patients Had Higher Incidence of *Cancer* »[718]

« PROSPER assessed lipid-lowering agents among 2804 men and 3000 women aged 70-82 randomized to pravastatin or placebo, followed up for a mean of 3.2 years, as either primary or secondary prevention. About half of the participants in this trial had CV disease and the others had CV risk factors...

Results reported the effect of lipid-lowering agents on CV events in women (CHD mortality, nonfatal MI, fatal stroke, and nonfatal stroke). The relative risk reduction of CV events among *women* treated with pravastatin was -3% and NS »[719] - « Age 75 is the age where the PROSPER trial [Medline 12457784] showed exactly *no mortality* difference in a higher-risk UK population--but a highly significant increase in "new cancers" »[720]

« Pravastatin showed no benefit over placebo for any outcome in elderly women and despite a change in composite CV outcomes, all cause mortality stayed the same (hazard ratio 0.97, 95% confidence interval 0.83 to 1.14[721] »

* Factual conclusion : despite a few numerical benefits of some endpoints (total MI), they are limited to men, they are too minuscule to be relevant in clinical practice, and total mortality is not reduced in either sex. The results are 'negative' clinically.

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Prosper
* Aucun bénéfice en terme de mortalité toute cause, tout comme dans les essais *Jupiter, Corona, Aurora et Gissi-HF*
* Cet essai est le seul qui inclut des patients de 70 ans et plus

* Dans cet esssai particulièrement bien présenté de la pravastatine, on constate que le risque d'événements du critère principal d'évaluation était de 3,8 par 100 patients-année dans le sous-groupe (66%) à risque élevé et de 6,8 par 100 patients-année dans le sous groupe à risque très élevé (34%). Il y avait dans l'ensemble 44% d'antécédents CV personnels, 62% d'hypertension, 27% de tabagisme, 11% de diabète; 48% d'hommes et un âge moyen de 75 ans...

La relative risk reduction fut de -2% pour la mortalité toute cause, -23% pour la mortalité CV et -29% pour les événements coronariens

* Conclusion factuelle : Désolé, *Prosper* ne passe pas la rampe d'une réduction du risque absolu de 1 événement CV majeur évité par 50 patients-année même en prévention secondaire pour un critère combiné d'événements hétérogènes…

Un NNT_{exp} annualisé de 74 pour la mortalité toute cause n'est pas cliniquement signifiant car il ne représente qu'une

[713] Wright et al. Thepareutics Newsleter 48 - http://www.ti.ubc.ca/PDF/48.pdf
[714] Vos & Rose. CMAJ 2005; 173(10) : 1207
[715] Eisenberg et al
[716] Vos E. BMJ 2005; 331(7509): 159 - doi: 10.1136/bmj.331.7509.159-a
[717] http://www.ravnskov.nu/myth6.htm
[718] Luis Gruberg/Shepherd J. http://www.medscape.com/viewarticle/444971#3
[719] Walsh & Pignone. JAMA 2004 ; 291 : 2243
[720] Eddie Vos. http://www.bmj.com/content/352/bmj.i1395/rapid-responses
[721] Mangin et al. BMJ. 2007 August 11; 335(7614): 285–287 - doi: 10.1136/bmj.39241.630741.BE1

prolongation de vie de 4,9 jours par année de traitement et le NNT_{clin} est prudemment postulé au delà de 100 patients-année (prolongation annuelle de 3,65 jours chez les traités), trop peu pour compenser les méfaits et les couts

* Seulement si une statine réduisait de -33% (RR = 0,67, p < 0,001) le risque relatif de mortalité totale en conditions expérimentales, et seulement si le risque des témoins sous placebo atteignait 3% par an (ou 30% par 10 ans), pourrait-on atteindre une réduction annuelle absolue de 1% (NNT = 100 patients-année) et pourrait-on utiliser le résultat au numérateur de la balance bénéfice-risque en gériatrie, avant de terminer l'évaluation en calculant les couts

* Les recommandations des instances officielles en faveur de la statinisation en prévention primaire de personnes ayant un risque CV annuel de 1% manquent de fondement scientifique voire de gros bon sens

PROVE IT-TIMI 22, THE TRIAL *Pravastatine 40 mg c. atorvastatine 80 mg – Prévention secondaire après syndrome coronarien aigu – Bénéfice annulé par des chiffres erronés*

Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22
* Princeps publication : Cannon/*NEJM*/2004[722]
* Private funding : Bristol Myers Squibb ; Sankyo

METHODOLOGY
* Sample size : 4162 randomized
* Age and sex : 58 years, all > 18 years ; 22% women

* Participants health : all within 10 days of hospitalisation for acute coronary syndrome ; 18% with prior MI ; 18% diabetics ; TC mean 4.6 mM , all < 6.21 mM, and < 5.18 mM if already under a statin; baseline LDL-C of 2.74 mM (109 mg/dL)
* Methodology : high risk of bias (see below)

* Follow-up : 2 years
* Comparison : atorvastatin 80 mg (intensive dosing) vs. pravastatin 40 mg (moderate dosing)

* Primary composite endpoint : [total mortality / MI / rehospitalization for unstable angina / revascularization / stroke], a priori an heterogenous endpoint, with soft outcomes exposed to subjective decisions and/or to unblinding by peeking into the cholesterol levels in the emergency room ; see below for a posteriori criticism

* Positive compliance (active group adherence) : 67%
* Negative compliance (control group adherence) : 69.6%

RESULTS
a) TOTAL MORTALITY : annual NNT = 104 patient-years
b) CHD mortality : annual NNT = 347 patient-years (6 fewer CHD deaths in high dose group, in a sample of 4162 patients)

c) non-fatal MI : annual NNT (high dose) = 149 patient-years
d) stroke : relative risk reduction = 1%, NS
e) « No reduction in prespecified secondary endpoints of : total death, CHD death, MI death, MI, stroke »[723]

Harms :
* Liver ALT elevation (> 3 ULN) : annual NNH (high dose) = 32 patient-years, clinically significant
* New onset diabetes not reported in princeps publication ; RRI of +1%, NS, reported by metanalyst Preiss
* Health related quality of life *not reported*

* Primary composite endpoint : absolute risk reduction of 1.95% fewer events per year for an NNT of 52 patient-years under experimental conditions, but this apparent success is weakened by 3 major biases, the last one (c) being overwhelming:

a) improper mixing of soft criteria – the only individually significant outcome differences being those of revascularizations and hospitalizations - with hard endpoints
b) minuscule absolute risk reductions in Death from all causes (total mortality) and IHD Deaths

[722] Cannon et al. N Engl J Med 2004; 350:1495 - DOI: 10.1056/NEJMoa040583 – URL http://www.nejm.org/doi/full/10.1056/NEJMoa040583
[723] DuBroff, *QMJ*, 1.11.2017

c) data corrections being published 2 years later without offering recalculations, a suficient motive to disqualify the trial. A difference of 2 CV deaths at the 24 month mark has been conflated thanks to the magic of relative risk calculation to a reduction of -33%. An erratum was published discreetly 2 years afterwards but the authors never corrected their calculations nor retracted the paper[724]:

« Go to Fig 4 on page 1501 of NEJM April 08, 2004; 350 (15) and calculate the absolute risk reduction for Death from all causes (total mortality) : 1% over 24 months (3.2% on Pravachol™ 40 mg minus 2.2% on Lipitor™ 80 mg), and Deaths from CHD: 0.3% (a difference of 2 patients) over 24 months (1.4% or 11 patients on Pravachol™ 40mg minus 1.1% or 9 patients on Lipitor 80mg) …[Annualized NNTs are 200 patient-years for Death from all causes (total mortality) and 666 patient-years for CHD Death]...

And 2 years afterwards the NEJM (Feb 16, 2006 ; 354(7) : 778) discretely published a correction in the far upper corner of the page, authors admitting they had made a mistake and omitted, for example, 184 patients at the 24 month-mark [a 68% mistake], and they have not redone the calculations of the Kaplan-Meir curve nor retracted the paper »[725] - Here are the corrections in question:

« Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (April 8, 2004;350:1495-1504). In Figure 2 on page 1500, several of the numbers of *patients at risk* for death or a major CV event in the pravastatin and atorvastatin groups were listed incorrectly. The numbers of patients should have read as follows:

1. for pravastatin :
a) 1701 (6 months) instead of 1688
b) 1542 (12 months) instead of 1536

c) 1449 (18 months) instead of 1423
d) 896 (24 months) instead of 810
e) 224 (30 months) instead of 138

2. for atorvastatin :
a) 1752 (6 months) instead of 1736
b) 1590 (12 months) instead of 1591

c) 1515 (18 months) instead of 1485
d) 950 (24 months) instead of 842
e) 231 (30 months) instead of 133 »[726]

* Bottom line : This trial has enough methodological and ethical flaws to be disqualified as a source of evidence favoring intensive statinization after an acute coronary syndrome and should be excluded from meta-analyses, it should be either retracted or reported again with the proper data

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : Yes but asked for response *not to be made public*

l'essai dit Prove It-Timi 22 / l'essai Prove It

* Mortalité totale : différence absolue de 0,5 par 100 patients-année, NNT annualisé = 200, taux annuel d'inefficacité = 99,5%, prolongation moyenne de vie de 1,83 jours ou 44 heures par année de traitement. Échec clinique

* Mortalité coronarienne : différence absolue de 0,15 par 100 patients-année, NNT annualisé = 666, taux annuel d'inefficacité de 99,85%, retard moyen d'une mort coronarienne de 0,55 jour ou 13 heures. Échec clinique

* Critère combiné : bénéfice numérique pour la statine fortement dosée, mais un NNT = 52 patients-année n'atteint pas la barre de 50 pour un critère combiné hétérogène associant des critères flous (les deux seuls à être améliorés) et des critères robustes…

La réduction de la mortalité totale et coronarienne est trop minuscule pour être cliniquement pertinente. De plus un doute important est jeté sur la validité des résultats par la correction tardive et trop discrète des données et l'impardonable absence

[724] Paul v Nguyen, 2014
[725] Paul van Nguyen, 2013 and Forbes/Larry Husten's blog
[726] Correction. N Engl J Med 2006 ; 354(7) : 778

de recalculation ou de rétraction[727]. Donc, un échec éthique par dessus un échec clinique

PUBLICATION BIAS
« In 2007, researchers looked at every published trial that set out to explore the benefit of a statin. This study found 192 trials in total, either comparing one statin against another, or comparing a statin against a different kind of treatment. Once the researchers controlled for other factors, they found that industry-funded trials were 20 times (+2.000%) more likely to give results favoring the test drug. Again, that's a very big difference »[728]

PULMONARY FIBROSIS AND STATINS
Statinovigilance
fibrose pulmonaire et statines
« Dans un cas les symptomes respiratoires et l'image radiologique se sont lentement améliorés à l'arrêt de la simvastatine puis sont réapparus à l'introduction de la pravastatine »[729], ce déchallenge positif est compatible avec un lien de causalité et représente peut être un effet de classe car d'autres pneumopathies interstitielles ont été associées à d'autres statines

RAMPANT STATIN OVERUSE
« Overuse of statin therapy was found among 69% of patients undergoing primary prevention, and among 47% of patients undergoing secondary prevention »[730]
surutilisation endémique de statines
« Depuis 2005 en France, la convention médicale signée entre la Caisse nationale d'assurance-maladie (CNAM) et les médecins libéraux prévoit une diminution des prescriptions des médicaments anticholestérol au nom de la 'maîtrise médicalisée' des dépenses de santé. En 2003, une étude de la CNAM pointait une 'énorme dérive par rapport aux recommandations' et estimait que 40 % des prescriptions n'étaient pas légitimes 'en l'état des connaissances scientifiques' »[731]

RANK OF HIGH TOTAL CHOLESTEROL AS A GLOBAL RISK FACTOR
Épidémiologie
rang du cholestérol total élevé en tant que facteur de risque à l'échelle mondiale
* selon une étude d'envergure de 67 facteurs de risque dans 21 régions du monde en 2010, en prenant comme critère les années de vies corrigées de l'incapacité, le cholestérol est au 16e rang en 2010 chez l'homme, loin derrière le tabagisme, l'hypertension, l'acoolisme, l'hyperglycémie, l'obésité et le sédentarisme ; et au 15e rang en 2010 chez la femme, loin derrière l'hypertension, l'obésité, le tabagisme, l'hyperglycémie, le sédentarisme[732]

RANK OF HIGH TOTAL CHOLESTEROL AS A RISK FACTOR IN 4 WEALTHIEST REGIONS *Épidémiologie mondiale*
rang de l'hypercholestérolémie parmi les facteurs de risque des 4 régions les plus riches
* L'hypercholestérolémie arrive, selon une étude d'envergure de 67 facteurs de risque dans 21 régions du monde en 2010, en prenant comme critère les années de vies corrigées de l'incapacité[733] :

a) au 8e rang en Australasie (AU, NZ)
b) au 8e rang en Europe de l'Ouest (18 pays…), derrière le tabagisme, l'hypertension, l'obésité, le sédentarisme, l'hyperglycémie

c) au 9e rang en Amérique du Nord anglophone (USA, CA)[734], derrière le tabagisme, l'obésité, l'hypertension, le diabète, le sédentarisme
d) au 12e rang en Asie Pacifique (Inde, Chine, Japon, Corée du Sud…)
* Ce ne sont pas des données sur les effets de la statinisation

RAW DATA HIDDEN
« The raw data on the efficacy and safety of statins are being kept secret and have not been subjected to scrutiny by other scientists. This lack of transparency has led to an erosion of public confidence. Doctors and patients are being misled about the true benefits and harms of statins, and it is now a matter of urgency that the raw data from the clinical trials are released. The egregious lack of transparency surrounding the raw data on statins has meant that doctors have been misled about the evidence.

[727] Paul v Nguyen, 2014
[728] Ben Goldacre. Scientific American 2013.2.13
[729] Prescrire 2005 ; 25(265) : 672
[730] Abookire SA et al. Arch Intern Med 2001; 161(1): 53 - doi:10.1001/archinte.161.1.53
[731] Sandrine Blanchard citant Michel de Lorgeril dans Le Monde 12.6.07
[732] Lim et al. Lancet 2012 ; 380 : 2224-2260 (36 pages)
[733] Lim et al. Lancet 2012 ; 380 : 2224-2260 (36 pages)
[734] Lim et al. Lancet 2012 ; 380 : 2224-2260 (36 pages)

Doctors prescribing statins should remain inherently sceptical because the majority of those taking statins are 'healthy' people at low risk, where the benefits are vanishingly small and the raw data on side effects are kept hidden[735]. »
données brutes cachées

RE-EVALUATION OF THE TRADITIONAL DIET-HEART HYPOTHESIS : Analysis of recovered data from Minnesota Coronary Experiment (1968-73) – (Article)
RAMSDEN CE et al. *BMJ* 2016; 353: i1246[736] at
Réfutation de l'hypothèse du cholestérol – Exploitation de données expérimentales non publiées – Synthèse méthodique en nutrition

« The MCE (1968-73) was a double blind RCT to test whether replacement of saturated fat with vegetable oil rich in linoleic acid reduces coronary heart disease and death by *lowering serum cholesterol*. Recovered MCE unpublished documents and raw data were analyzed and included …

unpublished documents with completed analyses for the randomized cohort of 9423 women and men aged 20-97; longitudinal data on serum cholesterol for the 2355 participants exposed to the study diets for a year or more; 149 completed autopsy files. The intervention group had significant reduction in serum cholesterol compared with controls.

a) Kaplan Meier graphs showed no mortality benefit for the intervention group in the full randomized cohort or for any prespecified subgroup.

b) There was a 22% higher risk of death for each 0.78 mmol/L reduction in serum cholesterol in covariate adjusted Cox regression models [arguing against the lifesaving properties of cholesterol reduction]

c) There was no evidence of benefit in the intervention group for coronary atherosclerosis or myocardial infarcts.

Findings in existing diet-heart RCTs were analysed through a systematic review and meta-analysis. Systematic review identified 5 RCTs for inclusion (n=10 808). In meta-analyses, these cholesterol lowering interventions showed no evidence of benefit on mortality from coronary heart disease or all cause mortality

Available evidence from RCTs shows that replacement of saturated fat in the diet with linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates to a lower risk of death from coronary heart disease or all causes. Findings from the MCE add to growing evidence that incomplete publication has contributed to overestimation of the benefits of replacing saturated fat with vegetable oils rich in linoleic acid »
Ré-évaluation de la traditionnelle hypothèse de la cardioprotection alimentaire : Analyse des données récupérées de l'essai contrôlé Minnesota Coronary Experiment (1968-73) – (Traduction libre)

REASSESSING THE BENEFITS OF STATINS IN THE PREVENTION OF CARDIOVASCULAR DISEASE IN DIABETIC PATIENTS - A systematic review and meta-analysis. - (Méta-analyse indépendante)
Statines chez diabétiques
CHANG YH, HSIEH MC, WANG CY, LIN KC, LEE YJ. *Rev Diabet Stud* 2013; 10: 157-70[737]

« When trials that investigated only diabetic patients (i.e., CARDS, 4D, and ASPEN) were included in the analysis, statin treatment was not found to reduce CVD significantly Furthermore, after performing subgroup analysis, no benefit of statin treatment was found in *primary* prevention or *secondary* prevention (OR = 0.89, NS) of CVD in diabetic patients »

REDUNDANT PUBLICATION
Revues savantes
duplicate publication
publication redondante
***** le marketing s'en charge ; à titre d'exemple l'essai dit Jupiter sur le Crestor™ (rosuvastatine) fut l'objet de quelques dizaines d'articles, après l'article princeps dans le NEJM, question de faire passer un message promotionnel dans plusieurs milieux professionnels. Les carriéristes et les leaders d'opinion s'en servent aussi pour gonfler leur CV

[735] Maryanne Demasi, 2018 - http://bjsm.bmj.com/content/bjsports/early/2018/01/16/bjsports-2017-098497.full.pdf?ijkey=Rsap0XafljfcOCR&keytype=ref
[736] http://dx.doi.org/10.1136/bmj.i1246
[737] http://www.ncbi.nlm.nih.gov/pubmed/24380090

RELATIVE RISK REDUCTION AVERAGES UNDER STATINS

* in the Zhou et al. 2006[738] systematic review of 8 statin controlled trials, the relative risk of fatal and non fatal IM is reduced by 25% in the treatment groups, the relative risk reduction is -18% for cerebrovascular + coronary deaths, and -15% for total mortality

réduction relative du risque moyenne sous statine

* Noter qu'avec un réduction relative de -25% telle que comptabilisée par Zhou et coll., il faut que le risque de base des infarctus fatal ou non, soit d'au moins 4% par année si l'on veut obtenir une réduction du risque absolu annuelle d'au moins 1%, ce qui correspond à un NNT annualisé de 100 patients-année et un retard moyen d'infarctus de 3,65 jours par année de traitement ou 88 heures…

RELATIVE RISKS GRADUAL LOWERING WITH AGING

Épidémiologie – Gériatrie

« Pooled epidemiological studies of CV disese risks who that the relative risk decreases with age The inverse age association is roughly log-linear. For risk factors such as hypertension, hyperglycemia, *hypercholesterolemia* and smoking, the relative risk reaches 1 soon after 100 years » which may partly explain why statinisation is useless, even in IHD patients, after their seventies[739]

diminution des risques relatifs avec le vieillissement

REPEAT REVASCULARIZATION AS AN ENDPOINT

Critère d'évaluation

« Repeat revascularization is a subjective end point that is due more to the vagaries of physician choice than to the disease process »[740] - «Researchers often use composite outcomes in an attempt to boost statistical power but the components might be subject to clinically subjective decisions, eg, the composite of death, myocardial infarction, or repeat revascularisation »[741]

reprise de revascularisation comme critère d'évaluation

* il en est de même pour une première revascularisation coronaire dans les essais de statines et ce critère ne devrait pas faire partie d'un critère d'évaluation primaire combinant des critères plus 'durs' comme la mort toutes causes et le décès coronarien ou par AVC

REPORTING OF ADRs IN STATIN TRIALS LACK IN CREDIBILITY

Statinovigilance

« The levels of adverse events reported in the statin trials contain worrying anomalies. For example, in the West of Scotland Coronary Prevention Study (WOSCOPS, the first primary prevention study done), the cumulative incidence of myalgia was 0.06% in the statin arm, and 0.06% in the placebo arm…

However, the METEOR study found an incidence of myalgia of 12.7% in the rosuvastatin arm, and 12.1% in the placebo arm. Whilst it can be understood that a different formulation of statin could cause a different rate of myalgia, it is difficult to see how the placebo could, in one study, cause a rate of myalgia of 0.06%, and 12.1% in another. This is a 200-fold difference in a trial lasting less than half as long...

Furthermore, the rate of adverse effects in the statin and placebo arms of all the trials has been almost identical. Exact comparison between trials is not possible, due to lack of complete data, and to variety of measures of adverse effects used. However, here is a short selection of major statins studies :

AFCAPS/TEXCAPS: Total adverse effects : pravastatin 13.6%, placebo 13.8%
4S: Total adverse effects : simvastatin 6%, placebo 6%
CARDS: Total adverse effects : atorvastatin 25%, placebo 24%
HPS: Discontinuation rates : simvastatin 4.5%, placebo 5.1%

METEOR: Total adverse effects : rosuvastatin 83.3%, placebo 80.4%
LIPID: Total adverse effects : 3.2% pravastatin, 2.7% placebo
JUPITER: Discontinuation rates : 25% rosuvastatin, 25% placebo. Serious Adverse Events : 15.0% rosuvastatin, 15.5% placebo
WOSCOPS: Total adverse effects : pravastatin 7.8%, placebo 7.0%

[738] Zhou et al. Am Heart J 2006 ; 151(2) : 273
[739] Lim et al. Lancet 2012 ; 380 : 2224-2260 (36 pages)
[740] Kazi & Hlatky. Circulation: Cardiovascular Quality and Outcomes 2012; 5: 249 - doi: 10.1161/ CIRCOUTCOMES.112.965764
[741] Ioannidis JPA et al. Lancet 2014 ; 383(9912): 166 - doi:10.1016/S0140-6736(13)62227-8

Curiously, the adverse effect rate of the statin is always very similar to that of placebo. However, placebo adverse effect rates range from 2.7% to 80.4%, a 39-fold difference »[742]
les comptes-rendus des EIM en cours d'essais statiniques manquent de crédibilité

RESULTS
* Health related quality of life *not reported*

Lipid reduction :
* TC 147 mg/dL under statin, from 212 mg/dL
* LDL-C mean of 72.9 mg/dL under statin, from 133 mg/dl

Relative risk results:
* RRI of +2% for total mortality, NS – 216/2365 in treated group and 211/2366 in placebo group over 4.9 years
* relative risk reduction of -16% for fatal and nonfatal stroke, the primary endpoint, NS
* relative risk reduction of -22% for ischemic strokes; 55 under atorvastastin and 33 under placebo

* RRI of +66 % hemorrhagic strokes; 218 under atorvastatin and 274 under placebo
* relative risk reduction of -32 % for CHD events
* RRI of +3% for CHD deaths

* RRI of +2 % for serious adverse events (SAE)
* RRI of +34% for new onset diabetes, not reported by authors, but retrieved by meta-analyst Waters
* Liver enzymes elevation were more common under atorvastatin

* Absolute risk results :
a) 5-year absolute risk reduction in risk for combined primary endpoint of fatal and nonfatal stroke = -2.2 % or 0.44 % per year by Kaplan-Meier analysis, for an annual NNT of 258 patients-years, amounting to a first stroke delay of 34 hours per year of treatment when benefit is averaged over 258 patients. A clinically irrelevant benefit, plausibly of 17 hours in a clinical setting

b) CHD events annual NNT = 296 patient-years
c) total mortality annual NNH = 2319 patient-years - « The 5-year trial had 5 fewer deaths on placebo than on top-dose atorvastatin »[743]

* Factual conclusion: The only trial suggesting a protection against ischemic strokes by intensive statinisation is not clinically significant since the minuscule delay of 34 hours for ischemic stroke under trial conditions is counterbalanced by inefficacy or harm on other outcomes. It has not been confirmed. There are no clinically relevant CHD benefits and no total mortality benefits. Because of the increased risk of hemorrhagic stroke, patients with a history of that condition should probably not be statinized
l'essai dit Sparcl
* le seul essai qui semble démontrer un quelconque effet protecteur contre l'angiopathie cérébrale a souffert de conflation. Il y eu 5 décès de plus sous atorvastatine fortement dosée que sous placebo, ainsi que 18 AVC hémorragiques de plus

REVASCULARISATION : A SOFT ENDPOINT
revascularisation, a subjective endpoint

« Some studies, including CTT publications, have increased statistical power by including 'softer' outcomes such as coronary revascularisation procedures. However, rates of revascularisation are less precise because of geographical variations in thresholds for intervention and because treatment allocation is largely unblinded, made apparent by the lower total and LDL cholesterol levels in people assigned to the statin arms of the clinical trials…

Bias resulting from unblinding has been documented for all outcomes except total mortality, particularly subjectively determined outcomes »[744]
la revascularisation, un critère d'évaluation 'mou'/subjectif

REVIEW OF CHOLESTEROL REDUCTION IN WOMEN – (Synthèse)

[742] Sir Richard Thompson et al. 10.6.2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf
[743] Vos E. Nutr Metab Cardiovas Dis 2007 ; 17 : e19
[744] Abramson et al. BMJ 2013; 347: f6123 - http://www.bmj.com/content/347/bmj.f6123

WALSH & PIGNONE / *JAMA* / 2004[745]

* Covering trials published 1966-2003, authors found that the risk for total mortality was not lower in women treated with lipid-lowering drugs, regardless of whether they had prior CV disease or not. In the secondary prevention trials :

a) The total mortality summary relative risk reduction in 4 trials (NHLBI Type II, 4S, PLAC-II and LIPID) totalling 2393 women was 0 %. Statins do not save lives in women with CHD

b) The summary relative risk reduction in CHD mortality in 7 trials (Scottish, Newcastle, Care, NHLBI Type II, 4S, PLAC-II and LIPID) among 3190 women was -26 % but numerical only

c) The summary relative risk reduction of nonfatal MI in 7 trials (Scottish Physicians, Newcastle Physicians, CARE, NHLBI Type II, 4S, PLAC-II and LIPID) was -29 % in 3190 women, but numerical only

d) The relative risk reduction of all CHD events in 4 trials (4S, CARE, LIPID and HPS) was -20%, NS. Composite CHD events are weakened by pooling both soft and hard endpoints in individual trials, and differing definitions across trials ; they are by themselves not valid enough to serve as a basis for prescribing statins

« For the trials reporting total mortality, lipid lowering did not appear to have a beneficial effect for women with or without previous CV disease over the 2.8 to 6-year study period in the available trials »
synthèse sur l'efficacité de la réduction du cholestérol chez les femmes

RHABDOMYOLYSIS *EIM fatal*
rhabdomyolyse
= atteinte musculaire aiguë, nécrose des cellules musculaires squelettiques (myocytes), diffusion du contenu (myoglobine) dans la circulation, blocage des glomérules rénaux, insuffisance rénale parfois fatale sans dialyse. C'est une complication très rare mais grave des statines

RISK EVALUATION : THE RIGHT WAY
Vraie prévention
la vraie évaluation du risque
« Le meilleur moyen de savoir si un patient est à risque de maladie CV, c'est de s'asseoir avec lui, et de regarder ses facteurs de risque traditionnel, comme l'hypertension, le diabète, s'il est fumeur, et de lui poser des questions sur ses habitudes de vie. 'Ce n'est pas difficile de mesurer un tour de taille, d'interroger quelqu'un sur ce qu'il mange et le nombre de fois qu'il fait de l'exercice dans la semaine'...

Cela ne sert à rien de donner des statines en prévention primaire à moins qu'il ne souffre d'hypercholestérolémie familiale sévère. Les personnes qui font de l'exercice sont plus à risque de souffrir des effets secondaires musculaires des statines. 'On ne parle plus de 7 %, mais de 15 à 20 %'. L'exercice démasque les douleurs musculaires chez les gens qui prennent des statines. Je pratique dans un centre où tous mes patients font de l'exercice, et je constate un très haut taux d'intolérance aux statines »[746]

« Selon les calculateurs actuels, un homme d'âge mûr est censé prendre des statines. Mais aucun ne tient compte des habitudes de vie et tant que ce sera le cas, ces outils ne vaudront rien ! »[747]

RISK FACTORS ALLEGED TO BE INDICATIONS FOR STATINISATION
a) Family history of premature coronary heart disease defined as CHD in male first degree relative <55 years (father, brother) or CHD in female 1st degree relative < 65 years (mother, sister)
b) Diabetes
c) Hypertension

d) Smoking
e) High cholesterol
f) Prior ischemic heart disease
g) Prior stroke

[745] Walsh & Pignone. JAMA 2004 ; 291(18) : 2243
[746] Martin Juneau cité par Fabienne Papin. ProfessionSanté 3.12.2013
[747] Martin Juneau

h) Obesity
i) Waist circumference
facteurs de risque allégués être des indications de la statinisation
* Malheureusement la statinothérapie ne prolonge la vie d'aucun d'eux, à moins que le risque annuel de mortalité totale n'approche 3 à 4%, ce qui est rare dans l'hypercholestérolémie polygénique

ROSUVASTATIN ON *WorstPillsBestPills's* BLACK LIST
« The *Health Research Group* made a formal presentation before the FDA's Endocrinologic and Metabolic Drugs Advisory Committee on July 9, 2003 strongly opposing the approval of rosuvastatin because of its unique kidney toxicity. We were also seriously concerned because of 7 cases of rhabdomyolysis that were common enough to have shown up in the pre-approval clinical trials of rosuvastatin in which the 80 milligram dose was used...

A number of patients taking primarily the 80 and 40 milligram doses of rosuvastatin had an increased frequency of persistent protein in the urine (proteinuria) and blood in the urine (hematuria), that in some subjects was also associated with another abnormal test result that is an early signal for kidney toxicity known as the serum creatinine level...

The FDA documents pointed out that there were two cases of kidney failure and one case of kidney insufficiency with 80 milligrams of rosuvastatin in which these patients also had experienced both protein and blood in the urine… An FDA medical officer reviewing rosuvastatin had sobering comments on the cases of kidney problems with the drug:

'The 3 cases of renal insufficiency of unknown etiology are of concern because they present with a clinical pattern, which is similar to the renal disease seen with rosuvastatin in these clinical trials. There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis [death of cells]...

All cases occurred at the 80 mg dose which was also associated with the greatest number of patients with abnormal renal findings in these clinical trials. Proteinuria and hematuria could be potentially managed with regular urinalysis screening. However, if they are the signals for the potential progression to renal failure in a small number of patients, this may represent an unacceptable risk since currently approved statins do not have similar renal effects'…

The *Endocrinologic and Metabolic Drugs Advisory Committee* recommended that kidney monitoring be required for patients taking 40 milligrams of rosuvastatin per day. The FDA failed to take this advice… We list rosuvastatin as a do not use drug for the following factors:

a) It has no proven health benefit, joining atorvastatin and fluvastatin as the statins that have not demonstrated a health benefit to the patients that use them in terms of reducing serious CV events

b) it can cause potentially serious kidney toxicity that is not seen with the other statins
c) it is the only statin that caused rhabdomyolysis, a life-threatening adverse drug reaction, in pre-approval clinical trials
d) there are already 3 statins on the market that are safer »[748]
rosuvastatine sur la liste noire de *WorstPillsBestPills*

ROSUVASTATIN TRIALS
CORONA, GISSI-HF, JUPITER, AURORA in secondary prevention ; JUPITER in primary prevention
essais de la rosuvastatine

RUN-IN PERIOD
« The rate of adverse effects in post-marketing studies is, in most cases, far higher than that found in the pre-marketing studies. In part this is due to the fact that the clinical trial populations studied in premarketing trials are highly selected. Furthermore, some industry sponsored trials include pre-randomisation run-in periods where those who fail to tolerate statins are excluded. RCT patients may therefore not represent the population that will actually take the drugs in the real world...

RCTs may thus grossly underestimate adverse effects such as myopathy or cognitive impairment and fail to detect drug interactions e.g. amlodipine and statins »[749]
période de qualification ; période-test
« Les essais de statines excluent de 60 à 90% des malades initialement recrutés, souvent après une période-test de 4 à 8 semaines sous placebo ou sous statines, ne retenant que des malades 'idéaux', pas trop vieux, sans pathologies associées, [sans

[748] http://www.worstpills.org/public/crestor.cfm
[749] Sir Richard Thompson et al. 10.6.2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf

polymédication], sans risques de complications musculaires, hépatiques, cutanées, neurologiques, psychiatriques ou sexuelles des statines, des patients assez graves pour risquer un ACV, mais pas trop pour ne pas en mourir rapidement »[750]

RUSSIANS ARE ARE NOT JAPANESE *Hypothèse lipidique*
« In 2006 Russian men under the age of 65 suffered 18 times (+1800%) the rate of CHD of men in Japan. I don't think this ratio has changed this much. By the way, the average total cholesterol level in Russian men in 2006 was 5.1mmol/l, in Japanese men it was startlingly different at ... 5.1mmol/l ! »[751]
les Russes ne sont pas des Japonais

SAGE, THE TRIAL
Atorvastatine 80 mg (forte dose) c. pravastatine 40 mg (dose moyenne) – Prévention secondaire – Gériatrie
Study Assessing Goals in the Elderly

* Princeps publication : Deedwania/Circulation/2007[752]
* Participants demography: 893 randomized ; aged 65 to 85 years, with stable coronary disease with at least 1 episode of ischemia lasting at least 3 minutes during 48-hour ambulatory ECG ; 30 % women
* Comparison : atorvastatin 80 mg versus pravastatin 40 mg

RESULTS
* Health related quality of life *not reported*
* No difference in primary outcome : mean duration of myocardial ischemia at 3 or 12 months ECG monitoring

* Not significant absolute risk reduction of 3.2% in major acute CV events under atorvastatin; also, the composite secondary endpoint was heterogenous and included 4 hard and 3 soft outcomes
* The relative risk reduction of 67% (HR = 0.33) in TOTAL MORTALITY is not coherent with the smaller reduction of the composite endpoint, neither with the bulk of the evidence from much larger trials concerning statinization and total death
l'essai dit Sage
* Cette comparaison d'une statine fortement dosée avec une autre modérément dosée en prévention secondaire en gériatrie s'est avérée négative quant au critère d'évaluation principal et quant au critère combiné secondaire. L'apparente réduction relative de la mortalité totale est incompatible avec les autres résultats de cet essai et avec l'ensemble des données factuelles sur la statinisation et la mortalité totale

SALES OF CHOLESTEROL-LOWERING DRUGS IN QUEBEC AND CANADA
* In 2012-13 Canadians spent 1 643 000 000 $ in drugstore sales for cholesterol-lowering drugs, of which an estimated 427 180 000 $ went to pharmacists. 70.1% was spent on branded Lipitor™ and Crestor™ and only 6.8% on generic simvastatin. 43% of spending was for women, 57% for men…[753]

[What a waste, considering that statins do not tangibly extend lives, that the benefit-risk balance is negative and the cost-effectiveness unacceptable except in rare familial hyperlipidemias]

The spending per capita 65.13$ in Quebec and 47$ in Canada. The age-adjusted per capita spending in Quebec was 45.9% higher than in the rest of Canada and ranked no. 1 in this respect among provinces. It also ranked no. 1 for choosing more expensive products (branded vs. generic), inflating spending by 13.3% « Residents were prescribed a more costly mix of drugs »[754]

[Evidence that promotion is more effective, and / or CME is more defective and / or statins are more costly and / or generics are underprescribed, in this province]
données sur les ventes d'hypocholestérolémiants au Québec et au Canada
* Parmi les provinces, le Québec arrive 2e pour les dépenses par habitant (non ajustées pour l'âge) en 2012-13, chez les deux sexes de tout âge, juste après Terreneuve, et 1re pour les dépenses chez les hommes de 40 ans et plus, et chez les femmes de 40 à 64 ans.

* En 2012 les rémunérations brutes des cardiologues ont coûté à la Régie de l'assurance maladie du Québec la somme de 182 M

[750] Philippe Even 2013
[751] http://drmalcolmkendrick.org/2016/03/01/what-causes-heart-disease-part-vii/
[752] Deedwania et al. Circulation 2007 ; 115(6): 700 – abstract on http://www.ncbi.nlm.nih.gov/pubmed/17283260
[753] Morgan et al. The Canadian Rx Atlas, 3rd ed. 2013 - http://www.chspr.ubc.ca/pubs/atlas/canadian-rx-atlas-3rd-edition
[754] Morgan et al. The Canadian Rx Atlas, 3rd ed. 2013 - http://www.chspr.ubc.ca/pubs/atlas/canadian-rx-atlas-3rd-edition

(490 cardiologues x 395 808$ par année)[755]. Statiniser toute la clientèle est peu laborieux et assure une clientèle de longue durée. On peut se poser la question des dépenses directes et indirectes induites par la prescription inutile de statines. Les généralistes sont courtisés (et désinformés) eux-aussi et sont souvent de gros prescripteurs de statines 'à vie'.

SALES OF CRESTOR™

« The marketing spend for Crestor™ alone was $1bn in the first year »[756] - « From October 2013 to September 2014, rosuvastatin (Crestor™) was the most prescribed brand-name drug in the U.S., with 22.3 M prescriptions filled and $5.8 billion in sales. However, even though the drug lowers cholesterol, it has no proven health benefit — such as a decreased risk of heart attack or stroke — in people with high cholesterol »[757]

ventes du Crestor

SALES OF LIPITOR™

« Lipitor™ sales alone exceeded $120 bn between 1996 and 2011 »[758] - « The patent on Pfizer's blockbuster statin drug Lipitor®, (atorvastatin) expired at the end of 2011. In its hay-day, worldwide annual Lipitor® sales hit $12.9 bn. In 2012 (post patent expiry) they collapsed to $3.9 bn, and in 2013 they dropped a further 41% »[759] - « The best-selling drug in the world, Lipitor™, peaked at $12 bn, but only after years on the market »[760] - « Atorvastatin (Lipitor™) at one point was making £13 bn a year »[761]

ventes du Lipitor™

SATURN, THE TRIAL

Critères angiomorphologiques – Rosuvastatine 40 mg (forte dose) c. atorvastatine 80 mg (forte dose)

* Study of Coronary Atheroma by Intravascular Ultrasound : Effect of Rosuvastatin vs Atorvastatin
* Princeps publication : Nicholls/NEJM/2011[762]
* Funding : private, AstraZeneca (Crestor™)

* Primary (surrogate) endpoint : progression of coronary plaque volume by serial intravascular ultrasonography at baseline and after 2 years
* Methodology : > 1000 patients, > 1 year ; surrogate endpoint

* Participants : 1039 randomized patients
* Participants' health : coronary disease
* Comparison : high dose atorvastatin 80 mg, high dose rosuvastatin 40 mg
* Duration : 104 weeks

RESULTS
* No difference in percentage of atheroma volume decrease (0.99% under atorvastatin and 1.22 % under rosuvastatin) after 2 years
* No difference in first major CV events : 52 under rosuvastatin or 7.5% ; 49 under atorvastatin or 7.1%
* New proteinuria : 1.7% under atorvastatin, 3.8% under rosuvastatin
* Health related quality of life *not reported*

* Authors' conflation : the two statins are efficacious in slowing progression of atheromatous plaques
* Factual conclusions :
(a) it is possible that neither statins slowed plaque progression, since there is no control group
(b) the amplitude of plaque volume reduction (only -0.99% and -1.22% over two years) was insufficient to have clinical consequences

(c) this surrogate endpoint is not correlated enough with CV events to serve, alone, as evidence of clinical efficacy; the authors themselves admit that « Intravascular ultrasonography remains a surrogate end point, and a reduction in plaque volume should

[755] SM 25, RAMQ 2013
[756] Malcom Kendrick, 2014
[757] WorstPillsBestPills, January 2015
[758] Ioannidis JPA. JAMA 2014; 311(5): 463 - doi: 10.1001/jama.2013.284657
[759] http://healthinsightuk.org/2014/03/04/sos-sanity-over-statins-sssssh-side-effects-pharmas-fingers-and-a-cunning-plan/
[760] FiercePharma, 8.4.2014
[761] Malcolm Kendrick, 2014
[762] Nicholls et al. NEJM 2011 ; 365(22) : 2078 - doi: 10.1056/NEJMoa1110874 – abstract on http://www.ncbi.nlm.nih.gov/pubmed/22085316 - full paper on http://www.stmarymed.com/site/wp-content/uploads/2012/10/journal04-12.pdf

not be interpreted as equivalent to a clinical benefit in terms of preventing CV events »
« Note that no published studies compare rosuvastatin clinical outcomes with another statin »[763]
l'essai dit Saturn

SCANDAL
« Some day, I suspect, we will regard statins as an unmitigated *scandal* in medicine »[764]
scandale

SCANDAL, DECEPTION, DECEIT AND CENSORSHIP
See CENSORSHIP IN LIPID LAND

SCIENCE AND ETHICS OUT OF CONTROL
dérapage scientifique et éthique
« Il n'y a aucun exemple dans toute l'histoire du médicament d'un dérapage scientifique et éthique comparable [aux tromperies sur le cholestérol et les escroqueries concernant les statines] »[765]

SCIENTIFIC LITERATURE CREDIBILITY QUESTIONED
la crédibilité de la documentation scientifique remise en question
* C'est un pavé dans la marre lancé par un éditorial de Richard Horton (*Lancet* 11.4.2015)[766]. Le cas contre la science est simple, une grande partie de la littérature scientifique, peut-être la moitié, est tout simplement *fausse*. Trop d'études [comme celles en statinologie] font que la science a pris un virage vers l'obscurantisme, car elles sont caractérisées par :[767]

a) des effets *minimes*,
b) des analyses exploratoires *invalides*,
c) des *conflits* d'intérêts évidents
d) l'obsession de suivre des tendances à la *mode* d'importance douteuse

SEARCH, THE TRIAL *Prévention secondaire chez coronariens stables – Simvastatine 80 mg c. 20 mg – Comparaison de doses – Sans placebo*
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Search
* Effectifs randomisés : 12 064
* Âges : moyenne de 64 ans (de 18 à 80)

* Suivi moyen : 6,7 ans
* LDL-C à l'inclusion : 2,54 mM (98 mg/dL)
* Critère d'évaluation principal combiné : décès coronariens, infarctus du myocarde, AVC, revascularisations [critère trop hétérogène par le regroupement des revascularisations avec les décès coronariens]

* Résultats numériques :
a) Un événement vasculaire majeur survint chez 24,5% sous haute dose et chez 25,7% sous faible dose, un avantage absolu de 1,2 % NS et relatif de 4,9% selon notre calcul et de 6% selon les auteurs. Il n'y a donc pas d'avantage clinique en utilisant une forte dose. Ce qui contredit l'hypothèse statinique

b) les décès CV furent de 9,4 % sous 80 mg et de 9,5% sous 20 mg, une relative risk reduction de -1%, NS et un avantage absolu de -0,1 % cliniquement nul

c) la plus grande chute des LDL sous haute dose (- 0·35 mM), critère de substitution, n'est pas accompagnée de bénéfice clinique en 6,7 ans, ce qui contredit l'hypothèse du cholestérol

[763] Green et al. JAMA Intern Med 2013 - doi:10.1001/jamainternmed.2013.1529
[764] Alan Cassels, 2012
[765] Even 2013, page 34
[766] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60696-1/fulltext
[767] Hervé Maisonneuve, 1.5.2015 - http://www.h2mw.eu

d) on confirme que les myopathies sont un EIM dose dépendant car il y en a 27 fois plus sous haute dose, soit 0,03% (2 cas) sous 20 mg contre 0,9% (53 cas) sous 80 mg de simvastatine

* Conclusion factuelle: résultats négatifs cliniquement quant à la prévention CV; comme la simvastatine fortement dosée augmente de 2 700% la iatrogénie musculaire, la balance avantage-risque n'en devient que plus négative

SECONDARY PREVENTION EARLY AFTER ACUTE CORONARY SYNDROME : A META-ANALYSIS *Prévention secondaire après syndrome coronarien aigu – Statine c. placebo ou soins usuels*
BRIEL M et al. *Int J Cardiol* (2011)[768]

* The Briel et al meta-analysis was based on 18 trials involving over 14 000 patients, who compared statin to control (placebo or usual care). Randomization had to be initiated within 2 weeks after onset of an ACS (myocardial infarction or unstable angina). Follow-up had to last at least 1 month. Risk ratios were calculated at 1 and 4 months following the ACS...

The primary combined endpoint chosen by the international group of reviewers included [total mortality + MI + stroke]: it was not significantly reduced short term, measured at 1 and 4 months...

The risk ratio for unstable angina at 4 months was the only secondary individual endpoint reaching significance at the 2% alpha level but a p value < 0.01 (even < 0.005 by the conservative Bonferroni correction), should have been required to account for the multiplicity of comparisons (total of 16, fig 2, page 5). Also there was moderate heterogeneity among trials for unstable angina (a component of ACS), that may be due to differences in the definition of the endpoint of unstable angina among trials
une méta-analyse de la prévention secondaire introduite tôt après syndrome coronarien aigü
* Nombre d'essais : 18
* Nombre de participants: 14 303
* Âge et sexe des patients : 53-69 ans, majoritairement hommes

* Statines : atorvastatin (4 essais), fluvastatine (3), simvastatine (3), pravastatine (7)
* Témoins : 6 soins usuels, 8 placebo
* Cholestérolémie : réduction relative de -15 à -53% des LDL, et de -9 à -37% du cholestérol total

* Résultats bénéfiques présentés en risques absolus : aucun
* Résultats bénéfiques présentés en risques relatifs, non significatifs même au seuil de 5% après 1 mois et après 4 mois :

a) critère principal combiné (décès, IM, AVC), NS
b) mortalité toutes causes, NS
c) infarctus myocardique fatal ou non-fatal, NS

d) AVC fatal ou non-fatal, NS
e) décès CV, NS
f) intervention de revascularisation (angioplastie ou pontage) , NS
g) défaillance cardiaque aigüe (de novo ou aggravée) , NS

* Conclusion factuelle : la statinothérapie amorçée peu après un syndrome coronarien aigu chez des hommes est inutile à court-terme (du moins à 4 mois). Cette forme de statinisation en prévention secondaire est cliniquement futile. En plus de contredire l'hypothèse lipidique et l'hypothèse statinique

SECONDARY PREVENTION IN GERIATRICS : NO LIFE EXTENSION *Étude observationnelle*
« The value of statins in people aged 75 and older, and particularly those aged 80 and older, is controversial. In a cohort of 1,262 older adults hospitalized with CAD, we found that statin therapy had no significant effect on long-term survival (median follow-up 3.1 years) after adjustment for between-group differences.

These findings call into question the benefit of statin therapy for secondary prevention in a real-world population of adults aged 80 and older »[769]
prévention secondaire en gériatrie : pas de prolongation de la vie

[768] Briel M, et al. Int J Cardiol (2011) - doi:10.1016/j.ijcard.2011.01.033 -
[769] Rothschild et al. J Am Geriatr Soc 2016 ; 64: 1475

SECONDARY PREVENTION IN STATINOLOGY
prévention secondaire en statinologie
= celle entreprise chez des patients ayant des antécédents CV personnels, i.e. des signes cliniques d'ischémie coronaire ou cérébrale ou d'une autre forme d'insuffisance macro-vasculaire (e.g. claudication). La statino-thérapie chez ces patients vise à retarder la récidive

* Dans une majorité de patients ayant des antécédents personnels de maladie coronaire ou d'autres maladies macro-vasculaires, il faudrait un risque d'événement vasculaire sévère très élevé, soit de ≥ 3 à 4 par 100 années-patients dans le groupe témoin, pour oser espérer un bénéfice clinique suffisant pour contrebalancer les inconvénients de la statinisation à vie

* Dans l'hyperlipidémie familiale, quand celle-ci n'a pas encore provoqué de coronaropathie clinique, la statinothérapie est au sens strict utilisée en prévention primaire, mais le risque est non seulement très élevé, il est extrême

SECONDARY PREVENTION OF TOTAL MORTALITY IN WOMEN *Méta-analyse spécifique au sexe*
prévention secondaire de la mortalité toute cause chez les femmes
* Selon la méta-analyse de Kostis et coll.[770] sur 18 essais statiniques contrôlés comprenant 40 275 femmes participantes, le rapport de cote est de 1,03 (+3%) et NS, confirmant que la statinisation des femmes même coronariennes ne prolonge pas leur vie

SECONDARY PREVENTION TRIALS OF STATINS AGAINST PLACEBO
* With > 1000 participants and lasting > 1 year, on adults with established CV disease:
SPARCL, 4S, LIPID, GISSI, GREACE, ALLIANCE, LIPS, HPS, CARE, PROSPER, A to Z, CORONA, J-STARS
« High-risk populations don't consistently benefit from lipid-lowering therapy and risk scores don't accurately identify patients who could *potentially* benefit from statin therapy… such as high coronary calcium score, diabetes, kidney disease, heart failure, post-MI and post-CABG[771] »
essais statiniques en prévention secondaire
* La maladie CV peut être coronaire (ischémie, insuffisance cardiaque par ischémie) ou cérébrovasculaire. La majorité des essais sont négatifs et les autres sont trop biaisés

SERIOUS ADRs REPORTED FOR SIX SUSPECTED STATINS (USA) *Statinovigilance*
« Statin harms statistics from serious ADR reports at FDA from Jan 1, 2004 to Sept 30, 2011 from FDA as reported by RxIsk.org[772]are as follows for Lipitor™, Crestor™, Zocor™, Pravachol™, Mevacor™ and Lescol™ combined:[773]

a) 25,565 related deaths
b) 25,200 life threatening reactions
c) 40,807 disabilities
d) 138,107 hospitalizations
EIM graves notifiés pour six statines suspectées (ÉU)
* le nombre d'ordonnances au cours de la période aux ÉU n'est pas présenté (secret industriel !)et les liens de causalité sont vraisemblablement variés

SHARP, THE TRIAL *Simvastatine 20 mg + ezetimibe 10 mg c. placebo – Dans l'insuffisance rénale chronique modérée à sévère dont un tiers en hémodialyse - Résultats négatifs cliniquement*
Study of Heart and Renal Protection

* Princeps publication : Baigent/Lancet/2011[774]
* Funding : Merck/Schering: £40M plus drug supply

METHODOLOGY
* Participants demography : 9270 randomized
* Participants' health : 3023 on dialysis, 6247 not dialyzed; no CHD history

[770] Kostis et al. J Am Coll Cardiol 2012; 59(6): 572 – doi: 10.1016/j.jacc.2011.09.067
[771] DuBroff, QJM 1.11.2017 - https://academic.oup.com/qjmed/advance-article-abstract/doi/10.1093/qjmed/hcx213/4587483?redirectedFrom=fulltext
[772] https://www.rxisk.org/Default.aspx
[773] Harriet Rosenberg, communication
[774] Baigent et al. SHARP Investigators. Lancet 2011 ; 377 ; 2181

* Unclear statistical analysis plan, poorly designed primary endpoint[775]

* Primary composite endpoint : total major CV events including : non-fatal MI, CHD death, non-haemorrhagic stroke, any arterial revascularisation procedure
* Duration : median (50th percentile) 4.9 years

RESULTS
* Composite endpoint : relative risk reduction -17%. There were 619 events under placebo, 526 under simvastatin + ezetimibe, mostly explained by differences in revascularisation (352 under placebo, 284 under simvastatin + ezetimibe), a procedure that is a subjective medical decision usually at high risk of unblinding of treatment allocation

* Health related quality of life *not reported*
* No benefit on CHD death, nonfatal AMI, major CHD event, or total mortality

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit Sharp

SHOULD MEDICAL SCIENCE IGNORE THE PAST? (Article) *Traduction de lettre au BMJ – Démolition du mythe du cholestérol*
Uffe RAVNSKOV. BMJ 2008; 337: a1681[776]
La science médicale peut-elle ignorer le passé ? (Traduction par Elena Pasca)
* Dans le *BMJ* du 20.9.2008, Uffe Ravnskov, porte-parole du réseau THINCS (critique du 'mythe du cholestérol'), répond par une lettre concise à un article portant sur l'hypercholestérolémie (excès de LDL) et ses traitements à tout va :

« Pour leur article sur l'hypercholestérolémie et son traitement, Bhatnagar et coll. n'ont retenu que les analyses comprenant une 'longue liste de références récentes' (Bhatnagar D et al. BMJ 2008; 337: a993) omettant ainsi d'importantes connaissances acquises de longue date (Ravnskov U. www.bmj.com/cgi/eletters/337/aug21_1/a993#201600). Je m'explique :

a) L'étude postmortem d'individus pris au hasard n'a trouvé aucune association entre le cholestérol et le degré d'athérosclérose
b) Un taux élevé de cholestérol n'est pas un facteur de risque pour les femmes, les patients en insuffisance rénale, les diabétiques ou les personnes âgées (Ravnskov U. *Q J Med* 2003; 96: 927-34)

c) Les personnes âgées ayant un taux élevé de cholestérol ont une espérance de vie plus longue que ceux qui ont un cholestérol bas (Ravnskov U. *Q J Med* 2003; 96: 927-34)
d) Aucune étude visant la baisse du taux de cholestérol, qu'elle soit randomisée, contrôlée, unifactorielle, basée sur un régime alimentaire, etc., n'a jamais réussi à faire baisser la mortalité coronarienne ou totale (Ravnskov U. *J Clin Epidemiol* 1998; 51: 443-60)

e) Aucun essai clinique ou angiographique n'a trouvé une causalité entre les réponses individuelles à des traitements hypolipémiants et le taux général de mortalité (Ravnskov U. *Q J Med* 2003; 96: 927-34)
f) Plus de 20 études de cohorte ont constaté que les patients souffrant de maladies coronariennes mangeaient la même quantité de graisses saturées que les personnes du groupe de contrôle (Ravnskov U. *J Clin Epidemiol* 1998; 51: 443-60)

g) Sur 10 études de cohorte, 7 ont constaté que les patients ayant souffert un accident vasculaire cérébral mangeaient moins de graisses saturées que les contrôles sains

h) La concentration d'acides gras à chaîne courte dans les tissus adipeux – qui est l'indice le plus fiable de l'ingestion de graisses saturées – est similaire, voire plus basse chez les patients souffrant de maladies coronariennes comparés aux contrôles sains, et ce dans 5 études cas-témoins

i) L'effet des statines est largement surévalué et n'est pas dû à la baisse du cholestérol (Ravnskov U. *Q J Med* 2003; 96: 927-34). Seul un petit pourcentage de patients tire un bénéfice de ce traitement : il s'agit d'hommes à haut risque CV; mais ce bénéfice ne tient pas longtemps si on le rapporte aux effets indésirables, qui sont plus fréquents et plus graves que ceux signalés dans les essais cliniques portant sur les statines – ces derniers ne signalant pas grand-chose (Ravnskov U. *BMJ* 2006; 332: 1330-2)

[775] http://www.trialresultscenter.org/study8081-SHARP.htm
[776] http://www.bmj.com/content/337/bmj.a1681?ijkey=rIAxXmCReGu9zU7&keytype=ref

Il est urgent que des scientifiques n'ayant pas de liens financiers avec l'industrie pharmaceutique et l'industrie alimentaire soumettent la campagne sur le cholestérol à une sérieuse révision. L'auteur Ravnskov déclare n'avoir aucun conflit d'intérêt »[777]

SHOULD THERE BE A MORATORIUM ON THE USE OF CHOLESTEROL LOWERING DRUGS ? – (Article) – *Médicament mortel*
DAVEY SMITH G, PEKKANEN J. *BMJ* 1992; 304: 431-4
* A meta-analysis of primary prevention trials
« Total mortality was lower among subjects in the intervention groups in the diet trials (OR 0.95, relative risk reduction = -5%) but higher in the intervention groups in the drug trials (OR 1.16, RRI +16%) »[778]

SILENT DELETERIOUS REACTIONS ON FITNESS *Statinovigilance*
effets délétères silencieux sur la forme physique
« Effets délétères silencieux : diabète, cancers, pathologies oculaires, dépression, déclin cognitif accéléré »[779]
adaptation à l'exercice et statinisation
* la simvastatine annule considérablement l'adaptation à l'entraînement physique. Il est raisonnable de croire que les autres statines en font autant

SIMVASTATIN IMPAIRS EXERCISE TRAINING ADAPTATION *– (Article) Statinovigilance – EIM étudié par essai clinique contrôlé – Condition physique cardiorespiratoire*
MIKUS et al. *J Am Coll Cardiol* 2013; 62: 709-14 – doi:10.1016/j.jacc.2013.02.074 - free on http://content.onlinejacc.org/article.aspx?articleid=1679527

« Simvastatin attenuates increases in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise training in overweight or obese patients at risk of the metabolic syndrome » - Similarly, vastus lateralis skeletal muscle citrate synthase activity increased by 13% in the exercise only group, but decreased by 4.5% in the simvastatin plus exercise group (group by time interaction). Simvastatin 40 mg per day attenuates increases in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise training »[780] - « The results reported add to the evidence that statins affect the ability of skeletal muscle to adapt to the stress of exercise training »[781] - « The RCT demonstrates that simvastatin significantly attenuates cardiorespiratory fitness as compared to placebo in overweight and obese patients »[782]

SIMVASTATIN TRIALS
* HPS, 4S, SEARCH
essais de la simvastatine

SINGLE OUTCOME CRITERIA VARIETIES IN STATIN RESEARCH
a) total mortality
b) fatal CHD ; fatal MI ; CHD mortality
c) fatal stroke
d) non fatal MI

e) non fatal stroke
f) acute coronary syndrome or ACS; unstable angina
g) hospitalisation for ACS
h) stable angina

i) revascularization procedure (angioplasty or bypass)
j) angioplasty ; percutaneous coronary intervention or PCI (with stent) ; stenting
k) bypass ; coronary artery bypass surgery

l) CHD event
m) CV event (coronary, cerebral, aneurysm, leg amputation, other)
n) CV mortality

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[777] Elena Pasca. Pharmacritique accessible sur http://pharmacritique.20minutes-blogs.fr/archive/2008/09/25/une-revision-des-directives-sur-le-cholesterol-et-les-statin.html
[778] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1881265/pdf/bmj00060-0042.pdf
[779] http://michel.delorgeril.info/
[780] Mikus et al. JACC 2013 – DOI 10.1016/j.jacc.2013.02.074
[781] Thompson & Parker. JACC 2013– DOI 10.1016/j.jacc.2013.03.030
[782] TI/ Therapeutics Letter # 89, 2014

variétés de critères d'évaluation uniques en recherche statinique
* par opposition aux critères combinés

SOCIOECONOMIC vs. BIOLOGICAL CARDIOVASCULAR RISK FACTORS
« The 10-year risk for fatal CVD varied substantially across countries. For instance, a 65-year-old Japanese (JA) man with diabetes, a systolic BP of 140 mm Hg, and TC of 6 mmol/L (232 mg/dL) would have a 10-year risk for fatal CVD of 5%. The same man in China (CN) would have a 24% risk »[783], an unequivocal demonstration that socio-economic determinants (SEEES) are more important – in this case 4.8 times - than biological markers such as glycemia, systolic and cholesterolemia
facteurs de risque CV socioéconomiques c. biologiques
« À la lumière des nouvelles études, les scores de risques traditionnels (tel que ceux de Framingham), qui ne tiennent pas compte des habitudes de vie, sont à mon avis complètement dépassés »[784] déclare un cardiologue expert en prévention

* à glycémie, systolique et cholestérolémie égales, un homme de 65 ans en Chine présent une risque annuel de décès CV de 2,4% tandis qu'au Japon le même homme a un risque de 0,5%, une différence relative de 4 800% ou 4,8 fois, assurément associée aux conditions de vie

SPARCL, THE TRIAL
Prévention secondaire des AVC - Atorvastatine 80 mg c. placebo – Forte dose

Stroke Prevention by Aggressive Reduction in Cholesterol Levels
* Funding : private, Pfizer

* Princeps publication : Amarenco/NEJM/2006[785] - Amarenco/Stroke/2007[786]
* Participants randomized : 4731 - 40 % women; average age 63 years

* Participants health: post-stroke (69%) or transient ischemic attack (31%), 1-6 months previously; TC mean of 212 mg/dL – LDL-C mean of 133 mg/dL
* Median duration (50th percentile): 4.9 years
* Comparison : atorvastatin 80 mg (high dose) vs placebo

RESULTS
* TOTAL MORTALITY : 216 deaths under statin; 211 died in placebo group, relative risk reduction is NS
* CHD mortality : 40 deaths in statin group, 39 died under placebo, relative risk reduction is NS

* Primary endpoint : stroke
« Initial analysis found no significant difference between the two groups, whether concerning fatal or non-fatal strokes. Secondary analyses included statistical adjustments and did not adjust the p level (to <0.01) for the number of interim analyses, but authors concluded this was a truly positive trial »[787]

« In the SPARCL trial of atorvastatin versus placebo after stroke or transient ischemic attack, an unadjusted analysis yielded a borderline result in favor of atorvastatin for the primary outcome of recurrent stroke. A prespecified, covariate-adjusted analysis that accounted for geographic region, entry event and duration, age, and sex yielded a hazard ratio of 0.84...

It is not clear which was the prespecified primary analysis. Under the *dubious premise* that a significance level of 5% should be of paramount importance, one might debate whether the trial is "positive." A more reasonable verdict is that overall there is modest evidence of a treatment benefit »[788]
l'essai dit Sparcl

SPCD, THE TRIAL
Financement public
l'essai dit Spcd

[783] Lancet 2015
[784] Martin Juneau, Promotion Santé, Mars 2015, page 38
[785] N Engl J Med 2006; 355: 549 - DOI: 10.1056/NEJMoa061894 - http://www.nejm.org/doi/full/10.1056/NEJMoa061894#t=articleResults
[786] Amarenco et al. Stroke 2007 ; 38(12) : 3198
[787] de Lorgeril 2014, op. cit.
[788] Pocock & Stone. N Engl J Med 2016; 375: 861-70 - DOI: 10.1056/NEJMra1510064

SPEAKERS' BUREAU UNWRITTEN RULES
* In her book, *The Truth About Statins*, cardiologist Barbara Roberts echoes others' experience. She agreed to speak about Pfizer's Lipitor™ (atorvastatin) and gender-specific aspects of heart disease in women, but told Pfizer 'that I wasn't interested in just getting up in front of a bunch of doctors and plugging one or another of Pfizer's medicines.' …

Declining to use Pfizer-supplied slides, she created her own slides for the speeches 'until one night a regional manager attended one of my talks—and suddenly I was no longer invited by Pfizer to give lectures'
règles non écrites des conférences au profit des firmes
* Le sponsoring met fin à la liberté universitaire et à l'impartialité des formateurs en matière de prévention CV

SPECTRUM OF ADRs
Statinovigilance
"The MHRA (UK) states that … there is sufficient evidence to support a possible causal relationship between statin use and the following adverse reactions [among other better known ADRs] : sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease[789]"

« The FDA has recently approved a new safety labelling change for the entire class of drug.[790] The FDA has warned that increases in glycosylated hemoglobin (HbA1c) and fasting serum glucose levels have been reported with statin use. Moreover, the FDA has added a safety warning about associated cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion)...

We have to bear in mind that statins have numerous interactions with CV and other drugs that may increase the toxicity of statins »[791]
* The best known statinovigilante in the USA is Beatrice Golomb of the University of California

« Statin therapy has been associated with a wide range of adverse events including liver dysfunction, acute renal failure, and cataracts; cognitive symptoms, neuropathy, and sexual dysfunction; decreased energy and exertional fatigue; and psychiatric symptoms, including depression, memory loss, confusion, and aggressive reactions »[792]

« Harms are documented and referenced in the detailed analysis by Golomb and Evans[793] and include : peripheral neuropathy, behaviour change, memory loss, depression, psychosis, interstitial lung disease, heart failure, Parkinson syndrome, lupus-like syndrome, dermatomyositis, other auto-immune syndromes, pancreatitis and others … They are often subtle, usually dose related, sometimes serious and require vigilance to detect. The magnitude of most remains uncertain at this time»[794]
le spectre / l'éventail des EIM
* l'experte la mieux connue dans le domaine de la statinovigilance est Beatrice Golomb de l'Université de la Californie
* la iatrogénie statinique ou pathologie statinique recouvre l'ensemble effets indésirables reliés aux statines. Il y a les effets directs sur la santé mais aussi les coûts directs et indirects, les risques d'interaction, et l'effet nocebo qui inclut l'étiquetage de personne à risque dont 'le cholestérol est malade', sorte de condamnation à une pharmacothérapie 'à vie'

SSSS / 4S, THE TRIAL *Simvastatine 20 ou 40 mg c. placebo – Prévention secondaire – Quelques résultats numériquement positifs - Résultats cliniquement non signifiants*
Scandinavian Simvastatin Survival Study ; 4S trial
* Funding : private, Merck « The trial was conducted by the sponsor's staff, the only statistician belonged to the sponsor's staff. This would not be acceptable today, with the new regulations »[795]

METHODOLOGY
* Princeps publication : Pedersen/*Lancet*/1994[796]
* Participants demography: 4444 randomized; 827 women or 18.6 %; mean age 59 (33% > 65 years), range 35-70 years

[789] WHO Pharmaceuticals Newsletter No. 6, 2009 & No. 1, 2010
[790] www.fda.gov/Drugs/DrugSafety/ucm293101.htm
[791] Hudzik B et al. CMAJ 2012 ; 184(10) – (Letter) - doi: 10.1503/cmaj.112-2051 - http://www.cmaj.ca/content/184/10/1175.1.full
[792] http://www.bmj.com/content/347/bmj.f6123
[793] Golomb & Evans. Am J Cardiovasc Drugs 2008; 8: 373
[794] http://www.ti.ubc.ca/sites/ti.ubc.ca/files/89.pdf
[795] de Lorgeril 2014, op. cit.
[796] Pedersen et al. (4S). Scandinavian Simvastatin Survival Study Group (SSSSG). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the scandinavian simvastatin survival study. Lancet 1994; 344(8934): 1383 - doi:10.1016/S0140-6736(94)90566-5 – full at https://www.biostat.wisc.edu/sites/default/files/Courses/542articles2006/08%204S.pdf or https://www.tandfonline.com/doi/full/10.1080/07853890.2018.1453233?scroll=top&needAccess=true&

* Participants' health : 100% with CHD history (angina, MI) ; TC mean 6.8 mM; TC range 5.5-8 mM (213-309 mg/dL); 80% with LDL-C > 4.2 mM (1.6 g/l); mean TC 6.8 mM; on a diet; 4.5% diabetics;
* Planned duration : endpoint driven, 440 deaths of any cause
* Control measures : double blinding, randomization; run-in period to select compliant participants

* 1 primary endpoint : all-cause mortality
* 1 secondary composite endpoint analyzed by time to first event : major CHD events [CHD death + non-fatal AMI + resuscitated cardiac arrest + definite silent MI], too heterogenous to be valid
* 5 tertiary, exploratory endpoints analyzed by time to first event : any CHD event; death *or* any atherosclerotic event; revascularisation; hospital admission for acute CHD event without diagnosis of MI; health economics aspect

* Follow-up : 5.58 years (67 months); stopped slightly prematurely by the trial statistician (Merck's…) because a third and final interim analysis showed a *statistically* significant reduction in total mortality (bilateral alpha of 5% adjusted for the three interim analyses) and the actual number of deaths, 438, had practically reached the prespecified number of 440

* Positive compliance (active group adherence) : 90%
* Negative compliance (control group adherence) : 87%

* Krauss comments « No information how patients were selected before randomisation, only that 'patient records' were used… The trial do not collect baseline data – and thus assess – for differences between patients in levels of physical fitness, of exercise, of stress and other alternative factors that can also affect the primary outcome and bias results… even on randomisation cannot evade an even balance of influencing factors (internal validity : comparable groups)… Some placebo patients (13% negative compliance) in the 4S trial stopped the study drug to obtain actual cholesterol-lowering treatment which shows that treatment allocation was at times unblinded by participants themselves checking cholesterol levels outside the trial. Such issues related to blinding, although often unpreventable, need to be more explicitly discussed in studies and particularly the extent to which they bias results… The use of a binary variable (died or not) can neglect the multiple ways in which participants perceive the quality of their life (external validity of endpoints) while receiving treatment[797] »

RESULTS
Surrogate endpoints (Lipid reduction) :
a) TC : relative risk reduction of -26 %, from 6.8 mM
b) LDL-C reduction : relative risk reduction of -36 %, from 4.9 mM

Clnical benefit outcomes :
* TOTAL MORTALITY: 182 deaths in 2221 treated patients and 256 in 2223 placebo patients over a median of 5.4 years; relative risk reduction of -30% - Absolute difference is 74 deaths (256 – 182 = 74) for 5.4 years or 13,7 death postponed annually in 2222 participants. The percentage absolute reduction in annual death rate = 0,62% for an NNT of 161 patient-years

« The 6-year probabilities of survival in the placebo and simvastatin groups were 87.6% and 91.3%, respectively », in other words a 6-year probabilities of death of 12.4% in the placebo and 8.7 % in the simvastatin group (3.7% absolute difference), equivalent to 2.07 % per year under placebo and 1.45 % per year under simvastatin (a 0.62% yearly difference), for an absolute risk reduction of -0.62 deaths per 100 patient-years, a NNT of 161 patient-years, an annual inefficacy rate of 99.38 % and a virtual life extension of 54 hours per year of treatment ([365 / 161] x 24 = 54). Unfortunately, such results…

(a) have never been replicated except in the HPS trial, a trial at high risk of bias
(b) are not clinically important, since 161 patient-years in experimental conditions is above our (arbitrary but reasonable and even generous) NNT threshold of 100 patient-years and reasonably larger in clinical settings (possibly 242 to 322 patient-years !)
(c) are limited to men who made up 81.4% of partipicants

* Kristensen et al. have used another method for estimating postponement of death, the *area between the survival curves* for the treated and the untreated. They calculated a relative risk reduction of -30%, a life extension of 112 hours or 4,7 days per year of treatment over 5,8 years of follow-up[798]

Since survival benefit is clinically trivial, author's emphasis on the -42 % relative risk reduction in coronary mortality is irrelevant, conflationary and misleading - « 4S is the most favorable statin trial from the standpoint of mortality, in middle-aged men (around 59) with heart disease (100%), but the asbolute magnitude of benefit should not be overconstrued, and is *relatively*

[797] Krauss, op. cit.
[798] Kristensen ML et al. BMJ Open 2015; 5: e007118 - doi:10.1136/bmjopen-2014-007118

modesthps[799]»

« The 4S trial showed decreased total mortality. The absolute decrease was 3.3% over 5.4 years [0.62% per year, NNT = 161 patient-years], expressed, as is popular, as a relative risk reduction of -30%. The small real benefit might still have merit if this benefit extends to the whole group over time »[800]… and to be *certain* of living one more year, it would require 1 patient to take 58 765 simvastatin tablets over 161 years

HARMS:
* New onset diabetes RRI = +3%, NS, *not reported* in princeps publication, later obtained by meta-analyst Sattar
* Health related quality of life *not reported*

Results in women, making up 18.6% of participants :
a) TOTAL MORTALITY : RRI of +11 %, NS « The 4S study ended with more deaths in women taking simvastatin »[801]

b) CHD MORTALITY : relative risk reduction of -21 %, NS - Since CHD mortality tended to decrease and total mortality to increase, non-CHD mortality must have increased under simvastatin
c) nonfatal MI : relative risk reduction of -34 %, NS
d) CHD events : relative risk reduction of -32 %, NS

Reproducibility :
« The 4S 'miracle' has not been reproduced »[802]

Transparency :
The BMJ has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE
l'essai dit 4S
* Comparaison : simvastatine 20 mg à 40 mg c. placebo
* Suivi : 5,58 années
* Participants: 4444 randomisés; tous coronariens, dont 79% avec antécédent d'IDM datant d'au moins 6 mois; 18,6 % de femmes; âges de 35-70 ans, 59 ans en moyenne, dont 33% > 65 ans; cholestérolémie totale entre 5,5 et 8,0 mmol/l

* Résultats cliniques:

a) relative risk reduction de -33% pour les événements coronariens; NNT annualisé = 53 patients-année, retard moyen de 6,9 jours par année de traitement – Ce critère combiné étant hétérogène (fréquence/valeur/objectivité), il n'est *pas valide* pour appuyer une décision thérapeutique
b) relative risk reduction de -42% pour la mortalité coronarienne

c) relative risk reduction de -29% pour la mortalité totale, réduction absolue de -0.62 % par année et NNT annualisé de 161 patients-année, prolongation vitale de 54 heures par année de traitement en situation expérimentale, et sensément moins en situation clinique, peut-être de 40 heures, de 27 heures…

Commentaires :

« 42% de réduction relative de la mortalité coronaire est le seul chiffre que les cardiologues aient retenu, peu importe qu'il n'ait jamais été confirmé par 31 autres essais et que le NNT annualisé fut de 161 patients-année pour la mortalité toute cause … La présentation en 1994 devant des milliers de cardiologues déclencha un délire d'enthousiasme, applaudissant debout »[803]

* l'effet de la simvastatine sur le risque relatif de mortalité totale, dans l'essai 4S, qu'elle soit obtenue par régression multiple non corrigée (relative risk reduction= 0.29 ou -29%) ou adaptée aux données de survie par la méthode de régression multiple de Cox ajustée (relative risk reduction = 0.30 ou -30%), est identique, en raison de l'importance de l'effectif et du très faible taux de

[799] BA Golomb. Clin Invest 2013 ; 3(10): 913
[800] Kinosian et al. J Am Coll Cardiol 1996; 27: 165A
[801] Eddie Vos, communication
[802] de Lorgeril 2014, op. cit.
[803] Even, pages 159, 224, 336

censures avant la fin de l'essai[804]. Malheureusement elle ne compense pas la faible validité externe dans l'interprétation pragmatique de cet essai.

« La mortalité non CV est identique dans les deux groupes. Un bénéfice est retrouvé en ce qui concerne les accidents coronariens non mortels, les besoins en angioplastie et en chirurgie coronarienne, et les AVC. Le bénéfice est également retrouvé dans les deux sexes et quel que soit l'âge (> ou < 60 ans) »[805]

* Dans l'essai de prévention secondaire 4S, au terme du suivi de 5,4 ans, la simvastatine est associée avec un gain en espérance de vie de 24 jours sur une durée de 5,4 ans[806], équivalent à une prolongation vitale de 4,4 jours par année de traitement. C'est cette variable qui devrait servir de départ à toute étude pharmaco-économique de la statinisation et à toute évaluation de l'effectivité prévue sur le terrain

* L'essai dit 4S fut exécuté avant la nouvelle règlementation régissant la façon dont les études doivent être faites et publiées, c'est-à-dire avant le scandale du Vioxx™…
* Les données brutes demeurent cachées[807]

STACKING UP AGAINST
« Facts that are stacking up against the cholesterol hypothesis remain ignored by the mainstream medical establishment »
s'accumulant contre
« Les faits s'accumulent contre l'hypothèse du cholestérol mais demeurent ignorés de la majorité du corps médical »

STATIN
statine
« Classe de médicaments hypocholestérolémiants qui sévissent dans le traitement de l'hypercholestérolémie polygénique, coutent les yeux de la tête et ne préviennent pas la maladie conarienne quand on analyse correctement les études d'abaissement des taux de cholestérol »[808]

STATIN CARCINOGENICITY
Toxicologie pré-clinique

« All members of the two most popular classes of lipid-lowering drugs (the fibrates and the statins) cause cancer in rodents, in some cases at levels of animal exposure close to those prescribed to humans. Results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be avoided except in patients at high short-term risk of coronary heart disease »[809]
carcinogénicité statinique

STATIN CONSUMPTION
Scandale pharmacoéconomique
« 8% percent of Americans aged 20 to 59, and 44% of those over 60, were prescribed statins in 2008 »[810]
consommation de statines
* Considérant que la majorité des ordonnances sont en prévention primaire, ou chez des femmes, ou chez des coronariens très âgés, le gaspillage est phénoménal

STATIN DEFICIENCY, A NEW DISEASE
Maladie inventée
« If it seems like the whole world is on statins, it's not your imagination. In 2014 the FDA approved AstraZeneca's Crestor™ for children as young as 10 and in March it approved Crestor™ for 6.5 M people who have no cholesterol or heart problems at all! (The three Fs : *fear, forever and faith*.) …

Many say, since lead investigator of the Justification for the Use of Statins in Primary Prevention study Paul Ridker of Brigham and Women's Hospital in Boston is co-patent holder/inventor of the C-reactive protein (CRP) test which "proves" Crestor's

[804] http://www.spc.univ-lyon1.fr/polycop/courbes%20de%20survie.htm
[805] DFM
[806] Ibidem et Kruth LH. Am J Cardiol 1998; 81(8): 1045 - DOI: 10.1016/S0002-9149(98)00084-8
[807] Paul Nguyen, communication
[808] Therrien, op. cit.
[809] Newman & Hulley. JAMA. 1996; 275: 55
[810] Joseph Dumit. Drug for Life, page 2

effectiveness, there's a COI. Others say, since CRP isn't necessarily even a marker for heart disease and statins can cause Type 2 diabetes, it's bad science along with a COI »[811]
la carence en statine, une nouvelle entité

STATIN DIABETES CONUNDRUM
« The statin diabetes conundrum forces medical providers to make clinical decisions based upon incomplete data. I believe the full effect of statins in diabetes and the risk of statin induced diabetes has been obfuscated by focusing upon short-term observations, combined clinical end points, and meta-analyses while quietly overlooking the lack of mortality benefit demonstrated in multiple well-conducted RCTs...

To some degree this lack of mortality benefit can be explained by the fact that many studies were neither designed nor powered to demonstrate a mortality advantage. Alternatively, it is also possible that there simply is no mortality benefit of statins in diabetes. The statin-centric approach to preventing CHD may distract us from other therapies of proven benefit...

Specifically, the Mediterranean diet has consistently been shown to both reduce CHD mortality and reduce the risk of developing type 2 diabetes mellitus. The statin diabetes conundrum may only be resolved by long-term RCTs but, until then, we must acknowledge that the evidence to support the use of statins in diabetes is inconsistent and the long-term risks of statins may have been under-appreciated »[812]
statines et diabète, une association problématique

STATIN DISCOVERER STOPS BEING STATINIZED
« A Japanese scientist who discovered an obscure cholesterol-fighting fungus will be awarded 'America's Nobel' for his contribution to today's blockbuster statin drugs.[SEP][SEP]Akira Endo, 74, will receive the Lasker Award and its $300,000 prize on Sept. 25, 2008 in New York… A 2006 profile of Endo noted that he briefly took Mevacor™, a Merck statin produced with a fungal byproduct close to the one he discovered...

But Endo stopped taking it, and when a doctor found he still had elevated LDL, he decreased his levels by exercising, he told the Wall Street Journal. When asked why, he gave the Journal a cryptic answer in the form of a Japanese proverb: 'The indigo dyer wears white trousers' »[813]
le découvreur des statines met fin à sa statinisation
* dans la même veine, le découvreur de l'APS pour dépister le cancer de la prostate s'est insurgé contre cette utilisation du test

STATIN IATROGENY
statinic iatrogeny
= burden of adverse reactions from statins ; statin related diseases ; statinic pathology
iatrogénie statinique

STATIN INTERACTIONS
statin drug-drug interactions
interactions statiniques (médicamenteuses)
* En termes d'aire sous la courbe (AUC en anglais), critère standard pour évaluer l'effet d'un produit sur la biodisponibilité de l'autre, ici une statine dont on mesure le taux sanguin après administration d'une dose. Les augmentations de l'aire sous la courbe de la concentration de statine dans le sang exposent aux toxicités musculaires bien connues comme étant dose-dépendantes[814]:

a) amiodarone (Cordarone™): +180% pour lovastatine et simvastatine
b) amlopidine (Norvasc™): +180% pour la simvastatine
c) conivaptan (Vaprisol™): +300% pour lovastatine et simvastatine

d) cyclosporine (tacrolimus / everolimus / sirolimus) : +600% à 1500% pour l'atorvastatine, 200% à 400% pour la fluvastatine, 500% à 20 000% pour la lovastatine, +500% pour la pitavastatine, 500% à 1000% pour la pravastatine, +7000% pour la rosuvastatine, +600% à +800% pour la simvastatine

e) digoxine : +20% pour l'atorvastatine

[811] Martha Rosenberg, 2015 - http://www.alternet.org/personal-health/8-invented-diseases-big-pharma-banking
[812] DuBroff RJ. Evid Based Med 2015 ; 20(4) : 1 – DOI: 10.1136/ebmed-2015-110236
[813] http://www.scientificamerican.com/blog/post.cfm?id=cholesterol-drug-scientist-receives-2008-09-12
[814] Wiggins et al. http://circ.ahajournals.org/content/circulationaha/early/2016/10/17/CIR.0000000000000456.full.pdf

f) diltiazem (Cardizem™): +51% pour l'atorvastatine, +360% pour la lovastatine, +460% pour la simvastatine
g) dronedarone (Multaq™): +360% pour lovastatine et simvastatine

h) fenofibrate (Lipanthyl™): +100% pour atorvastatine, +110% pour rosuvastatine et simvastatine, +120% pour pitavastatine
i) gemfibrozil (Lopid™): +140% pour atorvastatine, +200% à 300% pour lovastatine, +150% pour pitavastatine, +200% pour pravastatine, +160% à 190% pour rosuvastatine, +200% à 300% pour simvastatine

j) ranolazine (Ranexa™): +190% pour lovastatine, simvastatine
k) ticagrelor (Brilinta™) : +140% pour atorvastatine, +200% à 300% pour lovastatine
l) vérapamil (Isoptin™): +360% pour lovastatine, +250% pour simvastatine
m) warfarine (Coumadin™): jusqu'à +30% pour l'INR (d'où risque hémorragique)

* Cet article ne présente pas les effets des statines sur la biodisponbilité (les taux sanguins) de nombreux autres médicaments

STATIN MUSCLE COMPLAINTS *Statinovigilance*
« There are millions of people with statin-induced muscle complaints and they account for a growing portion of all patients seen for muscle problems[815]"

"Muscular problems are the major group of side-effects during statin treatment. They are known to occur much more frequently during and after exercise. Only 6, out of 22 professional athletes [in whom] treatment with different statins was attempted, finally tolerated at least one member of this family of drugs[816]"

"In an unselected population of 7924 hyperlipidemic patients receiving high-dosage statin therapy in a usual care, the odds ratios were 10x for muscular symptoms, 4x for unexplained cramps, 2x for creatine kinase elevation. Overall, muscular symptoms were reported by > 10% of patients, with a median time to onset of 1 month after first dose. In 3.8% moderate exertion was prevented and 0.4% were unable to work[817]"

"Almost 90 % of my patients now have apparent elevated cholesterol levels because of what I believe are unrealistic recommended levels of LDL cholesterol. I cannot tell you how many patients have had to take off statin drugs after they developed muscle aches, I warn all my patients to quit taking their medication at the first sign of unusual muscle pain or weakness[818]"

* Myalgia is a manifestation of myopathy "Many people taking statins seem to complain of disabling muscular discomfort or weakness[819]"
plaintes musculaires d'origine statinique
« Il y a des millions de personnes se plaignant de problèmes musculaires et ils constituent un proportion croissante des patients qui consultent en neurologie »
* La myalgie peut être aggravée par l'activité physique[820]

* La fréquence de la myalgie statinique chez les usagers est au strict minimum de 7% mais s'élève jusqu'à 17% quand on tente de la mesurer. Les chiffres disponibles proviennent de contextes expérimentaux où les promoteurs ne mesurent pas ou ne révèlent pas les myalgies, mais ils sont nettement plus élevés en situation clinique. Il n'est pas rare que les cliniciens nient le lien de causalité quand un patient statinisé s'en plaint

STATIN MYOPATHY RISK FACTORS *Statinovigilance*
facteurs favorisant la myopathie statinique
* certains sont endogènes comme l'âge avancé (> 80 ans), l'hypertension, le diabète, le faible poids, etc., alors que d'autres sont exogènes comme l'activité physique importante, un traumatisme, la prise de fibrate (interaction dangereuse), de warfarine, d'amiodarone, de bloqueur calcique, etc.[821]

[815] Oskarsson B. Neurology Clinical Practice 2011;76(Suppl 2):S14-19
[816] Helmut Sinzinger. Br J Clin Pharmacol. 2004 April; 57(4): 525–528
[817] Erick Bruckert. Cardiovasc Drugs Ther. 2005 Dec;19(6):379 & Statin-related muscle complaints: an underestimated risk, Corsini A, ibid.
[818] Ray Strand, 2003. Opus cité, pages 93 et 96
[819] Michael Oliver. BMJ 2009;338:603 & 338:b873
[820] Oskarsson B. Neurology Clinical Practice 2011;76(Suppl 2):S14
[821] Oskarsson B. Neurology Clinical Practice 2011;76(Suppl 2):S14

STATIN MYOPATHY *Statinovigilance*
« Statin-induced myopathy includes:
a) myalgia (muscle symptoms without elevation in CK),
b) myositis (elevated CK with or without muscle symptoms),
c) rhabdomyolysis (CK levels > 10 times the upper limit of normal)
Further, histopathologic findings of myopathy occur in patients with or without muscle symptoms and normal CK levels »[822]
myopathie statinique
« L'atteinte musculaire se définit par une myopathie (associant douleurs musculaires, une faiblesse, avec ou sans élévation des enzymes musculaires (créatine phosphokinase ou CK) pouvant aller, dans des cas extrêmes, jusqu'à un tableau de rhabdomyolyse avec une destruction massive des muscles pouvant conduire à l'insuffisance rénale. Sa prévalence reste faible, avec moins de quelques cas par 10 000 personnes traitées…

Ce risque augmente avec la dose prescrite de statines ainsi que lors de certaines interactions avec d'autres médicaments (rôle du cytochrome P450). Il semble également exister un terrain génétique à cette sensibilité musculaire, caractérisé par des mutations sur le gène SLCO1B1 codant une protéine intervenant dans le transport hépatique des statines »[823]

STATIN MYOPATHY TRUE INCIDENCE *Statinovigilance*
« Statin myopathy is a common dilemma not reflected in clinical trials but in real world conditions approximately 20% of statin users have muscle problems. Clinical trials, because of their short duration and unrepresentative populations, are unlikely to have the full story of side effects »[824]

« Although the excess risk of myopathy associated with statins reported in the 2012 CTT meta-analysis is 0.5 per 1000 patients over 5 years (NNH = 10 000 patient-years). However, a cross sectional analysis from the National Health and Nutrition Examination Survey[825] database shows that the prevalence of muscle pain in statin users is 50% greater than in non-users. In absolute terms, this increase in muscle pain is 100 times greater than that reported in clinical trials — 53/1000 patients, NNH = 19…

A retrospective cohort study[826] that included 13 626 people taking statins and 32 623 controls found a greater incidence of musculoskeletal disorders overall (OR = 1.19 or +19 %) and injuries (OR = 1.12 or +12 %) in those taking statins. The NNH for musculoskeletal disorders and injuries in people taking statins were 47 and 37, respectively…

A randomised controlled trial[827] found that improvement in cardiorespiratory fitness over 12 weeks of exercise training was significantly attenuated in 18 overweight or obese participants treated with simvastatin 40 mg (1.5% improvement) compared with the fitness in 19 treated with placebo (10% improvement, an 8.5 % difference) »[828]
la vraie incidence de la myopathie statinique

STATIN NATION : The Great Cholesterol Cover-Up **(USA) -** (Film)
= A film by Justin Smith exposing the over-prescription of cholesterol-lowering medications and the misrepresentation of medical evidence

« We are told that cholesterol is a major cause of heart disease. At least 40 M people are currently taking cholesterol-lowering medications, known as statins, and millions more people are avoiding foods that contain saturated fat and cholesterol. The basic idea is that dietary saturated fat raises cholesterol levels, and these two substances somehow clog-up our arteries, causing a heart attack…

This idea is often referred to as the diet-heart hypothesis. However, a numbers of doctors and researchers have been challenging this hypothesis for decades, and the latest heart disease statistics reveal some alarming facts. People with high cholesterol tend to live longer...

People with heart disease tend to have low levels of cholesterol. Cholesterol-lowering of a population does not reduce the rate

[822] Abramson et al. 2013
[823] Wiki
[824] Fernandez et al. Cleveland Clinic Journal of Medicine 2011 ; 78(6) : 393
[825] Buettner CA et al. J Gen Intern Med 2008;23:1182
[826] Mansi I et al. JAMA Intern Med 2013;73:1
[827] Mikus CR et al. J Am Coll Cardiol 2013;62:709
[828] Abramson et al. BMJ 2013;347:f6123 doi: 10.1136/bmj.f6123 available at http://www.abc.net.au/catalyst/heartofthematter/download/StatinsshouldNOTbebroadedtowiderpopulation.pdf

of heart disease. Statin medications do not extend life for the majority of people who take them, despite their widespread use and description as 'wonder drugs'…

Cholesterol-lowering has become a huge global industry, generating at least $29 billions each year. Have the facts about heart disease, cholesterol and cholesterol medications been distorted by pharmaceutical companies and food manufacturers keen to increase their profits? If the focus on cholesterol has been a mistake, then the greatest cost is associated with the lost opportunity to tackle heart disease »[829]
NATION STATINISÉE : Le grand camouflage du cholestérol (Traduction libre du titre du film)

STATIN POLYNEUROPATHY *Statinovigilance*
CASE REPORT : « We present an 18-year-old white female with type 1 diabetes for 5 years who, over several months, developed restless legs followed by parasthesias, nocturnal diarrhea, fecal incontinence, early satiety, and weight loss. Examination revealed loss of pinprick sensation to the upper arms and thighs accompanied by areflexia and loss of vibration sense, a fixed tachycardia, and orthostatic hypotension.

Neuroelectrophysiological studies showed evidence of axonal, sensory, and motor polyneuropathy but did not meet criteria for demyelination. Before further investigations began, it was noted that the subject had been taking atorvastatin despite very low lipid levels, and it was discontinued. Within 1 week, her symptoms improved dramatically. Within 6 months, the postural hypotension, diarrhea, and symptoms of gastroparesis had resolved, and all medicines other than insulin were discontinued. There remained a minimal decrease in vibration sense, areflexia, and loss of sensation to the wrist and ankle.

STATIN TRIALS BEFORE AND AFTER 2004-1005 NEW REGULATIONS
« Since the introduction of statins to clinical medicine in 1987, several kinds of statins were reported to be effective in lowering LDL-C and also preventing CHD events (mostly in 1990s). However, unfair and unethical problems were associated with clinical trials reported by industry-supported scientists [as repeatedly denounced by De Lorgeril] and new penal regulations on clinical trials came into effect in 2004 …

After 2004–2005, every clinical trials (performed by scientists *relatively* free of COI with pharmaceutical industries), reported that statins were effective in lowering LDL-C but no significant beneficial effects were observed for the prevention of CHD. Currently, the majority of scientists continue to claim that statins are effective in preventing CHD, but these claims are based on meta- analyses of reports, including those published before the EU regulation (mostly in 1990s) »[830]
essais statiniques avant et après la nouvelle réglementation de 2004-2005
* Les essais 'après nouvelle réglementation' incluent *Aspen, Enhance, 4D, Seas, Gissi-FH, Corona, Illuminate, Jupiter*
* Les essais 'avant nouvelle réglementation' incluent *4S, Lipid, Prove-It-Prv, Prove-It-Atv, Lipid, Care, Hps, Tnt-Atv80, Tnt-Atv10, Woscops, Ascot*

STATIN USE AND PAIN IN ELDERLIES WITH CANCER *Épidémiologie – Étude de prévalence trasnversale - Statinovigilance*
« In a univariate model for outpatient participants aged 80+ with cancer, statin use was associated with more than 3 times the odds of self-reported pain of 5 or greater (OR = 3.18) on a visual analogue scale of 10. After adjusting for age, sex, analgesic use, and CCI, statin users had 4 times the odds of pain of 5 or greater (OR = 4.09)…

This highlights the potential value of deprescribing statins in older people with cancer, particularly when benefit is likely to be minimal and ADEs are present. 49% of octogenarians were using statins in primary prevention (sic) »[831]
statinisation et douleur chez les vieillards cancéreux
* Chez des cancéreux ambulatoires âgés de 80 ans et plus, l'utilisation de statines est associée 3 à 4 fois plus souvent à des douleurs dépassant le niveau 5 sur une échelle visuelle analogue de 10. C'est rien de moins que 49% de ces octogénaires cancéreux qui étaient statinisés en prévention primaire : la stupidité n'a donc pas de limite…

Vivement la déstatinisation en gériatrie, en fin de vie, en soins palliatifs, en oncologie, en médecine générale, en médecine préventive, en attendant que ce soit en cardiologie, probablement la dernière spécialité qui abandonnera cette 'molécule qui tue les cellules une à la fois'

STATIN-ASSOCIATED ADVERSE COGNITIVE EFFECTS – (Article) *Statinovigilance*

[829] http://www.statinnation.net/
[830] Okuyama et al. Expert Rev Clin Pharmacol 2015 : 1 - doi: 10.1586/17512433.2015.1012494
[831] Turner et al. J Am Geriatr Soc 2014 ; 62: 1900

EVANS MA & GOLOMB BA. *Pharmacotherapy* 2009; 29(7): 800
« Patients completed a survey assessing statin-associated, cognitive-specific ADR characteristics and time course of symptom onset and recovery. Visual analog scales were used to assess the effect of the cognitive ADRs on 7 quality-of-life domains…

a) causality evaluation: 128 patients (75%) experienced cognitive ADRs determined to be *probably* or *definitely* related to statin therapy
b) time to onset : median 20 weeks, mean 53 weeks...

c) positive dechallenges and times to offset: of 143 patients who reported stopping statin therapy, 128 or 90% reported improvement in cognitive problems, sometimes within days of statin discontinuation (median time to first-noted *recovery* 2.5 wks and 8 wks of complete recovery). Of interest, in some patients, a diagnosis of dementia or Alzheimer's disease reportedly was reversed…

d) positive rechallenges and times to recurrence : 19 patients or 66 % who were rechallenged after a positive dechallenge reported a recurrence ; their *time to recurrence* averaged 6 weeks (whereas their previous time to onset was about 1 week.) Within this vulnerable group, a powerful relationship was observed between potency of the statin and fraction of trials with that agent resulting in cognitive ADRs.

Quality of life was significantly adversely affected for each of the 7 assessed domains. Findings from the survey suggest that cognitive problems associated with statin therapy have variable *onset* and *recovery* courses, a *clear relation* to statin *potency*, and significant *negative impact* on quality-of-life »
effets cognitifs indésirables associés aux statines
* le déchallenge fut positif pour les méfaits cognitifs dans 90% des cas, après une médiane de 2,5 semaines, le rechallenge fut positif dans 66% cas, après 6 semaines en moyenne
* on se rappellera que la qualité de vie n'est pas mesurée dans les essais contrôlés de statines ; à la lumière de ces résultats on comprend mieux pourquoi les sponsors évitent ce critère essentiel dans tout essai à visée pragmatique

STATIN-ASSOCIATED MYOPATHY WITH NORMAL CREATINE KINASE LEVELS *Myopathie – Physiopathologie – Essais à effectif unique*
PHILLIPS PS et al. *Ann Intern Med* 2002; 137(7): 581-5

« Four patients with muscle symptoms that developed during statin therapy and reversed during placebo use repeatedly distinguished blinded statin therapy from placebo [N of 1 trial]. Strength testing confirmed weakness during statin therapy that reversed during placebo use. Muscle biopsies showed evidence of mitochondrial dysfunction, including abnormally increased lipid stores, fibers that did not stain for cytochrome oxidase activity, and ragged red fibers...

These findings reversed [positive dechallenge] in the 3 patients who had repeated biopsy when they were not receiving statins. CK levels were normal in all 4 patients despite the presence of significant myopathy. In conclusion, some patients who develop muscle symptoms while receiving statin therapy have demonstrable weakness and histopathologic findings of myopathy despite normal serum creatine kinase levels. »
myopathie statinique sans élévation de la créatine kinase (Traduction libre du titre de l'article)
* ceci démontre que le dosage de la CK durant un essai clinique est un critère de substitution imparfait et que sa normalité n'exclut pas une myopathie. L'imputabilité statinique chez ces 4 patients est < 95% ou très probable (definite) tant par les déchallenges et rechallenges positifs que par la démonstration des lésions cellulaires

STATIN-ASSOCIATED POLYMYALGIA RHEUMATICA (PMR) *Statinovigilance*
statinic polymyalgia rheumatica

« We conducted a case/non-case study based on individual case safety reports (ICSR) in the WHO global ICSR database aka VigiBase. Case reports containing the adverse event term polymyalgia rheumatica were defined as cases. We identified 327 reports of PMR as cases and 1635 reports of other ADRs as non-cases…

Among cases, statins were more frequently reported as suspected agent (29.4%) compared to non-cases (2.9%). After adjustment for several covariates, statins were significantly associated with reports of PMR (reporting odds ratio of 14.21). The results of this study lends support to previous anecdotal case reports in the literature suggesting that the use of a statin may be associated with the occurrence of PMR »[832]
polymyalgie rhumatismale statinique

[832] De Jong et al. PLoS ONE 2012 ; 7(7): e41289 available at http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0041289

* quand une polymyalgie survient chez une personne statinisée, il y a 14 chances contre 1 que la statine soit en cause

STATIN-RELATED COGNITIVE PROBLEMS : DECHALLENGE-RECHALLENGE EXPERIMENT *Statinovigilance - Démence*
« Our pilot study found an improvement in cognition with discontinuation of statins and worsening with rechallenge. Statins may adversely affect cognition in patients with dementia[833] »
problèmes cognitifs sous statines : une expérience par déchallenge et rechallenge

STATIN-RELATED COGNITIVE PROBLEMS : VIGNETTES *Statinovigilance*

« It took me a long time to realize I had statin-related cognitive impairment because I had no idea what it was… A few years ago, I found myself slowly sinking into a sea of troubles. My work productivity gradually slumped, I had trouble remembering names and appointments, and I started having more trouble designing technical solutions for my clients. I had less energy for my family, and I felt grumpy and depressed about it…

I didn't connect my problems with the statin I'd been taking until I ran out of pills and kept forgetting to pick up my refill. One day, I noticed that driving was enjoyable again... The decline had been so gradual that I hadn't really noticed it. Then, suddenly, after failing to take my statin for a few days, I was processing information in my peripheral vision so much more efficiently that I could change lanes without feeling anxious. That's when I figured it out...

This wasn't the first time I had run out of pills and wondered whether my statin was to blame for my mental decline. At that time, my physician had reassured me that there was no evidence for such side effects. Now, I was sure that the drug was to blame… So we decided that I should give up the statins altogether…

There are a few things I'd like medical professionals to take away from reading this. Please take seriously any symptoms your patients think might be related to use of a statin. When it comes to known side effects, please make sure we understand what they are. Patients may not know what cognitive impairment is; if we have statin-related cognitive impairment, we're unlikely to recognize it unless you alert us »[834]

« A lawyer contacted Beatrice Golomb, a physician at the VA San Diego Healthcare Center, because he could no longer follow a normal conversation with his clients…
A radiologist told BG that he found himself suddenly unable to distinguish left from right…
A 3rd person told her he had grown so forgetful that his doctor assumed he had Alzheimer's…

All three had developed their memory problems after taking a cholesterol-lowering statin drug, and the symptoms improved after they stopped the medication ….[i.e. positive dechallenge]»[835]

« This personal misadventure started about 4.5 years ago when my doctor read me the 'riot act on my cholesterol numbers'. The upshot was that my doctor put me on a whopping dose of the most powerful statin drug, Crestor™ 40mg (rosuvastatin). I left his office feeling like my identity was transformed from a healthy normal person to a prisoner on death row…

Then I was having trouble remembering things, names especially, and at times felt like my brain was fogged. I developed neuropathies (tingling and numbness) in my hands and feet. I grew suspicious that these things were connected with the whopping dose of Crestor™ that I was on. I then decided to taper down and get off the stuff. By September it was out of my system. My doctor was rather cross with me...

He assured me that an LDL level above 70 mg (1.8 mM) was a death sentence, should I get back there. Over the next 6 months, the brain fog and the name-forgetting went away [positive dechallenge] »[836]

« I have a friend who was put immediately on Lipitor™ and the usual array of blood pressure and other meds after suffering a mild stroke. He instituted major lifestyle changes and was able to find a physician to do a drug review. Something he had complained about was cognitive deficits and difficulties reading and understanding different text which made me feel the Lipitor™ could be contributing significantly rather than the stroke impacts…

[833] Padala et al. Am J Geriatr Pharmacother 2012; 10: 296 - http://dx.doi.org/10.1016/j.amjopharm.2012.08.002
[834] Jonathan McDonagh. JAMA Intern Med 27, 2014 - doi:10.1001/jamainternmed.2014.5376
[835] http://www.washingtonpost.com/national/health-science/statins-keep-cholestrol-in-check-but-they-can-affect-memory-and-strength/2013/03/11/8b1ad74a-82b8-11e2-a350-49866afab584_story.html
[836] http://redgreenandblue.org/2012/03/20/james-howard-kunstler-all-is-swindle-from-goldman-to-statins/

He stopped the Lipitor™ a number of weeks ago and he describes his thinking as being totally different - clearer, more incisive- like his old self. He describes this as being miraculous [positive dechallenge]. His cholesterol levels are good. So how many people on statins are operating below par but don't even know it? He wouldn't have discovered it if I hadn't known about this adverse drug reaction, and talked to him, and if he hadn't been able to find a physician who was willing to explore it »[837]

« My doctor pointed out that my cholesterol levels were high and that I should take some sort of medication to reduce the cholesterol level. There was nothing wrong with me, apart from high cholesterol. I took the doctor's advice and began taking a statin. After about 2 weeks I was having a difficult time walking in the daytime, and at night I had trouble sleeping, my legs ached. I was definitely experiencing a memory loss...

I didn't feel that I could recall things as clearly as I did before I was taking the statin. I decided to stop taking the medication. I started feeling better after about 3 weeks to maybe a month afterwards [positive dechallenge]. It took 6 months to get 100% better »[838]

« I have always had an excellent memory and cherished this as part of my job as Professor of Biomolecular and Cellular Science. After I started to take atorvastatin 20 mg a day, I started to forget dates, places and even the names of close relatives. At work I was unable to recall the names of colleagues as well as of my PhD and undergraduate medical students. My confidence was drained and I became withdrawn - 'a hermit' in the workplace…

Things came to a head when I was travelling to an international scientific meeting in France, which I was chairing. I arrived by plane at Charles De Gaulle Airport and suffered a complete memory blackout and utter confusion. I had no idea why I was in France. It was not until I found TGV tickets in my pocket that I realised that I had a train to catch...

I slowly pieced together the reason that I was in France and attended the meeting. I went to see my GP and fortunately he had a healthy approach to this class of drugs - and more importantly, were willing to listen to me. We agreed that I should stop the statin, which I did. I've now been free of statins for four years and my cognitive function and memory have improved immensely [positive dechallenge]»[839]

vignettes de problèmes cognitifs par statinisation

* un déchallenge positif, tel qu'observé dans ces vignettes, est un argument fort en faveur d'un lien de causalité et ne peut être qualifié péjorativement d'anecdote, surtout que ces observations cliniques sont spécifiques et nombreuses

STATINATOR

= enthousiastic and uncritical prescriber of statins in patients unlikely to benefit medically from being dragged into statinotherapy for life ; that prescriber is implicitely a hypercholesterolist and often a key opinion leader

statinisateur ; statinateur ; statinien ; meneur d'opinion en statinisation et prescripteur convaincant

* ils peut être influent à l'échelle régionale, nationale ou mondiale

STATINIC BULLSHIT *Meneur d'opinion sponsorisé – Fausses affirmations – Dénigrement de la critique – Ignorance méthodologique, épidémiologique et pharmacologique*

« In Portugal, for example, scientific advances have pushed the average life expectancy from 68 years to 81 years between 1970 and 2017... About 80% of this improvement is due to the extraordinary advances in the diagnosis and treatment of CV diseases … and in the identification of "risk factors", especially *levels of fat.* Controlling these fat levels through medications called "statins" plays a critical role. In fact, most leading physicians today say that after antibiotics, *statins have contributed more* to prolonging life expectancy than any other type of medication (sic)...

Statins *dramatically* reduces the risk of "major vascular events", including *death* from heart attack and stroke. The use of a statin administered for 5 years to 10,000 people with known vascular disease would prevent major vascular events in 1,000 patients [NNT = 50 patient-years]. And this benefit increases for every year the medication is taken. Statins have side effects… the most serious are called "myopathies" (muscle pains, with evidence of muscle lesions) which occur in about 5 patients out of every 10,000 by the end of 5 years of continuous treatment [NNH = 10 000 patient-years]…

The world's major CV societies, including American, Canadian, European (which I chaired) and Asian, have expressed a clear position in support of statins in their respective clinical practice guidelines… The question then is: why do statin *disinformation campaigns* persist, some even organised by people linked to the medical profession? Why are they putting patient lives at risk?

[837] Janet Currie, 2013

[838] http://www.abc.net.au/catalyst/stories/3881441.htm#.UnKSgZv3koQ.twitter

[839] Andrew Demaine. http://www.bmj.com/content/348/bmj.g1520/rr/692195

Why do people insist on denying *irrefutable* evidence… on what has been one of the great successes of modern medicine…

We cannot forget that what took us out of the Middle Ages was the application of scientific method.. which has enabled the extraordinary health gains that we now enjoy. Challenging the value of statins is comparable to denying the extraordinary impact that antibiotics and vaccines have had on our civilisation. It's like *questioning whether man ever landed on the moon*...

The most serious consequence of this latest disinformation campaign is that we have clear evidence that when patients with heart disease stop taking their statins it significantly increases the number of cardiac events they are likely to suffer. In other words, many people will die, unfortunately, because they listened to the *statin naysayers*. Statins are the most precious weapon we have in the fight against CV diseases...[840] »

connerie statinique

* On aimerait bien savoir combien le personnage a reçu des fabricants de statines. On croirait lire un éditorial commandité préparé par une agence de marketing. Même remarque pour les sociétés de cardiologie. Mis à part les chiffres erronés, on mélange joyeusement *événements* avec *décès*, comme on le voit souvent dans les critères d'évaluation combinés

STATINIC MYALGIA FREQUENCY *Statinovigilance*

« Statin-induced myalgia is a major cause of statin intolerance and is common; it is reported in 27%[841] of subjects treated with statins … In a retrospectively studied a cohort of 1,160 subjects taking statins, 24%[842] developed statin-induced myalgia, myositis, myopathy, and/or myonecrosis »[843]

fréquence de la myalgie statinique

STATINIC TENDINOPATHIES

tendinopathies statiniques

« Il s'agit d'un effet de classe a priori non dose-dépendant avec un délai moyen d'apparition de 8 à 10 mois. On note une rupture dans un tiers des cas ainsi qu'une localisation calcanéenne dans 52% des cas, le plus souvent unilatérale (58,7% des cas). Les localisations similaires à celles rencontrées avec les fluoroquinolones comprennent en plus le tendon biceps brachial et le moyen fessier...

La physiopathologie bien que non établie, reposerait sur une altération de la composition de la matrice extracellulaire, une majoration de l'activité des métalloprotéases, une action délètère sur la croissance et la différenciation des téno- cytes possiblement lié à une modification de leur contenu lipidique intracellulaire et membranaire. Les facteurs de risque sont l'âge avancé, une tendinopathie préexistante, une activité physique intense ainsi que l'association à une FQ »[844]

« Une centaine de tendinopathies attribuées aux statines furent notifiées en France entre 1990 et 2005[845] :

a) 59% apparues dans la première année de traitement, délai moyen d'apparition de 8 mois
b) aucun ne prenait d'autre médicament reconnu capable d'entraîner cet EIM (telle une fluoroquinolone)
c) 21 ont présenté une rupture d'emblée, 12 une rupture après tendinite (la rupture apparaît surtout dans les 2 premières semaines), et 63 une tendinite sans rupture

d) 50 cas impliquaient le tendon d'Achille (calcaneum) et 14 cas le quadriceps fémoral
e) atteinte bilatérale chez 26 patients
f) délai moyen de régression de 23 jours après l'arrêt : le *déchallenge positif court* est un argument *fort* en faveur de la causalité

g) chez tous les 7 patients qui reprirent une statine, la tendinopathie est *réapparue dans 100%* des cas : ces *rechallenges positifs* sont des arguments *très forts* plaidant pour un lien de causalité de 4/4 (certain, *definite*)
h) les 5 statines impliquées étaient prises à dose normale

En date de 2009, les tendinopathies ne figurent pas dans les comptes-rendus d'essais cliniques, appuyant l'hypothèse que ces essais n'ont pas la puissance de détection suffisante pour s'assurer de la sécurité de ces produits. Au 31.3.2006 la FDA avait déjà recensé 247 observations, selon RC Pullan et coll. qui ont rapporté cet EIM sous simvastatin/ezetimibe (*Am J Car*diol 2007 ;

[840] Fausto Pinto, 19.10.2017 - Professor and director of the Faculty of Medicine of the University of Lisbon; director of the Cardiology Service and the Heart and Vessels Department of the North Lisbon Hospital Centre; president of the European Society of Cardiology (2014-16)
[841] Vandenberg BF, Robinson J. Curr Atheroscler Rep 2010; 12: 48
[842] Palamaner et al. PLoS One 2014; 9: e88877
[843] Maksim Khayznikov et al. N Am J Med Sci 2015 ; 7(3): 91
[844] Échos de Pharmacovigilance (Strasbourg), n. 11, Mai 2015
[845] Prescrire 2010 ; 30(315) : 29

100 :152). Marie et Noblet ont publié 96 notifications survenues entre 1990 et 2005 (*Arthritis Rheum* 2008 ; 59(3) : 367) »…

Noter que l'absence de tendinopathies dans les ECC statiniques peut relever soit de raisons méthodologiques inévitables (rareté de l'EIM, sélection des patients, effectif insuffisant, etc.), soit parce que ces EIM ont été volontairement *occultés* des publications en les noyant sous le vocable non spécifique de 'problèmes musculosquelettiques' ou en les excluant des EI, ce qui équivaut à tricher

STATINISATION IN LONG TERM CARE UNITS
la statinisation en unités de soins de longue durée
* Les réducteurs de cholestérol n'y ont guère leur place, même quand on utilise des produits génériques moins chers. Un psycho-gériatre[846] 'se demande pourquoi on s'obstine à donner de l'atorvastatine (Lipitor™), une statine vedette, à des personnes atteintes de démence à des stades avancés'

« Premièrement, parce qu'il est peu logique de vouloir retarder théoriquement la survenue d'un accident coronarien de quelques jours ou semaines ou mois, quand la qualité de vie est franchement négative, comme c'est le cas lorsqu'on ne marche plus, ne parle plus et ne comprend plus, ou quand l'espérance de vie est ostensiblement compromise par une polypathologie et le vieillissement de tous les organes...

Ce qui n'empêche pas, soit dit en passant, que dans des hôpitaux états-uniens pour vétérans[847], 52% des patients ainsi compromis reçoivent une statine durant les 6 derniers mois de leur vie », une pratique aberrante

« Secondement, parce que les statines en prévention primaire – donc chez des sujets sans antécédent de maladie coronaire - ne prolongent de façon tangible ni l'espérance de vie, ni sa qualité chez les femmes, majoritaires dans ce milieu, même en dehors des unités des soins de longue durée. Pas plus qu'elles ne prolongent la vie ou sa qualité en prévention secondaire dans les deux sexes »[848]

« Ceci est tellement bien établi que la FDA (Agence états-unienne du médicament) oblige dorénavant de mentionner dans la publicité sur l'atorvastatine - ne serait-ce qu'en caractères illisibles sans loupe grossissante - que le produit n'est pas indiqué pour prévenir la mortalité coronarienne et que les résultats (pourtant cités dans l'annonce) ne sont pas concluants chez les femmes »[849]. L'incohérence tolérée témoigne de la pharma-co-dépendance des patrons de la FDA, à la Maison Blanche…

« Pour rappel, chez les très âgés comme on en retrouve en unités de soins de longue durée, un trop bas cholestérol est biologiquement de mauvais présage car la mortalité augmente quand le cholestérol total est sous la barre de 5,5 mmol/l »[850] - « Il y a pourtant des prescripteurs au cerveau bien lavé par l'idéologie dominante, qui s'énervent devant un tel niveau »[851]

« C'est pourquoi l'on devrait exhorter les assurances publiques comme privées à ne plus rembourser aux unités de soins de longue durée les ordonnances de statines, sauf sur justification médicale chez des coronariens moins âgés et sans démence avancée, et à condition d'utiliser la version générique la moins chère...

Et j'exhorterais aussi les collègues à ne plus renouveler les ordonnances de statines dans ce milieu, sauf dans des cas d'exception. L'argent récupéré en cessant les statines permettrait d'engager davantage de personnel soignant et de mieux le former »[852]

STATINISATION IN PRIMARY PREVENTION, WHAT AN INCREDIBLE WASTAGE *Lipidologie – Prévention primaire – Pharmacoéconomie*

« Of 1000 people treated with a statin for 5 years, 18 would avoid a major CVD event »,[853] conclude the authors of a Cochrane

[846] Jacques Potvin interviewé par Denis Méthot dans L'Actualité médicale (Montréal) du 8.9.2010 page 6
[847] Silveira MJ et al. Statins in the last six months of life. J Palliat Med 2008;11(5)
[848] James Wright, Therapeutics Letter 77: Mars-Avril 2010 Do statins have a role in primary prevention? An update, disponible sur http://ti.ubc.ca/letter77
[849] http://pharmacritique.20minutes-blogs.fr/archive/2011/08/23/la-pharmaco-prevention-dans-les-unites-de-soins-de-longue-du.html
[850] LK Petersen, K Christensen, J Kragstrup. Age and Ageing 14.10.2010 p.1-7. Lipid-lowering treatment to the end? - E Vos & P de Groot. Neurology 11.6.2007 Low LDL cholesterol, statins, and brain hemorrhage: Should we worry? Disponible sur http://www.neurology.org/cgi/eletters/68/10/719#7946 – Noda et al. Circulation. 2009;119:2136-2145 The Ibaraki Prefectural Health Study
[851] Oliver M. BMJ 2009;338:b873
[852] Biron P. Site http://pharmacritique.20minutes-blogs.fr/archive/2011/08/23/la-pharmaco-prevention-dans-les-unites-de-soins-de-longue-du.html
[853] Taylor et al. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub5

meta-analysis published in issue I, 2013 of their Library, giving an NNT_{exp} of 277 person-years in experimental conditions and – accounting for all the numerous explicative and pragmatic biases known to plague statin controlled trials – a plausible NNT_{clin} of 416 to 554 person-years in daily clinical practice…

if you admit that *effectiveness* in real life is 1.5 to 2 times lower than efficacy in artifical conditions. If you dont admit it, its time to read the methodology section of those trials that were meta-analysed and look for biases and conflation …

« Based on a 2011 Cochrane[854] review of trials for primary prevention, there has been recent enthusiasm that for people without a history of heart disease statins can relatively reduce premature deaths by 17%, coronary heart disease by 28%, strokes by 22%, and revascularisation by 34%...

Yet a close reading of the tables from that systematic review suggests the estimated absolute risk reductions with around 4-5 years of drug taking are 0.5% for death, 1.9% for coronary heart disease, 0.5% for stroke, and 0.7% for revascularisation…

The estimated NNT for 4 to 5 years thus ranges from 50 to 200 depending on the outcome measure. So according to this evidence, most people taking long term statins for primary prevention gain no direct benefit »[855]

"Based on a 2011 Cochrane review of trials for primary prevention, most people taking long term statins for primary prevention gain no direct benefit. The magnitude of the benefit in absolute terms is extremely small for those at low risk"[856]
"Statins had not been found to reduce total or coronary mortality in women, men, or combined, for primary prevention"[857]

"Cardiologists like statins more than their patients[858]"
"Treating high cholesterol in older well people is unconscionable"[859]

« In individuals with 5-year risk of major vascular events lower than 10% [< 2% per year], each 1 mM reduction in LDL cholesterol produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years [or 11 per 5000 patient-years, NNT = 455 patient-years]. This benefit greatly exceeds any known hazards of statin therapy »[860] conclude the authors of a 2012 meta-analysis

* The direct and indirect costs are not justified and an NNT > 100 in experimental conditions is clinically irrelevant to medical practice (where it may reach 150 or 200 patient-years, who knows). At a conservative 500$ total expenditures per year (blood tests, medical visits, drug costs), avoiding one event costs 2.28 M dollars
« Healthy men should not take statins » titles a *JAMA* 2012 article[861]

"Cardiologists have told me to my face 'You cannot tell patients that [i.e. the large NNTs], because they will not take it [the statin]'. That is the degree of zeal they have… Research has not shown efficacy in the primary prevention setting … John PA Ioannidis, of Stanford, is leery of the use of industry-sponsored research to support the arguments for primary prevention… We do not really know if statin therapy works in primary prevention. It is just that the evidence is not available to support it"[862]

"Although Americans take billions of dollars worth of statins per year, their average life expectancy is less than Cubans who take none[863]"

« Dr. John Abramson, health policy lecturer at Harvard University, estimates that a person without existing CV disease can get as much benefit from a brisk daily 10-minute walk as from a daily statin pill – and without the potential side effects. Smoking cessation and weight loss would have even more dramatic effects. Statins are not magical medications for prevention of heart disease. They give the illusion of protection. It is a costly illusion that needs to be shattered »[864]

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[854] Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of CV disease. Cochrane Database Systematic Review 2011; 1: CD004816 - Deckers J, Blumenthal R. Statins for primary prevention of CV disease. BMJ 2011;342:d1048
[855] Ray Moynihan. http://www.bmj.com/content/343/bmj.d5160
[856] Taylor F et al. Statins for the primary prevention of CV disease. Cochrane Database Systematic Review 2011; 1: CD004816 - Deckers J & Blumenthal R. Statins for primary prevention of CV disease. BMJ 2011;342:d1048 - Cités par Ray Moynihan 2011
[857] S Mora. Circulation, 22.2.2010 on line, Medline 20176986
[858] Nortin Hadler. Worried Sick, p 41
[859] Hadler, Rethinking Aging, page 43
[860] CTT Collaborators, 17.05.2012 - http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60367-5/fulltext
[861] Rita F. Redberg & Mitchell H. Katz. JAMA. 2012; 307(14): 1491
[862] Mike Mitka 2011. Quoting Lee A Green, an Ann Arbor family hysician
[863] Colin Rose, communication
[864] André Picard, 2013 at http://www.theglobeandmail.com/authors/andre-picard

« We found no benefit in total mortality in primary prevention... in healthy people. Our job as physicians is to help them feel better or live longer. Statins do not help … Claims of benefit attributed to statin therapy in the primary prevention setting tend to be inferred from less-than-robust subset analyses or meta-analyses of clinical trials… leading to a costly lifetime drug regimen that may cause adverse effects and does not lenghten life »[865]

« Dr Rita Redberg of University of California in San Francisco argues against the current practice of prescribing statins to patients with CV risk factors, including individuals with elevated cholesterol levels. She said that there are too many low-risk individuals taking statins, and they simply don't get a benefit. In these low-risk/low-benefit patients, given the residual risk of statins, benefit is exceeded by harm…

Despite research that has included tens of thousands of people, there is no evidence that taking statins prolongs life, although cholesterol levels do decrease, she writes, using the most optimistic projections, for every 100 healthy people who take statins for 5 years, 1 or 2 will avoid a heart attack [NNT 250-500 patient-years, a ridiculously small average life extension of 35 to 18 hours]...

One will develop diabetes [NNH 500 patient-years]. But, on average, there is no evidence that the group taking statins will live any longer than those who don't »[866]

« Australia had one of the highest rates of statin use in the world, and people who were not at high risk of heart disease need to reconsider using them … Statins have long been touted as a miracle drug, with some doctors and researchers pushing for their use in all older people, but that is unwise », says Australian clinical pharmacologist David LeCouteur in 2012

« Statins have not been shown to provide an overall health benefit in primary prevention trials »,[867] concludes an independant Canadian clinical pharmalogist and drug evaluator

« Based on a Cochrane review of trials for primary prevention, there has been recent enthusiasm that for people without a history of heart disease statins can reduce premature deaths by 17%, coronary heart disease by 28%, strokes by 22%, and revascularisation by 34%...

Yet a close reading of the tables from that systematic review suggests the estimated absolute risk reductions with 4-5 years of drug taking are 0.5% for death, 1.9% for coronary heart disease, 0.5% for stroke, and 0.7% for revascularisation...

The estimated number needed to treat for 4-5 years thus ranges from 50 to 200 [NNT around 450 patient-years] depending on the outcome measure. So according to this evidence, most people [449 out of 450 annually] taking long term statins for primary prevention gain no direct benefit »[868]

« Primary prevention with statins provides only small and clinically hardly relevant improvement of CV morbidity/mortality » according to a 2003 meta-analysis[869]

« Statin use in primary prevention remains controversial »[870]
"For primary prevention, whatever the level of LDL cholesterol, men over 65 years of age, and women of any age who take statins receive no benefit"[871]
la statinisation en prévention primaire, quel incroyable gaspillage
* De plus en plus d'experts indépendants, dont Michel de Lorgeril en France et Uffe Ravnosk au Danemark sont des chefs de file, remettent en cause l'effectivité des statines, notamment chez les séniors (les plus de 70 ans pour faire simple), les femmes de tout âge, et les enfants

« Les statines tiennent un rôle critique dans le traitement de quelques maladies congénitales rares du métabolisme du

[865] Mike Mitka 2011. Quoting Rita Redberg
[866] Michael O'Riordan quoting Blumenthal RS & Redberg R. Should healthy people take cholesterol drugs to prevent heart disease? Wall Street Journal, January 23, 2012
[867] http://www.ti.ubc.ca/pages/letter48.htm
[868] Roy Moynihan. http://www.bmj.com/content/343/bmj.d5160
[869] Vrecer et al. Int J Clin Pharmacol Ther 2003; 41(12): 567 – Summary at http://www.ncbi.nlm.nih.gov/pubmed/14692706
[870] Morgan et al. The Canadian Rx Atlas, 3rd ed. 2013 - http://www.chspr.ubc.ca/pubs/atlas/canadian-rx-atlas-3rd-edition
[871] James Wright. Protégez-Vous, Fév. 2010, interview traduit par Carol Kuschner

cholestérol et un rôle moindre dans la prévention secondaire permettant d'éviter une deuxième crise cardiaque »[872] , mais il faut prendre garde d'extrapoler les bénéfices limités mais reconnus dans l'hyperlipidémie familiale, et reconnus mais minuscules en prévention secondaire ciblée sur les coronariens pas trop âgés

« Si on prend l'exemple des statines, une bonne partie des prescriptions sont inutiles, ne devraient pas avoir lieu »[873] déplore en France un pharmaco-épidémiogiste ex-doyen de faculté

* Quand un cardiologue prescrit de bonne foi une statine à une personne à faible risque, donc en prévention primaire, il croit se baser sur la science sans réaliser qu'il est alors motivé par le santéisme biologique, en plus d'être manipulé par un savoir médical dévoyé par les entreprises et leurs complices

« L'hypolipémiant, médicament symbolique puisque protecteur autant qu'une hostie, mange la plus grosse part du budget pharmacie de nos Sécus. On sait qu'il faut traiter 1 000 patients hyperlipémiques pendant 5 ans pour éviter 18 événements CV graves [NNT = 278 personnes-année]...

Comme dans tout médecin, il y a un docteur Knock qui sommeille, l'hypertension et l'hypercholestérolémie, affections sans symptômes, ont pris les premières places dans quasi tous les pays du monde comme raisons de rencontre avec le médecin[874] », commente le père de la prévention quaternaire

* Les statines en prévention primaire, quelle futilité. D'utilité probablement minime à nulle en prévention secondaire chez les femmes, et chez les hommes > 75 ans. Les NNT dépassent trop souvent le seuil de 50 à 100 personnes-année en situation expérimentale (et probablement le seuil de 75 à 200 personnes-année en situation clinique) ; cette ineffectivité s'accompagne de coûts directs et indirects inacceptables, sans compter les EIM dont la fréquence est sous-estimée par les prescripteurs…

« Le paradoxe est que les pays où l'exposition aux statines est la plus élevée sont aussi parmi ceux qui ont la plus forte mortalité cardio-vasculaire »,[875] les ÉU ont occupent le 2e rang pour le taux de mortalité coronarienne < 50 ans parmi les pays riches[876] --- « Il serait facile d'économiser des fortunes – directement et indirectement en coût iatrogène - en restreignant les statines »[877] et pourquoi pas celui des cholestérolémies de dépistage !

STATINIZATION
statinisation (UK)

1. At the population level
« = massive use at the population level. It is uncertain whether this would be one of the greatest achievements or one of the worst disasters of medical history »[878]
statinisation

2. At the client/patient level
statinisation
« La science indépendante dit qu'en prévention secondaire, les statines ne sont probablement pas utiles et qu'en prévention primaire, les statines n'ont pas d'utilité »[879]

STATINIZATION FOR LIFE
= prescription of statinotherapy for a lifetime

* too often in persons unlikely to benefit medically (qualify of life, lifespan) such as healthy men and women, coronary women of any age, men > 75 years (even coronary men's benefit is marginal and doubtful); often exposing them to adverse reactions; always costing much more than public drug plans can reasonably afford
statinisation pour la vie
= la mise en statinothérapie pour la vie; trop souvent de personnes qui n'en tireront pas de service médical tangible (qualité de

[872] Hadler. Le dernier des bien portants, p. 43
[873] Bernard Bégaud. Cité par Éric Favereau 3.1.2005 pour Libération
[874] Marc Jamoulle 2013 sur http://pratiques.fr/-Pratiques-No-63-En-faire-trop-.html
[875] Marc Girard. http://www.rolandsimion.org/spip.php?article275
[876] http://www.nap.edu/catalog.php?record_id=13497
[877] Marc Girard. http://www.rolandsimion.org/spip.php?article275
[878] Ioannidis JPA. JAMA 2014; 311(5): 463 - doi: 10.1001/jama.2013.284657
[879] Mikael Rabaeus, 2012

vie, espérance de vie), comme les bien portants de tout sexe et de tous âges, les coronariens > 75 et les coronariennes de tous âges (il n'y a pas d'essais ayant randomisé seulement des femmes, par crainte des résultats…)

« Faudrait s'interroger sur cette étrange perversité qui conduit les gens en parfaite santé à dilapider une part sans cesse croissante de leurs ressources (je ne parle pas de leur qualité de vie) sous le vaseux prétexte d'une prévention tentaculaire par les hypocholestérolémiants »[880]

STATINIZATION OF ELDERLIES
« Evidence of protection by primary prevention with statins in the elderly is lacking … Preventive use of statins shows no overall benefit in elderly people as CV mortality and morbidity are replaced by cancer[881]», a good reason to stop cholesterol screening after 75 even in men

« Data support removing older men from the cholesterol guidelines if extending life is a patient criterion »[882]
« In an Australian cohort of 677 community-dwelling well-elderly (mean 78.3 years), statin-use was associated with greater decline in memory at 4 years (-0.27, p<0.001) »[883]

« Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy. There is no evidence that hypercholesterolemia, or low HDL-C, is an important risk factor for all-cause mortality, coronary heart disease mortality, hospitalization for myocardial infarction or unstable angina in persons > 70 years...

In fact, studies show that elderly patients with the lowest cholesterol have the highest mortality after adjusting other risk factors. In addition, a less favorable risk-benefit ratio may be seen for patients older than 85, where benefits may be more diminished and risks from statin drugs more increased (cognitive impairment, falls, neuropathy and muscle damage)[884] »
statinisation des gens âgés
« La preuve n'est pas faite que la prévention primaire statinique protège les gens âgés », une bonne raison pour abandonner le dépistage du cholestérol après 75 ans même chez les hommes

STATINIZATION OF MYOCARDIAL INFARCTION SURVIVORS *Prévention secondaire*

« The most recent and less objectionable clinical trials have demonstrated no impact of cholesterol reduction on the risks of MI or stroke recurrence. Only self-delusional blindness could excuse advocating that MI survivors take a statin. It is a scientific aberration and doctors should case to prescribe statins to these patients, without exception, and whatever their underlying pathology : renal failure, heart failure or diabetes »[885]
la statinisation des survivants d'un infarctus du myocarde

STATINIZATION OF WOMEN AND SCIENTIFIC TRANSPARENCY
« Petretta et al. have revealed the disturbing persistence of an on-going problem of non-disclosure of gender-specific results, which has affected previous meta-analyses... Criqui and Golomb raised the urgent issue of their unsuccessful attempts to access gender-specific total mortality data from the Cholesterol Treatment Trialists Collaboration... Similar frustration was also expressed by Walsh and Pignone…

In 2007, Abramson and Wright urged the release of data on total mortality, total serious adverse events, total incidence of cancer, and total CV events for primary prevention subpopulations including women… We see a pattern of overestimation of benefit [aka conflation], aggressive marketing, failure to disclose relevant data and an insufficient attention to adverse events »[886]
statinisation des femmes et transparence scientifique

STATINIZATION SCAM
l'arnaquerie / l'escroquerie de la statinisation

STATINIZATION, CORONARY CALCIFICATION AND CARDIOMYOPATHY *Statinovigilance – EIM paradoxaux*

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[880] Marc Girard. http://www.rolandsimion.org/spip.php?article275
[881] Mangin et al. BMJ 2007 ; 335 : 285
[882] Vos E. NMCD 2007 ; 17 : e19
[883] Samaras et al. at https://endo.confex.com/endo/2014endo/webprogram/Paper14285.html
[884] http://www.choosingwisely.org/wp-content/uploads/2013/09/AMDA-5things-List_Final.pdf
[885] de Lorgeril 2014, op. cit.
[886] Rosenberg et al. Int J Cardiol 2009 : 145 - doi:10.1016/j.ijcard.2008.12.122

« In contrast to the current belief that cholesterol reduction with statins decreases atherosclerosis, we present a perspective that statins may be causative in *coronary artery calcification* and can function as mitochondrial toxins that *impair muscle function* in the heart and blood vessels through the depletion of coenzyme Q_{10} and 'heme A', and thereby ATP generation...

Statins inhibit the synthesis of vitamin K_2, the cofactor for matrix Gla-protein activation, which in turn protects arteries from calcification. Statins inhibit the biosynthesis of selenium containing proteins, one of which is glutathione peroxidase serving to suppress peroxidative stress. An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure, reminiscent of the dilated cardiomyopathies seen with selenium deficiency...

Thus, the epidemic of *heart failure* and *atherosclerosis* that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs. We propose that current statin treatment guidelines be critically reevaluated »[887]
statinisation, calcification coronaire et affaiblissement du muscle cardiaque

STATINIZED CHILDREN *Surmédicalisation - Surmédicamentation*
statinated children
« Giving statins to children is like teaching fat kids to practice bulimia; it will be of unproven benefit to all, somewhat harmful to many, very harmful to some, and fatal to a few; exercise and sensible eating make rather more sense »[888]
enfants statinisés
« Donner une statine à un enfant est déraisonnable car leur cerveau est encore en développement et a besoin de la production intracellulaire de cholestérol. Et les autres cellules, ne pouvant incorporer le cholestérol circulant à cause de la déficience du récepteur de LDL-C, ont encore plus besoin du cholestérol produit 'localement', cad intracellulairement mais bloqué par la statine, donc 'doublement bloqué'»[889]
SCREENING IN CHILDREN *Recommandations incohérentes – Collusions institutionnelles – Lipidémie de dépistage - Surdiagnostic*
« Universal pediatric lipid screening is advised by the National Heart, Lung, and Blood Institute (NHLBI) for those aged 9 to 11 years and 17 to 21 years, in addition to the selective screening advised by the American Academy of Pediatrics (AAP) and the American Heart Association (AHA). In contrast, the US Preventive Services Task Force (USPSTF) did not find sufficient evidence to recommend any pediatric lipid screening »[890]
dépistage chez l'enfant
* une connerie de plus en lipidologie ; seule une institution en dépendance financière, politique ou intellectuelle avec les fabricants peut promouvoir ce dépistage

STATINIZED WOMEN *Médicalisation – Médicamentation – Pharmaco-prévention futile et nuisible*
statinated women

« Far too many healthy women are taking statins… that may be more likely to cause serious side effects in women … 'If you're going to tell a healthy person to take a medicine every day for the rest of their life, you should have really good data that it's going to make them better off' said Dr. Rita Redberg, a cardiologist at the University of California, San Francisco, and the editor of JAMA Internal Medicine….

Lowering cholesterol should not be not an end in itself, she added, and cholesterol may not play the same role in heart disease in women as in men. 'You can have high cholesterol and still be really healthy and have a low risk of heart disease' she said… Women tend to develop heart disease about 10 years later in life on average than men; women's risk begins to equal that of men when they reach their mid-70s...

Studies have found that healthy women who took statins to prevent CV disease did experience fewer episodes of chest pain and had fewer treatments like stents and bypass surgery. But statins didn't prevent healthy women from having their first heart attacks and didn't save lives.. The Jupiter trial, which included 6,801 women age 60 and older, found a significantly lower risk of so-called soft endpoints, like hospitalization for unstable angina, among healthy women taking statins...

But the absolute number of these health setbacks was small, and there was no significant reduction in heart attacks, strokes and deaths among these women. 'The data are underwhelming, to say the least' said Dr. Barbara Roberts, author of The Truth About Statins: Risks and Alternatives to Cholesterol-Lowering Drugs and an associate professor of medicine at Brown University...

'Women who are healthy derive no benefit from statins, and even those women who have established heart disease derive only

[887] Okuyama et al. Expert Rev Clin Pharmacol 11.1.2015 - doi: 10.1586/17512433.2015.1011125
[888] Warren Bell. Communication. Author is general practitioner in British Columbia (CA)
[889] Paul v Nguyen, 2014
[890] Vinci et al. JAMA 2014; 311(17):1804 -doi:10.1001/jama.2014.241

half the benefit men do'…

The debate has taken on added urgency because of the risks associated with statins, which often are supposed to be taken daily for the rest of one's life. The drugs have long been known to cause muscle pain in some people and, more rarely, liver and kidney damage, as well as cognitive side effects like memory loss and confusion...

In 2010, Johns Hopkins researchers discovered that statins could, in rare instances, make the body produce antibodies against its own proteins, engendering a painful and debilitating muscle disease that actually gets worse when patients stop taking the drugs...

But the most common side effect is diabetes. In 2012, researchers published a study showing that postmenopausal women who took part in the Women's Health Initiative were much more likely to develop diabetes if they took statins, and diabetes itself increases the risk of heart disease considerably. Despite the concerns, women are heavy users of statins, especially in midlife — when the gap in heart disease risk between men and women happens to be greatest…

'I have women come to me who were put on statins in their 30s by their physician because their cholesterol was a point or two above what's said to be normal' Dr. Roberts said. 'This is insane'. She advises women that they can reduce their heart risk by watching their weight, exercising and following a diet rich in fish, fruits and vegetables, nuts and olive oil — and, if they've never had heart trouble, forgetting statins...

'We know you can get the benefit and relative risk reduction from adhering to a Mediterranean-style diet' she said »[891]
« Studies have not shown that statin treatment reduces total mortality in women »[892]

« The meta-analyses of primary prevention clinical trials show benefits for men but not for women, and a difference between men and women. The analyses do not support statin use to reduce heart attacks in women based on extrapolation from men… Billions of health-care dollars may be being wasted on statin use by women but the current regulatory regime does not create incentives to prevent such behavior »[893]

* Even in secondary prevention statins did not reduce relative risk of total mortality in women (RR, 0.92, NS) vs. men (RR, 0.79, significant) or stroke (RR, 0.92, NS in women) vs. RR, 0.81 [95% CI, significant in men)… In secondary prevention, according to a 2012 meta-analysis by Guttierez :[894] « The stratification by sex showed no relative risk reduction for women taking statins compared with women taking placebo for the reduction of total mortality and any type of stroke »

"There are no statin trials with even the slightest hint of a total mortality benefit in women and women should be told so[895]"
« When you actually look at the evidence, there are no good studies showing that statins are a benefit for women at any age »[896]

"Every week in clinic I see patients who are suffering severe adverse effects of statins, and most of them are incredibly low-risk patients, most of them are women, who I think, unfortunately, suffer more adverse effects from statins, which is ironic because women are at a much lower risk than men from coronary disease anyway…

None of the trials in primary prevention have shown a reduction in heart disease and none of them in women. None of them have shown a reduction in total mortality in men or women. What this means for women is that they are much more likely to be getting adverse events and not likely to get any benefit at all from treatment"[897]

« Statin studies are often not planned to reveal possible differences in treatment effects between women and men. No primary preventive reduction of CV mortality or incidence of nonfatal AMI has been shown in women »[898]

« Right now the evidence has not supported benefit to women, even if they have heart disease, in terms of mortality and total

[891] Roni Caryn Rabin. New York Times 5.5.2014 - http://well.blogs.nytimes.com/2014/05/05/a-new-womens-issue-statins/?_php=true&_type=blogs&_r=0
[892] Morgan et al. The Canadian Rx Atlas, 3rd ed. 2013 - http://www.chspr.ubc.ca/pubs/atlas/canadian-rx-atlas-3rd-edition
[893] Eisenberg & Wells. Journal of Empirical Legal Studies 2008 ;5(3): 507
[894] Gutierrez J et al. Arch Intern Med. 2012;172(12):909
[895] Eddie Vos. CMAJ 2005; 173(10):1207
[896] Mike Mitka 2011. Quoting Lee A Green of University of Michigan
[897] Rita Redberg, heartwire interview
[898] Nilsson et al. Journal of Negative Results in BioMedicine 2011 ; 10(6) – DOI 10.1186/1477-5751-10-6

morbidity. It has not shown benefit to elderly, even if they have heart disease. In fact, in the 4S trial, there was a 12% increase in total mortality in the women in that group who were assigned to statin rather than placebo...

So the evidence really doesn't support that the benefit is the same for women and for men. And on top of that, women are at higher risk of complications from statins »[899]
« An 8.9-year study[900] of women exposed to statins and hormone therapy found a doubling of breast cancer »[901]
femmes statinisées
« Chez les femmes sans antécédents de maladie du cœur, il n'existe aucune preuve clinique concluante que les statines réduisent le nombre de cardiopathies ou de décès, peu importe l'âge … Aucune preuve clinique de qualité ne confirme que le recours aux statines pour diminuer la cholestérolémie présente des bienfaits pour la majorité des femmes qui en prennent actuellement »[902]

« Eisenberg & Wells in 2008[903] assessed the statistical evidence for primary prevention statin use for women. No evidence of benefit was demonstrated. Extrapolating benefit from men is unwarranted »[904]

STATINIZING GUIDELINES (UK)
« Announcing its most recent lipid guideline, the National Institute for Health and Care Excellence (NICE) estimated that, if everyone eligible took treatment, then we would also give statins to 4 448 000 patients for no benefit »[905]
directives statinisantes
A HYPOTHESIS OUT-OF-DATE : The Diet-Heart Idea – (Article)
Uffe RAVNSKOV. *J Clin Epidemiol* 2002; 55: 1057[906]

« An almost endless number of observations and experiments have effectively falsified the hypothesis that dietary cholesterol and fats, and a high cholesterol level play a role in the causation of atherosclerosis and cardiovascular disease. The hypothesis is maintained because allegedly supportive, but insignificant findings, are inflated, and because most contradictory results are misinterpreted, misquoted or ignored »

STATINOLOGY AT STAKE
"For cholesterol experts and the cholesterol industry, recent cholesterol-lowering drug trials have definitely been very disappointing. The most recent trials were either negative (ENHANCE, SEAS, GISSI-HF, CORONA), or not clinically consistent and probably biased (JUPITER) because of premature termination. Taken together, in the light of other negative trials (ASPEN, 4D, PREVEND IT, IDEAL, ILLUMINATE)… these trials are puzzling…

They suggest that the positive trials published before 2005 should be urgently re-examined. At a minimum, experts independent of industry and free of conflict of interest should be asked to carefully check all the raw data recorded in the datasets and redo the statistical analyses. The next question would then be: is it not time for a full reappraisal of the cholesterol theory?"[907]

« Large trials designed to achieve marginal gains in a near saturated therapeutic field typically overestimate potential benefits (because trial samples are unrepresentative and, if the trial is overpowered, effects may be statistically but not clinically significant) and underestimate harms (because adverse events tend to be underdetected or underreported)...

The 74 year old who is put on a high dose statin because the clinician applies a fragment of a guideline uncritically and who, as a result, develops muscle pains that interfere with her hobbies and ability to exercise, is a good example of the evidence based tail wagging the clinical dog....

In such scenarios, the focus of clinical care shifts insidiously from the patient (this 74 year old woman) to the population subgroup (women aged 70 to 75) and from ends (what is the goal of investigation or treatment in this patient?) to means (how

[899] Beatrice Golomb 2013 at http://www.abc.net.au/catalyst/stories/3881441.htm#.UnKSgZv3koQ.twitter
[900] Beck et al. J Clin Epidemiol 2003 ; 56 : 280
[901] Rosenberg H et al. Int J Cardiol 2009 : 145 - doi:10.1016/j.ijcard.2008.12.122
[902] H Rosenberg & AD Allard. Prudence oblige : l'emploi des statines chez les femmes. Action pour la protection de la santé des femmes, 2007
[903] J Empirical Legal Stud 2008 ; 5 : 507
[904] Rosenberg et al. Int J Cardiol 2009 : 145 - doi:10.1016/j.ijcard.2008.12.122
[905] Treadwell J & McCartney M. Br J Gen Pract 2016; 66(644): 116-7 - doi: 10.3399/bjgp16X683881
[906] http://www.jclinepi.com/article/S0895-4356(02)00504-8/pdf
[907] Michel De Lorgeril. World Rev Nutr Diet. 2009(100):80

can we ensure that everyone in a defined denominator population is taking statins?) »[908]
statinologie en danger

STATINOMANIA
statinomanie
N.d.T. néologisme proposé par Michel de Lorgeril

STATINOVIGILANCE
statinovigilance
= surveillance des effets indésirables chez les personnes statinisées en prévention primaire ou secondaire, hommes ou femmes, diabétiques ou non, jeunes / matures / âgés ou non

STATINOVIGILANCE : REAL-WORLD INCIDENCE ADVERSE REACTIONS
* A recent 'real world' study of 150 000 patients who were taking statins (Zhang et al. *Ann Intern Med* 2013; 158: 526) showed 'unacceptable' side effects in 17.4 % of participants — including myalgia, gastrointestinal upset, sleep and memory disturbance, and erectile dysfunction—, resulting in discontinuation of the drug in 9% of the study population. This is massively at odds with the major statin trials that report significant side effects of myopathy or muscle pain in only 1/10 000[909]

« We're told over and over again that statins are extremely safe. And when you look at the results of the clinical trials, you would conclude that they are safe. Problem is that the clinical trials are not designed to pick up all the side effects. The CTT collaboration, for example, uses mostly drug company data, and report very low levels of muscle side effects from statins. But when you look at the side effects in the general population, it's 100 times higher »[910]

« Based on review of structured electronic medical record categories and automated review of unstructured narratives from follow-up visits of 107 835 patients over 8 years, 18 778 of all study patients (17.4%) had a statin related event documented during the study. Among those who experienced a statin related event, only 59.2% [= 10.3% of all study patient] had statin therapy discontinued at least temporarily...

However, because of possible miscategorisation resulting from the limited options in the electronic medical record for recording reasons for discontinuation of statin therapy, Zhang et al concluded that 'as many as 87% of these discontinuations could have been due to statin-related events. This equates to up to 9% [= 10.3% x 87%] of the study population having possibly discontinued statin therapy as a consequence of statin related events »[911]
statinovigilance : incidence des effets indésirables dans la vraie vie

STATINOVIGILANTE
statinovigilant
= surveillant des effets indésirables des statines. On peut dire que les membres du groupe de réflexion *Thincs* animé par Uffe Ravnskov, est composé de statinovigilants

STATINS AND ALL-CAUSE MORTALITY IN HIGH-RISK PRIMARY PREVENTION: A meta-analysis of 11 randomized controlled trials involving 65,229 participants – (Méta-analyse indépendante)
RAY KK et al. *Arch Intern Med* 2010, 170: 1024–1031 – Full paper at :
http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/416105

« This literature-based meta-analysis did not find evidence for the benefit of statin therapy on total mortality »
« A well-done meta-analysis of statins for primary prevention, showing no mortality benefit »[912]
« A meta-analysis of 11 statin trials in high-risk primary pevention found no mortality benefit and no correlation between the degre of LDL lowering and mortality rates[913] »
Statines et mortalité de toute cause en prévention primaire à haut-risque : Une méta-analyse de 11 essais contrôlés aléatoires impliquant 65 229 participants (Traduction libre)

STATINS AND MUSCULOSKELETAL CONDITIONS, ARTHROPATHIES, AND INJURIES – (Article) *Statinovigilance – Étude*

[908] Greenhalgh et al. BMJ 2014; 348: g3725 - doi: http://dx.doi.org/10.1136/bmj.g3725
[909] Aseem Malhotra. BMJ 2013;347:f6340 - doi: 10.1136/bmj.f6340
[910] John Abramson 2013 at http://www.abc.net.au/catalyst/stories/3881441.htm#.UnKSgZv3koQ.twitter
[911] Editorial correction. BMJ 2014;348:g3329
[912] Rita Redberg, 2012, Editor of Archives of Internal Medicine - http://www.nejm.org/doi/full/10.1056/NEJMc1207079
[913] Robert DuBroff, 2016, op. cit.

observationnelle
MANSI I et al. *JAMA Intern Med* 2013 - DOI:10.1001/jamainternmed.2013.6184[914]

* By retrospective cohort study with propensity score matching, treatment with a statin was associated with a 19% increased risk of any type of musculoskeletal injury, a 13% increased risk of dislocations, strains, and sprains, and a 9% increased risk of musculoskeletal pain...

This is biologically plausible, based on the known problems of muscle weakness, concerns about associated tendinopathies, and inhibition of coenzyme Q10 synthesis (which affects muscle metabolism)
Statines et affections musculosquelettiques, arthropathies et blessures (Traduction libre du titre de l'article)

STATINS AND RISK OF TREATED INCIDENT DIABETES IN A PRIMARY CARE POPULATION – (Méta-analyse) *Statinovigilance*
ZAHARAN NL, WILLIAMS D, BENNETT K. *Br J Clin Pharmacol*. 2013; 75(4): 1118-1124

« A earlier by Ireland's national health agency involving about 240,000 patients beginning treatment with various statins found that rosuvastatin was associated with the highest increase in risk of new-onset diabetes compared with other statins »[915]
Statines et risque de nouveau diabète traité dans une population de soins primaires – (Traduction libre du titre de l'article)

STATINS ARE CREATED EQUAL - (Méta-analyse par comparaisons indirectes) *Pharmacoéconomie*
« We were unable to detect differences either in outcomes for fatal and nonfatal strokes, all CV deaths, and all-cause mortality. Evidence from published statin randomized placebo-controlled trials suggests that pravastatin, simvastatin, and atorvastatin, when used at their standard dosages, show no difference in their effect on long-term CV prevention »[916]

« After much-loved Lipitor™ sailed over the 'patent cliff' did Canada's doctors, who had been responsible for writing $1.2 billion worth of Lipitor™ scripts every year, switch everyone to generic atorvastatin? More than half the former Lipitor™ patients have been switched to the newest still-patented anti-cholesterol drug, Crestor™, which is not proven to be any more effective than generic atorvastatin, and it's certainly *more exp*ensive than the lower priced generic »[917]
les statines se valent
* en matière de réduction lipidique et de réduction relative sur la mortalité coronarienne, l'IDM non fatal, les AVC fatals ou non, les décès CV et la mortalité totale ; si on insiste encore pour statiniser, prescrire la moins chère, génériquée, demeure la meilleure solution pour réduire les dépenses médicamenteuses… la moitié des médecins canadiens ne semblent pas le savoir car…

« … plus de la moitié des patients qui prenaient du Lipitor™ se sont vu prescrire du Crestor™, un nouveau médicament breveté, dont les avantages, comparativement au générique atorvastatine, restent à prouver. Ce qui est certain, par contre, c'est qu'il coûte bien plus cher qu'un générique … L'éducation de nos médecins ne doit plus dépendre de l'industrie, car ses 'cours particuliers' coûtent de plus en plus cher à la collectivité »[918]

STATINS FOR ACUTE CORONARY SYNDROME – (Méta-analyse indépendante) *Prévention secondaire*
VALE et al. *Cochrane Library*. 1.9.2014[919]

* 18 studies (14,303 patients) compared early statin treatment versus placebo or no treatment in patients with ACS. There were some concerns about risk of bias and imprecision of summary estimates. Based on moderate quality evidence, early statin therapy did not decrease the combined primary outcome of death, non-fatal myocardial infarction, and stroke at 1 or 4 months (relative risk reduction -7%, NS) of follow-up when compared to placebo or no treatment...

There were no relative risk reduction from statins for total mortality, total MI, total stroke, CV death, revascularization procedures, and acute heart failure at 1 or 4 months. Moderate quality evidence suggests that the incidence of unstable angina was reduced at 4 months following ACS (RR 0.76). There were 9 individuals with myopathy (CK levels > 10 ULN) in statin-treated patients (0.13%) versus one (0.015%) in the control groups. Serious muscle toxicity was mostly limited to patients treated with simvastatin 80 mg »

[914] http://archinte.jamanetwork.com/article.aspx?articleid=1691918 - DOI: 10.1002/14651858.CD006870.pub3
[915] WPBP, January 2015
[916] Zhou et al. Am Heart J 2006 ; 151(2) : 274
[917] Alan Cassels, evidencenetwork, 2012
[918] Alan Cassels, ibidem
[919] http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006870.pub3/abstract

STATINS IN DIABETICS : USEFULNESS CALLED INTO QUESTION – (Synthèse méthodique)
Michel de LORGERIL/*Rev Recent Clin Trials*/2012[920]

« Randomised studies found no clear benefit of statins in patients who had diabetes :
a) The 4D (Die Deutsche Dialyse Studie) or German Diabetes and Dialysis Study: 1255 patients with diabetes on dialysis were assigned to atorvastastin or placebo for about 4 years. There was an -8 % relative risk reduction in the primary endpoint and a -15% relative risk reduction in MI…

b) The ASPEN study, in type 2 diabetics : there was a -10 % relative risk reduction in the primary endpoint, and a -26 % relative risk reduction in MI, not clinically relevant …

c) The CORONA trial, where 30% of the participants had diabetes, reported an 8 % relative reduction in the primary endpoint and a 17% relative risk reduction in MI, not clinically relevant

Treatment decisions should be based not on the relative risk reduction but on the absolute risk reduction or its reciprocal, the NNT. And one should consider life expectancy, concomitant diseases and quality of life, and lifestyle changes such as cessation of smoking, healthy diet and regular exercise »[921] according to a 2008 short review of statins in people with diabetes

« Cholesterol-lowering drugs are often prescribed to patients with T2DM despite uncertainty about the benefits of this treatment in the prevention of CV complications. We here systematically review (PRISMA guidelines) the results of high-quality double blind trials testing whether cholesterol-lowering drugs (statins and fibrates) reduce total mortality and CV complications specifically in type 2 diabetics…

Trials with premature termination without pertinent medical justification or using nonrandomized subgroups of diabetics were excluded from the review…

Only 4 trials met our predefined inclusion criteria. Among the 3 statin trials, CARDS was discontinued 2 years before the anticipated end, and in the absence of significant effect on both total and CV mortality, suggesting that the trial should not have been prematurely stopped…

The 2 other statin trials showed no significant effect on the primary endpoint (relative risk 0.92, 95% CI 0.77 to 1.10 in 4D and 0.90, 95% CI 0.73 to 1.12 in ASPEN) and on both CV and total mortality. Finally, the fibrate trial (FIELD) showed no significant benefit on the primary endpoint (relative risk 0.89, 95% CI 0.75 to 1.05) and total mortality (relative risk 1.11, 95% CI 0.95 to 1.29)…

Because of a huge medical heterogeneity between patients in the selected trials, it was consensually decided to stop the analysis at this stage. This review does not support the use of cholesterol-lowering drugs (such as statin and fibrate) to reduce total mortality and CV complications in type 2 diabetics. Official guidelines should be re-examined and reformulated by experts independent from the pharmaceutical industry »

« To date, no large clinical studies have examined the association of statin therapy with microvascular disease »[922]

« We urgently propose that statins are contraindicated in diabetics and their prescription should be restricted to special cases for which doctors rationally decide to be necessary, such as familial hypercholesterolemic cases with enlarging xanthomas have been considered although without firm evidence base…

Even if statins exhibited no significant benefit for the prevention of CHD in the trials performed by scientists independent of industries after 2004, when a new regulation on clinical trials took effect in EU, in 2012 the Japanese Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic CV Diseases recommends diabetics to maintain LDL-C levels below 3 mM (120 mg/dL) »[923]
statines chez les diabétiques : utilité remise en question

STATINS IN GERIATRICS

[920] de Lorgeril et al. Rev Recent Clin Trials. 2012; 7(2): 150 - available at http://www.ncbi.nlm.nih.gov/pubmed/22353198#
[921] Cheung BMY. Lancet 2008 ; 371 : 94
[922] Preiss et al. JAMA 2011; 305(24): 2556 – Full paper at http://jama.jamanetwork.com/article.aspx?articleid=646699
[923] Harumi Okuyama et al. J Lipid Nutr 2013 ; 22(2) : 173 – In Japanese, English Summary

« A meta-analysis addressed studies on the effect of statins in elderly subjects (above age 65) without established CVD[924]. The absolute risk reduction for one year was 0.34% for MI. The corresponding NNT for a year will be 294 patient-years. It is important to acknowledge that the NNT was miscalculated by a factor of 10 in the original publication[925]
les statines en gériatrie

STATINS IN THE LAST SIX MONTHS OF LIFE : A Recognizable, Life-Limiting Condition Does Not Decrease Their Use – (Article) *Gaspillage – Statinisation non factuelle - Déprescription*
SILVEIRA MJ et al. *J Palliat Med* 2008; 11(5): 695 - DOI: 10.1089/jpm.2007.0215

« A large proportion of patients (52.3%) receive statins during their last year of life at the Veterans Health Administration (USA). The diagnosis of a recognizable, life limiting illness does not change the timing of or likelihood that a statin will be discontinued prior to death, even for patients without cardiovascular disease. All subjects were receiving statins from the VHA during 6 months prior to death...

By the time of death, 51% of cases and 64% of controls were still receiving statins. However, there was no significant difference in the days without statins between cases (with life limiting condition) and controls. Those subjects taken off statins had statins discontinued a mean of 65 days prior to death for cases and 64 days prior to death for controls. Our results did not change after stratifying our analyses by illness subgroup (i.e., cancer, CHF, and COPD) »

STATINS STIMULATE ATHEROSCLEROSIS AND HEART FAILURE : PHARMACOLOGICAL MECHANISM – (Article) *Insuffisance cardiaque – Statinovigilance - Athérosclérose*
OKUYAMA H et al. *Expert Rev Clin Pharmacol* 2015; 8(2): 189 - doi: 10.1586/17512433.2015.1011125

« From 6673 consecutive individuals - 2413 on statin therapy and 4260 not on statin therapy - with no known coronary heart disease and available statin use status, Nakasato et al. (2012)[926] studied the relationship between statin use and the presence and extent of specific plaque composition types. Statin use is associated with an increased prevalence and extent of coronary plaques possessing calcium …

The epidemic of CHF and atherosclerosis that plagues the modern world may paradoxically be aggravated by the *pervasive* use of statin drugs. Current statin treatment guidelines should be *critically and urgently* reevaluated… Statins with or without other cholesterol lowering drugs are effective in lowering LDL-C, but essentially ineffective in preventing CHF… Statins are mitochondrion toxic, making all cells depleted in ATP which is essential for normal heart muscle function… Statins are general cell toxins…

They can produce skeletal muscle weakness, pain and cell death (with elevated CK levels). In animals statins have been shown to increase mortality in cardiomyopathic hamsters… The first reported cases of statin-related heart failure were published in 1990 (Folkers et al. *PNAS USA* 1990 ; 87(22) : 8931), 5 patients had a dramatic deterioration in myocardial function and clinical status after starting lovastatin, and returned to their previous condition after stopping the statin and taking supplemental CoQ_{10}…

It has been demonstrated that diastolic dysfunction developed in 10/14 healthy hyperlipidemic patients after 3-6 months of atorvastatin (Silver et al. *Am J Car*diol 2004 ; 94(10) : 1306), an early finding in CHF. The dysfunction reversed to normal after 3 months of supplemental CoQ_{10}…. In an ongoing study, patients on statin for an average of 6 years presented with overt and often permanent CHF

Fifty consecutive patients with severe statin ADRs were followed for 28 months (Langsjoen et al. *Bio Factors* 2005 ; 25(1-4) : 147), had their statin discontinued and were supplemented with CoQ_{10}, and then followed for 2 years : 50% of those with CHF showed significant improvement in heart muscle function…

Statin cardiomyopathy is not uncommon after long-term treatment (average 6 years), 130 cases were identified during a 4-year period presenting to a solo cardiology practice. Physicians in general are not aware that statins can cause heart failure and are clearly not recognizing it
Les mécanismes d'action qui sous-tendent l'athérogénie et la cardiomyopathie statiniques – (Traduction libre du titre de l'article)

STATINS STIMULATE ATHEROSCLEROSIS AND HEART FAILURE: PHARMACOLOGICAL MECHANISMS – (Article) *Synthèse –*

[924] Savarese et al. J Am Coll Cardiol. 2013; 62(22): 2090 - doi:10.1016/j.jacc.2013.07.069
[925] Sigurdsson A. J Am Coll Cardiol. 2014; 63(21): 2302 - doi:10.1016/j.jacc.2014.02.605
[926] Nakasato et al. Atherosclerosis 2012 ; 225 : 148 - http://dx.doi.org/10.1016/j.atherosclerosis.2012.08.002

Statinovigilance - Toxicologie
OKUYAMA H et al. *Exp Rev Clin Pharmacol* 2015 ; 8(2) : 188-199 - DOI:10.1586/17512433.2015.1011125

« In contrast to the current belief that cholesterol reduction with statins decreases atherosclerosis, we present a perspective that statins may be causative in coronary artery calcification and can function as mitochondrial toxins that impair muscle function in the heart and blood vessels through the depletion of coenzyme Q_{10} and 'heme A', and thereby ATP generation...

Statins inhibit the synthesis of vitamin K_2, the cofactor for matrix Gla-protein activation, which in turn protects arteries from calcification. Statins inhibit the biosynthesis of selenium containing proteins, one of which is glutathione peroxidase serving to suppress peroxidative stress. An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure, reminiscent of the dilated cardiomyopathies seen with selenium deficiency...

Thus, the epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs. We propose that current statin treatment guidelines be critically reevaluated »[927]
Les statines favorisent l'athérosclerose et l'insuffisance cardiaque : pharmacodynamie (Traduction libre)

STATINS, SENIORS AND PUBLIC DRUG PROGRAMS IN CANADA IN 2012[928] - (Rapport d'enquête) *Taux d'utilisation – Gériatrie - Dépenses publiques*
statines, personnes âgées et régimes publics d'assurance-médicaments au Canada en 2012[929]
* 46,6 % furent statinisées au moins un mois, 41,3 % toute l'année ; soit un taux relatif d'utilisation chronique de 88,5 % (par ces ordonnances plutôt absurdes dites 'pour la vie')
* 53 % des hommes et 41,5% des femmes de 65 + ont été statinisés en 2012 (même si les statines n'ont jamais prolongé la vie d'une femme même coronarienne)

* 46,1 % des 65-74 ans, 50,8 % des 75-84 ans et 39,1 % des 85 + ont été statinisés (même si en prévention secondaire chez les hommes, il n'y a pas de bénéfices démontrés après 70-75 ans et même si ceux avant cet âge sont minuscules)

* les statines ont occasionné la plus grande part des dépenses des régimes publics, soit 7,9 % des dépenses totales des régimes d'assurance-médicaments publics chez les personnes âgées
* ces dépenses s'élèvent à 344,7 M $, équivalentes à 212 $ par bénéficiaire

* en établissements de soins de longue durée, les statines se classent au 7e rang pour l'utilisation, avec un taux de 29,8 % (alors qu'elles devraient arriver aux derniers rangs)
* les statines se classent au 1er rang, soit 48%, pour les personnes âgées habitant dans la collectivité

STATINS, THE BMJ, JEANNE LENZER AND EDITORIAL FREEDOM : AN OPEN LETTER *Transparence - Revues savantes – Harcèlement – Liberté de presse*

* The following letter was prepared in June 2014 by a group of physicians, scientists, and others in response to the controversy about two recent articles in The BMJ[930] on the use of statins for primary prevention of heart disease. We believe the calls for The BMJ to retract the papers are unwarranted, and we hope the independent panel[931] appointed to review any retraction decision will allow these papers to remain as part of the ongoing scientific conversation about statins :

« The BMJ stands out among the top medical journals of the world as a beacon in the best tradition of science through its willingness to publish articles and studies that question orthodoxy. Many of these articles question the results of industry-funded research, and while The BMJ publishes its share of industry-funded research, it has also given space and voice to those who question the output of such studies, including those published by The BMJ itself...

The journal was among the first to call for open access to clinical trial data, much of which is left unpublished, held secret or misanalysed. The BMJ became one of the first medical journals in history to establish a medical investigative unit geared to understanding when research data represent some of the true and valuable breakthroughs of medicine, and when they are part of the sad history of spin trumping real science...

[927] http://www.tandfonline.com/doi/full/10.1586/17512433.2015.1011125 - Texte complet gratuit
[928] https://secure.cihi.ca/free_products/Drug_Use_: in_Seniors_on_Public_Drug_Programs_2012_EN_web.pdf
[929] https://secure.cihi.ca/free_products/Drug_Use_in_Seniors_on_Public_Drug_Programs_2012_FR_web.pdf
[930] http://www.bmj.com/content/348/bmj.g3306
[931] http://www.bmj.com/about-bmj/independent-statins-review-panel

This willingness to give voice to careful skeptics, and to insist on data transparency, has triggered the ire of industry and the recipients of its largesse on more than one occasion, leading to accusations and threats against The BMJ. Now, The BMJ is being attacked once again, over a paper involving statins, that should not be retracted as demanded by its critics. The BMJ was correct in publishing the paper, and did what was necessary in correcting an error...

We, as doctors, researchers, scientists, patient advocates, journalists and others from around the globe, want to stand with The BMJ in its effort to elevate scientific and honorable dialogue about the issues of the day »[932]
statines, le BMJ, Jeanne Lenzer et la liberté éditoriale: une lettre ouverte

STICS, THE TRIAL
* Comparison : rosuvastatin (2011-2014)
* Funding : AstraZeneca: $ 100 K
l'essai dit Stics

STOPPING STATIN THERAPY : IS THERE A RISK ?
« Collins et al.[933] claim that statin therapy can be devastating but we suggest that cholesterol lowering per se plays little role in mortality and that is is incorrect to state that stopping statins can be devastating »[934]
cesser la statinisation comporte-t-il un risque ?

STOPPING STATINS IN SECONDARY PREVENTION *Déstatinisation*
« In individuals with a prior history of heart attack or stroke ('secondary prevention') statins do reduce the relative risk of death (particularly from heart attack). However this benefit needs to be taken in the context of underlying risk. The data[935] show that if 200 people were to be treated with statins for a year about 1 person would be spared a heart attack. If 100 people were treated, only about 1 life would be saved over the next 5 years [annualized NNT = 500 person-years]…

Taking all benefits into consideration, over 5 years of treatment, 96% of people would not benefit at all. This means, again, that if even if someone has had a prior heart attack, stopping statins is actually quite unlikely to usher in a heart attack or earlier demise. It's only by taking a cold hard look at the data and understanding it in real [absolute] terms that we can make an accurate judgment about the supposed risks of stopping statins...

STROKE AND CHOLESTEROL *Épidémiologie*
« Neither TC nor non-HDL cholesterol are associated with increased risk of stroke in observational studies… Evidence from randomized controlled trials[936] suggests that statins may confer a degree of protection against stroke independent of baseline low-density lipoprotein level »[937]

« In the Rotterdam population-based cohort study, TC/HDL ratio was not associated with the risk of stroke in the expected direction: with the quartile of participants with the lowest TC/HDL ratios as the reference category, the hazard ratios were :

a) 0.83 (95% CI 0.69–0.99) for the second quartile (absolute risk reduction of -17%)
b) 0.84 (95% CI 0.70–1.00) for the third quartile (absolute risk reduction of -16%, NS)
c) 0.97 (95% CI 0.82–1.16) for the fourth quartile (absolute risk reduction of -3%, NS, with highest TC/HDL ratio)

The participants who used cholesterol-lowering medication (prevalence 2.3%) had a slightly lower risk of stroke than those in the lowest quartile of the TC/HDL ratio distribution, a relative risk reduction of -29%, not cinically significant. There was no association between HDL or non-HDL cholesterol with the risk of stroke when assessed separately »[938]
AVC et cholestérol ; angiopathie cérébrale et cholestérol
* Selon la rédaction[939] de *PloS Medicine* commentant l'étude de Rotterdam[940] :

[932] 30.6.2014 - http://lowninstitute.org/news/blog/open-letter-to-the-bmj/
[933] Lancet 2016 ; 19(388) : 2532
[934] Eddie Vos, 2016, comunication
[935] http://www.thennt.com/nnt/statins-for-heart-disease-prevention-with-known-heart-disease/
[936] Baigent et al. Lancet 2005 ; 366: 1267
[937] Burch D. PLOS Medicine 2014 ; 11(4): e1001637 - doi:10.1371/journal.pmed.1001637-
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001637
[938] Bos et al. PloS Medicine 29.4.2014 - DOI: 10.1371/journal.pmed.1001634 -
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001634
[939] Burch D. Op. cit.
[940] Bos et al. Op. cit.

a) il y a absence de corrélation entre cholestérolémie et AVC (ce qui contredit l'hypothèse lipidique)
b) la protection des statines va de cliniquement futile à numériquement nulle dans les essais contrôlés, même quand les LDL sont élevées au départ (contredisant l'hypothèse statinique)

* Dans la même étude, le risque d'AVC diminue légèrement à mesure que le rapport TC/HDL augmente, et pris séparément, le cholestérol total et les lipoprotéines non-HDL ne sont pas associées aux AVC (contredisant l'hypothèse lipidique).
* Et la statinisation n'a pas modifié le risque d'AVC numériquement (contredisant l'hypothèse statinique)

STROKE AND MISLEADING GUIDELINES
AVC et recommandations trompeuses
a) Données expérimentales :

* Les justifications de prescrire de statines à fortes doses pour prévenir la récidive d'AVC - sont simplement ridicules puisque le seul essai ayant montré un minuscule effet favorable (l'essai SPARCL) n'est pas crédible … ce qui fait qu'il n'y a aucun argument justifiant la prescription de statines chez ces patients. L'effet nocif des statines sur le risque d'AVC hémorragique a été observé dans d'autres essais cliniques[941] - Voir aussi SPARCL, THE TRIAL

b) Données observationnelles:

* En avril 2014, les investigateurs de la grande Étude de Rotterdam ont publié les résultats de 13 ans de suivi d'une large cohorte (près de 7000 personnes), parmi lesquelles plus de 1000 ont présenté un AVC, ischémique (confirmé chez 600) ou hémorragique (confirmé chez 100). On notera surtout que le cholestérol [y compris le supposé mauvais LDL] n'est pas associé à une augmentation du risque d'AVC ischémique; mais qu'il est *inversement associé* au risque d'AVC hémorragique ...

Dit autrement, plus le cholestérol est bas et plus le risque d'AVC hémorragique augmente. Pour ceux qui avaient le cholestérol le plus haut, le risque d'AVC hémorragique était 70% inférieur par rapport à ceux qui avaient le cholestérol le plus bas...

Ce cholestérol abaissé avait une cause naturelle ou était un effet thérapeutique, l'effet d'une statine évidemment... Dans une perspective de prévention des AVC ischémiques et hémorragiques, il ne ne faut pas diminuer le cholestérol. Les médecins devraient ils prescrire des statines chez les patients qui ont survécu à un AVC ?[942]

STROKE AND STATINS
« Certain researchers funded by the pharmaceutical industry have asserted that statins have a beneficial anti-inflammatory effect on carotid lesions (Crisby et al. *Circulation* 2001; 103: 926)[943]. Other researchers of international renown such as Renu Virmani, not financed by industry, reported that statins had no effect after studying nearly 400 patients (Verhoeven et al. *Stroke* 2006; 37: 2054)[944] …

Two types of stroke exist : occlusion of a cerebral artery or rupture of a cerebral artery. The first result from formation of a clot/thrombus and the others consist of a haemorrhage. It is totally absurd to apply the same prenventative treatment to these two forms of stroke »[945]
AVC et statines

STROKE RISK AND CHOLESTEROLEMIA IN WOMEN *Étude de cohorte – Hypothèse lipidique réfutée*
* Cholesterol levels at baseline as predictors of total stroke in women in a Swedish population followed prospectively for 32 years are associated with :[946]

a) by Cox regression : relative risk reduction of -11%, NS of total stroke - relative risk reduction of -30%, NS for the subset of haemorragic strokes
c) by multivariate Cox regression : relative risk reduction of -12% for total stroke - relative risk reduction of -29%, NS for haemorragic strokes – relative risk reduction of -8%, NS for ischaemic stroke
risque d'AVC et cholestérolémie chez les femmes
* c'est clair dans ce suivi épidémiologique de haute qualité méthodologique que l'augmentation de la cholestérolémie n'est pas

[941] Michel de Lorgeril. 3.5.2014 - http://michel.delorgeril.info/nutrition/diete-mediterraneenne/prevention-de-laccident-vasculaire-cerebral
[942] Michel de Lorgeril, op. cit.
[943] http://circ.ahajournals.org/content/103/7/926.full
[944] http://stroke.ahajournals.org/content/37/8/2054.full
[945] de Lorgeril 2014, op. cit.
[946] Blomstrand et al. BMJ Open 2014; 4: e005173 - doi:10.1136/bmjopen-2014-005173 - http://bmjopen.bmj.com/content/4/10/e005173.full

un prédicteur d'AVC chez les femmes; on y observe même une tendance associant l'hypocholestérolémie au risque d'accidents vasculaires cérébraux, notamment hémorragiques

* à la lumière de cette enquête populationnelle où les diagnostics d'AVC ont été validés, doit-on continuer de statiniser les femmes victimes d'un d'AVC hémorragique, ou encore les femmes à haut risque comme les hypertendues sous anticoagulant ? Pourtant on continue de prescrire et dispenser sans broncher. D'autant plus que la statinisation n'a jamais été démontrée capable de prolonger la vie des femmes

SUDDEN DEATH AND CHOLESTEROL LEVELS *Hypothèse lipidique contredite*
mort subite et niveaux de cholestérol
* Une enquête cas-témoins chez les hommes recrutés dans la Physician's Health Study n'a pas permis de trouver de relation entre la mort subite et le cholestérol total : 5.77 mM (223 mg/dl) chez les cas et 5.64 mM (218 mg/dl) chez les témoins (p=0.51)[947]

SWEEPING ASIDE ON-STATIN PATIENTS COMPLAINTS *Statinovigilance - Pratique*
dismissing statin ADRs reported by patients
« I encountered many patients whose doctors had dismissed a possible statin connection to their problem »[948] **-** « Sweeping away patients' complaints under the carpet »
écarter d'emblée / rejeter / balayer du revers de la main / balayer sous le tapis les plaintes de patients statinisés
* Écarter d'emblée la contribution d'une statine dans l'apparition d'une fatigue, d'une douleur musculaire, de faiblesse, de trouble de mémoire, de paresthésie ou d'arthralgie, est une attitude des médecins que les statinisés ne cessent de déplorer dans les forums et les médias sociaux ; il est temps que leurs voix soient entendues

syndrome coronarien aigu et statines

THE CHOLESTEROL CONSPIRACY – (Livre) *Hypothèse lipidique*
RUSSEL L SMITH. St-Louis (USA): Warren Green; 1991 - ISBN-13: 978-0875274768 - ISBN-10: 0875274765

THE CHOLESTEROL CONTROVERSY – (Livre) *Hypothèse lipidique*
Edward PINCKNEY. Los Angeles: Sherbourne Press; 1973 – ISBN 0820201553

THE CHOLESTEROL MYTH – (Extrait de livre et article de revue) *Hypothèse du cholestérol dénoncée*
Thomas J MOORE. *The Atlantic Monthly* 1989 ; 264 : 37 (Article drawn from the book Heart Failure)

« Diet has hardly any effect on your cholesterol level; the drugs that can lower it often have serious or fatal side effects; and there is no evidence at all that lowering your cholesterol level will lengthen your life »
Le mythe du cholestérol (Traduction libre)
« L'alimentation n'a pas pratiquement pas d'effet sur votre cholestérolémie ; les réducteurs du cholestérol ont souvent des effets indésirables graves; et il n'y a aucune preuve qu'abaisser votre cholestérolémie prolongera votre vie » - « Gigantesque article qui insiste sur l'aspect mythique entourant le cholestérol et ou l'auteur se demande comment nous en étions arrivés à faire croire toutes ces inepties sur le cholestérol et les graisses alimentaires »[949]

THE EFFECT OF STATINS ON AVERAGE SURVIVAL IN RANDOMISED TRIALS : An Analysis Of End Point Postponement – (Article)
Méta-analyse ciblée – Mortalité totale – Aire sous la courbe - Survie
ML KRISTENSEN, PM KRISTENSEN, J HALLAS. *BMJ Open* 2015; 5:e007118 - doi:10.1136/bmjopen-2014-007118

« Statin treatment was compared to placebo. The average postponement of all-cause death as represented by the area between the survival curves. 6 studies for primary prevention and 5 for secondary prevention with a follow-up between 2.0 and 6.1 years were identified. The relative risk reduction of selected trials was -11%. Death was hastened/postponed between −5 and +19 days in primary prevention trials and between −10 and +27 days in secondary prevention trials...

The median postponement of total death for primary and secondary prevention trials were 3.2 days (76.8 hours) and 4.1 days (98 hours), respectively. Statin treatment results in a surprisingly small average gain in overall survival within the trials' running time. For patients whose life expectancy is limited or who have adverse effects of treatment, withholding statin therapy should be considered »

[947] Albert et al. Circulation 2002 ; 105 : 2595
[948] Beatrice Golomb, 2014
[949] Therrien, op. cit.

« Even when researchers demonstrate a statin mortality benefit, the findings are underwhelming. A recent meta-analysis[950] concluded that statins would only postpone death by a median of 3.2 days and 4.1 days for primary and secondary preventions respectively over 5 years[951] »

* Here are the postponement days obtained by the 'area under the curve' method introduced by the authors, standardized for each year of treatment, of statin trials compared with placebo or no treatment, and where a Kaplan-Meier curve for total mortality was published, highlighted in red. In brackets ( ) are the postponement days per treatment-years calculated by the simpler *arithmetic method* used in this Statinization Annex: [(365 days / annual NNT) x 24 hours] :

In primary prevention
a) ALLHAT-LLT 2002: postponement of 20 hours per treatment-year
(5.8 hours, since 365 days / annual NNT of 1500 patients = 0.24 days = 5.8 hours, by the *arithmetic method*)
b) ASCOTT-LLA 2003 : postponement of 13,6 hours per treatment-year (12.5 hours, by the *arithmetic method*)

c) CARDS 2004 : postponement of 93 hours per treatment-year (27.4 hours, by the *arithmetic method*)
d) JUPITER 2008 : postponement of 44 hours per treatment-year (70 hours, by the *arithmetic method*)
e) MEGA 2006 : postponement of 21 hours per treatment-year (9.6 hours, by the *arithmetic method*)
f) WOSCOPS 1995 : postponement of 45 hours per treatment-year (15.8 hours, by the *arithmetic method*)

In secondary prevention :
g) 4S 1994 : postponement of 112 hours per treatment-year (54 hours, by the *arithmetic method*)
h) GISSI-HF 2008 : paradoxically, a *hastening* of all-cause death by 52 hours per treatment-year (14 hours, by the *arithmetic method*) ; a not unexpected result since patients were in heart failure, and rosuvastatin / Crestor™ just worsened their condition

i) GISSI-P 2000 : postponement of 91 hours per treatment-year (33 hours, by the *arithmetic method*)
j) LIPID 1998 : postponement of 87 hours per treatment-year (44 hours, by the *arithmetic method*)
k) CORONA 2007 : postponement of 36 hours per treatment-year (45.6 hours, by the *arithmetic method*)

* It is clear that their method does correlate with the simpler arithmetic method, using the NNTs presented by the Danish authors in Table 1 and standardized for trial duration; for example, in CORONA's the trial NNT is 71, the cut point is 2.7 years, the postponement is 1.5 day or 36 hours per treatment-year, and the annual NNT = 192 (71 x 2.7 years). Applying the arithmetic method (365 days / 192 patients) the postponement is 1.9 day or 45.6 hours per treatment-year

* A rough correlation also exist in secondary prevention albeit of smaller amplitude. It must also be kept in mind that the *experimental* NNTs are sensibly and presumably smaller, maybe 1.5 to 2 fold, than the *clinical* NNTs obtained in medical practice ; therefore any postponements of death calculated from trials in hours per treatment-year are sensibly and presumaby smaller than those derived from trials.

« While a Pfizer ad is silent on the impact of Lipitor on our longevity, the *British Medical Journal* was not. A 2015 study published in the journal examined the impact of statins (like Lipitor) on longevity. The study reviewed the results of 11 detailed studies of statins and longevity. Its conclusion: The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively[952] »
L'effet des statines sur la survie moyenne dans les essais randomisés : Une analyse du retard de la mortalité comme critère d'évaluation (Traduction libre)
MISINTERPRETED SURVEYS *Hypothèse du cholestérol*
enquêtes mal interprétées
« Aujourd'hui, un nombre croissant de spécialistes affirment que les études fondatrices 'Des sept pays' et celle 'De Framingham', du nom de la petite cité ouvrière proche de Boston où elle fut menée, établissant la distinction entre bon et mauvais cholestérol sont biaisées. Selon eux, la postérité leur a fait dire le contraire de ce qu'elles démontraient »[953]

THE EMPEROR CHOLESTEROL HAS NO CLOTHES
« Physicians are now writing 250 M prescriptions a year for cholesterol-lowering drugs; that's about one per every child, woman

[950] Kristensen et al. op. cit.
[951] Robert DuBroff, 2016, op. cit.
[952] Wanda Morris. http://www.carp.ca/2017/11/28/grey-matters-seniors-shouldnt-quietly-take-medicine/
[953] Anne Crignon. http://teleobs.nouvelobs.com/la-selection-teleobs/20151006.OBS7198/a-voir-ce-soir-le-danger-du-cholesterol-mythe-ou-realite.html

and man every year (USA). We are now spending $18.5 billion a year on cholesterol-lowering drugs, and for what? To lower a number. Yes, your LDL level is only a number that by itself means very little. If it were so important wouldn't you expect most heart attack victims to have high LDL levels? If fact, most of them don't »[954]
L'empereur cholestérol est nu

THE GREAT CHOLESTEROL BLUFF – (Traduction libre d'un documentaire exceptionnel)
See LE GRAND BLUFF DU CHOLESTÉROL

THE GREAT CHOLESTEROL CON : Why Everything You've Been Told About Cholesterol, Diet and Heart Disease is Wrong **(AU)** – (Livre)
Anthony COLPO. 2006 - www.Lulu.com – 448 pages - ISBN 978-1-4116-9475-0[955]

« The primary force behind the anti-cholesterol paradigm is not public health, but greed. Drug companies, food companies, the medical profession, and health organizations all make billions in dollars of profit from the cholesterol theory. The shocking, sordid tale of the cholesterol scam - a mind-boggling saga of ignorance, corruption, deceit and greed - is a subject worthy of an entire book! »[956]

"There is every reason in the world to encourage people to exercise frequently, stop smoking, eat minimally processed foods, and find ways to get a handle on the stresses of modern life. The evidence for low-fat diets, on the other hand, is based on a mixture of erroneous assumptions, half-truths and downright lies"[957]
La grande supercherie du cholestérol : Pourquoi tout ce qu'on vous a dit sur le cholestérol, l'alimentation et la maladie cardiaque est faux (Traduction libre)

« Ce livre explique pourquoi les mensonges à propos du cholestérol sont présents dans toutes les sociétés civilisées où les intérêts pharmaceutiques et agro-alimentaires sont supérieurs à l'intérêt du citoyen… et démontre par plus de 1 400 références que le cholestérol n'est presque jamais relié (et pas linéairement) au risque cardiaque, en analysant les études qui existent déjà, mais qui ne sont jamais citées »[958]

« Parmi les études les plus célèbres, certaines (MRFIT, Framingham) ont été présentées de manière avantageuse (spinned) pour l'hypothèse lipidique, c'est-à-dire de manière à affirmer que le cholestérol et les graisses sont fortement liés numériquement aux maladies CV»[959]

« Je vous demande de tout cœur de lire ce livre en entier, il pourrait vous sauver la vie de par les précieux renseignements qu'il apporte du début jusqu'à la fin »[960] selon un médecin rebelle de la NASA qui a alerté au sujet de pertes de mémoire induites par les statines

« Dans ce livre opportun et qu'il était urgent d'écrire, Colpo commence en soulignant les nombreuses contradictions inhérentes à l'hypothèse lipidique. Méticuleusement, il dissèque les arguments fallacieux des auteurs des campagnes anti-cholestérol et met en lumière leur manipulation flagrante des statistiques »[961] selon un dénonciateur renommé de l'argumentation fallacieuse du paradigme du cholestérol

THE GREAT CHOLESTEROL MYTH: Why Lowering Your Cholesterol Won't Prevent Heart Disease - and the Statin-Free Plan That Will – (Livre)
Stephen T SINATRA & Jonny BOWDEN. USA: Fair Winds Press; 2012

« Heart disease is the #1 killer. However, traditional heart disease protocols--with their emphasis on lowering cholesterol--have it all wrong. Emerging science is showing that cholesterol levels are a poor predictor of heart disease and that standard prescriptions for lowering it, such as ineffective low-fat/high-carb diets and serious, side-effect-causing statin drugs, obscure the real causes of heart disease…

[954] Dove Michaeli. http://healthworkscollective.com/dov-michaeli/92041/emperor-cholesterol-has-no-clothes
[955] http://www.Lulu.com/shop/anthony-colpo/the-great-cholesterol-con/paperback/product-18915662.html
[956] Anthony Colpo. http://www.thegreatcholesterolcon.com/
[957] Joel Kauffman. http://www.jpands.org/vol11no4/bookreviews.pdf
[958] Lecteur non identifié
[959] Sylvain Duval citant Colpo, sur http://www.formindep.org/Cholesterol-le-bon-le-mauvais-et.html
[960] Duane Graveline
[961] Uffe Ravnskov, chercheur indépendant, auteur, bloguiste (Thinks)

Even doctors at leading institutions have been misled for years based on creative reporting of research results from pharmaceutical companies intent on supporting the $31-billion-a-year cholesterol-lowering drug industry »

LE GRAND MYTHE DU CHOLESTÉROL : La vérité sur les gras, les sucres, l'inflammation et les statines – (Livre traduit ; préfaces de Marc Zaffran et de Michel de Lorgeril)
Stephen T SINATRA & Jonny BOWDEN. Montréal: Edito (Gallimard); 2014 – 368 pages – ISBN : 978-2-924402-24-5

« Le cholestérol : l'invention d'un mythe par l'industrie pharmaceutique et comment lutter efficacement contre les maladies cardio-vasculaires. Le cholestérol, une cause de mortalité ? En France, Michel de Lorgeril puis Philippe Even ont commencé à lever le voile sur une imposture médicale qui fait du cholestérol un épouvantail destiné à nourrir l'industrie pharmaceutique. Aux États-Unis, Jonny Bowden et Stephen Sinatra continuent l'enquête...

Ils dévoilent comment le cholestérol a été 'construit' en problème de santé publique, et l'inutilité des traitements longtemps préconisées : les statines (déjà dénoncées par de Lorgeril puis par Even), mais pas seulement. Alors comment lutter contre les maladies cardio-vasculaires ? …

En arrêtant de se battre contre le seul cholestérol, et en s'attaquant aux vraies origines des MCV : les sucres, qui causent inflammation et stress oxydatif. L'ouvrage propose donc un programme de rééquilibrage par l'alimentation, la relaxation, des traitements doux… »

« Les médecins, il est toujours possible d'induire leur décision dans un sens ou un autre en leur donnant des informations tendancieuses, incomplètes, biaisées ou, carrément, mensongères… Transformer le cholestérol, ce composant normal de notre physiologie, en poison lent ou violent est probablement la plus grand escroquerie des 50 dernières années. Elle a rapporté, et rapporte, à ceux qui en bénéficient plus d'argent que les spéculations criminelles qui mirent naguère les banques en danger...

Des médecins prescrivent, par bienveillance ou par conscience professionnelles, pensent-ils, des médicament inutiles et dangereux à des personnes qui n'en ont pas besoin. Les mécanismes de cette escroquerie planétaire ? Le livre de Bowden et Sinatra les décrit en détail…»[962]

« Le cholestérol et les traitements anticholestérol ont engendré une corruption massive et une mise en danger de la population, sous le prétexte fallacieux de la protéger de maladies qu'elle n'a pas. Pour de sombres raisons commerciales, les mensonges et la propagande règnent en maître pour imposer des traitements anticholestérol inutiles et toxiques à des millions d'innocents : environ 7M en France, plus de 30M aux É-U…

La culpabilité du cholestérol est un mythe et les médicaments anticholestérol ne servent à rien sinon à empoisonner… Les médicaments anticholestérol ont rapporté des centaines de milliards de profits à l'industrie pharmaceutique tansnationale au cours des dernières décennnies, nous l'appelons la plus énorme et ignoble arnaque scientifique de l'histoire de la médecine… Nos cris et révoltes sont longtemps restés inaudibles…

Nous étions comme asphyxiés par la propagande massive orchestrée par les plus grands noms des Académies et autres corporations professionnelles qui ne vivent (luxueusement) que des subventions versées par l'industrie du médicament… »[963]

THE INTERNATIONAL NETWORK OF CHOLESTEROL SKEPTICS **; THINCS** – (Groupe de réflexion) *Hypothèse du cholestérol – Statinovigilants*
« For decades, enormous human and financial resources have been wasted on the cholesterol campaign, more promising research areas have been neglected, producers and manufacturers of animal food all over the world have suffered economically, and millions of healthy people have been frightened and badgered into eating a tedious and flavorless diet or into taking potentially dangerous drugs for the rest of their lives…

As the scientific evidence in support of the cholesterol campaign is non-existent, we consider it important to stop it as soon as possible...THINCS is a steadily growing group of scientists, physicians, other academicians and science writers from various countries. Members of this group represent different views about the causation of atherosclerosis and CV disease, some of them are in conflict with others, but this is a normal part of science...

What we all oppose is that animal fat and high cholesterol play a role. The aim with this website is to inform our colleagues and the public that this idea is not supported by scientific evidence; in fact, for many years a huge number of scientific studies have

[962] Marc Zaffran, préfacier, page 10
[963] Michel de Lorgeril, préfacier, page 13

directly contradicted it »[964]

« Skepticism is very far from denial, the stubborn refusal to admit the truth in the face of overwhelming evidence for it. Statinators are deniers. Skeptics beg to be convinced but they are adepts of the philosophy of English-Austrian philosopher Karl Popper whose most famous saying is 'Science is not to prove, but to disprove'. Healthy skepticism, especially if scientifically and rigorously argued is essential for the evolution of science and of conscience, because without the latter science will be ruinous »[965]
Le réseau international des sceptiques du cholestérol (Traduction libre du titre de l'association)
* Leur porte-parole Uffe Ravnskov est danois, interniste, néphrologue, ancien professeur de l'Université de Copenhague, devenu chercheur indépendant. Il a obtenu une reconnaissance internationale pour ses recherches et de nombreuses études scientifiques, menant à la publication d'un livre déclarant que l'hypothèse lipidique largement popularisée est scientifiquement invalide. Sa pensée va dans le même sens que celle Michel de Lorgeril, cardiologue grenoblois

THE STATIN INSANITY[966] - (Blogue)
L'absurdité statinique

THE STATINIZED WOMAN *Pharmacovigilance*
* Title of a book yet to be written… but badly needed. A true 'unmet need'
La femme statinisée
***** Titre d'un livre qu'il faudrait vivement écrire… pour révéler au grand jour l'histoire de toutes ces femmes qui souffrent de malaises musculaires chroniques reliés à la prise inutile de statine en prévention primaire voire en prévention secondaire, qui se font dire par leur prescripteur que le produit n'est pas en cause, qui se font dire que si elles cessent elles devront se chercher un autre médecin, voire qu'elles mettent leur vie en danger …

alors qu'aucune étude fiable ne montre clairement qu'une statine prolonge la vie d'une femme à faible comme à haut risque coronarien et qu'il n'y a aucune preuve de prolongation de l'espérance de vie chez les femmes statinisées en vertu d'hypercholestérolémie polygénique avec ou sans antécécents coronariens, quel que soit leur âge

THE TRUTH ABOUT STATINS: Risks and Alternatives to Cholesterol-Lowering Drugs - (Livre)
Barbara H ROBERTS. New York; Gallery Books : 2012 – 256 pages

« Smoking, diabetes, obesity, high blood pressure, a sedentary lifestyle and strong family history of heart disease are far more significant, Roberts says. She has researched and treated lipid disorders since the 1970s and is an outspoken critic of widespread statin usage with her book…

Roberts has led studies over the last 40 years and criticizes the way pharmaceutical companies interpret data. In particular, women and men are vastly different with how cholesterol levels and medication impact them, she says. In men a risk factor is high LDL. In women, high LDL levels are not shown to cause any increase in heart disease, Roberts says...

Then there are the side effects of statins, including muscle pain, muscle damage, increased risk of diabetes and cataracts, fetal defects when taken during pregnancy, liver and kidney damage. These are not innocuous medicines, Robert says, and we know that just eating a plant-based Mediterranean-style diet lowers your risk…with no side effects...

You can game the system, these randomized double-blind controlled trials are supposed to be the gold standard for clinical research, but there are lots of problems with them »[967]
La vérité sur les statines : risques et alternatives aux réducteurs de cholestérol (Traduction libre du titre du livre)

THREE REASONS TO ABANDON LOW-DENSITY LIPOPROTEIN TARGETS: An Open Letter to the Adult Treatment Panel IV of the National Institutes of Health - (Article)
HAYWARD RA, KRUMHOLZ HM. *Circ Cardiovasc Qual Outcomes* 2012; 5: 2
Trois raisons pour abandonner les cibles de LDL (Traduction libre du titre de l'article)
« L'idée souvent avancée d'ajuster dose de statine et cible de LDL pour obtenir la LDL la plus basse possible, relève d'une hypothèse qui n'est fondée sur aucun des grands essais d'intervention : tous utilisaient une dose fixe de statines, éventuellement avec des ajustements modestes…

[964] http://www.thincs.org/
[965] Paul v Nguyen, 2014
[966] David Newman 2013. http://www.huffingtonpost.com/david-h-newman-md/statins_b_4277001.html?utm_hp_ref=tw
[967] Barbara Turnbull, The Star, 28.10.2014

et la sécurité de 'traiter à la cible' (treat to target) est loin d'être démontrée, comme le rappelaient récemment encore deux cardiologues Américains de l'Université de Yale, peu suspects d'être des 'anti statines' systématiques »[968]

THRESHOLD VALUES LOWERING *Santéisme biologique*
* In 1998, WHO lowers the threshold for total cholesterol from 240 mg/dl (6,2 mmol/l) to 200 mg/dl (5,2 mmol/l), creating 42 M new american patients in 24 hours, making them candidates to statinisation for life, 'for better, for worse, in sickness, in health'
« Perhaps the biggest threat to the concept of (true) prevention is the progressive lowering of thresholds for 'prediseases', particularly hypertension, *serum choles*terol and blood sugar »[969] - « So what does it mean to be normal if no one is ? »[970]
abaissement des valeurs-seuil
« La plus grande menace au concept de (la vraie) prévention est l'abaissement progressif des valeurs seuils des 'prémaladies', notamment la tension artérielle, le cholestérol sérique et la glycémie »
* Cet abaissement concerne le diagnostic et les objectifs du traitement; il relève du *santéisme biologique*

« En manipulant des membres influents de la communauté médicale, les lobbys industriels ont peu à peu modifié les normes de certaines valeurs biologiques – comme le taux de cholestérol et la tension artérielle – afin d'augmenter le nombre de patients susceptibles d'êtres traités »[971] et on devrait ajouter le diabète léger chez patients à faible risque

TNT, THE TRIAL *Prévention secondaire - Coronariens stables – Atorvastatin 10 mg c. atorvastatin 80 mg – Comparaison de doses*
Treatment to New Targets
* Princeps publication : LaRosa/*NEJM*/2005[972]
* Private funding : Pfizer

METHODOLOGY
* Participants demography : 10 001 randomized; 4045 or 80.8% men; 19.2% women
* Participants health : 100% with CVD - Baseline lipids : LDL-C < 3.36 mM (130 mg/dL)

* Inclusion criteria : stable CHD; LDL-C < 3.4 mM (130 mg/dL)
* Duration : 4.9 years median (58.8 months)

* Comparison : atorvastatin 80 mg vs. 10 mg
* Control group : atorvastatin 10 mg

* Primary composite endpoint defined with 5 major CV events, whichever component occurs first : [death from CHD + nonfatal non-procedural MI + resuscitation after cardiac arrest + fatal stroke + nonfatal stroke] - Validity is decreased somewhat by mixing fatal with non fatal events, leading to heterogeneity in seriousness and in frequency

Participants health :
* LCL-C were 2.0 mmol/l in the group treated with atorvastatin 80 mg once daily and 2.6 mmol/l in the group treated with atorvastatin 10 mg once daily

Run-in period, open label :

« The trial had run-in periods, which means that people who complained of side effects from statins were excluded from the trial. For example, 35% of the statin users were excluded during the open-label run-in in TNT. Thus, the actual adverse events rate are certainly higher than in the trials[973] », a major flaw in the external validity of patient selection and a form of *cheating* by omitting this manipulation in the abstract

"Randomised patients were screened carefully and pre-exposed to the active drug through a run-in period thus excluding those intolerant to the study drug, up to 30% of eligible patients in the case of the TNT trial"[974], making the detection of ADRs irrelevant to a clinical setting and compromising external validity with regards to the target real-life population

[968] Jean-Pierre Vallée. Éditorial. Médecine 2013 ; 9(4) : 148
[969] Starfield et al. JECH 2008;62 :580-3
[970] Nortin Hadler. Worried Sick, page 52
[971] Martin Winckler. Postface. Les inventeurs de maladies. Jörg Blech. Paris : Actes Sud, 2005 - page 257
[972] LaRosa et al. N Engl J Med 2005; 352: 1425 - http://www.nejm.org/doi/pdf/10.1056/NEJMoa050461
[973] Rita Redberg, JAMA Intern Med editor
[974] Paul v Nguyen, 2014

* Positive compliance (active group adherence) : 92.8%
* Negative compliance (control group adherence) : 94.7%

RESULTS
In relative risks for the high dose :

* Primary end point : relative risk reduction = -22%
* Nonfatal MI : relative risk reduction = -22%
* Fatal or nonfatal stroke : relative risk reduction of -25 %

* Major coronary event : relative risk reduction of -20%
* Cerebrovascular event : relative risk reduction of -23%
* Hospitalisation for congestive heart failure : relative risk reduction of -25%

* Any CV event : relative risk reduction of -19%
* CV mortality relative risk reduction of -20%, NS
* No change in TOTAL MORTALITY
* Serious adverse events : No difference

* Any coronary event : relative risk reduction of -21%
* Primary composite endpoint : 8.7% on high dose, and 10.9% on low dose – relative risk reduction of 22% - absolute risk reduction of -2.2%, annual absolute risk reduction of 0.49% and annual NNT of 204 patient-years, amounting to an inefficacy rate of 99.51% under trial conditions; in daily practice the NNT could rise to 300, even 400 patient-years

* TOTAL MORTALITY : 5.6% on high dose or 1.14% per year; 5.7% or 1.12% per year on low dose (NS) – relative risk reduction = -2% - annual absolute risk reduction = 0.02% and NNT = 5000 patient-years; annual inefficacy rate of 99.98%

Reporting of harms :
* Liver aminotransferase : ARI of +0.8% on 80 mg daily dose

* New onset diabetes not reported in princeps publication ; RRI of +19%, reported by metanalyst Preiss
* Health related quality of life *not reported*
* Serious adverse events : not reported

* Cancer mortality relative risk increase in women, p= 0.004 – « The findings of increased incidence of breast cancers is documented in the TNT trial »[975] …

« The secondary analysis[976] of the TNT study reported a large excess in cancer mortality in women (p=0.004). Alarmingly, annualized cancer mortality was 1 in 1000 patients in the low-dose atorvastatin group and 4 in 1000 patients in the high-dose group. Furthermore, there was a trend (HR = 1.10, NS) towards increased total mortality in the high-dose compared to the low-dose atorvastatin group, neutralizing any benefit in CV mortality »[977]

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE

l'essai dit TNT
* Comparaison : forte dose (80 mg) d'atorvastatine c. faible dose (10 mg) servant de groupe témoin
* Publication princeps : LaRosa/*NEJM*/2005[978]
* Financement : privé, Pfizer
* Suivi moyen : 4.9 ans (58.8 months)

* Structure : randomisation, sans groupe placebo, double insu; plus de 1000 participants; plus d'un an de suivi
* Démographie des participants: 7595 randomisés ; âge moyen 61 ans, de 35 à 75

[975] Paul v Nguyen, 2014
[976] Wenger et al. Heart 2008 ; 94 : 434
[977] Rosenberg et al. Int J Cardiol 2009 : 145 - doi:10.1016/j.ijcard.2008.12.122
[978] LaRosa et al. NEJM 2005; 352(14): 1425 – DOI: 10.1056/NEJMoa050461 - Complet sur http://www.nejm.org/doi/full/10.1056/NEJMoa050461

* Santé des participants : maladie coronarienne documentée ; LDL-C entre 3,4 et 6,5 mM au départ (réduit à moins de 3.4 mM après 8 semaines de qualification (run-in period) sous atorvastatine 10 mg selon NICE 2014)

Résultats des critères d'évaluation :
* Mortalité totale : augmentation relative du risque de +10%, NS, sous forte dose
* Mortalité CV : relative risk reduction de -20%, NS

Résultats de statinovigilance:
* Nouveau diabète : 659 sur 7595 ou 8.68% ont présenté un nouveau DT2
* Rhabdomyolyse : aucune observation sous faible ou forte dose, ce qui soulève un doute sérieux sur la surveillance des EIM

* Transaminases hépatiques (> 3x la limite supérieure) : augmentation relative de 3.9 x ou 390 %
* Cancer chez les femmes : Augmentation relative de 4x ou 400%, et augmentation absolue de 3 / 1000 femmes-année pour un NNH = 333 femmes-année

* Conclusion : résultats cliniquement négatifs ; numériquement il y a une réduction de plusieurs événements CV mais on observe davantage d'EIM ainsi qu'une tendance numérique de cancérogénécité chez les femmes

TOO HIGH NNTs, TOO MANY ADRs *Rapport bénéfice/risque*
« If you look at the "published data", if you have established heart disease and you got heart attack, taking a statin every day for 5 years, there's a one in 83 chance that that will save your life [annual NNT = 415]. That information isn't something that is given by chance to any patient. That is really important. Actually that's a much more *informative* and *transparent* way to understand the benefit they're going to get…

Statins are essentially mitochondrial poison. They inhibit an enzyme called HMG-CoA reductase, which is how they work to lower cholesterol. But that same enzyme is also responsible for a number of other things like making coenzyme Q, which is responsible for the muscle pain and the fatigue. Then it also facilitates the conversion of vitamin K1 to K2, another important nutrient for heart health.

Finally, it actually blocks the formation of ketones, which is really an essential part of mitochondrial nutrition and overall health. If you can't make ketones, you're really impairing your whole body metabolism and raising your risk for a variety of other diseases »[979]
NNT trop élevés, trop d'EIM
* un NNT annualisé de 415 est un bénéfice qui équivaut à une extension de vie de 21 heures par année de traitement en prévention secondaire (365 jours de plus pour 1 personne, répartis parmi 415 années de traitement = 21 heures et 6 minutes). Ces 21 heures doivent être comparées aux EIM (de plus en plus admis par les promoteurs depuis l'échance des brevets et le développement des PCSK9), à l'effet nocebo et aux couts directs (achat) et indirects (consultations, cholestérolémies), bref à la qualité de vie durant une année

TOTAL AND CORONARY MORTALITY IN PRIMARY PREVENTION
« Before the JUPITER trial, statins had not been found to reduce total or coronary mortality in women, men, or combined for primary prevention. Moreover, the recent MEGA study enrolled more women than men in large numbers, but the reduction in events was significant only in men »[980]

« JUPITER was halted at a median follow-up of 1.9 years after showing a reduction in overall mortality. Although the trial was unblinded at the time, subsequent mortality data would be interesting to review because early stopping is known to inflate estimates of benefit »[981]
mortalité totale et coronarienne en prévention primaire

TOTAL MORTALITY AND TOTAL CHOLESTEROL IN SOUTH KOREA *Hypothèse du cholestérol réfutée*
« My study of TC and all-cause mortality by sex and age in 12.8 M Korean adults found a U-curve relationships between TC and mortality regardless of sex and age. TC ranges associated with the lowest mortality were 210-249 mg/dL in each sex-age subgroup. Inverse associations in the range <200 mg/dL (5.17 mmol/L) were more than 3-fold stronger than positive associations for cholesterol levels ≥200 mg/dL. Positive associations in the upper TC range were strongest for youngest adults

[979] Aseem Malhotra. http://mercola.fileburst.com/PDF/ExpertInterviewTranscripts/Interview-Aseem-Malhotra-SaturatedFats.pdf
[980] Walsh JM, Pignone M. JAMA 2004; 291: 2243 - Petretta M et al. Int J Cardiol. 2010; 138: 25 - Thavendiranathan P et al.. Arch Intern Med. 2006; 166: 2307
[981] Vinay Passad. Ann Intern Med 2014; 160: 867

and weakened with advancing age. *TC levels <200 mg/dL (5.17 mmol/L) may not necessarily be a sign of good health*.[982] »
mortalité totale et cholestérol total en Korée du Sud
* il est 3 fois plus malsain d'avoir un bas cholestérol que d'en avoir un élevé quand la mortalité toute cause est choisie comme critère d'évaluation pertinent et robuste

TOTAL MORTALITY IN PRIMARY PREVENTION *Statinisation inutile, nuisible et couteuse*
"The claimed mortality benefit for statins for primary prevention is more likely a measure of bias than a real effect[983]" according to the only independent drug bulletin in Canada
« Total mortality was not reduced for either men or women »[984] in primary prevention

"For primary prevention, whatever the level of LDL cholesterol, men over 65 years of age, and women of any age who take statins receive no benefit",[985] a good reason to stop repeatedly screening healthy people for cholesterol levels
"Statins had not been found to reduce total or coronary mortality in women, men, or combined, for primary prevention »[986]

« When patients with prior CV disease are excluded, there is no evidence of benefit from statin therapy on total mortality. The mortality from CV disease has decreased by at least 80% in the last 50 years, mostly before the introduction of statins »[987]

« Statins are not associated with a decrease in total mortality in a high-risk primary prevention setting »[988]
« Statins and total mortality in high-risk primary prevention: a 2010 meta-analysis of 11 randomized controlled trials involving 65,229 participants did not find evidence for the benefit of statin therapy »[989]

« Statins might alter what is written on your death certificate but they are extremely unlikely to change the date »[990]
« There are no studies showing atorvastatin saves lives »[991]
« Atorvastatin (Lipitor™) has never been demonstrated to reduce total mortality for primary prevention in any clinical study »[992]
mortalité toute cause en prévention primaire
« Le risque CV fait intervenir de nombreux facteurs dont l'hypercholestérolémie n'est pas le composant principal. Alors que les statines sont en plein essor en prévention primaire, leur bénéfice sur la mortalité globale n'est pas établi. Leur prescription devrait donc être réservée aux sujets à haut risque »[993]

* Elles ne prolongent pas la vie parce que le risque annuel d'événement cardiovasculaire est inférieur à 4 % chez les sujets sans antécédents CV même quand ils sont dits 'à haut risque'. ...

Voici mon argumentaire :

(a) Même en assumant généreusement que la statinisation puisse réduire de 25% le risque relatif de mortalité générale - ce qui d'ailleurs n'a jamais été démontré, et

(b) En assumant que le NNT annualisé (en conditions expérimentales) ne doive pas dépasser 100 personnes-année pour atteindre un seuil quelconque de signifiance clinique, cela équivaut à une réduction absolue du risque de 1% par année de traitement, soit une prolongation de vie de 3,65 jours (ou 88 heures) si on répartit le bénéfice aux 100 sujets statinisés 1 an…

En termes de pharmacoéconomie, si 1 an de statinisation coute directement et indirectement 1000 $, il en coute 274 $ pour ajouter une journée de vie ou 100 000 $ par QUALY, soit le double du plafond recommandé par le NICE (50 000 $) et par d'autres instances sanitaires qui font autorité

(c) Alors il est impossible d'atteindre ce seuil si le risque absolu annuel n'est pas de 4%, puisque 0,75 x 0,04 = 0,03 et que 0,04 – 0,03 = 0,01 ou 1%

[982] Yi Sang-Wook, communication, 2018
[983] Therapeutics Letter 2010;77 - www.ti.ubc.ca/letter77, cité par Ray Moynihan 2011.
[984] Rosenberg et al. citant Petretta et al.
[985] James Wright. Protégez-Vous, Feb 2010, interview translated by Carol Kuschner
[986] S Mora. Circulation, 22.2.2010 on line, Medline 20176986
[987] Jane Smith. http://www.australianprescriber.com/magazine/34/6/169/72
[988] Kaess BM & Vasan RS. Evid Based Med 2011 ; (1):8
[989] Ray et al. Arch Intern Med 2010 ; 170(12): 1024
[990] Malcolm Kendrick. The Great Cholesterol Con
[991] Vos E. Nutr Metab Cardiovas Dis 2007 ; 17 :e19
[992] 10.6.2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf
[993] D Vital-Durand. Rev Med Interne 2014; 35: 151 - http://dx.doi.org/10.1016/j.revmed.2013.11.004

« Les nombres de sujets à traiter 3,5 ans avec une statine pour éviter un décès sont de 151 en prévention primaire et de 68 en prévention secondaire »[994], pour des NNT_{exp} annualisés de 528 années-patients en prévention primaire et de 238 en prévention secondaire. Déjà le bénéfice vital apparaît futile en situation expérimentale forcément artificielle ; si on doublait ces chiffres pour les extrapoler à la pratique courante, les NNT_{clin} annualisés seraient encore plus élevés…

La position dominante des statines dans les profils d'ordonnance et les budgets pharmaceutiques (Top Ten) témoigne de l'inquiétant succès de la promotion directe ou indirecte, ouverte ou insidieuse, et de l'échec d'une formation continue en pharmacothérapie inféodée qui transmet un savoir médical dévoyé, la majorité des ordonnances étant faites - initiées mais surtout renouvelées - dans un contexte de prévention primaire par des médecins de famille influencés par des cardiologues

« Ray et collaborateurs ont publié en juin 2010 une méta-analyse de 11 études en prévention primaire dans des populations relativement à haut risque et ont conclu que 'cette méta-analyse n'a pas trouvé d'évidence d'un bénéfice de l'utilisation de statines sur toutes les causes de mortalité dans un environnement de prévention primaire d'une population à haut risque »[995]

TOTAL MORTALITY IN WOMEN
« No statin trial has ever succeeded in lowering mortality for women »[996] - Eddie Vos reviewed the question in 2006[997] :

a) Two reviews of trials – Criqui & Golomb in J Am Coll Cardiol 2004 ; 44(5) : 1009 and Walsh & Pignone in JAMA 2004 ; 291(18) : 2243 – found no reduction in total deaths and CHD deaths from statin over placebo in women with or without CHD

b) The J-LIT observational study in 41,801 hypercholesterolemic Japanese (mean cholesterol 7 mM, two thirds were women) in Matsuzaki et al. in Circ J 2002 ; 66(12): 1087 - found the 6-year mortality in the lowest on-statin cholesterol categories to be higher (6% dead with < 4 mM) than in persons remaining at high cholesterol (4.1% dead with >7.4 mM)

c) The 4S Scandinavian trial of 4444 coronary patients in Lancet 1994 ; 344(8934) : 1383 – with 19% women, ended with 3 more dead women on simvastatin vs. placebo

d) Another 'successful' study – BMC Med 2005 ; 3 : 6 – found no significant mortality benefit in women
e) In the ASCOT trial, the mortality curves touch until mean study end at 3,3 years. And the study ended with 2 more heart attacks in women, one of which was fatal, on atorvastatin (Lipitor™)

The cited data support removing women[998] from the cholesterol guidelines and from lifelong cholesterol screening if life extension is a patient criterion
mortalité toutes causes chez les femmes statinisées

TOTAL MORTALITY PLACEBO-STATIN DIFFERENCES AT 21-MONTHS ACROSS TRIALS
* Jupiter was stopped prematurely (and without sound medical or ethical reasons) shortly after around 21 months.[999] The 21-month total mortality rates can be compared between the placebo arm and the statin group in 11 trials. Differences are formated in absolute death rates per 100 patients…

« JUPITER was halted at a median follow-up of 1.9 years after showing a reduction in overall mortality. Although the trial was unblinded at the time, subsequent mortality data would be interesting to review because early stopping is known to inflate estimates of benefit »[1000]

In no instances are absolute total mortality reductions as high as 1% or NNTs as low as 100 for 21 months, equivalent to an annual absolute risk reduction of at least 0.57% or an annual NNT as low as 175 patient-years; no difference is observed in 4 trials, and a nominal increase in 2 of them ; statins do not prolong lives:

a) JUPITER : minus 0.6%, NNT = 167 patients for 21 months (equivalent to 292 patient-years)
b) CARDS : minus 0.8%, NNT = 125 (equivalent to 219 patient-years)

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[994] Michel Lievre. BIP31.fr 2011 ; 18(3) : 28 citant HAS 2010
[995] François Melançon, Clinicien plus, mars 2013
[996] http://www.ravnskov.nu/newsletters#Feb%202012
[997] Vos E. Statins for women, elderly : Malpractice ? Nutr Metab Cardiovas Dis 2007; 17: e219
[998] Vos & Rose. CMAJ 2005; 173(10) : 1207
[999] Victor L Serebruany. Cardiology 2011; 120(2): 84 (Editorial) - DOI:10.1159/000330507
[1000] Vinay Passad. Ann Intern Med 2014; 160: 867

c) PROVE IT : minus 0.9%, NNT = 111 (equivalent to 194 patient-years)
d) ALLHAT : plus 0.1%, NNH = 1000 (equivalent to 1750 patient-years)

e) ASPEN : 0 difference
f) ASCOT : 0 difference
g) PREVEND IT : plus 0.2%, NNH = 500

h) HYRIM: 0 difference
i) WOSCOPS : minus 0.3%, NNT = 333 (equivalent to 583 patient-years)
j) AFCAPS : 0 difference
h) MEGA : minus 0.1%, NNT = 1000 (equivalent to 1750 patient-years)
différence entre placebo et statine pour la mortalité toutes causes à 21 mois selon les essais

TOTAL MORTALITY REDUCTIONS ACROSS TRIALS IN PRIMARY PREVENTION
a) « In JUPITER, rosuvastatin showed a relative risk reduction of 20% for total mortality, when compared to placebo (HR 0.80, 95% CI 0.67 to 0.97; P=0.02) »[1001] [but] the baseline rate, taken hereby as the rate in the placebo group, was 1.25% per year. The rate was 1% per year in the rosuvastatin arm…

Therefore the absolute risk reduction (absolute risk reduction) of total mortality was 0.25% per year, amounting to a NNT of 500 person-years, an inefficacy rate of 99.75% per year of treatment, 182 500 rosuvastatin tablets leading to an average life extension of 17.5 hours (10 429 tablets needed to prolong life by 1 hour)…

if you accept the reasoning that one year has 365 days, that delaying death by 1 year is delaying it by 365 days in one lucky person out of 500 person-years, and spreading 365 days over the 500 persons exposed to rosuvastatin, it leads to a negligible 0.73 day of life extension per person (365 / 500 = 0.73) or 18 hours under experimental conditions…

A baseline risk should reach 5% per year if a 20% relative risk reduction were to produce a 1% absolute risk reduction (5% x 0,20 = 1%) amounting to an NNT of 100 patient-years and common sense tells us that 100 is the largest yearly NNT that can reasonably be tolerated for justifiying the term clinically meaningful under experimental conditions (the NNT is most likely higher in clinical settings considering the poor internal and external validities of Jupiter)...

Furthermore the p value is not significant at an alpha threshold of, at the very least 1%, that is warranted when endpoints are multiplied (and manipulated) as in Jupiter…

Finally, the onus of the proof rests on the promoter and, if a clinician wishes to be 95% confident about the evidence relied upon for treating his patients, he should use the upper 95% CI (0.97 in Jupiter), equivalent to a mere 3% relative risk reduction leading to a futile absolute risk reduction and consequently an 'astronomical' annual NNT, well befitting the trial's acronym !
réduction de la mortalité de toute cause dans les essais de prévention primaire

TOWARDS A PARADIGM SHIFT IN CHOLESTEROL TREATMENT : A Re-examination of the Cholesterol Issue in Japan – (Synthèse méthodique) *Épidémiologie – Hypothèse du cholestérol*
Hamazaki/Okuyama/Ogushi/Hama. *Ann Nutr Metab* 2015; 66(suppl 4): 1–116 - DOI: 10.1159/000381654

« All-cause mortality is the most appropriate outcome to use when investigating risk factors for life-threatening disease. We discuss all-cause mortality according to cholesterol levels, as determined by large epidemiological studies in Japan. Overall, an inverse trend is found between *all-cause mortality* and total (or LDL) cholesterol levels: mortality is highest in the lowest cholesterol group without exception...

If limited to elderly people, this trend is universal... Elderly people with the highest cholesterol levels have the highest survival rates irrespective of where they live in the world...

Based on the evidence we have presented in this issue, we believe it is time for a paradigm shift in the way we view and treat cholesterol. And it does look like this is starting to happen. In 2013, the *American College of Cardiology* and the *American Heart Association* released a new guideline for cholesterol, stating that :

'*...the Expert Panel was unable to find RCT evidence to support titrating cholesterol-lowering drug therapy to achieve target LDL-C or non-HDL-C levels, as recommended by Adult Treatment Panel III*'... This statement by ACC/AHA in itself destroys the

[1001] Davis & Dietrich. BMJ 2014; 348: g1795 - doi: 10.1136/bmj.g1795 (26.2.2014)

mainstay of guidelines promoting target LDL-cholesterol levels…

Our fervent wish is that, through this supplementary issue, people can see that the *cholesterol hypothesis* relies on very weak data—and sometimes considerably distorted data. Indeed, many studies in Japan actually show that cholesterol plays a very positive role in health...

We hope that professionnal societies and health authorities will move toward recognizing cholesterol as a friend not an enemy. In the meantime, we will continue pushing for acceptance of the anti-cholesterol hypothesis, to reverse what we see as the biggest mistake made by medical science in the previous century. »
Vers un changement de paradigme dans le traitement du cholestérol : Un ré-examen de la question du cholestérol au Japon
(Traduction libre du titre de la synthèse)
* Synthèse méthodique magistrale qui démolit l'hypothèse du cholestérol, réfute les arguments justifiant sa réduction pharmacologique et blâme les sociétés professionnelles et les autorités de santé qui promouvoient la réduction médicamenteuse de la cholestérolémie. Publiée en avril 2015, accessible gratuitement en ligne

TOXICITY FROM DRUG INTERACTION *Pharmacocinétique – Étude populationnelle de coho*rte
« In older adults, coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 increases the risk for statin toxicity. Compared with azithromycin, coprescription of a statin with clarithromycin or erythromycin was associated with a higher risk for hospitalization with rhabdomyolysis (absolute risk increase or ARI of +0.02%, NNH = 5 000) or with acute kidney injury (ARI of +1.26%, NNH = 79) and for total mortality (ARI of +0.25%, NNH = 400) »[1002]
toxicité par interaction médicamenteuse

TRANSIENT GLOBAL AMNESIA *Sémiologie - Statinovigilance*
amnesic stroke / ictus
ictus amnésique; amnésie globale transitoire
= trouble mnésique transitoire et d'installation brutale, d'une durée de 1 à 24 heures par définition. Peut constituer un EIM (quand un médicament est soupçonné) ou un ÉI (sans soupçon d'un médicament). Étrangement, les *statines* peuvent en provoquer, lisez ce qu'en dit un médecin astronaute pour la NASA, Duane Graveline[1003]

TRANSPARENCY LACK AT THE CCT (UK)
« Sharing the individual patient level data from the statin trials would be another fine contribution by this highly respected group of research leaders and a strong message that no single person or group should have exclusive access to trial data. In the end, the sharing of these data by the trialists may do more to advance their interpretation of the data and promote consensus than anything else they could do[1004] »

« *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them... The reply in 2015 with the record of the status and nature of response, was NO RESPONSE from the principal investigators of the following trials: AURORA, BIP, CARE, CORONA, FIELD, GISSI-HF, GISSI P HPS, IDEAL, LIPS, MEGA, POST-CABG, PROSPER, 4S, SEARCH, SHARP, TNT, WOSCOPS[1005], and PROVE IT-TIMI 22 investigators asked response not to be made public
défaut de transparence à la CCT (R-U)

TREATING TO TARGET DOSING
targeted adjusted dose

a) 4S trial[1006] : to TC <5.2 mM (LDL <3.8mM) – In women, no valid numerical reductions in total or coronary mortality, nonfatal MI or CHD events, and 3 more dead women on simvastatin than on placebo – No clinical significant benefits, even if relative risk reduction of CHD deaths was -42%, a finding hyped for decades but never confirmed in 31 other trials

b) AFCAPS trial : to LDL <2.8 mM – lovastatin vs placebo in primary prevention, associated with some relative risk reduction but no clinically significant absolute risk reduction
c) GREACE trial : to LDL <2.6 mM : comparing atorvastatin in unblinded patients, by unblinded caregivers, against usual care in

[1002] Patel et al. Ann Intern Med 2013; 158(12): 869 - doi:10.7326/0003-4819-158-12-201306180-00004
[1003] http://www.spacedoc.net/statin_amnesia_true_cost.html
[1004] Harlan M Krumholz. BMJ 2016;354:i4963 doi: 10.1136/bmj.i4963
[1005] http://www.bmj.com/campaign/statins-open-data
[1006] SSSS. Lancet 1994 ; 344(8934) : 1383

secondary prevention
posologie ajustée sur cible

TRIGLYCERIDES THRESHOLD FOR PHARMACOTHERAPY *Seuil de traitement*
« 500 mg/dl fasting is the new threshold recommended in 2011 by the AHA… Why are doctors prescribing fibrates with growing enthusiasm when data from negative drug trials support an increasingly conservative approach to drug treatment ?[1007]»
* Note that 500 mg/dl [5.6 mmol/l] carries a risk of pancreatitis and warrants lowering for that reason, irrelevant to CV prevention. But the CV benefits from reducing triglycerides with drugs have yet to be demonstrated…
seuil de triglyridémie à traiter pharmacologiquement
« 5,6 mmol/l à jeun est le nouveau seuil recommandé en 2011 par l'Association américaine de cardiologie… Pourquoi les médecins prescrivent-ils des fibrates avec un enthousiasme croissant alors que les données qui ressortent d'essais négatifs militent en faveur d'une approche de plus en plus conservatrice vis-à-vis de la pharmacothérapie? »

« A ce jour, la baisse des triglycerides ou l'augmentation du HDL-C par des moyens pharmacologiques n'a pas été associée à une prévention de la survenue d'évènements CV voire à une diminution de la mortalité totale »[1008]
* Noter que 5,6 mmol/l comporte un risque de pancréatite et mérite un abaissement pour ce motif, sans égard à la prévention CV

TRIPARANOL SAGA
See MER/29 SAGA

TRUNCATED TRIAL *Essais - Méthodologie*
« It is now well acknowledged – Bassler et al. *JAMA* 2012; 303 :1180 - de Lorgeril et al. *Arch Intern Med* 2010; 170 : 1032 - Pocock & Hughes *Control Clin Trials* 1989; 10(suppl) : 209S - that truncated trials overestimate the reported benefits of any treatment »[1009]

* Truncated trials overestimate the reported benefits of any treatment. This overestimation is independent of prespecified rules and greater in truncated trials having fewer than 500 events[1010]
« Truncated trials overestimate the reported benefits of any treatment. This overestimation is independent of prespecified rules and greater in truncated trials having fewer than 500 events....

Therefore a 5-year (or a 10-year) NNT based on extrapolation from data obtained by meta-analyses that included truncated trials with a relatively short duration, like ASCOT-LLA, or CARDS, JUPITER, whose median follow-ups were 3.3 years, 3.6 years, and 1.8 years respectively, may overestimate the benefits and cannot be considered a reliable indicator for decision-making when considering starting a "lifelong" treatment for a specific patient »[1011]
essais tronqués
* Jupiter (1,8 an) est l'exemple flagrant d'arrêt prématuré, mais il y a aussi Cards (3,9 ans), 4S, Afcaps, Gissi-P, Ascot-Lla (3,3 ans), Illuminate, dal-Outcome

TRUTHS ABOUT CHOLESTEROL *Hypothèse lipidique – Hypothèse statinique*
a) Diet has hardly any effect on your cholesterol level
b) There is no evidence at all that lowering your cholesterol level will lengthen your life
c) The drugs that can lower it often have serious side effects, and always reduce quality of life in some way or another
d) Cholesterol is probably just a marker for an underlying imbalance that is not being addressed by just lowering cholesterol »[1012]
vérités à propos du cholestérol

UK-HARP-I, THE TRIAL
First United Kingdom Heart and Renal Protection

ULTRASTRUCTURAL DAMAGE IN SKELETAL MUSCLE *Statinovigilance – Myopathie – Pathologie*

[1007] http://www.cardioexchange.org/screen-with-nonfastingtriglycerides/
[1008] BIP 2014 no 2 page 5
[1009] de Lorgeril et al. RRCT 2012 ; 7(2) : 1
[1010] Bassler et al. JAMA 2010 : 303 : 1180
[1011] Nguyen & Biron. BMJ 2014;349:g4980 - doi: http://dx.doi.org/10.1136/bmj.g4980 - http://www.bmj.com/content/349/bmj.g4980/rr/763032
[1012] http://www.drfranklipman.com/what-is-your-take-on-cholesterol/

* People on statins without any symptoms may have microscopic evidence of muscular damage : « To investigate further the mechanism that mediates statin-induced skeletal muscle damage, skeletal muscle biopsies from statin-treated and non-statin-treated patients were examined using both electron microscopy and biochemical approaches. We report clear evidence of skeletal muscle damage in statin-treated patients, despite their being asymptomatic...

Though the degree of overall damage is slight, it has a characteristic pattern that includes *breakdown* of the T-tubular system and subsarcolemmal *rupture*. These characteristic structural abnormalities observed in the statin-treated patients were reproduced by extraction of cholesterol from skeletal muscle fibres *in vitro*..

These findings support the hypothesis that statin-induced cholesterol lowering *per se* contributes to *myocyte damage* and suggest further that it is the specific lipid/protein organization of the skeletal muscle cell itself that renders it particularly vulnerable »[1013]
lésions ultrastructurelles dans le muscle squelettique

UNBLINDING IN STATIN TRIALS
loss of blinding in statin trials

« Electronic health records may threaten blinding in trials of statins. Records of changes in cholesterol can show whether patients are receiving intervention or not—biasing trials to make statins look more beneficial than they really are… Newly released US guidelines on cholesterol that promote more use of statins have been criticised as being over-reaching and biased. These guidelines are based on a meta-analysis of individual data from many randomised trials...

But a previously overlooked problem may also have inflated the perceived benefits of statins: a lack of concealment of patient allocation. In randomised controlled trials of the clinical efficacy of CV drugs in general—and statins in particular—a key control measure is the double blinding of patients, caregivers, and especially investigators and outcome assessors...

A lack of blinding may significantly bias results in favour of the drug under study, particularly if clinical efficacy is based mostly on 'soft outcomes' (those influenced by judgment or perception), such as the diagnosis of angina, or decisions on admission to hospital or on cardiac catheterisation or revascularisation. Unblinding can occur inadvertently in clinical trials when patient data are available in electronic health records »[1014]

« As pointed out in the BMJ[1015], incidental unblinding of patients data by electronic records indeed happen. Often trial participants remain under care of their family physicians who ought to look at their patients' blood results...

It is not uncommon that individuals under stress with disordered breathing or after indigestion referred for cardiology review because of perceived high CV risk and if cholesterol levels are elevated or HDL-C is low then perception of risk escalates because epidemiological observations and animal studies indicated association of cholesterol which by many considered causative for atherosclerosis based CV events...

These perceptions prompt stress testing or direct coronary catheterization and subsequent PCI's on coronary arteries because of oculomotor reflex, sometimes without induced ischemia due to incidental discovery of suitable 'lesion'. It well may be that by this mechanism many revascularizations have occurred in the placebo arms of primary prevention statin trials making composite primary end point look good...

But this as evidenced by every primary prevention statin RCT hasn't benefited CV mortality. Agree, only hard end points should be used for evidence of benefit of intervention in primary prevention trials »[1016]

« We found some risk of bias for each of 12 reviewed RCTs. Loss of blinding to treatment allocation probably occurred in all 12 RCTs, because statins predictably lower LDL-C and the physicians managing the patients knew the lipid parameters. This loss of blinding likely biased clinical decisions regarding revascularization procedures and how outcomes were categorized (e.g. transient ischemic attack or reversible ischemic neurological deficit)...

Fewer revascularization procedures in the statin group as a result of loss of blinding would result in fewer complications

[1013] Draeger et al. J Pathol 2006; 210: 94 - DOI: 10.1002/path.2018
[1014] Paul v Nguyen. BMJ 2014; 349 ; g5239 (20.8.2014) - doi: http://dx.doi.org/10.1136/bmj.g5239
[1015] Paul v Nguyen, op. cit.
[1016] Alexei Chataline, communication, 2014

secondary to the procedures, e.g. myocardial infarctions »[1017]

« 43% of major vascular events are coronary revascularizations, an outcome that is highly subject to loss of blinding bias and thus the benefit observed could partially or completely be a measure of bias. Loss of blinding occurs in all statin trials because the statins are so good at lowering cholesterol the investigators know who is receiving the drug »[1018]

levée de l'insu / perte de l'insu dans les essais statiniques

« La majorité des essais cliniques sont rapidement (généralement après < 6 mois) décodés par les investigateurs eux-mêmes [sous prétexte de vérifications variées, notamment la survenue d'EIM sévères] ou par les patients eux-mêmes (avec ou sans la complicité de leur médecin traitant) puisqu'il suffit d'une prise de sang et d'une mesure du cholestérol pour savoir si on reçoit la statine (et pas le placebo) ; sans parler des multiples EIM qui eux-aussi dénoncent le médicament »[1019]

ACADEMIC PHARMA-CO-DEPENDENCE: CTT and CTSU (UK) *La connection Oxford – Collusion universitaire*

« Collins detailed the grants received by his unit to fund research over the past 20 years (until one year ago) [*Editor's note: this refers to the time of writing, May 2015]*. Merck (which makes many hundreds of millions of dollars every year from cholesterol-lowering drugs) has funded the Unit's work to the tune of £179,700,000 [C$ 300 million in 2016] over the past 20 years. The next biggest funder has been Schering-Plough – which was acquired by Merck in 2009 – at £40m...

That combined total is equivalent to a run rate of £900,000 per month [C$ 1,5 million in 2016] every month for 20 years; in today's money that amount is almost certainly more than £1 million per month, on average. After Merck/Schering, the next biggest funder in Collins's declaration was the Medical Research Council at £13,700,000 over the 20-year period...

That money does not of course go into Prof Collins's pocket: it is to fund the research; but he is right to declare such funding as a potential *conflict of interest*. Trials included in the *Cholesterol Treatment Trialist's Collaboration* (CTTC) were, as Abramson noted, funded by statin manufacturers (a fact acknowledged by Prof Collins and the CTTC)[1020] » states the *Committee on Publication Ethics* (COPE - UK) on April 15th, 2016

« The CTT or Cholesterol Treatment Trialists is part of the CTSU or Clinical Trial Service Unit and Epidemiological Studies Unit and conducts periodic meta-analyses of individual participant data on mortality and morbidity from all relevant large-scale randomised trials of lipid-modifying treatments »[1021]

« CTT is tasked with conducting research on statin drugs. Mainly, it pools together the results of industry-funded statin studies, and then occasionally makes pronouncements on this class of drugs. I don't think I would be mischaracterising the CTT to say that it is a staunchly pro-statin body (or lobby group) »[1022]

« A serious concern is that the data driving NICE 2014 guidance on statins comes almost entirely from pharmaceutical company funded studies. Furthermore, these data are not available for review by independent researchers, only those who work for the Oxford CTT Collaboration ...

The CTT has commercial agreements with pharmaceutical companies which apparently means that they cannot release data to any other researchers who request to see it. Which, in turn, means that the latest reviews of the data by NICE (2014) and also by the Cochrane group are totally reliant on the CTT 2012 meta-analysis[1023] of this concealed data »[1024]

« As a contributor to lipidsonline.org, Rory Collins declares support from AstraZeneca, Bristol-Myers Squibb, Merck, Sanofi. No such interests were declared in this 'game-changing' statin paper[1025]. I found a 'current and recent grants' declaration from fellow CTT Collaboration secretariat member, Colin Baigent, on his and Collins' behalf, to be particularly enlightening:

Merck & Schering £39M; Merck £52M; British Heart Foundation £9M + £2.7M; Medical Research Council £13.8M (recent MRC appointees being Senior Vice-President and Chief Scientific Officer of Pfizer Neusentis, and Executive Vice President of Innovative Medicines at AstraZeneca)[1026] ; Bayer £965,000 ; Solvay £978,000 - That's £116 M [US$ 197 M] before you get

[1017] TI/ Therapeutics Letter # 77, 2010
[1018] James Wright, communication 2013
[1019] Michel de Lorgeril, 2014 - http://michel.delorgeril.info
[1020] Documents relating to a complaint about The BMJ made to COPE by Jane Armitage, Rory Collins et al, October 2014 - April 2016
[1021] http://www.ctsu.ox.ac.uk/research/meta-trials/ctt/ctt-website
[1022] John Briffa. http://www.drbriffa.com/2014/03/27/if-statins-are-so-safe-why-wont-some-researchers-let-us-see-their-data/
[1023] Mihaylova et al. Lancet 2012; 380(9841): 581
[1024] Thompson et al. 2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf
[1025] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437972/
[1026] http://www.mrc.ac.uk/Newspublications/News/MRC008756

into the small change »[1027]

« CTT is a part of the CTSU in Oxford, which has carried out many very large studies on statins, and other lipid modification agents with pharmaceutical company support, and has received hundreds of millions in funding over the years. To consider just one such study (REVEAL) is being funded by Merck Sharp & Dohme, which developed anacetrapib. A grant of £96 M towards the cost of this multi-million dollar study has been provided to the University of Oxford…

We are concerned that financial conflicts of interest and major commercial bias may have corrupted the database on statins, resulting in an underestimate of the incidence of statin side-effects »[1028] - « They hold all the trial data on statins including ADRs and will not allow anyone else to see it. They have signed confidentialy agreements with the companies, these data are kept secret and have never been seen by any other independent researchers » bemoans Malcolm Kendrick[1029]

« Commercial Grants to Oxford University for any Clinical Trial Service Unit (CTSU) trials or other commercially-funded research over the past 20 years (but excluding CTSU core support from MRC, CR-UK and BHF for these and other studies, as well as other non-commercially funded research) :

a) ASCEND trial of aspirin and fish oils (2004-ongoing) : Abbott/Solvay: £2.0M plus drug supply - Bayer: £1.7M plus drug supply
b) ATLAS trial of tamoxifen duration (1997-ongoing) AstraZeneca: £1.0M plus drug supply
c) CCS-2 trial of metoprolol and clopidogrel (1999-2005) : AstraZeneca: £1.1M plus drug supply - Sanofi: £1.1M plus drug supply
d) China Kadoorie Biobank (2002-ongoing) : AstraZeneca: $300K - GlaxoSmithKline: £2.2M - Merck: £200K

e) Elinogrel feasibility trial (2010-2011) : Novartis: £500K
f) Establishing Fuwai-Oxford research centre (2010-ongoing) : Merck: £1.1M
g) Heart Protection Study or HPS (1993-2002) : Merck: £5.5M plus drug supply - Roche: £5.5M plus drug supply
g) Heart Protection Study or HPS follow-up studies (2003-ongoing) : Merck: £1.2M - GlaxoSmithKline: $400K - Liposcience: £50K

h) HPS2-THRIVE trial of niacin/laropiprant (2005-ongoing) : Merck: £53M plus drug supply
i) HPS3/TIMI55-REVEAL trial of anacetrapib (2010-ongoing) : Merck: £96M plus drug supply
j) Pfizer Innovation Award (2004) : Pfizer: £50K to CTSU for unrestricted research
k) PROCARDIS genetic study (1998-2011) : AstraZeneca: £1.7M

k) SEARCH trial of simvastatin dose (1997-2010) : Merck: £22.7M plus drug supply
l) SHARP trial of simvasatin/ezetimibe (2002-2013) : Merck/Schering: £40M plus drug supply
m) STICS trial of rosuvastatin (2011-2014) : AstraZeneca: $100K
n) 3-C trial of transplant rejection (2009-2017) : Pfizer: £500K - Novartis: £350K

o) Patents : Myopathy-related genetic variant; licensed by Oxford University to Boston Heart Diagnostics; all personal income waived in favour of the University and CTSU to support research
p) Note: The CTSU conducts, analyses and interprets its clinical trials and other research independently of industry and other funders, with the datasets held by the CTSU rather than by the funders…

In accordance with CTSU's long-term policy (see attached), honoraria, consultancy or other payments have not been received directly or indirectly from industry, either personally by Professor Collins or by the University (except for reimbursement of travel and accommodation costs for taking part in relevant scientific meetings) »

« We are compelled to address the issue of financial conflicts of interest as a potential source of bias, as well. An example is the cholesterol guidelines published in 2012 by the *Cholesterol Treatment Trialists'* (CTT) Collaborators [64]. This group is part of the *Clinical Trials Service Unit* (CTSU) in Oxford, which has received hundreds of millions of pounds over recent years to conduct research on behalf of the pharmaceutical companies...

Their conclusion was that 'in individuals with 5-year risk of major vascular events lower than 10%, each 1 mmol/l reduction in LDL cholesterol produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years. This benefit greatly exceeds any known hazards of statin therapy' »[1030]
pharma-co-dépendance universitaire : CTT et CTSU (RU)

[1027] http://www.bmj.com/content/348/bmj.g3306?page=1&tab=responses
[1028] Thompson et al. 2014 - http://www.nice.org.uk/media/877/AC/NICE_statin_letter.pdf
[1029] drmalcolmkendrick.org 2014.12.1
[1030] Diamond & Ravnskov, op. cit.

« Le CTSU d'Oxford (RU), est le groupe de statisticiens de loin le plus favorable aux statines et pour cause, car, malgré ses apparences officielles et publiques, le CTSU est une officine privée, certes liée par contrat à la Radcliffe Infirmery d'Oxford, qui lui confère son apparence publique, mais il est pour la plus grande part, et de loin, financé statutairement par Merck, Sharp & Dome et au cas par cas, par les firmes Glaxo-SmithKline, Astra-Zeneca et Bristol-MyersSquibb, fabricants de statines…

Le CTSU a été fondé par Sir Richard Doll, lourdement condamné peu avant sa mort pour malversations et falsifications graves … C'est une société-écran »[1031] - « Les méta-analystes du CTSU d'Oxford ont donné de nombreux exemples de licences, dérives et falsifications »[1032]

* En plus des subventions directes, ces chercheurs recoivent des sommes de fondations publiques ou gouvernementales majoritairement financées par les mêmes firmes, sommes que certains considèrent comme de l'argent blanchi…

UNDER-REPORTING OF ADVERSE REACTIONS IN SPONSORED TRIALS
« Company-funded studies show side effects in <1% of patients. Independent studies show them in at least 20%. Inquiries have suggested adverse effects can be minimised in drug company trials by excluding patients if they fail to tolerate statins during run-in periods or if they have certain pre-existing health problems...

Evidence from drug company sponsored trials have been shown to play down the risk of statin side effects including diabetes, impotence, cataracts, muscle pains, mental impairment, fatigue and liver dysfunction »[1033]
sous-évaluation / sous-estimation des effets indésirables dans les essais sponsorisés
* On peut dire que la statinovigilance expérimentale ne se porte pas bien…

UNDERESTIMATION OF MYOPATHIES BY MISCODING IN PHARMACOVIGILANCE DATABASES *Statinovigilance – Codage dans MedDRA – Présentation trompeuse*

« A way to *minimize* the muscular symptoms is to separate them into numerous categories. According to the FDA Adverse Event Reporting System (FAERS), [which uses the very 'granular' MedDRA terminology for ADRs], adverse muscular symptoms are recorded in 11 categories (muscle disorder, myopathy, muscle tightness, musculoskeletal stiffness, myalgia, muscular weakness, muscle cramp, muscle enzyme, muscle fatigue, muscle necrosis and muscle spasm)...

In most of them, a low incidence of adverse effects is reported, which disperses the total number of adverse event reports across many subtypes of pathology. Taken together, however, the total number of myopathy-related adverse events is substantial »[1034]

« Amongst classical means to fraud in clinical research (and also to respond to a paper by Goldacre B. *BMJ* 2014 ; 348 : g2940) rightly lamenting the lack of reliability of clinical research as it is published, one may mention the incredible area for data manipulation offered by coding [in MedDRA terminology] : for example and as far as statins are concerned, patent rhabdomyolyses (with CK > 15 000 U/L) being transformed into 'enzyme increase', or 'CK increase', or 'liver/kidney disorder'»[1035]
sous-estimation des myopathies par codage erroné dans les bases de données de pharmacovigilance

UNE HISTOIRE INVENTÉE : Essai sur le cholestérol – *Hypothèse lipidique*
THERRIEN, Jean-Marie. Montréal : Carte-Blanche ; 2014 - 262 pages – ISBN 978-2-89590-226-3 (imprimé, numérique)
« Le Dr. Jean-Marie Therrien a passé les 30 dernières années à lire tout – ou presque ! – ce qui s'est écrit sur le cholestérol. Il avait dès le départ une intuition qui, au fil de ses milliers d'heures d'étude, s'est muée en une certitude : le cholestérol n'est pas le dangereux tueur que l'on prétend...

Sa diabolisation est une *histoire inventée* qui a permis à un lucratif marché de médicaments de voir le jour. Une vaste supercherie véhiculée par des médias en mal de sensations et par des médecins trop débordés pour remettre en question la conformité des études commandées par les compagnies pharmaceutiques… Un livre extrêmement bien documenté, qui donne l'heure juste et sonne l'alarme »

[1031] Philippe Even. http://www.lanutrition.fr/bien-dans-sa-sante/les-maladies/le-cholesterol/polemique-sur-l-arret-des-statines.-le-commentaire-du-pr-even.html
[1032] Philippe Even. La vérité sur le cholestérol, page 217
[1033] Lucy Johnston. Express (UK) 2.3.2014 - http://www.express.co.uk/news/health/462607/Health-chief-slams-statins-Millions-face-terrible-side-effects-as-prescription-escalates
[1034] Diamond & Ravnosk, op. cit.
[1035] Marc Girard, 2014

UNFOUNDED GUIDELINES FROM PREVENTIVE SERVICES TASK FORCE (USA)
« Researchers searched 3 databases, including the Cochrane Library, and reference lists of retrieved articles, hoping to identify randomized controlled trials, cohort studies, and case-control studies of the screening for or treatment of asymptomatic dyslipidemia in adults aged 21 to 39 years...

No studies. Zero. So, any recommendations regarding lipid screening and subsequent treatment is based on *speculation* or *extrapolation* from research on older populations. Both approaches are fraught.

There are no studies of screening or treating adults younger than 40 years for lipid disorders. Yet the current 2016 USPSTF[1036] recommends that screening begin at age 35 years in all men (A recommendation), and at age 20 years for men and women at risk for coronary heart disease (B recommendation). Treatment, though, is not recommended until age 40 » adding incoherence to bias.
recommandations non fondées par le groupe de travail sur les services de prévention (É-U)

USUAL-CARE COMPARISON STATIN TRIALS
* ALLHAT-LLT, GREACE, GISSI-P
essais comparant la statinisation aux soins usuels

UTILISATION REVIEW : STATIN WASTAGE IN BRITISH COLOMBIA 1999-2004 (CA)
« There were 211,964 new statin users between 1999 and 2004 :

a) 35% had evidence of Ischemic heart disease (IHD) only
b) 5% had neither diabetes or IHD but had atherosclerosis (cerebral, peripheral)
c) 20% had diabetes but no IHD [even if statins are proven useless in diabetes without IHD, which the authors do not seem to know]

d) 22% had disorders of lipid metabolism only
e) 18% had none of the medical conditions evaluated »[1037]

* Actually, only 35% may have been at very high baseline risk (see that term) while the other 65% were given a futile, ineffective and inefficient drug with more ADRs than sponsors and prescribers will admit

VA-HIT, THE TRIAL *Prévention secondaire – Diabète – Fibrate – Gemfibrozil*
Veterans Affairs High-Density Lipoprotein Intervention Trial[1038]
l'essai dit Va-Hit

VADT, THE TRIAL *Calcification des coronaires – Effet paradoxal*
Veterans Affairs Diabetes Trial
« More frequent statin use is associated with accelerated coronary artery calcification in diabetes type 2 patients with advanced atherosclerosis »[1039]
l'essai dit Vadt

VENOUS THROMBO-EMBOLISM AND STATINS – (Méta-analyse indépendante)
Kazem RAHIMI et al. *Effects of statins on venous thromboembolic events : a meta-analysis of published and unpublished evidence from randomized controlled trials*. *PloS Med* 2012; 9: e1001310[1040]

« In trials of statin versus control, allocation to statin therapy did not significantly reduce the risk of venous thromboembolic events : 465 or 0.9% on statin versus 521 or 1.0% in control group, NS. There was no evidence that higher dose statin therapy reduced the risk of venous thromboembolic events compared with standard dose statin therapy : 198 or 1.0% versus 202 or 1.0%, NS »
thrombo-embolie veineuse et statines
* Les statines n'exercent pas d'effet protecteur dans cette situation clinique, le risque d'événements thrombo-emboliques est

[1036] Chou et al. Ann Int Med 2016 ; 165 : 560
[1037] Raymond et al. Clinical Therapeutics 2007 ; 29(9) : 2107 – abstract at http://www.sciencedirect.com/science/article/pii/S0149291807003037
[1038] Rubins et al. NEJM 1999 ; 342 ; 410 - Arch Intern Med 2002 ; 162 :2597
[1039] Salemi et al. Diabetes Care 2012 ; 35: 2390
[1040] http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001310 - DOI: 10.1371/journal.pmed.1001310

de 0.9% sous statine et de 1% sous placebo et les fortes doses ne font pas mieux que la posologie standard.

VERY LOW BASELINE RISK *Prévention primaire*
risque de base très faible
= risque de 0 à 0,9 événement par 100 patients-année selon notre définition; équivaut à < 1 % par année ou < 10 % en 10 ans
* Il est impossible qu'une statinothérapie soit cliniquement utile quand le risque des témoins est aussi faible car il est impossible, même si la chute invraisemblable du risque relatif était de 90% (RR de 0,10 chez les statinisés), d'obtenir une réduction du risque absolu d'au moins 1 événement par 100 patients-année

* Si on applique cette échelle à l'essai dit :
a) JUPITER, utilisant le critère combiné secondaire (IM, AVC, décès CV) des auteurs, on trouve sous placebo un risque d'événement principal combiné de 0,85 par 100 AP (risque très faible).

b) ASCOT-BPLA, on découvre que le risque d'un événement principal combiné du groupe témoin (sous aténolol) était de 0,91 par 100 AP (risque très faible)

c) ASCOT-LLA, on observe que le risque de base des témoins (sous antihypertenseurs) était de 0,94 événement principal combiné par 100 AP (risque très faible)

d) DIAD[1041], un essai de diabétiques de 60 ans en moyenne, 55% hommes, LDL moyen de 2,9 mmol/l, on constate que le risque annuel est de 0,6 événement CV par 100 AP (risque très faible), ce qui démontre bien que le simple fait d'être diabétique ne mérite pas le qualificatif automatique de risque élevé quand d'autres faceurs de risque ne sont pas concomitants, nombreux et élevés

VIOLENCE AND AGRESSIVITY *Statinovigilance*
« A professor of psychiatry, David Healy noted the potential for aggression after undertaking a study of case reports submitted to the FDA. He found 310 reports of aggression and *violence*, and 62 reports of homicidal behavior involving Lipitor™. There were 309 reports of irritability, 256 reports of personality change and 68 of paranoia...

In another study, researchers from the University of California looked at 1,000 people and found a link between statins such as Lipitor™ and *aggression* - particularly in postmenopausal women over the age of 45. Researchers found that women most likely to become *aggressive* were normally more placid than average...

Among the study participants was a 46-year-old woman who admitted treating her husband rather badly for the duration of time she was on statins - about 9 months. 6 weeks after stopping, she was back to her normal self »[1042]
violence et agressivité

VIVRE AVEC DU CHOLESTÉROL – (Livre) *Dénonciation de l'hypothèse du cholestérol*
Marian APFELBAUM. Paris : Rocher; 1997 – 153 pages - ISBN 9782268025568
« Un seul dosage dans votre vie montrant que votre cholestérol est au-dessous de 7,7 mmol/l (3 g) suffit. N'y revenez plus… si vous n'avez pas d'hypercholestérolémie familiale »[1043]
* L'auteur est l'un des trois dénonciateurs français les plus notoires de la supercherie (*deception*) du cholestérol et de l'escroquerie (*swindle*) des statines, après Michel de Lorgeril et, plus récemment, Philippe Even

VORARLBERG COHORT STUDY (OE) *Étude prospective observationnelle de population - Épidémiologie*
« In the Austrian province of Vorarlberg, 149,650 individuals (67,413 men and 82,237 women) were followed from 1985 to 1999. The median survival time from first examination was 5.75 years in men and 6.25 years in women...

The relationship between *low* total cholesterol level and total *mortality* is confirmed for both men and women > 50 years and in men < 50 years. Total cholesterol level was not a significant independent predictor in women > 50 years. The role of *high* cholesterol in predicting *death from CHD* could be confirmed in men of all ages and in women < 50 »[1044]
l'étude de cohorte de Vorarlberg
* L'*hypo*cholestérolémie est un faible prédicteur de mortalité de toute cause > 50 ans dans les deux sexes et chez les hommes de < 50 ans ; mais pas chez les femmes de < 50 ans (préménauposées)

[1041] Young et coll. JAMA. 2009;301(15):1547
[1042] http://www.lawyersandsettlements.com/articles/Lipitor-diabetes-lawsuits-mdl/lipitor-diabetes-lawsuits-mdl-margaret-clark
[1043] Cité par Even, La vérité sur le cholestérol, page 15
[1044] Ulmer et al. J Womens's Health 2004 ; 14(1) : 41 – complet sur http://www.health-heart.org/eve-not-adam.pdf

* L'*hyper*cholestérolémie est un faible prédicteur de maladie cardiaque prématurée chez les hommes de tout âge et chez les femmes préménopausées mais pas chez les femmes ménopausées

* Si l'hypocholestérolémie – et non l'hypercholestérolémie - prédit la mortalité chez les femmes ménopausées, pourquoi sont-elles si nombreuses à consommer des réducteurs du cholestérol ?

PRECAUTIONS WITH STATINS *Statinovigilance*

a) Potential *interactions* deserve attention : « If a person taking a statin starts taking additional drugs, or needs treatment for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions, consider reducing the dose of the statin, or temporarily or permanently stopping it » – This an admission that interactions may pose serious risks, that statins are 'last line' drugs, and may be stopped permanently without harm

b) Statin *myalgias* deserve medical attention : « People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured » - Not mentioned is that myalgias may occur without elevation of creatine kinase

c) *Neuropathy* is an ADR and deserves medical attention : « If a person develops an unexplained peripheral neuropathy, statins should be discontinued and specialist advice sought » – Before calling on a neurologist, better stop the statin, wait a few weeks or months and watch for a positive dechallenge

précautions avec les statines

VRECER ET AL, THE META-ANALYSIS[1045]

* This 2003 publication is based on 15 trials published between 1985 and 2002, studying 63 410 participants followed for a mean of 3.6 years. Abstract contains relative risks overall (primary and secondary prevention):

a) Coronary events relative risk reduction of -37%
b) CV mortality relative risk reduction of -22%
c) Non fatal stroke relative risk reduction of -26%
d) Stroke relative risk reduction of -23%

e) TOTAL MORTALITY relative risk reduction of -15%

la méta-analyse de Vrecer et coll.

* ne peut être commentée sans lire l'article en entier pour découvrir les réductions absolues des risques et les convertir en NNT annualisés afin d'en faire l'évaluation pragmatique et assurer une comparaison impartiale des différents essais

WARNINGS IN 2014 LIPITOR™ MONOGRAPH

« The following are reasons why Lipitor may not be suitable for you:

a) if you have had a previous stroke with bleeding into the brain, or have small pockets (lacunae) of fluid in the brain from previous strokes
b) if you have kidney problems

c) if you have an under-active thyroid gland (hypothyroidism)
d) if you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems
e) if you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines)

f) if you regularly drink a large amount of alcohol
g) if you have a history of liver disease
h) if you are older than 70 years »[1046]

mises en garde dans la monographie 2014 du Lipitor™

* Depuis que le promoteur est à mettre au point des plus puissants réducteurs du cholestérol, il concède enfin que sa statine n'est pas indiquée > 70 ans, qu'elle est contre indiquée après AVC hémorragique, dans hypothyroïdie, chez l'alcoolique, et qu'elle peut causer des problèmes musclaires, hépatiques, rénaux

* Comme toujours 'c'est le marketing qui décide', il faut commencer à dénigrer les statines maintenant génériquées si l'ont veut prendre leur part de marché avec une nouvelle classe de produits beaucoup plus rentables, les PCSK9

ACADEMIC COLLUSION : NIH INVESTIGATES MERCK (USA)

[1045] IJCPT 2003 ; 41(12) : 567-577 – Abstract only online - PubMed 14692706
[1046] http://www.medicines.org.uk/emc/medicine/2498/PIL/Lipitor+10mg,+20mg,+40mg,+80mg+Tablets/

« Dual relationships have come under scrutiny from lawmakers and regulators in the past. In 2009, Sen. Charles Grassley (Republican-Iowa) asked the National Institutes of Health (NIH) to investigate *university physicians* who were paid by Merck to work on a campaign for the cholesterol drug Vytorin™ (ezetimibe) even though an internal study had showed it was no more effective than cheaper drugs. The relationships were first reported by the Chronicle of Higher Education »[1047]
collusion universitaire : le Nih enquête auprès de merck (ÉU)

WEIGHT GAIN ASSOCIATED WITH STATINISATION *Statinovigilance – Effet nocebo - Épidémiologie*
« Besides the risks of muscle aches, diabetes, and cognitive dysfunction, I have observed over the years that for many patients, statins provide a *false reassurance*, as people seem to believe that statins can compensate for poor dietary choices and a sedentary life. In an elegantly performed analysis of NHANES data from 1999 to 2010, Sugiyama and colleagues[1048] have documented exactly such behavior...

They found that compared with statin nonusers, statin users significantly increased their fat intake and calorie consumption, along with their BMI, in the last decade. This article raises concerns of a potential moral hazard of statin use [i.e. gluttonery], in addition to the already known adverse effects. Focusing on cholesterol levels can be distracting from the more beneficial focus on healthy lifestyle to reduce heart disease risk »[1049]
gain pondéral associé à la statinisation
* élégante démonstration de l'effet nuisible d'une statinisation futile sur l'une des véritables formes de prévention, une saine alimentation
Voir aussi DIFFERENT TIME TRENDS….

WHO, THE TRIAL *Prévention primaire*
World Health Organisation Cooperative Trial[1050]
l'essai dit de l'OMS

WITHDRAWAL DURING DEVELOPMENT
« The failure of torcetrapib has not ended the development of new cholesterol medications—the potential market is simply too huge »[1051], even if its development came to a halt in 2006 after phase III studies showed greater total mortality in the treatment group receiving a combination of atorvastatin (Lipitor™) *and* torcetrapib
retrait durant la mise au point

WOLFSON INSTITUTE (UK) REVIEW OF IHD MORTALITY AND CHOLESTEROL LEVELS *Hypothèse lipidique réfutée – Enquête écologique*

* Mortality from IHD in 1992 compared to 1990 mean serum TC in men aged 50-70 :[1052]
a) 13 countries presented in order of ascending IHD mortality rates :
Japan, France, Italy, Belgium, Netherlands, Australia, Sweden, Iceland, United States, Norway, Ireland, Britain, Finland

b) IHD mortality rates per 100 000, and mean TC (mM) in brackets, in the same order :
58 (5.2) JA, 128 (6.1) FR, 204 (5.8) IT, 228 (6.2) BE, 275 (6.0) NE, 311 (5.9) AU, 329 (6.2) SW, 333 (6.2) IC, 345 (5.6) USA, 405 (6.3) NO, 482 (5.9) IR, 489 (6.2) UK, 547 (6.3) FI

c) Note the huge variations in IHD mortality, from 58 (JA) to 547 (FI) per 100 000, a 9.4-fold difference at extremes and a constant increase
d) Note the small variations in cholesterol levels, from 5.2 to 6.3, a 2.5 fold difference at extremes but within 5.8-6.2 in 9 countries
synthèse de l'Institut Wolfson sur la mortalité par cardiopathie ischémique et la cholestérolémie
« En dépit d'énormes différences en mortalité coronaire, les taux de cholestérol étaient pratiquement les mêmes dans tous les pays sauf aux extrêmes »[1053]
* En France la densité d'incidence de la mortalité coronarienne annuelle chez l'homme mûr (50-70 ans) est de 128 / 100 K et le cholestérol total moyen est 6,1 mM tandis qu'au Royaume-Uni elle est de 547 / 100 K et le cholestérol de 6,2 mM

[1047] http://www.propublica.org/article/double-dip-doctors-paid-to-advise-promote-drug-companies-that-fund-research
[1048] Sugiyama T et al. 24.4.2014 JAMA Intern Med -doi:10.1001/jamainternmed.2014.1927.
[1049] Rita F Redberg. 24.4.2014 JAMA Intern Med - doi:10.1001/jamainternmed.2014.1994
[1050] WHO. Br Heart J 1978 ;40 : 1069 - Lancet 1980 ; 2 : 379
[1051] Jonah Lehrer. Site http://www.wired.com/magazine/2011/12/ff_causation/4/
[1052] Law & Wald. BMJ 1999; 318(7196): 1471 (Table 3) - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1115846/#!po=17.2222
[1053] Even, page 144

WOMEN AND ROSUVASTATIN
« Physicians and *women* patients should be informed that rosuvastatin has thus far not been shown to reduce the risk of CV death, myocardial infarction, or stroke in high-risk primary prevention patients[1054] »
les femmes et la rosuvastatine

WOSCOPS, THE TRIAL *Prévention primaire – Résultats cliniquement négatifs – Pravastatine 40 mg c. placebo*
West of Scotland Coronary Prevention Study

* Princeps publication : Shepherd/NEJM/1995[1055] is one of the 10 most cited randomised trial (as of June 2016)[1056]
* Comparison : pravastatin 40 mg vs. placebo
* Funding : mixed (public and BMS)

* Participants' demography : 6595 Scottish men (therefore located in only one district in the UK), no women ; middle age men (mean 55 years ; 45 to 64). Les conclusions ne peuvent s'appliquer aux femmes ni aux hommes de > 70 ans

* Participants' health : 0% with CHD disease - 16 % with history of non-coronary angiopathies – (Scotland had one the highest rate of CHD deaths in Europe and is not representative of all men and women broadly treated with pravastatin around the world) – 16% with hypertension – 1 % with diabetes – baseline TC 7.0 mM, all > 6.5 mM ; LCL-C from 4.5 tp 6.0 mM, average 5.0 mM

« This trial states that their results could be "applicable to typical middle-aged men with hypercholesterolemia". But it does not indicate if the results would only apply to typical men in the particular sub-population within the West of Scotland (where the trial was run) given the specific lifestyle, nutrition and other traits of people in this region and the capacity of participating clinics[1057] »

* Follow-up : 4.9 years
* Methodology : randomized ; size > 1000 ; duration > 1 year
* Dropout rate of 33% in each group, a major *source of bias* in interpreting both internal validity (about causality) and external validity (about relevance)

« This cholesterol trial reported that 51% recruited to participate appeared for the first screening, after which only 4% of the recruited sample was randomised into the study – and later about 30% of participants dropped out[1058] » (The randomised are therefore not representative of the people to whom conclusions were thereafter applied – Dropout rates to that extent invalidate the randomisation purpose (internal validity) and emphasize the necessity of using only the intention to treat analysis (external validity) for the main outcome since the dropout rate in daily practice is likely to be as high.

RESULTS
Lipid reduction
relative risk reduction for TC : -20 %
relative risk reduction for LDL-C : -26 %, from 5 mM

Benefits (hard outcomes):
* TOTAL MORTALITY : relative risk reduction of -22 %, NS
Comment : « Allowing that the claimed reduction in total mortality in the large WOSCOPS trial is indeed real (absolute risk reduction of 0.9%/5 years and of 0.18 percentage points per year, NNT = 555 patient-years, average life extension of 36.5 hours per year of treatment; relative risk reduction of -22%; NS), their calculated average extension of life after 5 years on pravastatin is about 1 week [but is NS]. To extend their average life by 1 year would require each patient to take pravastatin for 260 years »[1059]

[1054] Vos, Rose & Biron. Circulation 2010; 122: e576 - doi: 10.1161/ CIRCULATIONAHA.110.954016 - http://circ.ahajournals.org/content/122/23/e576.full
[1055] Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med. 1995;333:1301–1308
[1056] Krauss A, op. cit.
[1057] Krauss A, 2017 - https://doi.org/10.1080/07853890.2018.1453233 - https://www.tandfonline.com/doi/full/10.1080/07853890.2018.1453233?scroll=top&needAccess=true&
[1058] Krauss, op. cit
[1059] Bassan M, Panush N. Am J Cardiol 1997; 79: 1001

* CHD death: relative risk reduction of -33%, NS

Benefits (softer endpoints)
* relative risk reduction of CHD events : -31%, ; absolute risk reduction of 0.49% per year, NNT = 204 patient-years, equivalent to a delay of 43 hours if this benefit is spread over the 204 patients treated for one year. The reduction was concentrated in the 16% of patients with prior non-coronary angiopathies

Harms
* New onset diabetes *not reported* in princeps publication but by Freeman/Circ/2001 and by meta-analyst Sattar
* Health related quality of life *not reported*

* Transparency : *The BMJ* has written in 2014 to the principal investigators of the trials included in the CTT analysis asking them whether they have the patient level data and under what circumstances they would be willing to share them. The reply in 2015 (http://www.bmj.com/campaign/statins-open-data), as is a record of the status and nature of response, is : NO RESPONSE

* Commentary : « WOSCOPS [Medline 7566020], is a Scottish trial that excluded women, that invited 160,000 men and that after dietary advice and a 4th screening randomized about 6600 men for 4.9 years [mean baseline age 55 years, cholesterol 7 mmol/L and 16% with prior CV disease] to find a *mortality* difference that *did not reach* statistical significance »[1060]

* Factual conclusion : no clinically significant benefit are observed that could counterbalance the ADRs and the costs
l'essai dit Woscops
* Essai clinique contrôlé de la pravastatine contre placébo en prévention dite primaire chez 6 595 hommes, âgés d'environ 55 ans, suivis environ 4,9 ans. Dans les faits, 16% étaient atteints de trouble CV (donc en prévention secondaire) et ce 16% a contribué pour une bonne part à la relative risk reduction des évènements coronariens. Cela réduit la validité externe quand on extrapole à la prévention primaire.

De plus, l'Écosse ne fut pas un choix innocent. L'Écosse est un des pays d'Europe du Nord où la mortalité coronarienne est la plus élevée et cela réduit la validité externe quand on extrapole.

En Europe du Sud "pour un même taux de cholestérol le risque absolu de mortalité coronarienne est de 30 à 50% inférieur à celui de l'Europe du Nord. La différence est même de l'ordre de 70% pour l'Europe du Sud méditérranéenne. »[1061] Si l'on ajustait les résultats écossais de WOSCOPS en fonction du risque de référence du reste de l'Europe, les avantages observés deviendrait insignifiants en valeur absolue.

L'Écosse est par ailleurs un pays où l'excès de maladies coronaires n'est pas explicable par une prédominance des facteurs de risques traditionnels.[1062]

* Le risque du groupe placebo était de 1,6 événement coronarien par 100 AP (risque *faible* selon nos critères)

* La réduction du risque absolu d'un événement coronarien est de -2,4% en 4,9 ans (-0,49 % par an), d'où un NNT annualisé de 204 personnes-année, ce qui équivaut virtuellement à retarder cet événement de 1,8 jours (ou 43 heures) pour chaque année de traitement, chez chacun des 204 sujets traités, sans prolonger leur vie ni leur épargner un décès coronarien ni améliorer leur qualité de vie

* Conflation des auteurs avec conflation : Ils concluent à un succès et la majorité des innombrables hypercholestérolistes qui citeront *Woscops* par la suite le qualifieront d'essai positif, ce que les cardiologues trop occupés ne prendront pas la peine de vérifier

WRITTEN CONSENT BEFORE PRESCRIBING? *Éthique clinique*
« There are now calls for patients to give written consent before taking a statin. If you do plan to give statins to women, to elderlies, to people at low risk, they should sign a consent form saying they understand that they're receiving a drug that will not extend their life, but will only shift the cause of death. I think patients have a right to know that before they agree to take on a medication »[1063]

[1060] Eddie Vos. http://www.bmj.com/content/352/bmj.i1395/rapid-responses
[1061] Société Française de Cardiologie, Thérapie 1996;51 :611
[1062] MITCHELL. Epidemiol Community Health 2005;59 :565
[1063] Prescripteur anonyme

consentement écrit avant de prescrire ?