REseau de MEDecins - réunion scientifique
Genève, le 6 juin 2013

Statin or not statin ?
Que dire à son patient ?

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Service de Cardiologie

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UNIVERSITÉ DE GENÈVE
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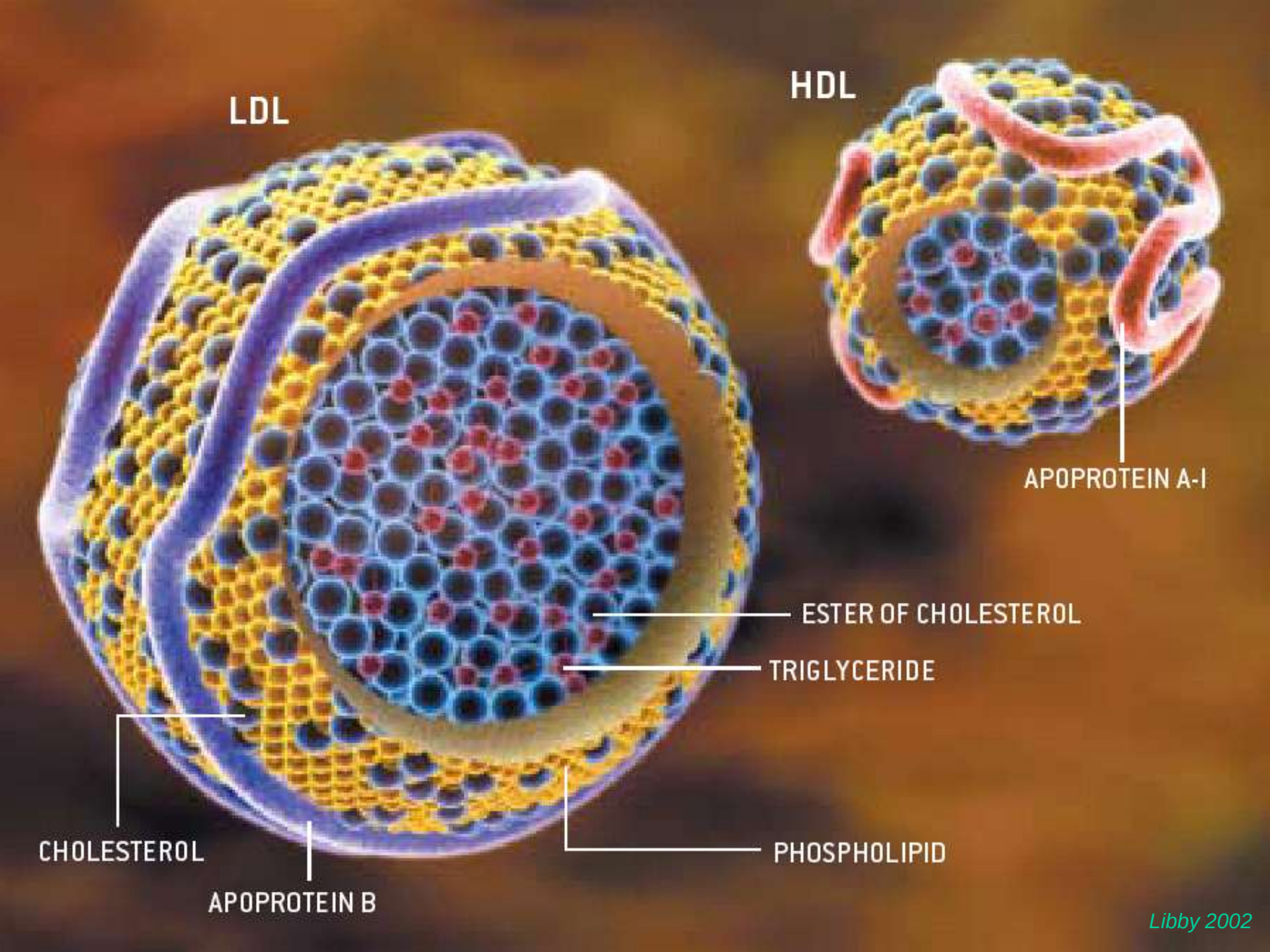

LDL
HDL
APOPROTEIN A-I
ESTER OF CHOLESTEROL
TRIGLYCERIDE
CHOLESTEROL
PHOSPHOLIPID
APOPROTEIN B

Libby 2002

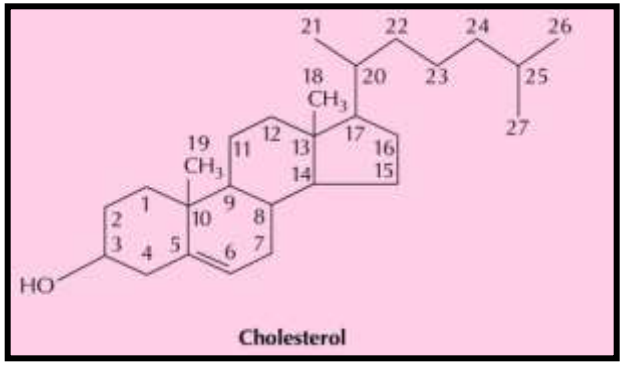
Cholestérol

Chole: bile *Stereos:* solide

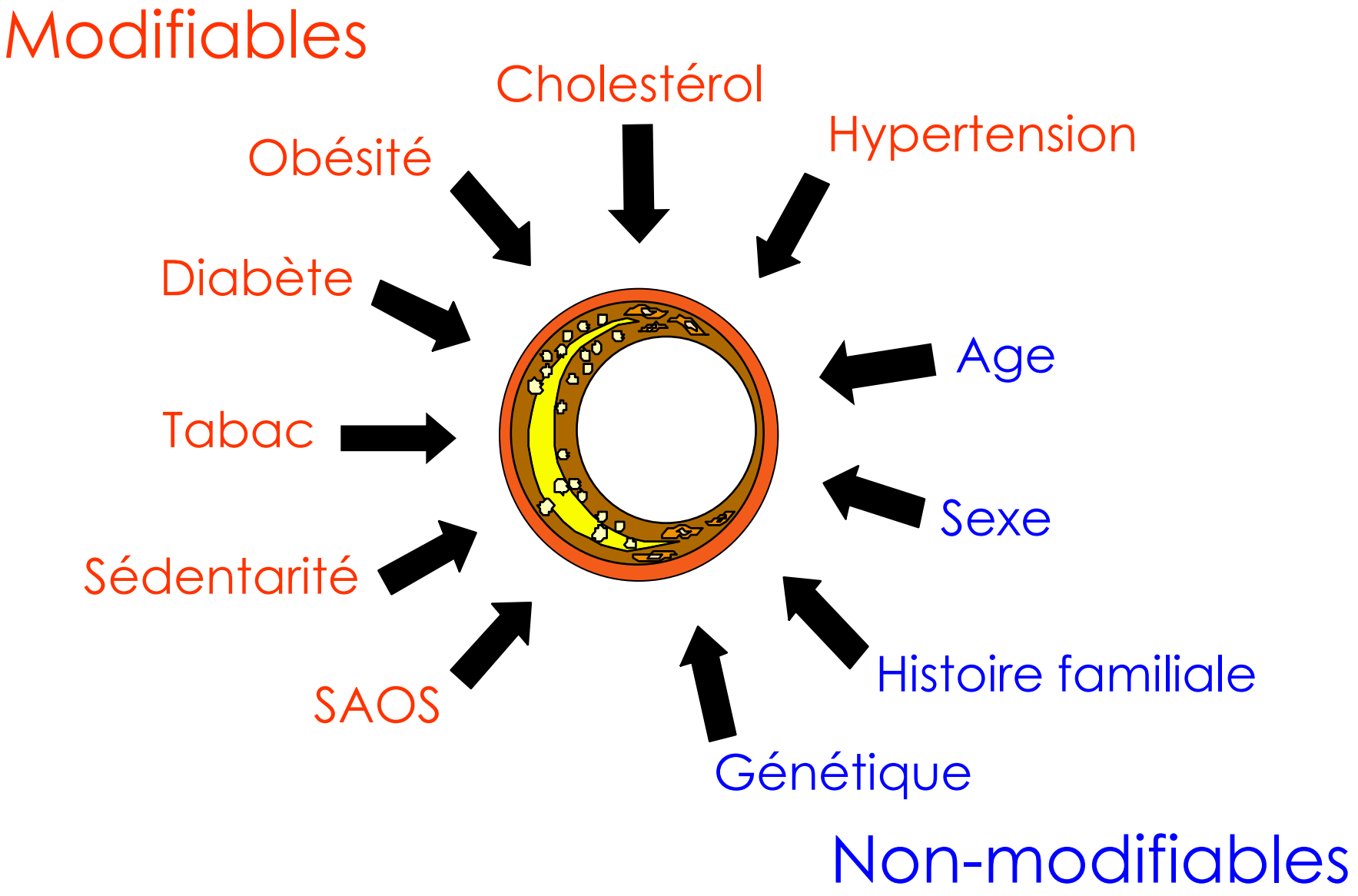
Fait partie des substances fondamentales de l'organisme et est un composant de tous les tissus

Le cholestérol est important en tant que:

- Elément des membranes cellulaires
- Substance de base pour:
  - les acides biliaires (digestion de certains aliments)
  - vitamine D (formation des os)
  - hormones (oestrogènes et testostérone)



Facteurs de Risque Cardio-vasculaire



Le nouvel Observateur

Du 14 au 20 février 2013

LA VÉRITÉ SUR LE CHOLESTÉROL

Et s'il n'était pas dangereux...

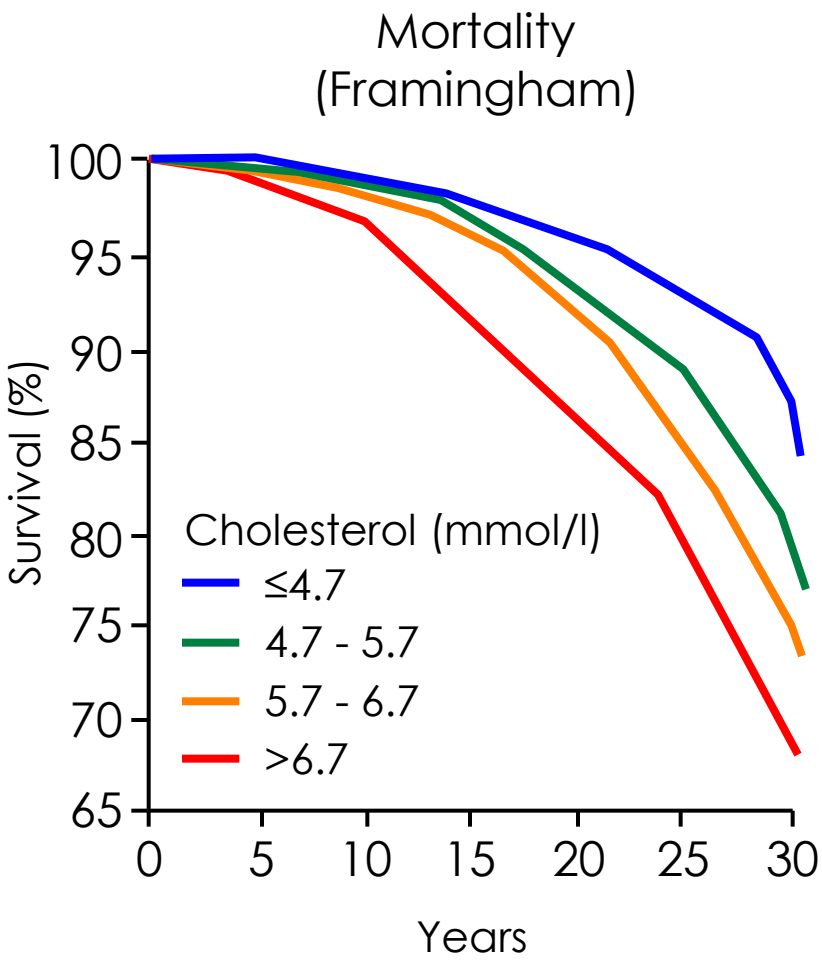
LE PROFESSEUR EVEN LANCE LA POLÉMIQUE

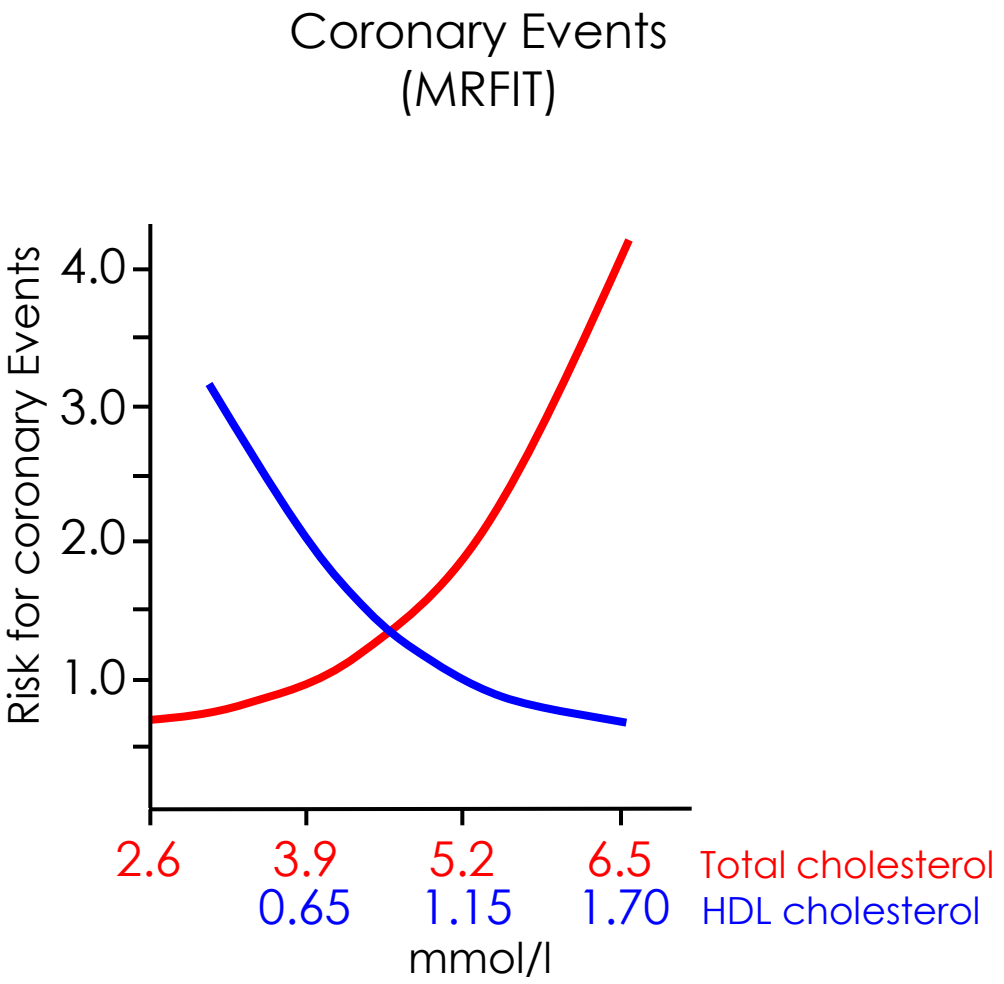
Avec BFMTV NEWS 24/7

BENOÎT XVI LES COULISSES D'UNE DÉMISSION SURPRISE

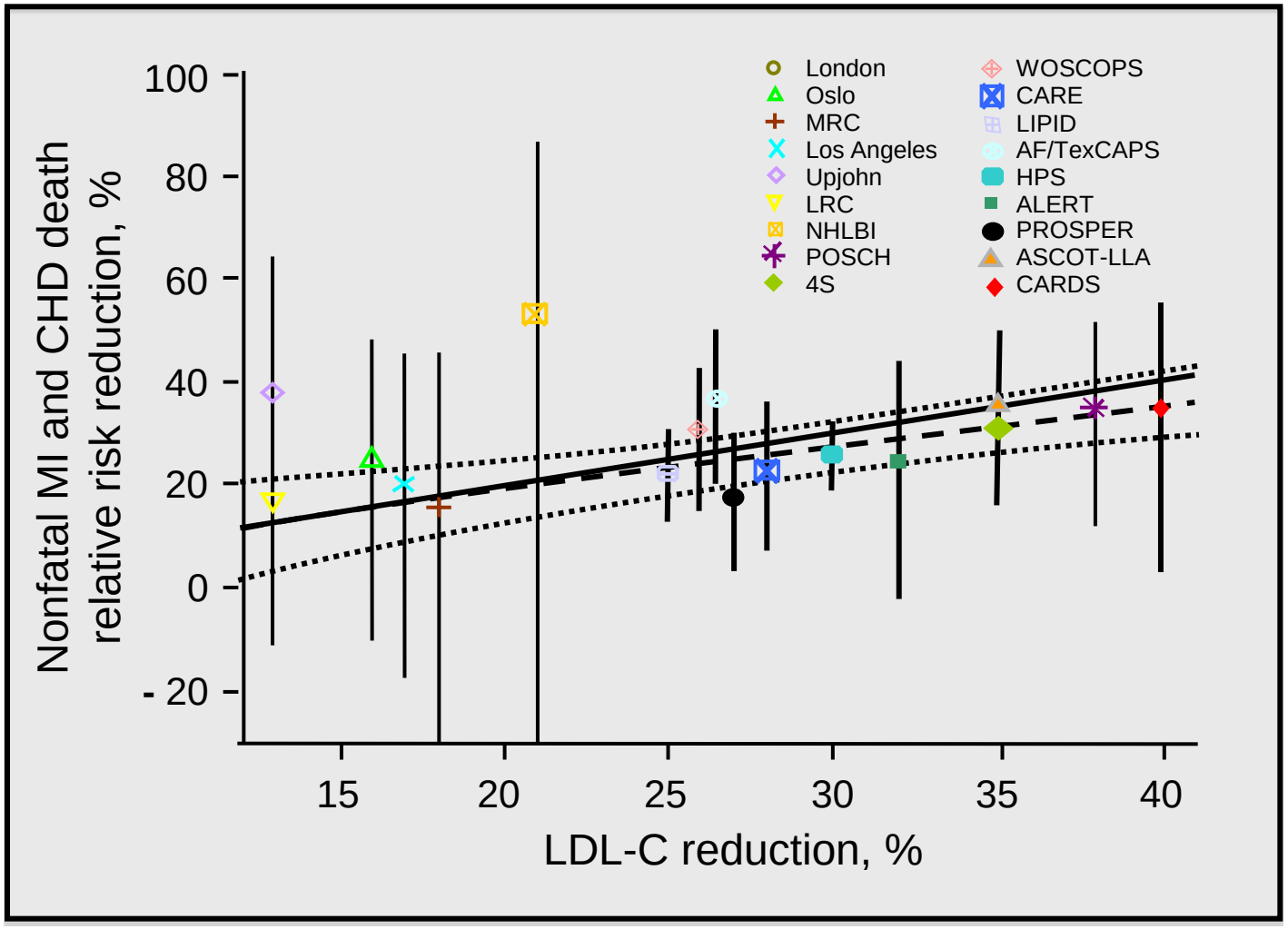
M 02228 - 2519 - F: 3,50 €

Facteurs de Risque Cardio-vasculaire





Lowering LDL-C by any Interventions Reduced the Risk for CHD

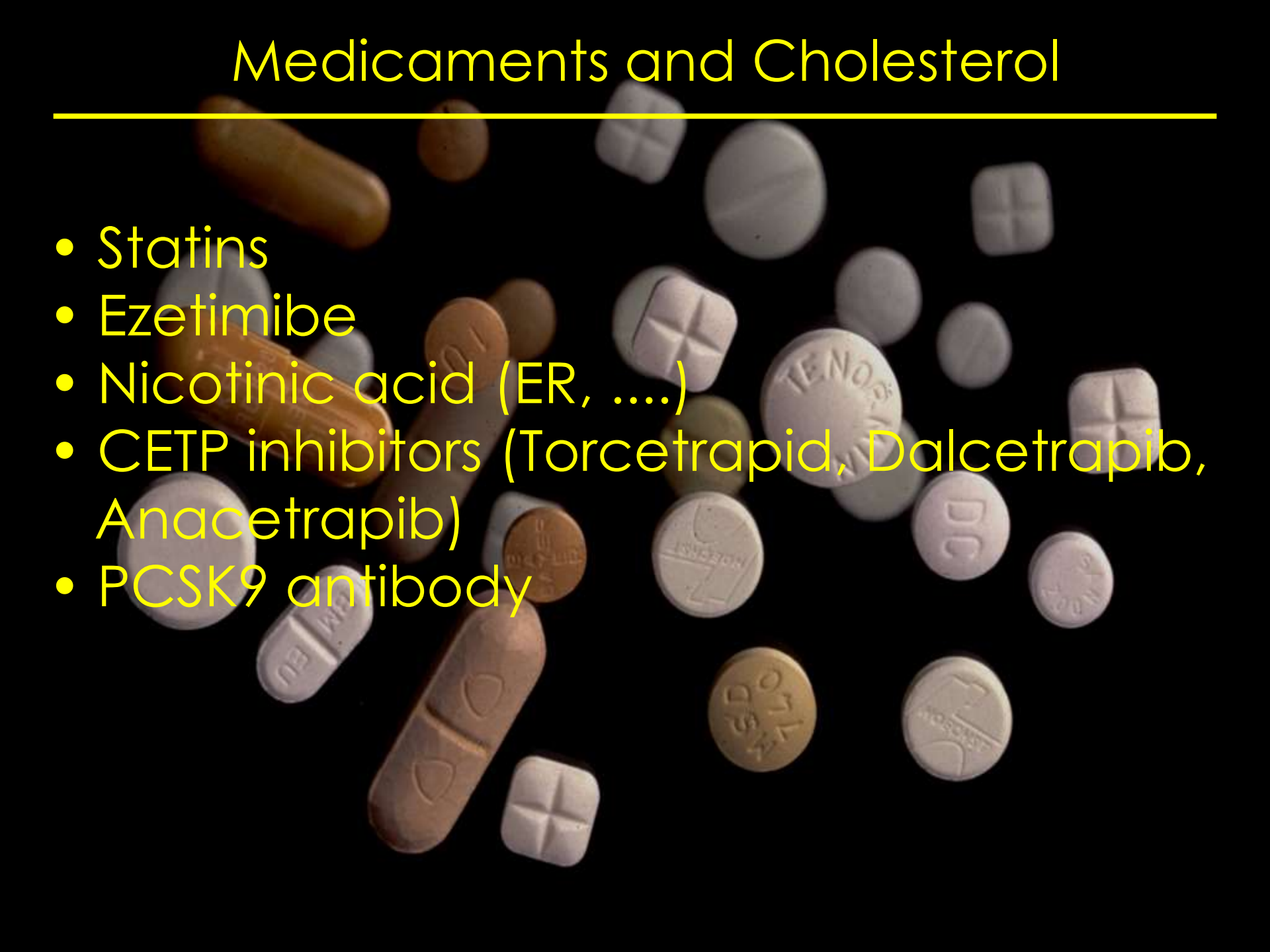


Interventions:

- Statins
- Diet
- Surgery
- Bile acid sequestrants

Adapted *JACC* 2005;46:1855

Medicaments and Cholesterol



- Statins
- Ezetimibe
- Nicotinic acid (ER, ...)
- CETP inhibitors (Torcetrapid, Dalcetrapib, Anacetrapib)
- PCSK9 antibody

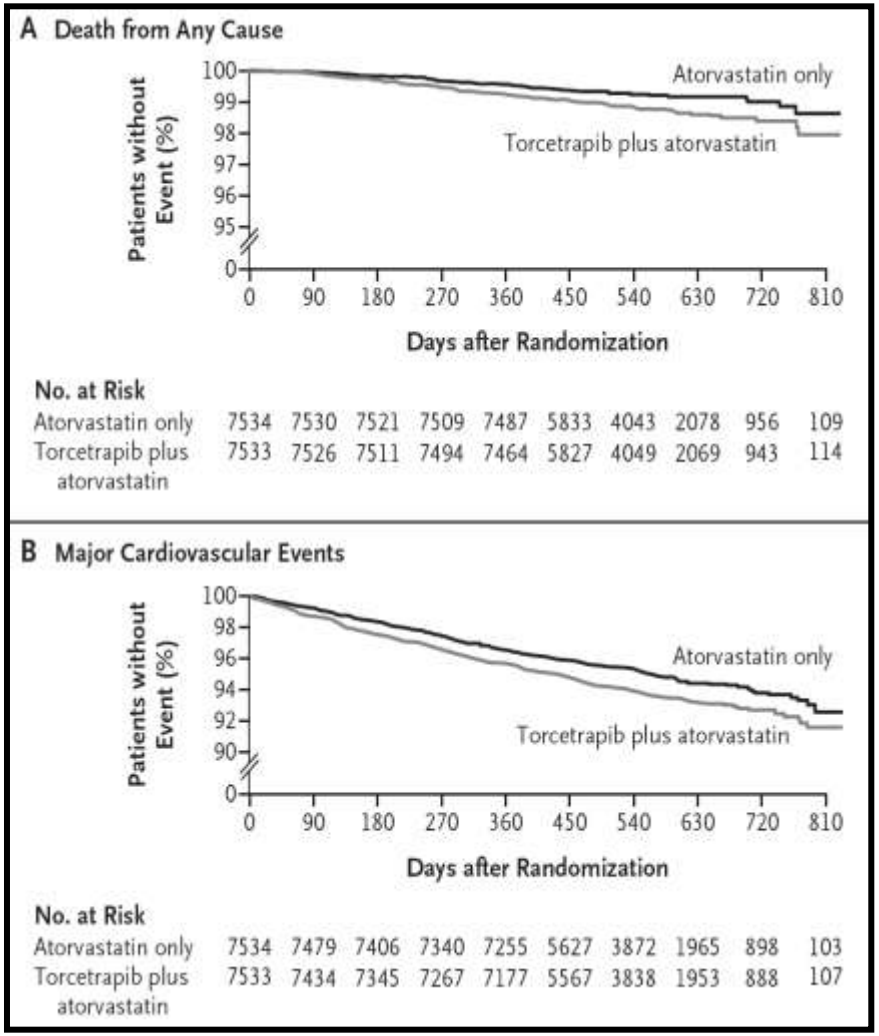
Augmenter le HDL (CETP-inhibitor)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 22, 2007 VOL. 357 NO. 21

Effects of Torcetrapib in Patients at High Risk for Coronary Events

Le ttt de Torcetrapib augmente le risque d'événements CV et la mortalité !



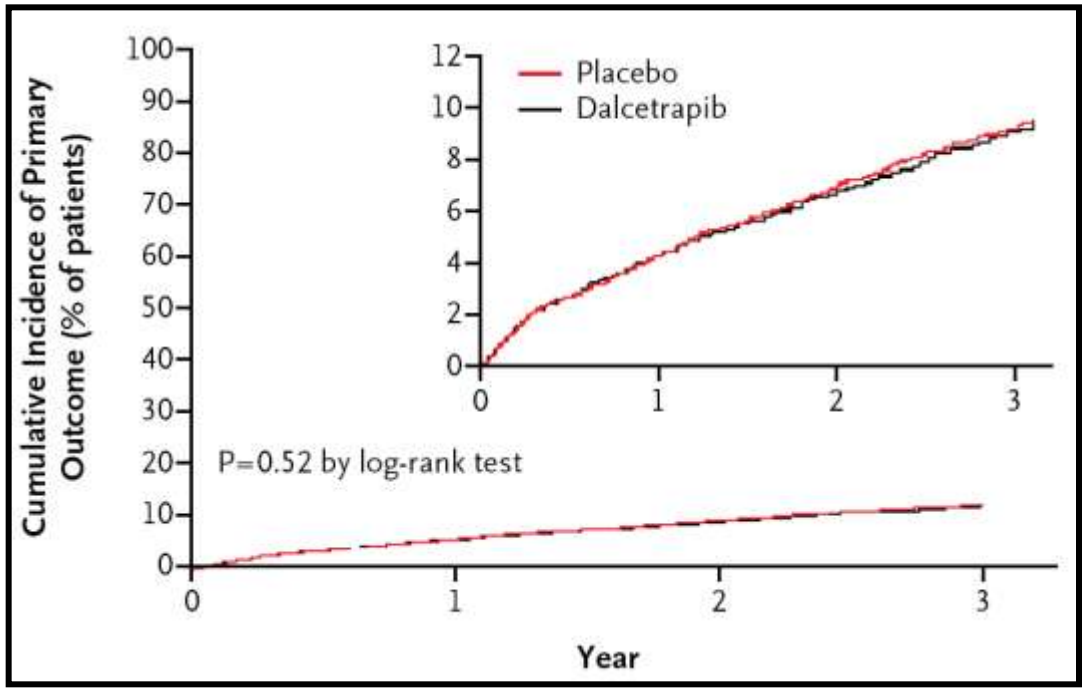
N Engl J Med 2007;357:109

Augmenter le HDL (CETP-inhibitor)

ORIGINAL ARTICLE

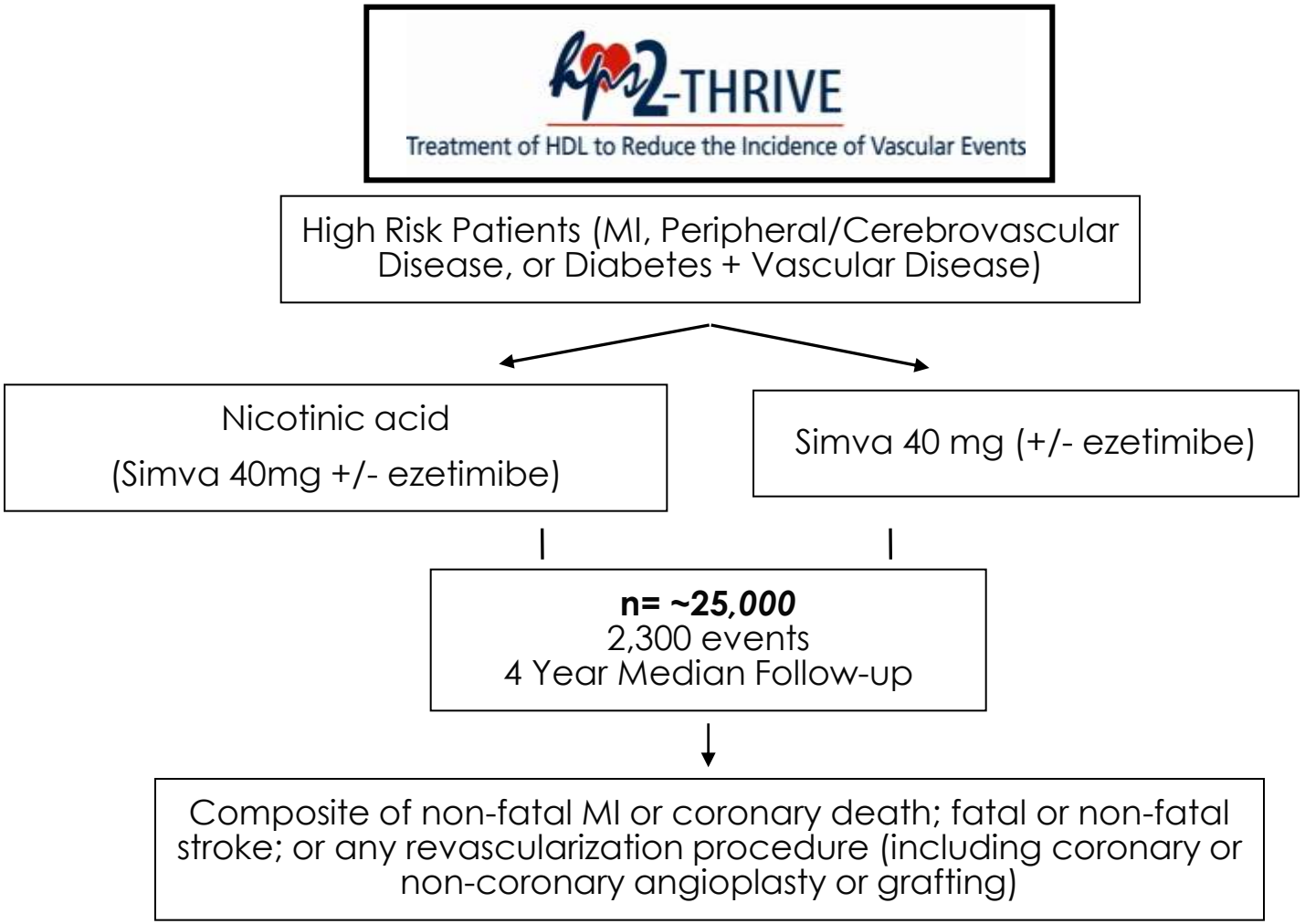
Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Le ttt de Dalcetrapib n'a aucun effet sur la prévention des d'événements CV !



N Engl J Med November 9, 2012

Augmenter le HDL (acide nicotinique)



Résultats en mars 2013

Increasing HDL (nicotinic acid)

On January 11, 2013, Merck/MSD announced it is taking steps to suspend the availability of TREDAPTIVE™ (extended-release niacin (ERN)/laropiprant (LPT)) tablets worldwide. Merck/MSD is taking these steps based on the current understanding of the preliminary data from the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) study, and in consultation with regulatory authorities. The decision to suspend the availability of the medicine was aligned with the recommendation of the European Medicine Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) based on the trial's results. See News Release.

On January 18, the EMA's Committee for Medicinal Products for Human Use (CHMP) issued a decision confirming the PRAC recommendation to suspend the marketing authorizations of TREDAPTIVE, PELZONT or TREVACLYN in the European Union (EU). In addition, the CHMP advised:

- Doctors to no longer prescribe TREDAPTIVE and to review patients' treatment options.
- Patients currently taking TREDAPTIVE to make a non-urgent appointment with their doctor to discuss their treatment.

Les statines en question…

Tribune de Genève

Trop prescrites, les statines éveillent des soupçons

Efficaces pour réduire le cholestérol chez les patients à risque, les statines ne sont pas toujours utiles

Anne-Muriel Brouet

60 MILLIONS DE CONSOMMATEURS

CHOLESTÉROL : LA FOLIE DES STATINES

Les fabricants font leur beurre avec ces pilules stars prétendument miracles. Leur efficacité est pourtant très contestée

Qui arrêtera cette folle course ? En France, rares sont les experts qui s'opposent à cette apologie moléculaire.

Allez vous reprendrez bien encore un peu de statine...

Les statines en question…

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LISTE NOIRE

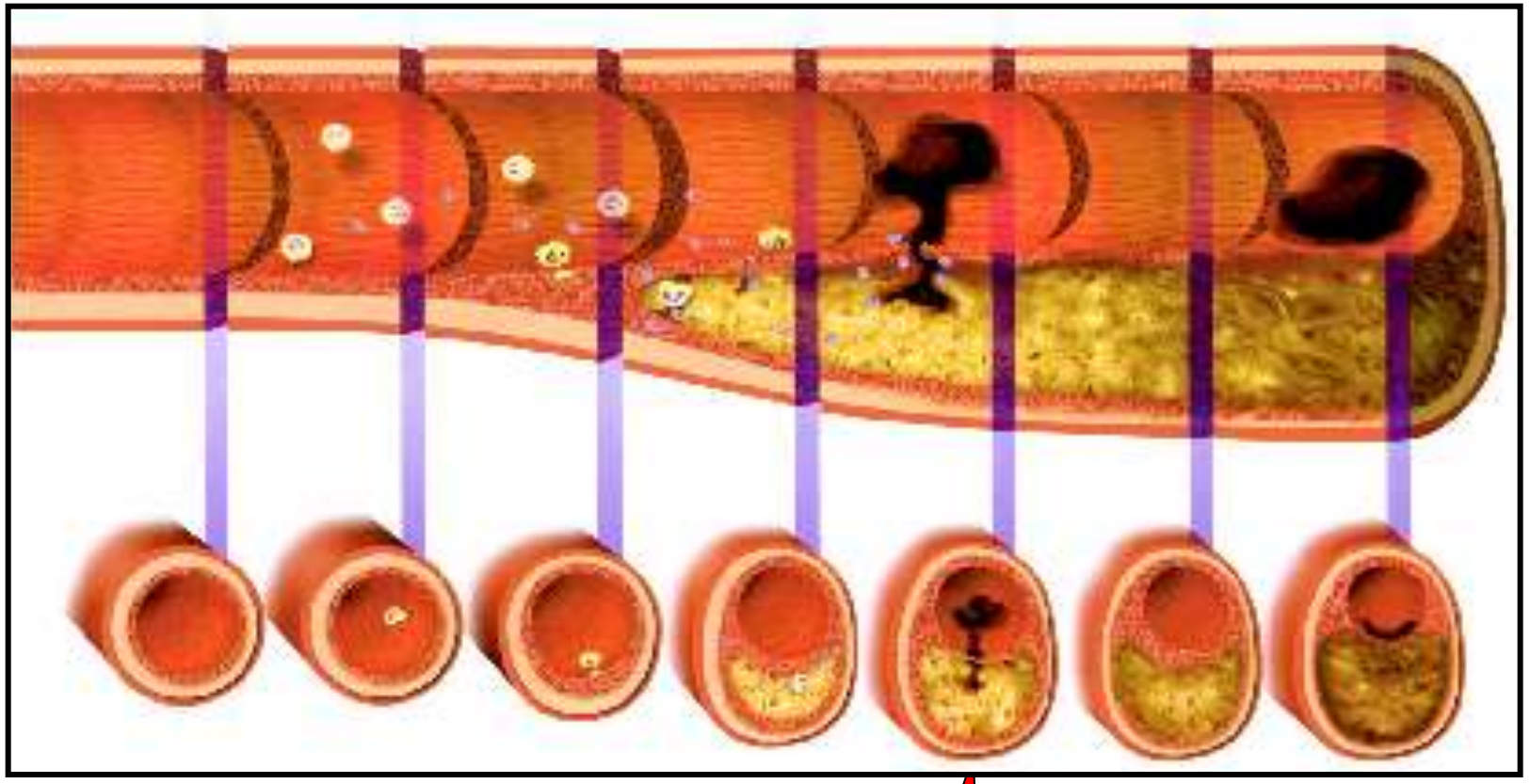
LES 58 MÉDICAMENTS DANGEREUX

Ces spécialités à haut risque sont à proscrire immédiatement. Inefficaces ou inutiles, elles peuvent être aisément remplacées par d'autres, moins dangereuses et souvent moins chères

Classe de médicaments	Nom	Nombre	Commentaire
Antiinflammatoires	Indocide (MSD), Nexen (Therabel), Ketum cutané (Ménarini), Celebrex (Pfizer), Arcoxia (MSD)	5	A remplacer par les autres anti-inflammatoires, pour éviter nécroses cutanées et hépatites. Le Celebrex et l'Arcoxia, cousins du Vioxx, retirés du marché provoquent des accidents vasculaires.
Médicaments cardiovasculaires	– 4 vasodilatateurs coronaires et artériels : Adancor (Derono), Ikorel(Sanofi), Vastarel et Trivastal (Servier) – 1 Anti-insuffisance cartiaque : Procoralan (Servier) – 1 Antiarythmique : Multas (Sanofi) – 3 anti-coagulants ou antiagrégants : Ticlid (Sanofi), Pradaxa (Boehringer) et Xigris (Lilly)	8	Les vasodilatateurs, l'anti-insuffisance cardiaque et l'antiarythmique sont inutiles et présentent des compliçations cardiaques multiples – hypotension, troubles du rythme, infarctus. Les anticoagulants ou antiagrégants doivent être remplacés par les molécules plus anciennes, aussi efficaces, moins dangereuses : Aspirine, Plavix, héparines, Préviscan.
Antidiabétiques	Byetta (Lilly) et Victoza (NovoNordisk) – 8 Gliptines : Galvus et Eucrers (Novartis), Januvia et Janumet (MSD), Xenuvia et Velmétia (P. Fabre), Trajenta et Onglyzia (Boehringer). – 2 glitazines : Actos et Competact (Takeda) suspendues en France, mais maintenues par l'Agence Européenne.	12	L'Actos, avec ses hépatites et ses cancers de la vessie et le Byetta, aux complications multiples, sont très dangereux. Les gliptines sont en nombre croissant, mais sans efficacité. Les associations à la metformine, le médicament original, comme le Janumet présentent des risques d'hépatite mortelle et sont dix fois plus chers.

Statines ≠ médicaments dangereux…

Athérosclérose - Processus dynamique



Prévention Primaire

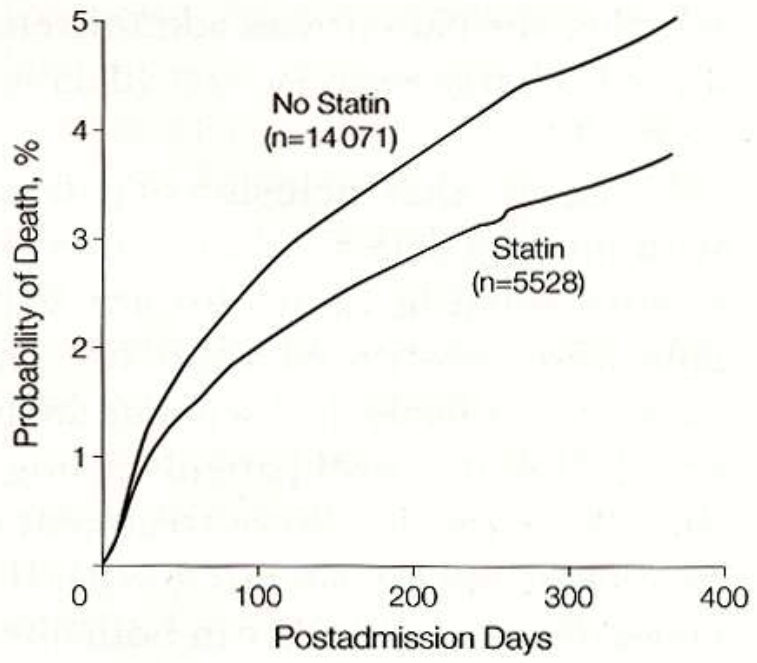
Prévention Secondaire

Evénement cardiovasculaire
Diagnostique d'athérosclérose/Diabète

Statine et infarctus

Early Statin Treatment Following Acute Myocardial Infarction and 1-Year Survival

Figure. Adjusted Probability of Mortality by Statin Treatment



Data were calculated using multiple Cox regression analysis (relative risk, 0.75; 95% confidence interval, 0.63-0.89; *P*=.001).

Context Randomized trials have established statin treatment as secondary prevention in coronary artery disease, but it is unclear whether early treatment with statins following acute myocardial infarction (AMI) influences survival.

Objective To evaluate the association between statin treatment initiated before or at the time of hospital discharge and 1-year mortality after AMI.

Design and Setting Prospective cohort study using data from the Swedish Register of Cardiac Intensive Care on patients admitted to the coronary care units of 58 Swedish hospitals in 1995-1998. One-year mortality data were obtained from the Swedish National Cause of Death Register.

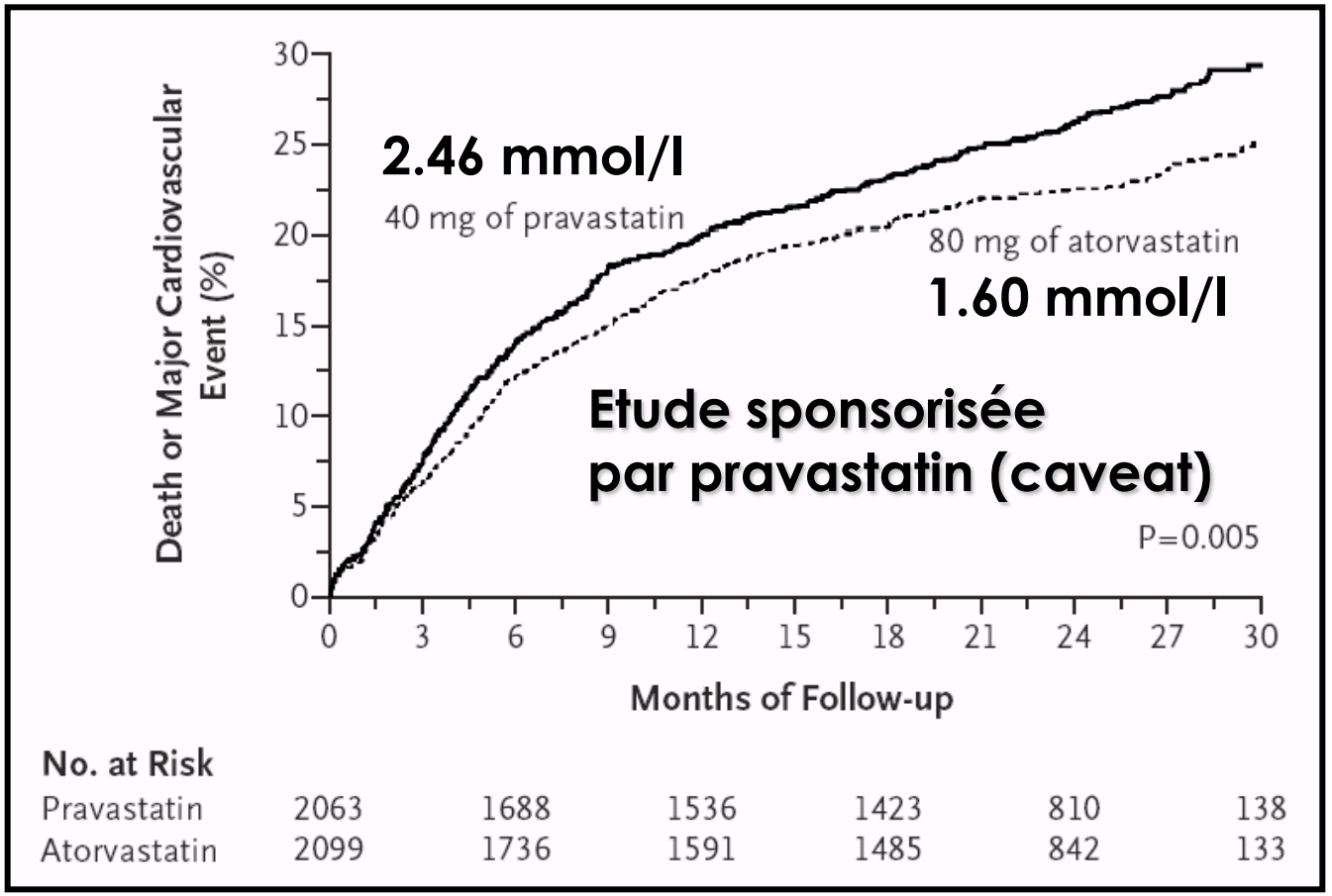
Patients Patients with first registry-recorded AMI who were younger than 80 years and who were discharged alive from the hospital, including 5528 who received statins at or before discharge and 14071 who did not.

Le traitement de statine après infarctus sauve des vies.

JAMA 2001;285:430

Is lower LDL-c better ?

Après un infarctus, le traitement de statine avec abaissement significatif de LDL-c diminue les futurs événements CV.



N Engl J Med 2004;350:15

Cholestérol et Athérosclérose
The lower the better ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Two Intensive Statin Regimens on Progression of Coronary Disease

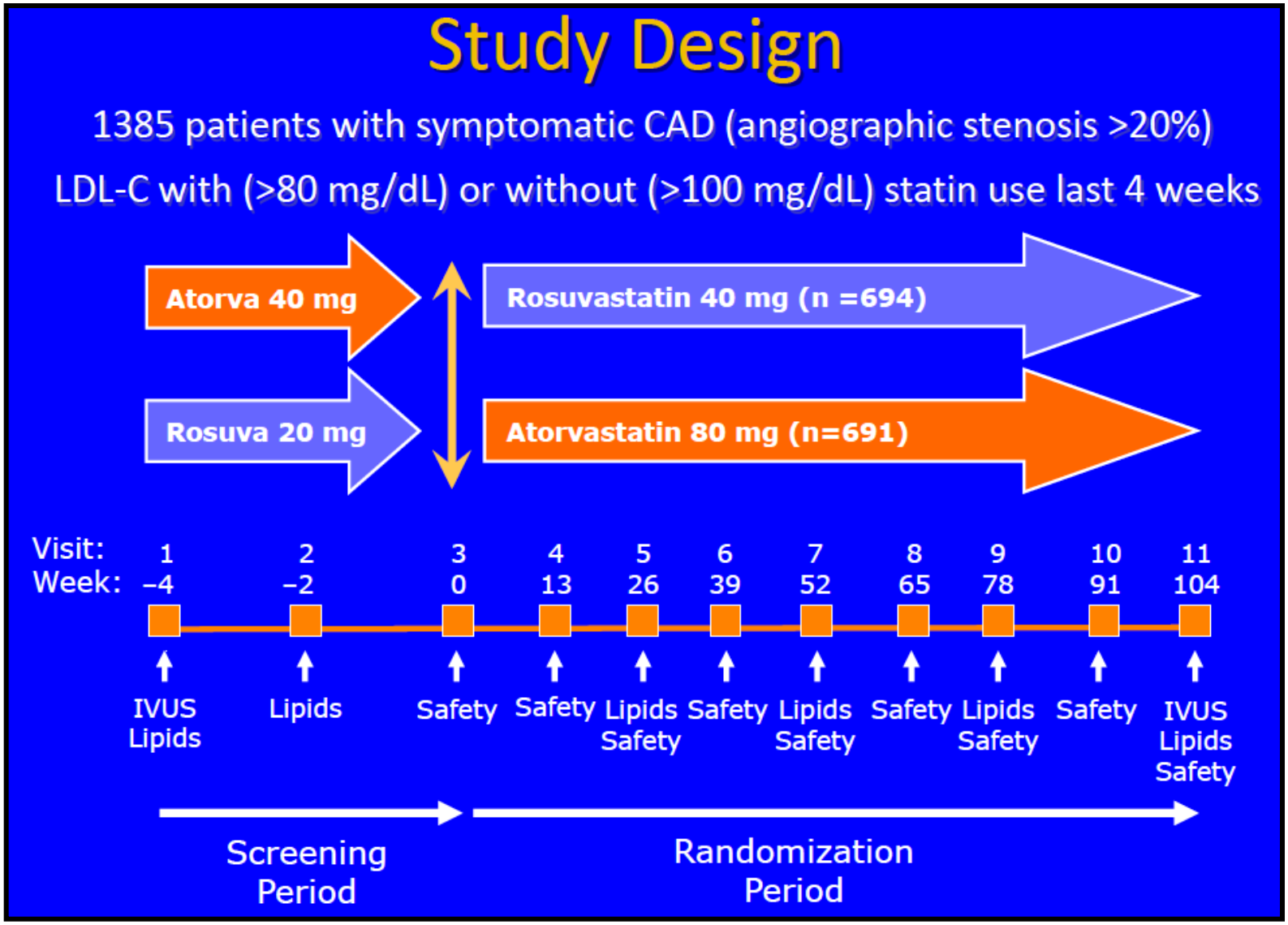
Stephen J. Nicholls, M.B., B.S., Ph.D., Christie M. Ballantyne, M.D., Philip J. Barter, M.B., B.S., Ph.D., M. John Chapman, Ph.D., D.Sc., Raimund M. Erbel, M.D., Peter Libby, M.D., Joel S. Raichlen, M.D., Kiyoko Uno, M.D., Marilyn Borgman, R.N., Kathy Wolski, M.P.H., and Steven E. Nissen, M.D.

METHODS

We performed serial intravascular ultrasonography in 1039 patients with coronary disease, at baseline and after 104 weeks of treatment with either atorvastatin, 80 mg daily, or rosuvastatin, 40 mg daily, to compare the effect of these two intensive statin regimens on the progression of coronary atherosclerosis, as well as to assess their safety and side-effect profiles.

New Engl J Med 2011;online

Cholestérol et Athérosclérose
The lower the better ?

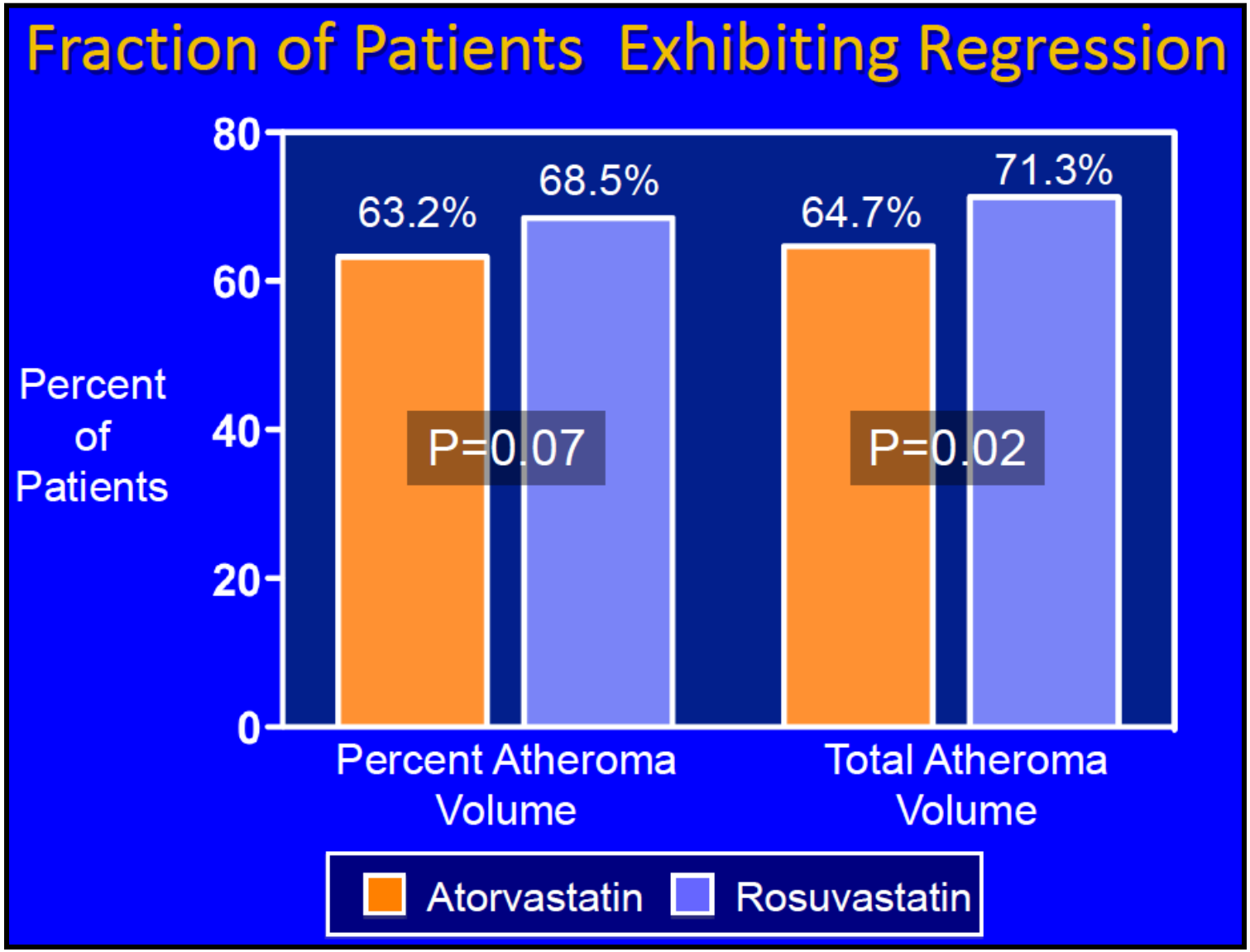


Cholestérol et Athérosclérose
The lower the better ?

Time-Weighted Lipid Levels and hsCRP

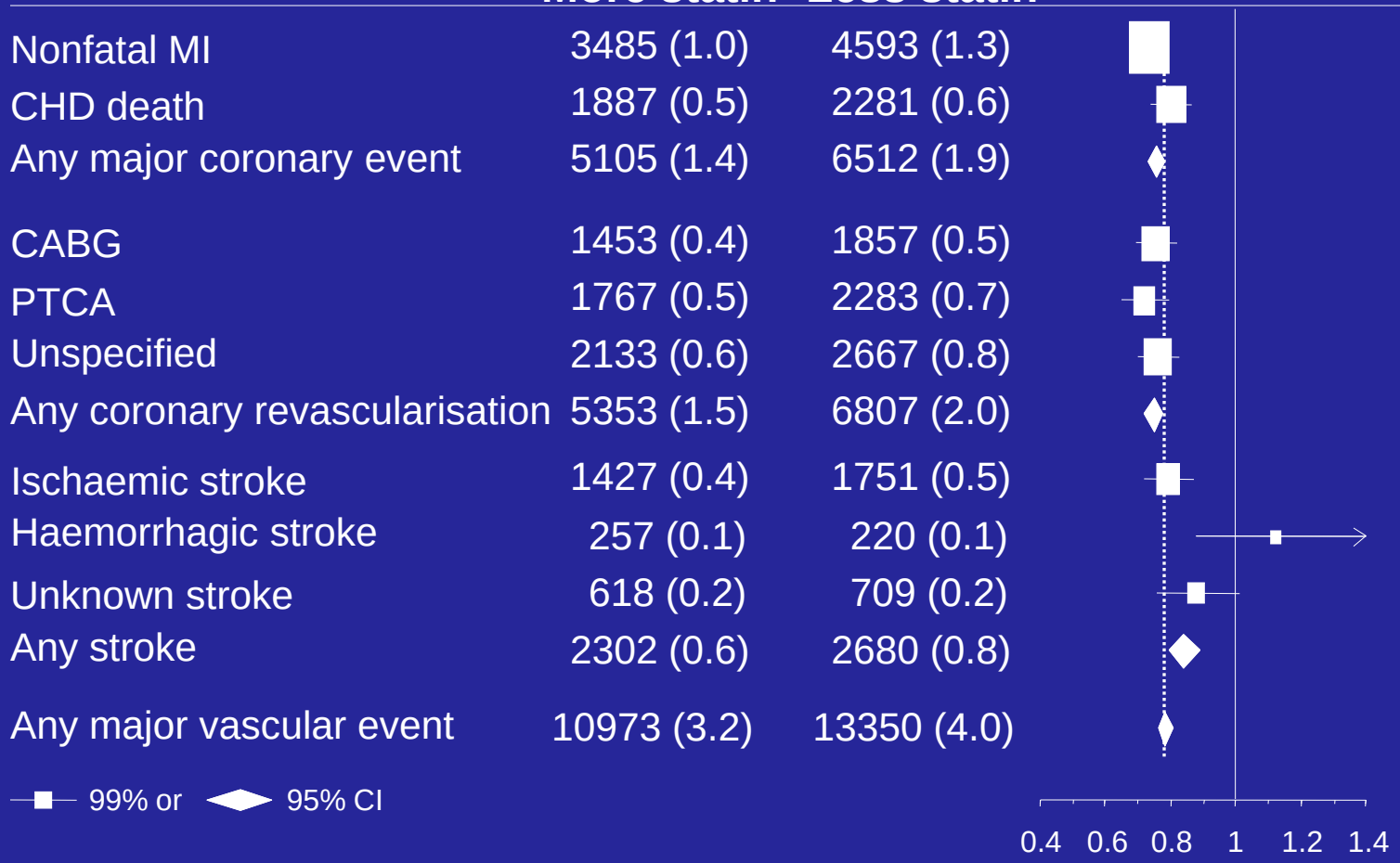
Parameter	Atorvastatin (n=519)	Rosuvastatin (n=520)	P Value
LDL cholesterol (mg/dL)	1.82 mg/L	1.62 mg/L	**<0.001**
HDL cholesterol (mg/dL)	1.26 mg/L	1.30 mg/L	**0.01**
Triglycerides (mg/dL)*	110	120	0.02
LDL:HDL cholesterol	1.5	1.3	<0.01
hsCRP (mg/L)*	1.0	1.1	0.05

Cholestérol et Athérosclérose
The lower the better ?



Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol

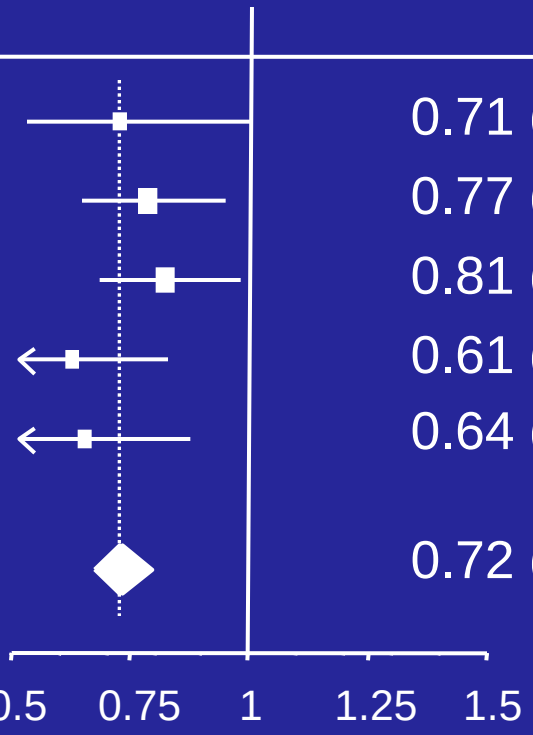
	No. of events (% pa) Statin/ More statin	Control/ Less statin	Relative risk (CI)
Nonfatal MI	3485 (1.0)	4593 (1.3)	0.73 (0.69 - 0.78)
CHD death	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Any major coronary event	5105 (1.4)	6512 (1.9)	0.76 (0.73 - 0.78)
CABG	1453 (0.4)	1857 (0.5)	0.75 (0.69 - 0.82)
PTCA	1767 (0.5)	2283 (0.7)	0.72 (0.65 - 0.80)
Unspecified	2133 (0.6)	2667 (0.8)	0.76 (0.70 - 0.82)
Any coronary revascularisation	5353 (1.5)	6807 (2.0)	0.75 (0.72 - 0.78)
Ischaemic stroke	1427 (0.4)	1751 (0.5)	0.79 (0.72 - 0.87)
Haemorrhagic stroke	257 (0.1)	220 (0.1)	1.12 (0.88 - 1.43)
Unknown stroke	618 (0.2)	709 (0.2)	0.88 (0.76 - 1.01)
Any stroke	2302 (0.6)	2680 (0.8)	0.84 (0.79 - 0.89)
Any major vascular event	10973 (3.2)	13350 (4.0)	0.78 (0.76 - 0.80)



CTT *Lancet* 2010;376:1670

More vs less trials: Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by baseline LDL cholesterol

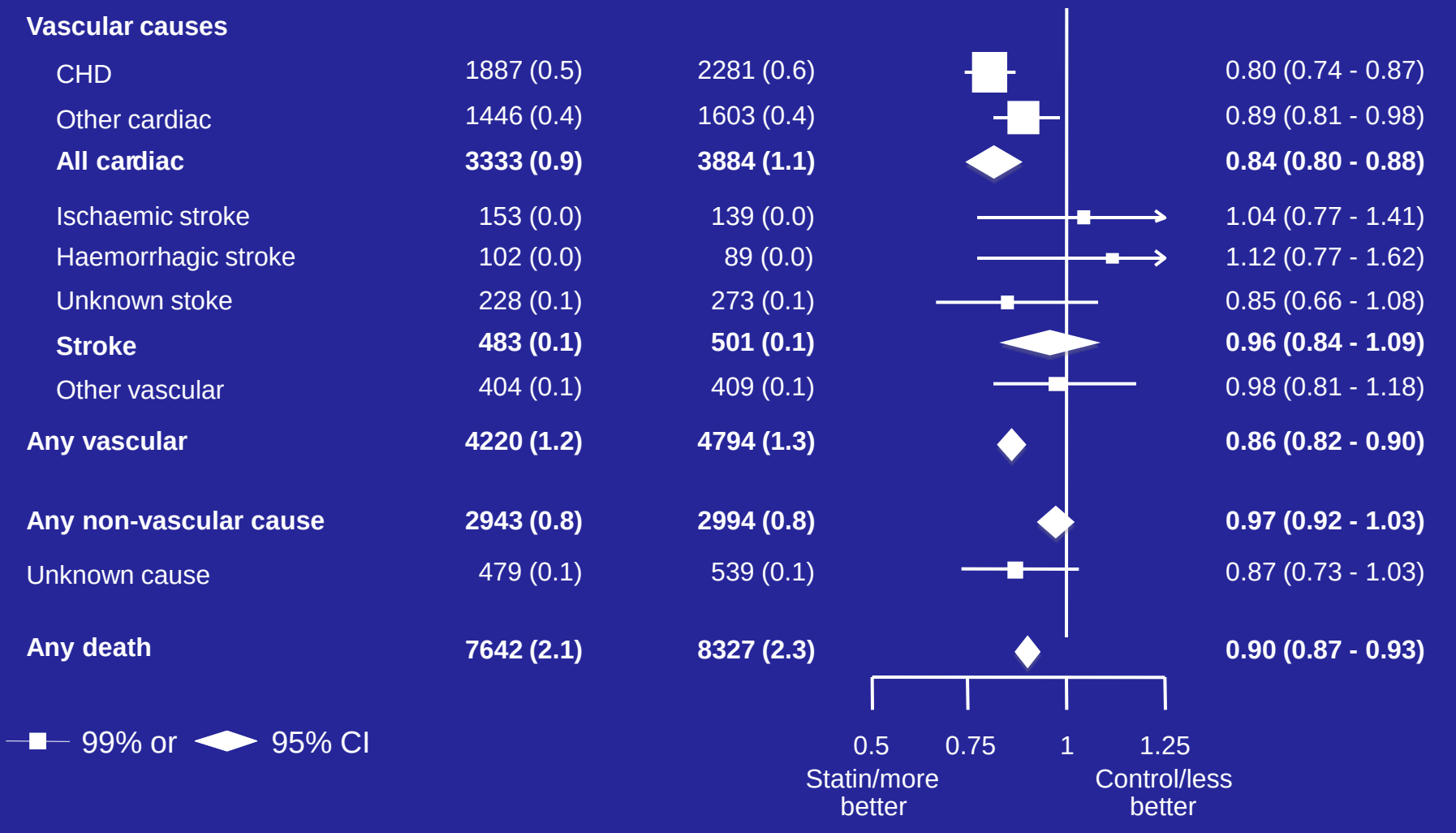
	No. of events (% pa)		
	More statin	Less statin	Relative risk (CI)
<2	704 (4.6)	795 (5.2)	0.71 (0.52 - 0.98)
≥2,<2.5	1189 (4.2)	1317 (4.8)	0.77 (0.64 - 0.94)
≥2.5,<3.0	1065 (4.5)	1203 (5.0)	0.81 (0.67 - 0.97)
≥3,<3.5	517 (4.5)	633 (5.8)	0.61 (0.46 - 0.81)
≥3.5	303 (5.7)	398 (7.8)	0.64 (0.47 - 0.86)
Total	3837 (4.5)	4416 (5.3)	0.72 (0.66 - 0.78)



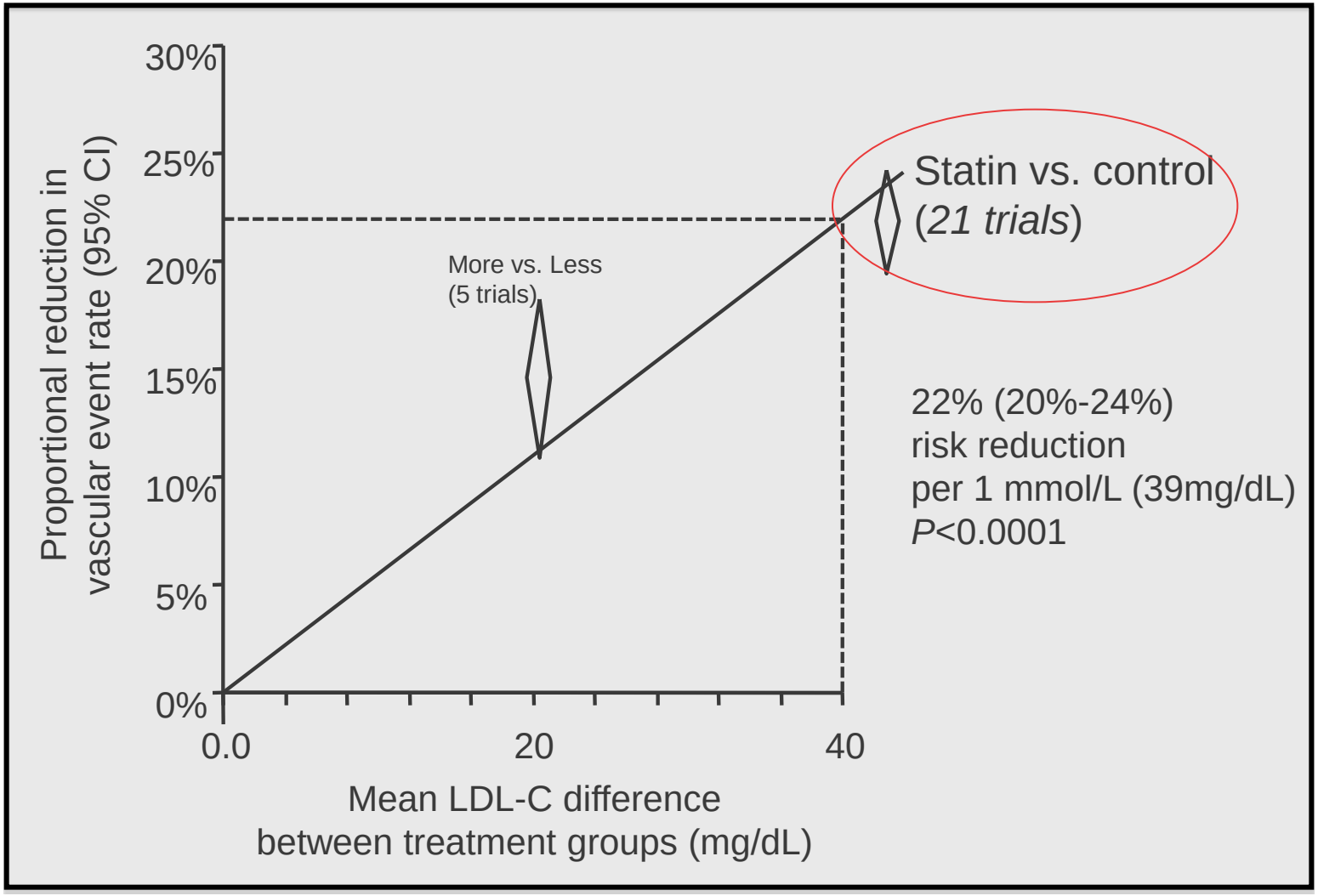
99% or 95% CI

Proportional effects on CAUSE-SPECIFIC MORTALITY per mmol/L LDL-C reduction

Cause of death	Events (% p.a.) Statin/more	Events (% p.a.) Control/less	RR (CI) per 1 mmol/L reduction in LDL-C
Vascular causes			
CHD	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Other cardiac	1446 (0.4)	1603 (0.4)	0.89 (0.81 - 0.98)
All cardiac	**3333 (0.9)**	**3884 (1.1)**	**0.84 (0.80 - 0.88)**
Ischaemic stroke	153 (0.0)	139 (0.0)	1.04 (0.77 - 1.41)
Haemorrhagic stroke	102 (0.0)	89 (0.0)	1.12 (0.77 - 1.62)
Unknown stoke	228 (0.1)	273 (0.1)	0.85 (0.66 - 1.08)
Stroke	**483 (0.1)**	**501 (0.1)**	**0.96 (0.84 - 1.09)**
Other vascular	404 (0.1)	409 (0.1)	0.98 (0.81 - 1.18)
Any vascular	**4220 (1.2)**	**4794 (1.3)**	**0.86 (0.82 - 0.90)**
Any non-vascular cause	**2943 (0.8)**	**2994 (0.8)**	**0.97 (0.92 - 1.03)**
Unknown cause	479 (0.1)	539 (0.1)	0.87 (0.73 - 1.03)
Any death	**7642 (2.1)**	**8327 (2.3)**	**0.90 (0.87 - 0.93)**

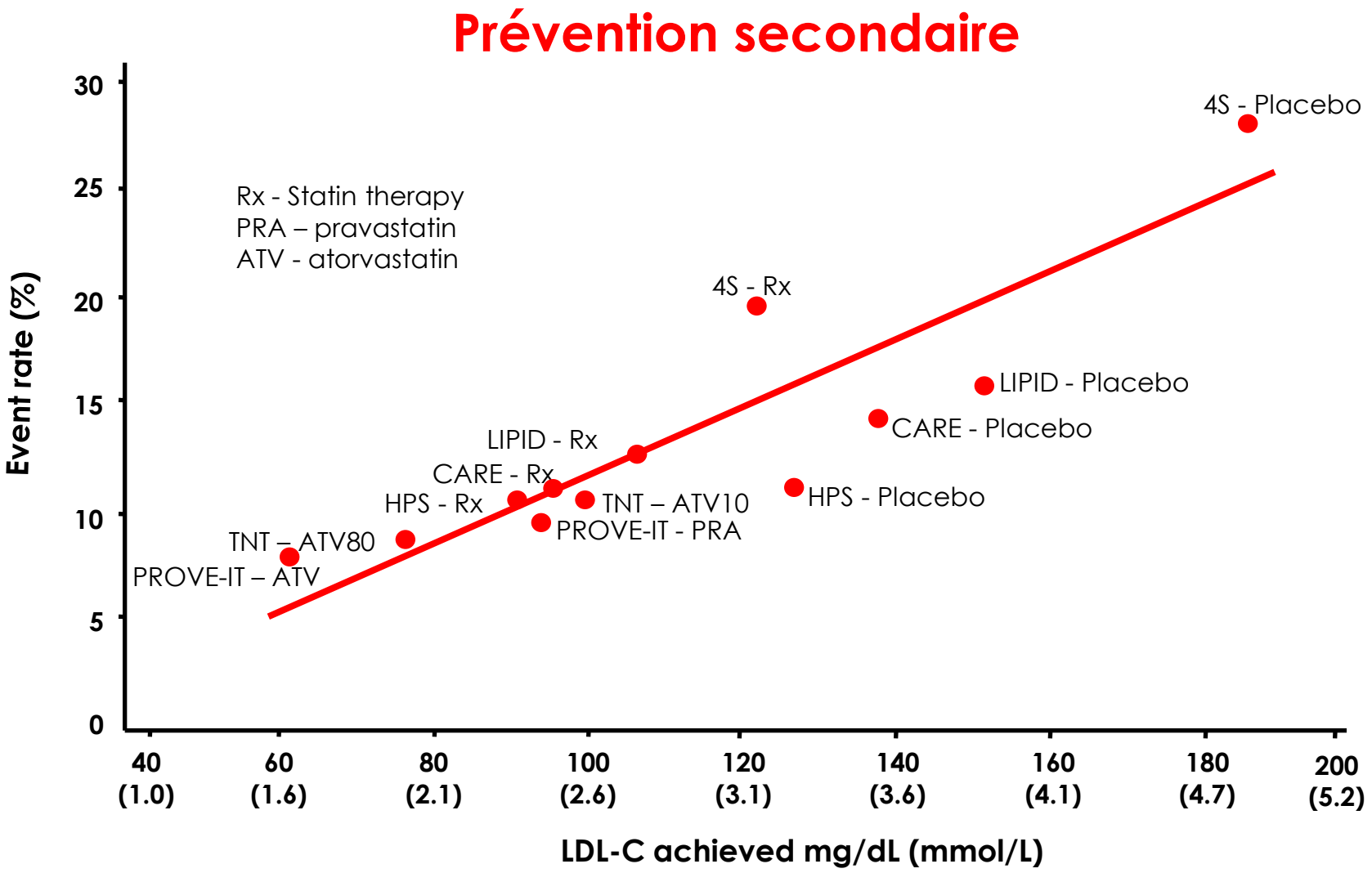


Most evidence for the benefit of LDL-C lowering is from statin vs placebo trial designs



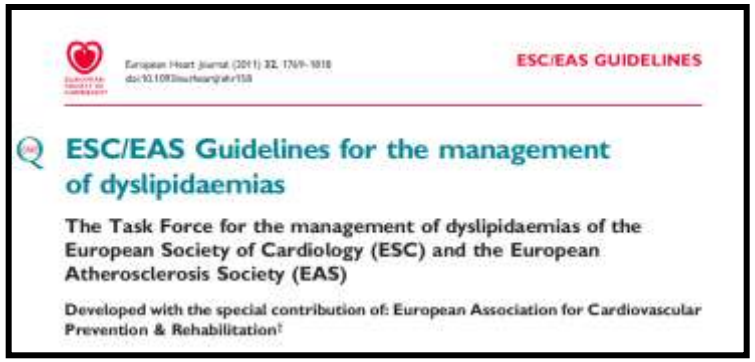
CTT Collaboration Lancet 2010;376:1670.

Statine et prévention secondaire



Exp Opin Emerg Drugs 2004;9(2):269
N Engl J Med 2005;352:1425

LDL-cholesterol levels



ESC/EAS GUIDELINES

ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

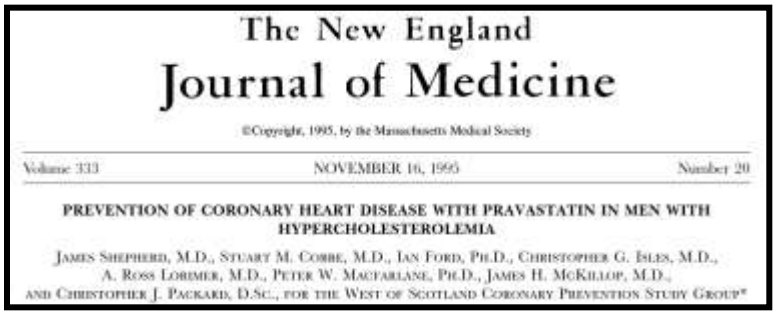
Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation

ESC/EAS guidelines for the management of dyslipidemias.
European Heart Journal 2011;32:1769

Table 8 Recommendations for treatment targets for LDL-C

Recommendations	Class[a]	Level[b]	Ref[c]
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I	A	15, 32, 33
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	IIa	A	15, 16, 17
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C	-

Statine et prévention primaire



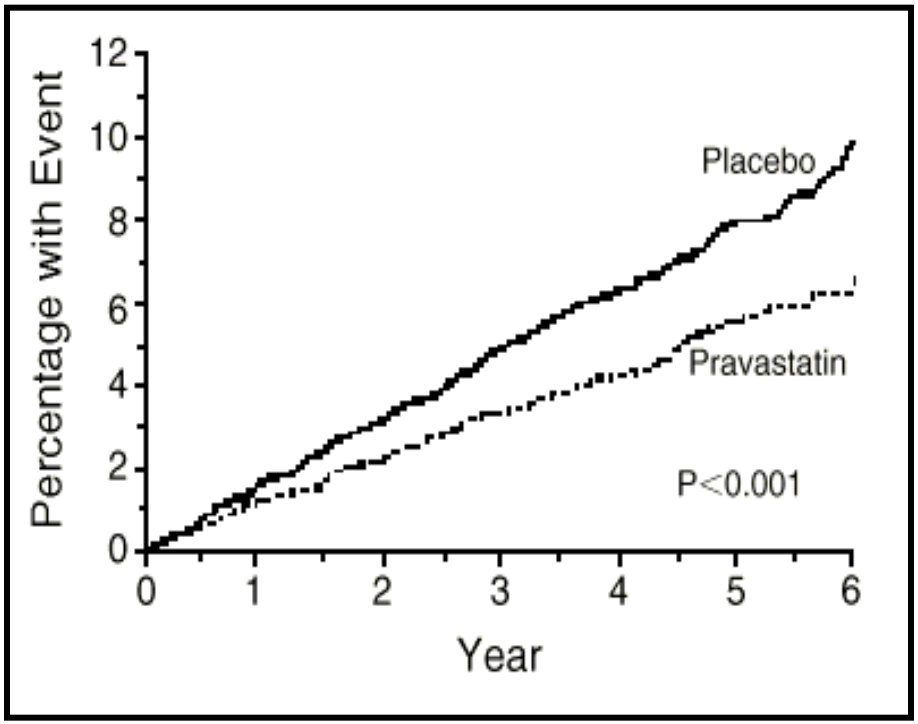
The New England
Journal of Medicine

Volume 333 NOVEMBER 16, 1995 Number 20

PREVENTION OF CORONARY HEART DISEASE WITH PRAVASTATIN IN MEN WITH HYPERCHOLESTEROLEMIA

JAMES SHEPHERD, M.D., STUART M. COBBE, M.D., IAN FORD, PH.D., CHRISTOPHER G. ISLES, M.D., A. ROSS LORIMER, M.D., PETER W. MACFARLANE, PH.D., JAMES H. MCKILLOP, M.D., AND CHRISTOPHER J. PACKARD, D.SC., FOR THE WEST OF SCOTLAND CORONARY PREVENTION STUDY GROUP*

En présence d'hypercholestérolémie, le traitement de statine diminue le risque d'événements CV.



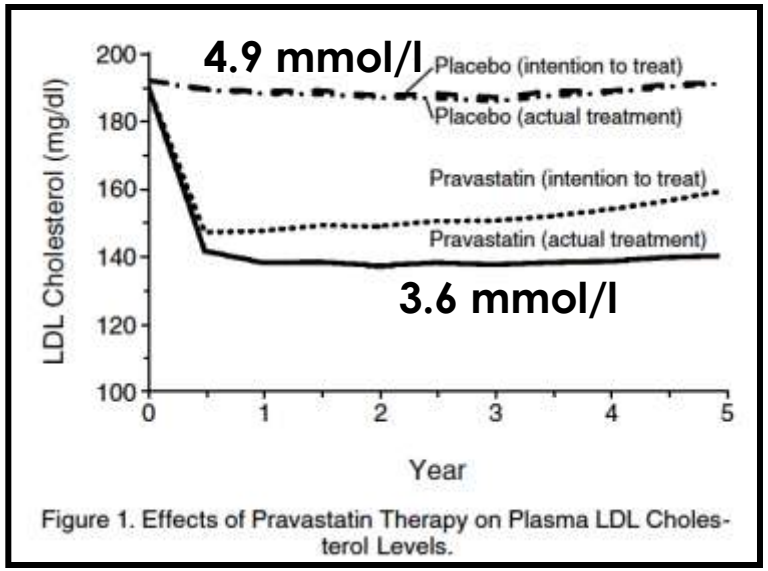
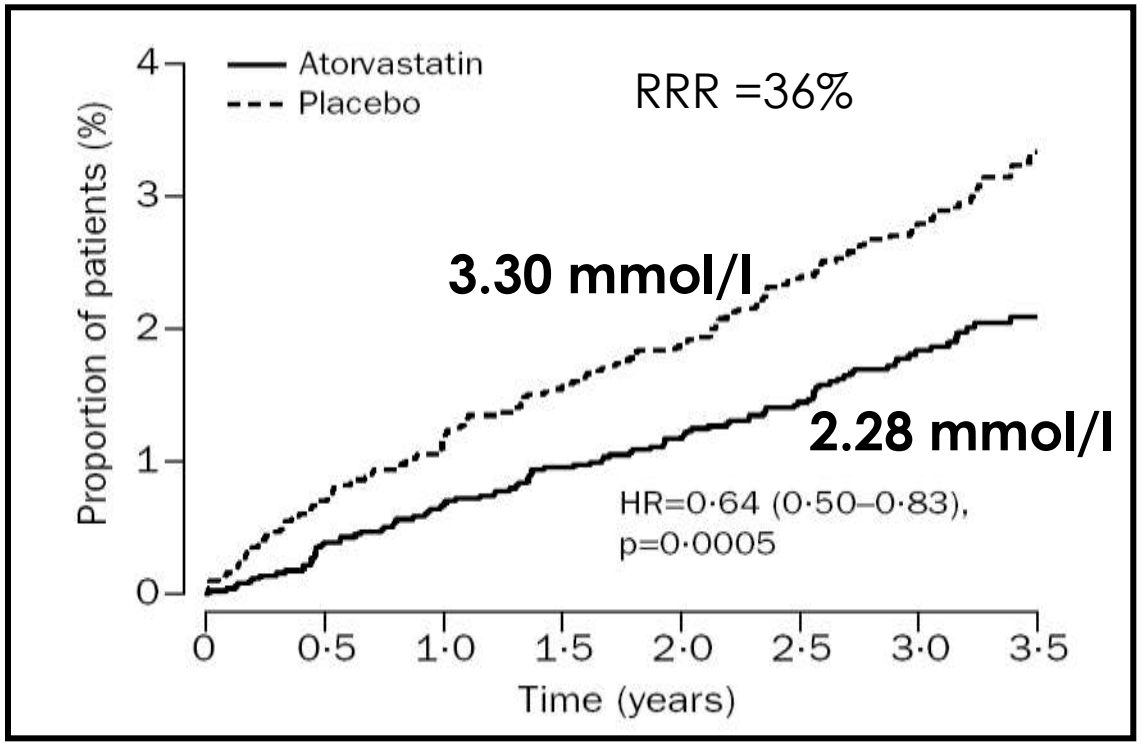


Figure 1. Effects of Pravastatin Therapy on Plasma LDL Cholesterol Levels.

WOSCOP *N Engl J Med* 1995;333:1301

Statine et prévention primaire

En présence d'HTA et d'autres FRCV, le traitement de statine diminue le risque d'événements CV.



Infarctus nonfatal et mortalité CV

ASCOT –LLA *Lancet* 2003;361:1149

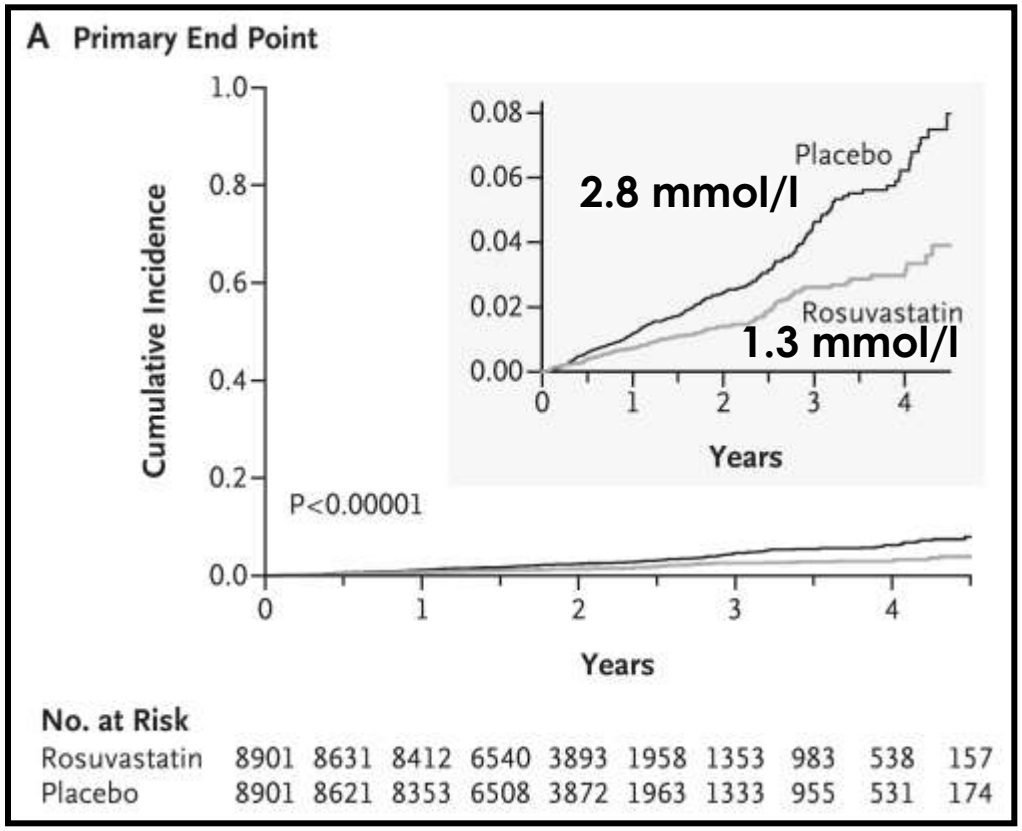
Statine et prévention primaire

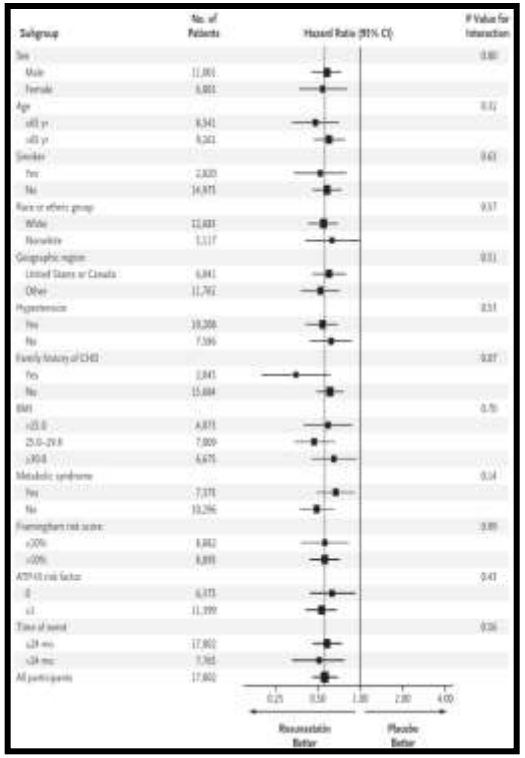
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2008 VOL. 359 NO. 21

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

En présence d'un syndrome métabolique et d'inflammation, le traitement de statine diminue le risque d'événements CV.

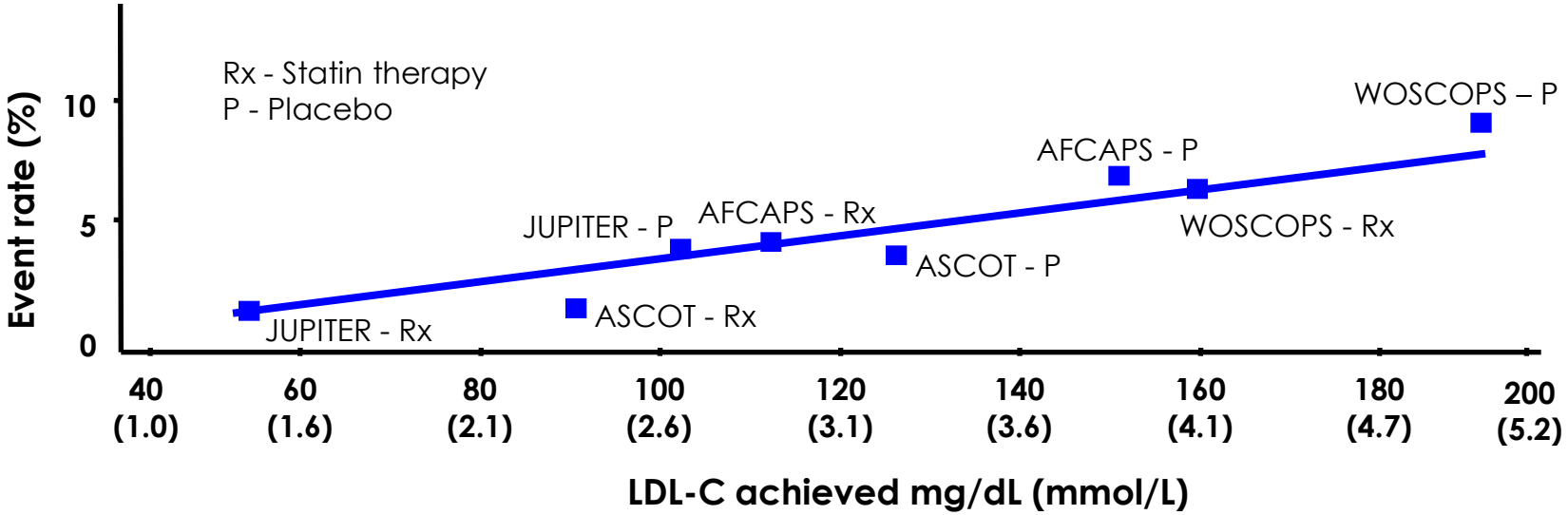




N Eng J Med 2008;359:2195

Statine et prévention primaire

Prévention primaire



Exp Opin Emerg Drugs 2004;9:269
N Engl J Med 2005;352:1425

Statine et prévention primaire

BMJ **RESEARCH**

Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis

JP Greving, research fellow in clinical epidemiology,[1] FLJ Visseren, internist and professor of vascular medicine,[2] GA de Wit, associate professor of health technology assessment,[1,3] A Algra, professor of clinical epidemiology[1,4]

Results Over a 10-year period, statin treatment cost €35 000 (£30 000, $49 000) per QALY gained for men aged 55 years with a 10-year vascular risk of 10%. The incremental cost-effectiveness ratio improved as risk for vascular disease increased. The cost per QALY ranged from approximately €5000 to €125 000 when the 10-year vascular risk for men aged 55 years was varied from 25% to 5%. The incremental cost-effectiveness ratio slightly decreased with age after the level of vascular risk was specified. Results were sensitive to the costs of statin treatment, statin effectiveness, non-adherence, disutility of taking medication daily, and the time horizon of the model.

Coût-efficacité du ttt de statine...

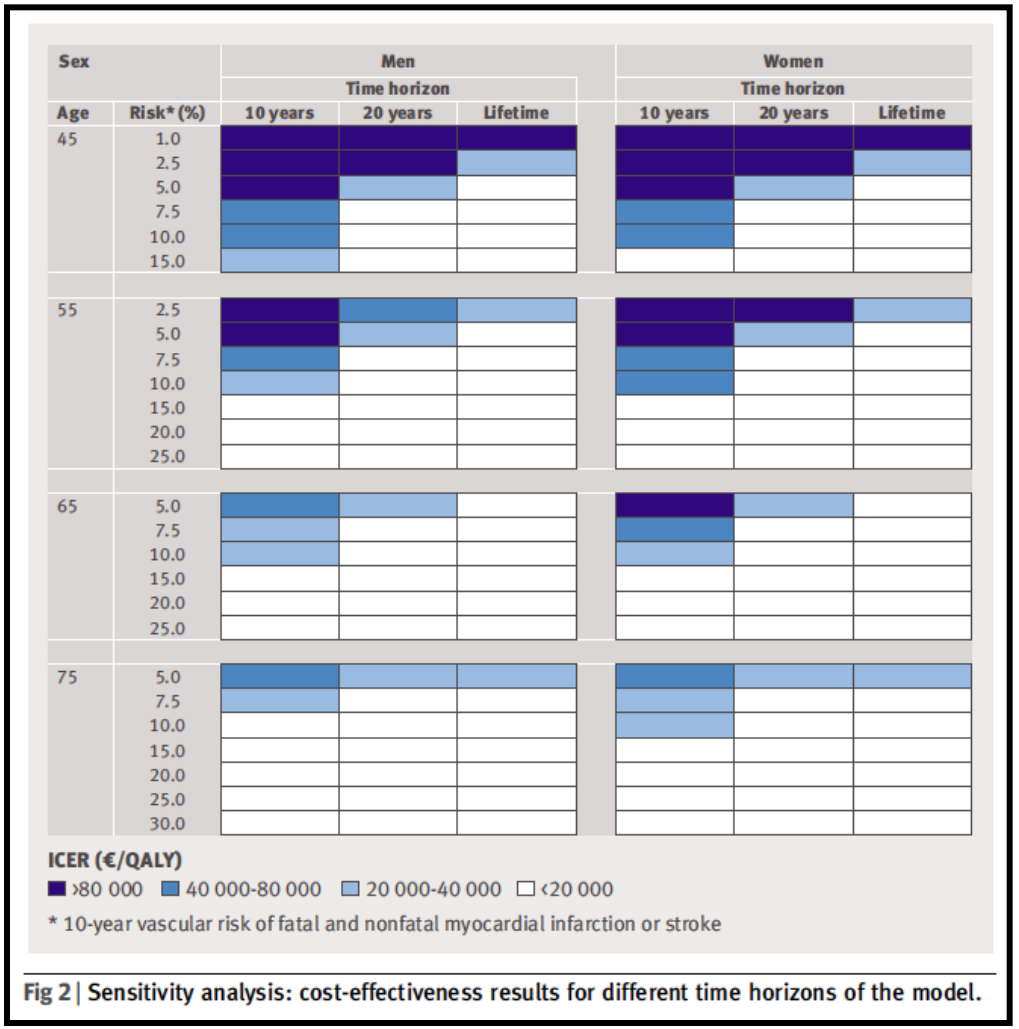


Fig 2 | Sensitivity analysis: cost-effectiveness results for different time horizons of the model.

BMJ 2011;342:1672

Statine et prévention primaire

WHAT IS ALREADY KNOWN ON THIS TOPIC?

Statins reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease.

Overall risk of vascular disease events, rather than single risk factors, determines the absolute benefits of statin therapy.

Adherence to statin treatment in daily practice is suboptimal and may impair cost-effectiveness.

WHAT THIS STUDY ADDS?

Statin treatment seemed not to be cost-effective for low risk primary prevention populations, despite low costs of generic drugs

Adherence to statins needs to be improved to enhance cost-effectiveness.

Efficace, mais pas coût-efficace si risque faible...

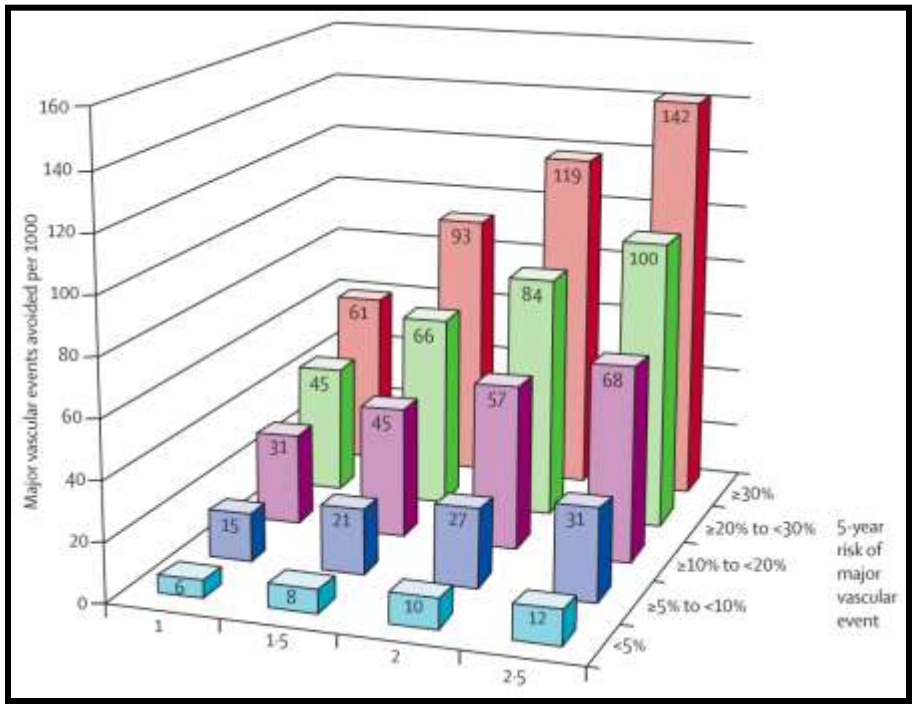
BMJ 2011;342:1672

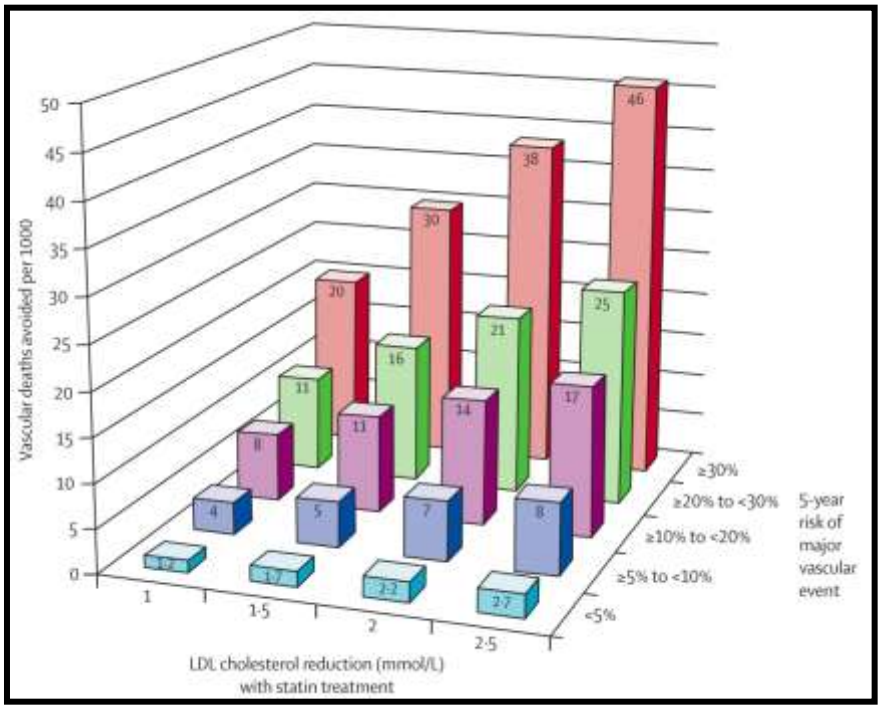
Statine et prévention primaire

The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

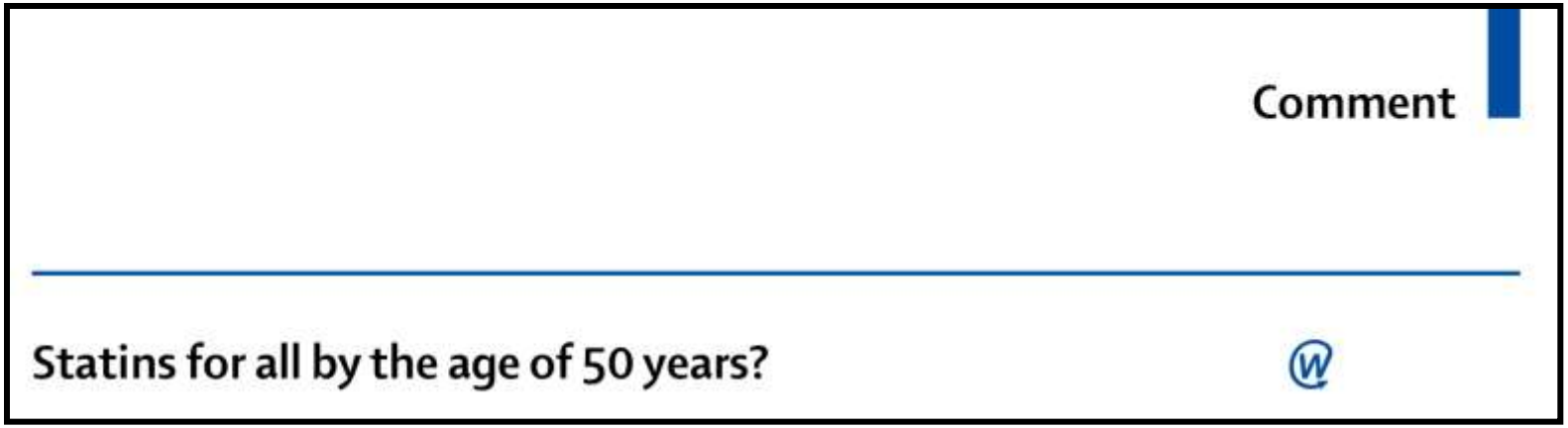
*Cholesterol Treatment Trialists' (CTT) Collaborators**

Lancet May 17, 2012;380:581





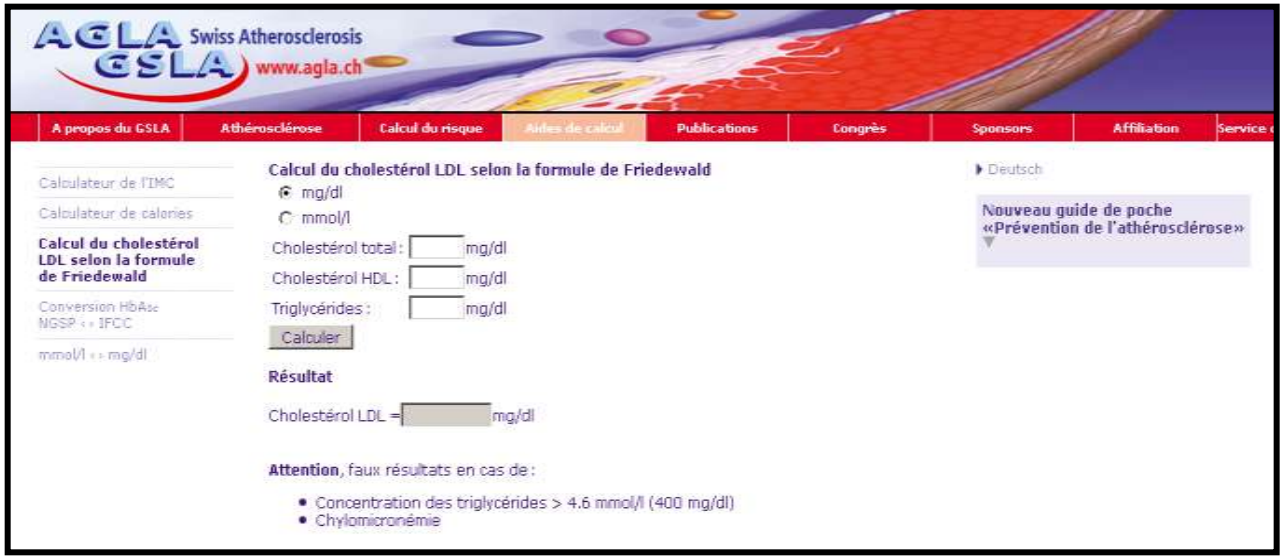
Statine et prévention primaire



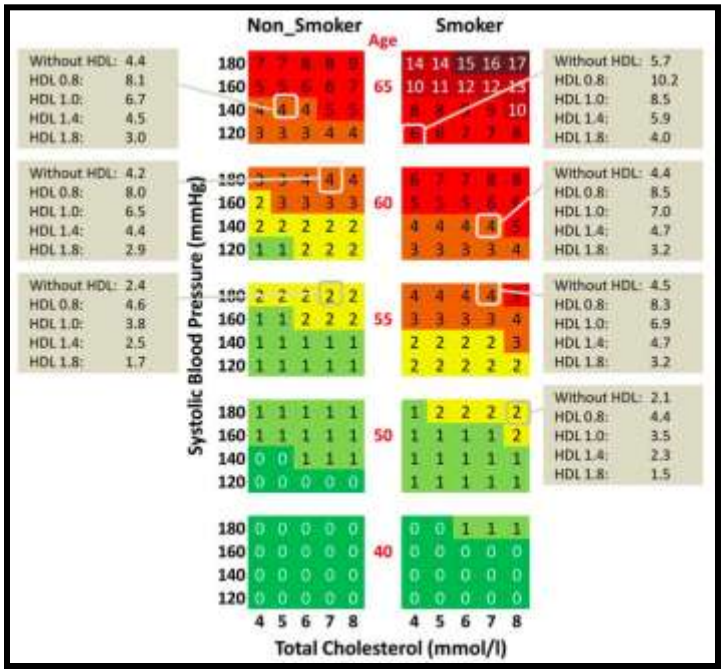
Lancet May 17, 2012;380:545

Pas vraiment « Evidence-Based-Medicine »…

Risque cardiovasculaire en prévention primaire

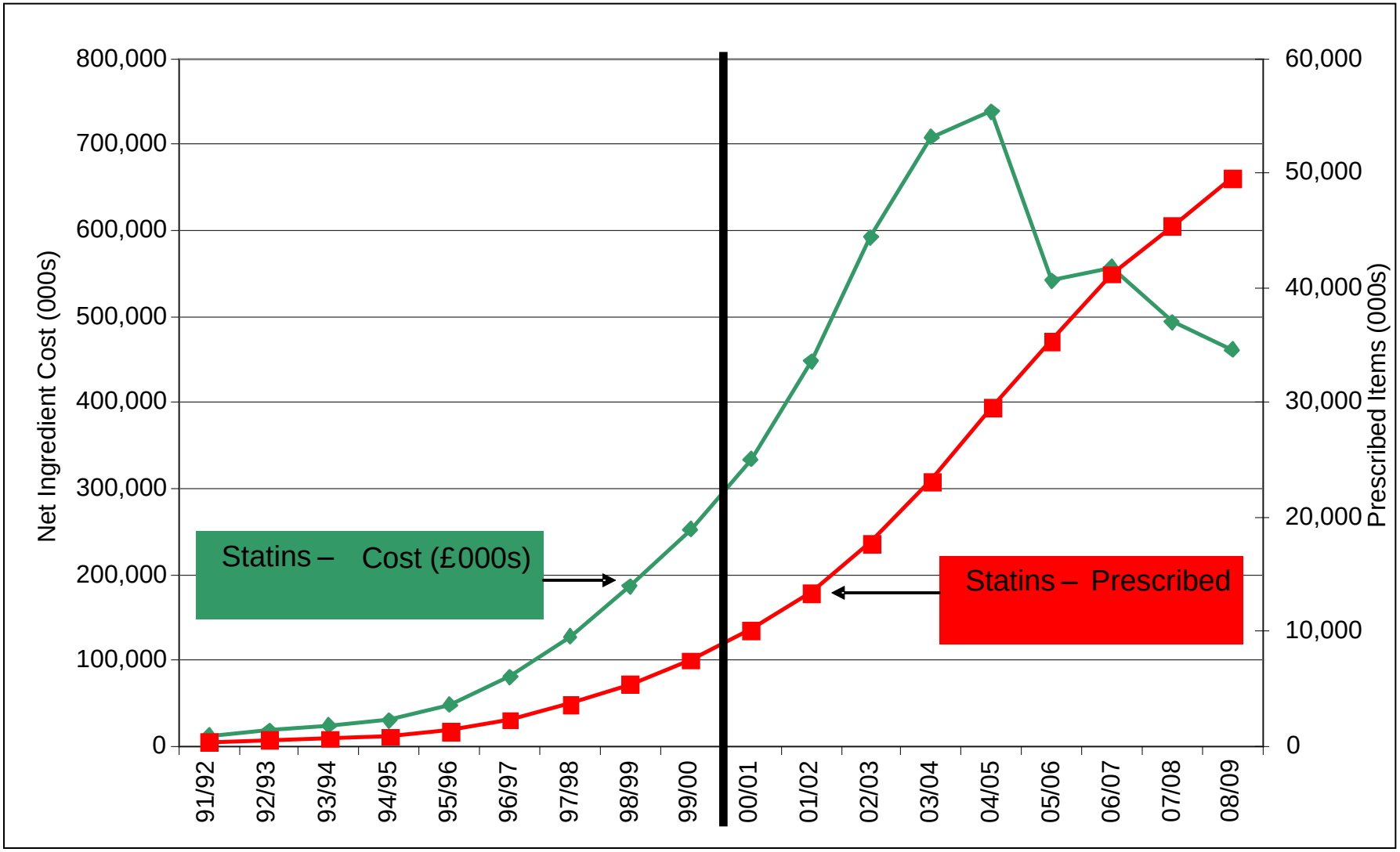


www.agla.ch

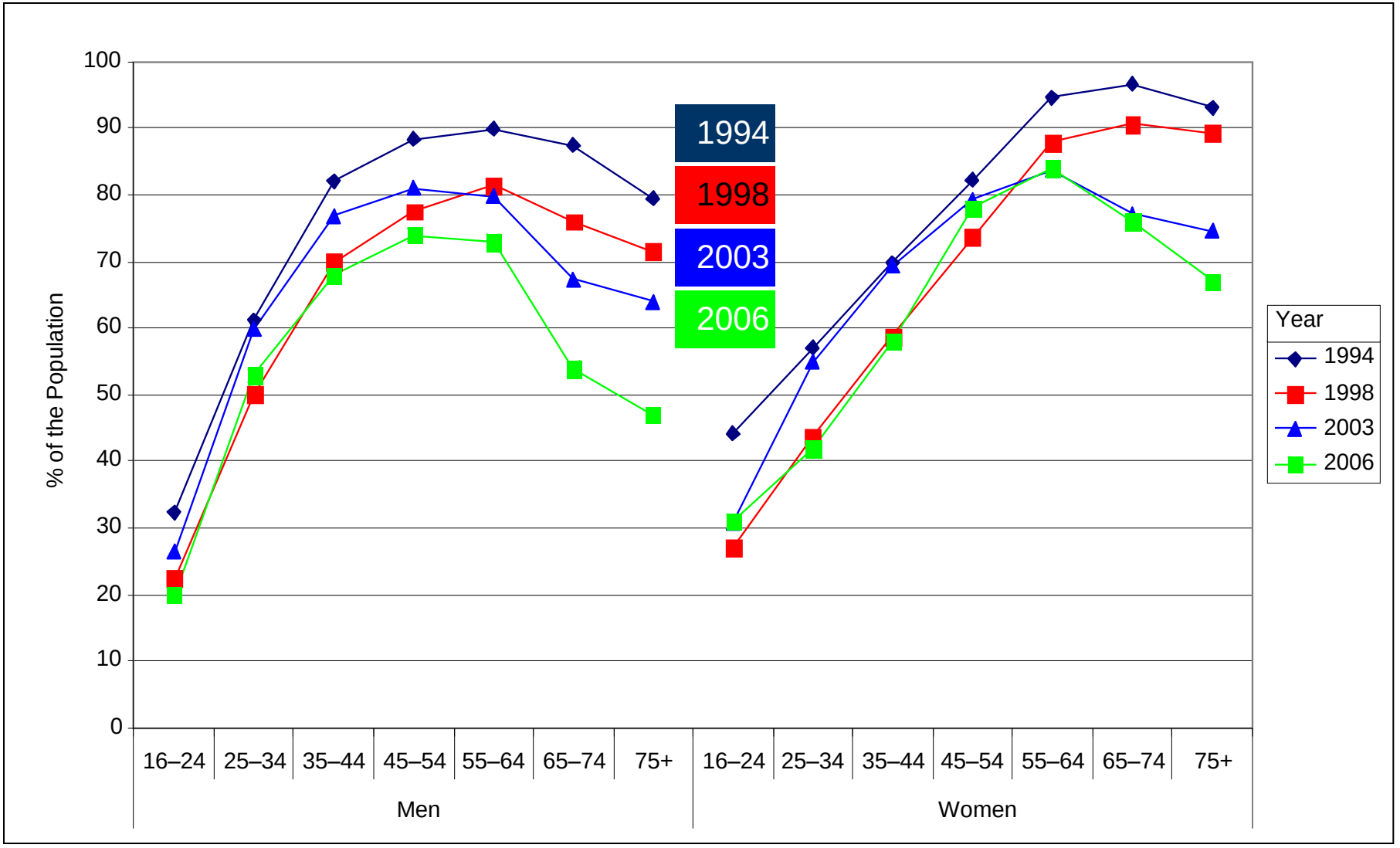


www.escardio.org

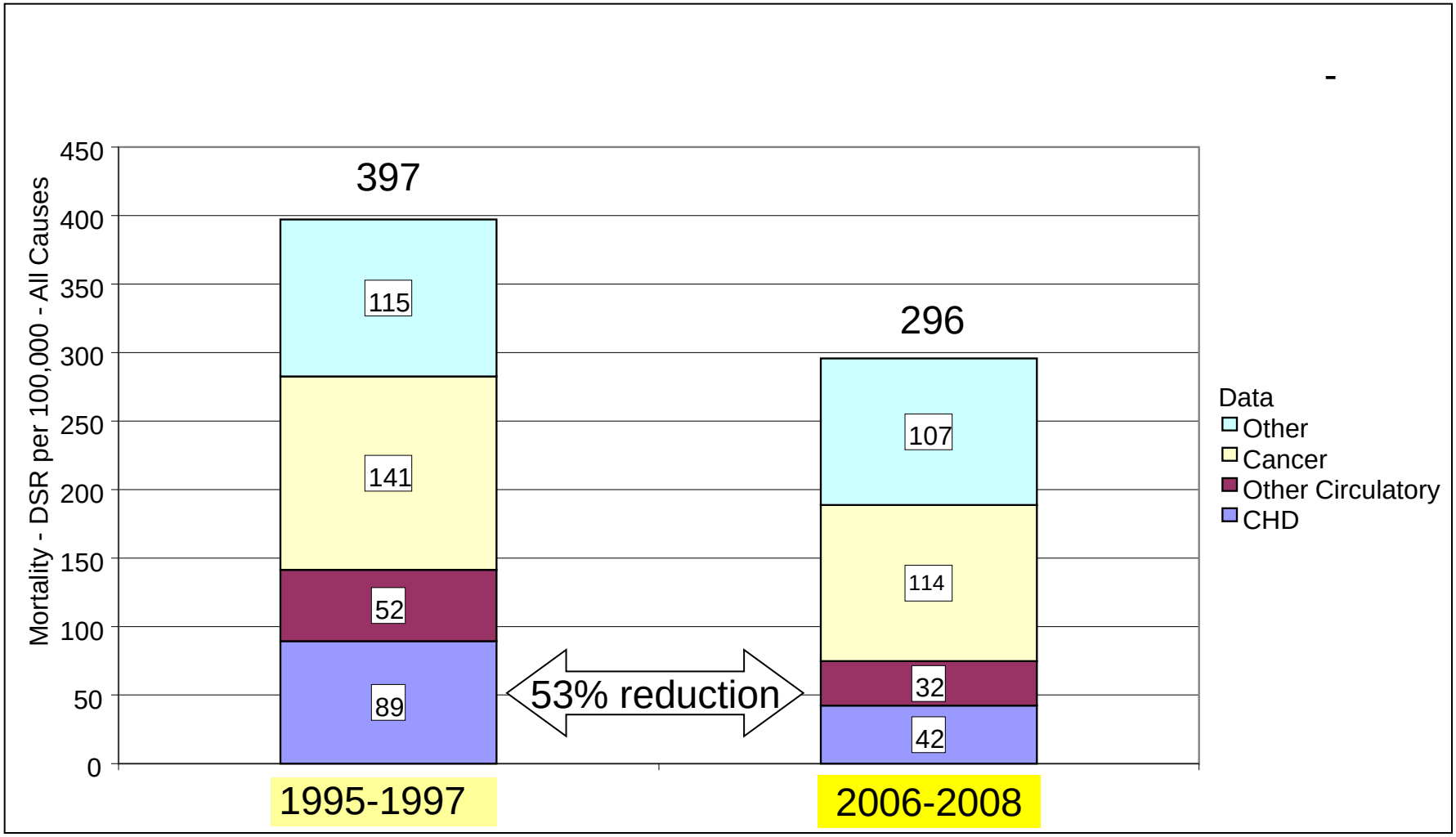
Statin Prescription in the UK



Percentage of the UK-population with TC > 5 mmol/l

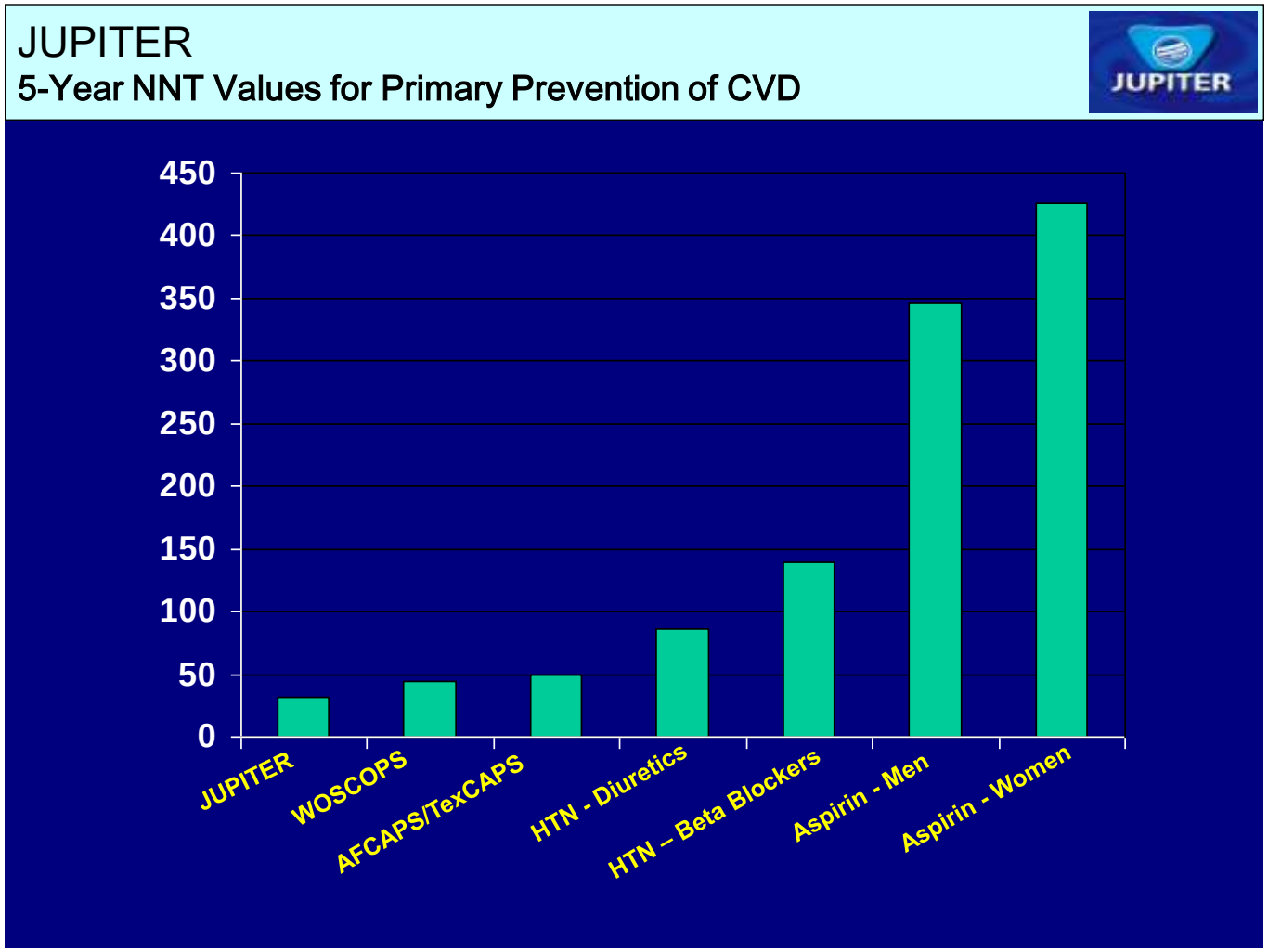


All-Cause Mortality in the UK in those < 75 Years



Statine et prévention primaire

NNT (Number Needed to Treat) comparé à d'autres thérapies CV



ACC March 30, 2009

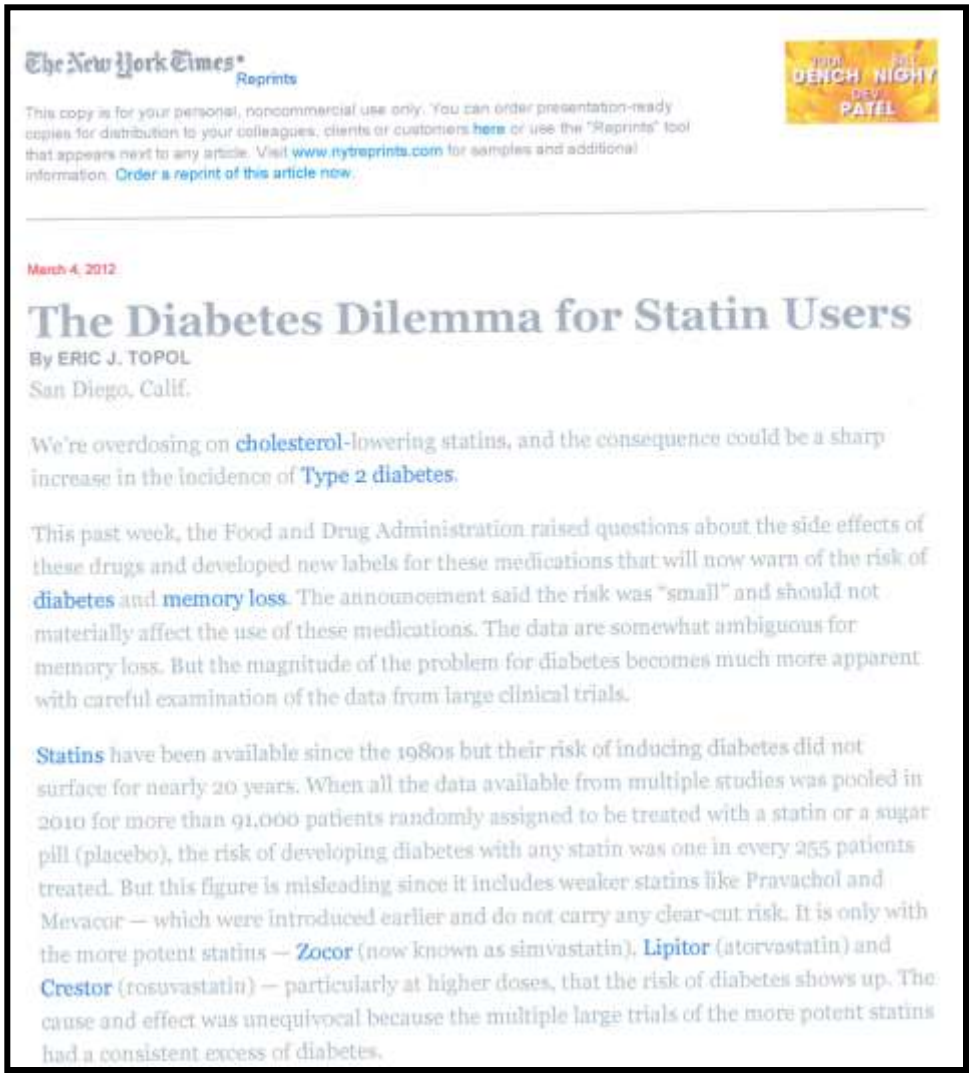
Prevention and LDL-c

Table 3 Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

ESC/EAS guidelines for the management of dyslipidemias. *European Heart Journal* 2011;32:1769

Statines et risque de diabète…



March 4, 2012

The Diabetes Dilemma for Statin Users

By ERIC J. TOPOL
San Diego, Calif.

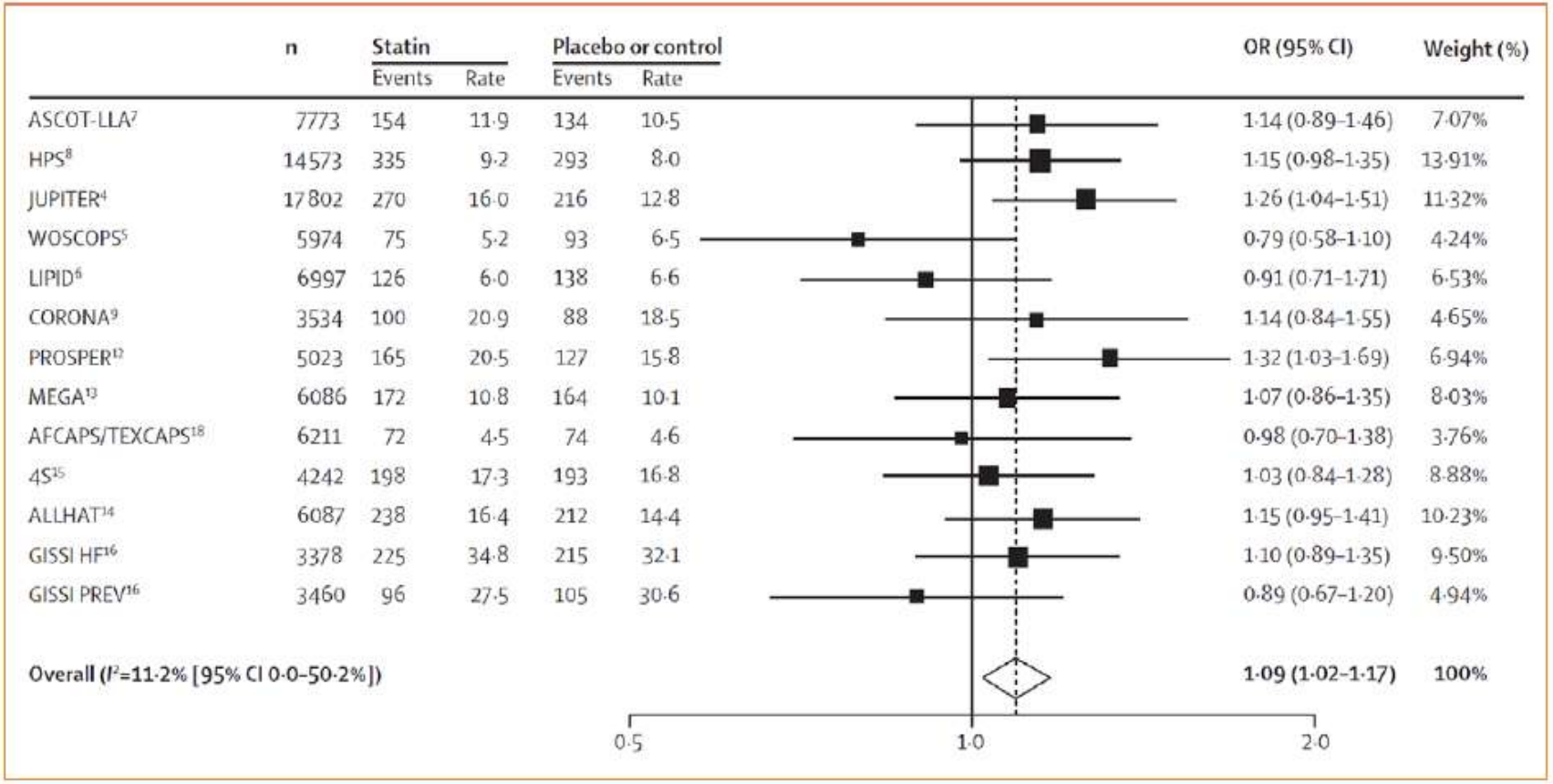
We're overdosing on cholesterol-lowering statins, and the consequence could be a sharp increase in the incidence of Type 2 diabetes.

This past week, the Food and Drug Administration 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 announcement said the risk was "small" and should not materially affect the use of these medications. The data are somewhat ambiguous for memory loss. But 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 one in every 255 patients treated. 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 (now known as 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.

Sous statines, le risque de diabète est significativement augmenté

En moyenne **1** nouveau patient avec un diabète pour **5,4** événements cardiovasculaires évités



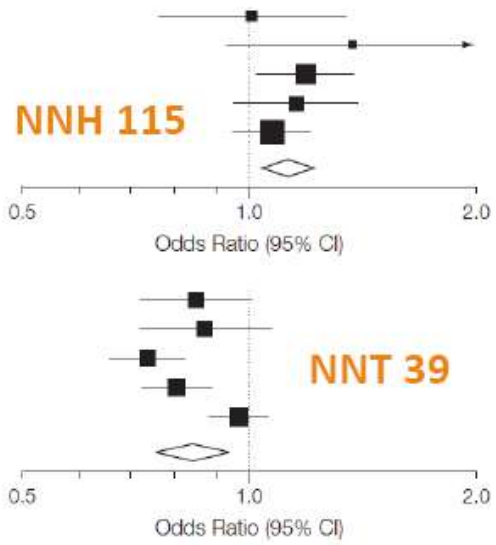
Lancet 2010;375:735

Risque de diabète sous statines– augmentation avec la dose de statines

Doses élevées de statines: **1** nouveau patient avec un diabète pour **3** événements cardiovasculaires évités

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	**1449/16408 (8.8)**	**1300/16344 (8.0)**	**1.12 (1.04-1.22)**
Heterogeneity: $I^2=0\%$; $P=.60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	**3134/16408 (19.1)**	**3550/16344 (21.7)**	**0.84 (0.75-0.94)**
Heterogeneity: $I^2=74\%$; $P=.004$			



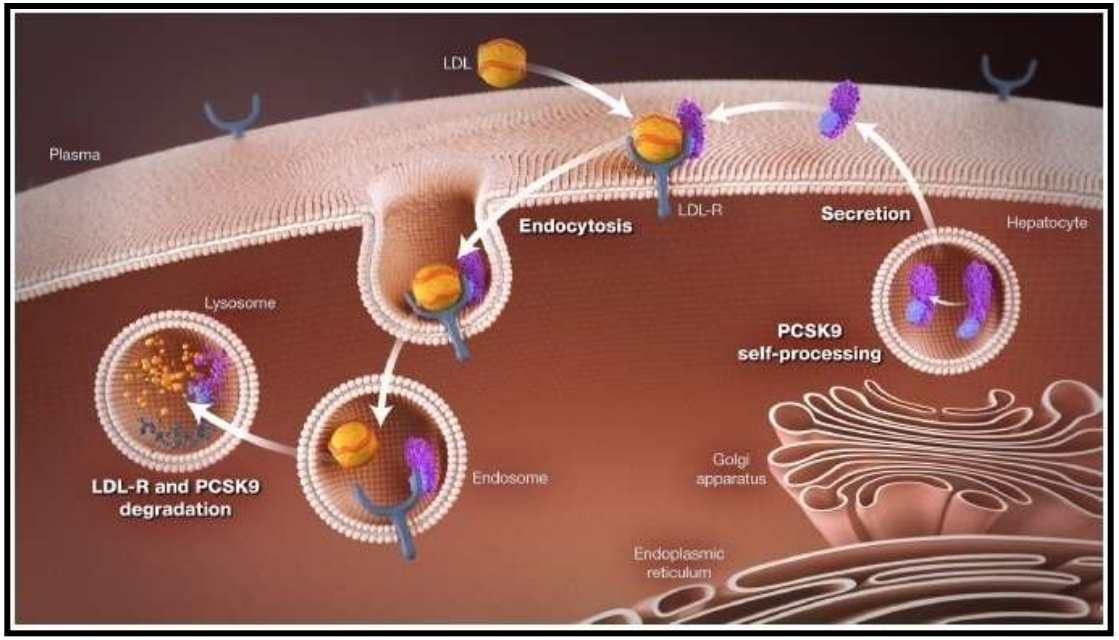
Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

JAMA 2011;305:2556

PCSK9 ???

Contexte - PCSK9

- Nouveau régulateur hépatique du LDL-R
- Diminue le LDL-R, induit une augmentation du LDL-c
- Une fonction PCSK9 abaissée entraine une diminution du LDL-c
- Nouvelle cible pour le traitement de l'hypercholestérolémie ?



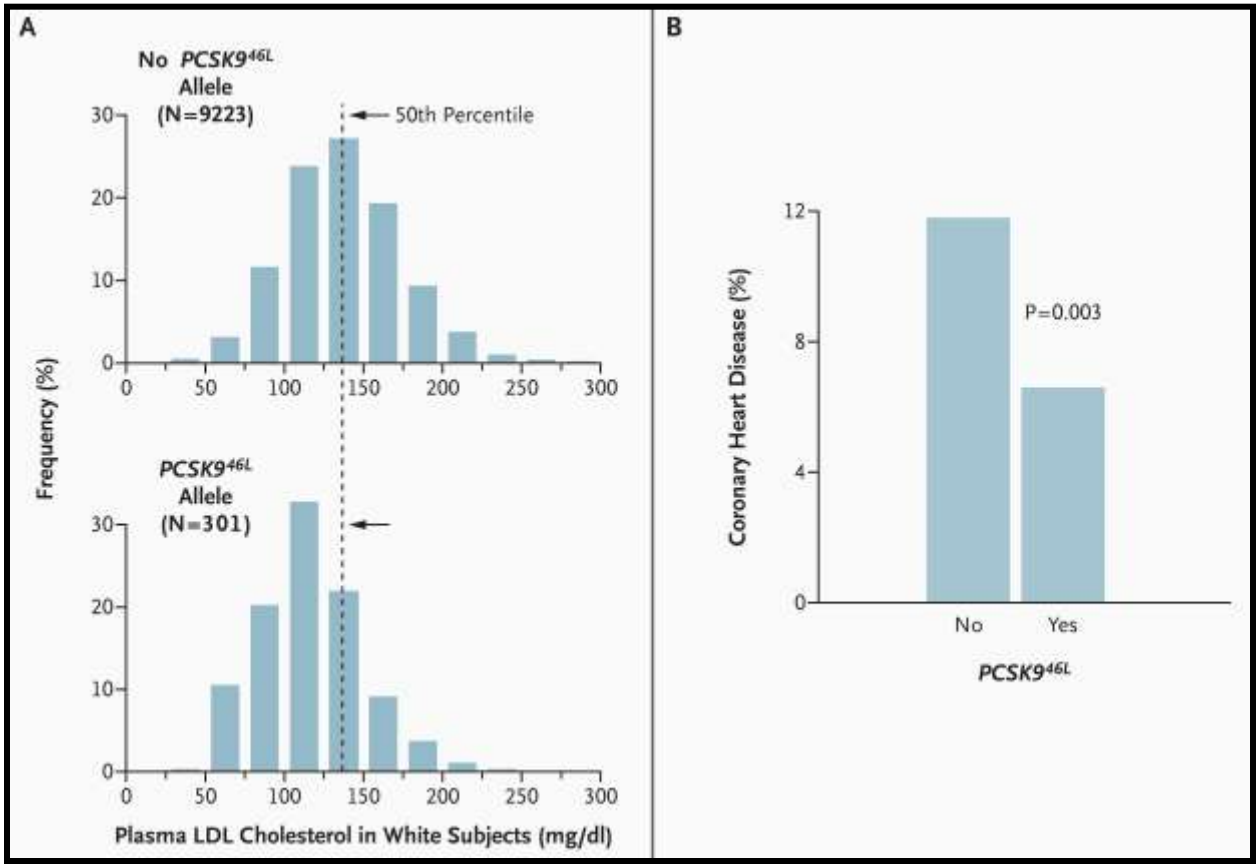
PCSK9 ???

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

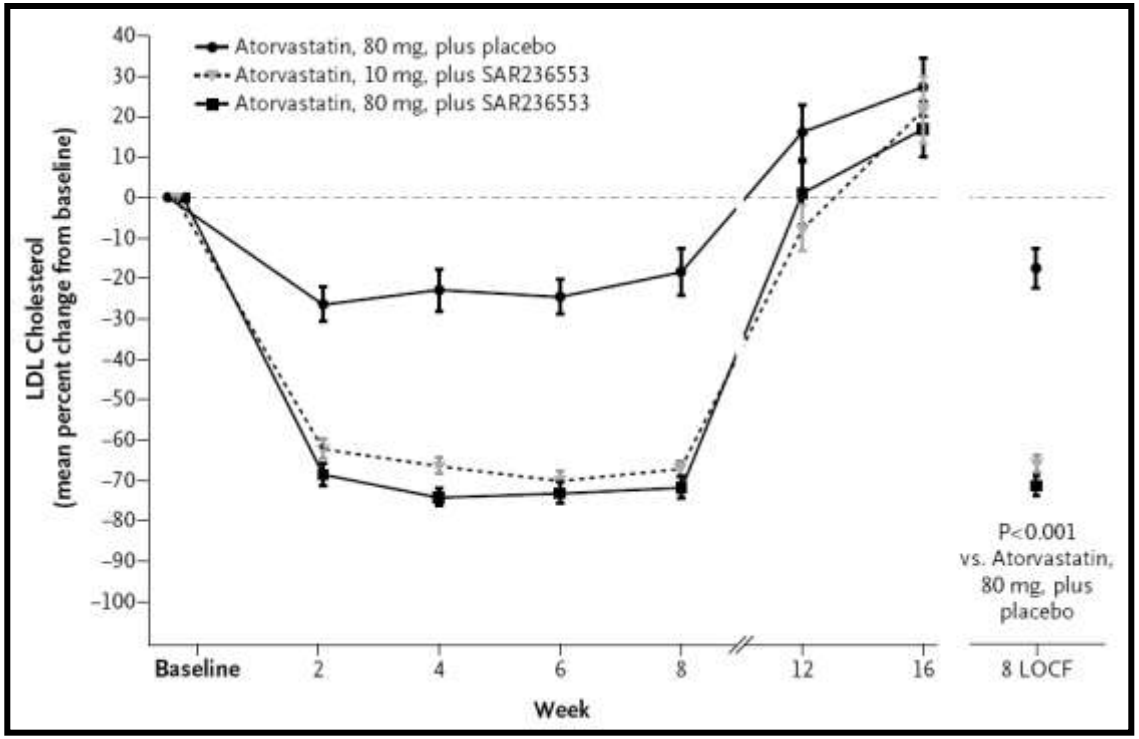
NEJM 2006;354:1264



Anticorps anti-PCSK9 et LDL-c

ORIGINAL ARTICLE

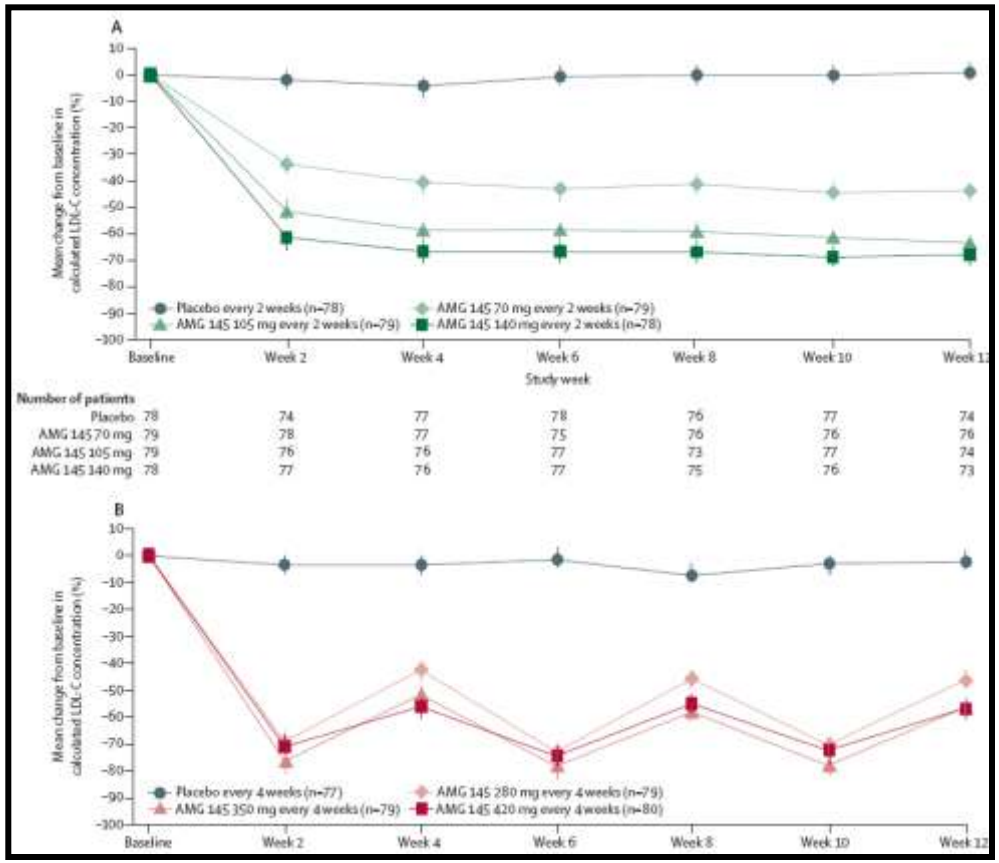
Atorvastatin with or without an Antibody to PCSK9 in Primary Hypercholesterolemia



New Engl J Med November15, 2012;367:1891

Anticorps anti-PCSK9 et LDL-c

Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study



Lancet November6, 2012

Anticorps anti-PCSK9 et LDL-c

Into the future: diversifying lipid management

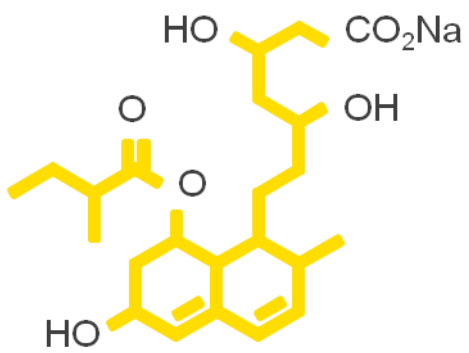
Lancet November 6, 2012

LIPIDS

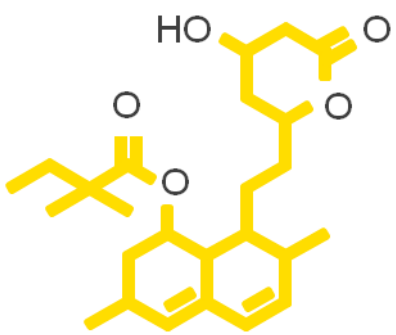
Antibodies against PCSK9—a new era of therapy

Nature Review Cardiology November 20, 2012

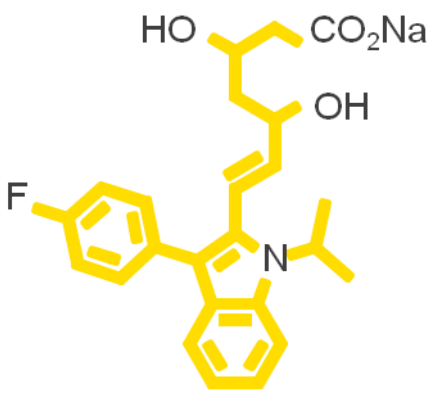
Statines - Nouveautés



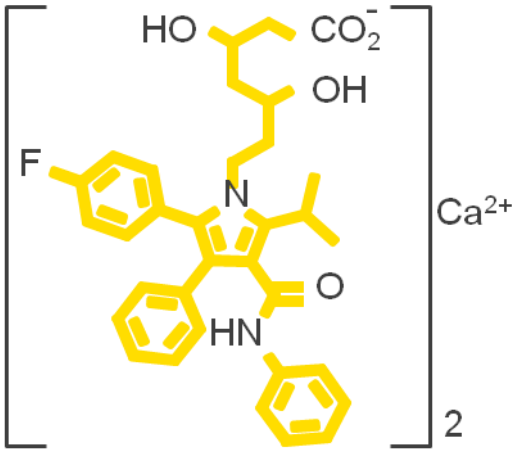
Pravastatin



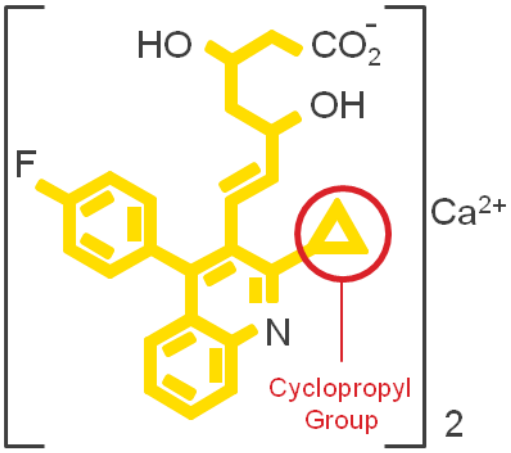
Simvastatin



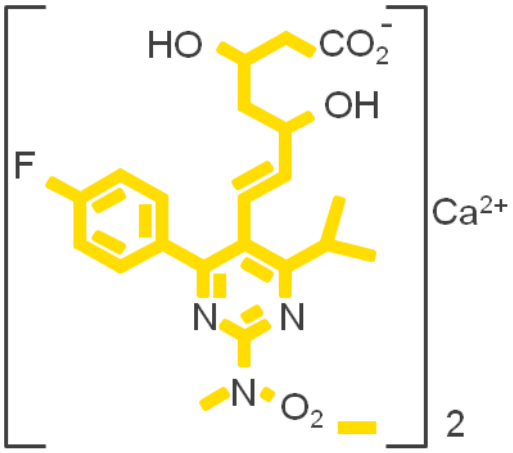
Fluvastatin



Atorvastatin



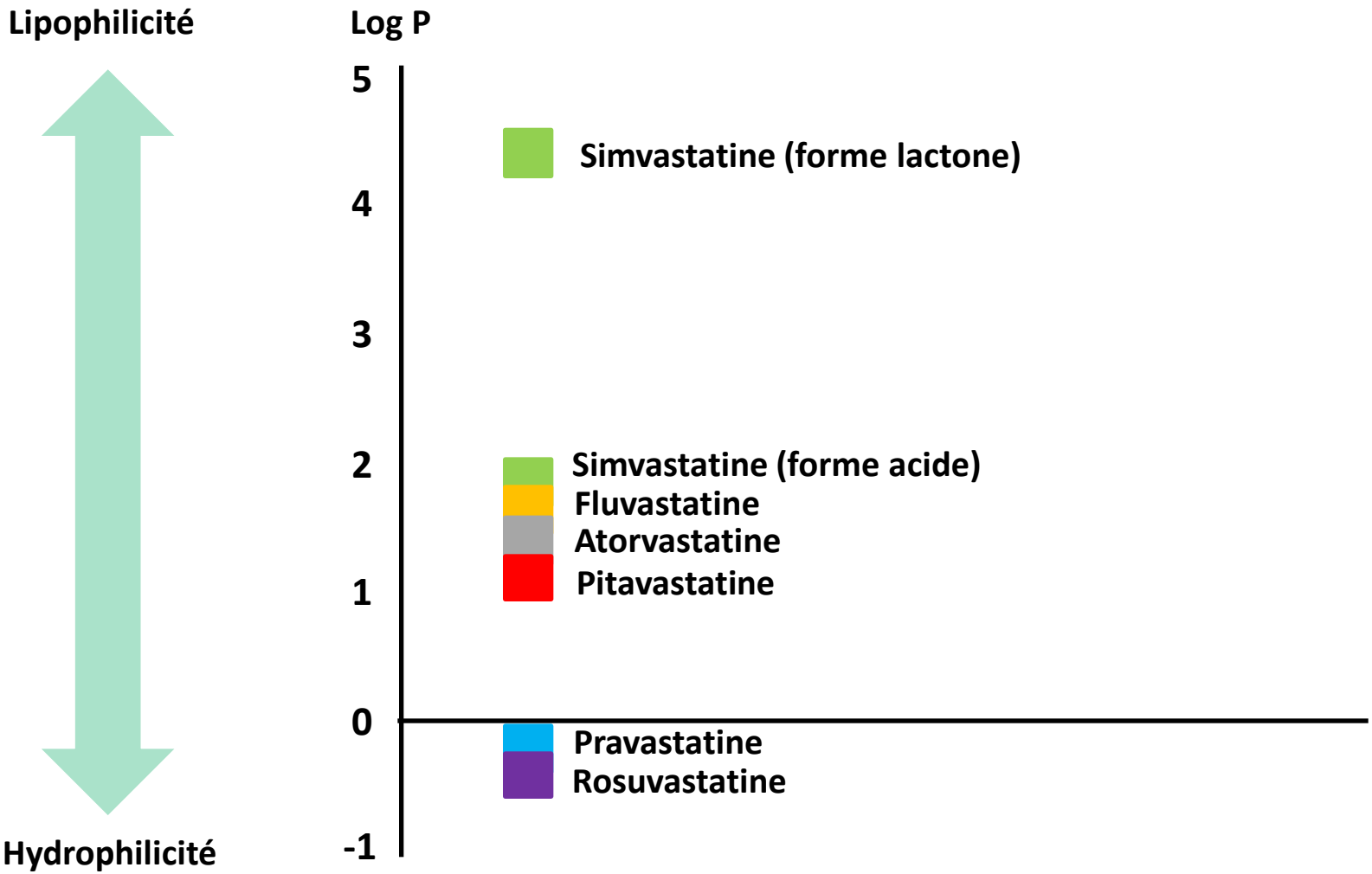
Pitavastatin



Rosuvastatin

Adapté de Kawai et al. Drug Design, Development and Therapy 2011;5:283–297: Place of pitavastatin in the statin armamentarium: promising evidence for a role in diabetes mellitus

Statines - Nouveautés



Déjà **5.6 MILLION** patients-années

Mis sur le marché

JAPON
2003

ETATS-UNIS
2010

EUROPE
2011

77 Etudes cliniques

- **44** en Europe et **33** au Japon
- **>7200** Patients traités avec LIVAZO (1,2,4mg) dans des études cliniques

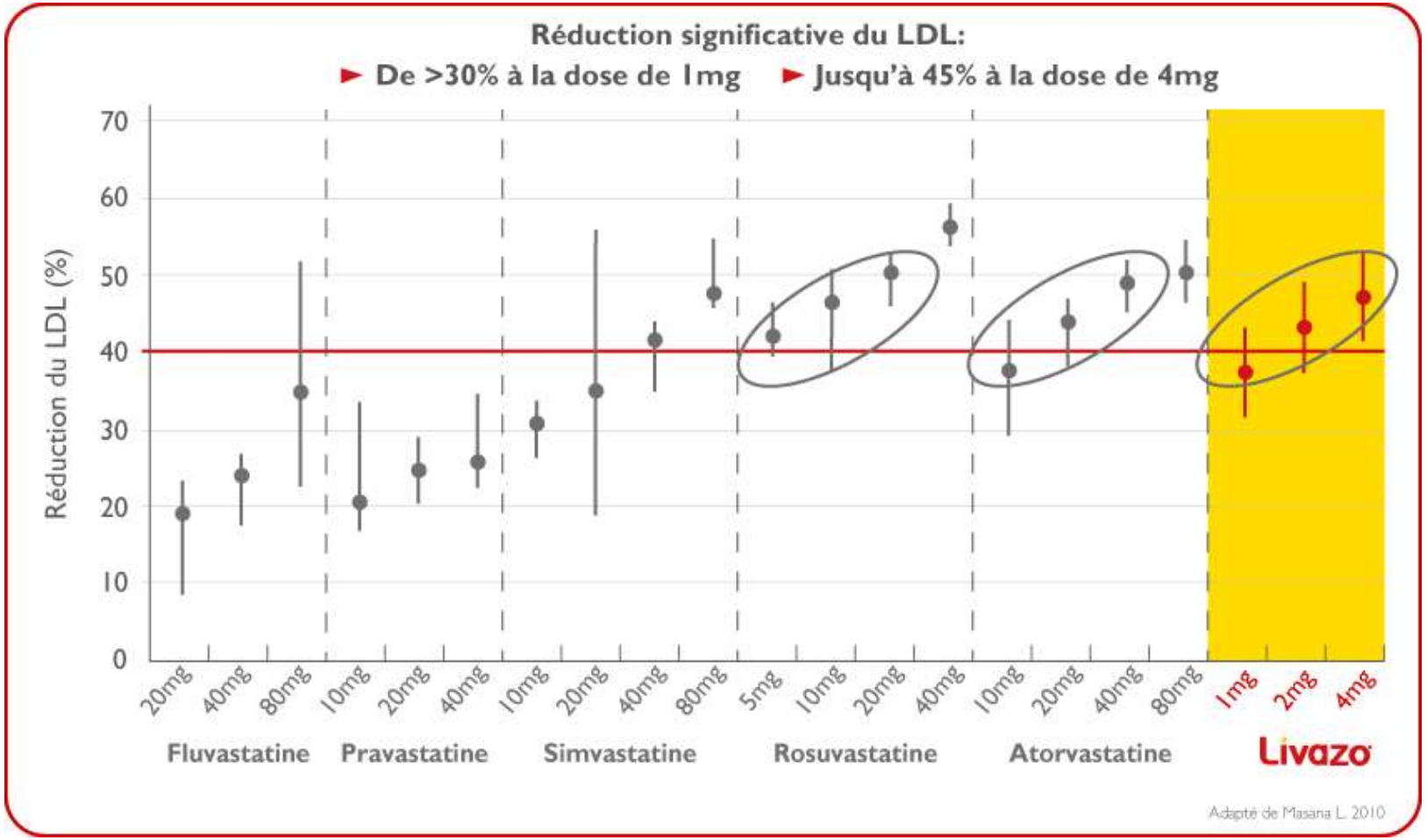
Livazo
pitavastatin

Statines - Nouveautés

	Atorva	Fluva	Pitava	Prava	Rosuva	Simva
Fraction absorbée (%)	30	98	75	34	50	60-80
Tmax (h)	2-3	4	1.2	0.9-1.6	3	1.3-2.4
Cmax (ng/ml)	27-66	55	18.2	45-55	37	10-34
Biodisponibilité (%)	12	6	51	18	20	5
Effet de la nourriture sur la biodisponibilité (%)	↓13	0	0	↓30	↑20	0
Lipophilicité	Oui	Oui	Oui	Non	Non	Oui
Substrat de transporteur	Oui	Oui	Oui	Oui	Oui	Oui
Liée aux protéines (%)	>98	>99	>99	43-55	88	94-98
Extraction hépatique	>70	>68	>70	46-66	63	78-87
Métabolites	Active	Inactif	Inactif	Inactif	Actif (mineur)	Actif
Clearance (ml/min)	291.6	4433	410	945	805	525
Clearance rénale (ml/min)	Non	Non	Non	>400	226	Non
T1/2 (h)	15-30	4.7	13	1.3-2.8	20.8	2-3
Excrétion fécale (%)	70	90	78	71	90	58
Excrétion urinaire (%)	2	6	<4	20	10	13

Statines - Nouveautés

Effet des statines sur le LDL-C

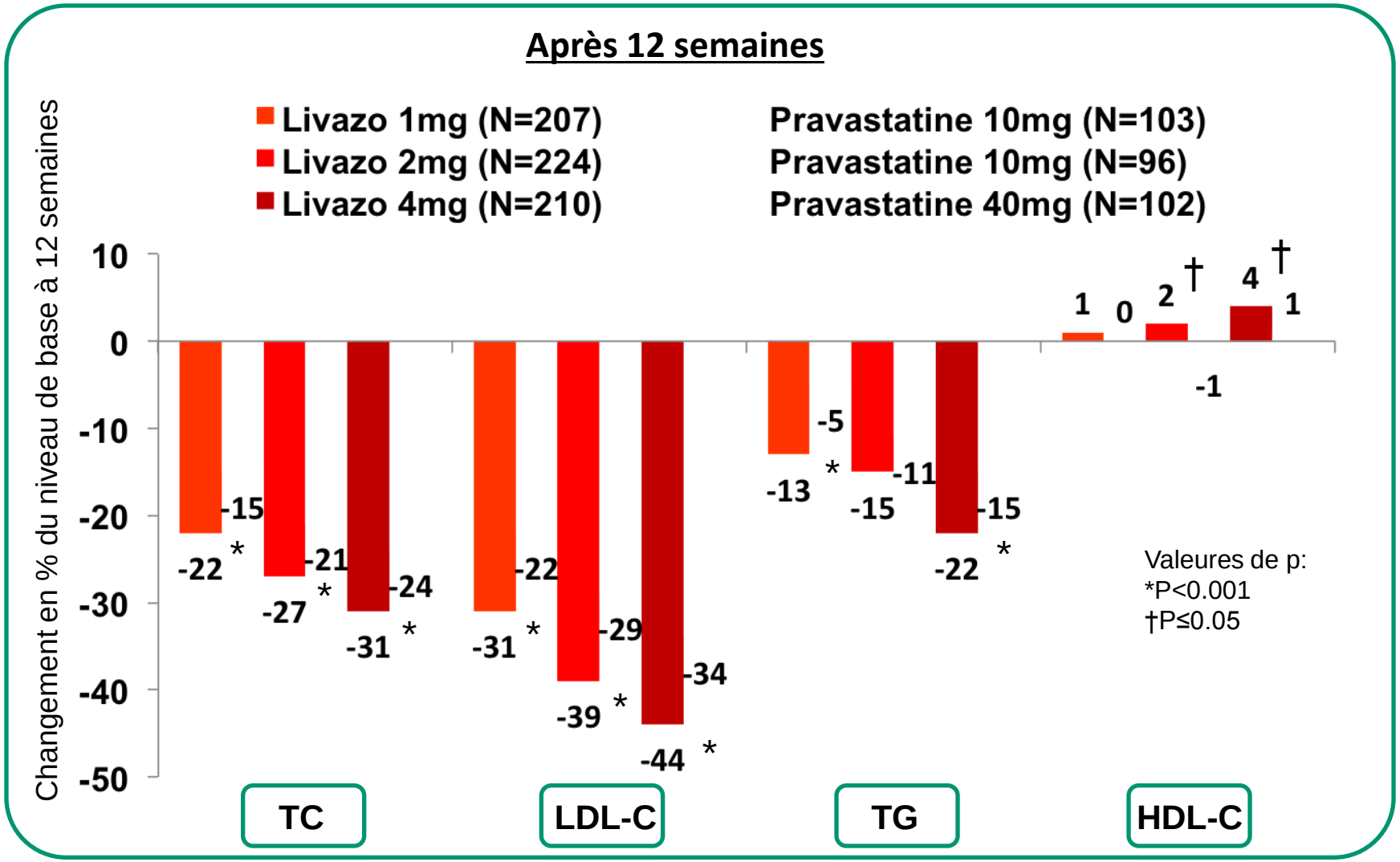


LDL-C: Low Density Lipoprotein Cholesterol

Adapté de Masana L. Atherosclerosis Supplements 2010;11(3):15–22: Pitavastatin – from clinical trials to clinical practice

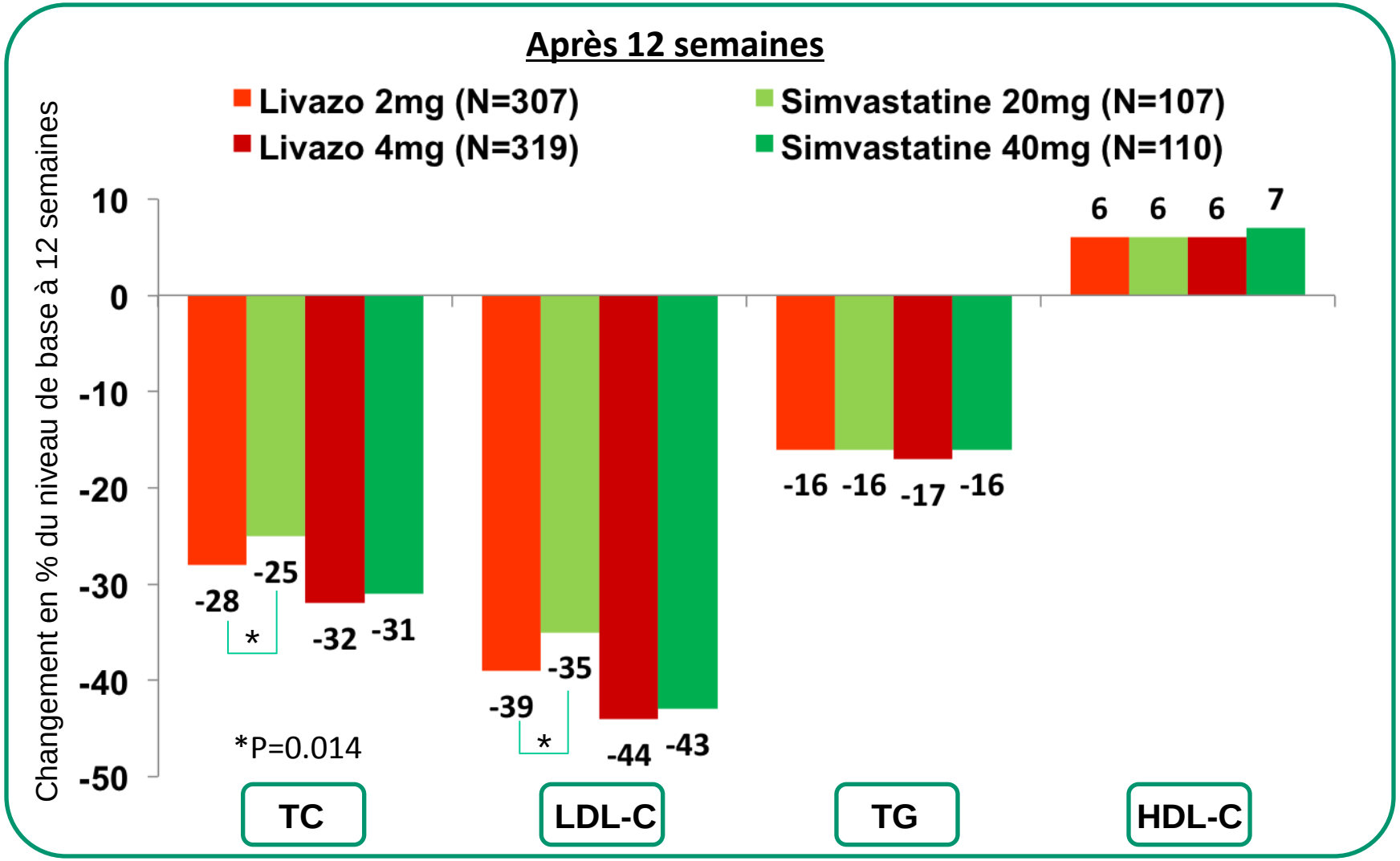
Statines - Nouveautés

Supérieur à la Pravastatine



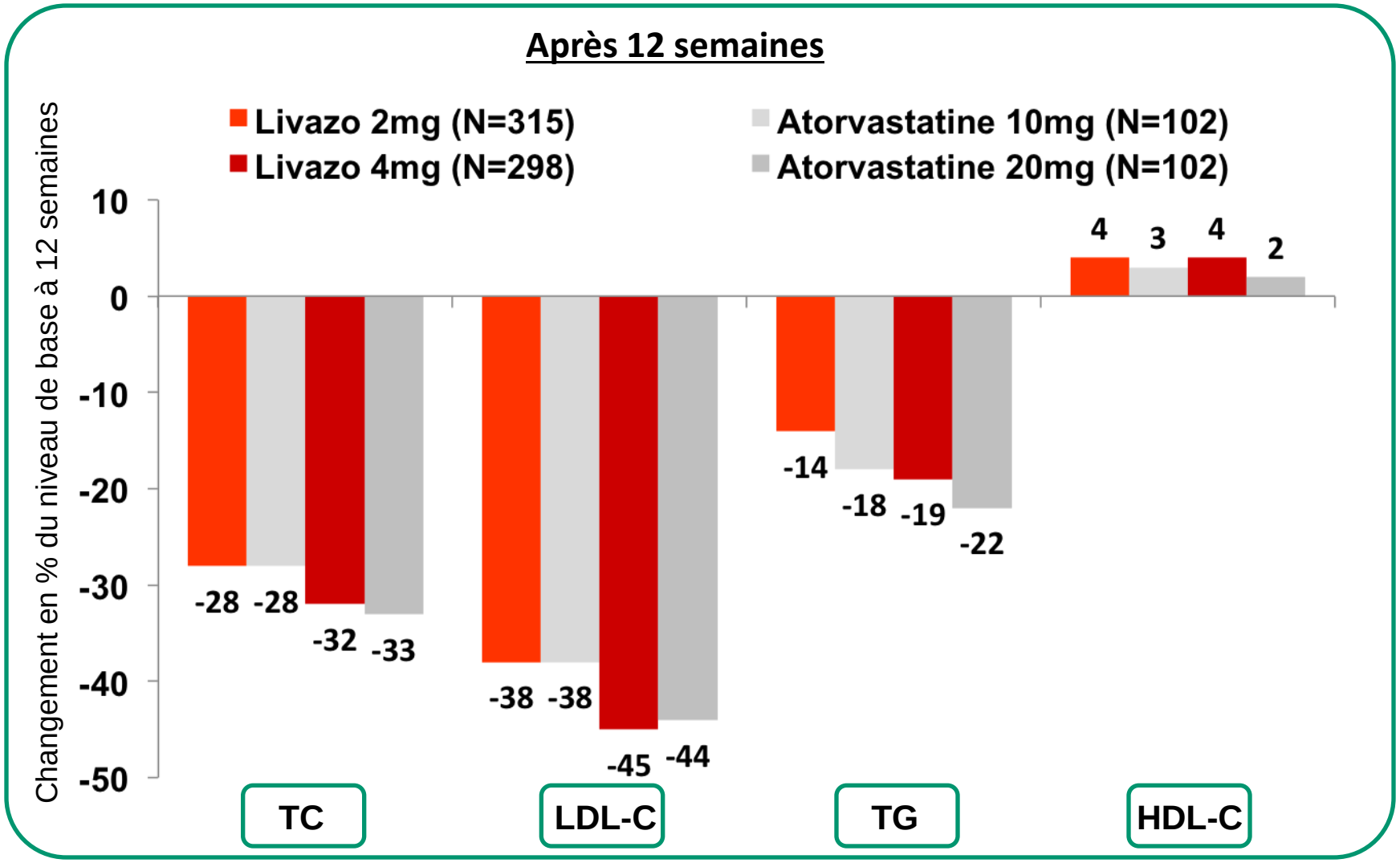
Statines - Nouveautés

Livazo 2mg: supérieur à 20mg Simvastatine



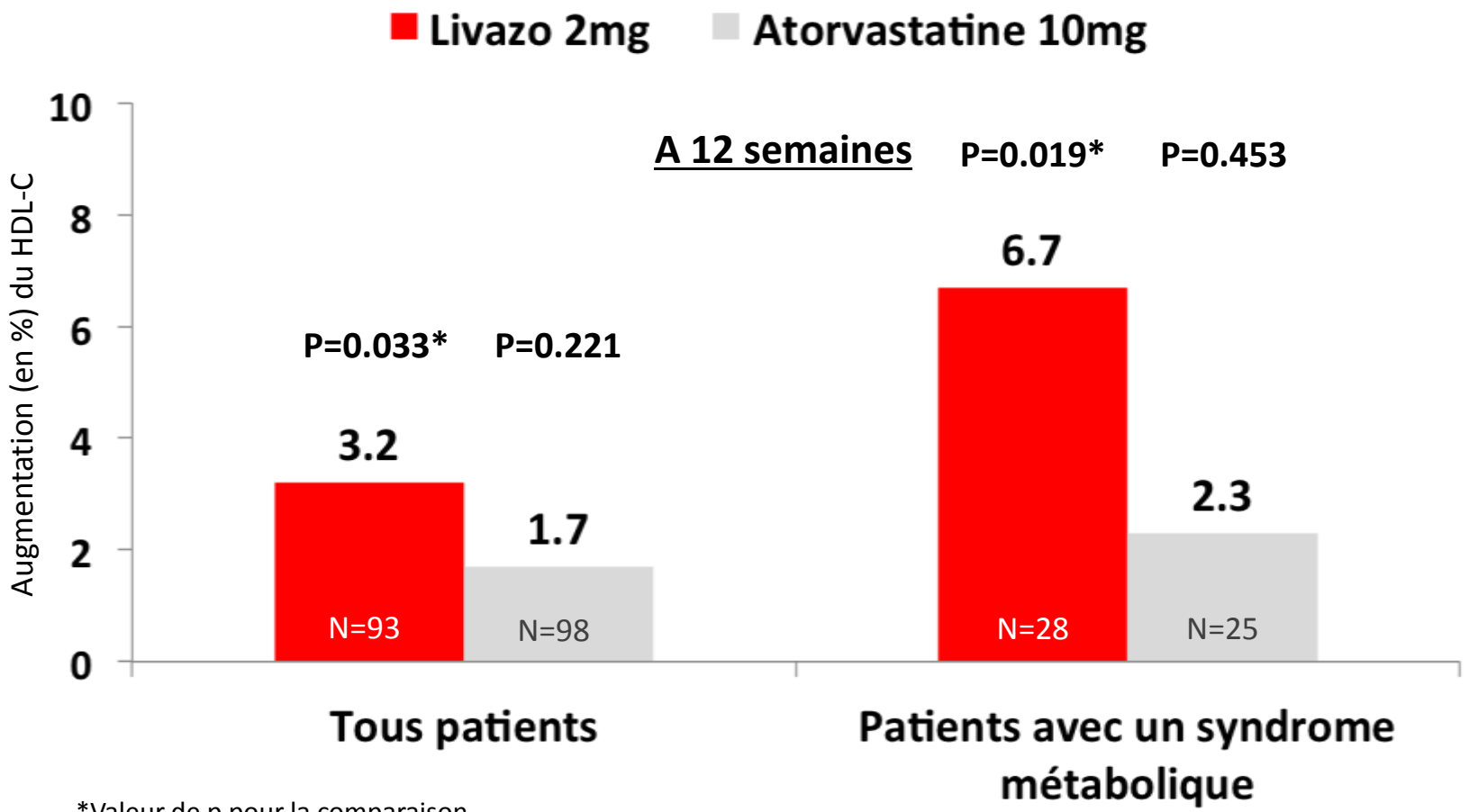
Statines - Nouveautés

Aussi efficace que l'Atorvastatine



Statines - Nouveautés

Etude CHIBA: Effet favorable sur le HDL-C

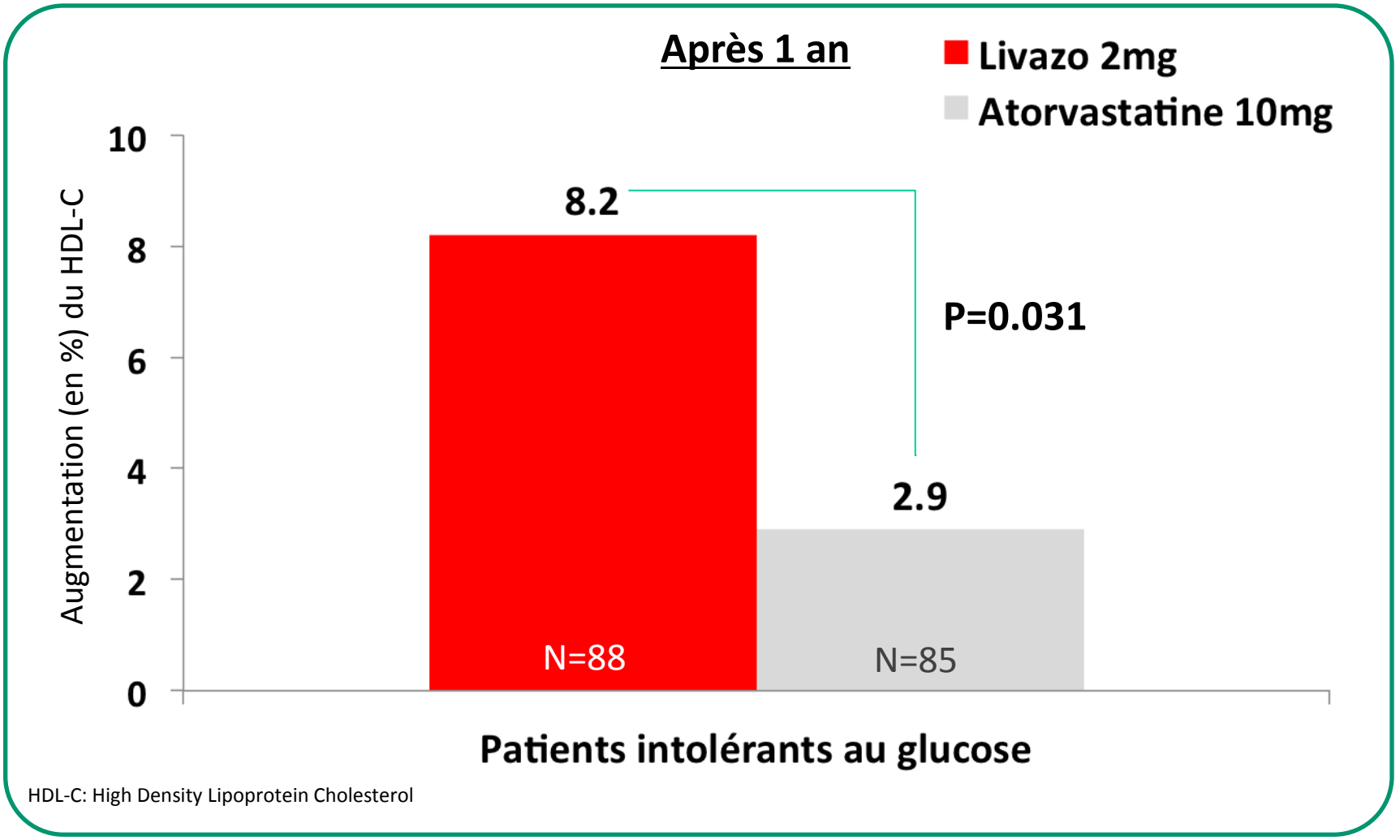


*Valeur de p pour la comparaison 12 semaines vs niveau de base

Atherosclerosis 2008;201:345

Statines - Nouveautés

Etude PIAT: Augmentation du HDL-C chez les patients intolérants au glucose

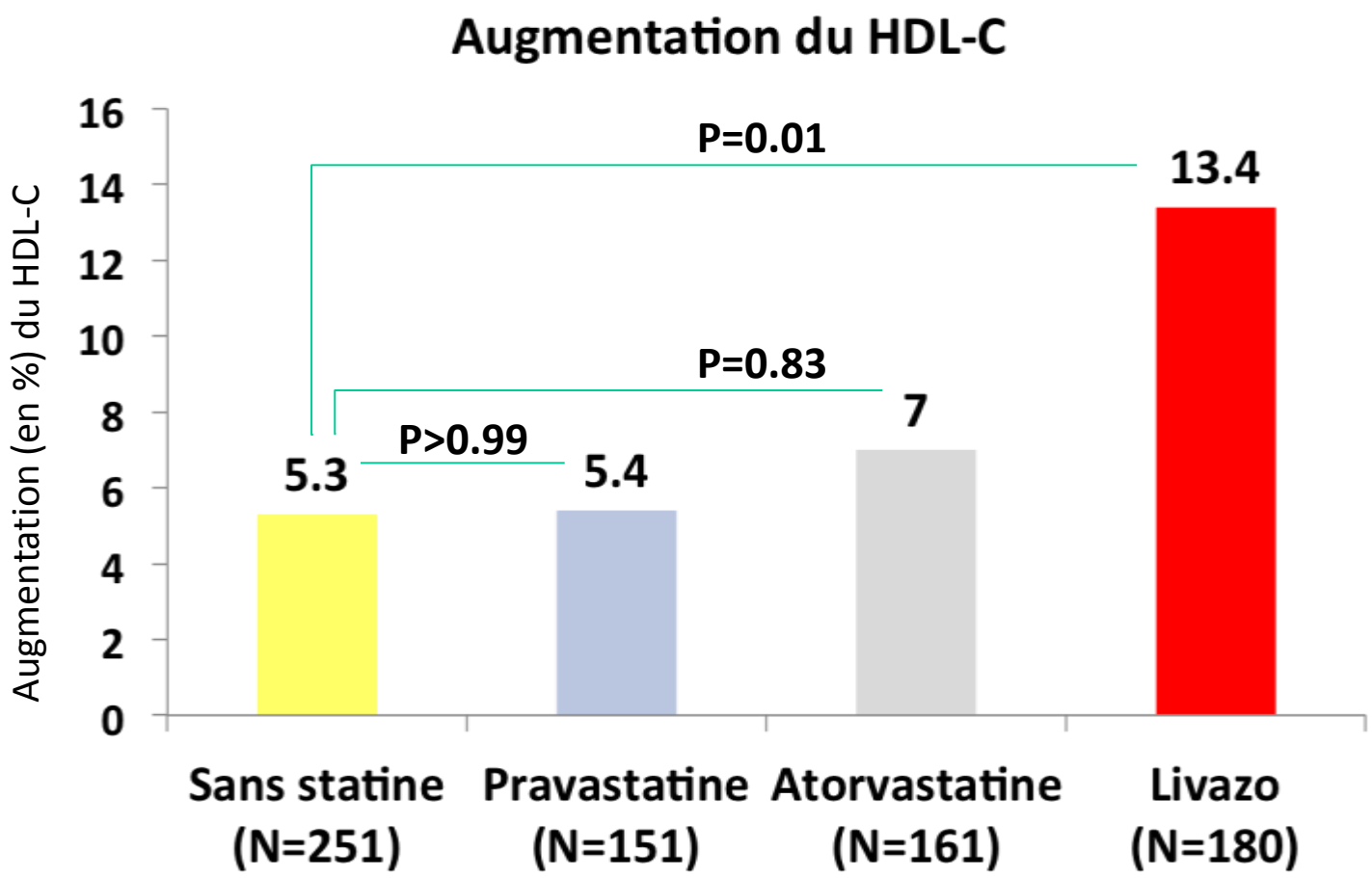


HDL-C: High Density Lipoprotein Cholesterol

Clinical Therapeutics 2008;30:1089

Statines - Nouveautés

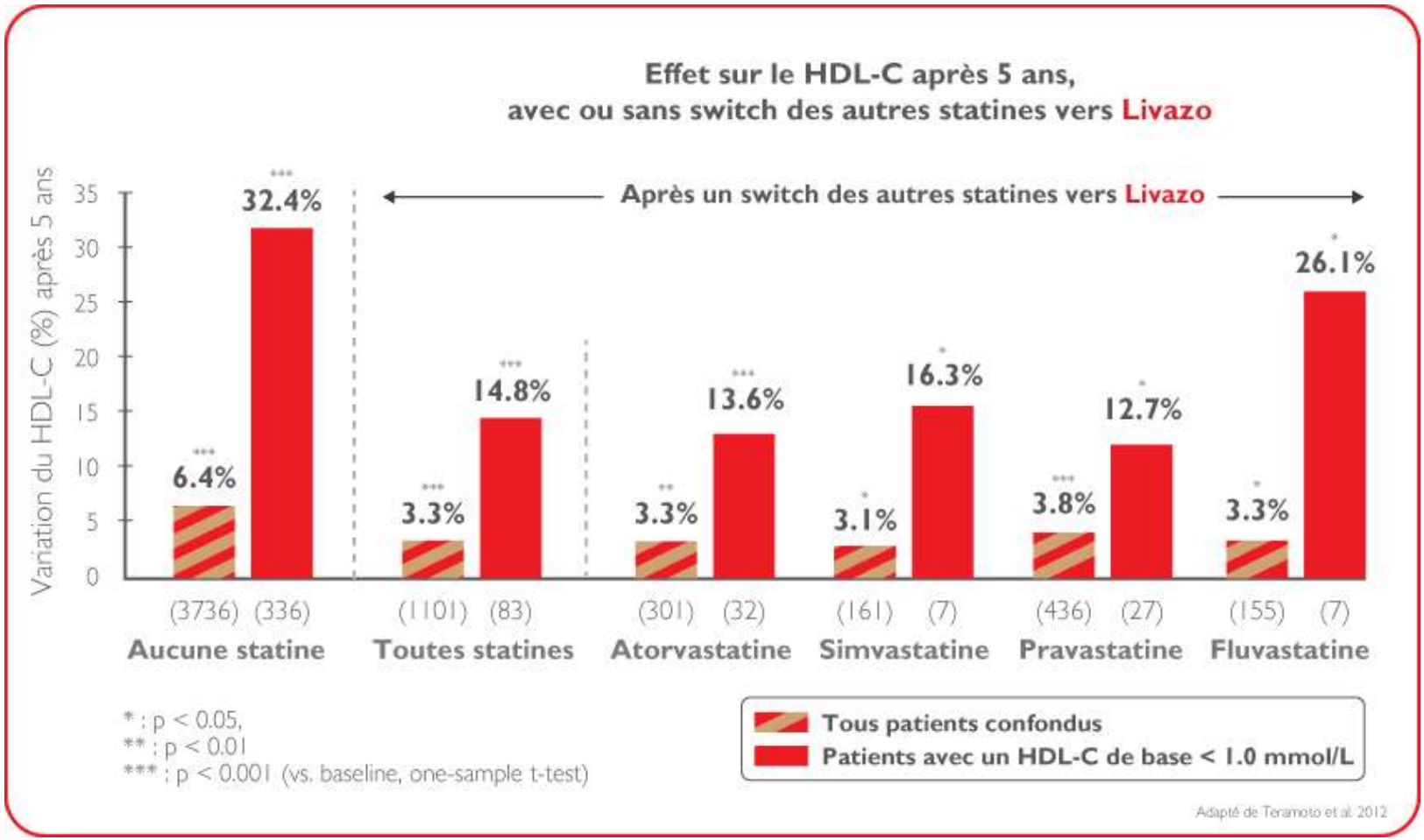
Etude CIRCLE : Augmentation du HDL-C chez les patients après PCI



Circ J 2011;75:1951

Statines - Nouveautés

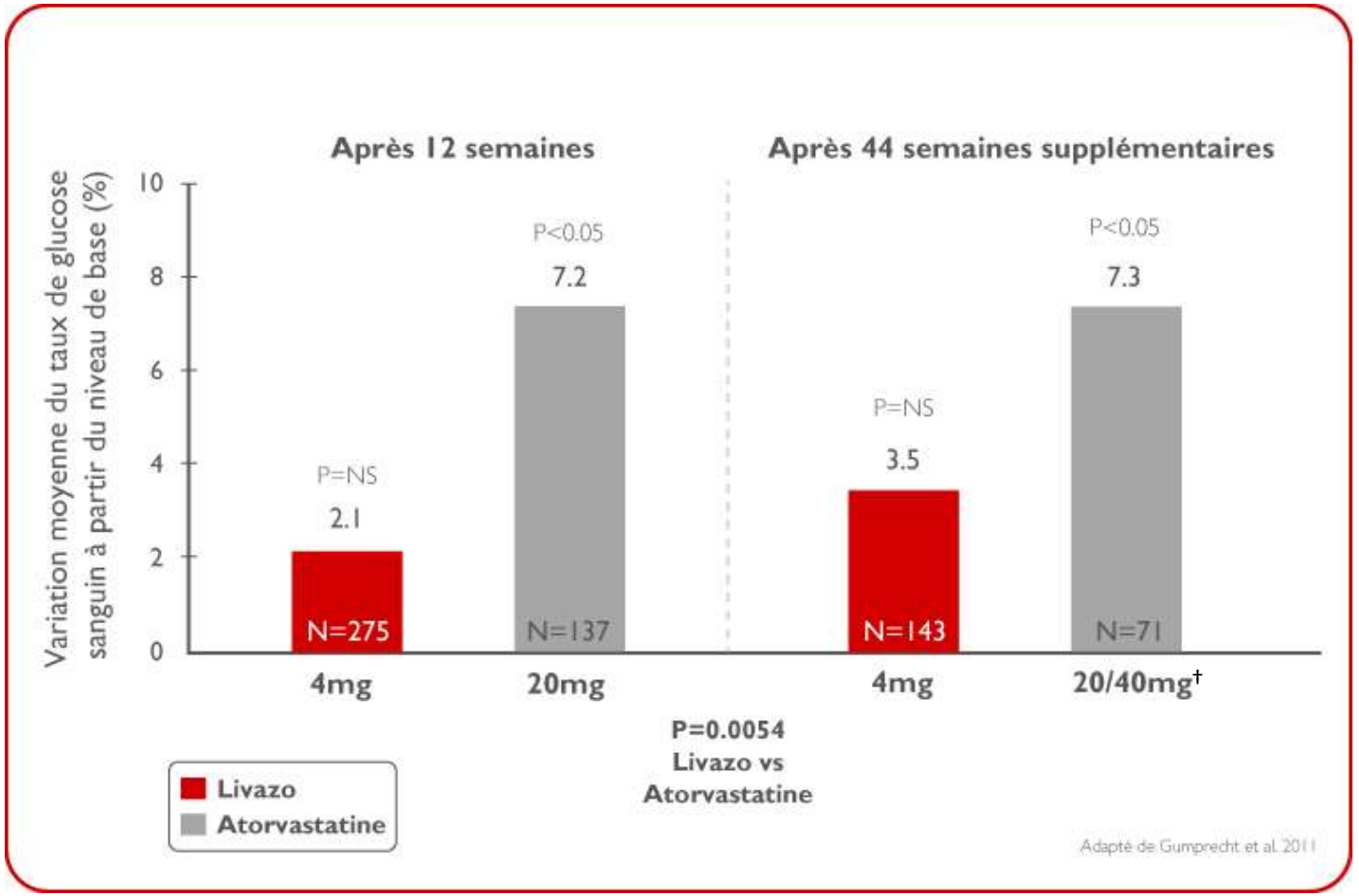
Etude LIVES: Augmentation du HDL-C à 5 ans même après traitement par d'autres statines



Expert Opin Pharmacother. 2012;13:859

Statines - Nouveautés

Diabétiques: Pas d'impact significatif sur le glucose sanguin vs Atorvastatine



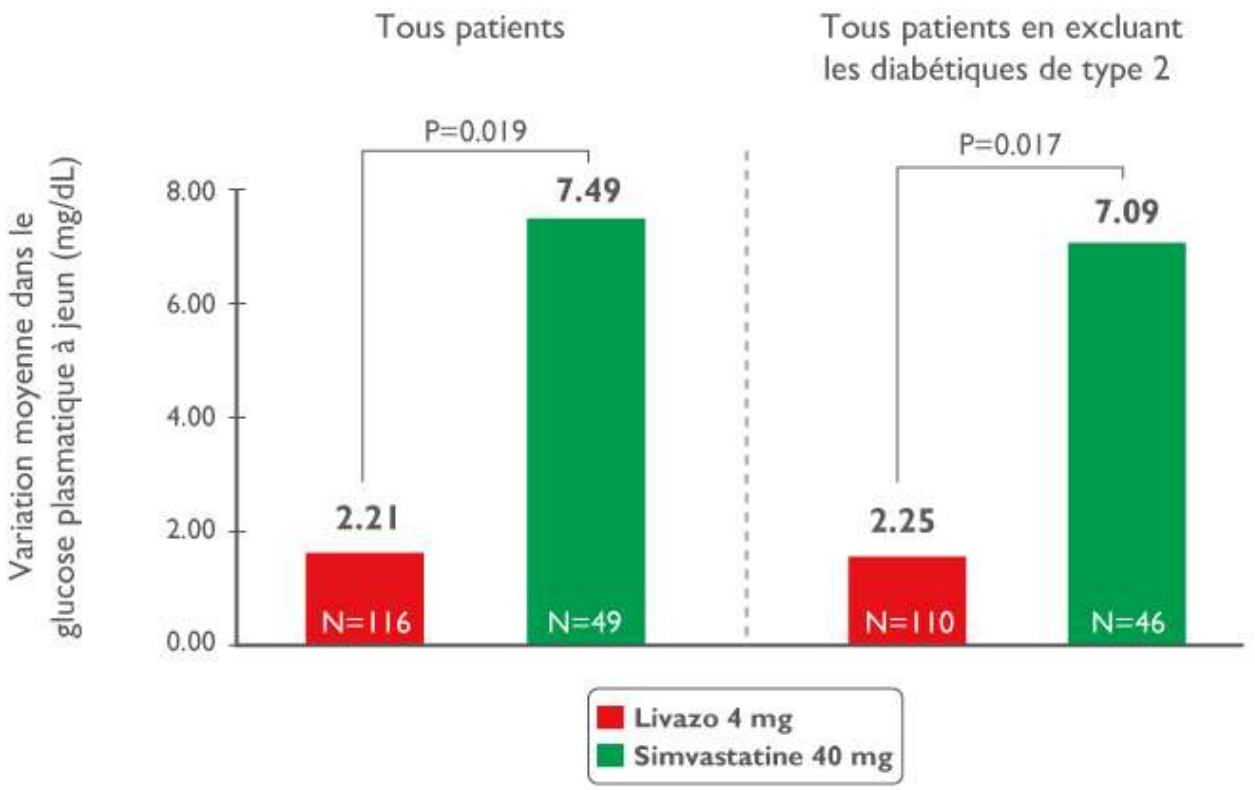
†Sept patients ont augmenté leur dose of atorvastatine de 20 à 40 mg/jour au début de l'étude d'extension.

Diabetes, Obesity and Metabolism 2011;13:1047

Statines - Nouveautés

Pas d'impact sur le glucose plasmatique à jeun vs Simvastatin

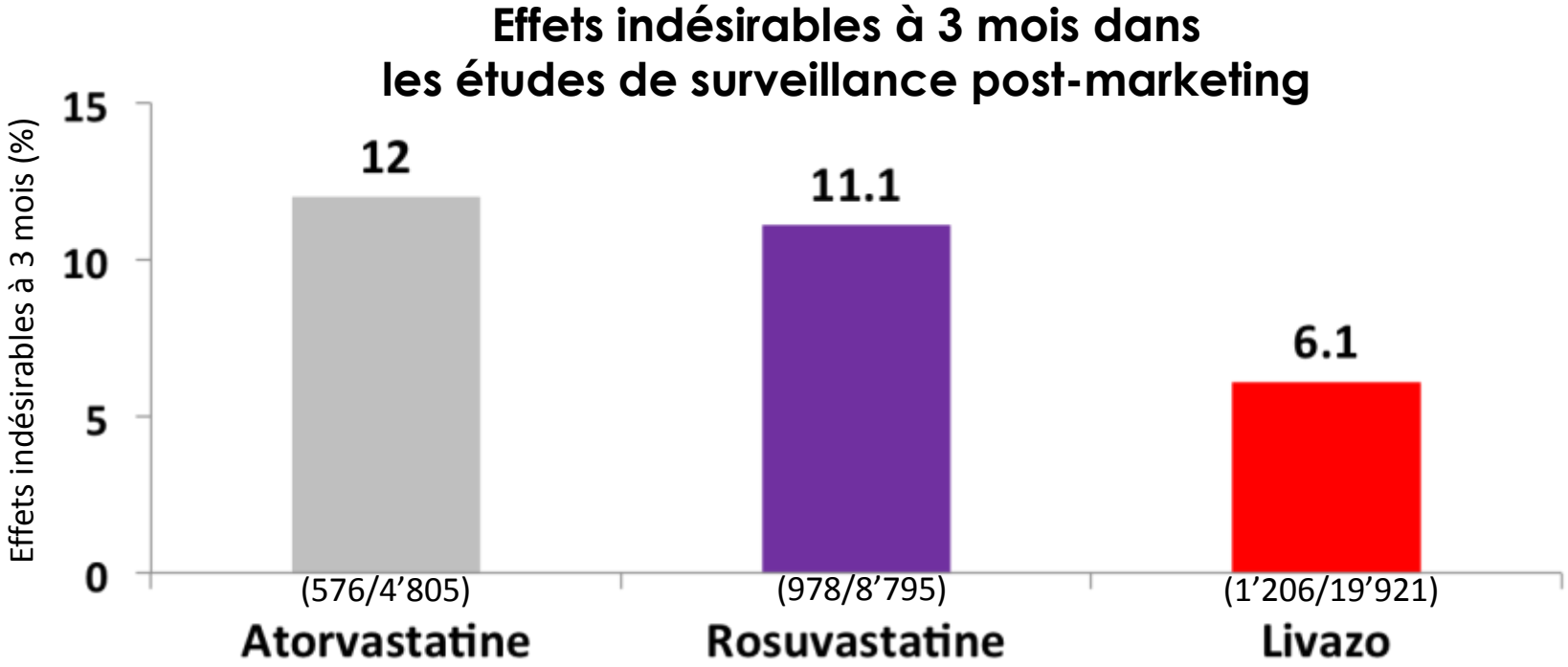
Variation moyenne dans le glucose plasmatique à jeûn après 56 semaines



JACC 2012:59;Suppl 27

Statines - Nouveautés

Livazo: Un traitement bien toléré en pratique clinique



Elévation de CPK		2.19%	2.29%
AST		1.14%	0.53%
ALT		1.83%	0.69%
Myalgie	0.5%		1.43%

Drug Design, Development and Therapy 2011:5;283

Statines - Nouveautés

Livazo: Un traitement bien toléré chez les patients ≥ 65 ans

A 12 semaines	Livazo			Pravastatine		
Effets indésirables	1mg (N=207)	2mg (N=224)	4mg (N=210)	10mg (N=103)	20mg (N=96)	40mg (N=102)
Sévères	1 (0.5%)	2 (0.9%)	3 (1.4%)	0 (0.0%)	1 (1.0%)	3 (2.9%)
Discontinuation	9 (4.3%)	11 (4.9%)	8 (3.8%)	8 (7.8%)	2 (2.1%)	4 (3.9%)
Effets indésirables les plus fréquents						
Nasopharyngite	15 (7.2%)	16 (7.1%)	19 (9.0%)	6 (5.8%)	5 (5.2%)	7 (6.9%)
Constipation	10 (4.8%)	6 (2.7%)	9 (4.3%)	5 (4.9%)	4 (4.2%)	3 (2.9%)
Maux de tête	8 (3.9%)	9 (4.0%)	4 (1.9%)	3 (2.9%)	4 (4.2%)	2 (2.0%)
Myalgie	3 (1.4%)	11 (4.9%)	4 (1.9%)	3 (2.9%)	2 (2.1%)	3 (2.9%)

Eur J Prev Cardiol 2012

Pitavastatin ongoing clinical trials JAPAN

Trial	Title	Indication	Population
PEARL	Pitava vs statin free in 500 patients	HC and heart failure	Japanese
DIALYSIS	Differential Intervention triAL bY Standard therapy versus pItavastatin in Subjects with chronic hemodialysis, 2-4 year follow up of 1550 patients	Renal failure	Japanese
PEACH trial	Coronary artery calcification + dyslipidaemia, 12 month evaluation in 240 patients	CAD	Japanese
J-PREDICT	Japan PREvention Trial of Diabetes by PItavastatin in Patients With Impaired GluCose Tolerance, 3-5 year fu in 1240 patients	IGT	Japanese
EPI-CENTRE	Dyslipidaemia, 6 month evaluation in 40 patients	Dyslipidaemia	Japanese
SAMURAI-Study	CAD + Hypercholesterolaemia 52 week evaluation in 100 patients	CAD	Japanese
STANP-trial	ACS, aortic dissection patients (Stanford Type B), 12 month evaluation in 100 patients	ACS	Japanese
TOHO-LIP	Hypercholesterolaemia, 5 year endpoint study in 600 patients	Primary hypercholesterolaemia	Japanese
HARMONY	Hypercholesterolaemia, 2 year C-IMT follow up on 300 patients		Japanese
CRYSTAL	PCI patients, coronary plaque volume change. 45 month follow up of 300 patients		Japanese
HIJ-PROPER	Outcomes study in ACS, 3-5 year follow up of 3000 patients	ACS	Japanese
REAL-CAD	Outcomes study in stable CAD, 3-5 year evaluation of 12,600 patients	CAD	Japanese

Pitavastatin clinical trials US and Korea

Trial	Title	Indication	Population
US 4.01	Renal Impairment Trial (PK)		US renal impaired and healthy
US 4.02	Lopinavir/Ritonavir DDI Trial		US healthy
US 4.03	Pitavastatin vs. Rosuvastatin effect on Warfarin-induced Anticoagulation		US healthy
PREVAIL	Pitavastatin 4 mg vs. pravastatin 40 mg	Primary hypercholesterolemia	US
INTREPID	Pitavastatin 4 mg vs. pravastatin 40 mg	HIV and dyslipidemia	US
LAMIS	prospective clinical observation study in patients with AMI	Hypercholesterolemia+AMI	Korean
LAMIS 2	Pitavastatin 2 mg vs. Pitavastatin 4 mg incidence of major cardiovascular events	Hypercholesterolemia+AMI	Korean
SAPHIRE	Pitavastatin vs Pravastatin Rate and number of hospitalization for cardiovascular cause; Lipid profile	Chronic Heart Failure	Korean

Livazo (pitavastatin) tablets

Clinical trials in EU and MENA

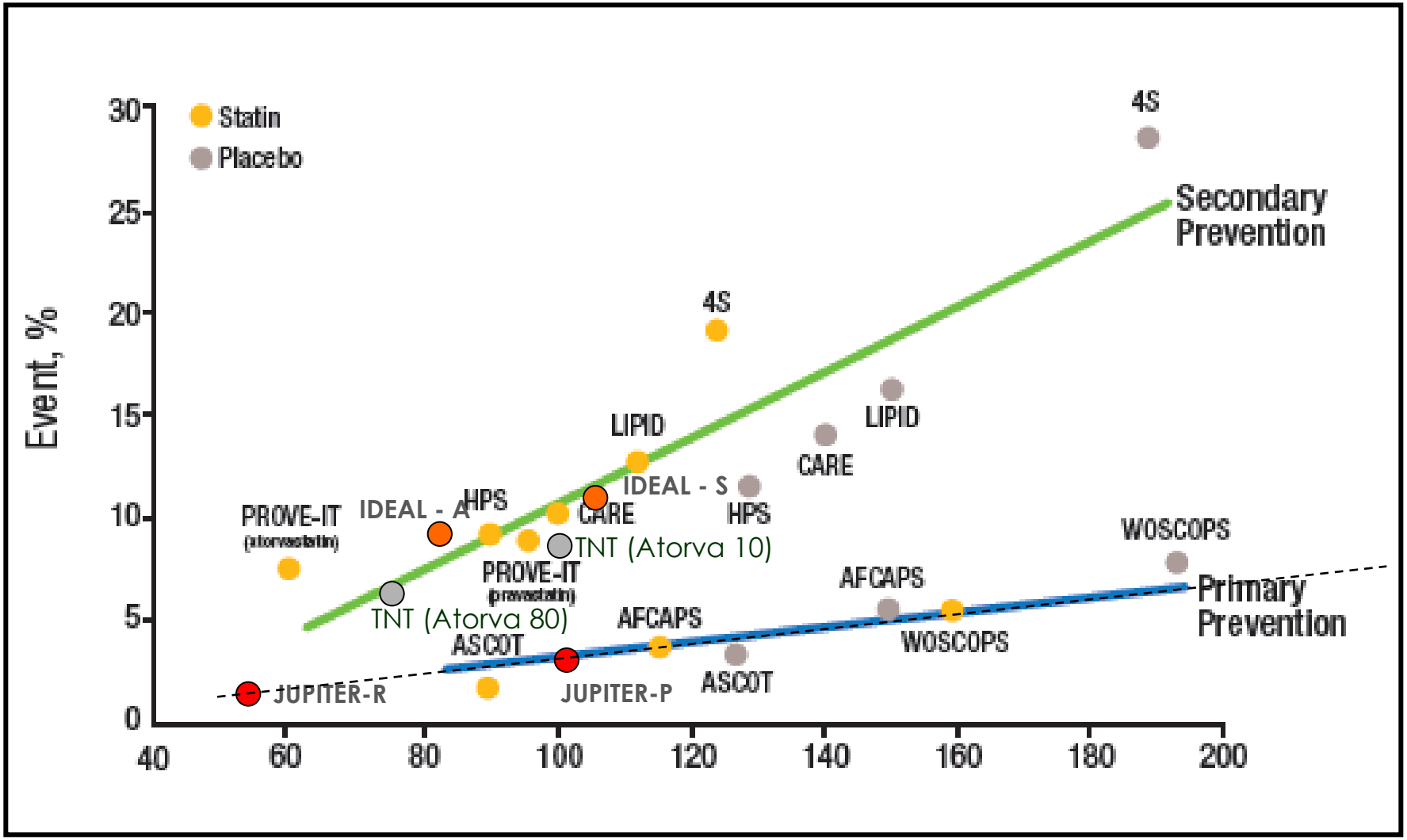
Country	Company	Title	Population	No. of patients	Duration	Start	Endpoints	Status
France	KRE	CAPITAIN NK-104-4.03 EU	Metabolic Syndrome	20	6 month	Sep.2009	Monocytes HDL-C fractions Biomarkers Lipidomics	ongoing
EU	Recordati	Pepita	Primary HL	1000	12 month	2012	lipids and safety	preparing
Lebanon	Algorithm		Primary HL	200	3 month	Apr.2011	lipids and safety	completed
Lebanon	Algorithm		Primary HL	1000		Nov.2011	lipids and safety	preparing
EU	KRE	Pediatric	age 6-17 FH, mixed dislipideamia , Diabetes	96	12+ 52week	Dec.2011	lipids and safety and tolerability	preparing
EU	KRE	DUS	Prescription Database	2000	Retro-spective	2012/13?	Demo-graphics	Protocol
EU	KRE	PASS	Medical Database	15000	Retro-spective	2014/15?	Hepatic, Rhabdo-myolysis, renal, interstitial pneumonia	Protocol

Livazo (pitavastatin) tablets

Conclusions/Messages

Les statines diminuent les événements CV lorsque le traitement est bien indiqué, et que l'observance thérapeutique est optimale.

Statins reduce CV events in primary and secondary prevention

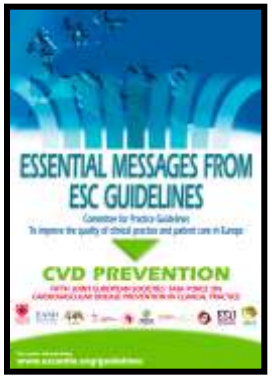


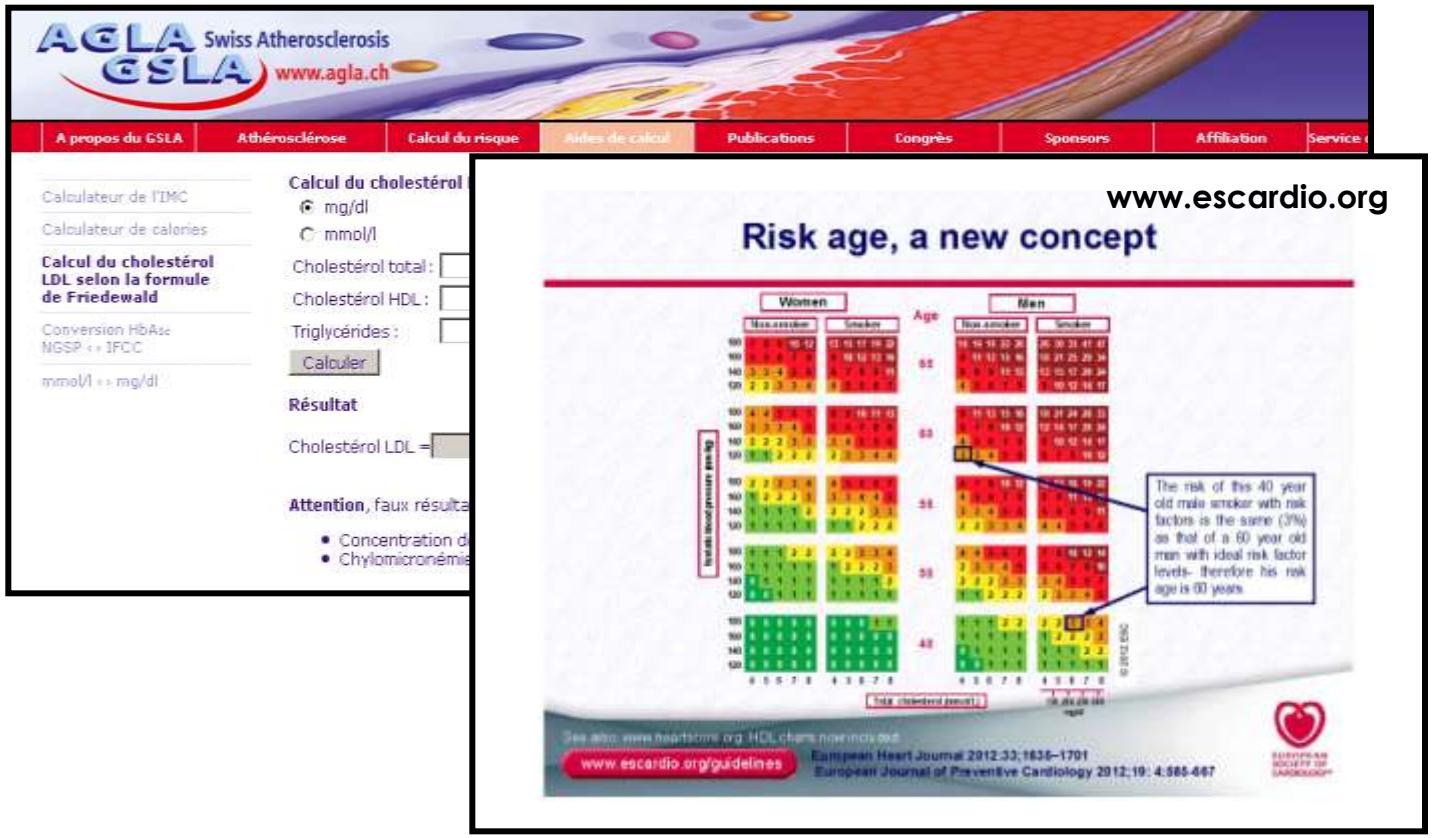
Conclusions/Messages

Prévention secondaire = Statine avec valeurs cibles de LDL-c

+ Eventuellement Ezetrol

Prévention primaire = Evaluation du risque CV (statine si nécessaire)





A practical approach to reach LDL-C goal

ESC pocket guidelines 2011:

Attainable avec
statine + ezetimibe

Attainable avec
statine monotherapie

Table Percentage reduction of LDL-C requested to achieve goals as a function of the starting value

STARTING LDL-C		% REDUCTION TO REACH LDL-C		
mmol/L	~mg/dL	<1.8 mmol/L (~70 mg/dL)	<2.5 mmol/ (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–

Education thérapeutique


ESC congress news

SUNDAY 26 AUGUST

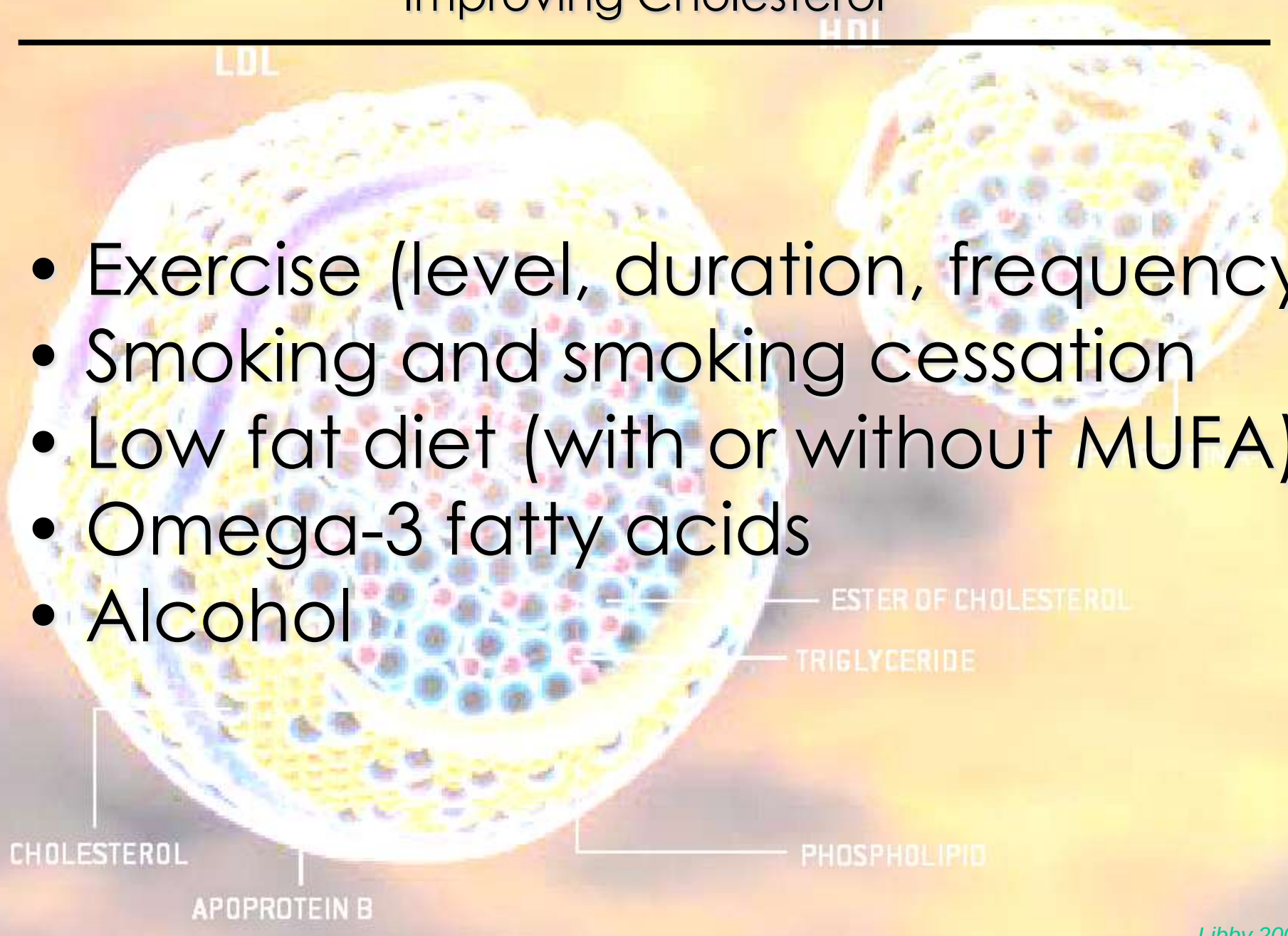
Medical education remains ESC's 'top priority', as new programme is announced

www.elips.hug-ge.ch

www.elips-e-learning.org

Improving Cholesterol

- Exercise (level, duration, frequency)
- Smoking and smoking cessation
- Low fat diet (with or without MUFA)
- Omega-3 fatty acids
- Alcohol



Libby 2002

REseau de MEDecins - réunion scientifique
Genève, le 6 juin 2013

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