Les statines en prévention primaire

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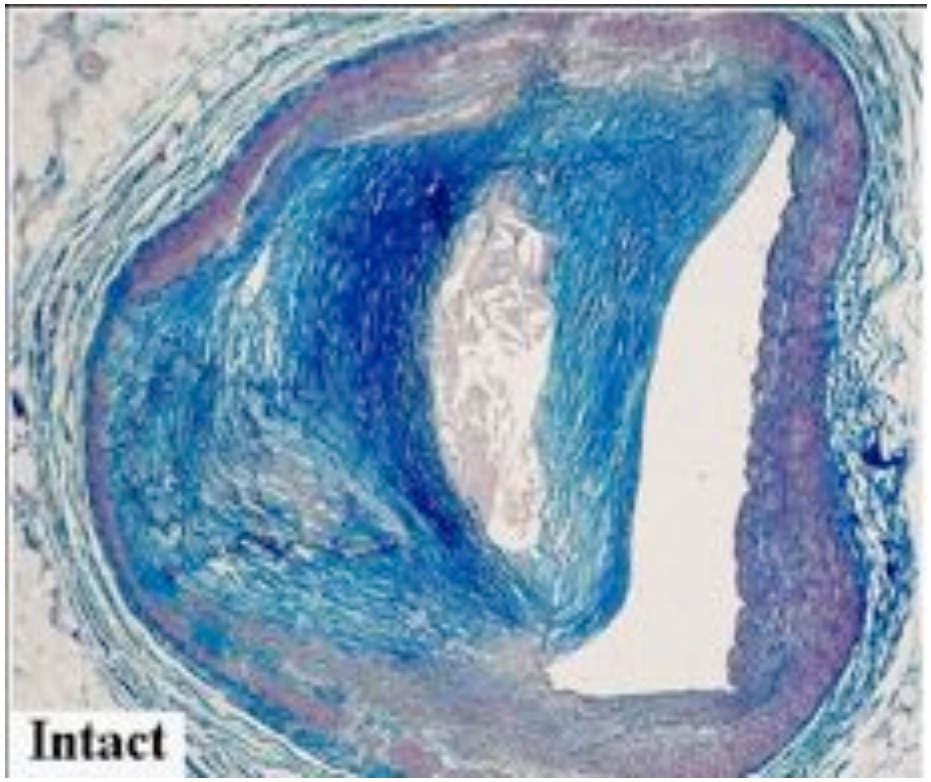
Past Chairman of the Scientific Advisory Committee of the French National Health Insurance Body

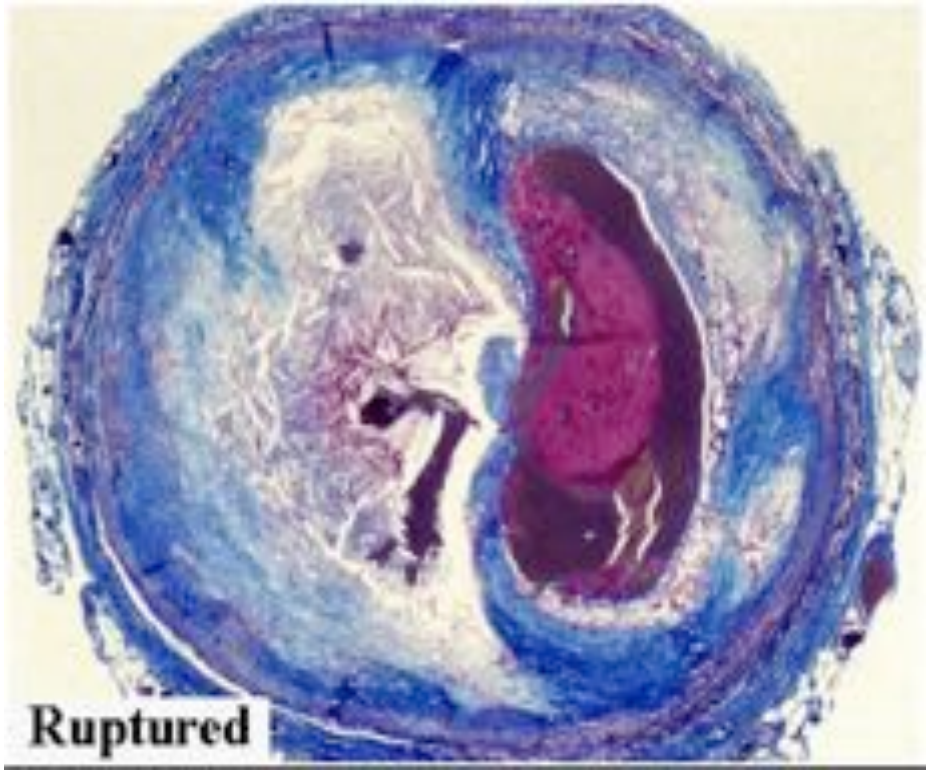
Le Dr Michel de Lorgeril a été le premier à montrer que les études « miraculeuses » sur les médicaments contre le cholestérol sont, comme le dit le Dr Horton, biaisées. En réalité, les statines n'empêchent ni les infarctus ni les AVC.

Le rationnel :

lipides et athérosclérose

Atherosclérose : plausibilité anatomique





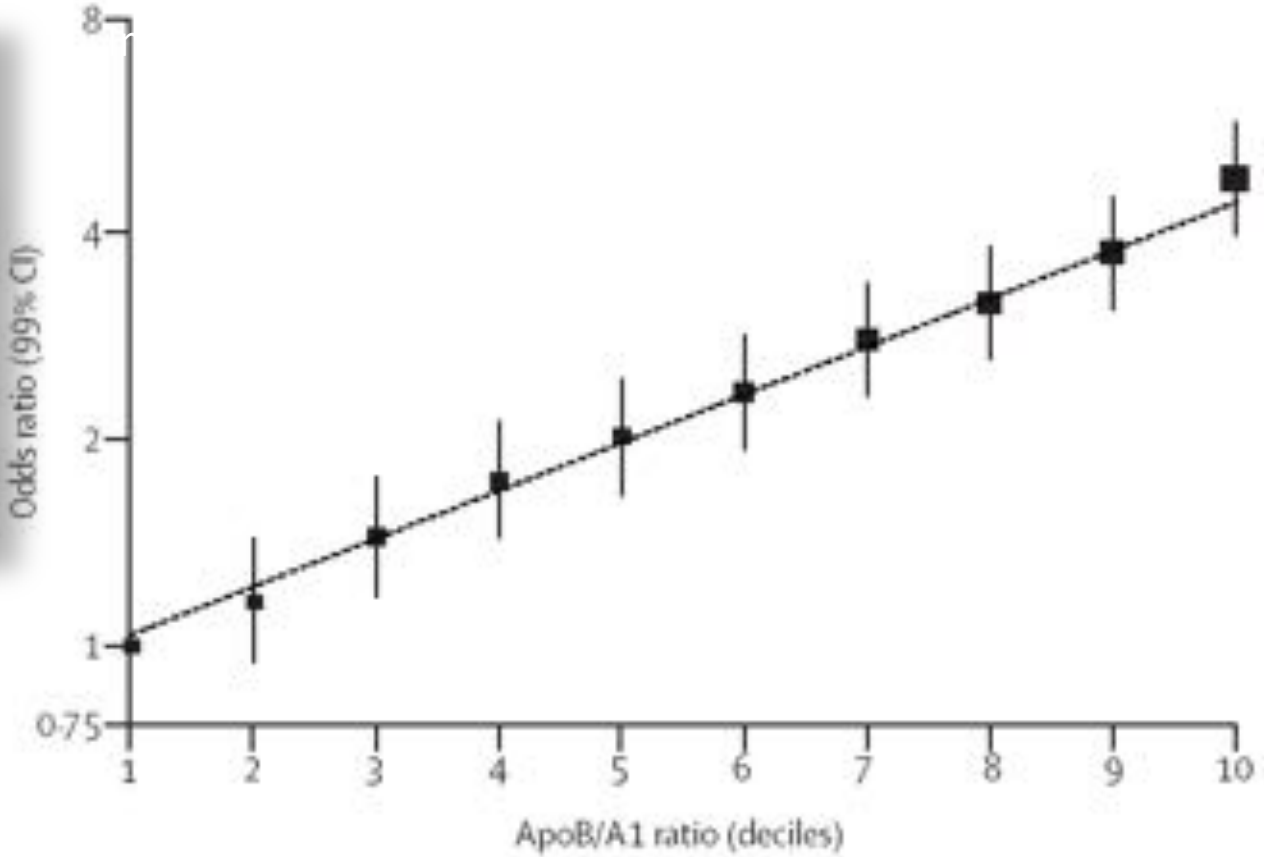
Courtesy Z. Mallat

Plausibilité épidémiologique : Etude cas-témoins INTERHEART

Hommes et femmes

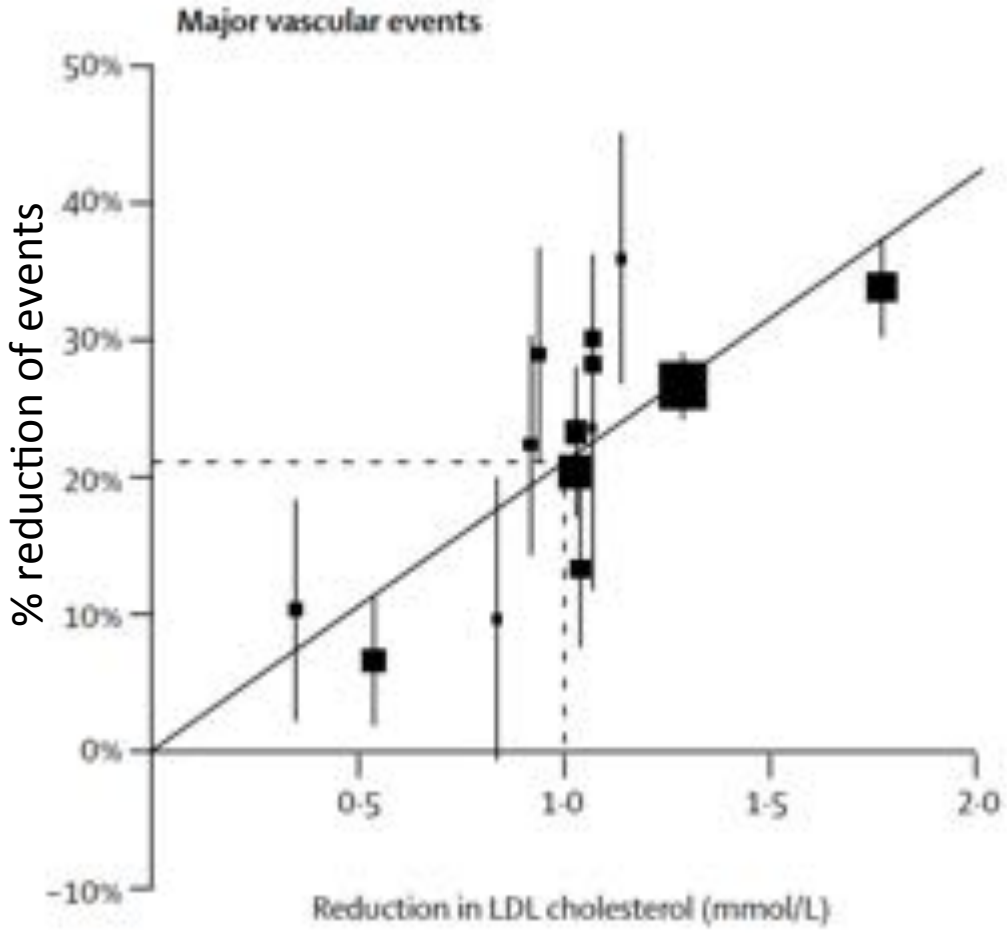
15 152 avec infarctus
14 820 contrôles

Etude mondiale, dans 52 pays, à faible ou haut risque CV



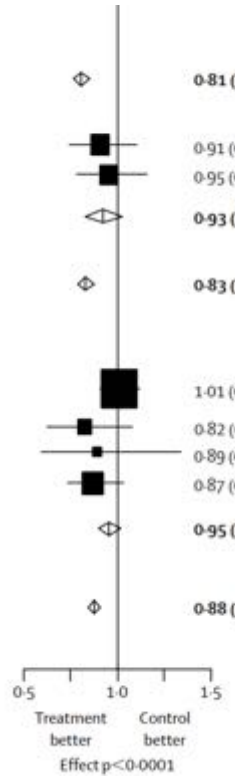
Number of controls	1210	1206	1208	1207	1210	1209	1207	1208	1208	1209
Number of cases	435	496	610	720	790	893	1063	1196	1366	1757
Median	0·43	0·53	0·60	0·66	0·72	0·78	0·85	0·93	1·04	1·28

Plausibilité thérapeutique : la baisse du LDL réduit les événements CV et la mortalité



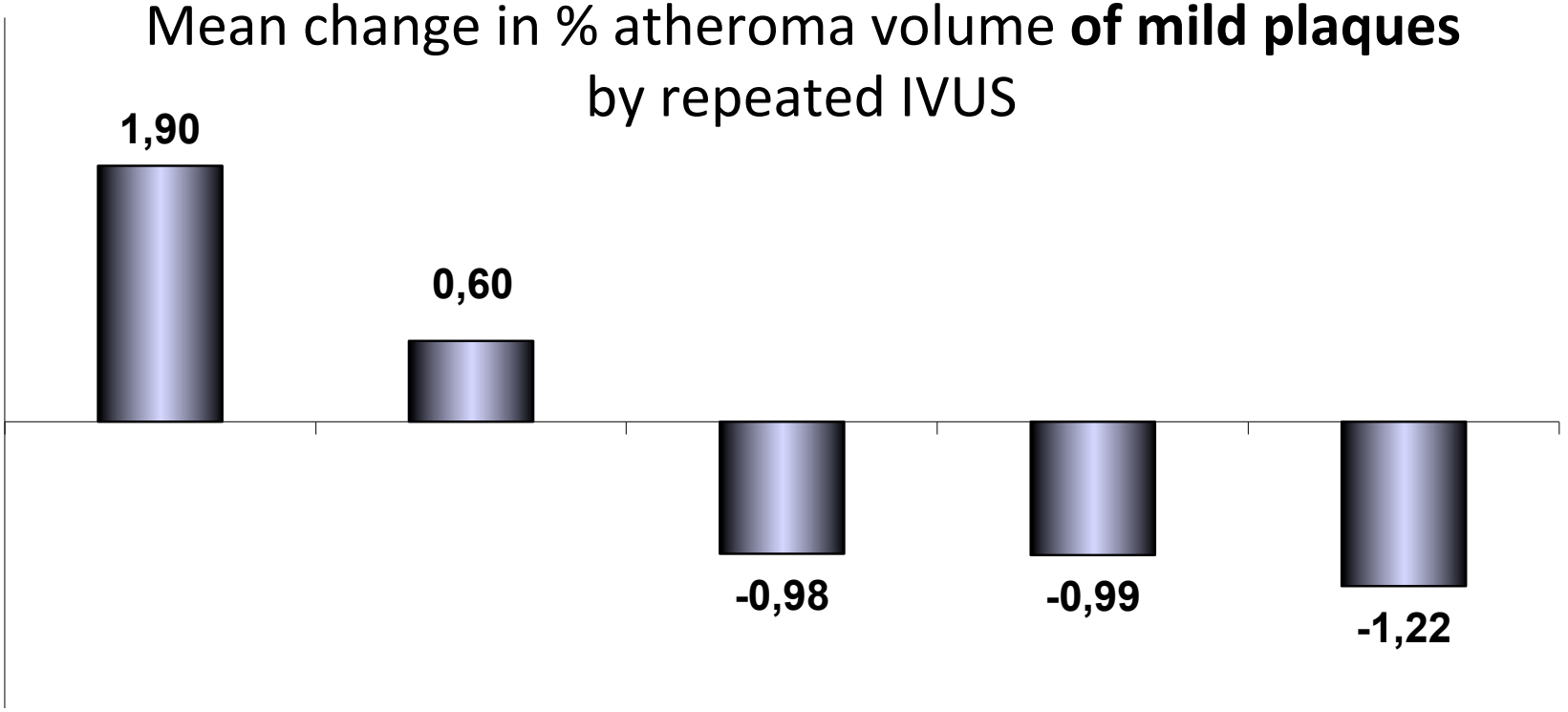
Mortality

Vascular causes:			
CHD	**1548 (3·4%)**	**1960 (4·4%)**	**0·81 (0·76 –0·85)**
Stroke	265 (0·6%)	291 (0·6%)	0·91 (0·74 –1·11)
Other vascular	289 (0·6%)	302 (0·7%)	0·95 (0·78 –1·16)
Any non-CHD vascular	**554 (1·2%)**	**593 (1·3%)**	**0·93 (0·83 –1·03)**
Any vascular	**2102 (4·7%)**	**2553 (5·7%)**	**0·83 (0·79 –0·87)**
Non-vascular causes:			
Cancer	1094 (2·4%)	1069 (2·4%)	1·01 (0·91 –1·12)
Respiratory	98 (0·2%)	125 (0·3%)	0·82 (0·62 –1·08)
Trauma	51 (0·1%)	57 (0·1%)	0·89 (0·59 –1·34)
Other/unknown	487 (1·1%)	550 (1·2%)	0·87 (0·73 –1·03)
Any non-vascular	**1730 (3·8%)**	**1801 (4·0%)**	**0·95 (0·90 –1·01)**
Any death	**3832 (8·5%)**	**4354 (9·7%)**	**0·88 (0·84 –0·91)**



CTT collaborators Lancet 2005

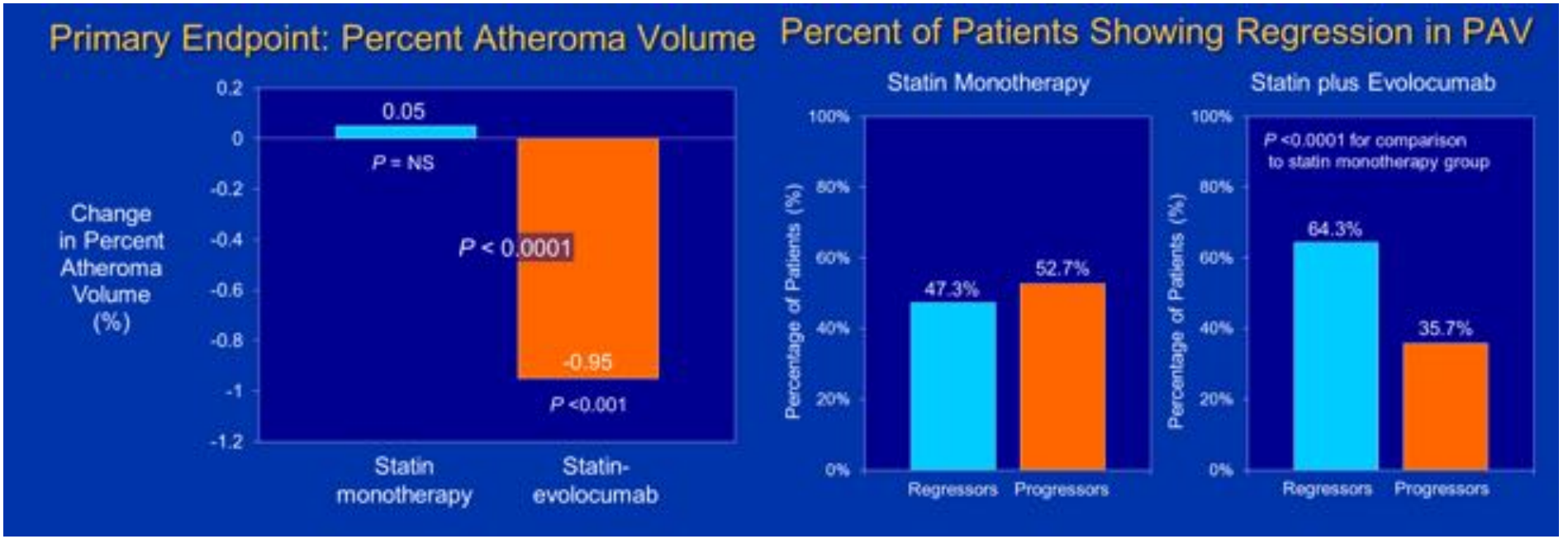
Réversibilité des plaques
Essais REVERSAL, ASTEROID et SATURN



LDL :	REVERSAL		ASTEROID	SATURN	
	Pravastatin	Atorvastatin	Rosuvastatin	Atorvastatin	
Rosuvastatin 18/24 mths	110 mg	79 mg /dL	61 mg/dL	70 mg/dL	63 mg/dL

Nissen SE, et al. JAMA 2004; JAMA 2006, NEJM 2011

GLAGOV: evolocumab vs placebo on top of statins

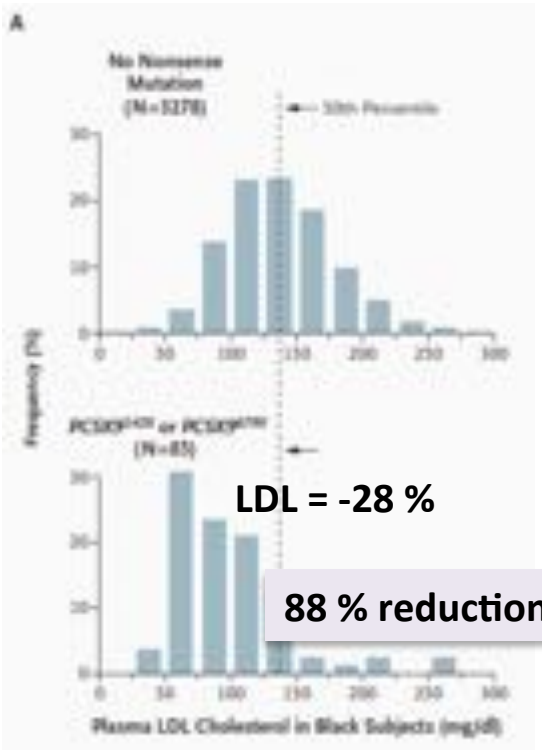


Nissen et al. JAMA 2016

Plausibilité génétique
PCSK9 gene mutation: ARIC study

Favorable mutations (nonsense) of the proprotein convertase subtilisine kexine 9 gene are associated with lower LDL-cholesterol levels

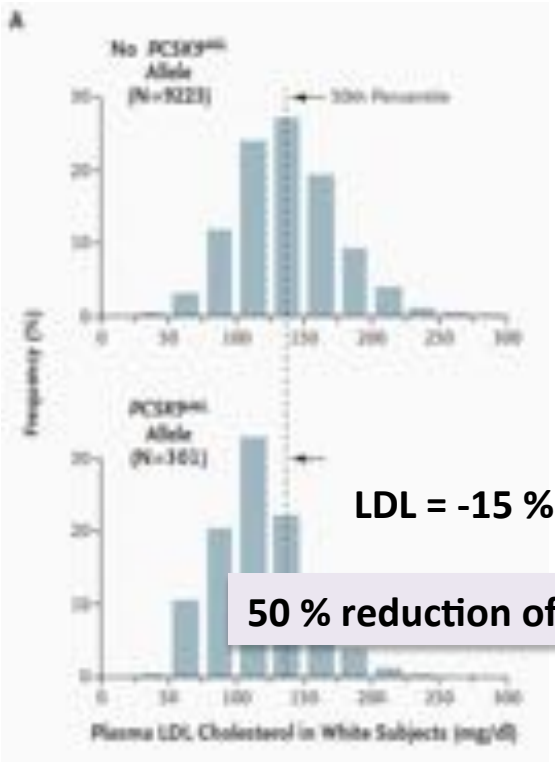
Blacks



LDL = -28 %

88 % reduction of CV events

Whites

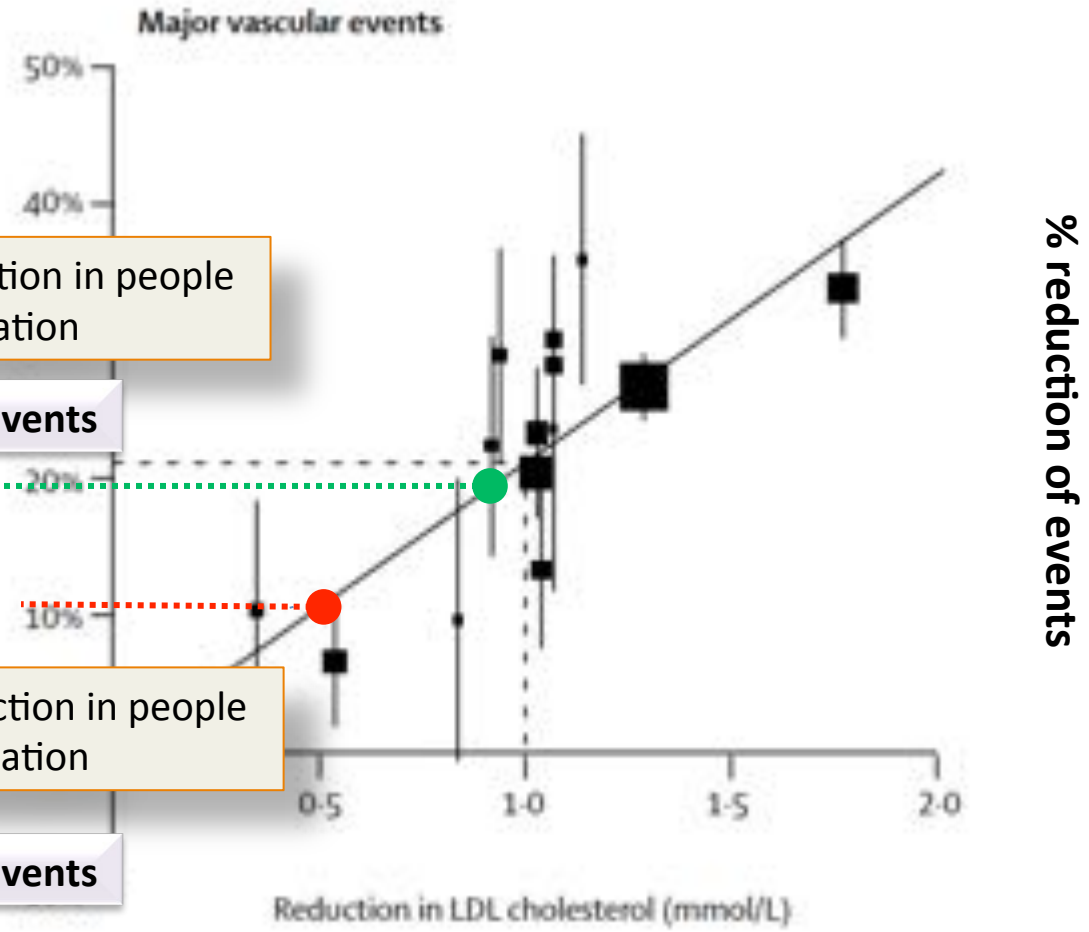


LDL = -15 %

50 % reduction of CV events

NEJM 2006

Plausibilité génétique : abaisser le LDL-c diminue le risque CV



Blacks : 38 mg/dl reduction in people with the favorable mutation

88 % reduction of CV events

Black: 138 -> 100 mg/dl

White: 137 -> 116 mg/dl

Blancs : 21 mg/dl reduction in people with the favorable mutation

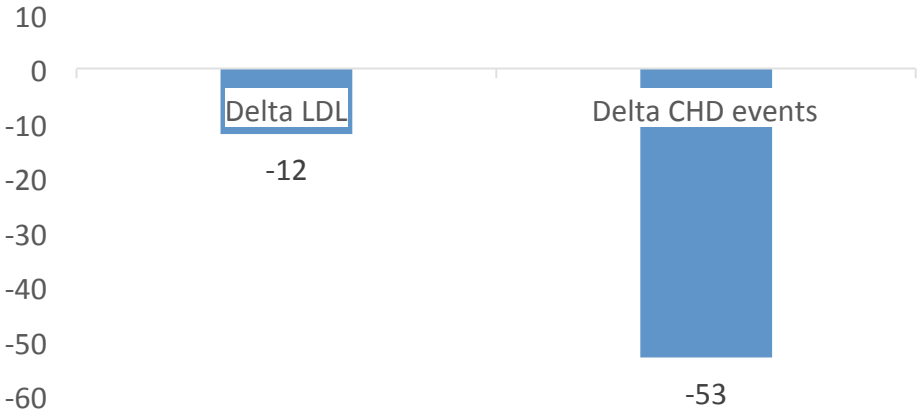
50 % reduction of CV events

CTT collaborators Lancet 2005

Effect of NPCIL1 gene mutations on CHD

- NPCIL1 is a protein implicated in the transport of cholesterol from the gut lumen into the enterocytes, and is inhibited by ezetimibe
- Case-control and cohort studies in 7,364 CHD patients and 14,728 controls

- 15 inactivating mutations:



Myocardial infarction genetics consortium. NEJM 2014

Le rôle du HDL

Les polymorphismes génétiques responsables d'une hausse du LDL sont associés à une hausse des événements CV, ainsi que cela est observé dans les études observationnelles

Contrairement aux résultats des études observationnelles, **les polymorphismes associés à un HDL élevé n'ont pas d'impact sur les événements => l'association rapportée par les études observationnelles est biaisée**

	Observational epidemiology		Genetically raised	
	Odds ratio (95% CI) per 0·03 mmol/L (1 mg/dL) increase in plasma HDL cholesterol	p value	Odds ratio (95% CI) per 0·03 mmol/L (1 mg/dL) increase in plasma HDL cholesterol	p value
Cohort				
Atherosclerosis Risk in Communities Study	0·97 (0·96–0·98)	7×10⁻¹⁴	0·96 (0·86–1·07)	0·44
Copenhagen City Heart Study	0·98 (0·98–0·99)	6×10⁻¹⁴	1·09 (0·95–1·26)	0·21
Malmo Diet and Cancer Study, Cardiovascular Cohort	0·97 (0·96–0·98)	1×10⁻⁸	0·82 (0·66–1·01)	0·06
Framingham Heart Study	0·96 (0·94–0·98)	4×10⁻⁴	1·17 (1·00–1·37)	0·06
Health Professionals Follow-up Study	–	–	1·84 (0·39–8·63)	0·16
Danish Diet, Cancer, and Health Study	–	–	1·05 (0·79–1·43)	0·71
Meta-analysis of cohort studies				
Per 0·03 mmol/L (1 mg/dL) increase in plasma HDL cholesterol	0·98 (0·97–0·98)	4×10⁻¹⁶	1·02 (0·95–1·09)	0·64
Per 0·39 mmol/L (15 mg/dL) increase in plasma HDL cholesterol	0·70 (0·66–0·74)	4×10⁻¹⁶	1·28 (0·46–3·61)	0·64

Table 3: Instrumental variable analysis estimate of the association of genetically raised HDL cholesterol and risk of myocardial infarction using LIPG Asn396Ser as an instrument

	Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*	Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†
LDL cholesterol	1·54 (1·45–1·63)	2·13 (1·69–2·69), p=2×10⁻¹⁰
HDL cholesterol	0·62 (0·58–0·66)	0·93 (0·68–1·26), p=0·63

Voight *Lancet* 2012; 380:572-80

En somme

- Le cholestérol est à la fois un constituant de la plaque d'athérome, et un facteur de risque.
- C'est un facteur de risque majeur dans l'hypercholestérolémie familiale.
- En dehors de cette situation, l'impact du niveau de LDL-c sur l'athérome est modulé par les autres facteurs de risque : schématiquement, plus l'endothélium est abîmé, plus le cholestérol peut passer dans la paroi artérielle et constituer des plaques. Cela explique pourquoi on peut avoir de l'athérome même en présence de niveaux "normaux" de LDL-c.

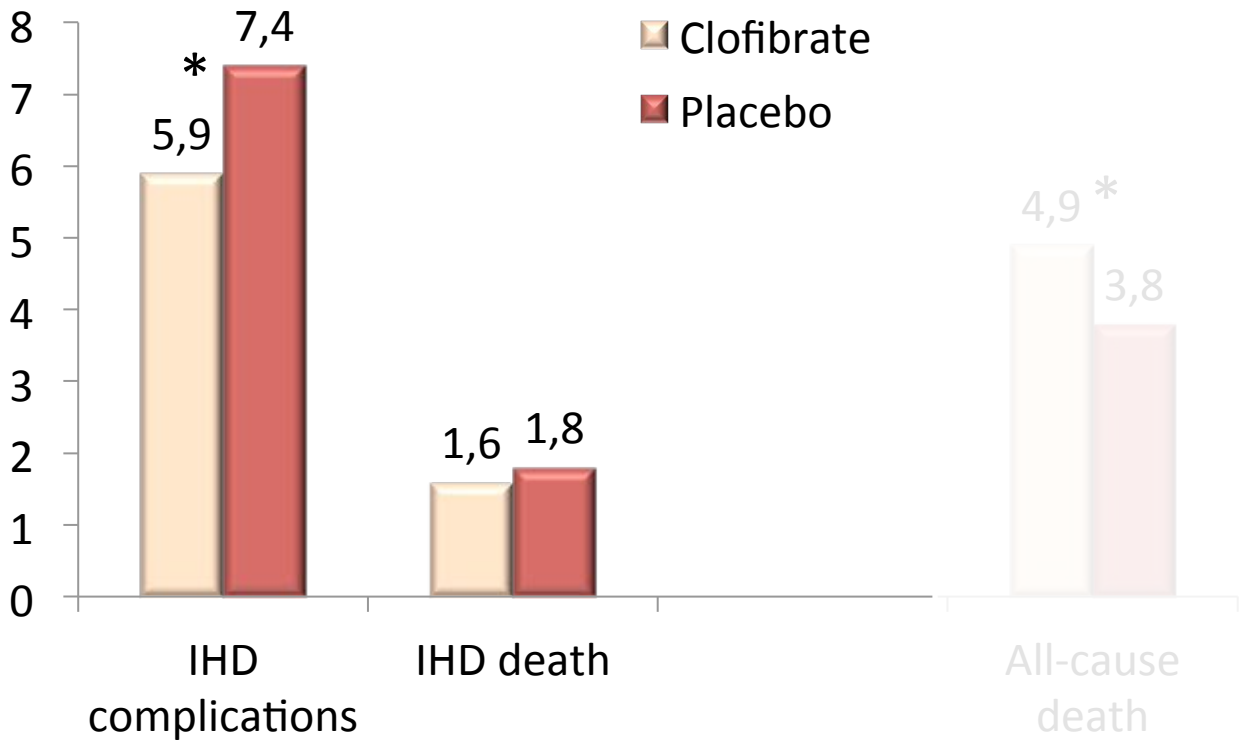
Traitement hypolipémiant en prévention primaire

WHO clofibrate trial in primary prevention

WHO trial
Men in Budapest, Prague, Edinburgh

- 5331 clofibrate
- 5296 placebo

5-year F/U



Mean decrease in cholesterol level on clofibrate: 9%

Br Heart J 1978; 40: 1069

Les statines en prévention primaire

MEGA : pravastatine à faible dose dans une population japonaise en prévention primaire

- 8214 sujets (hommes 40-70 ans, femmes méonopause-70 ans) avec CT 2,3-2,7 g/l.

  Randomisation régime vs régime + prava 10-20 mg

  Suivi 5,3 ans

- LDL réduit de 18 % dans le groupe pravastatine

- Critère principal : - 33 % (3.3% vs 5.0%), P=0,01
  - Infarctus : - 48 %
  - AVC : - 17 %
  - Décès : 2.7 % vs 3.8 % - 28 % (p=0,055)

Décès groupe contrôle : 0.72 % / an

Lancet 2006

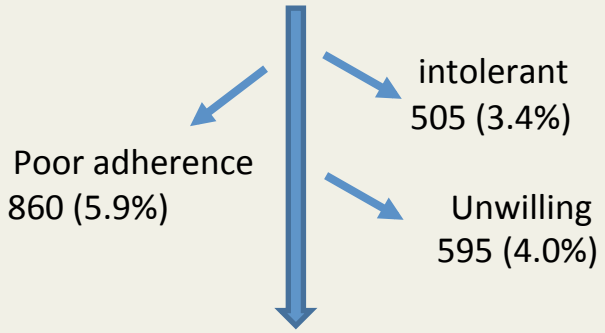
HOPE 3

Inclusion criteria
- Women aged ≥ 65 y* and men aged ≥ 55 y
- At least 1 of the following additional CV risk factors:
  - Waist-to-hip ratio ≥ 0.85 in women and ≥ 0.90 in men
  - History of current or recent smoking (regular tobacco use within 5 y)
  - Low HDL-C (< 1.0 mmol/L in men and < 1.3 mmol/L in women)
  - Dysglycemia (impaired fasting glucose, impaired glucose tolerance, or uncomplicated diabetes treated with diet only)
  - Early renal dysfunction†
  - Family history of premature coronary heart disease in first-degree relatives (age < 55 y in men or < 65 y in women)
  - Provision of informed consent

Recruitment 2007-2010

15,469 screened

14,665 active run-in (4 wks)



12,705 randomised

Randomisation : plan factoriel 2x2

Rosuvastatin 10 **v.** placebo

Candesartan/HCTZ 16/12.5 **v.** placebo

228 centres, 21 pays

1st Primary end-point P<0.04

CV death, MI or stroke

Follow-up

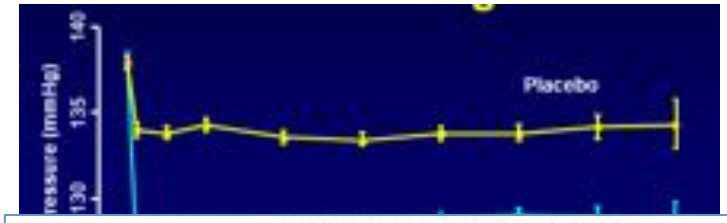
5.6 years (99.1%)

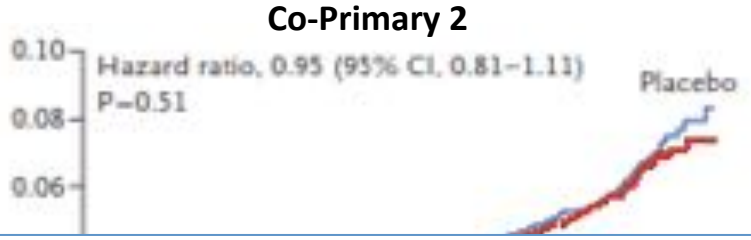
2nd primary outcome: P<0.02

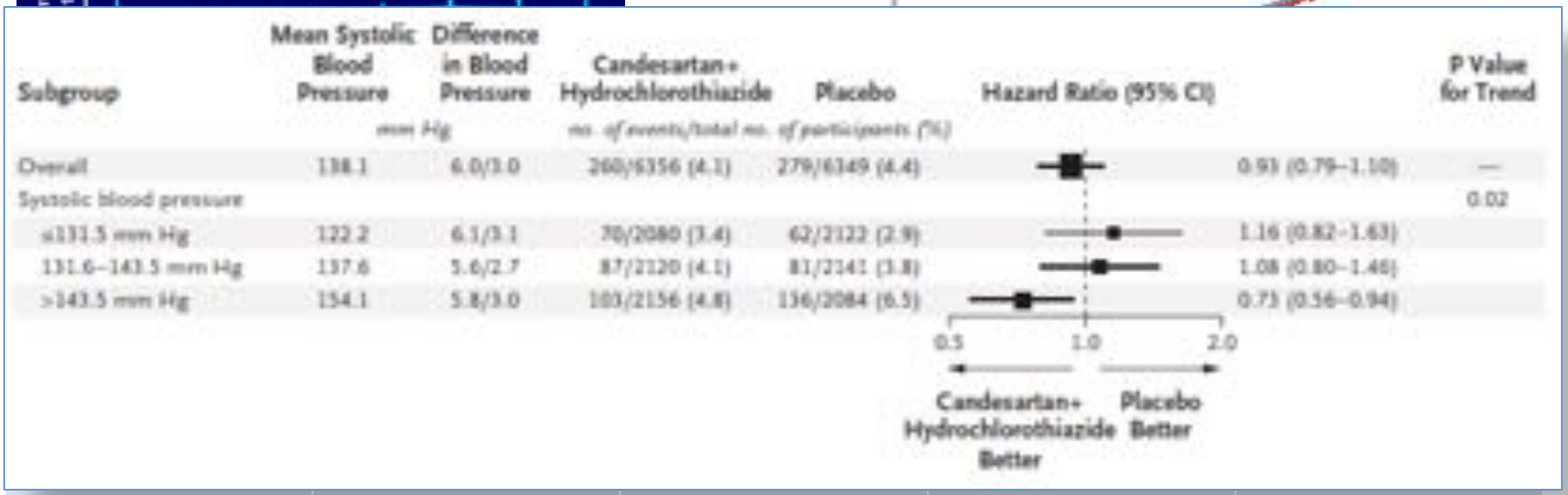
+ CHF, cardiac arrest, revasc

Lonn E et al. Can J Cardiol 2016

HOPE 3 : traitement antihypertenseur



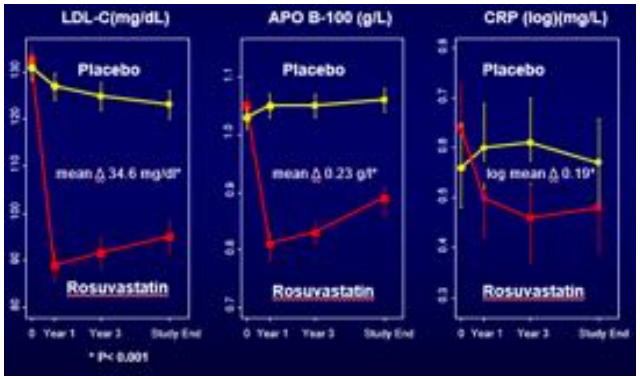


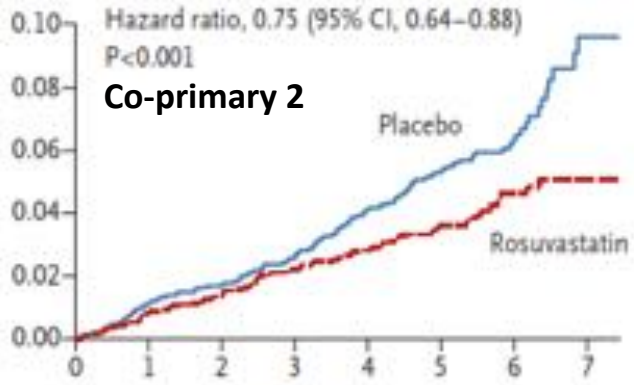


Secondary	335 (5.3%)	364 (5.7%)	0.92 (0.79-1.06)	0.26
CV Death	155 (2.4%)	170 (2.7%)	0.91 (0.73-1.13)	0.40
MI	52 (0.8%)	62 (1.0%)	0.84 (0.58-1.21)	0.34
Stroke	75 (1.2%)	94 (1.5%)	0.80 (0.59-1.08)	0.14
CV Hosp.	319 (5.0%)	331 (5.2%)	0.96 (0.83-1.12)	0.63

Lonn E et al. New Engl J Med 2016

HOPE 3 : rosuvastatine 10 vs placebo

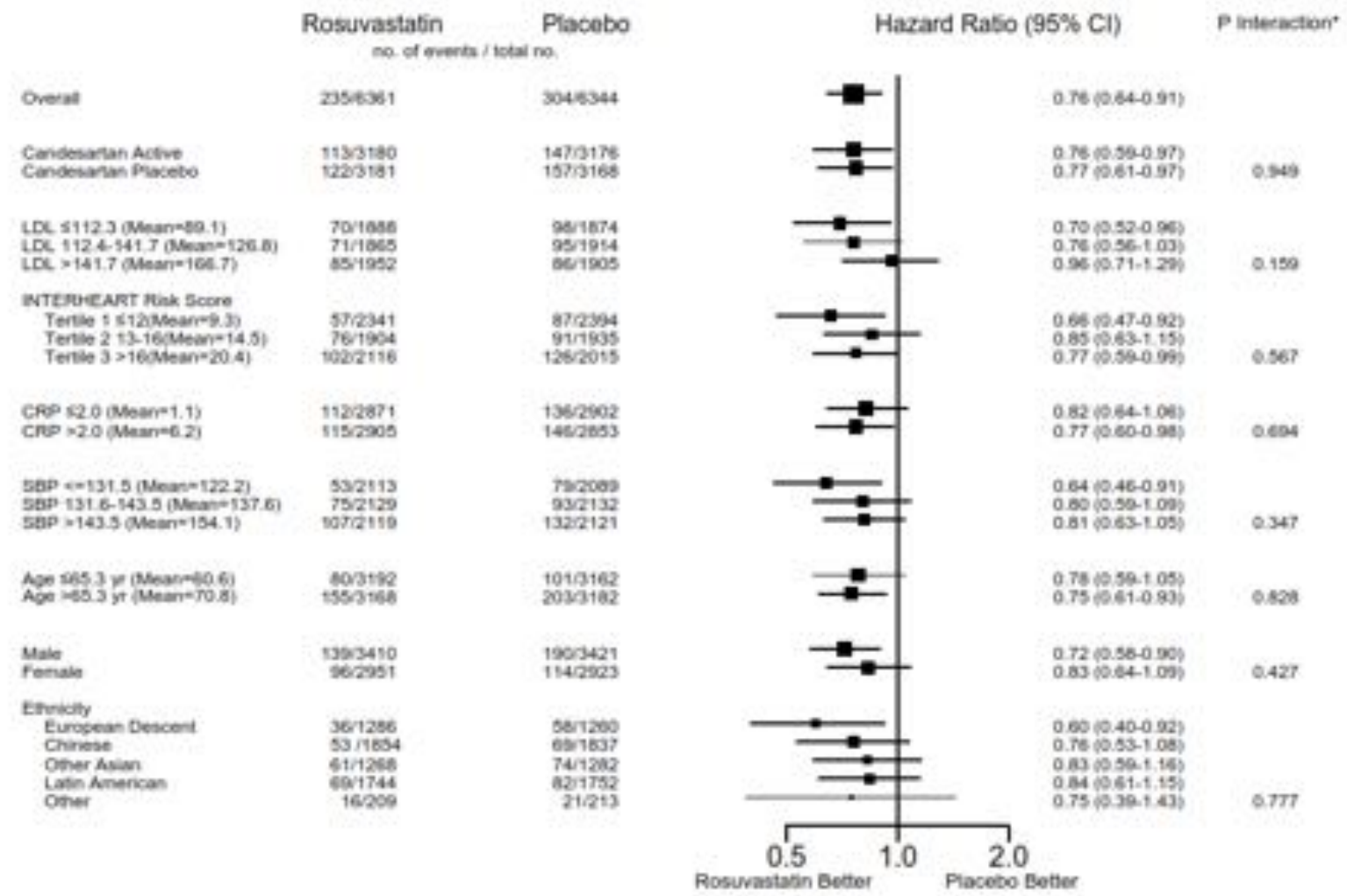




Outcome	Rosuvastatin N (%)	Placebo N (%)	HR (95% CI)	p
Co-Primary 1	235 (3.69)	304 (4.79)	0.76 (0.64-0.91)	0.002
Co-Primary 2	277 (4.35)	363 (5.72)	0.75 (0.64-0.88)	0.0004
Secondary 1	306(4.81)	393 (6.19)	0.77 (0.66-0.89)	0.0006
CV Death	154 (2.4)	171 (2.7)	0.89 (0.72-1.11)	0.31
MI	45 (0.7%)	69 (1.1)	0.65 (0.44-0.94)	0.02
Stroke	70 (1.1%)	99 (1.6%)	0.70 (0.52-0.95)	0.02
CV Hosp.	281 (4.4)	369 (5.8)	0.75 (0.64-0.88)	0.0003
All cause death	334 (5.3)	357 (5.6)	0.93 (0.80-1.08)	0.32

Yusuf S et al. New Engl J Med 2016

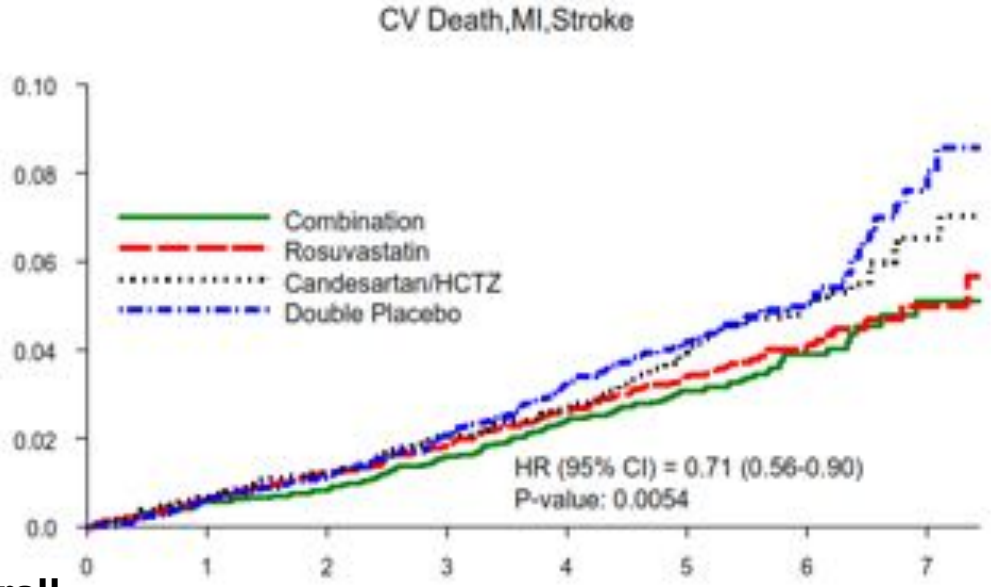
HOPE 3 : rosuvastatine 10 vs placebo

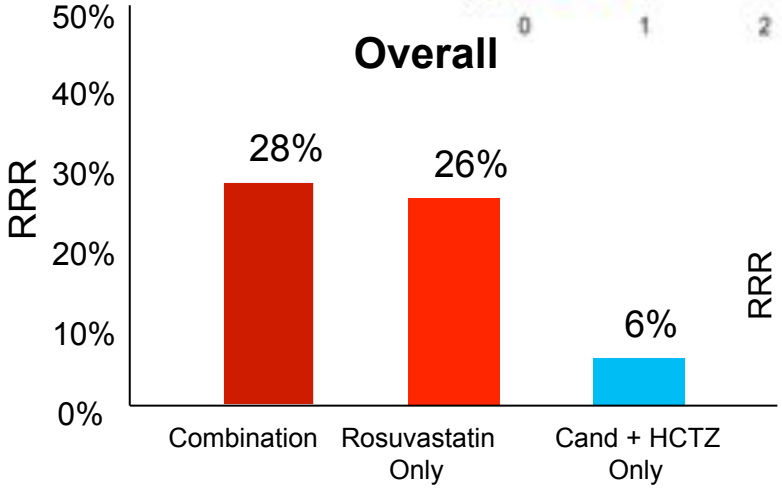


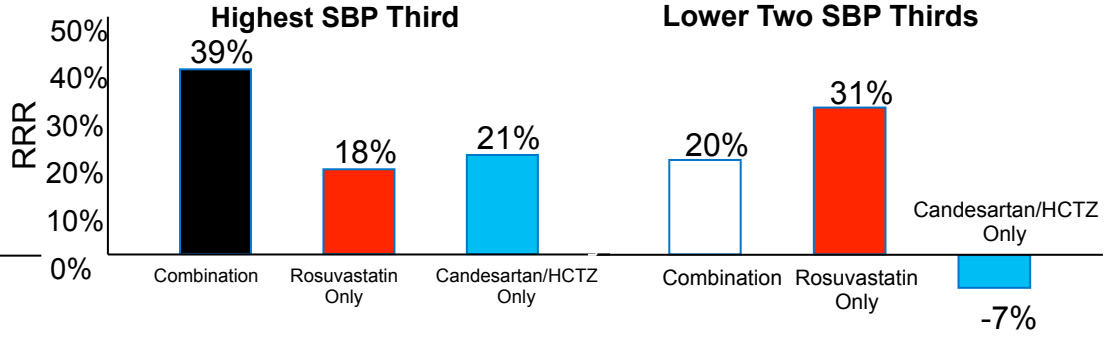
Yusuf S et al. New Engl J Med 2016

HOPE 3 : combinaison des 2 traitements

Pas de synergie ni d'antagonisme







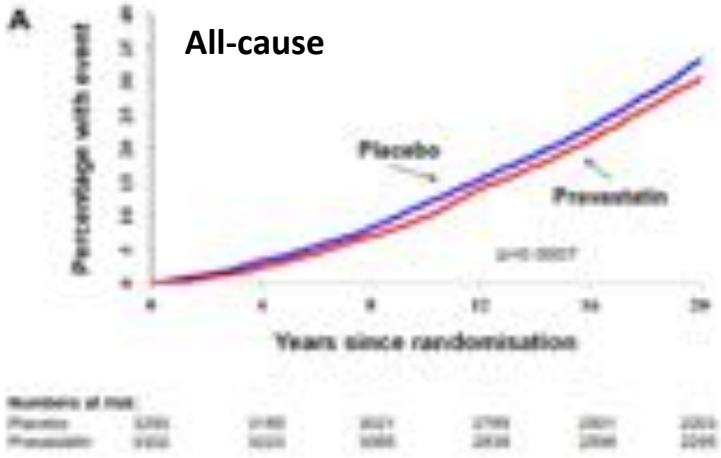
Yusuf S et al. New Engl J Med 2016

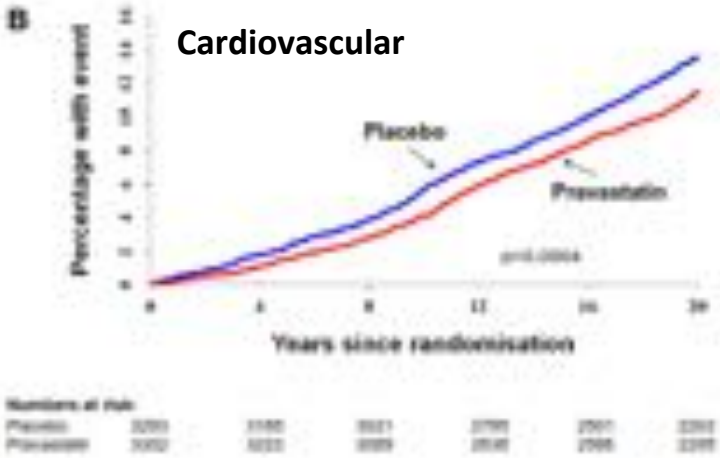
HOPE 3 : sécurité de la rosuvastatine 10

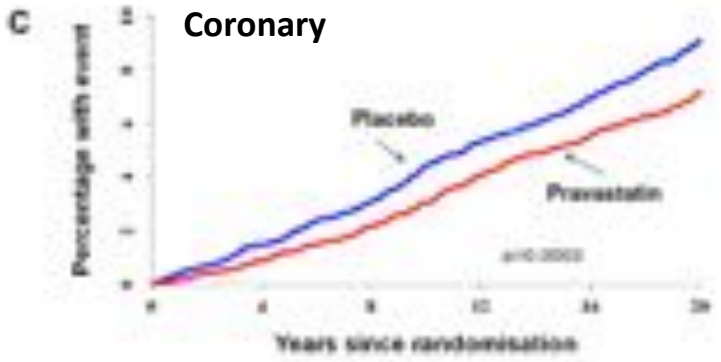
	Rosuvastatin N (%)	Placebo N (%)	p
Permanent Discontinuation	1510 (23.7)	1664 (26.2)	0.001
Rhabdomyolysis/Myopathy	2 (0.1)	1 (0)	1.0
Muscle pain/ weakness	367 (5.8)	296 (4.7)	0.005
Cataract Surgery	202 (3.3)	159 (2.6)	0.02
New Diabetes	232 (3.9)	226 (3.8)	0.82
DVT/ pulmonary embolism	14 (0.2)	31 (0.5)	0.01

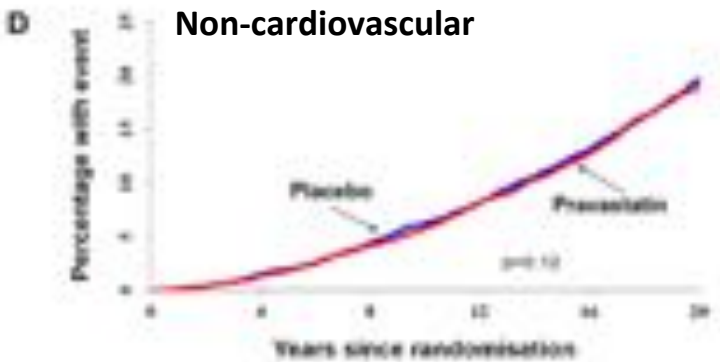
Yusuf S et al. New Engl J Med 2016

WOSCOPS : suivi de mortalité à 20 ans





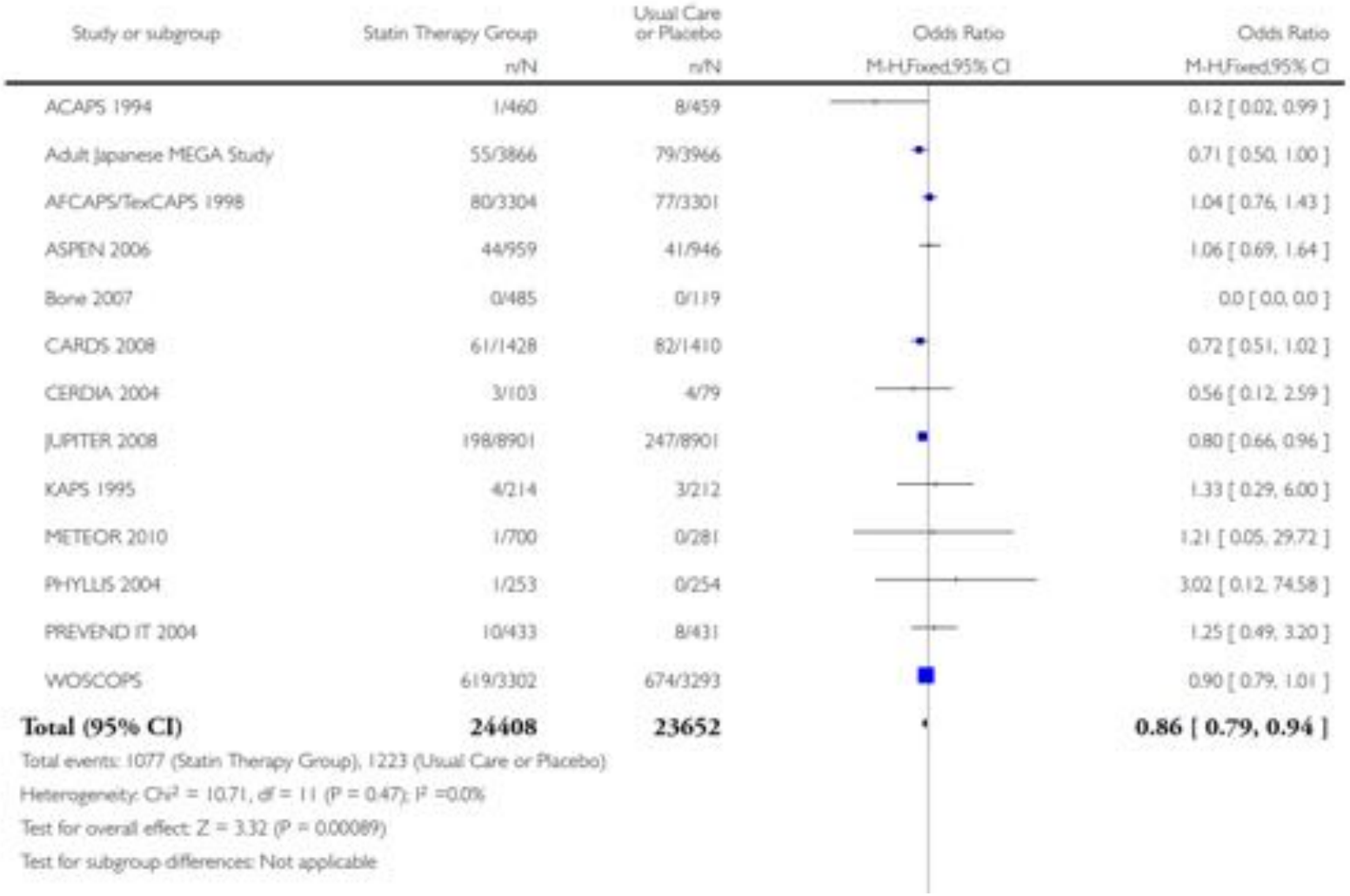




Ford I. et al. Circulation 2016

Méta-analyse de toutes les études statines en prévention primaire : mortalité

Cochrane Collaboration. Statins for the primary prevention of cardiovascular disease. 2013



Our previous conclusion urging caution in the use of statins in people at low risk of cardiovascular events is no longer tenable in light of the CTT Collaboration findings. Several issues remain to be considered before widespread use of statins could be recommended in people at low risk (Ebrahim 2012; Smeeth 2012). These include: i) the feasibility and desirability of having to treat the majority of people over the age of 50 with a statin; ii) the cost-effectiveness of such a strategy using a conventional healthcare delivery system; iii) diversion of attention from achieving coverage in people at high risk of events; iv) use of alternative public health strategies to lower blood cholesterol; v) the views of patients on life-long drug therapy; and vi) limited evidence on less serious but nonetheless potentially important adverse effects and quality of life.

Un choix de santé publique doublé d'un choix individuel

Cochrane Collaboration. Statins for the primary prevention of cardiovascular disease. 2013

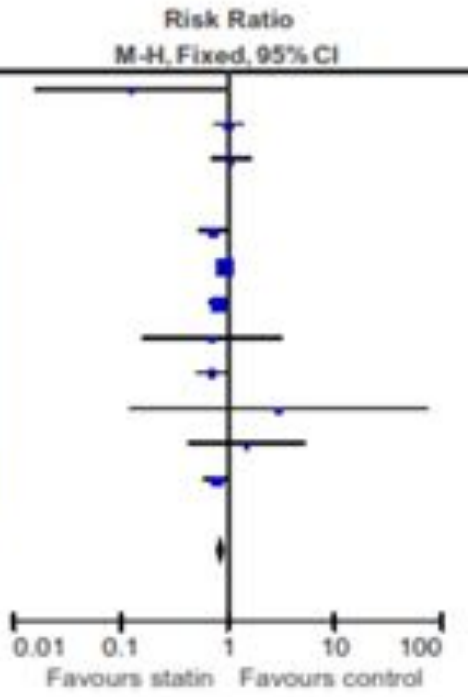
Mortalité dans les essais statines en prévention primaire

1.1 All-cause death

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACAPS	1	460	8	459	0.8%	0.12 [0.02, 0.99]
AFCAPS/TEXCAPS	80	3304	77	3301	7.4%	1.04 [0.76, 1.41]
ASPEN	44	959	41	946	4.0%	1.06 [0.70, 1.60]
Bone	0	239	0	119		Not estimable
CARDS	61	1428	82	1410	8.0%	0.73 [0.53, 1.01]
HOPE 3	334	6361	357	6344	34.5%	0.93 [0.81, 1.08]
JUPITER	198	8901	247	8901	23.9%	0.80 [0.67, 0.96]
KAPS	3	224	4	212	0.4%	0.71 [0.16, 3.13]
MEGA	55	3866	79	3966	7.5%	0.71 [0.51, 1.00]
PHYLLIS	1	254	0	254	0.0%	3.00 [0.12, 73.30]
PREVEND IT	6	433	4	431	0.4%	1.49 [0.42, 5.25]
WOSCOPS	106	3302	135	3293	13.1%	0.78 [0.61, 1.01]
Total (95% CI)		**29731**		**29636**	**100.0%**	**0.86 [0.79, 0.94]**
Total events	889		1034			

Heterogeneity: $Chi^2 = 11.47$, $df = 10$ ($P = 0.32$); $I^2 = 13\%$

Test for overall effect: $Z = 3.40$ ($P = 0.0007$)

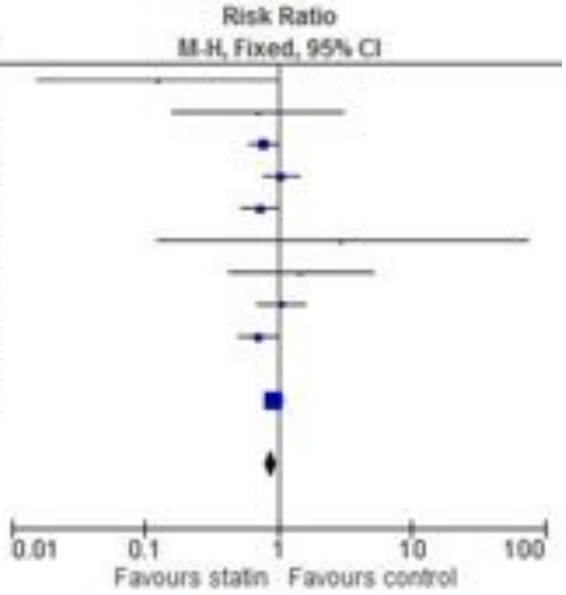


Mortalité des essais statines en prévention primaire après exclusion de l'étude JUPITER, terminée prématurément

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
ACAPS 1994	1	460	8	459	1.0%	0.12 [0.02, 0.99]	1994
KAPS 1995	3	224	4	212	0.5%	0.71 [0.16, 3.13]	1995
WOSCOPS 1997	106	3302	135	3293	17.2%	0.78 [0.61, 1.01]	1997
AFCAPS/TEXCAPS 1998	80	3304	77	3301	9.8%	1.04 [0.76, 1.41]	1998
CARDS 2004	61	1428	82	1410	10.5%	0.73 [0.53, 1.01]	2004
PHYLLIS 2004	1	254	0	254	0.1%	3.00 [0.12, 73.30]	2004
PREVEND IT 2004	6	433	4	431	0.5%	1.49 [0.42, 5.25]	2004
ASPEN 2006	44	959	41	946	5.2%	1.06 [0.70, 1.60]	2006
MEGA 2006	55	3866	79	3966	9.9%	0.71 [0.51, 1.00]	2006
Bone 2007	0	239	0	119		Not estimable	2007
HOPE 3 2016	334	6361	357	6344	45.4%	0.93 [0.81, 1.08]	2016
Total (95% CI)		20830		20735	100.0%	0.88 [0.79, 0.97]	
Total events	691		787				

Heterogeneity: $Chi^2 = 10.70$, $df = 9$ ($P = 0.30$); $I^2 = 16\%$

Test for overall effect: $Z = 2.58$ ($P = 0.010$)



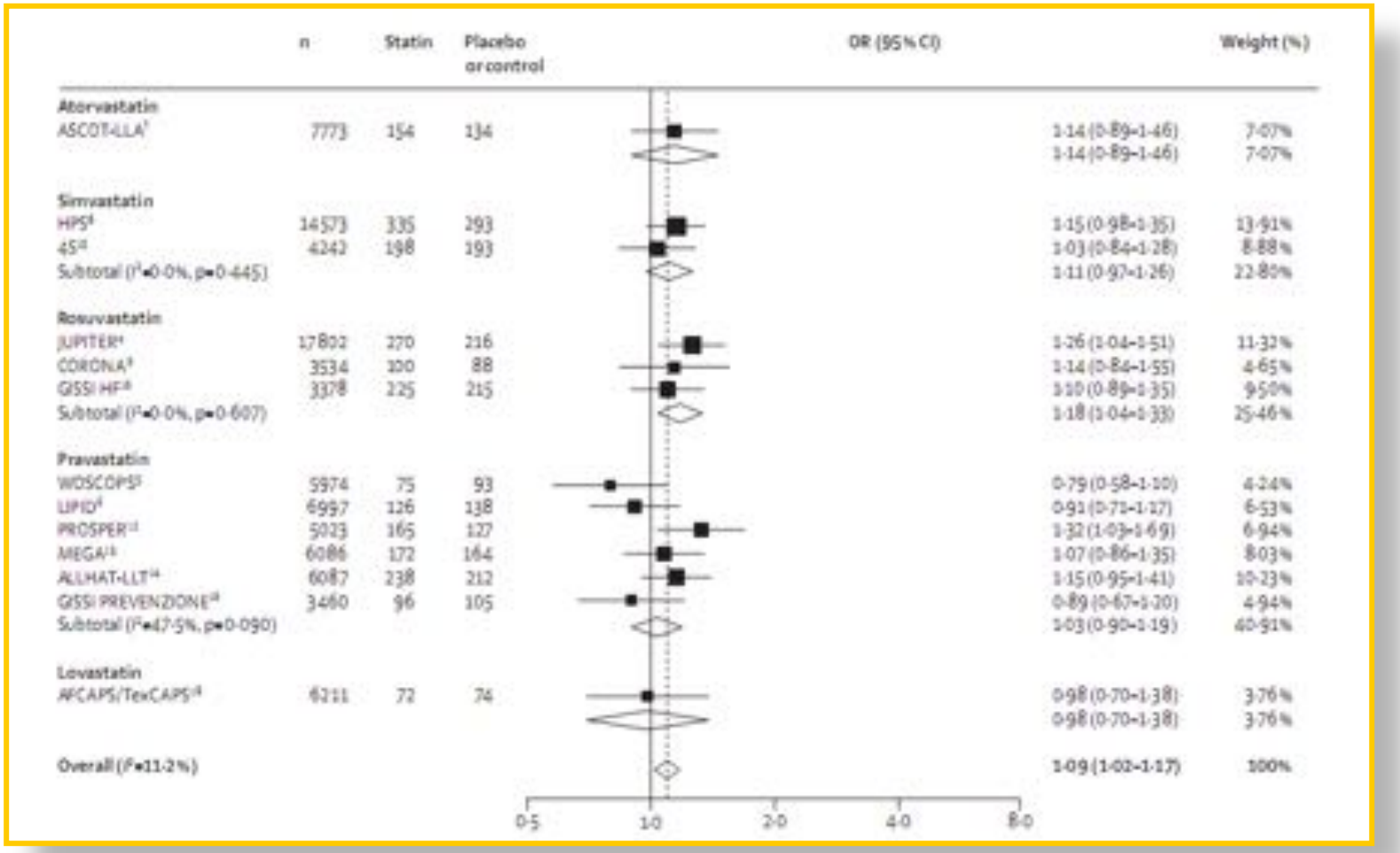
Les risques potentiels du traitement

HOPE 3 : sécurité de la rosuvastatine 10

	Rosuvastatin N (%)	Placebo N (%)	p
Permanent Discontinuation	1510 (23.7)	1664 (26.2)	0.001
Rhabdomyolysis/Myopathy	2 (0.1)	1 (0)	1.0
Muscle pain/ weakness	367 (5.8)	296 (4.7)	0.005
Cataract Surgery	202 (3.3)	159 (2.6)	0.02
New Diabetes	232 (3.9)	226 (3.8)	0.82
DVT/ pulmonary embolism	14 (0.2)	31 (0.5)	0.01

Yusuf S et al. New Engl J Med 2016

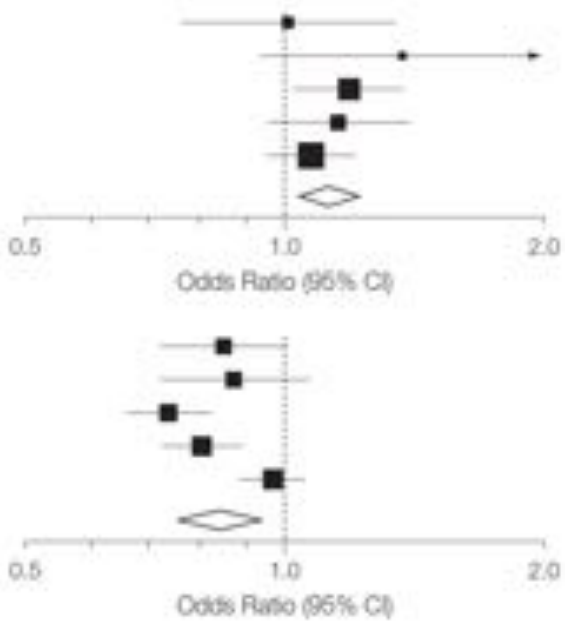
Statins and new onset diabetes



Lancet 2010

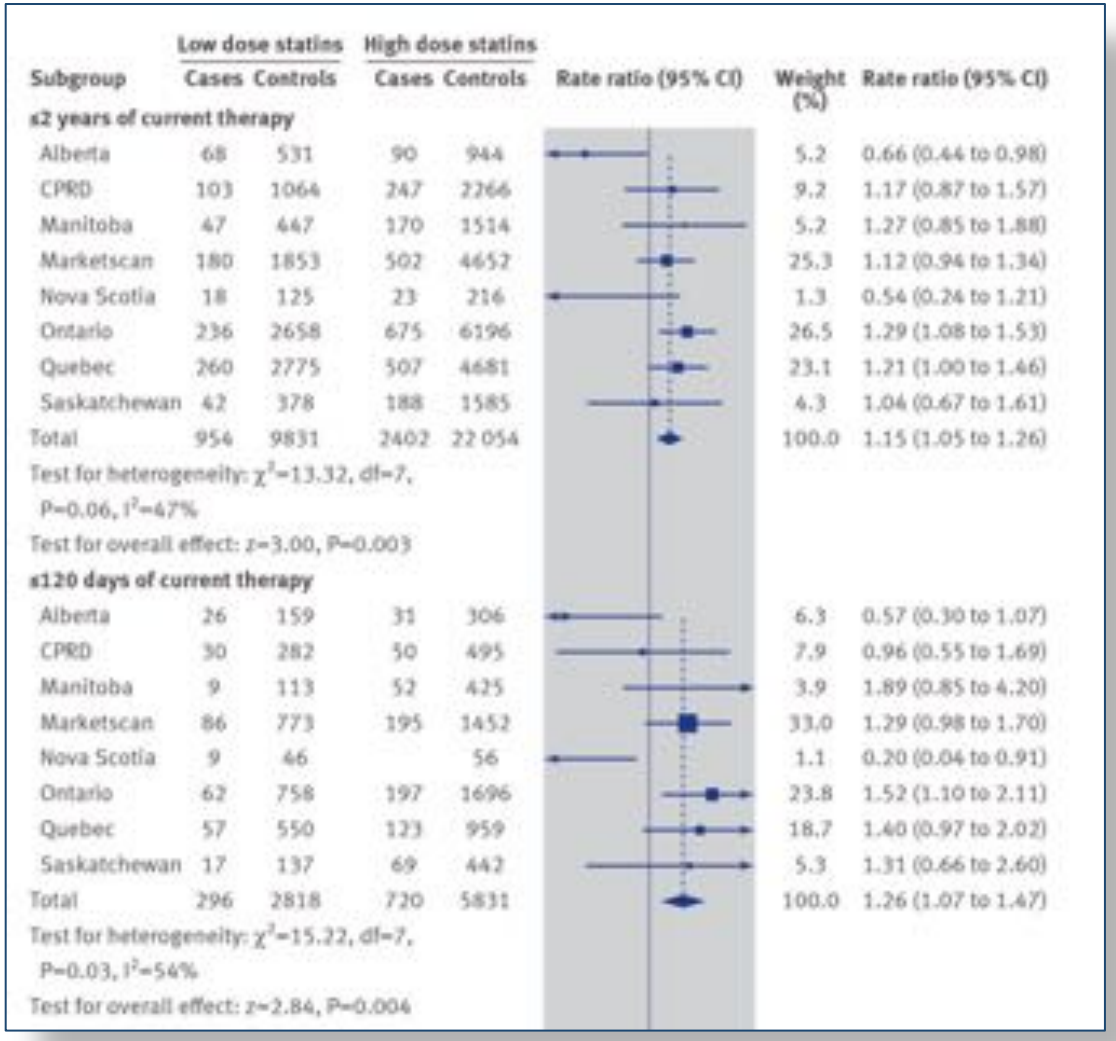
Statin dose and new onset diabetes

	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	**1449/16 408 (8.8)**	**1300/16 344 (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	**3134/16 408 (19.1)**	**3550/16 344 (21.7)**	**0.84 (0.75-0.94)**
Heterogeneity: $I^2 = 74\%$; $P = .004$			



Preiss et al. JAMA 2011

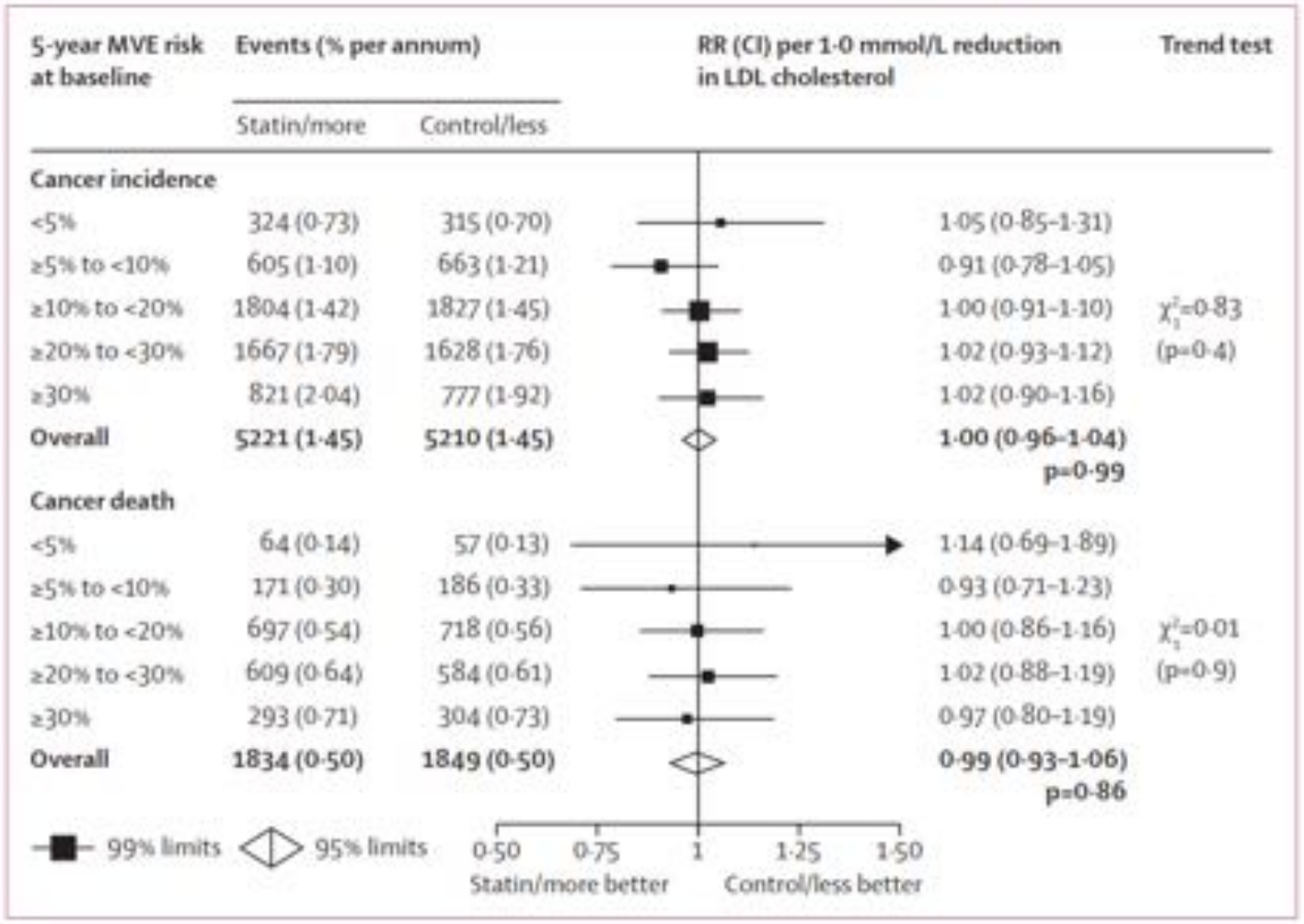
Risque de diabète avec les statines puissantes : bases de données de remboursement



Subgroup	Low dose statins Cases	Low dose statins Controls	High dose statins Cases	High dose statins Controls	Rate ratio (95% CI)	Weight (%)	Rate ratio (95% CI)
≤2 years of current therapy							
Alberta	68	531	90	944		5.2	0.66 (0.44 to 0.98)
CPRD	103	1064	247	2266		9.2	1.17 (0.87 to 1.57)
Manitoba	47	447	170	1514		5.2	1.27 (0.85 to 1.88)
Marketscan	180	1853	502	4652		25.3	1.12 (0.94 to 1.34)
Nova Scotia	18	125	23	216		1.3	0.54 (0.24 to 1.21)
Ontario	236	2658	675	6196		26.5	1.29 (1.08 to 1.53)
Quebec	260	2775	507	4681		23.1	1.21 (1.00 to 1.46)
Saskatchewan	42	378	188	1585		4.3	1.04 (0.67 to 1.61)
Total	954	9831	2402	22 054		100.0	1.15 (1.05 to 1.26)
Test for heterogeneity: χ^2=13.32, df=7, P=0.06, I^2=47%							
Test for overall effect: z=3.00, P=0.003							
≤120 days of current therapy							
Alberta	26	159	31	306		6.3	0.57 (0.30 to 1.07)
CPRD	30	282	50	495		7.9	0.96 (0.55 to 1.69)
Manitoba	9	113	52	425		3.9	1.89 (0.85 to 4.20)
Marketscan	86	773	195	1452		33.0	1.29 (0.98 to 1.70)
Nova Scotia	9	46		56		1.1	0.20 (0.04 to 0.91)
Ontario	62	758	197	1696		23.8	1.52 (1.10 to 2.11)
Quebec	57	550	123	959		18.7	1.40 (0.97 to 2.02)
Saskatchewan	17	137	69	442		5.3	1.31 (0.66 to 2.60)
Total	296	2818	720	5831		100.0	1.26 (1.07 to 1.47)
Test for heterogeneity: χ^2=15.22, df=7, P=0.03, I^2=54%							
Test for overall effect: z=2.84, P=0.004							

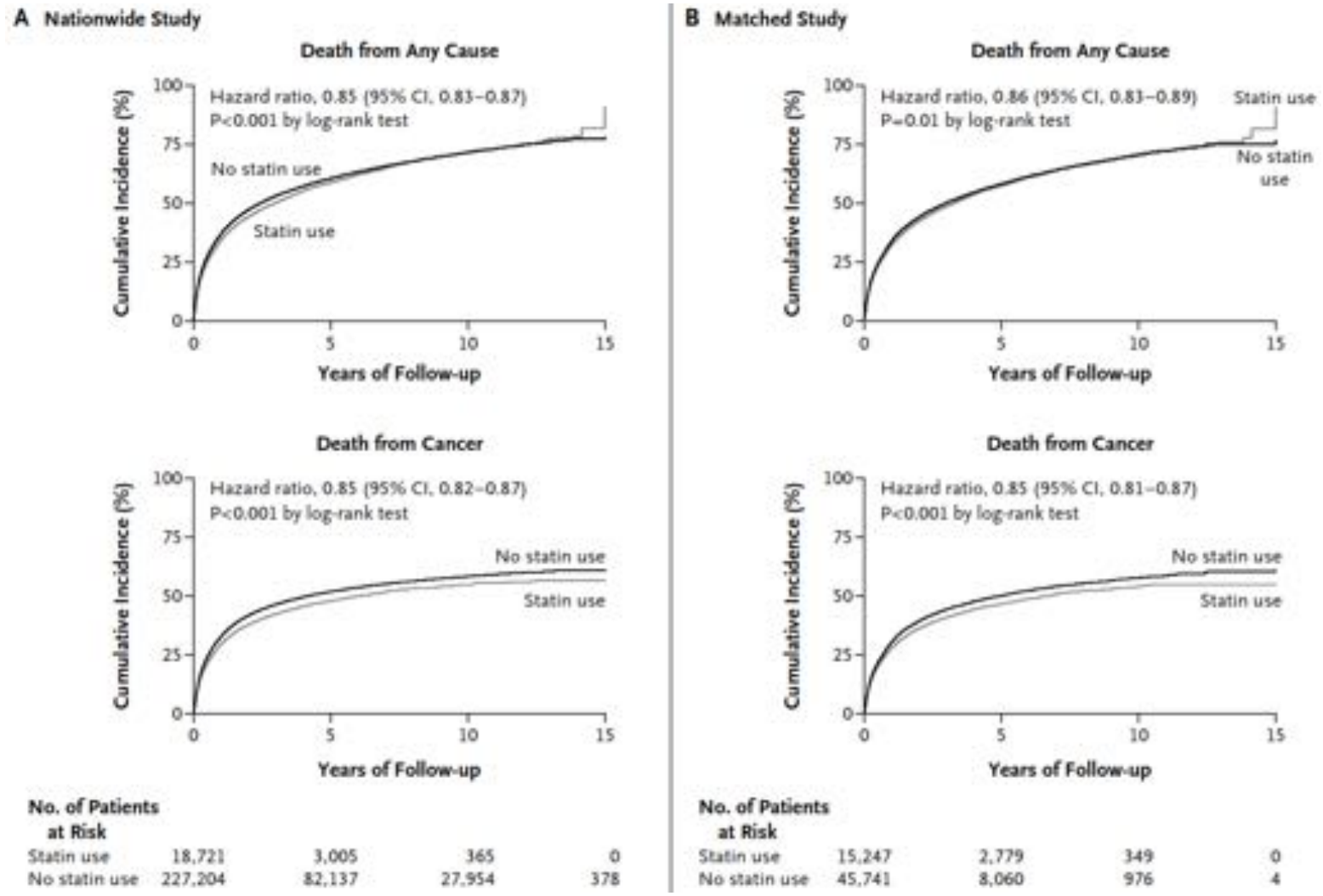
Dormuth CR et al. BMJ 2014

Statines et cancer :
Pas d'augmentation d'incidence ni de mortalité



CTT collaborators Lancet 2012

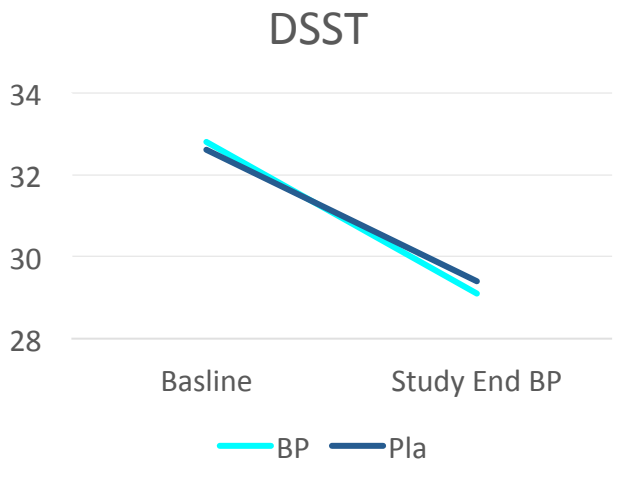
Statines et survie après diagnostic de cancer : Registre Danois

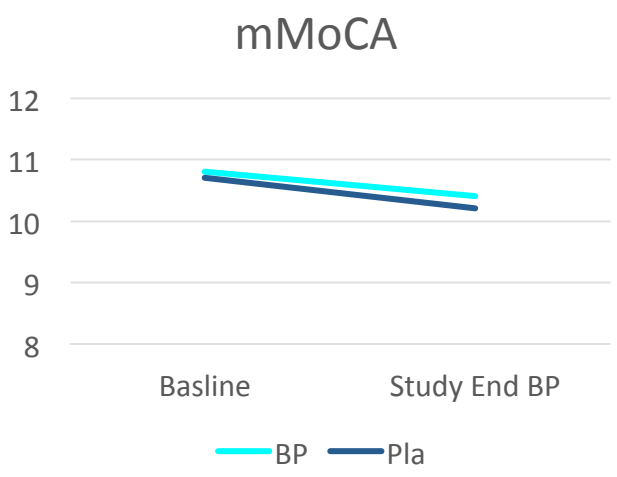


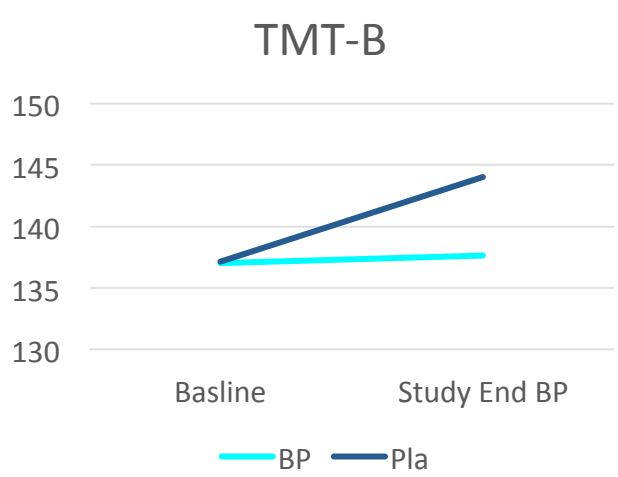
Nielsen et al. NEJM 2012

HOPE 3: Change in Cognitive Outcome substudy

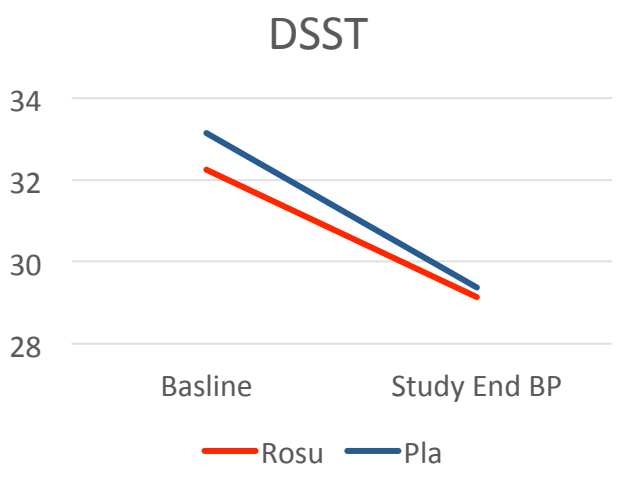
BP Lowering

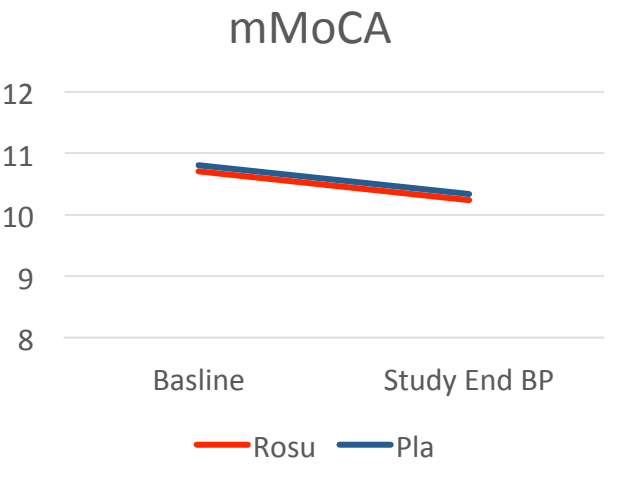


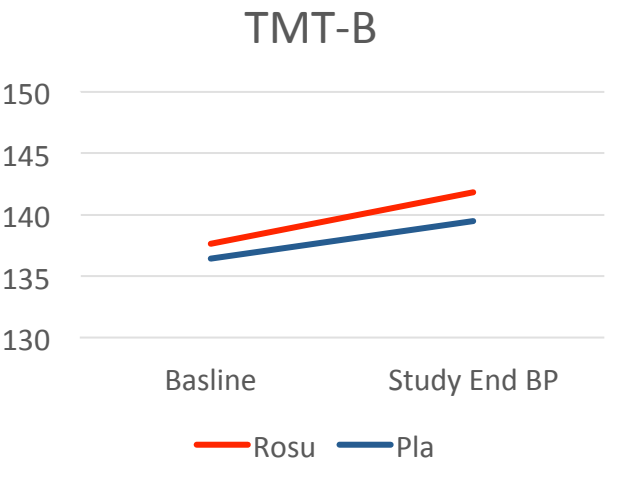




Cholesterol Lowering



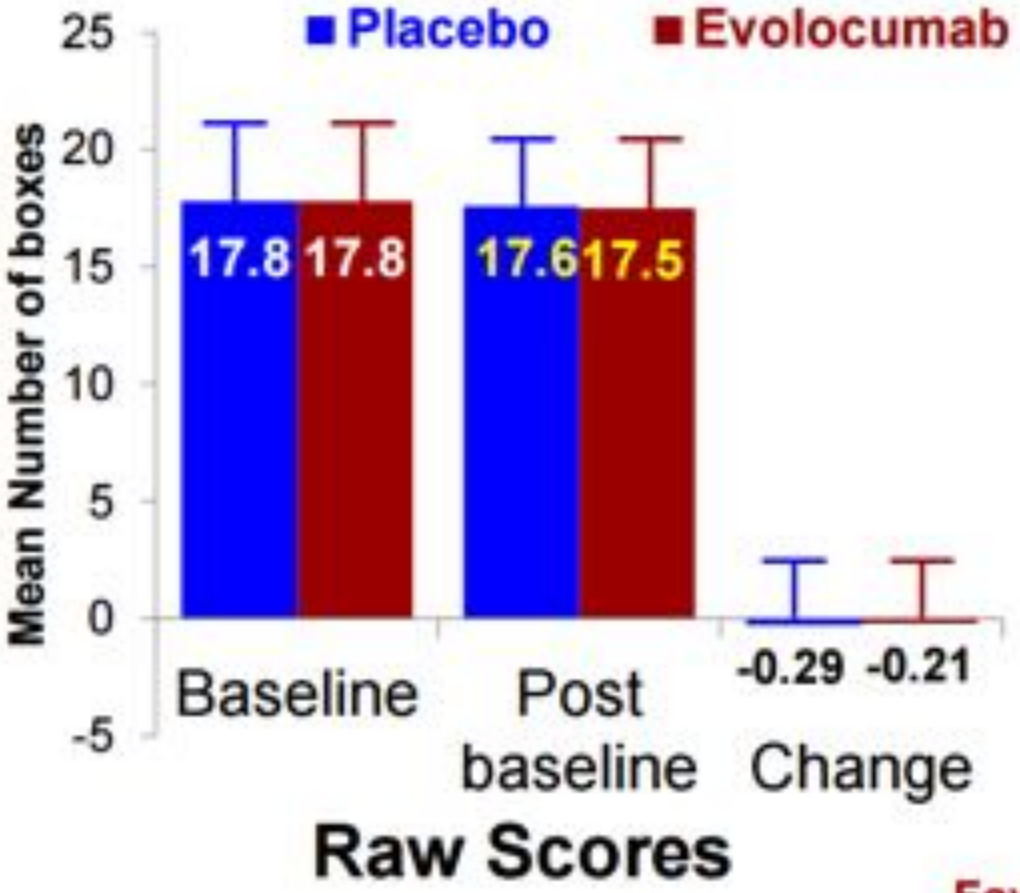




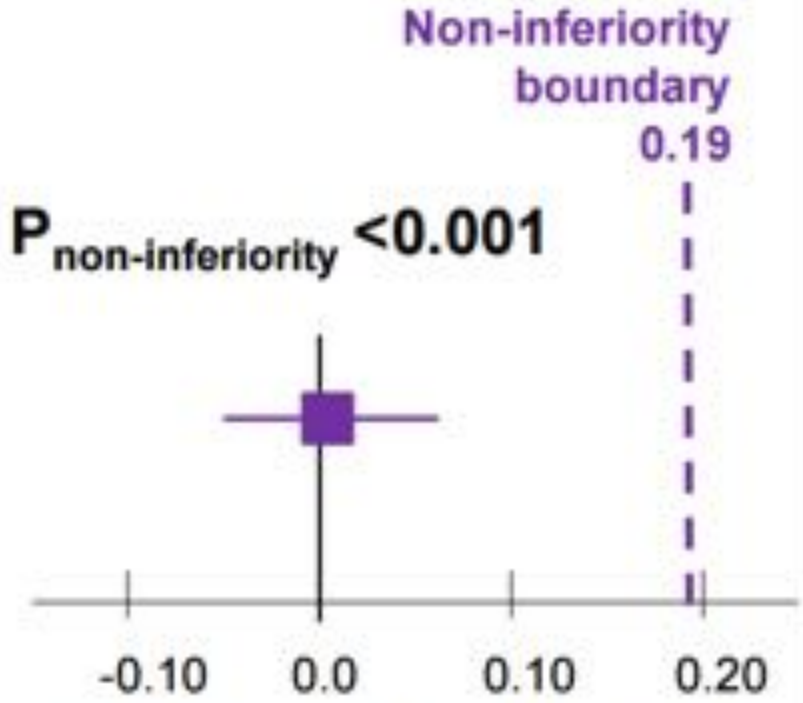
Primary Endpoint

Spatial Working Memory Strategy Index

ebbinghaus



Raw Scores



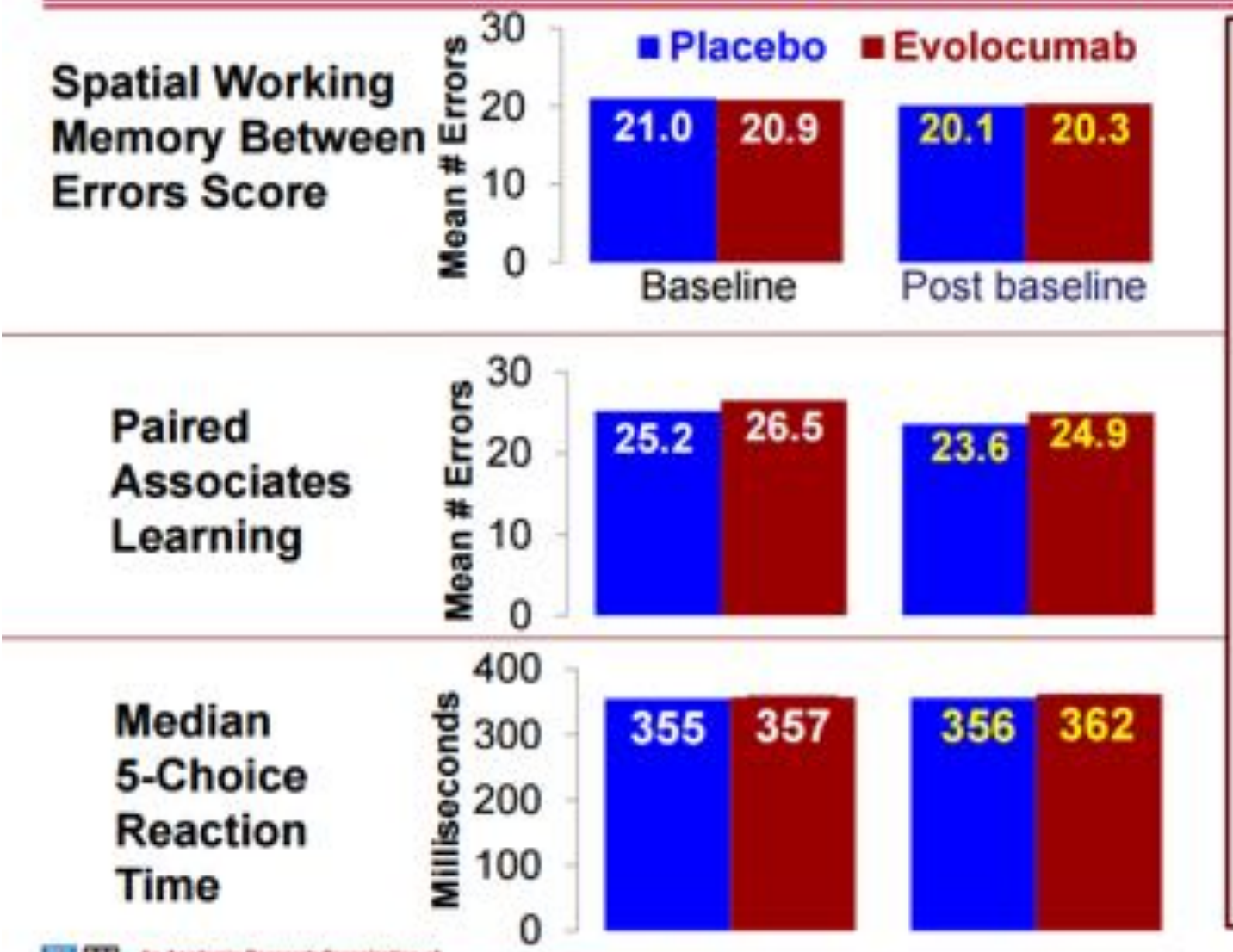
Treatment Difference in Z score (Placebo minus Evolocumab)

Favors Evolocumab **Favors Placebo**

P_{NI} is from fixed estimate

Secondary Endpoint Results

ebbinghaus



	Trt diff of Δ in Z-scores	$P_{superiority}$
Spatial Working Memory Between Errors Score	0.033	**0.36**
Paired Associates Learning	0.023	**0.49**
Median 5-Choice Reaction Time	0.073	**0.06**

Lower raw scores (fewer errors, faster time) are better

Effets secondaires des statines selon la dose

SEARCH	Simvastatine 80 mg (n=6031)	Simvastatine 20 mg (n=6033)
CPK >5 à ≤10 fois normale	77 (1·3%)	31 (0·5%)
CPK >10 à ≤ 40 fois normale	45 (0·7%)	12 (0·2%)
CPK>40 fois normale	23 (0·4%)	0
Myopathie a minima	82 (1·4%)	2 (0·0%)
Myopathie**	53 (0·9%)	2 (0·0%)
TNT	**Atorvastatine 80 mg (n=4995)**	**Atorvastatine 10 mg (n=5006)**
Tout effet secondaire	406 (8.1%)	289 (5.8%)
Arrêt traitement pour effet 2^{ndaire}	7.2%	5.3%
ASAT/ALAT > 3x Normale	60 (1.2%)	9 (0.2)
Méta-analyse JAMA 2011	**Forte dose (n=16408)**	**Dose plus faible (n=16344)**
OR apparition diabète (IC 95%)	1.12 (1.04-1.22)	

SEARCH collaborative group Lancet 2010; LaRosa et al. NEJM 2005; Preiss et al. JAMA 2011

Douleurs musculaires après introduction d'un traitement par statines

32,225 HMO members
1997-2004
Matched on age and year

	Subjects With Diabetes			Subjects Without Diabetes		
Myopathic Event	Statin Initiators (n = 10,247)	No Statin Exposure (n = 10,247)	*P*	Statin Initiators (n = 21,978)	No Statin Exposure (n = 21,978)	*P*
Myalgia[a]						
Proportion experiencing event, %	5.82 (5.36–6.27)	4.70 (4.29–5.11)	<0.001	6.66 (6.33–6.99)	3.29 (3.05–3.52)	<0.001
Prevalence rate/1000 person-years	18.0 (16.4–19.6)	15.8 (14.3–17.4)	0.055	20.0 (18.8–21.3)	10.8 (9.9–11.8)	<0.001
Mild myositis[†]						
Proportion experiencing event, %	1.72 (1.47–1.97)	0.59 (0.44–0.73)	<0.001	1.95 (1.76–2.13)	0.27 (0.20–0.34)	<0.001
Prevalence rate/1000 person-years	4.7 (3.9–5.6)	1.7 (1.3–2.3)	<0.001	4.5 (3.9–5.2)	0.8 (0.6–1.1)	<0.001
Severe myositis[‡]						
Proportion experiencing event, %	0.21 (0.13–0.30)	0.14 (0.07–0.21)	0.182	0.30 (0.23–0.38)	0.07 (0.04–0.11)	<0.001
Prevalence rate/1000 person-years	0.4 (0.2–0.7)	0.3 (0.1–0.5)	0.359	0.8 (0.6–1.1)	0.2 (0.1–0.4)	<0.001
Rhabdomyolysis[§]						
Proportion experiencing event, %	0.13 (0.06–0.20)	0.12 (0.05–0.18)	0.841	0.12 (0.08–0.17)	0.07 (0.03–0.10)	0.064
Prevalence rate/1000 person-years	0.1 (0.1–0.3)	0.2 (0.1–0.5)	0.425	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.999
Any myopathic event						
Proportion experiencing event, %	7.89 (7.35–8.40)	5.54 (5.10–5.99)	<0.001	9.03 (8.65–9.41)	3.69 (3.45–3.94)	<0.001
Prevalence rate/1000 person-years	24.2 (22.4–26.2)	18.9 (17.3–20.7)	<0.001	26.8 (25.4–28.2)	12.6 (11.6–13.7)	<0.001

Adjusted HR = 1.29 (1.15-1.45)

HR = 2.12 (1.92-2.35)

Nichols GA et al. Clin Ther 2007

GAUSS 3 : evolocumab vs ezetimibe chez des patients intolérants aux statines

Résultats de la phase A

Table 2. Patients Experiencing Intolerable Muscle-Related Symptoms During Phase A of GAUSS-3 Trial[a]

Category, No. (%)	Atorvastatin Followed by Placebo (n = 245)[b]	Placebo Followed by Atovastatin (n = 246)	All Randomized Patients (n = 491)[b]
Symptoms with atorvastatin but not placebo	126 (51.4)	83 (33.7)	209 (42.6)
Symptoms with placebo but not atorvastatin	42 (17.1)	88 (35.8)	130 (26.5)
Symptoms with both placebo and atorvastatin	22 (9.0)	26 (10.6)	48 (9.8)
No symptoms with either treatment	47 (19.2)	38 (15.4)	85 (17.3)
Did not start period 2 treatment	8 (3.3)	11 (4.5)	19 (3.9)

Lorsque le traitement est administré en aveugle, 36 % des patients dits "intolérants aux statines" (au moins deux essais de statines avec abandon avant l'étude) ont des symptômes musculaires sous placebo (26 % ont même des symptômes sous placebo, mais pas sous statine …)

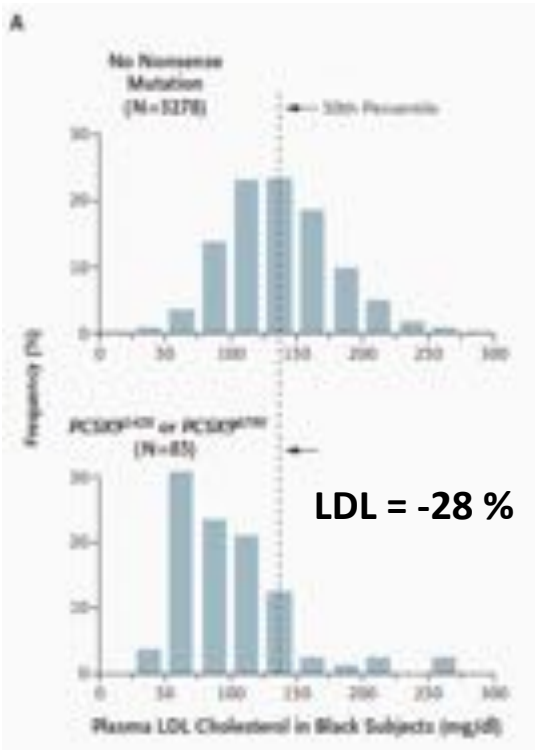
Quand débuter le traitement ?

Cholesterol as plaque substrate

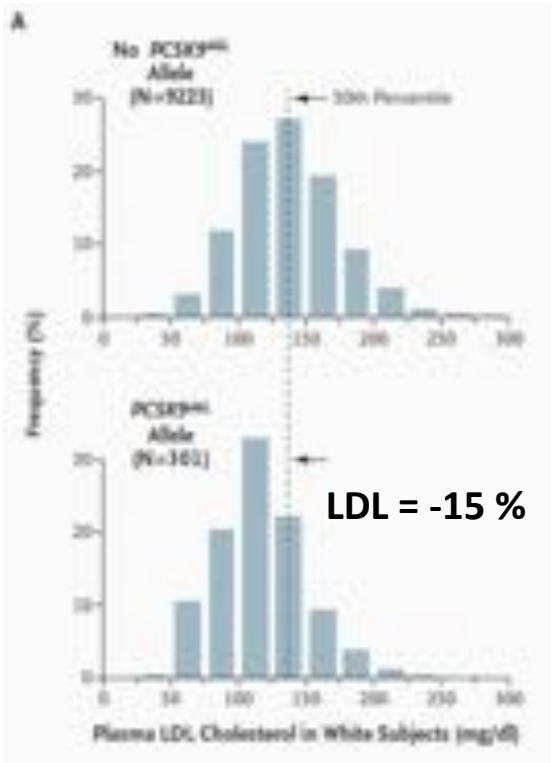
PCSK9 gene mutation: ARIC study

Favorable mutations (nonsense) of the proprotein convertase subtilisine kexine 9 gene are associated with lower LDL-cholesterol levels

Blacks

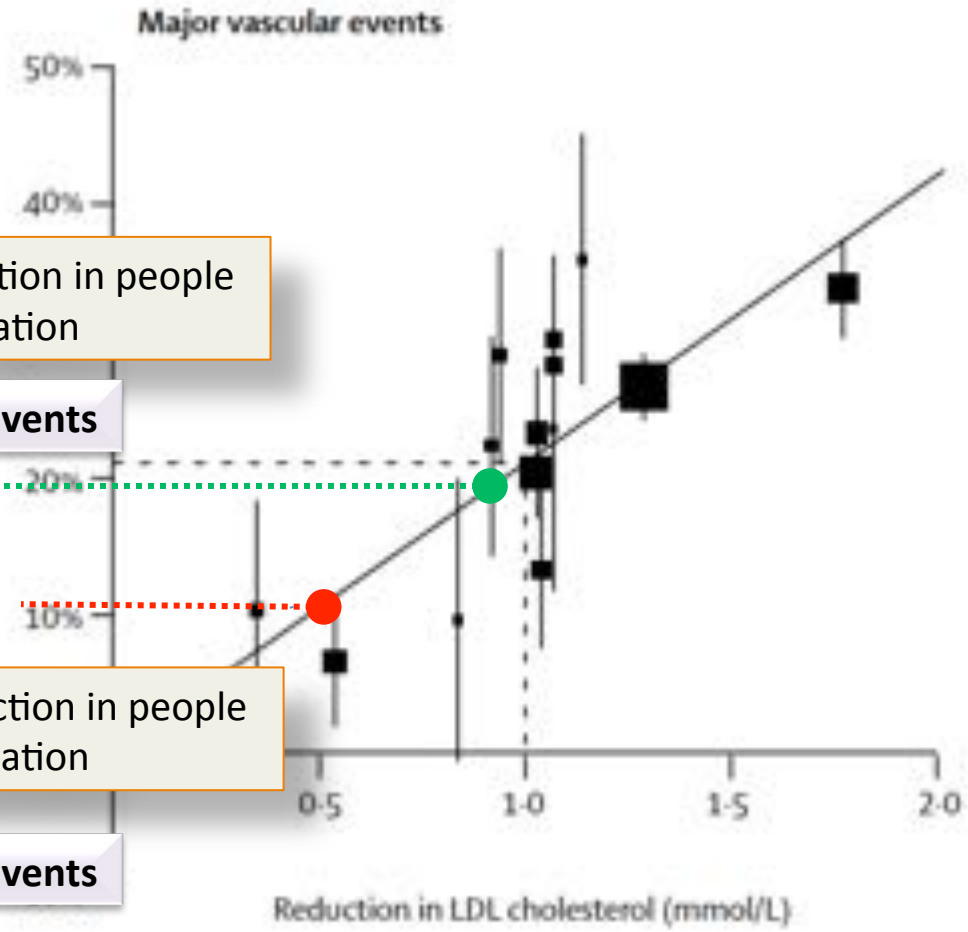


Whites



NEJM 2006

Lowering LDL-c decreases CV events and mortality



Blacks : 38 mg/dl reduction in people with the favorable mutation

88 % reduction of CV events

Black: 138 -> 100 mg/dl

White: 137 -> 116 mg/dl

Blancs : 21 mg/dl reduction in people with the favorable mutation

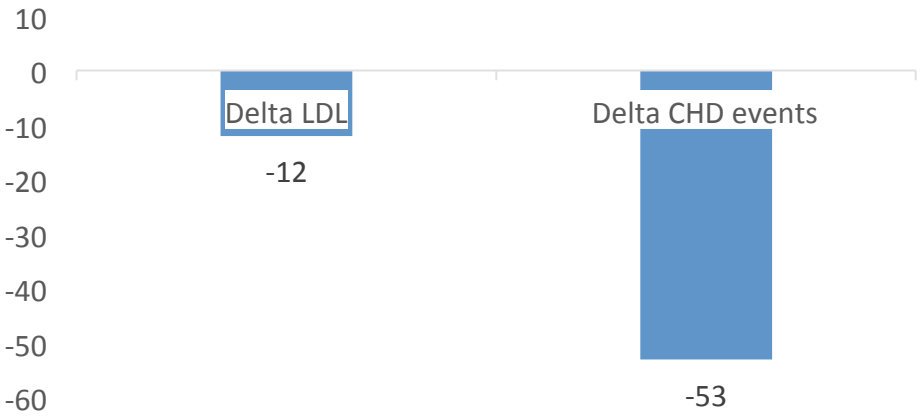
50 % reduction of CV events

CTT collaborators Lancet 2005

Effect of NPCIL1 gene mutations on CHD

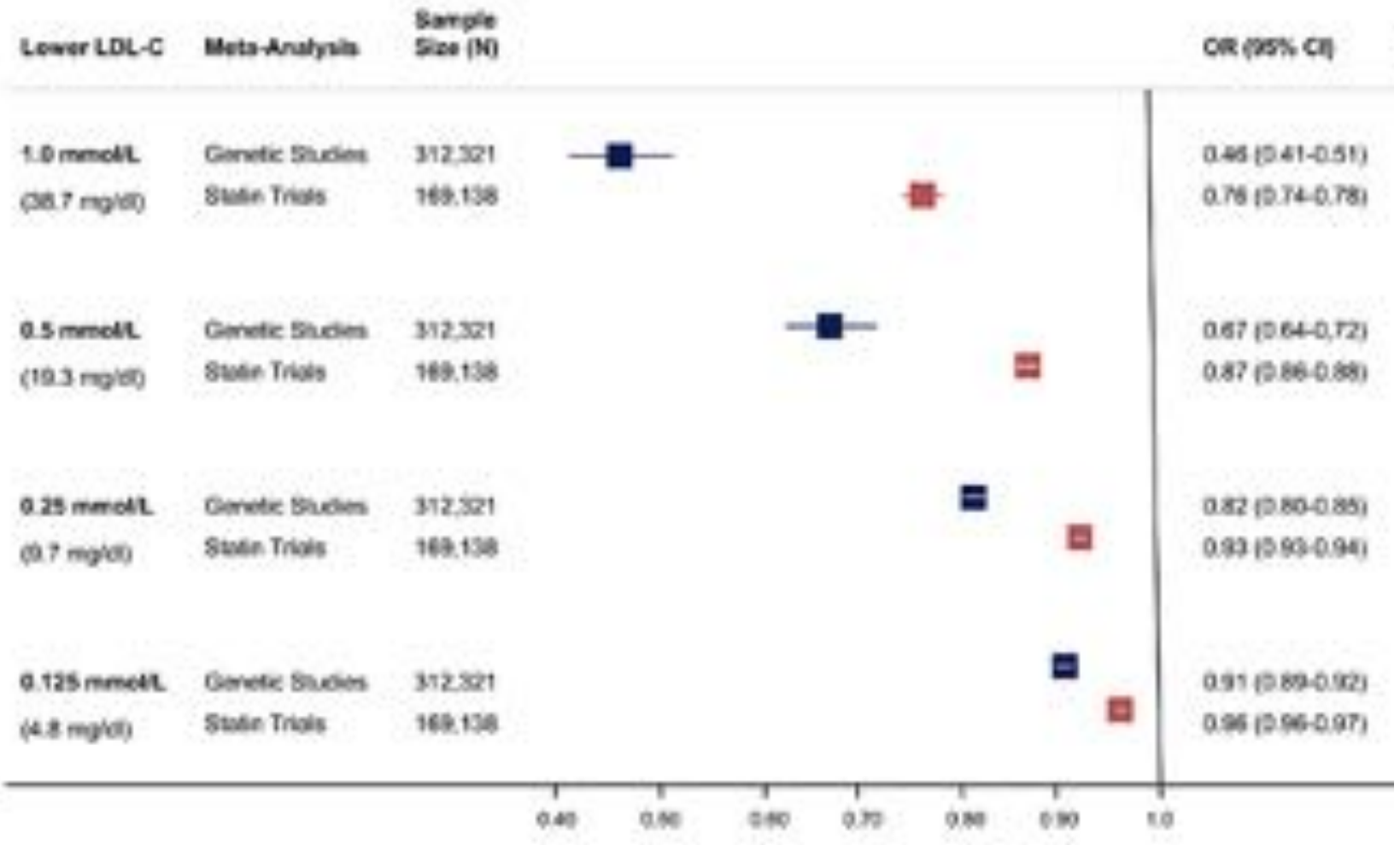
- NPCIL1 is a protein implicated in the transport of cholesterol from the gut lumen into the enterocytes, and is inhibited by ezetimibe
- Case-control and cohort studies in 7364 CHD patients and 14,728 controls

- 15 inactivating mutations:



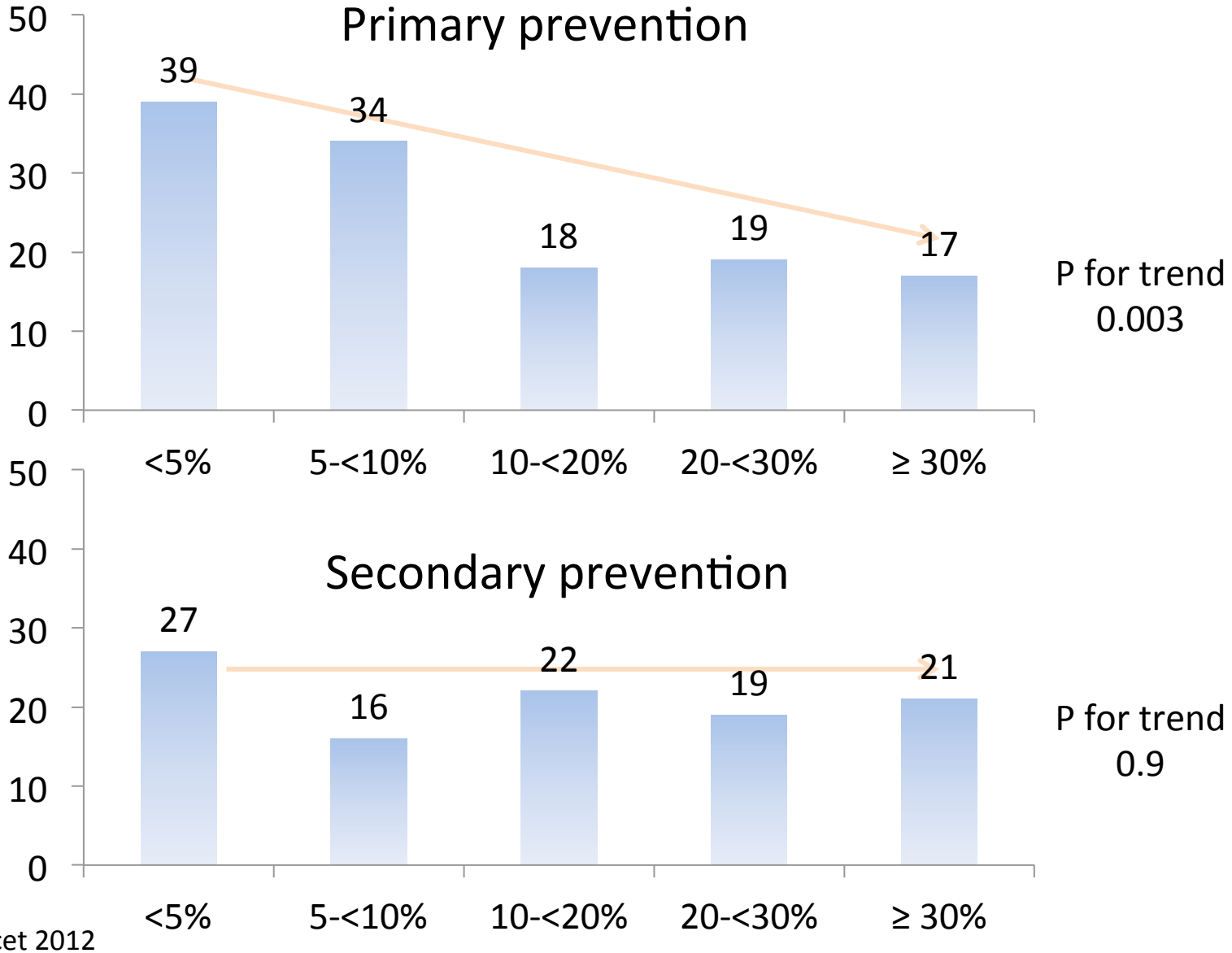
Myocardial infarction genetics consortium. NEJM 2014

Le concept de charge en cholestérol : la maladie met des décennies à se développer, agir tard est moins efficace



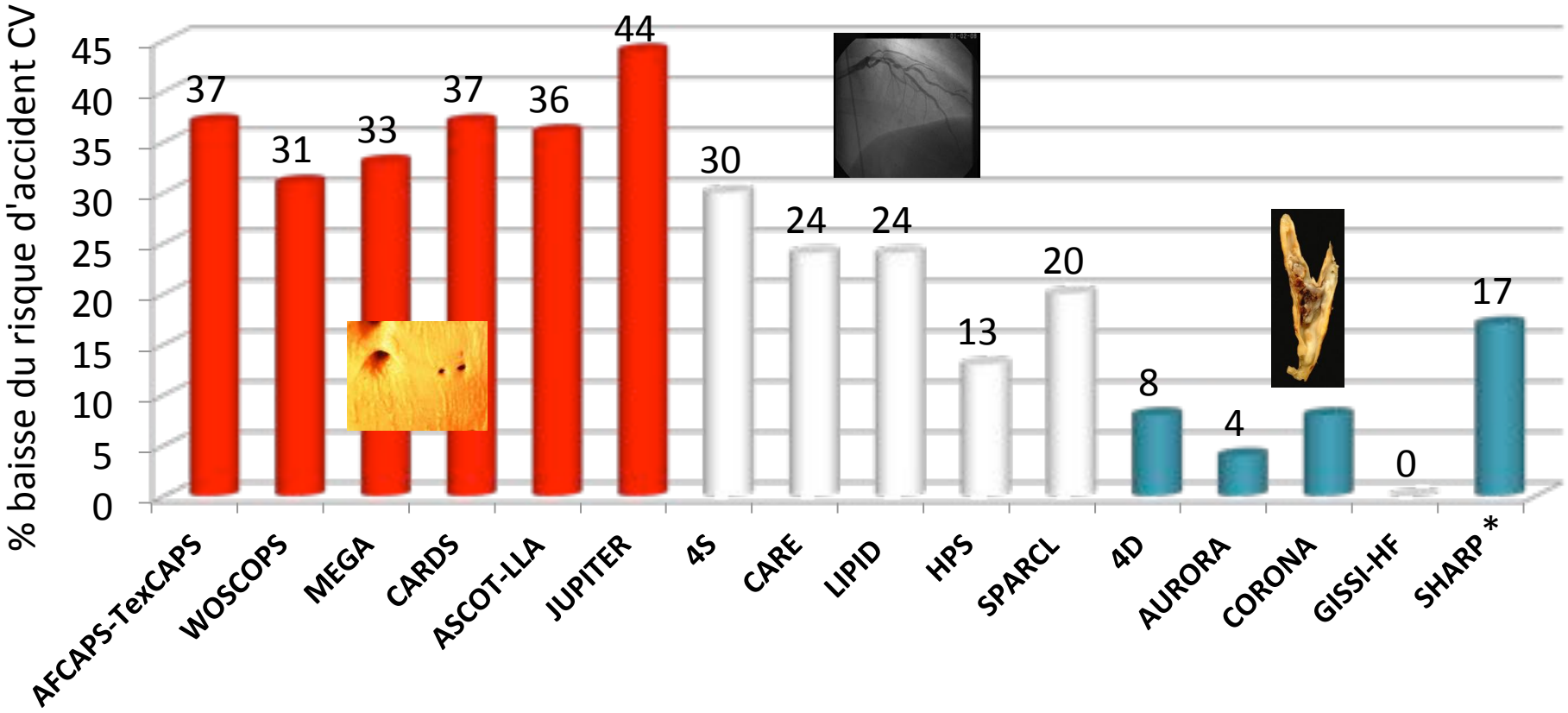
*Ference **JACC** 2012;60:2631-9.*

Relative risk reduction of CV events according to risk level of the trial populations



CTT collaborators Lancet 2012

Réduction de risque avec les statines en fonction du degré initial de maladie athéroscléreuse : le bénéfice relatif est d'autant plus grand que l'intervention commence à un stade précoce



Etudes en prévention primaire

Etudes chez des coronariens stables

Etudes chez des patients avec cardiopathie ou athérosclérose avancée

* simva+ ezetimibe vs PCB

Conclusion

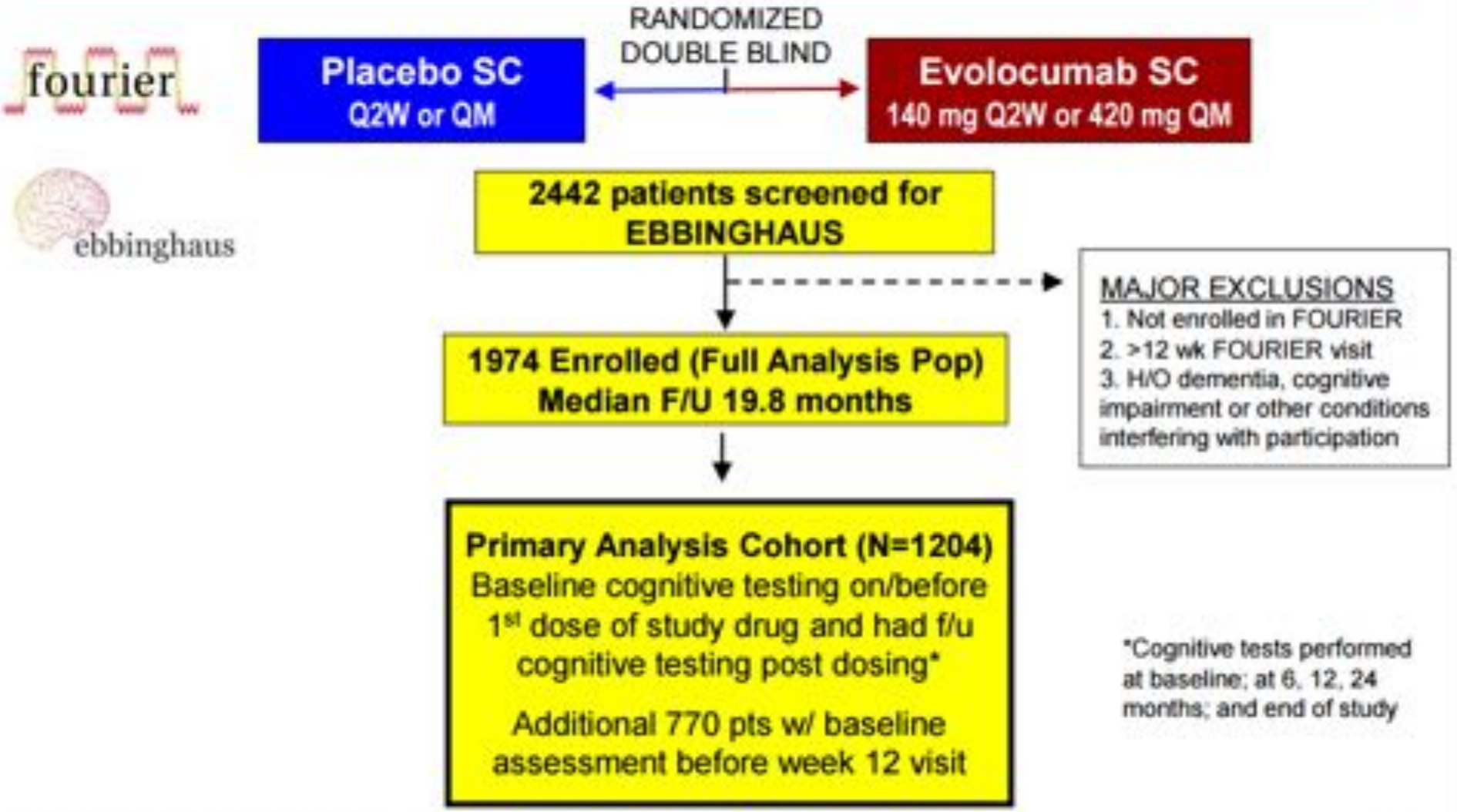
- Avoir un LDL-c plus bas tout au long de sa vie réduit considérablement le risque CV.
- Les statines sont efficaces en prévention primaire : elles réduisent le risque d'événements CV et augmentent l'espérance de vie dans les essais randomisés.
- L'effet protecteur des statines est d'autant plus grand que le traitement est débuté à un stade précoce de la maladie athéromateuse.

Conclusion

- La tolérance des statines à dose faible à modérée est excellente, même si des intolérances musculaires peuvent exister.
- La vraie question sur le traitement par satines est donc plus philosophique que médicale :

Souhaite-t-on, dès un âge jeune, prendre constamment un traitement médicamenteux pour réduire son risque des décennies plus tard et augmenter (statistiquement) son espérance de vie ?

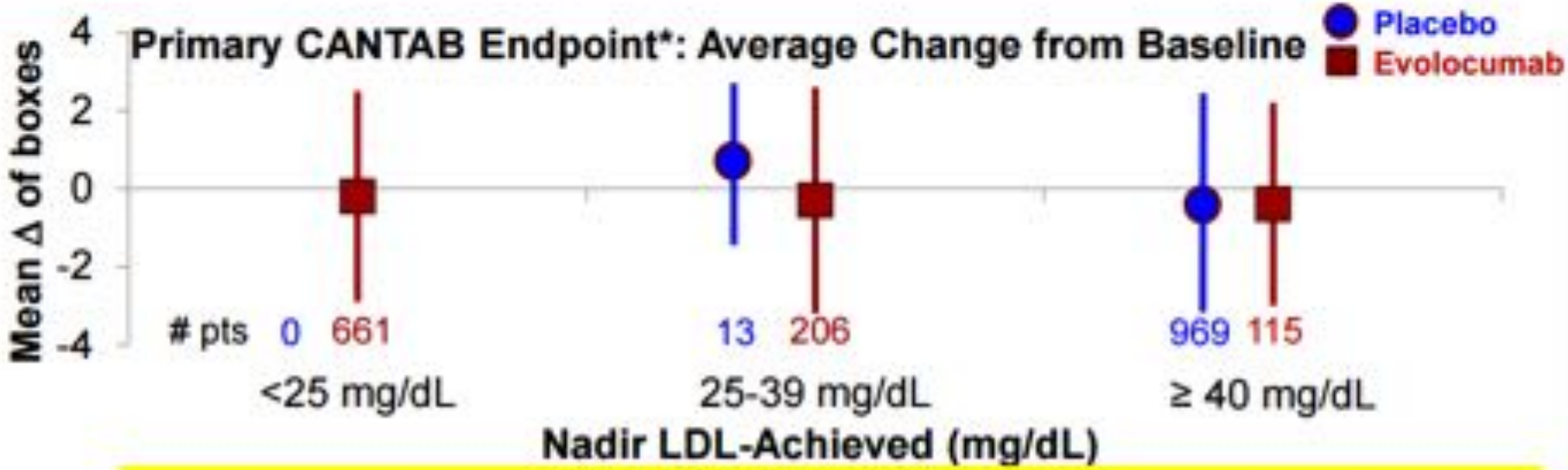
Trial Design



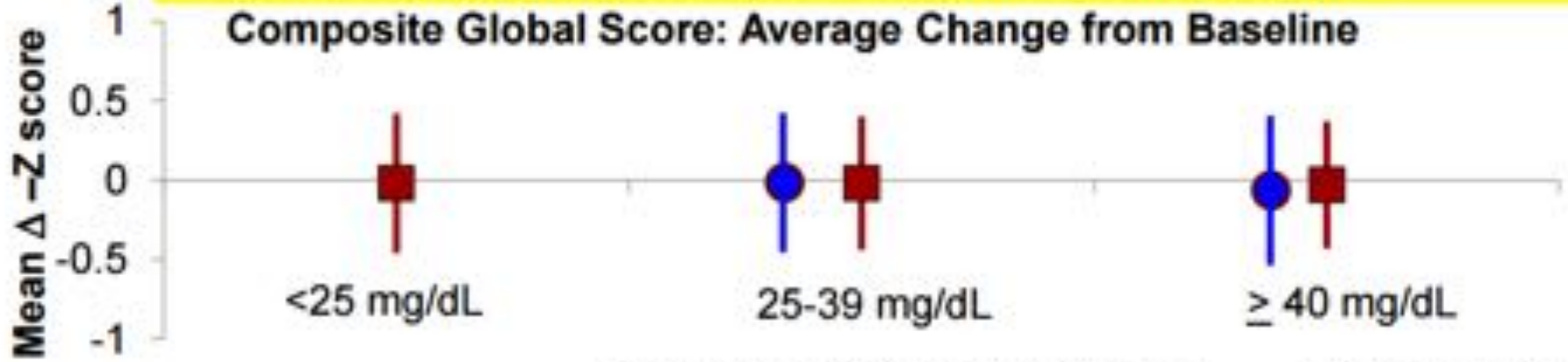
Giugliano RP et al. *Clin Card* 2017;40:59–65

Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)

ebbinghaus



P=NS across LDL values achieved and also between treatments



Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

Patient Self-Report: 23 Questions Regarding Everyday Cognition

ebbinghaus

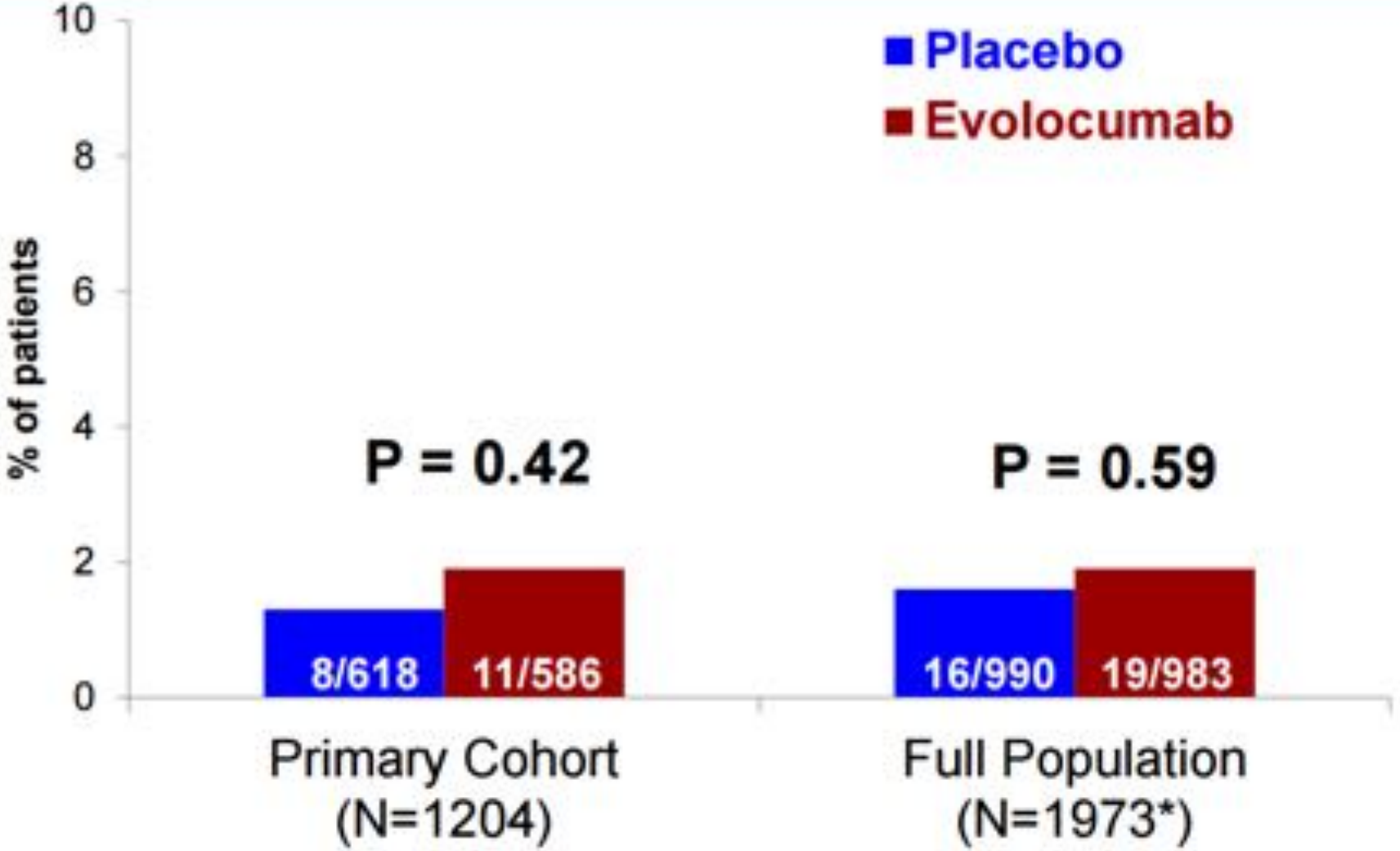
All Patients	Placebo (N=781) Mean (SD)	Evolocumab (N=800) Mean (SD)	P-Value
Memory	1.16 (0.39)	1.17 (0.39)	0.81
Executive functioning total score	1.11 (0.32)	1.12 (0.32)	0.28
Planning	1.08 (0.31)	1.10 (0.32)	0.20
Organization	1.09 (0.32)	1.10 (0.33)	0.57
Divided attention	1.15 (0.42)	1.16 (0.41)	0.54
Total Score	**1.13 (0.33)**	**1.14 (0.33)**	**0.42**

Patient self-report at end of study as compared to randomization, graded as

1. *Better or no change*
2. *Questionable / occasionally worse*
3. *Consistently a little worse*
4. *Consistently much worse*

Lower scores represent better cognition

Investigator Reported Cognitive Adverse Events



Data shown are % of patients with at least 1 event

*1 patient who did not take study drug is excluded from the evolocumab group

Conclusion

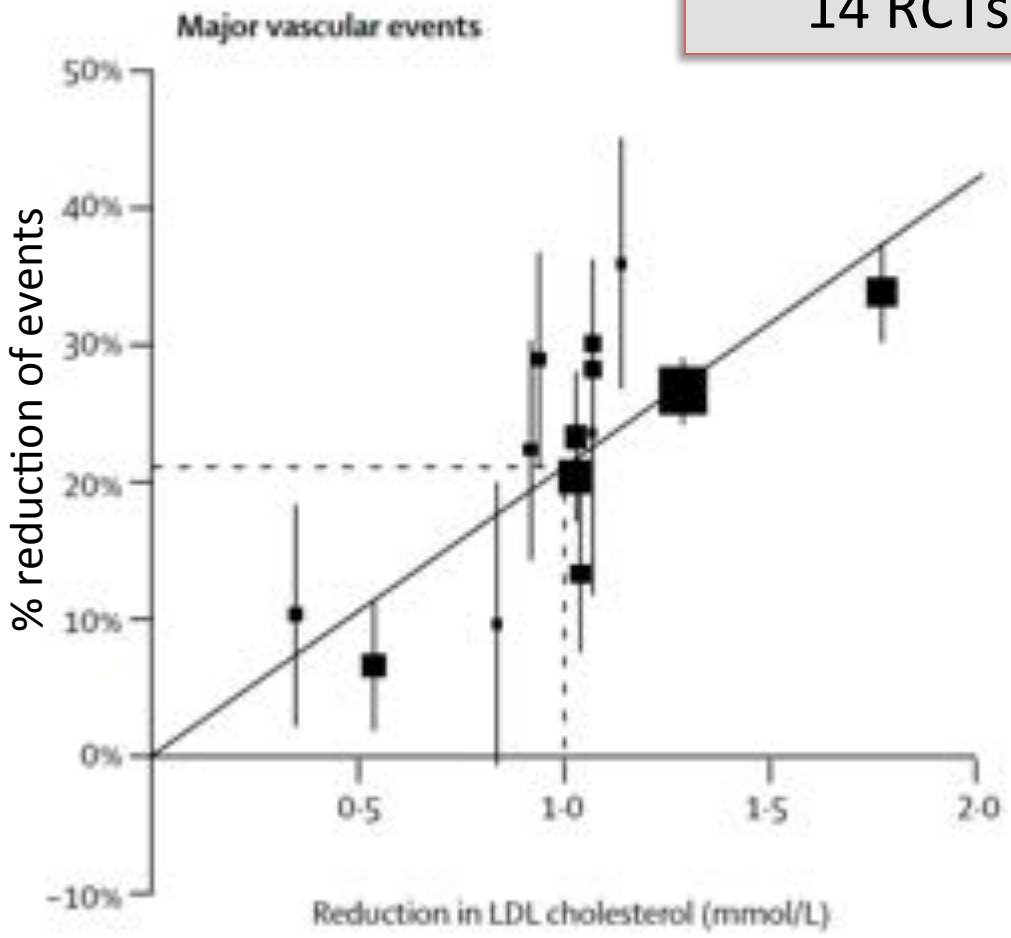
- FOURIER confirme, s'il était besoin, la relation entre LDL-c et maladie athéromateuse.

- Une réduction de 20 % des événements ischémiques graves est observée sous traitement.

- Malgré cela, aucune réduction de mortalité n'est constatée…

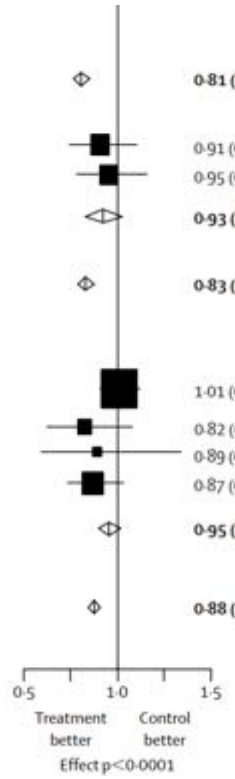
La baisse du LDL réduit les événements CV et la mortalité

90 056 patients
14 RCTs



Mortality

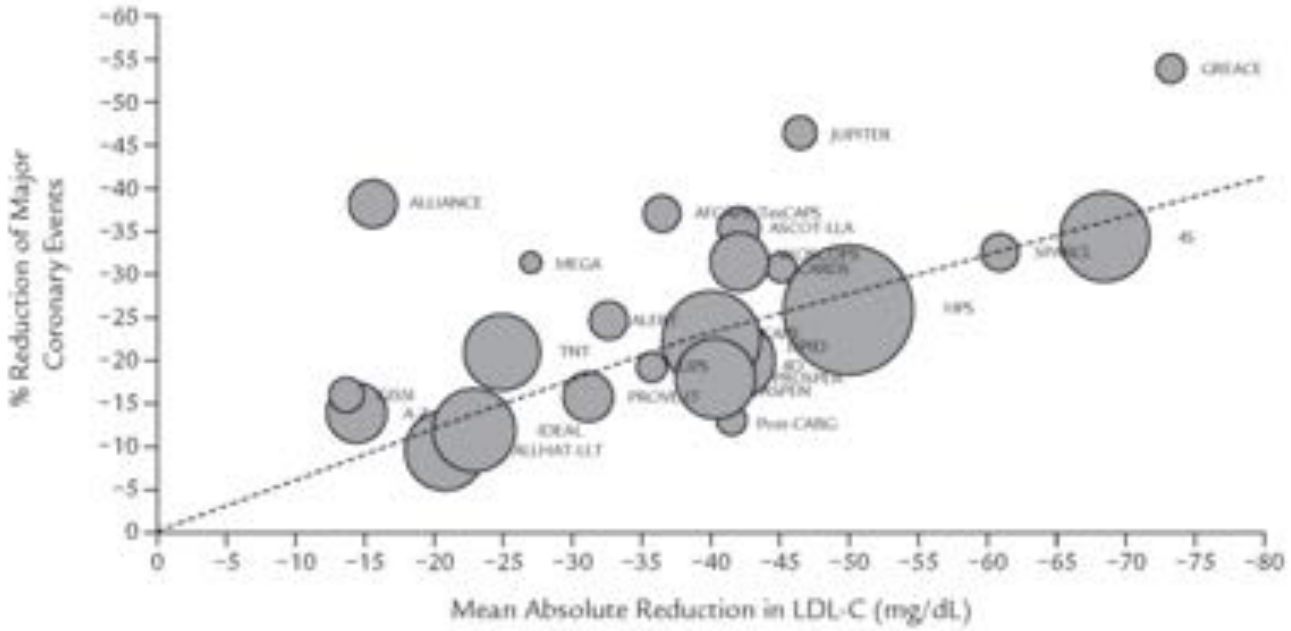
Vascular causes:			
CHD	**1548 (3·4%)**	**1960 (4·4%)**	**0·81 (0·76 –0·85)**
Stroke	265 (0·6%)	291 (0·6%)	0·91 (0·74 –1·11)
Other vascular	289 (0·6%)	302 (0·7%)	0·95 (0·78 –1·16)
Any non-CHD vascular	**554 (1·2%)**	**593 (1·3%)**	**0·93 (0·83 –1·03)**
Any vascular	**2102 (4·7%)**	**2553 (5·7%)**	**0·83 (0·79 –0·87)**
Non-vascular causes:			
Cancer	1094 (2·4%)	1069 (2·4%)	1·01 (0·91 –1·12)
Respiratory	98 (0·2%)	125 (0·3%)	0·82 (0·62 –1·08)
Trauma	51 (0·1%)	57 (0·1%)	0·89 (0·59 –1·34)
Other/unknown	487 (1·1%)	550 (1·2%)	0·87 (0·73 –1·03)
Any non-vascular	**1730 (3·8%)**	**1801 (4·0%)**	**0·95 (0·90 –1·01)**
Any death	**3832 (8·5%)**	**4354 (9·7%)**	**0·88 (0·84 –0·91)**



CTT collaborators Lancet 2005

Réduction du LDL et pronostic
Données récentes

Méta-analyse 2009
155,613 sujets



Delahoy PJ et al. Clin Therap 2009

Réduction du LDL et pronostic
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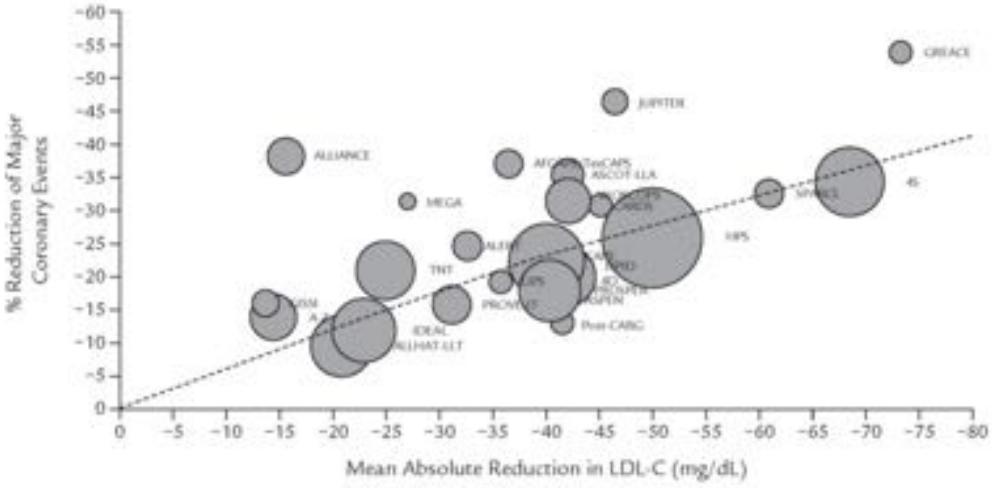
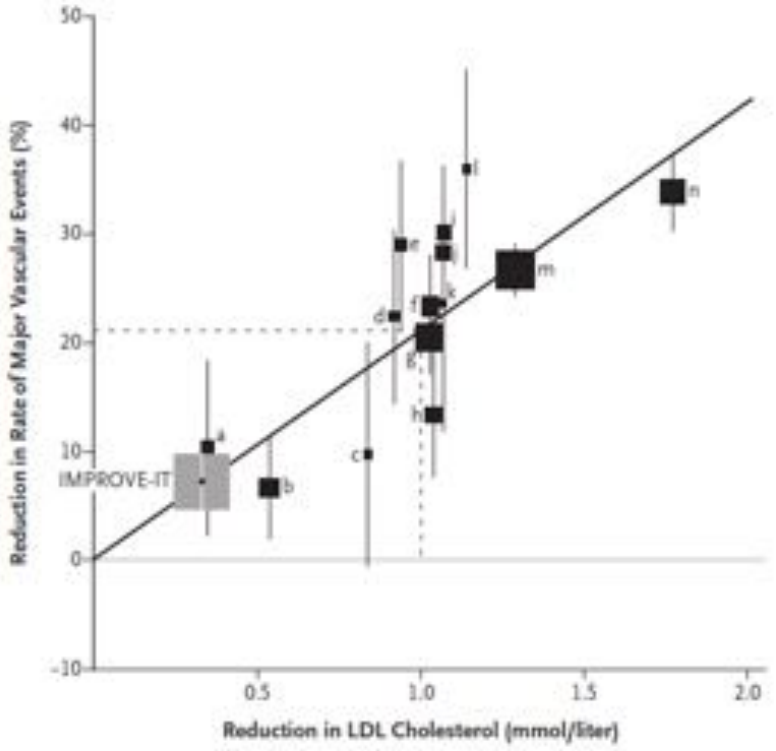
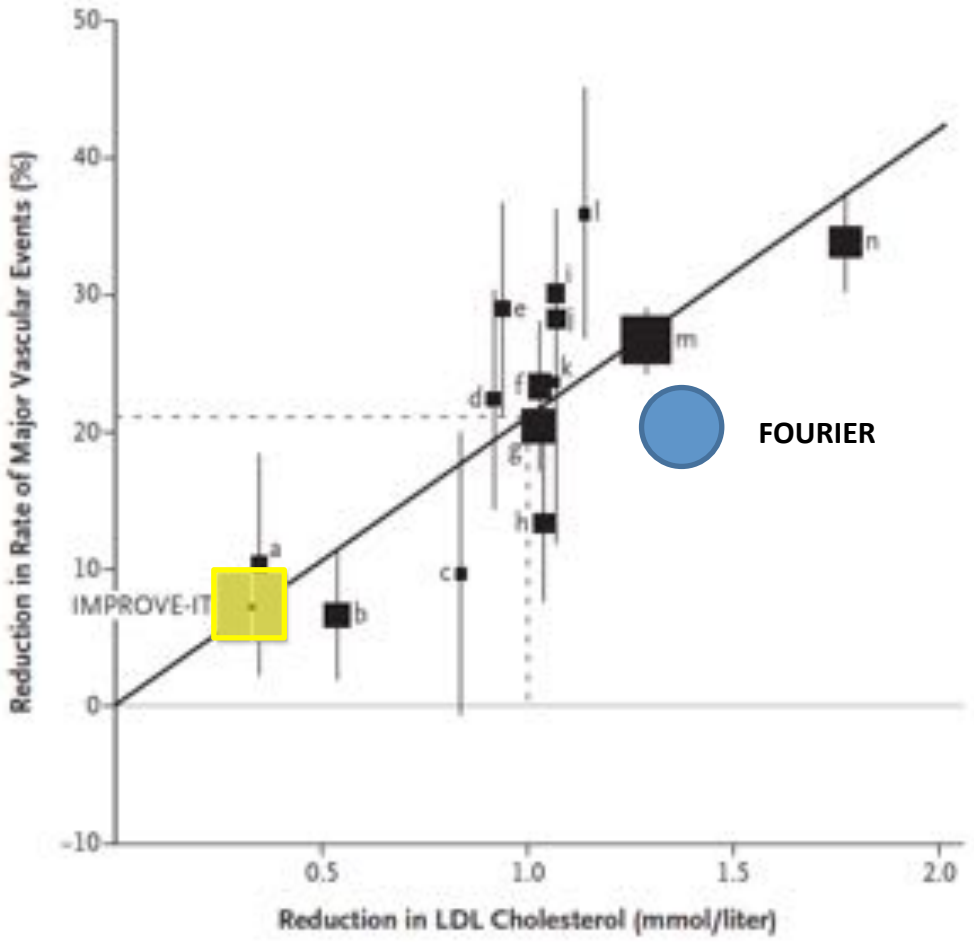


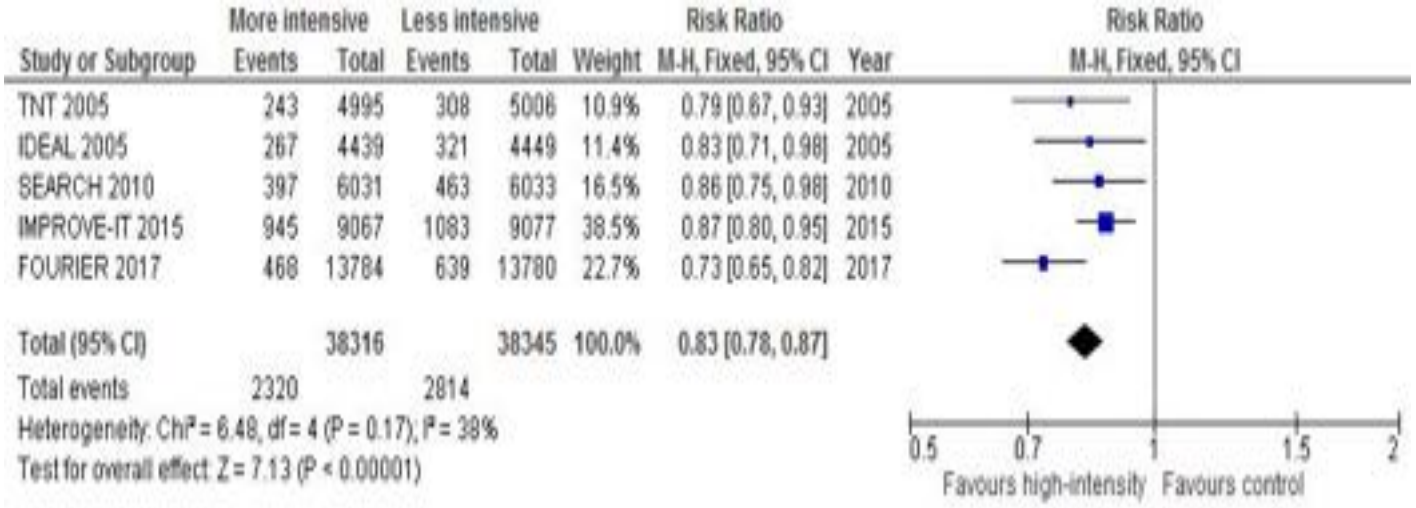


Delahoy PJ et al. Clin Therap 2009; Cannon CP et al. NEJM 2015

Relative reduction in major vascular events by LDL-c reduction



Infarctus et AVC dans les essais traitement intense vs standard (maladie stable)

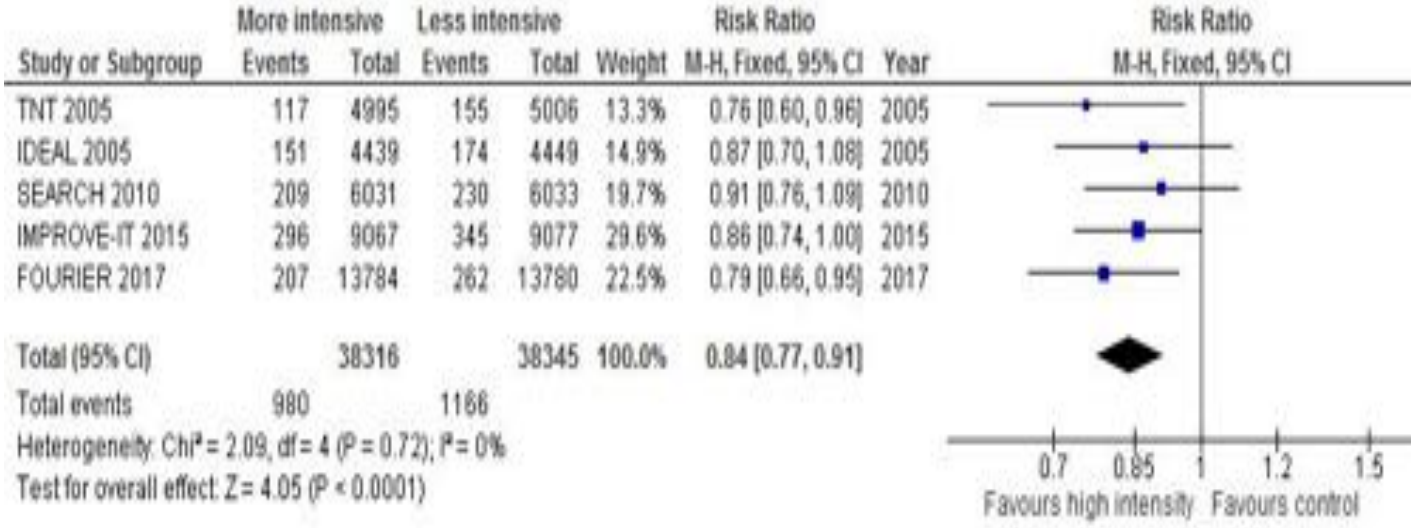


Study or Subgroup	More intensive Events	Total	Less intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
TNT 2005	243	4995	308	5006	10.9%	0.79 [0.67, 0.93]	2005
IDEAL 2005	267	4439	321	4449	11.4%	0.83 [0.71, 0.98]	2005
SEARCH 2010	397	6031	463	6033	16.5%	0.86 [0.75, 0.98]	2010
IMPROVE-IT 2015	945	9067	1083	9077	38.5%	0.87 [0.80, 0.95]	2015
FOURIER 2017	468	13784	639	13780	22.7%	0.73 [0.65, 0.82]	2017
Total (95% CI)		38316		38345	100.0%	0.83 [0.78, 0.87]	
Total events	2320		2814				

Heterogeneity: Chi² = 6.48, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 7.13 (P < 0.00001)

Risk Ratio M-H, Fixed, 95% CI
0.5 0.7 1 1.5 2
Favours high-intensity Favours control

AMI



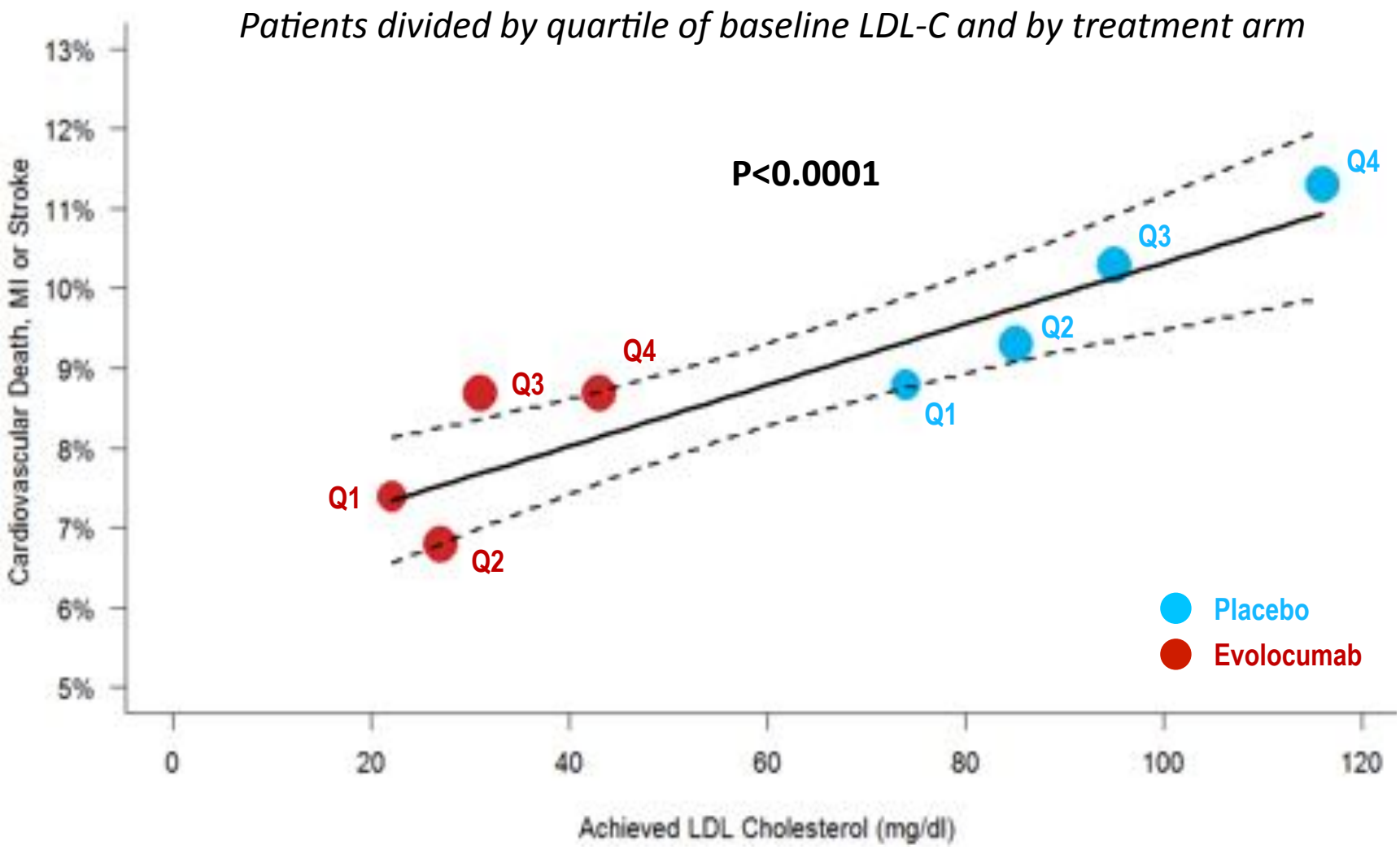
Study or Subgroup	More intensive Events	Total	Less intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
TNT 2005	117	4995	155	5006	13.3%	0.76 [0.60, 0.96]	2005
IDEAL 2005	151	4439	174	4449	14.9%	0.87 [0.70, 1.08]	2005
SEARCH 2010	209	6031	230	6033	19.7%	0.91 [0.76, 1.09]	2010
IMPROVE-IT 2015	296	9067	345	9077	29.6%	0.86 [0.74, 1.00]	2015
FOURIER 2017	207	13784	262	13780	22.5%	0.79 [0.66, 0.95]	2017
Total (95% CI)		38316		38345	100.0%	0.84 [0.77, 0.91]	
Total events	980		1166				

Heterogeneity: Chi² = 2.09, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.05 (P < 0.0001)

Risk Ratio M-H, Fixed, 95% CI
0.7 0.85 1 1.2 1.5
Favours high intensity Favours control

Stroke

Lower LDL-C Is Better



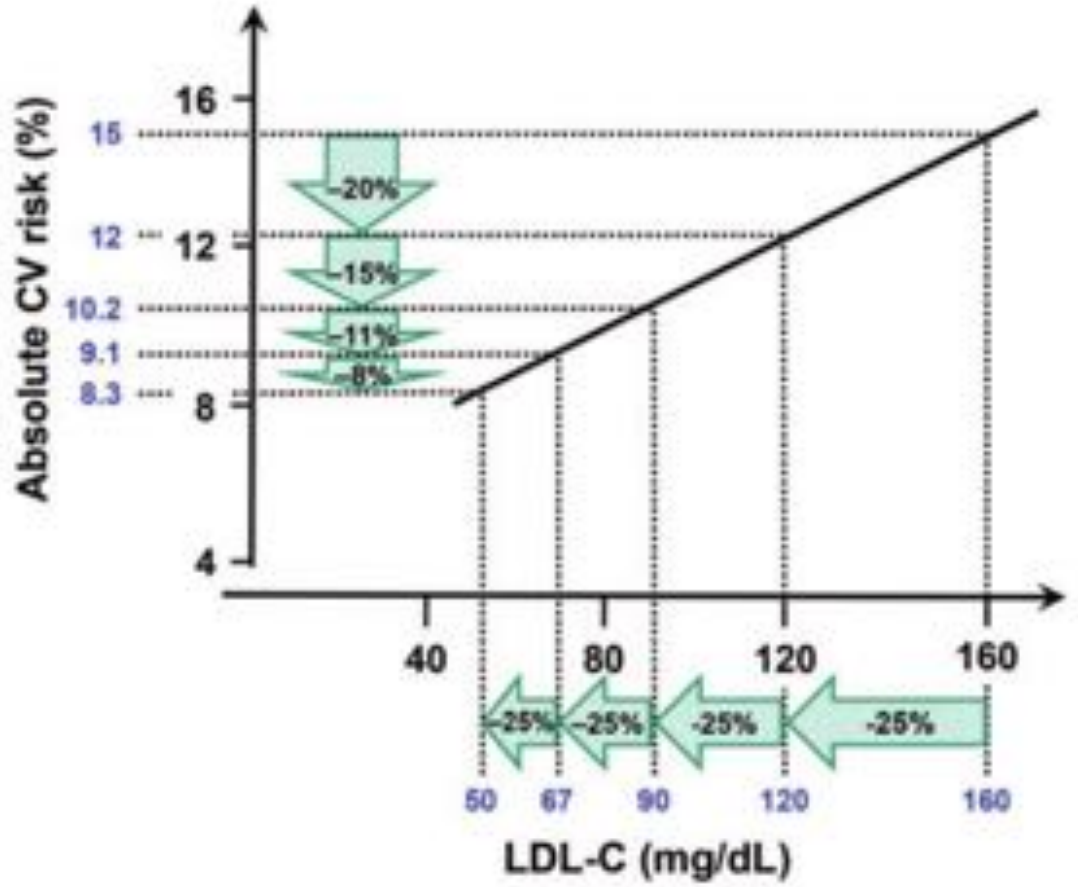
Meta-analysis of statin trials by achieved LDL-c concentration

TABLE 1 Risk for Major Cardiovascular Events, by Achieved LDL-C Concentration

	Achieved On-Trial LDL-C Concentration, mg/dl (mmol/l)						
	<50 (<1.29) (n = 4,375)	50–<75 (1.29–<1.94) (n = 10,395)	75–<100 (1.94–<2.58) (n = 10,091)	100–<125 (2.58–<3.23) (n = 8,953)	125–<150 (3.23–<3.88) (n = 3,128)	150–<175 (3.88–<4.52) (n = 836)	≥175 (≥4.52) (n = 375)
Major cardiovascular events	194 (4.4)	1,185 (11.4)	1,664 (16.5)	1,480 (16.5)	557 (17.8)	184 (22.0)	123 (32.8)
Unadjusted HR (95% CI)	0.20 (0.16–0.25)	0.40 (0.33–0.48)	0.50 (0.42–0.60)	0.48 (0.40–0.58)	0.51 (0.42–0.62)	0.64 (0.51–0.81)	1.00 (ref)
Adjusted HR (95% CI)*	0.44 (0.35–0.55)	0.51 (0.42–0.62)	0.56 (0.46–0.67)	0.58 (0.48–0.69)	0.64 (0.53–0.79)	0.71 (0.56–0.89)	1.00 (ref)
Major coronary events	129 (2.9)	918 (8.8)	1,431 (14.2)	1,336 (14.9)	492 (15.7)	170 (20.3)	107 (28.5)
Unadjusted HR (95% CI)	0.15 (0.12–0.20)	0.36 (0.29–0.43)	0.50 (0.41–0.61)	0.51 (0.42–0.62)	0.53 (0.43–0.65)	0.69 (0.54–0.88)	1.00 (ref)
Adjusted HR (95% CI)*	0.47 (0.36–0.61)	0.53 (0.43–0.65)	0.58 (0.48–0.71)	0.62 (0.51–0.75)	0.67 (0.55–0.83)	0.78 (0.61–0.99)	1.00 (ref)
Major cerebrovascular events	72 (1.6)	315 (3.0)	302 (3.0)	205 (2.3)	91 (2.9)	21 (2.5)	23 (6.1)
Unadjusted HR (95% CI)	0.47 (0.29–0.74)	0.62 (0.41–0.95)	0.52 (0.34–0.79)	0.38 (0.25–0.58)	0.47 (0.30–0.75)	0.41 (0.23–0.74)	1.00 (ref)
Adjusted HR (95% CI)*	0.36 (0.22–0.59)	0.46 (0.30–0.71)	0.49 (0.32–0.75)	0.45 (0.29–0.69)	0.58 (0.36–0.91)	0.43 (0.24–0.78)	1.00 (ref)

Boekholdt SM, et al. JACC 2014

Absolute CV risk reduction by LDL-c reduction



Laufs et al. EHJ 2014

Mortalité et LDL-c

ARIC:
PCSK9 mutations in the general population

Table 1. Nonsense Mutations in *PCSK9* and Cardiovascular Risk Factors among 3363 Black Participants in the Study.*

Variable	Noncarriers	Carriers			P Value†
		$PCSK9^{G31X}$	$PCSK9^{Y77X}$	$PCSK9^{G31X}$ or $PCSK9^{Y77X}$	
Mutation status — no. of subjects (%)	3278 (97.4)	26 (0.8)	60 (1.8)	85 (2.6)‡	
Age — yr§	53±6	54±6	53±6	54±6	0.61
Male sex — %	37	42	27	31	0.22
Body-mass index	29.6±6.1	28.7±4.4	29.7±5.5	29.5±5.2	0.88
Total cholesterol — mg/dl	215±44	177±44	172±45	173±44	<0.001
Triglycerides — mg/dl	113±81	97±38	94±39	94±38	0.04
LDL cholesterol — mg/dl	138±42	103±39	100±45	100±43	<0.001
HDL cholesterol — mg/dl	55±17	55±14	54±17	55±16	0.72
Hypertension — %¶	55	42	36	37	0.001
Diabetes — %‖	18	12	13	13	0.26
Smoking — %**	30	38	23	27	0.62
Carotid-artery intima–media thickness — mm	0.73±0.16	0.72±0.17	0.69±0.11	0.70±0.13	0.04
Coronary heart disease — no. of subjects	319	0	1	1	0.008
Stroke — no. of subjects (%)	217 (6.6)	3 (11.5)	3 (5.0)	6 (7.1)	0.87
Death — no. of subjects (%)	580 (17.7)	4 (15.4)	8 (13.3)	12 (14.1)	0.39

CSK9 and Cardiovascular Risk Factors among 9524 White Subjects in the Study.*

	Noncarriers	Carriers of $PCSK9^{***}$	P Value†
	9223 (96.8)	301 (3.2)	
	54±6	54±6	0.56
	45	46	0.84
	26.9±4.9	26.8±4.5	0.51
	214±40	194±37	<0.001
	133±87	135±89	0.79
	137±37	116±33	<0.001
	51±17	52±17	0.64
	25.0	24.6	0.87
	8.0	7.3	0.68
	24.6	25.2	0.80
— mm	0.73±0.18	0.71±0.16	0.005
cts	1089	19	0.003
	267 (2.9)	9 (3.0)	0.92
	988 (10.7)	25 (8.3)	0.18

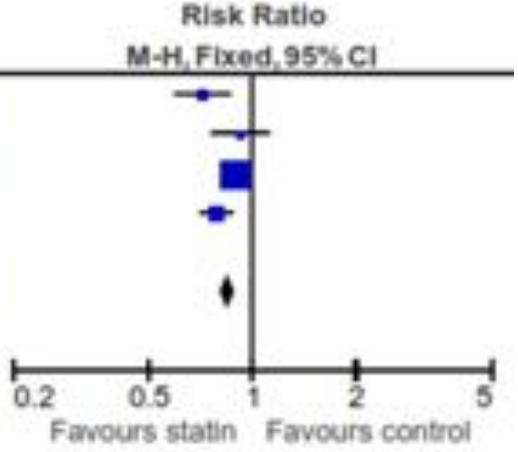
Mortalité dans les essais statines en prévention secondaire

1.1 All-cause death

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4S	182	2221	256	2223	9.9%	0.71 [0.59, 0.85]
CARE	180	2081	196	2078	7.6%	0.92 [0.76, 1.11]
HPS	1328	10269	1507	10267	58.1%	0.88 [0.82, 0.94]
LIPID	498	4512	633	4502	24.4%	0.78 [0.70, 0.88]
Total (95% CI)		**19083**		**19070**	**100.0%**	**0.84 [0.80, 0.89]**
Total events	2188		2592			

Heterogeneity: $Chi^2 = 7.32$, $df = 3$ ($P = 0.06$); $I^2 = 59\%$

Test for overall effect: $Z = 6.27$ ($P < 0.00001$)



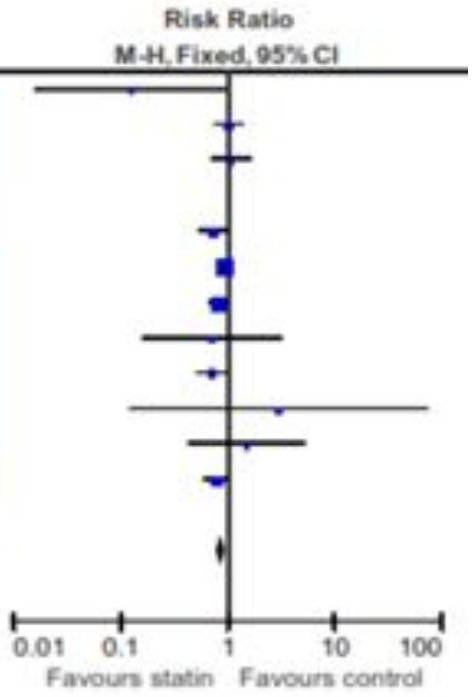
Mortalité dans les essais statines en prévention primaire

1.1 All-cause death

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACAPS	1	460	8	459	0.8%	0.12 [0.02, 0.99]
AFCAPS/TEXCAPS	80	3304	77	3301	7.4%	1.04 [0.76, 1.41]
ASPEN	44	959	41	946	4.0%	1.06 [0.70, 1.60]
Bone	0	239	0	119		Not estimable
CARDS	61	1428	82	1410	8.0%	0.73 [0.53, 1.01]
HOPE 3	334	6361	357	6344	34.5%	0.93 [0.81, 1.08]
JUPITER	198	8901	247	8901	23.9%	0.80 [0.67, 0.96]
KAPS	3	224	4	212	0.4%	0.71 [0.16, 3.13]
MEGA	55	3866	79	3966	7.5%	0.71 [0.51, 1.00]
PHYLLIS	1	254	0	254	0.0%	3.00 [0.12, 73.30]
PREVEND IT	6	433	4	431	0.4%	1.49 [0.42, 5.25]
WOSCOPS	106	3302	135	3293	13.1%	0.78 [0.61, 1.01]
Total (95% CI)		**29731**		**29636**	**100.0%**	**0.86 [0.79, 0.94]**
Total events	889		1034			

Heterogeneity: $Chi^2 = 11.47$, $df = 10$ ($P = 0.32$); $I^2 = 13\%$

Test for overall effect: $Z = 3.40$ ($P = 0.0007$)



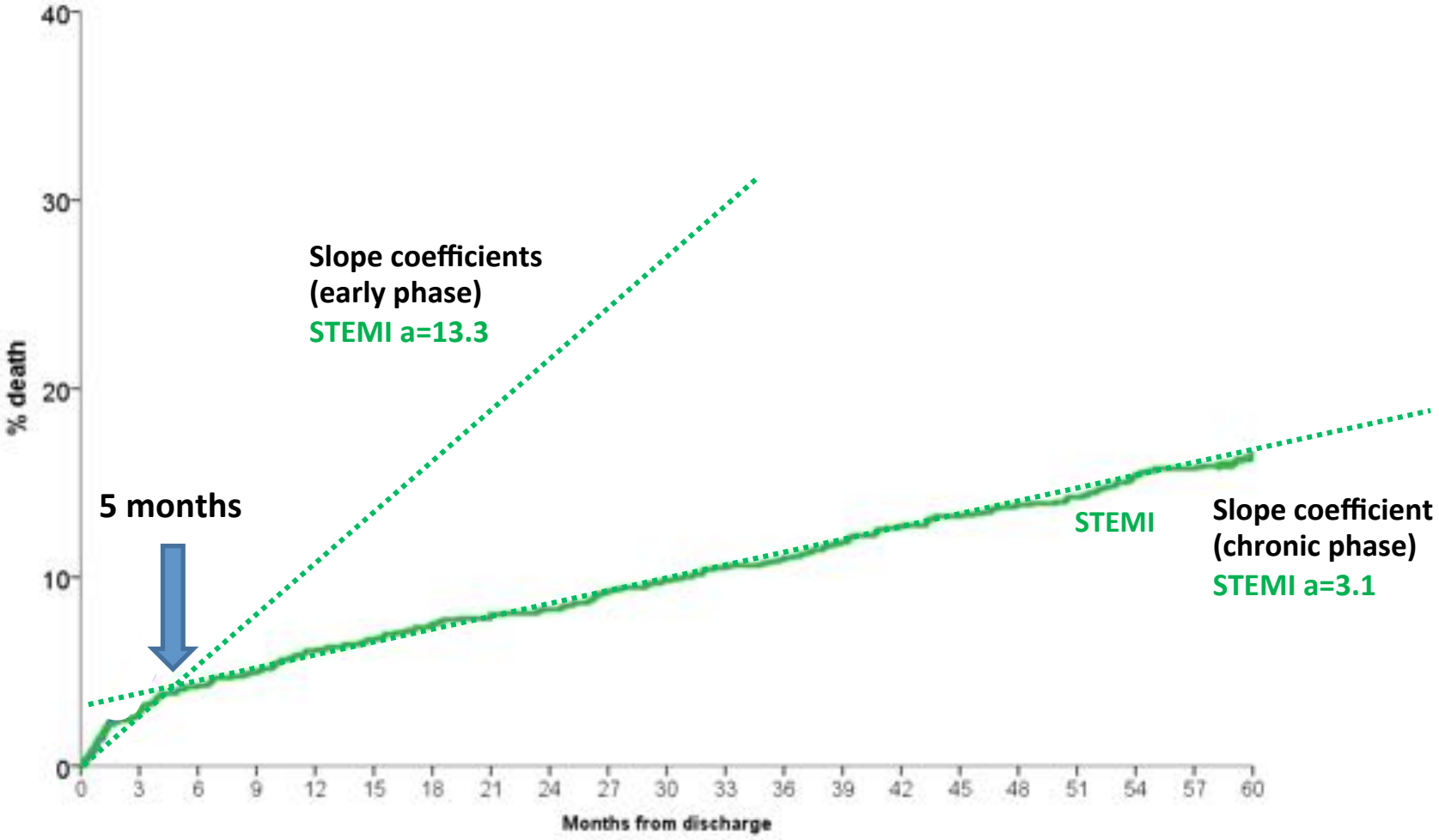
Essais forte intensité vs statines standard chez les patients coronariens

- 3 études post SCA : forte intensité vs dose standard
  - PROVE IT (A 80 mg vs P 40 mg)
  - A to Z (S 40 puis 80 mg vs S 20 mg après 4 mois)
  - IMPROVE IT (ezetimibe 10 vs PCB)
- 6 grandes études comparant traitement hypolipémiant plus intensif vs standard:

	average LDL-c in high-dose arm
TNT (A 80 mg vs A 10 mg)	77 mg/dl
IDEAL (A 80 mg vs S 20 mg)	81 mg/dl
SEARCH (S 80 mg vs S 20 mg)	83 mg/dl
IMPROVE IT (ezetimibe 10 vs PCB)	54 mg/dl
FOURIER (evolocumab vs PCB)	30 mg/dl
SPIRE 1 et 2 (bococizumab vs PCB) *	69 mg/dl

Mortality curves in STEMI patients

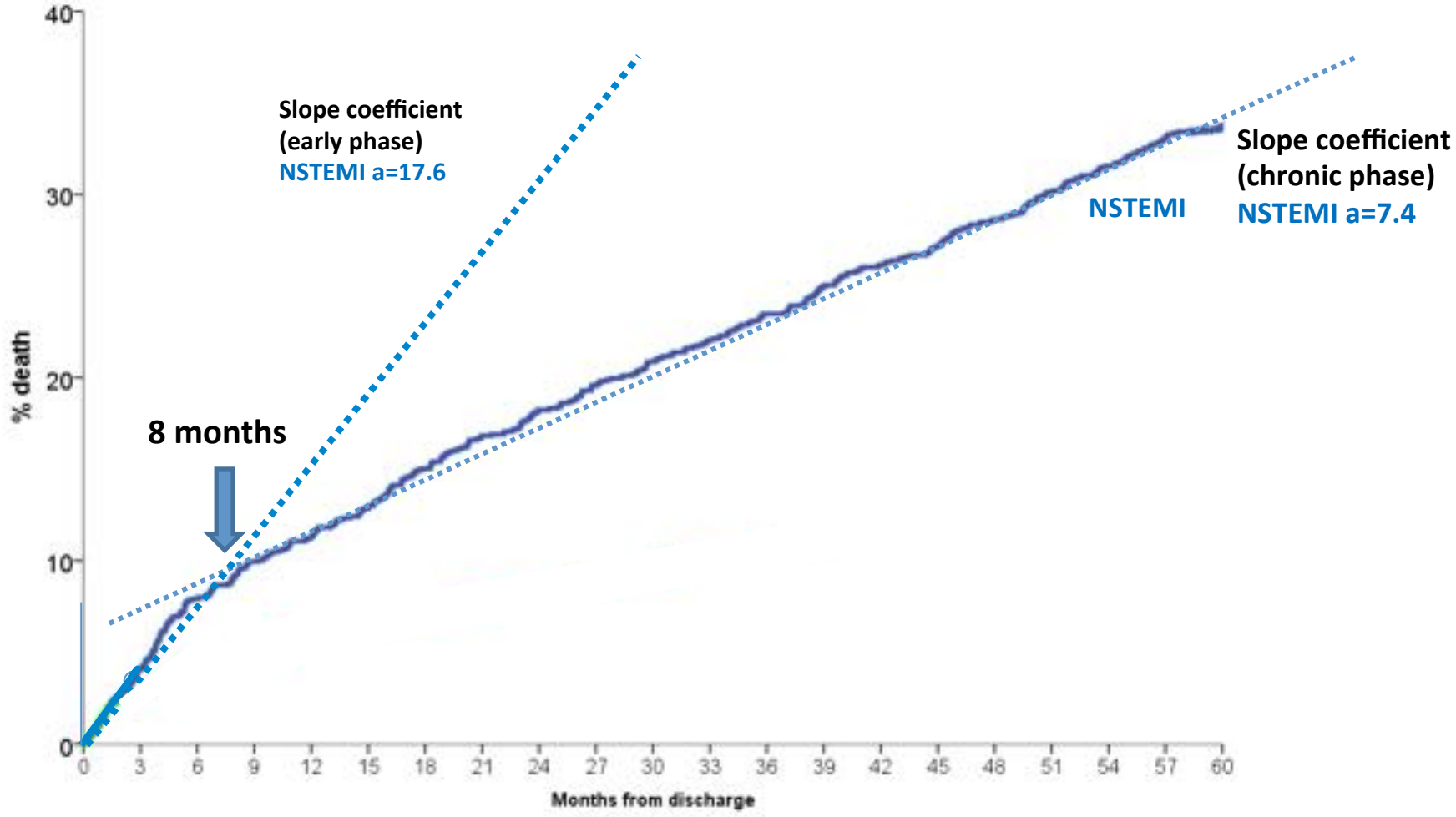
Simplified equations: one knot at 5 months



Danchin et al. ESC 2015

Mortality curves in NSTEMI patients

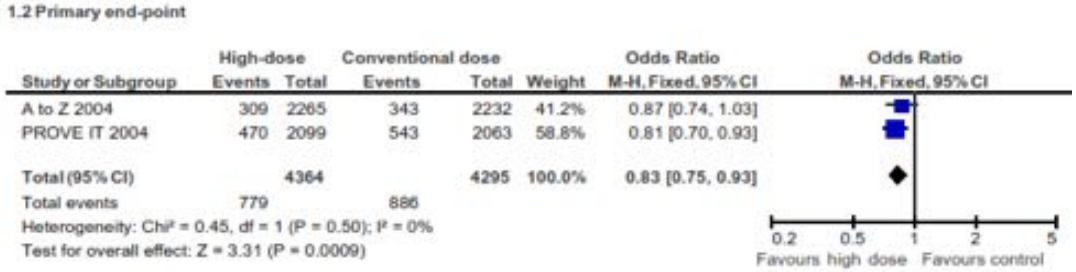
Simplified equations: one knot at 8 months



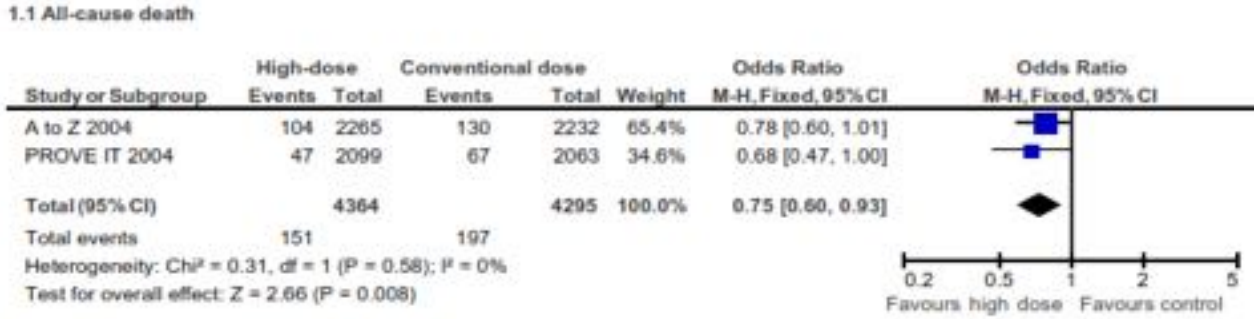
Danchin et al. ESC 2015

Hautes doses après SCA

- Evénements ischémiques :

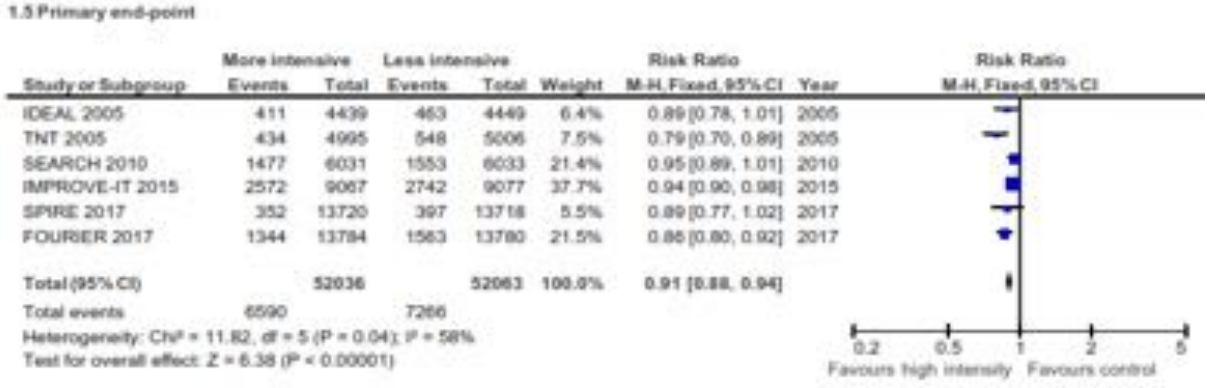


- Mortalité globale

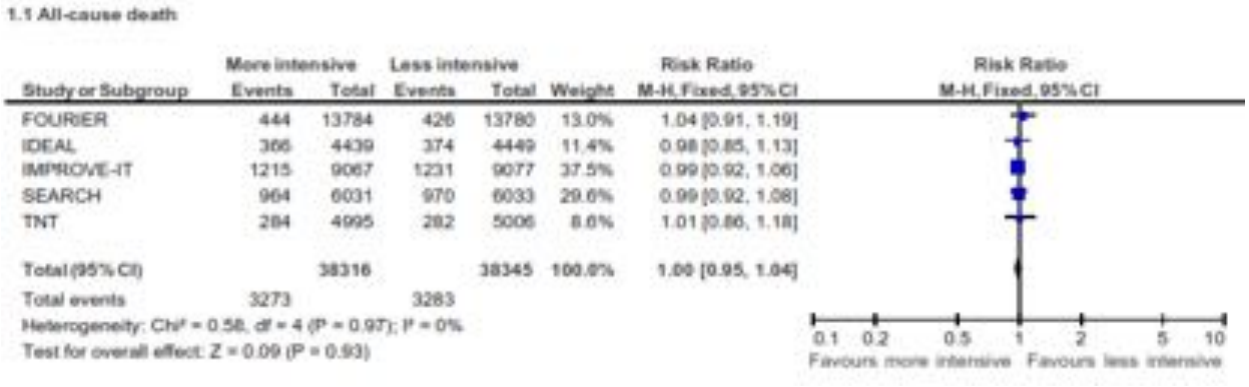


Hautes doses dans la maladie stable

- Evénements ischémiques :



- Mortalité globale



Annual mortality rates in clinical trials

Trial	Age (years)	Follow-up (years)	All-cause death % per year	% CV death
High-intensity lipid lowering vs conventional doses				
TNT	61	4.9	**1.14**	55
IDEAL	62	4.8	**1.75**	58
SEARCH	64	6.7	**2.40**	59
IMPROVE IT	64	6.0	**2.55**	44
FOURIER	62.5	2.2	**1.45**	53
Initial statin trials in secondary prevention				
4S	58	5.4	**2.13**	81
CARE	59	5	**1.89**	61
LIPID	62*	6.1	**1.81**	87
HPS	64	5	**2.94**	62
Statin trials in primary prevention				
ACAPS	62	2.8	**0.3**	75
MEGA	59	5	**0.4**	23
AFCAPS	58	5.2	**0.45**	32
ASPEN	60	2.4	**1.8**	46
CARDS	62	3.9	**1.5**	--
KAPS	57	3	**0.8**	75
PREVEND IT	51	3.8	**0.5**	50
WOSCOPS	55	4.9	**0.8**	54
JUPITER	66	1.9	**1.5**	--
HOPE 3	66	5.6	**1.0**	48
Contemporary non-lipid-lowering trials in secondary prevention				
LEADER [$]	64	3.8 *	**2.52**	63
EMPA-REG [$$]	63	3.1	**2.68**	71

En résumé

- Les statines ont un impact majeur, tant en prévention primaire que secondaire, en réduisant les accidents CV et en augmentant l'espérance de vie.

- L'effet du traitement sur les événements cliniques n'est pas instantané, ce qui est plausible sur le plan physiopathologique

- L'intensification du traitement hypolipémiant s'accompagne d'une réduction supplémentaire des événements cliniques, mais pas d'une réduction de la mortalité.

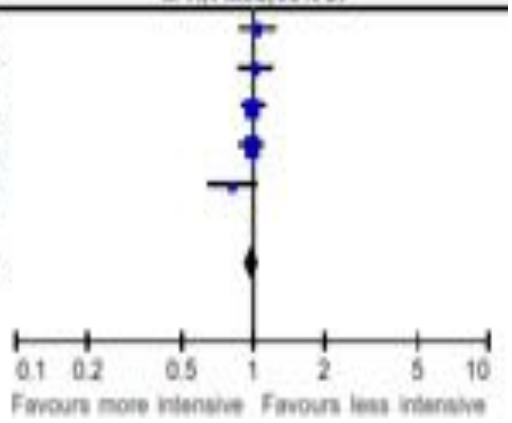
Causes de mortalité

1.3 CV death

Study or Subgroup	More intensive Events	Total	Less intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FOURIER	251	13784	240	13780	13.9%	1.05 [0.88, 1.25]
IDEAL	223	4439	218	4449	12.6%	1.03 [0.85, 1.23]
IMPROVE-IT	537	9067	538	9077	31.2%	1.00 [0.89, 1.12]
SEARCH	565	6031	572	6033	33.2%	0.99 [0.88, 1.10]
TNT	126	4995	155	5006	9.0%	0.81 [0.65, 1.03]
Total (95% CI)		38316		38345	100.0%	0.99 [0.93, 1.05]
Total events	1702		1723			

Heterogeneity: $Chi^2 = 3.25$, $df = 4$ ($P = 0.52$); $I^2 = 0\%$

Test for overall effect: $Z = 0.34$ ($P = 0.73$)

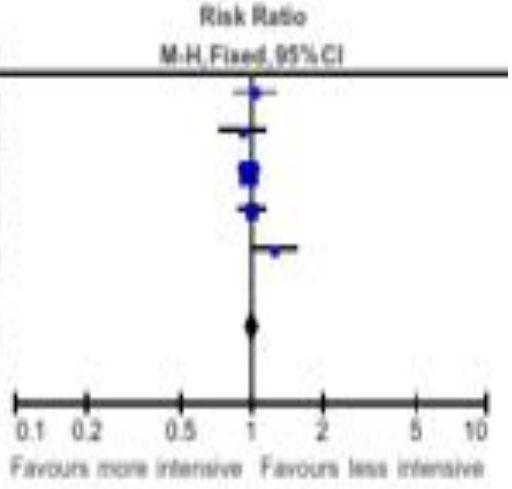


1.4 Non-CV death

Study or Subgroup	More intensive Events	Total	Less intensive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FOURIER	193	13784	186	13780	11.9%	1.04 [0.85, 1.27]
IDEAL	143	4439	156	4449	10.0%	0.92 [0.74, 1.15]
IMPROVE-IT	678	9067	693	9077	44.4%	0.98 [0.88, 1.08]
SEARCH	399	6031	398	6033	25.5%	1.00 [0.88, 1.15]
TNT	158	4995	127	5006	8.1%	1.25 [0.99, 1.57]
Total (95% CI)		38316		38345	100.0%	1.01 [0.94, 1.08]
Total events	1571		1560			

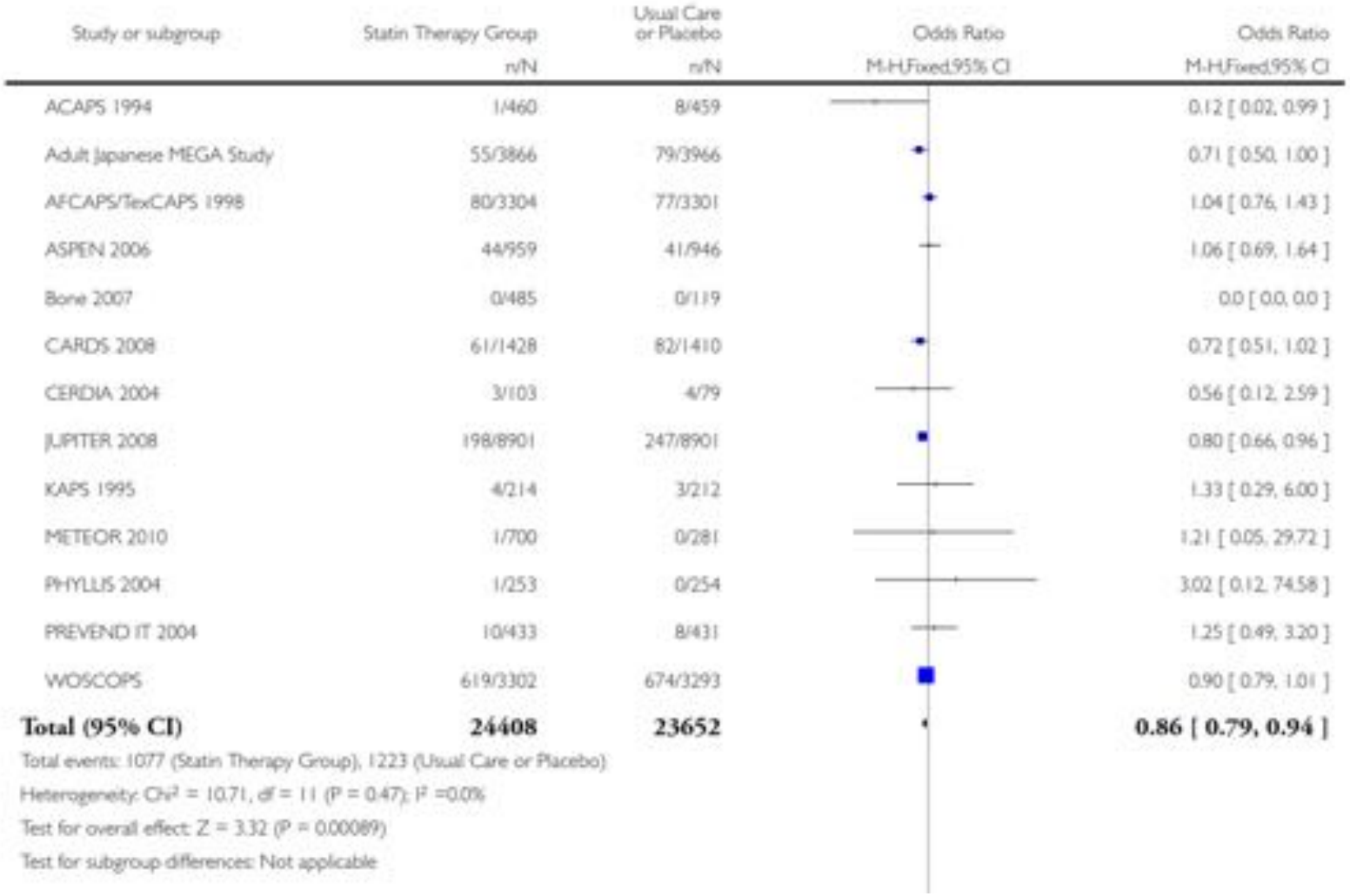
Heterogeneity: $Chi^2 = 4.33$, $df = 4$ ($P = 0.36$); $I^2 = 8\%$

Test for overall effect: $Z = 0.23$ ($P = 0.82$)



Méta-analyse de toutes les études statines en prévention primaire : mortalité

Cochrane Collaboration. Statins for the primary prevention of cardiovascular disease. 2013



Our previous conclusion urging caution in the use of statins in people at low risk of cardiovascular events is no longer tenable in light of the CTT Collaboration findings. Several issues remain to be considered before widespread use of statins could be recommended in people at low risk (Ebrahim 2012; Smeeth 2012). These include: i) the feasibility and desirability of having to treat the majority of people over the age of 50 with a statin; ii) the cost-effectiveness of such a strategy using a conventional healthcare delivery system; iii) diversion of attention from achieving coverage in people at high risk of events; iv) use of alternative public health strategies to lower blood cholesterol; v) the views of patients on life-long drug therapy; and vi) limited evidence on less serious but nonetheless potentially important adverse effects and quality of life.

Un choix de santé publique doublé d'un choix individuel

Cochrane Collaboration. Statins for the primary prevention of cardiovascular disease. 2013