Statin

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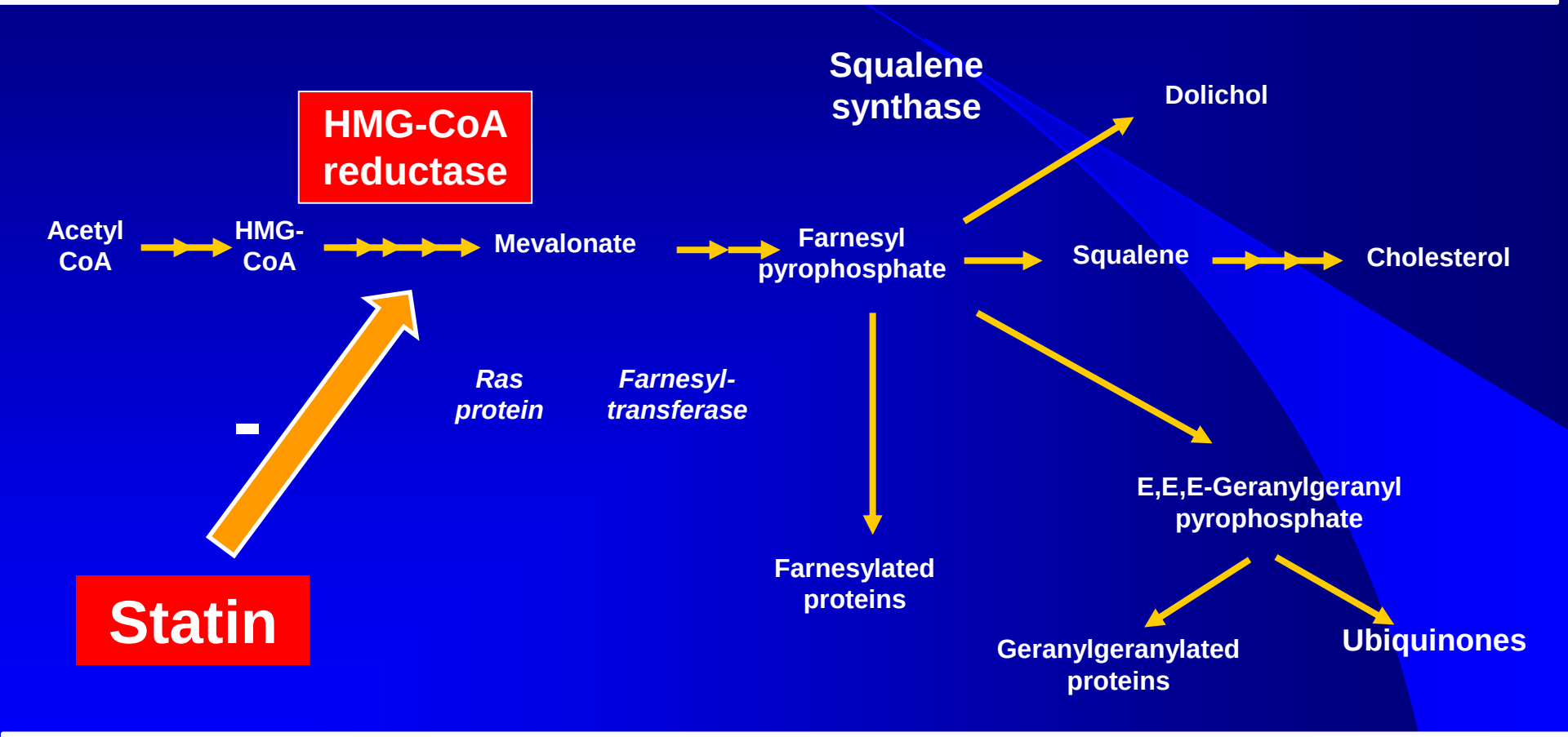
Statin

Simvastatin, Pravastatin, Fluvastatin, Lovastatin, Atorvastatin, Rosuvastatin, Pitavastatin



A unique class of drug: Millions of patients being treated, Unprecedented proven efficacy on CVD prevention, Few data to understand the main side effect, big media crisis
The main problem with statin is now poor compliance responsible of a large number of avoidable CV events despite a low cost for developed countries

Effect of statins on lipid parameters

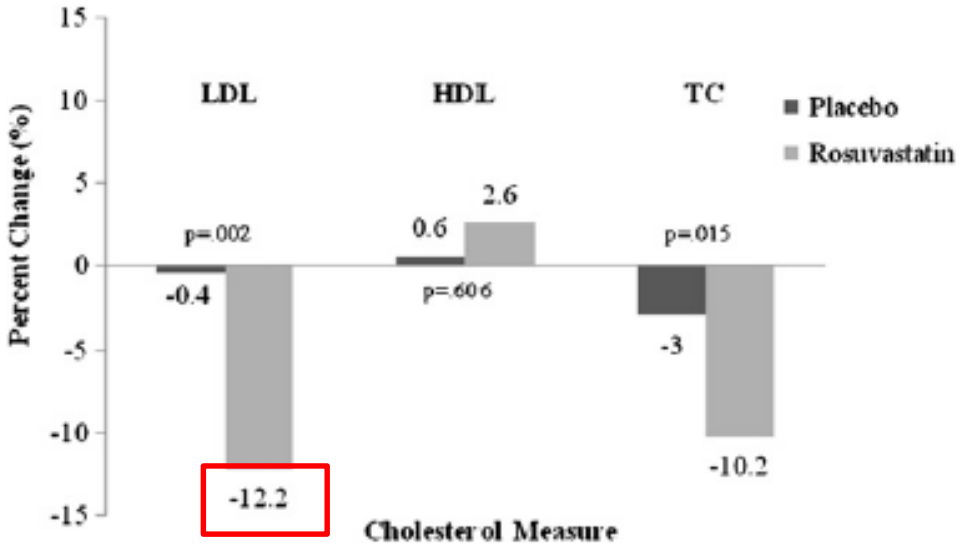
Effect of statin on LDL-c according to dose: 164 double-blind trials with 38 000 patients

	5mg	10mg	20mg	40mg	80mg
Fluvastatin	10%	15%	21%	27%	33%
Pravastatin	15%	20%	24%	29%	33%
Lovastatin	-	21%	29%	37%	45%
Simvastatin	23%	27%	32%	37%	42%
Atorvastatin	31%	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	58%

Law MR et al. BMJ 2003

Low-dose statin regimen in statin-intolerant patients

- Randomized, double-blind, placebo-controlled crossover study
- N=17 Veterans Affairs (VA) primary care patients with a diagnosis of hyperlipidemia and a history of myalgias on statin therapy who were not at LDL goal
- Two 8-week treatment phases rosuvastatin 5 mg once-weekly or PCB, with a dose titration to 10 mg once-weekly if not at LDL goal at week 4
- Primary efficacy outcome was the difference in the mean % change in LDL from baseline between rosuvastatin and placebo



HDL: High-density Lipoprotein
LDL: Low-density Lipoprotein
TC: Total Cholesterol

Figure 3 Mean percentage change in cholesterol values from baseline for study population (n = 17).

Kennedy SP et al. J Clin Lipidol 2011

Statin potency

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

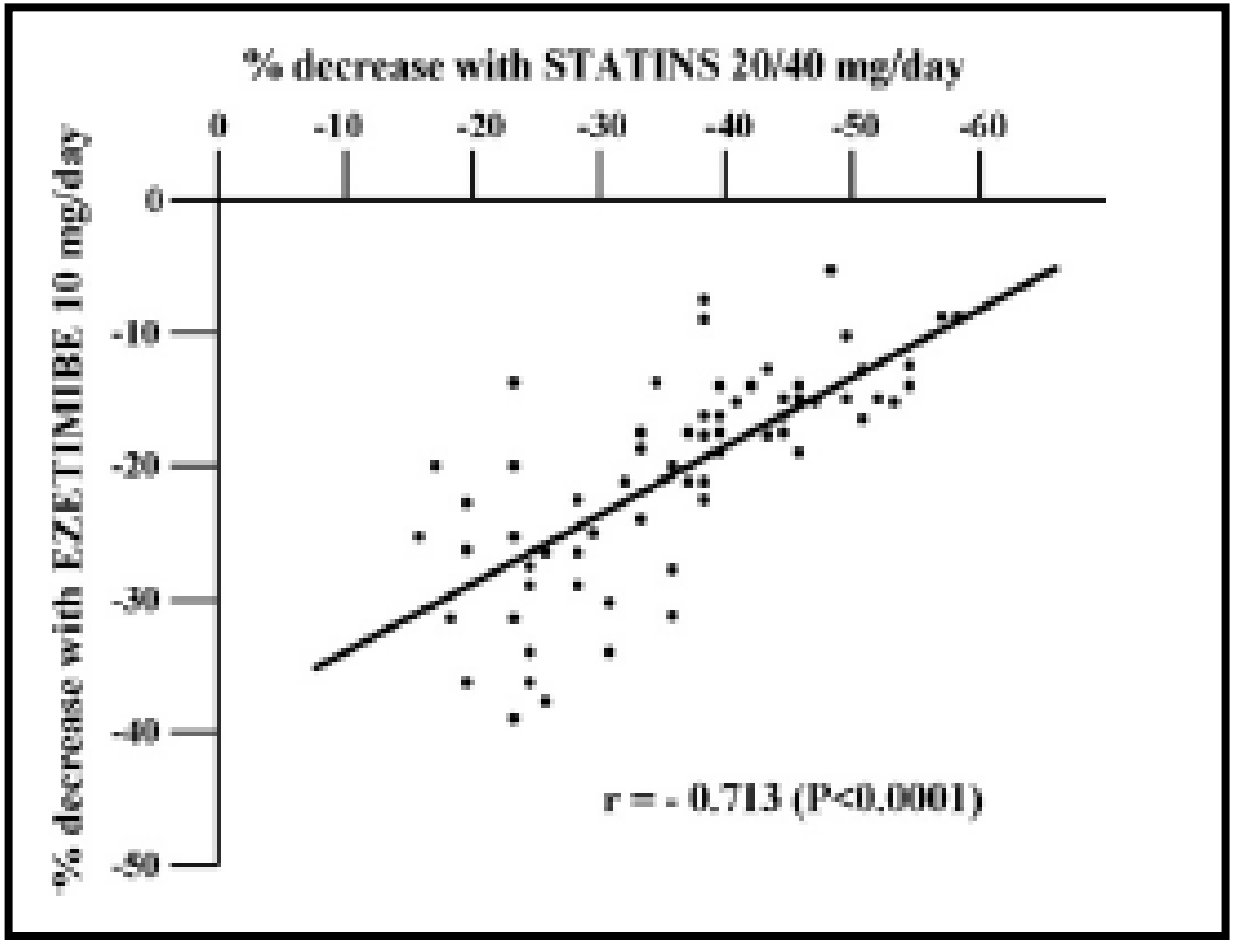
High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

American Heart Association
Circulation

Circulation 2013

Variability of statin effect on LDL-c

Variability of the effect of statin
Example in FH patients



Pisciotta et al, Atherosclerosis , 2007

LDL-c lowering according to demographics

- **Male and female participants limited to 14 trials 10 mg/d of atorvastatin. Small statistically significant increase in effect in females (7% greater) as compared with males (consistent with the effect of rosuvastatin 10 mg/d greater in females than in males (Adams 2014))**

- **Familial vs heFH decreased efficacy of atorvastatin in lowering LDL-c among FH. Consistent evidence of decrease efficacy in hoFH for all statins (approx – 20%)**

- **Ethnicity. LDL-c reduction with rosuvastatin 10 mg in Chinese patients greater than in Westerners (-52,8% versus -40,9 to 49,7%) while there were no differences for atorvastatin**

Adams SP, Tsang M,Wright JM *Cochrane Database of Systematic Reviews* 2015
Naito R et al. J Atheroscler Thromb 2017

Chronotherapy versus conventional therapy

8 RCTs (767 participants in morning and evening arms) (lovastatin: 2 trials; simvastatin: 3 trials; fluvastatin: 2 trials; pravastatin: 1 trial)

High risk of bias.

No data on CV mortality, CV morbidity, incidence of CV events, or deaths from any cause

No evidence of a difference in TC (MD 4.33, 95% CI -1.36 to 10.01), n = 514, 5 trials, mean follow-up 9 weeks, low-quality evidence), LDL-C (MD 4.85 mg/dL, 95% CI -0.87 to 10.57, n = 473 participants, 5 trials, mean FU 9 weeks, low-quality evidence), between morning and evening statin administration.

No differences in adverse events (OR 0.71, 95% CI 0.44 to 1.15, 556 participants, 5 trials, mean FU 9 weeks, low-quality evidence)

Izquierdo-Palomares JM ***Cochrane Database of Systematic Reviews*** **2016**

Statin effect on LDL-c and pharmacogenetic

- **Pharmacogenetic meta-analysis of GWAS in studies addressing the LDL-c response to statins, including up to 18,596 statin-treated subjects.**
- **Most promising signals validated in a further 22,318 statin recipients**
- **Two loci, SORT1/CELSR2/PSRC1 and SLCO1B1, not previously identified in GWAS. Confirmation of the previously described associations with APOE and LPA.**

Table 1 | Genome-wide significant associations in stage 1, stage 2 and combined meta-analysis.

Chr	Position	Lead SNP	Gene	Coding allele	Noncoding allele	Phase	*N*	Frequency-coding allele	Beta*	s.e.	% Extra reduction†	*P* value
1	109620053	rs646776	*SORT1/ CELSR2/ PSRC1*	C	T	Stage 1	16,697	0.230	−0.015	0.003	1.5	6.70×10^{-7}
						Stage 2	21,902	0.216	−0.010	0.003	1.0	2.43×10^{-4}
						Combined	38,599		−0.013	0.002	1.3	1.05×10^{-9}
6	160930108	rs10455872	*LPA*	G	A	Stage 1	12,981	0.069	0.041	0.006	−4.1	1.95×10^{-11}
						Stage 2	18,075	0.087	0.059	0.005	−5.9	7.14×10^{-35}
						Combined	31,056		0.052	0.004	−5.2	7.41×10^{-44}
12	21260064	rs2900478	*SLCO1B1*	A	T	Stage 1	16,749	0.165	0.016	0.003	−1.6	2.26×10^{-6}
						Stage 2	7,504	0.164	0.017	0.006	−1.7	3.54×10^{-3}
						Combined	24,253		0.016	0.003	−1.6	1.22×10^{-9}
19	50107480	rs445925	*APOE*	A	G	Stage 1	13,909	0.098	−0.043	0.005	4.3	1.58×10^{-18}
						Stage 2	3,613	0.157	−0.088	0.011	8.8	1.41×10^{-15}
						Combined	17,522		−0.051	0.005	5.1	8.52×10^{-29}

Postmus I et al. Nat Commun 2014

Statin and other lipid parameters

Statin and HDL

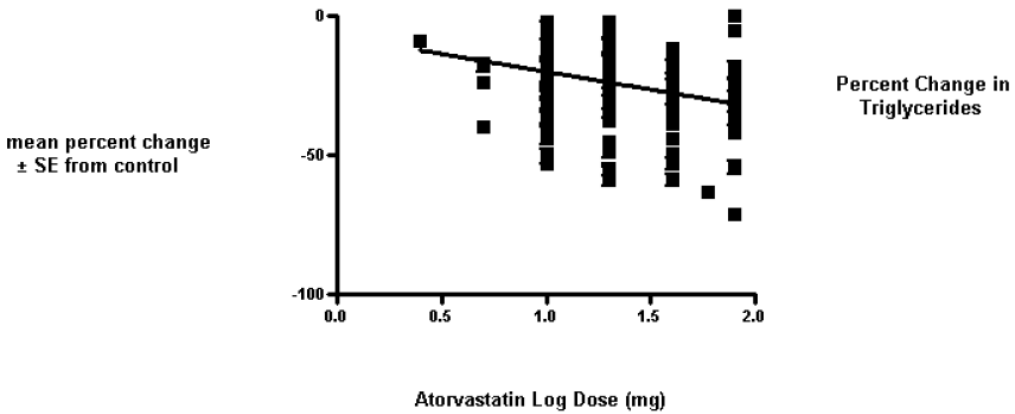
- HDL-c levels still predict CV outcome in statin treated patients*
- Statins increase modestly HDL-c levels
- The effect on HDL-c is greater if hyperTg
- Changes in HDL-c upon statin do not translate into decrease in CVD**
- Impact of statin on HDL functionality controversial***
- The only associations of genome-wide significance ($p<5\times10^{-8}$) were between minor alleles at the CETP locus and greater HDL-C response to statin treatment****

*Boekholdt SM et al. Circulation 2013, ** Briel M et al BMJ 2009 *** Arsenault BJ et al. Curr Atheroscler Rep 2014 ****Messas N et al. Pharmacogenomics 2012

Effect of statin according to dose on Tg and HDL-c

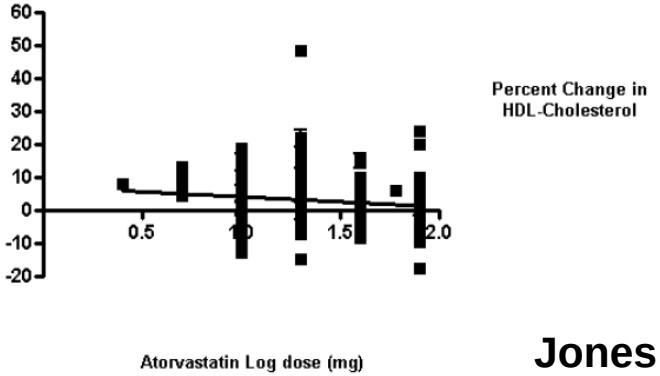
Triglyceride

Log dose-response curve of atorvastatin 2.5-80 mg/day

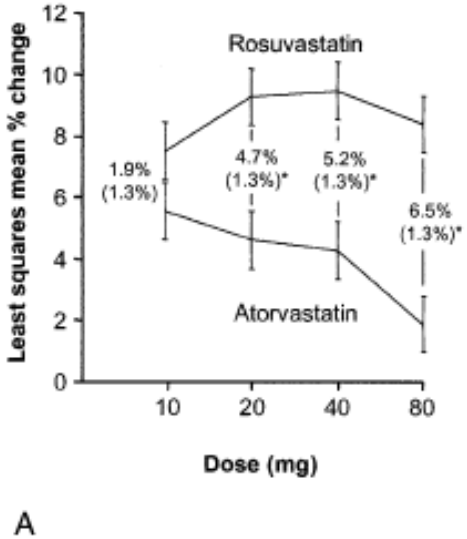


HDL-c

Log dose-response curve of atorvastatin 2.5-80 mg/day



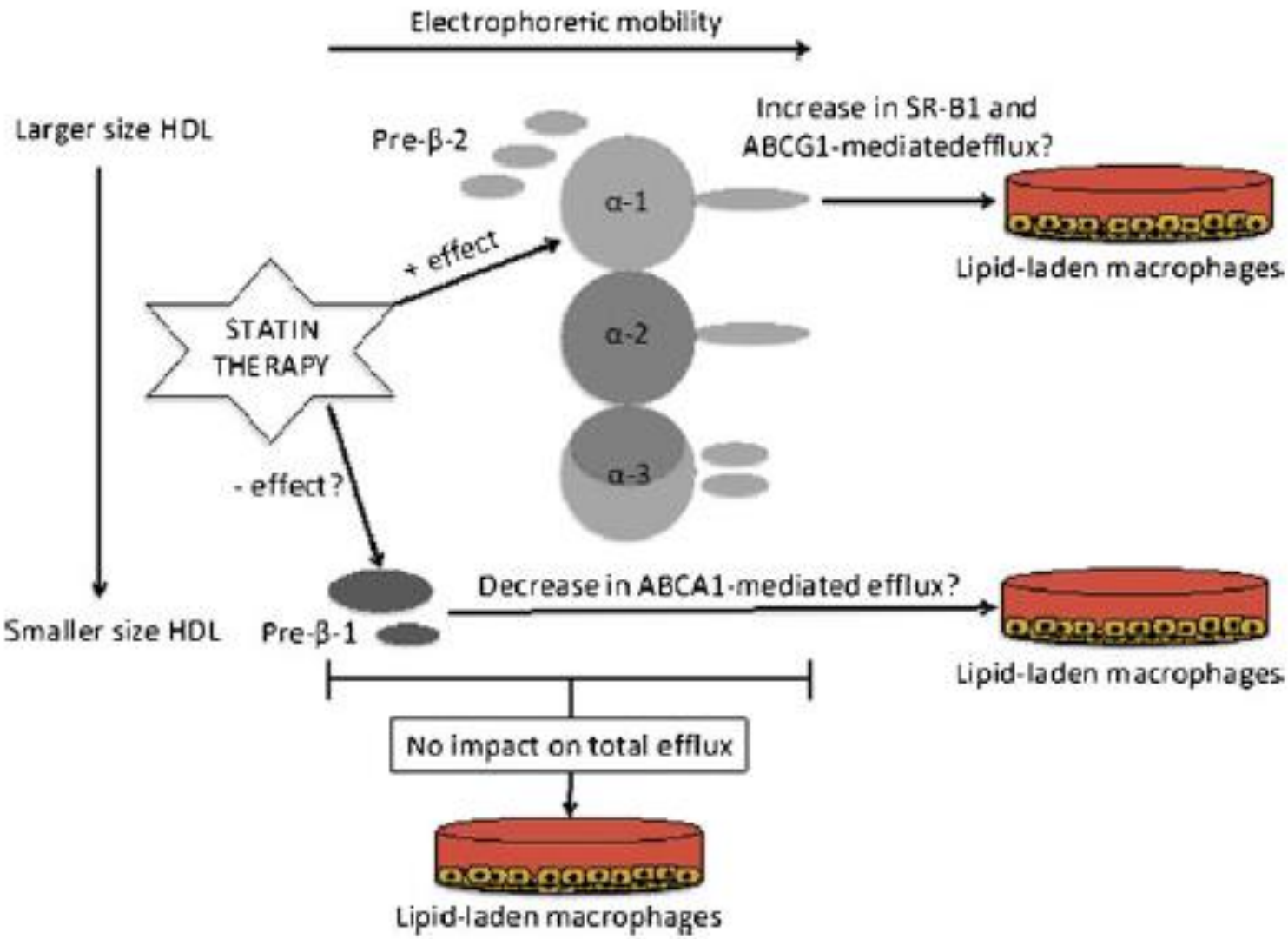
HDL-c ATORVA VS ROSUVA STELLAR



Jones P et al Am J Cardiol 2003

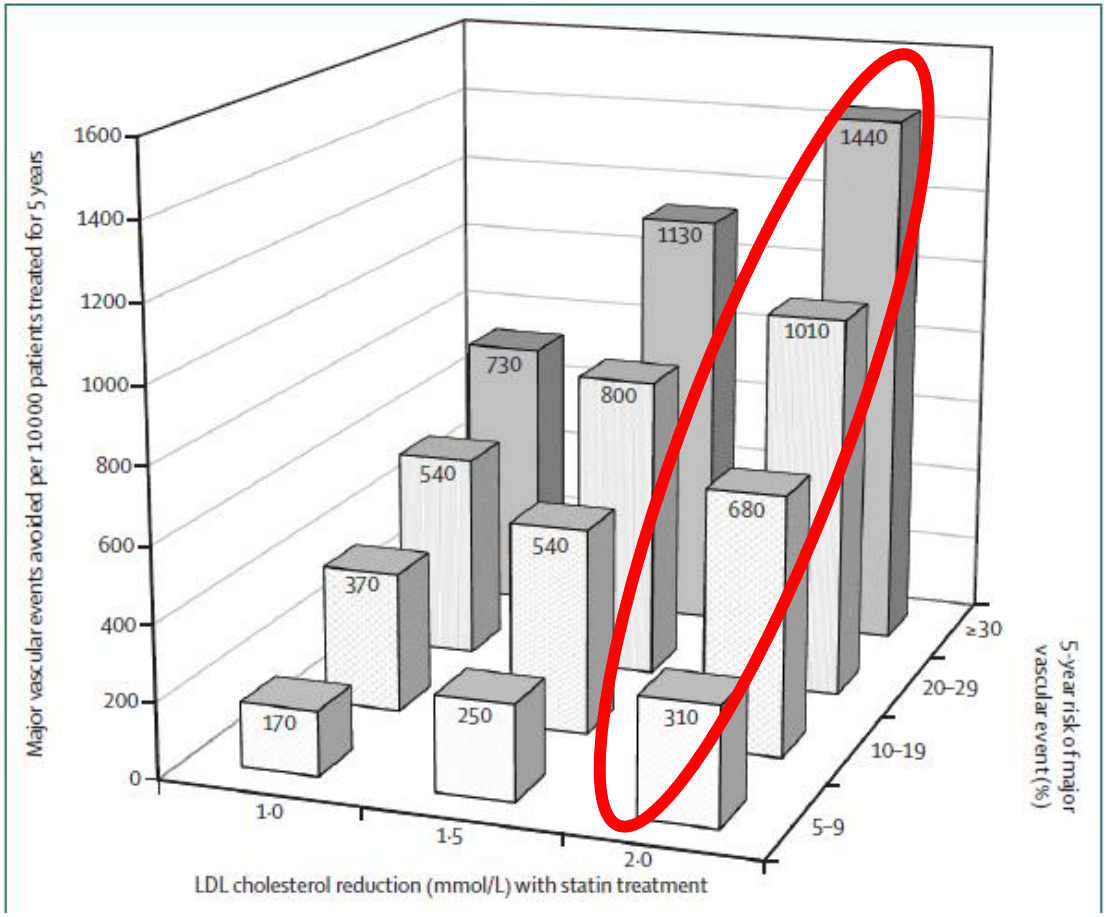
Adams SP, Tsang M,Wright JM *Cochrane Database of Systematic Reviews* 2015

Statin and HDL-c subfractions



Statin treatment decreases CVD
NTT is a direct function of risk

Benefit Risk ratio of statin treatment (effective regimen)



Interpretation of the evidence for the efficacy and safety of statin therapy

Rory Collins, Christina Reith, Jonathan Emberson, Jane Armitage, Colin Baigent, Lisa Blackwell, Roger Blumenthal, John Danesh, George Davey Smith, David DeMets, Stephen Evans, Malcolm Law, Stephen MacMahon, Seth Martin, Bruce Neal, Neil Poulter, David Preiss, Paul Ridker, Ian Roberts, Anthony Rodgers, Peter Sandercock, Kenneth Schulz, Peter Sever, John Simes, Liam Smeeth, Nicholas Wald, Salim Yusuf, Richard Peto

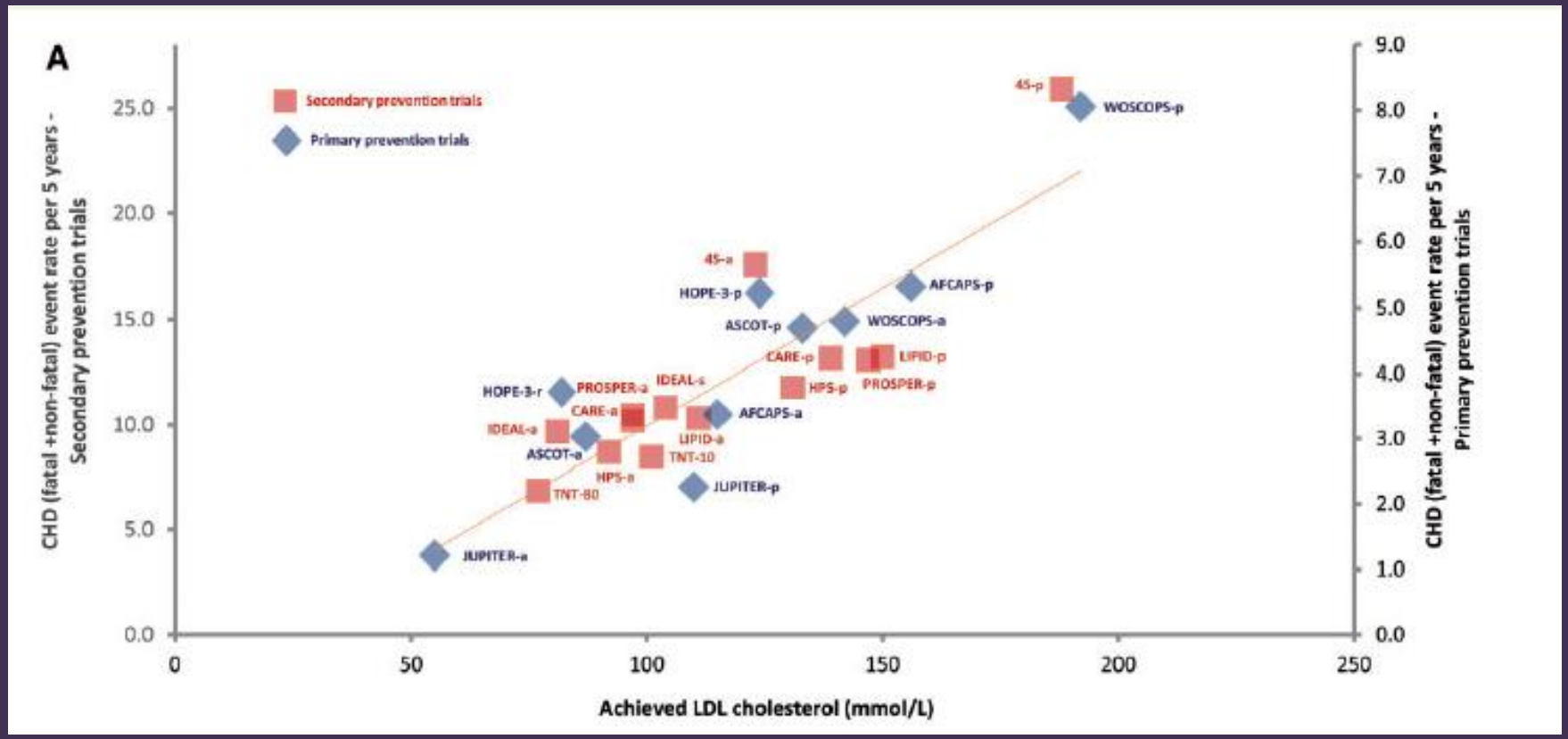
Treatment of 10 000 patients for 5 years (eg, atorvastatin 40 mg daily)

would cause about 5 cases of myopathy, 50–100 new cases of diabetes, and 5–10 hemorrhagic strokes

would avoid between 340 and 1440 serious CV events

Lancet septembre 2016

Relationship between on-treatment LDL-c and risk of CV event



Expected risk reduction according to baseline LDL-c, absolute LDL-c reduction and duration of treatment

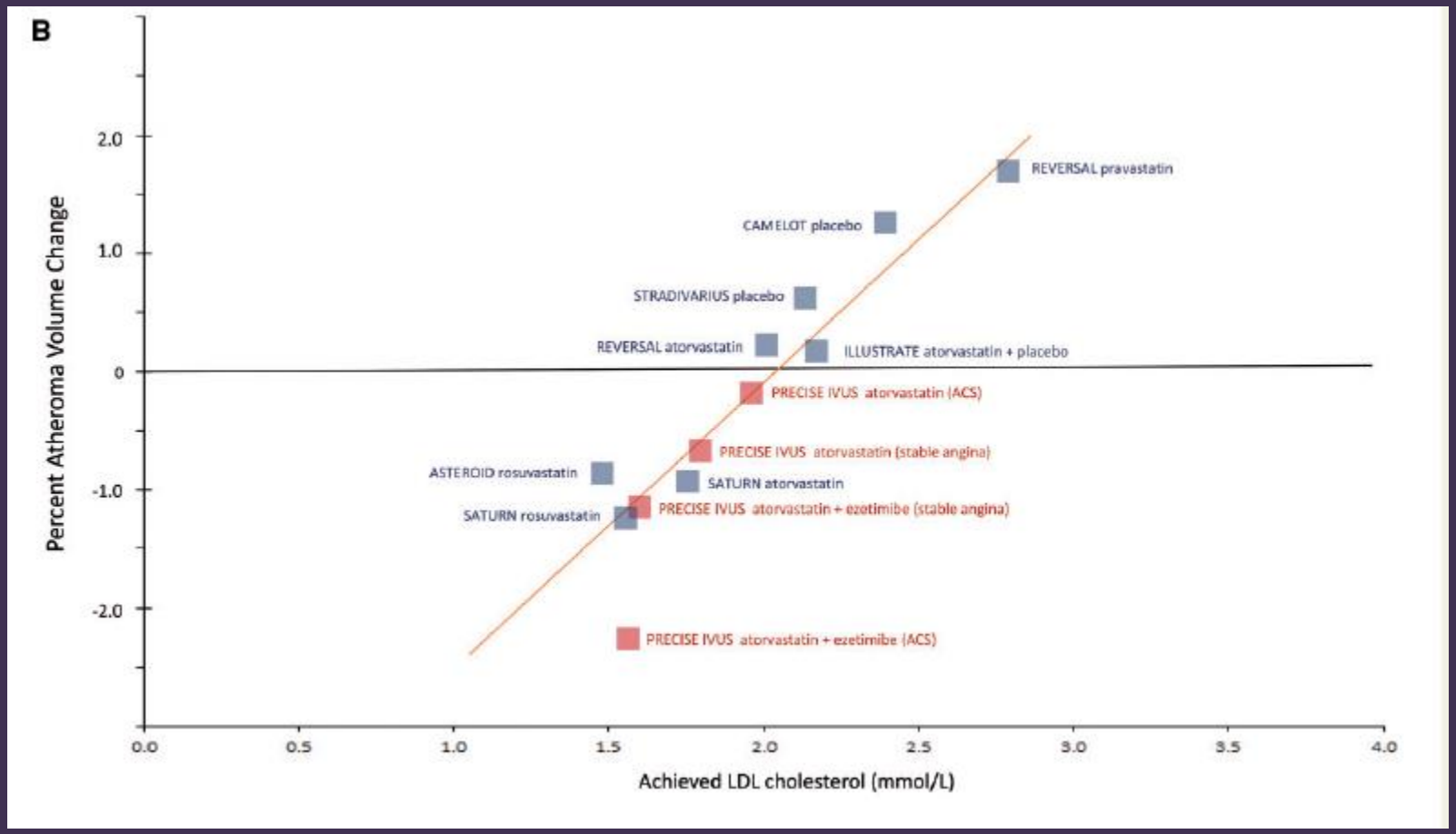
Table 2 Expected proportional risk reduction based on pre-treatment low-density lipoprotein cholesterol (LDL-C), absolute magnitude of LDL-C reduction, and total duration of therapy

Baseline LDL-C (mmol/L)	Absolute reduction LDL-C (mmol/L)	Duration of treatment exposure [expected proportional risk reduction (%)]					Guideline recommended treatment[51,52]
		5 years	10 years	20 years	30 years	40 years	
7	3.5	58	68	81	89	93	Yes (due to markedly elevated LDL-C)
7	3.0	53	62	76	85	90	
7	2.5	46	56	70	79	86	
7	2.0	39	48	61	71	79	
7	1.5	31	39	51	61	69	
5	2.5	46	56	70	79	86	Yes (due to markedly elevated LDL-C)
5	2.0	39	48	61	71	79	
5	1.5	31	39	51	61	69	
5	1.0	22	28	38	46	54	
3	1.5	31	39	51	61	69	Depends on risk of ASCVD
3	1.0	22	28	38	46	54	
3	0.5	12	15	21	27	32	
2	1.0	22	28	38	46	54	Depends on risk of ASCVD
2	0.5	12	15	21	27	32	

Trials with statin which failed to show positive outcomes

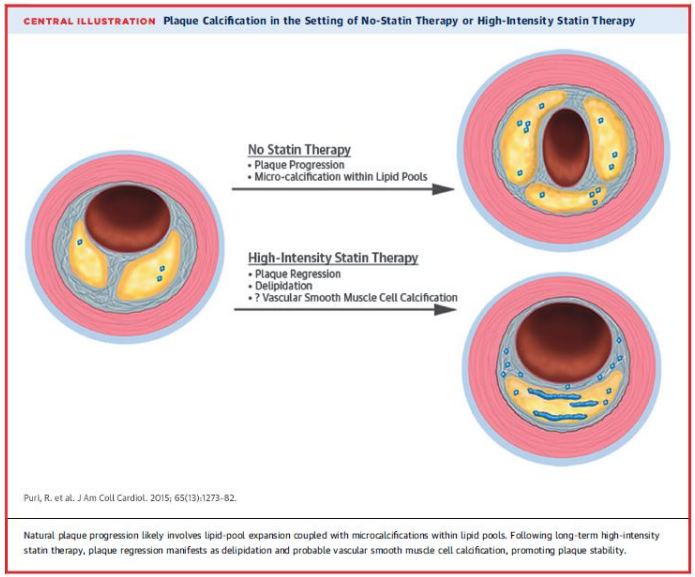
			N=	Primary outcome	RR
4D	Atorva 20	Dialysis	1225	CV death, MI, stroke	0.92 (NS)
AURORA	Rosuva 10	Dialysis	2776	CV death, MI, stroke	0.96 (NS)
CORONA	Rosuva 10	Cardiac failure	5011	CV death, MI, stroke	0.92 (NS)
GISSI-HF	Rosuva 10	Cardiac failure	4574	Death and hospitalisation for CV events	1.01 (NS)

Relationship between on-treatment LDL-c and plaque change in IVUS trials



Statins increase plaque calcification

- In a post-hoc patient-level analysis of 8 prospective randomized trials using serial coronary intravascular ultrasound, serial changes in coronary percent atheroma volume and CaI were measured across matched coronary segments in patients with CAD



Independent of their plaque-regressive effects, statins promote coronary atheroma calcification

Puri R et al. JACC 23015

Beyond potency (and cost), Which statin should we choose for a given patient?

Comparative pharmacokinetics of statins in healthy volunteers

	Atorva	Fluva	Lova	Prava	Rosuva	Simva
Lipophilicy (logp)	4.06	3.24	4.30	-0.23	0.13	4.68
Bioavailability (%)	12-14	9	< 5	18	20	< 5
Protein binding (%)	> 98	> 98	> 95	43-54	88	95
Metabolic enzyme	CYP3A4	CYP2C9	CYP3A4	Enzymatic and nonenzymaztic	Minimal CYP	CYP3A4
Active metabolites (number)	Yes (2)	No	Yes (3)	No	Minimal	Yes (3)
Renal excretion	< 2	< 6	> 10	20	10	13
T1/2 (h)	14-15	3.0	2.0	2.0	20	1.4-3.0

Statin and Safety including Muscle Associated Symptoms

Statin and Safety

- **278 unique non-CVD outcomes from 112 meta-analyses of observational studies and 144 meta-analyses of RCTs**

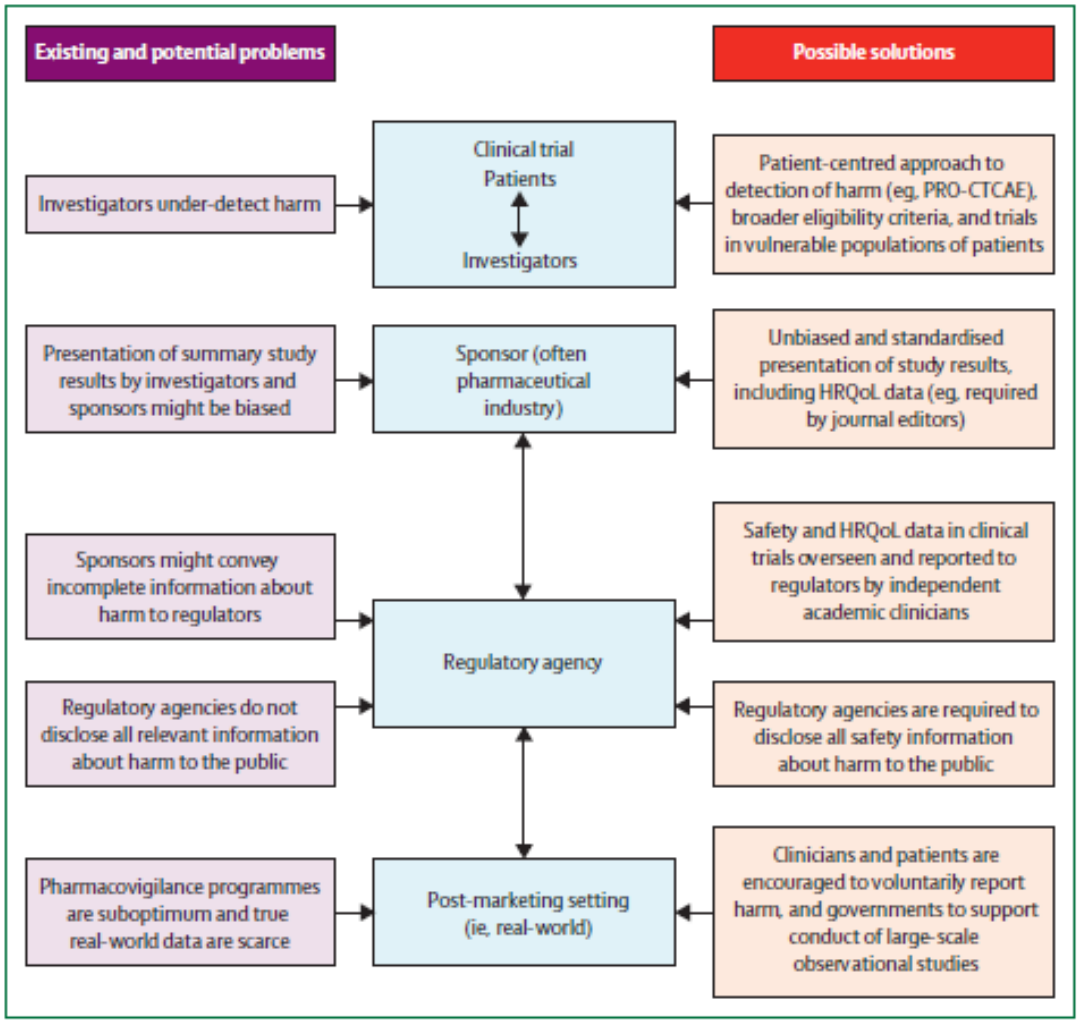
- **Observational studies: no convincing (class I) evidence, 2 highly suggestive (class II) associations (decreased cancer mortality in patients with cancer and decreased exacerbation in patients with chronic obstructive pulmonary disease), 21 suggestive (class III) associations, and 42 weak (class IV) associations**
- **For adverse events, observational studies showed suggestive evidence that statins increase the risk for diabetes and myopathy**

- **One outcome from the RCTs (decreased all-cause mortality in patients with chronic kidney disease) attained a sufficient amount of evidence with no hints of bias. Among the RCTs, no statistically significant effects were found on myopathy, myalgia, or rhabdomyolysis.**

He Y et al Annals of Internal Medicine 2018

Under-reporting of harm in clinical trials

Under-Reporting of harms during drug development, drug approval, and post-marketing, and suggested solutions to mitigate it



Lancet Oncol 2016

When reporting harm, agreement between clinician is low (interclass coefficient 0,46-0,69)[1] and agreement between clinician and patient is event lower with under-reporting 41-74%[2]

Agreement is lower for symptoms considered as non severe

1 Atkinson et al Qual Life Res 2012

2 Di Maio et al. J Clin Oncol 2015

Summary of bias of RCTs to evaluate SAMS

- Patients highly selected. The usual patient who do not tolerate anything will not accept to or will not be asked to participate in trials
- Exclusion of patients unlikely to adhere or using interacting drugs or with several co-morbidities
- Exclusion of patients with previous intolerance and/or run-in period to exclude intolerant patients
- Definitions of muscle adverse effects differ
- Motivated trial patients may minimize symptoms
- No systematic assessment of muscle side effects. Doctors may be reluctant to report frequent non-specific symptoms. Muscle aches and pains are common in placebo group
- Awareness (mediatisation) of side effect was low in first outcome trials

Risk Factors for Statin Induced Myopathy Patient Characteristics

- ***Statin***
  - *Dose of statin++*
  - *Type of statin (?)*
- ***Demographics***
  - Older Age,
  - Female gender
  - Asian race
- **Drug-drug and grape-fruit interaction**
- ***Genetic Predisposition***

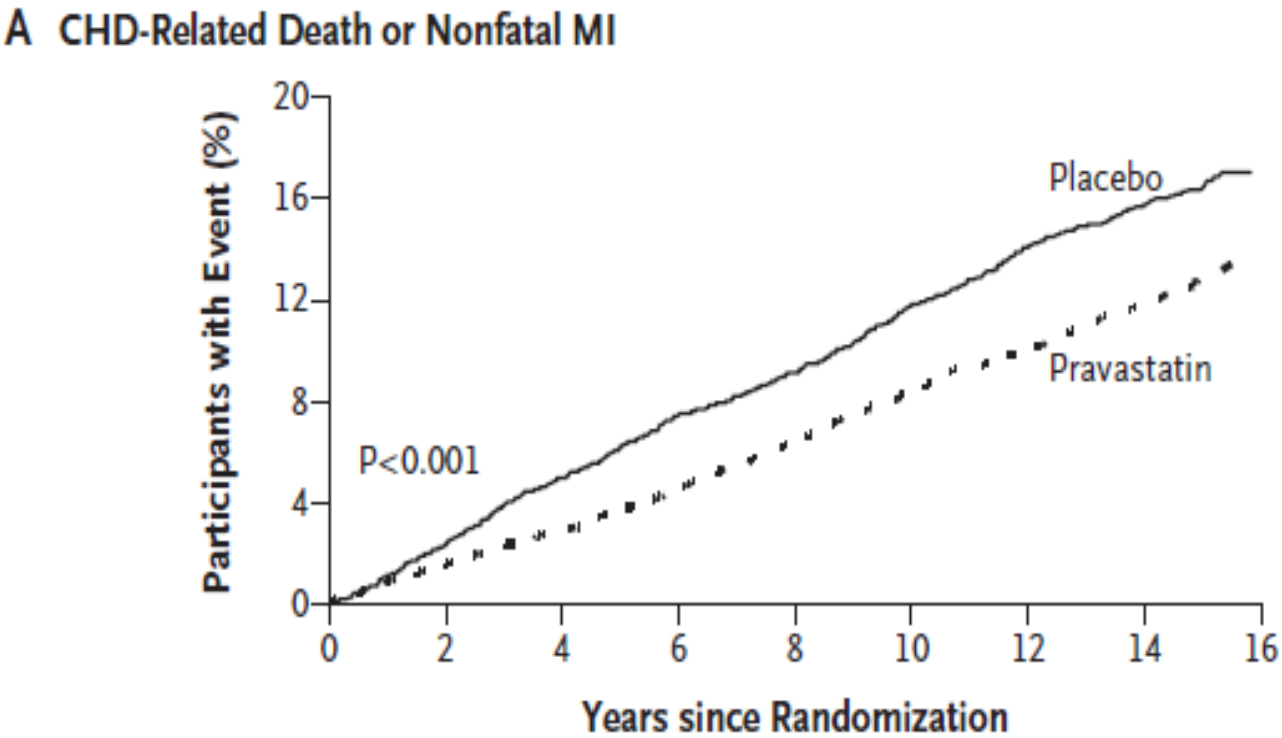
- ***Comorbidities***
  - Hypothyroidism
  - Systemic disease
  - Alcoholism / drugs
  - Major surgery
  - Myopathy
    - Hereditary (PYGM, CTP II, AMPD)
    - Acquired

Long term treatment with Statin

Long term follow-up in the WOSCOPS trial (5 years)

5 years after the trial ended, 38.7% of the original statin group and 35.2% of the original placebo group were being treated with a statin.

There were no excess deaths from nonCV causes or excess fatal or incident cancers.



No. at Risk

Placebo	3293	3199	3071	2953	2841	2691	2549	1903
Pravastatin	3302	3237	3157	3065	2943	2819	2675	2026

Ford I et al. N Engl J Med 2007

Long term follow-up in the WOSCOPS trial (20 years)

20 years

Death from all cause (A), cardiovascular (B) coronay heart disease (C) and non cardio-vascular (D)

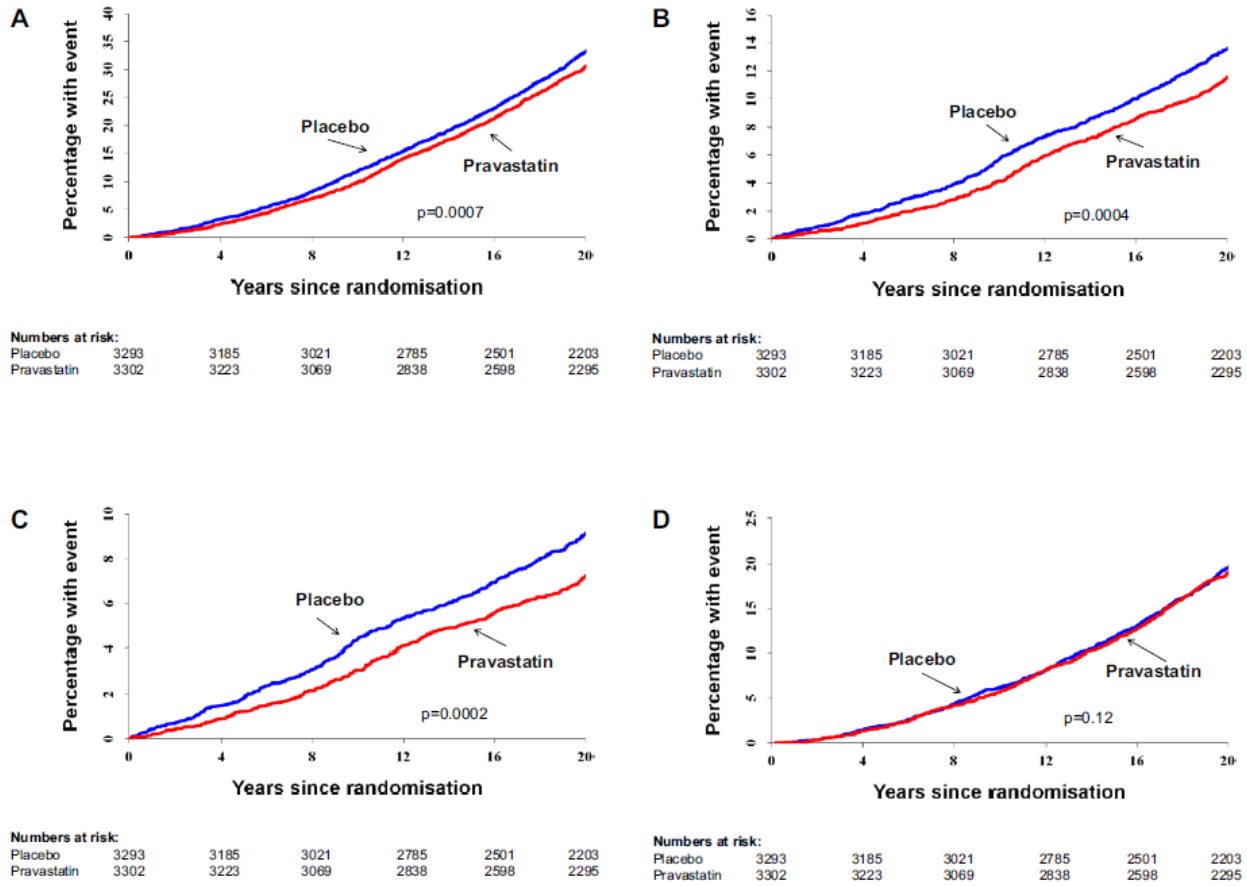


Figure 1. Cumulative events over the 20-year follow-up period. Cumulative incidence functions are provided for the outcomes of death resulting from (**A**) all causes, (**B**) cardiovascular disease, (**C**) coronary heart disease, and (**D**) noncardiovascular disease. *P* values were determined by Cox proportional hazards model.

Ford I et al. Circulation 2016

Statin in subpopulations

Children
hoFH
Elderly
Diabetic patients
Patients with CKD
Pregnant and breast feeding women

Meta-analysis of statin trials in FH children

476 statin treated patients and 322 upon PCB, 60% male patients, 8 to 18 years

Lipid/ lipoprotein	Nb statin treated pts	Nb PCB treated pts	% change (95% CI)
TC	464	306	-23.27% (-27.31%/-19.22%)
LDL-c	464	306	-29.67% (-35.61%/-23.72%)
HDL-c	464	306	+3.64% (+1.33%/+5.94%)

	Nb statin treated pts	Nb PCB treated pts	Relative risk (95% CI)
All adverse events	205/299	108/153	0.99 (0.79-1.25)
Tanner stage changes	121/348	92/217	0.96 (0.79-1.17)
CPK increase	2/454	1/308	1.38 (0.18 – 10.82)

Arterioscler Thromb Vasc Biol 2007

Effect of statin on IMT

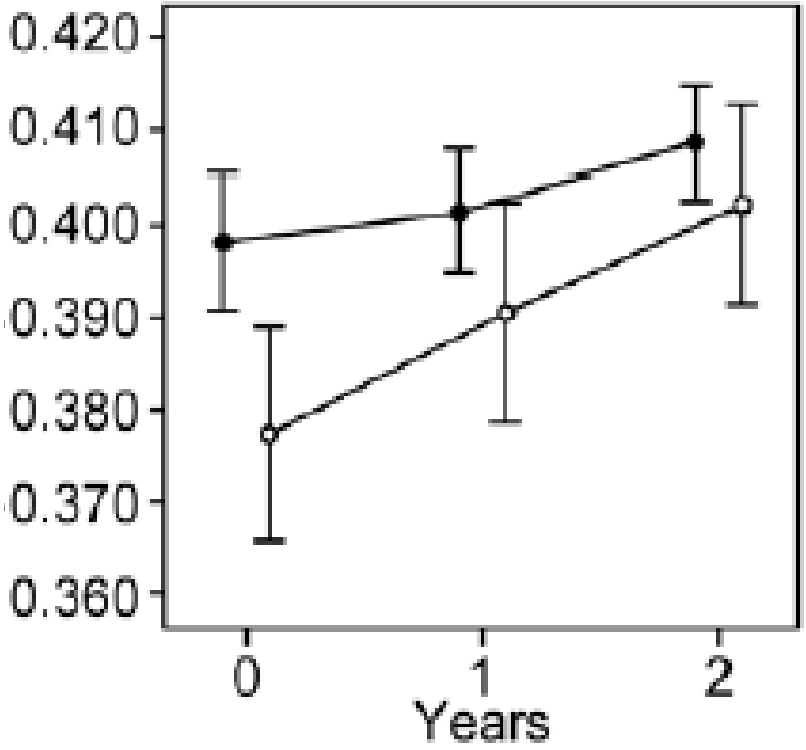
Children with HeFH (6–18 years) Rosuvastatin for 2 years, 5 mg uptitrated to 10 mg (6–10 years) or 20 mg (10–18 years)

Carotid IMT baseline, 12 & 24 months

Baseline: mean carotid IMT significantly greater for the 197 FH children vs 65 unaffected siblings *P*=0.001

2 years FU, change in IMT 0.0054 mm/y (95% CI, 0.0030–0.0082) in FH and 0.0143 mm/y (95% CI, 0.0095–0.0192) in siblings (*P*=0.002)

End-of-study difference in mean carotid IMT no longer significant



Braamskamp M et al. Circulation 2017

Effect of treatment in patients with hoFH

Table 1. Cardiovascular Morbidity and Mortality Characteristics of Patients With Homozygous Familial Hypercholesterolemia Pre-1990 and Post-1990

	Pre-1990 (n=36)	Post-1990 (n=113)
Females/males, n	24/12	58/55
Age at death, y, mean±SD		
All causes	18.4±10.1 (n=27)	32.9±15.5 (n=38)*
Cardiovascular cause	17.7±10.1 (n=22)	31.7±13.3 (n=28)†
Age at first nonfatal MACE, y, mean±SD	12.8±5.9 (n=6)	28.3±10.8 (n=44)‡
Nonfatal cardiovascular events, No. of patients	6 (14 Events)	44 (90 Events)
Myocardial infarction	5 (7 MIs)	10 (11 MIs)
Coronary procedures (CABG, AVR, PTCA, stent)	5 (7 Procedures)	43 (69 Procedures)
Other vascular procedures (carotid surgery, aortoiliac bypass surgery)	None	5 (8 Procedures)
Cerebrovascular events (TIA, stroke)	None	2 (2 Events)

MACE indicates major adverse cardiac event; MIs, myocardial infarctions; CABG, coronary artery bypass surgery; AVR, aortic valve replacement; PTCA, percutaneous coronary angioplasty; and TIA, transient ischemic attack.

*$P < 0.0001$.

†$P < 0.001$.

‡$P < 0.01$.

Raal FJ et al. Circulation nov 2011

A dose-titration and comparative study of rosuvastatin and atorvastatin in hoFH

Table 2

Baseline levels and percent changes from baseline in lipids and apolipoproteins in HoFH patients who received daily treatment with rosuvastatin 20 mg (first 6 weeks), 40 mg (week 6–12) and 80 mg (week 12–18)

	Baseline		Percentage change from baseline			
	Mean (S.D.) (mmol/L) ($n=41$)	Median (range) (mmol/L) ($n=41$)	Week 6 (obs), rosuvastatin 20 mg; mean (S.D.) ($n=41$)	Week 12 (obs), rosuvastatin 40 mg; mean (S.D.) ($n=37$)	Week 18 (LOCF), rosuvastatin 20–80 mg; mean (S.D.) ($n=41$)	Week 18 (LOCF), rosuvastatin 20–80 mg; median (range) ($n=41$)
LDL cholesterol[a]	13.3 (3.0)	13.2 (7.6–20.5)	−18.8 (15.8)***	−22.5 (15.3)***	−21.4 (21.0)***	−22.8 (−58.5 to +52.5)
Total cholesterol	15.0 (3.2)	15.0 (8.8–23.9)	−17.7 (12.5)***	−20.9 (12.3)***	−20.0 (17.6)***	−20.5 (−52.1 to +29.0)
HDL cholesterol	0.93 (0.27)	0.91 (0.52–1.7)	+5.1 (24.5) NS	+4.2 (17.2) NS	+3.1 (20.7) NS	+4.9 (−43.1 to +63.6)
Triglycerides	1.6 (1.4)	1.1 (0.5–6.1)	−7.5 (29.7) NS	−9.6 (26.9)*	+3.3 (46.2) NS	−7.6 (−57.2 to +187.1)
Apo B[b]	396 (88)[c]	400 (210–602)[c]	NA	NA	−20.0 (18.0)***	−25.2 (−49 to +28)
Apo A-I[d]	106 (24)[c]	103 (65–175)[c]	NA	NA	+5.2 (18.5) NS	+5.5 (−35 to +47)

LOCF, Last observation carried forward; obs, observed values at the timed measurement; LDL, low-density lipoprotein; HDL-C, high-density lipoprotein; apo, apolipoprotein; NS, not statistically significant. *$p<0.05$; ***$p<0.0001$.

[a] $n=40$ for baseline and LOCF.

[b] $n=38$ for baseline and LOCF.

[c] These values are in mg/dL.

[d] $n=40$ for LOCF.

Marais et al Atherosclerosis 2008

Statin in subpopulations

Children
hoFH
Elderly
Diabetic patients
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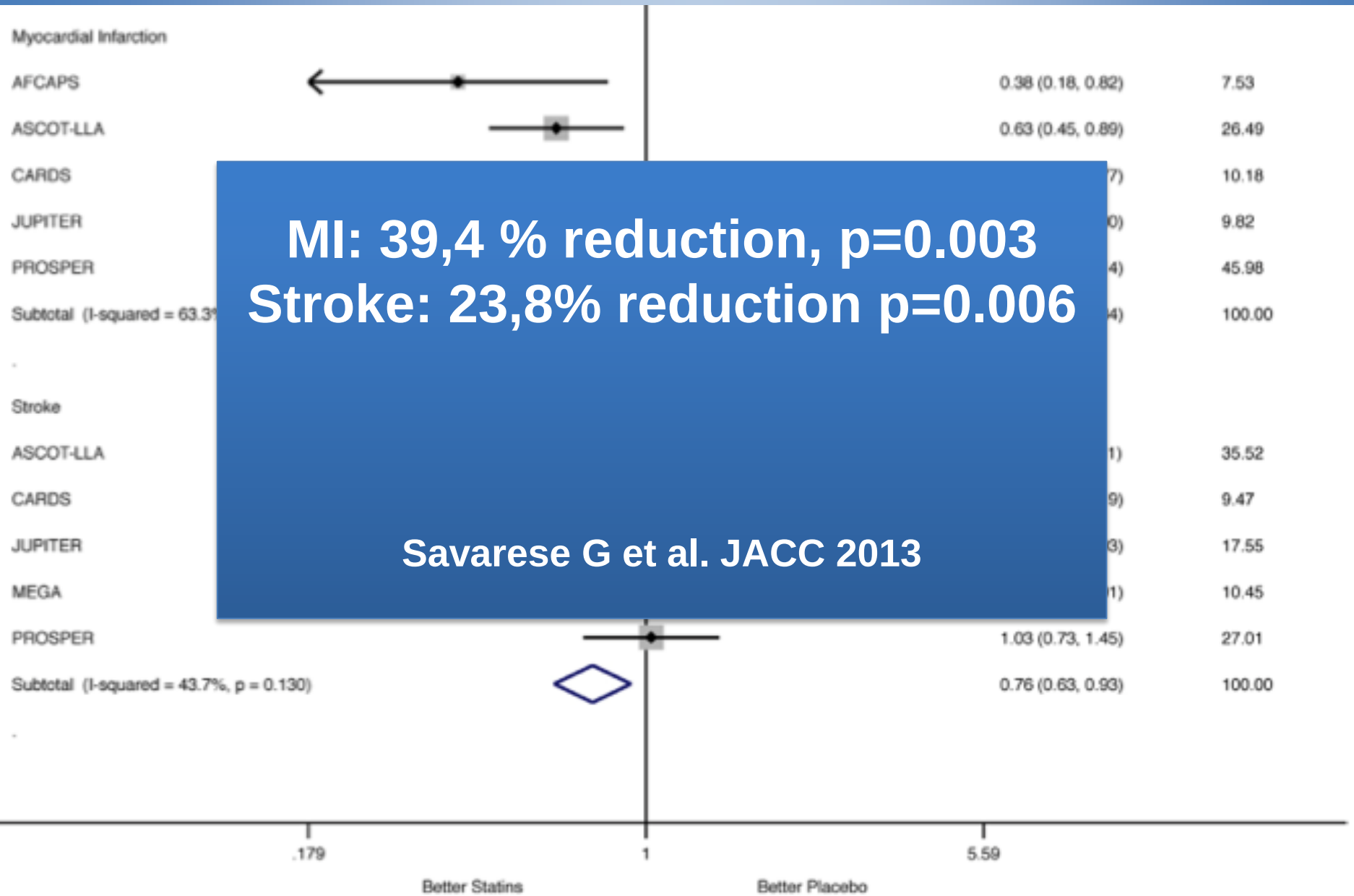
Pregnant and breast feeding women

Meta-analysis of the effect of statin in the Elderly



MI: 39,4 % reduction, p=0.003
Stroke: 23,8% reduction p=0.006

Savarese G et al. JACC 2013

Meta-analysis of the effect of statin in the Elderly

Meta-analysis studies with more than 1000 subjects and more than 2 years duration

	Statin more intensive	control	RR
≤65 Yrs	6056	7455	0.78 (0.75-0.82)
65 à <75 Yrs	4032	4908	0.78 (0.74-0.83)
≥75 Yrs	885	987	0.84 (0.73-0.97)

CTT collaboration Lancet nov 2010

EAS/ESC 2016

Table 24 Recommendations for the treatment of dyslipidaemia in older adults

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment with statins is recommended for older adults with established CVD in the same way as for younger patients.	I	A	334, 337
Since older people often have co-morbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger subjects.	IIa	C	
Statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia.	IIa	B	62, 64, 65

CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

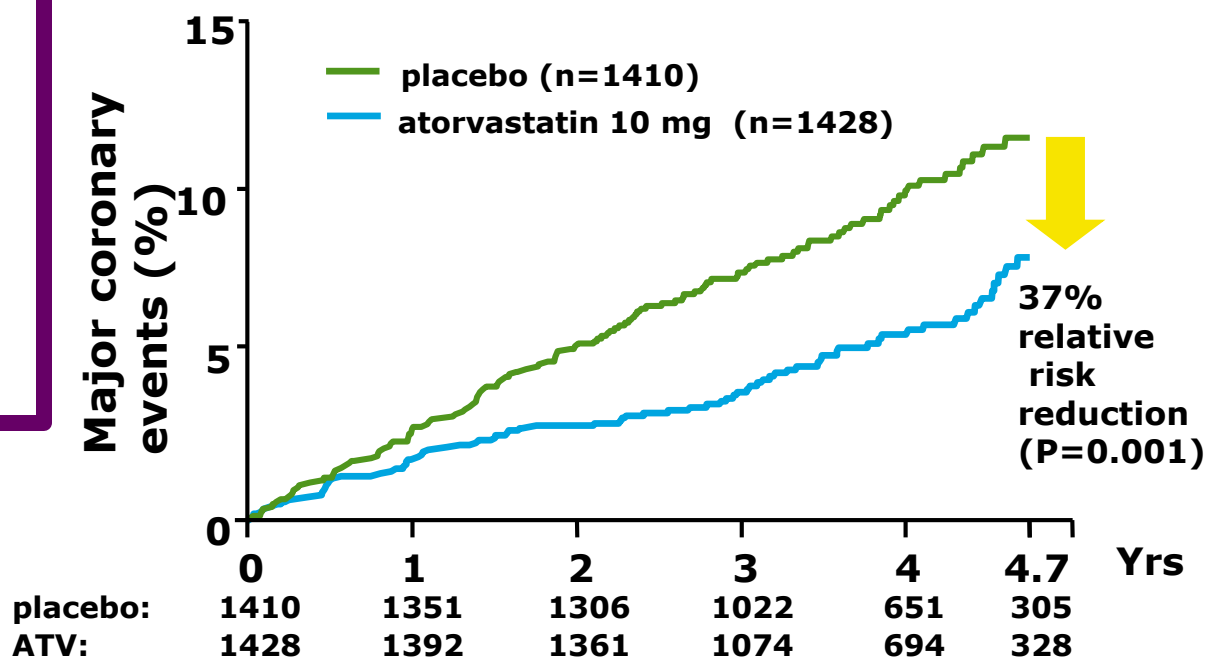
Statin in subpopulations

Children
hoFH
Elderly
Diabetic patients
Patients with CKD
Pregnant and breast feeding women

Major Coronary Event Rates in Patients with/without Diabetes

- 12 prosp. studies, follow-up at least 3 years
- **Primary prevention**
  - PCB n= 5385 / Active treatment n= 5453
  - Events in the PCB group: 543 (10%)
- **Secondary prevention**
  - PCB n= 2720 / active treatment n= 2720
  - Events in the PCB group: 922 (30%)

CARDS: Primary Prevention of CVD with Atorvastatin in Patients with Type 2 Diabetes



Costa J et al. BMJ May 2006

Colhoun HM et al. Lancet 2004

Statin in patients with CKD

- **Meta-analysis (11 RCTs, 21,295 participants, 6857 on dialysis.**
- **Statin reduced**
  - **death from all causes (RR 0.66; 95% CI: 0.55–0.79; p < 0.0001),**
  - **death from cardiac causes (RR: 0.69; 95%CI: 0.55–0.68; p = 0.0012),**
  - **cardiovascular events (RR: 0.55; 95%CI: 0.4–0.75; p = 0.0001)**
  - **stroke (RR: 0.66; 95%CI:0.5–0.88; p = 0.0022)**

- **Patients on dialysis: non-significant effect on death from all causes (RR: 0.99; 95%CI: 0.88–1.11; p = 0.85) and stroke (RR: 1.31; 95%CI: 0.9–1.89; p > 0.05), but had the effect of reducing death from cardiac causes (RR: 0.79; 95%CI: 0.64–0.98; p < 0.05) and CV events (RR: 0.81; 95%CI: 0.7–0.94; p < 0.05)**

Barilsky M et al. Pharmacol Res 2013

Statin in patients with CKD

- Patients with CKD are at high or very high CV risk
- Patients with CKD are at higher risk than those without CKD of side-effects due to reduced renal excretion, polypharmacy, and comorbid conditions
- Meta-analysis, (23 trials, 39 419 participants): statins reduced the rates of microalbuminuria, proteinuria, and deaths, but did not slow the clinical progression of non-end stage CKD*
- The KDIGO guidelines recommend the use of moderate-intensity statins (e.g. atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 40 mg, pravastatin 40 mg, fluvastatin 80 mg or pitavastatin 2 mg) in this population

Zhang Z et al Pharmacol Res 2016;105:74-83,

Statin in subpopulations

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Statin, pregancy and breast feeding

- **Statin is contra-indicated during pregnancy**

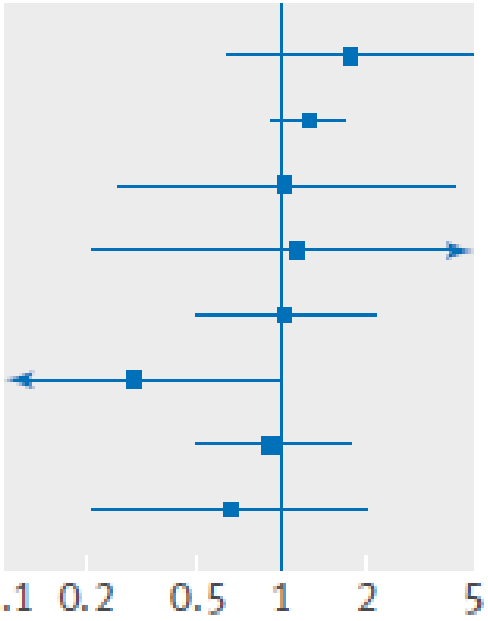
- **The current recommendation is that statins should be discontinued 2-3 months before pregnancy and should not be used during breastfeeding**

- **One pregnancy in a woman with FH = 12-15 months without statin. Women with FH may develop very high lipid levels**
- **Since age at which women have children has increase, some women have a high cholesterol and possibily atherosclerotic burden during pregnancy**

Statin and pregnancy

Meta-analysis and systematic review in women: no teratogenic effect when taken during first trimester* ans when adjusted on comorbidities including diabetes**

Outcome	Propensity score stratified	Relative risk (95% CI)
Central nervous system malformations	1.76 (0.64 to 4.86)	
Cardiac malformations	1.25 (0.93 to 1.70)	
Respiratory malformations	1.02 (0.25 to 4.09)	
Cleft palate and lip	1.14 (0.21 to 6.14)	
Gastrointestinal malformations	1.02 (0.49 to 2.14)	
Genitourinary malformations	0.29 (0.09 to 1.01)	
Musculoskeletal malformations	0.91 (0.48 to 1.72)	
Other	0.65 (0.21 to 1.99)	



***Karalis DG et al. J Clin Lipidol 2016**
****Bateman BT et al. BMJ 2015**

Statin and breast feeding

- **Rosuvastatin and pravastatin are both hydrophilic statins with theoretically lower transfer into breast milk**
- **Rosuvastatin has a higher degree of protein binding, higher molecular weight and higher volume of distribution than pravastatin and may therefore be preferable**
- **Even if breast milk were to contain statins, systemic absorption by the infant would be very limited, with a low risk of pharmacological effects**
- **No data on the impact of statin on breast milk composition. According to one study, breast milk from a woman with hoFH contained 3 times as much cholesterol as that of healthy control women**

Conclusion

- **This talk was an attempt to summarize 44810 publications of which 35268 in human**

Thanks for your attention!!