

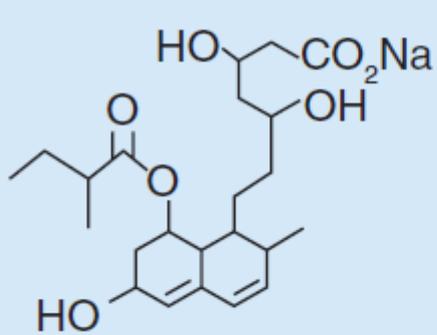
Statins

Lale Tokgozoglu MD FACC FESC

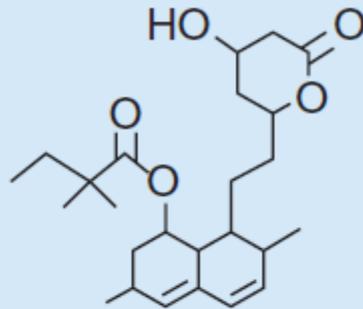
Professor of Cardiology

Hacettepe University

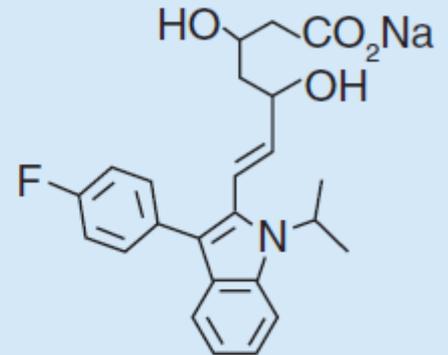
President EAS



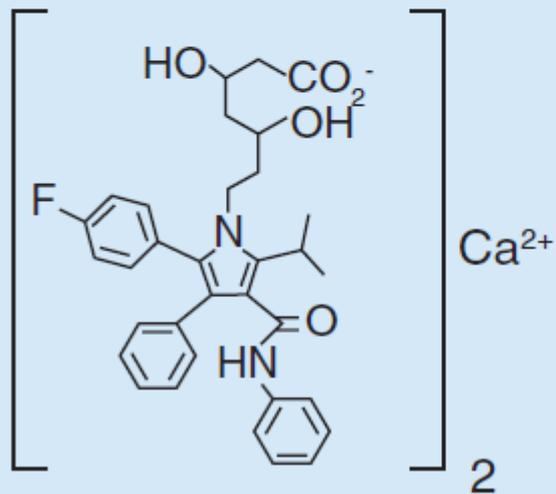
Pravastatin



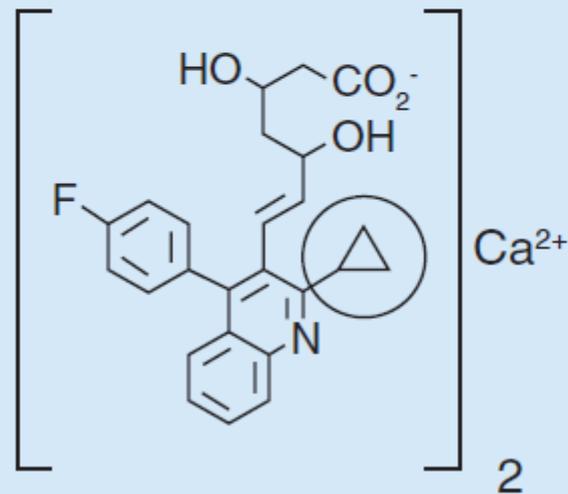
Simvastatin



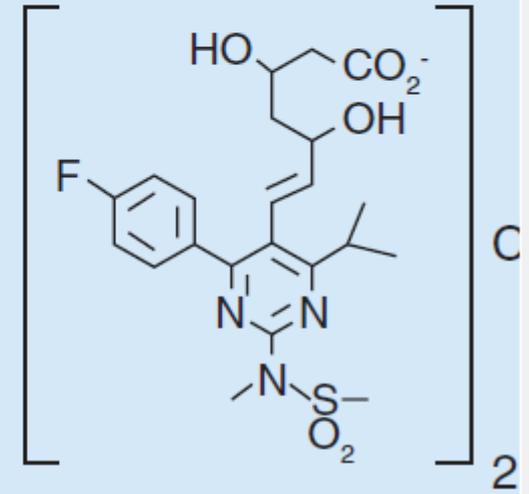
Fluvastatin



Atorvastatin



Pitavastatin

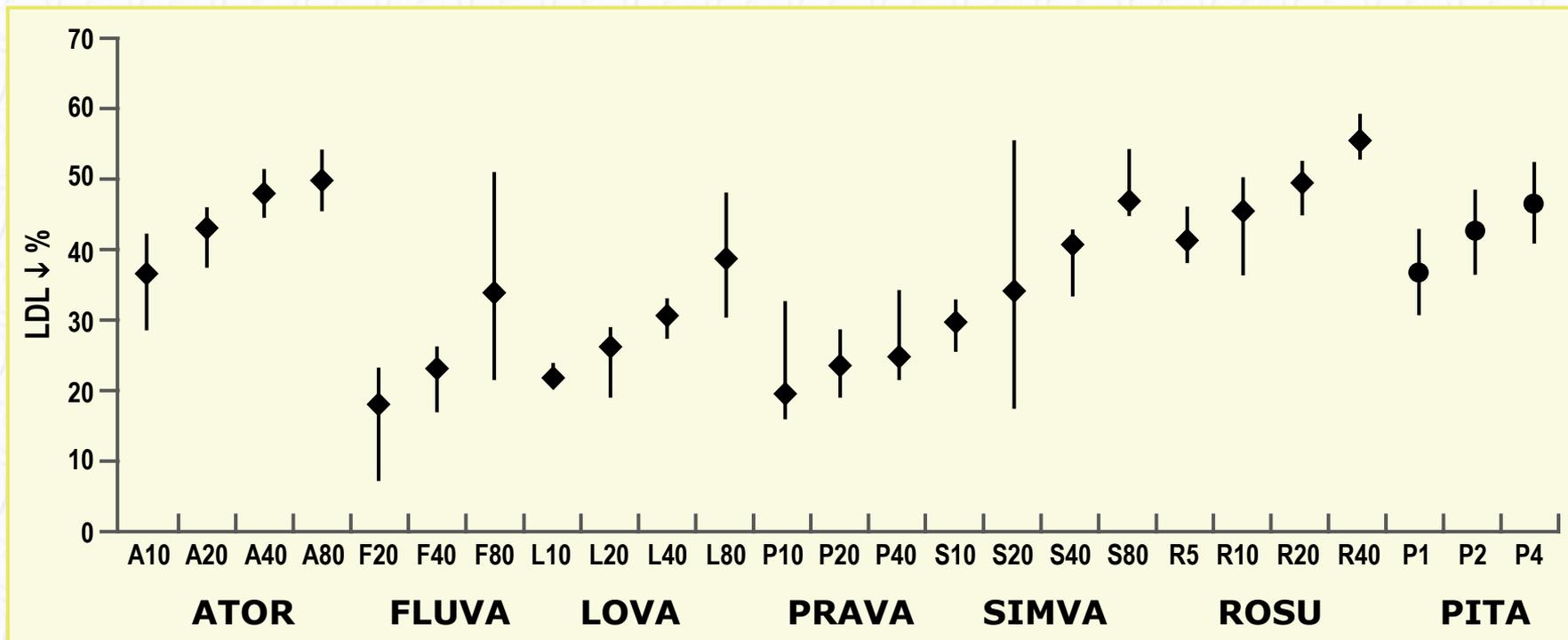


Rosuvastatin

Statin Pharmacokinetics

	Bio-Availability	Half-Life, h	CYP450 Metabolism	Solubility
Lovastatin	< 5%	2 to 3	3A4	Lipophilic
Simvastatin	< 5%	2	3A4	Lipophilic
Pravastatin	17%	1.5 to 2	none	Hydrophilic
Fluvastatin	24%	1	2C9	Hydrophilic
Atorvastatin	12%	14	3A4	Lipophilic
Rosuvastatin	20%	20	2C9	Hydrophilic
Pitavastatin	43% to 51%	12	2C9, 2C8	Slightly Hydrophilic

A systematic review and meta-analysis of the therapeutic equivalence of statins



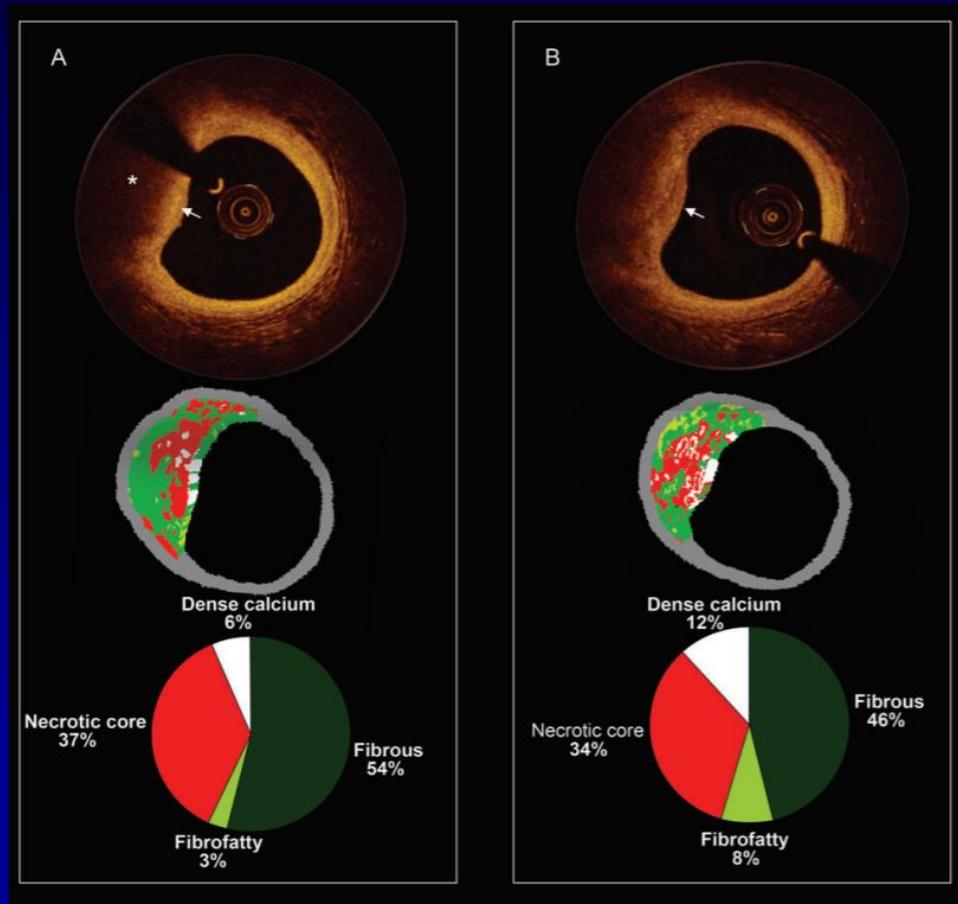
Weng TC, et al. *J Clin Pharm Ther.* 2010;35;139-151

Mukhtar RY, et al. *Int J Clin Pract.* 2005;59(2):239-252

Most ACS results from rupture of vulnerable plaques
Big lipid core, thin fibrous cap, inflammation and neovascularisation

Data not available

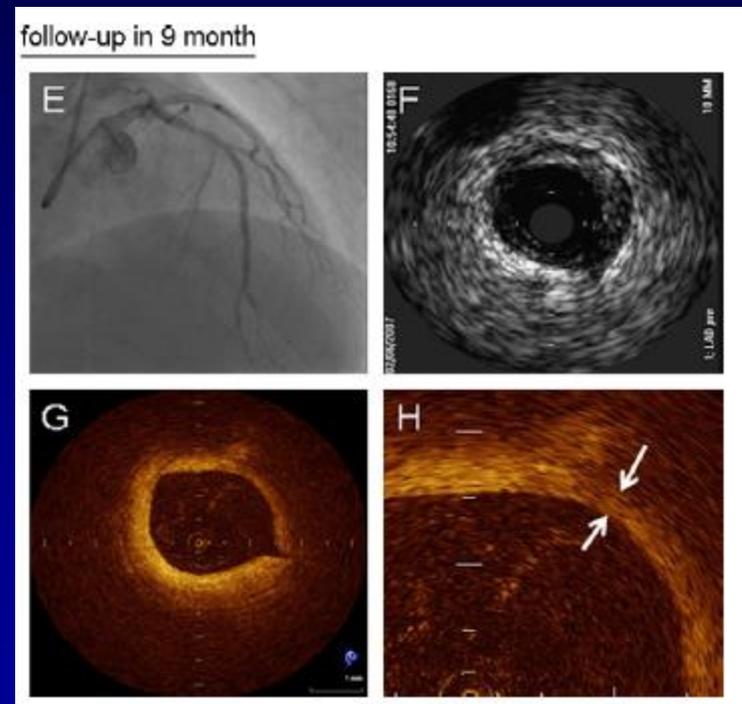
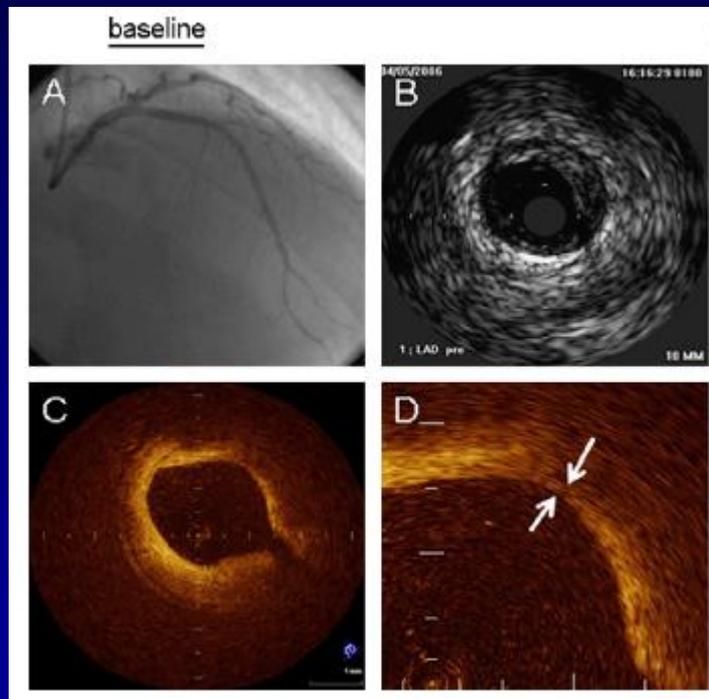
Statins cause plaque stabilization: OCT and VH one year after statin



Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: Assessment by optical coherence tomography study

Shigeho Takarada, Toshio Imanishi, Takashi Kubo, Takashi Tanimoto, Hironori Kitabata, Nobuo Nakamura, Atsushi Tanaka, Masato Mizukoshi, Takashi Akasaka*

Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama, Japan

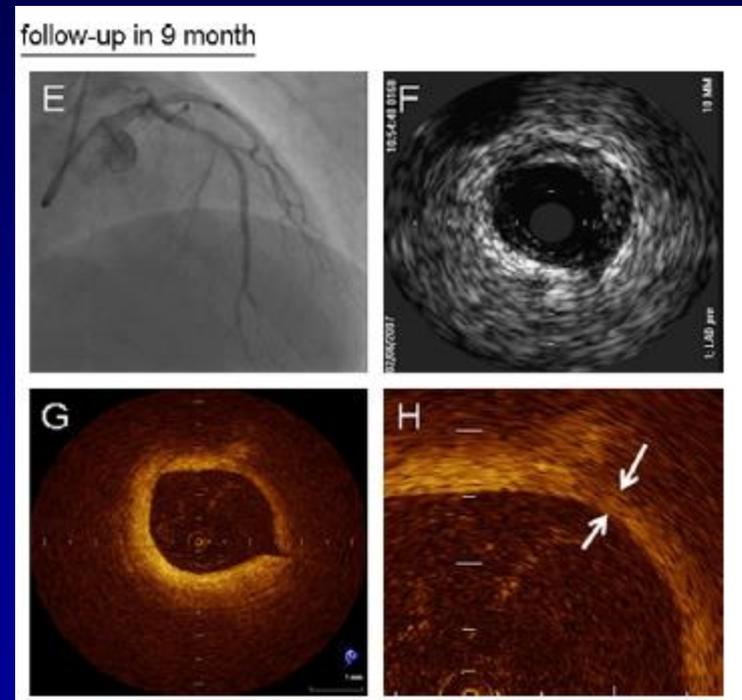
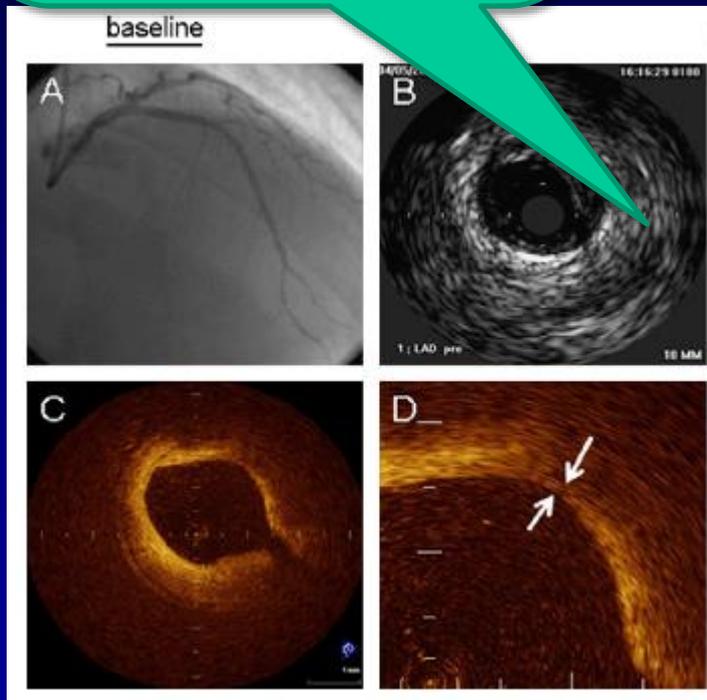


**Fibrous cap
thickens in 9
months**

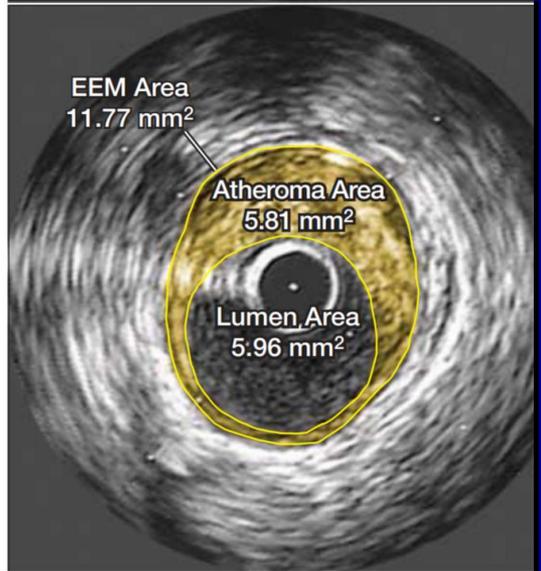
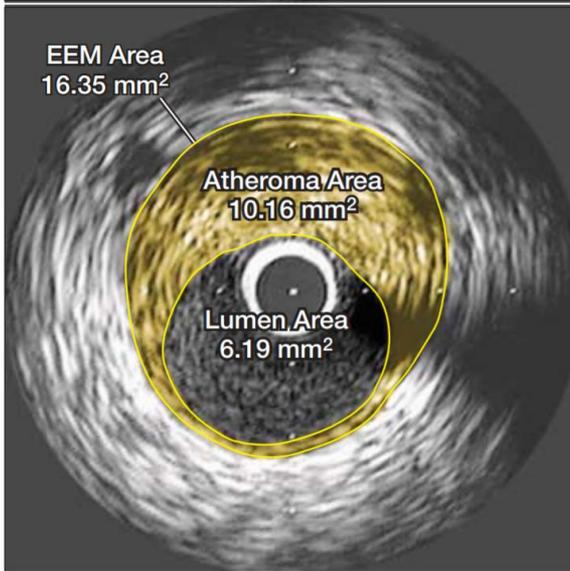
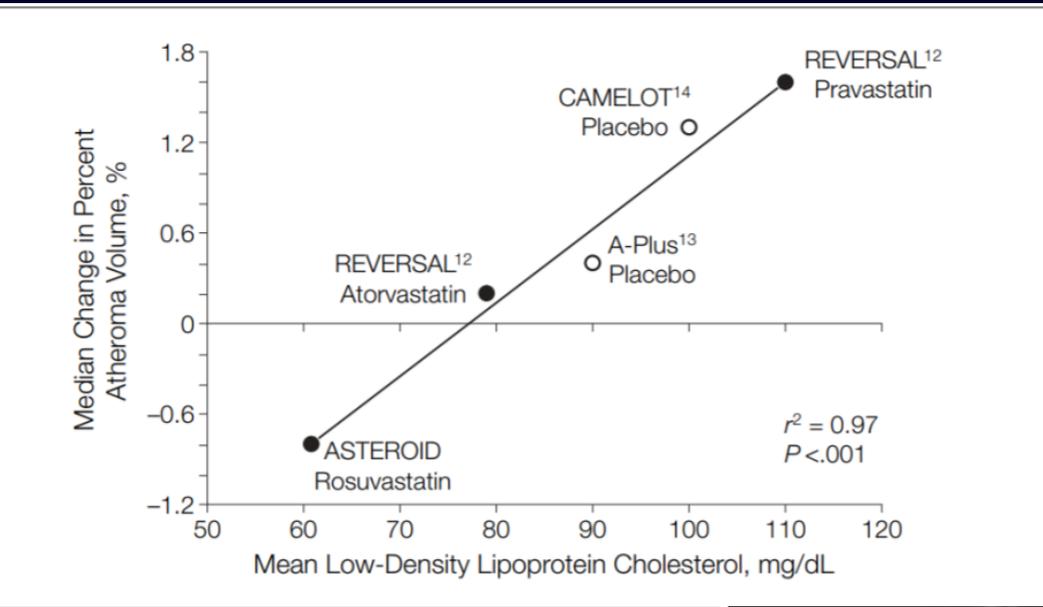
Study on coronary fibrous-cap thickness in patients with acute coronary syndrome: Assessment by optical coherence tomography study

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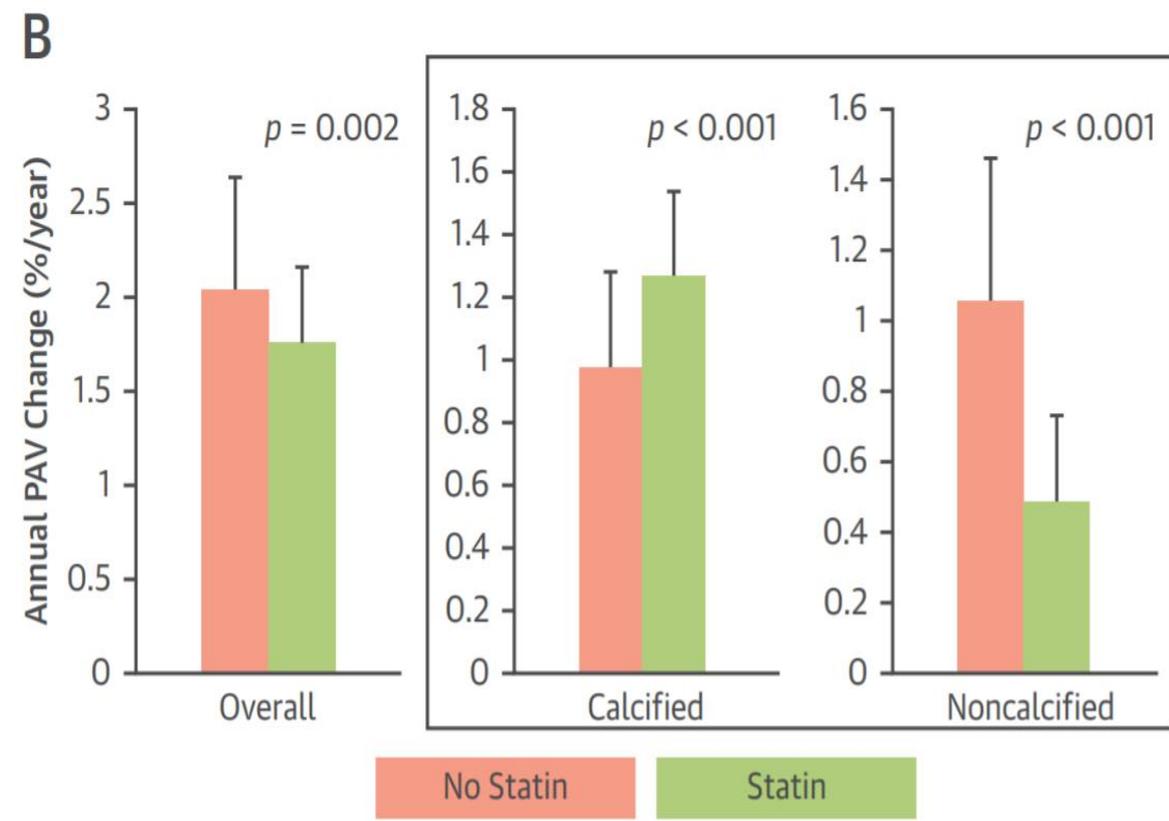
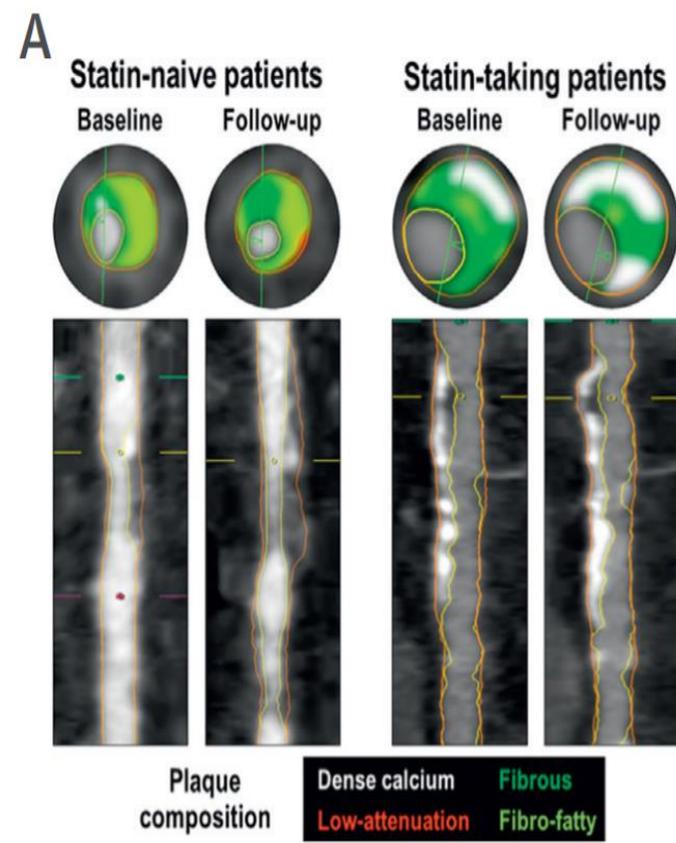
Journal of Intensive Cardiology, Wakayama Medical University, Wakayama, Japan



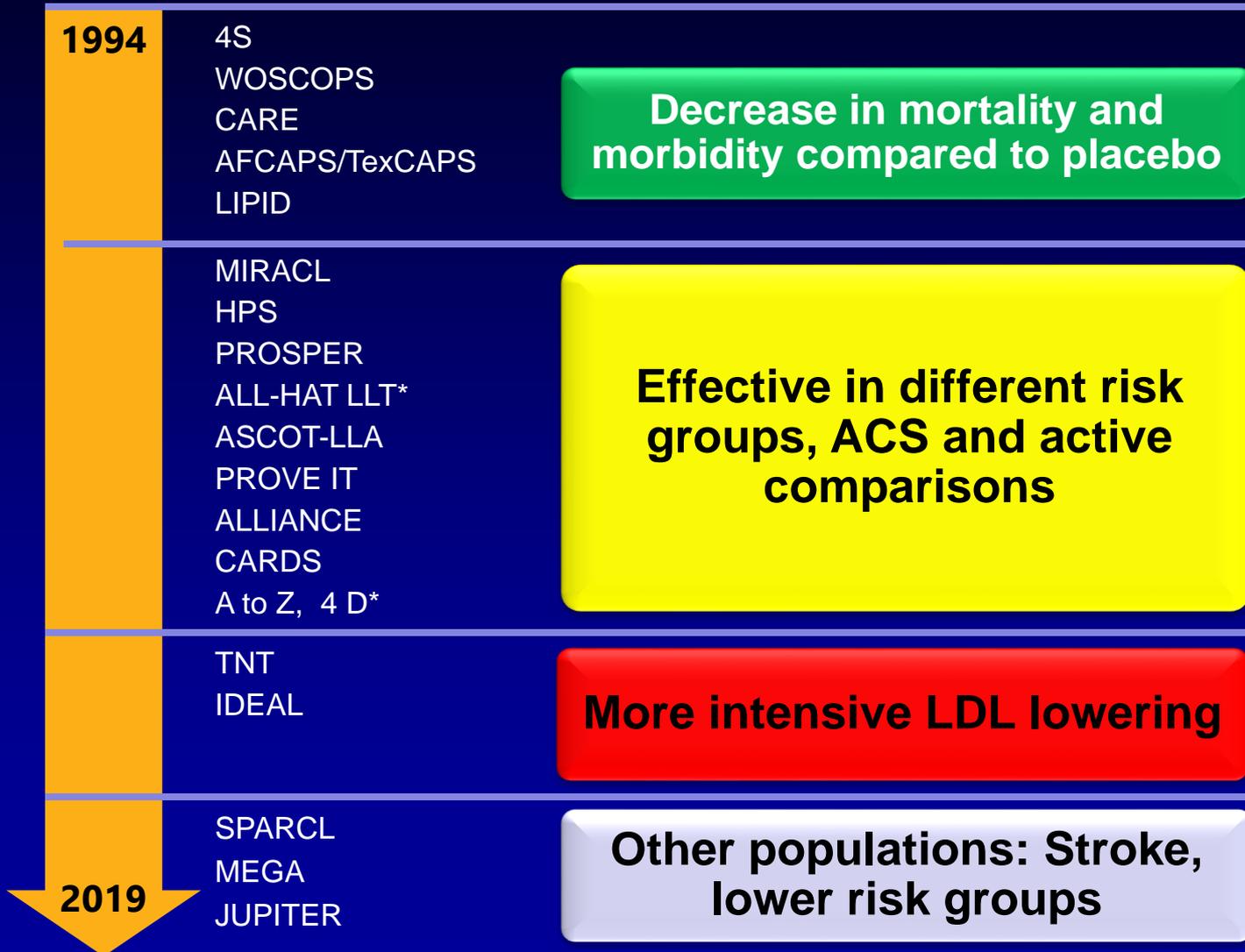
Relation between LDL and PAV:



Statins decrease atheroma volume and increase calcification: PARADIGM Study n=1255 CT at least 2 years apart

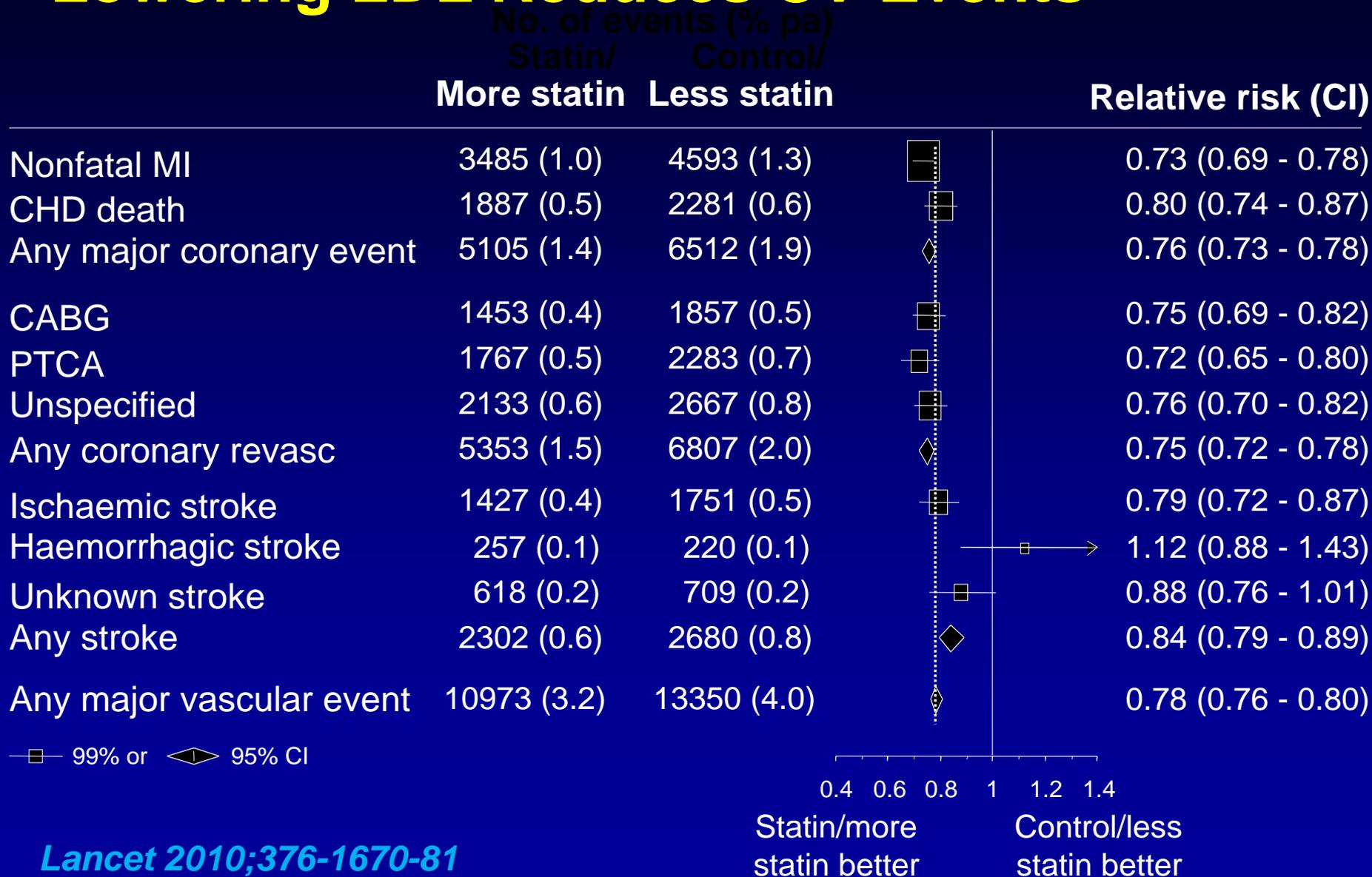


Clinical Outcome Studies With Statins



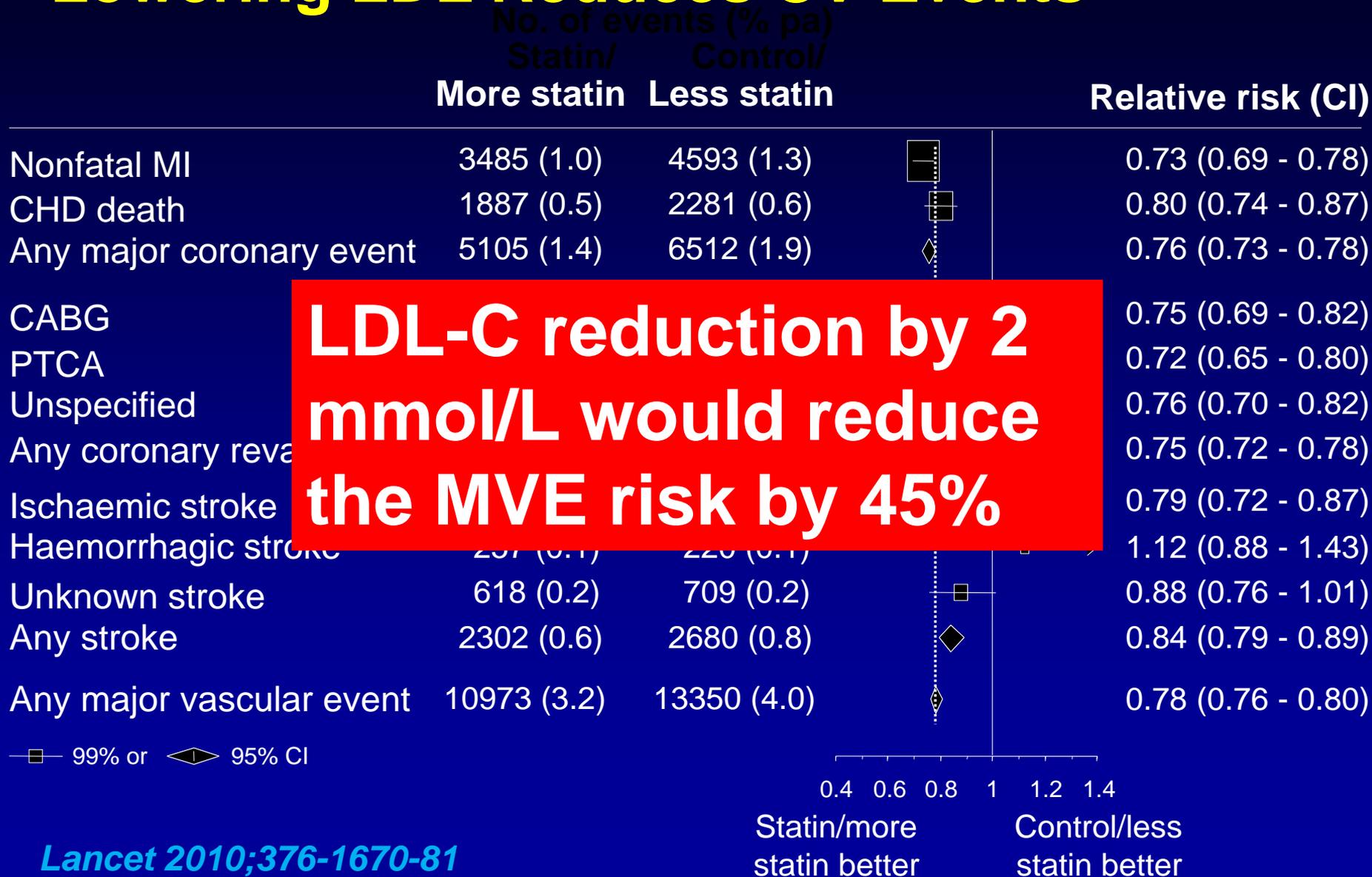
Key Lessons From Statin Trials (>160,000 pts)

Lowering LDL Reduces CV Events

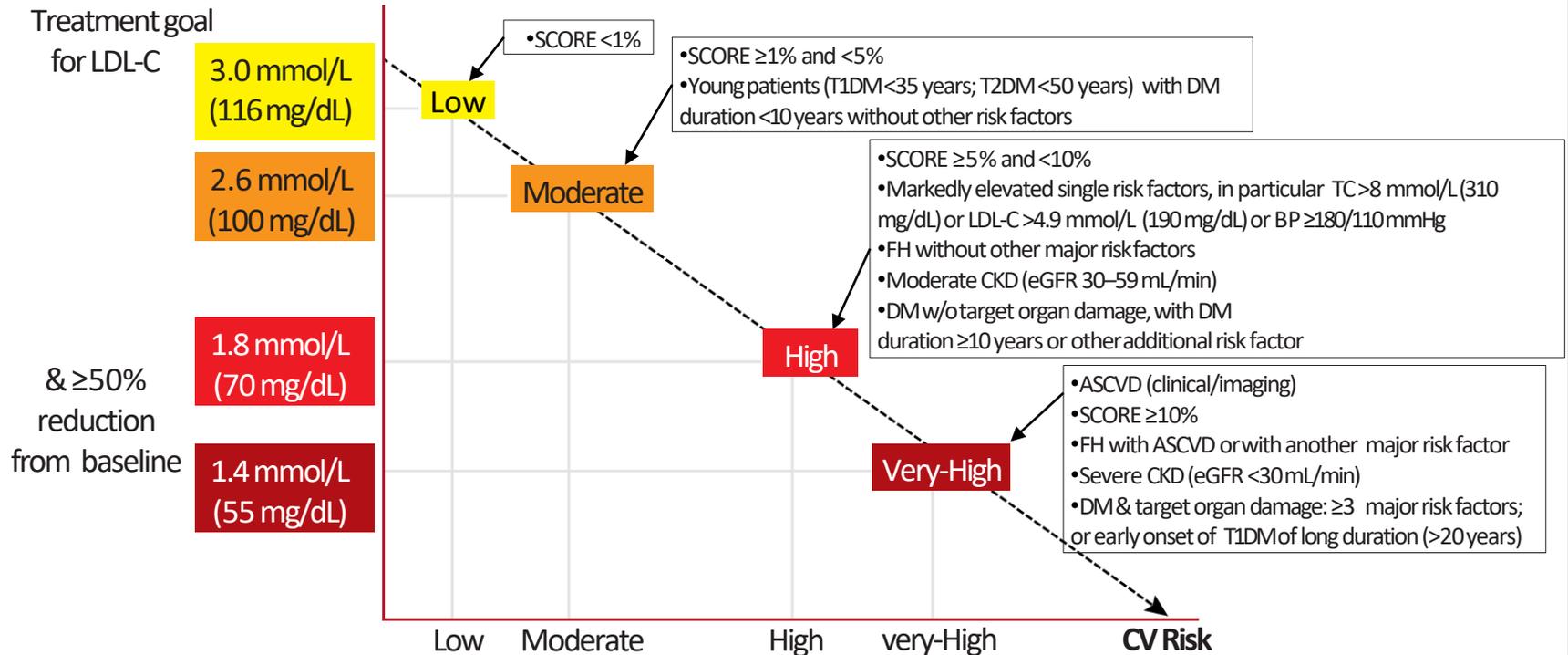


Key Lessons From Statin Trials (>160,000 pts)

Lowering LDL Reduces CV Events



Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



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Recommendations for pharmacological low-density lipoprotein cholesterol lowering (1)

Recommendations	Class	Level
It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals ^c set for the specific level of risk.	I	A
If the goals ^c are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	Ib	C

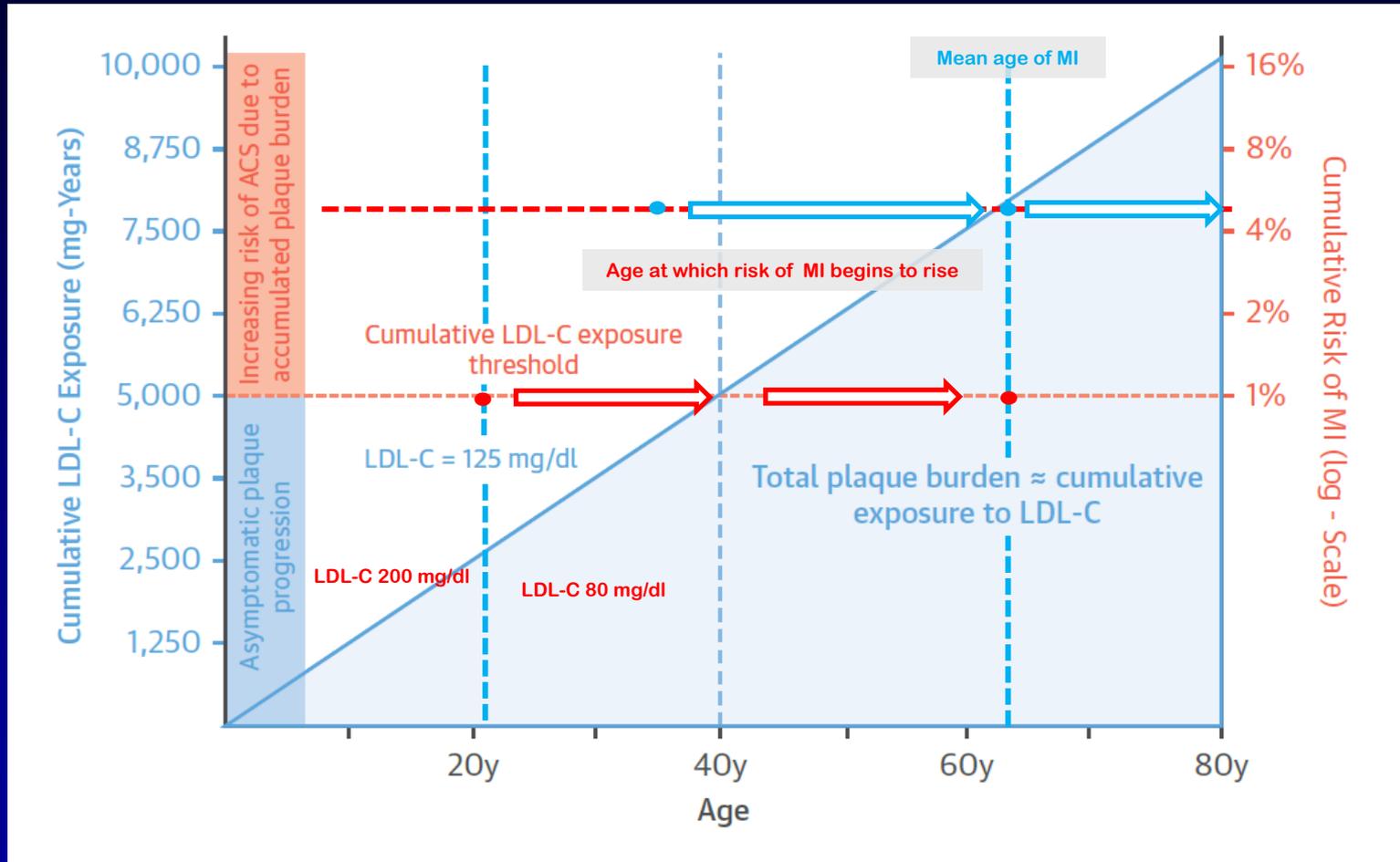
^c For definitions see Full Text.

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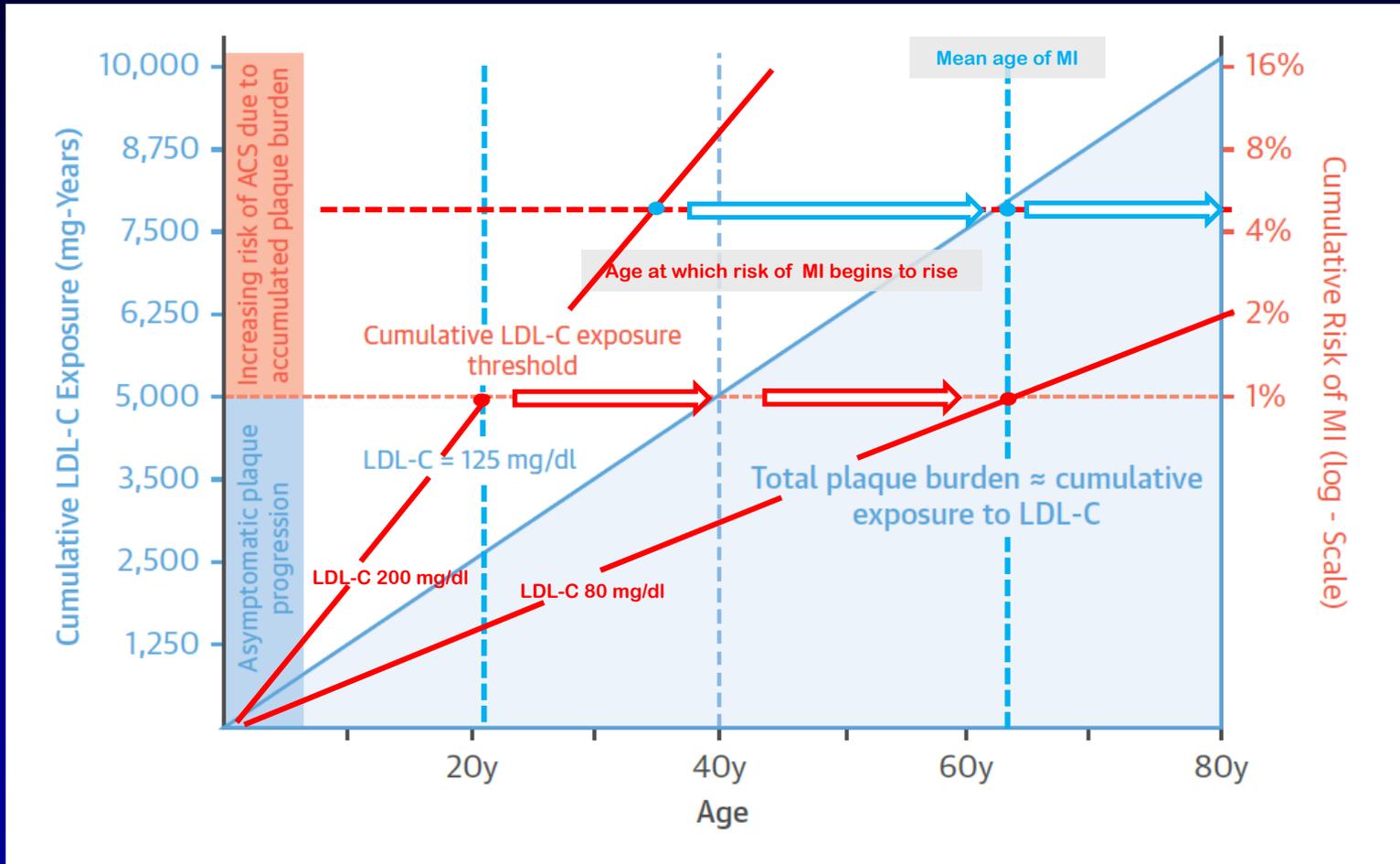
Is there any debate about when to use statins ?

- ♥ Primary prevention with high LDL-C
- ♥ Primary prevention with low CV risk
- ♥ Elderly over 75 years
- ♥ CKD

Effect of Cumulative Exposure to LDL on Plaque Burden and CV Risk

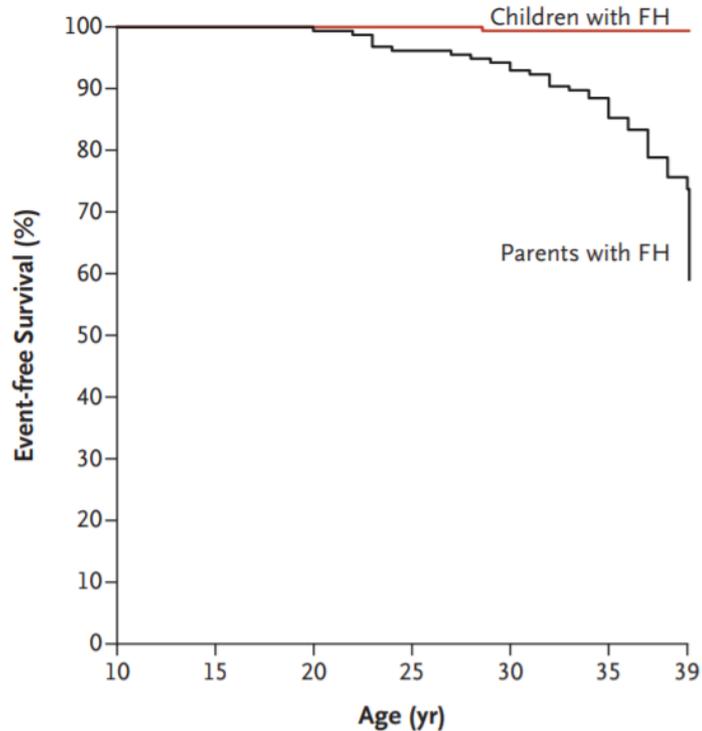


Effect of Cumulative Exposure to LDL on Plaque Burden and CV Risk



20 year follow-up of children with FH

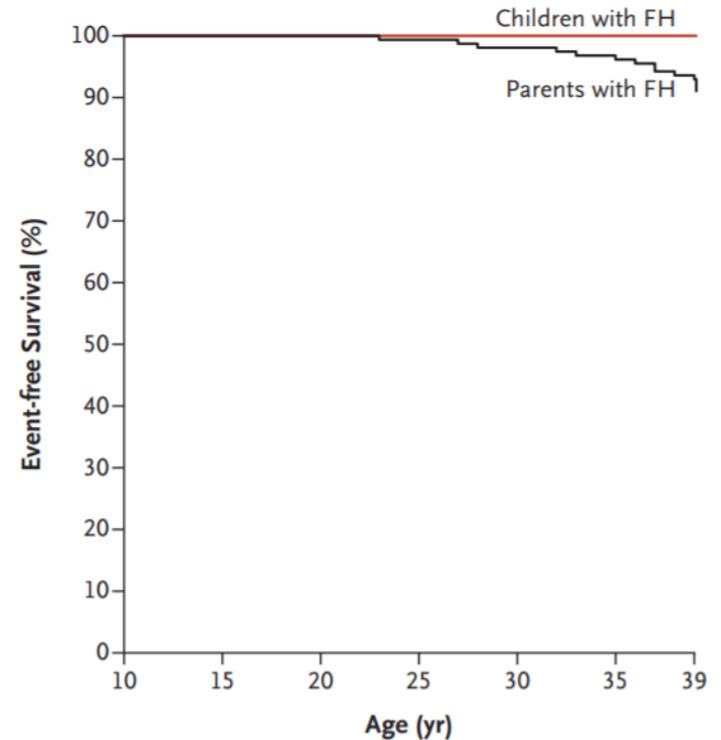
A Freedom from Cardiovascular Events



No. at Risk

Children with FH	214	213	213	206	134	44	1
Parents with FH	156	156	155	150	145	133	115

B Freedom from Death from Cardiovascular Causes



No. at Risk

Children with FH	214	213	213	213	143	45	1
Parents with FH	156	156	156	155	153	150	145

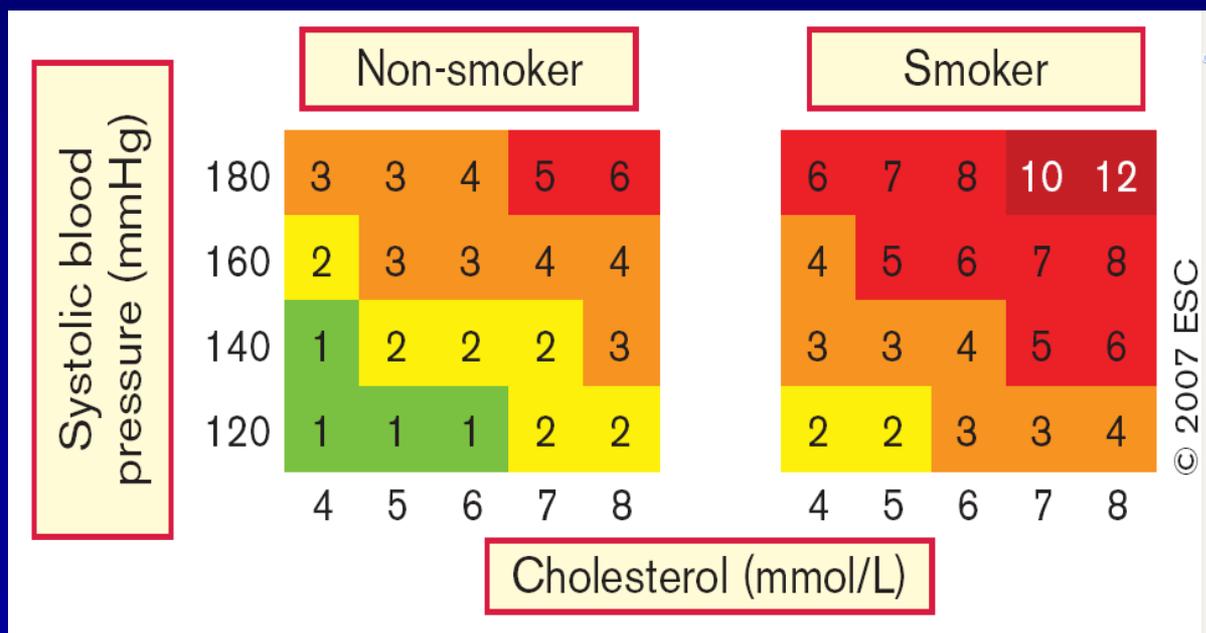
Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

Total CV risk (SCORE) %		Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
Primary Prevention	<1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	I/C	I/C	Ia/A	Ia/A
	≥1 to <5, or moderate risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	Ia/A	Ia/A	Ia/A	Ia/A
	≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	Ia/A	Ia/A	Ia/A	Ia/A	Ia/A	Ia/A
Secondary Prevention	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	Ia/B	Ia/A	Ia/A	Ia/A	Ia/A	Ia/A
	Very-high risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention			
Class ^a /Level ^b	Ia/A	Ia/A	Ia/A	Ia/A	Ia/A	Ia/A	

What about subjects with low risk ?

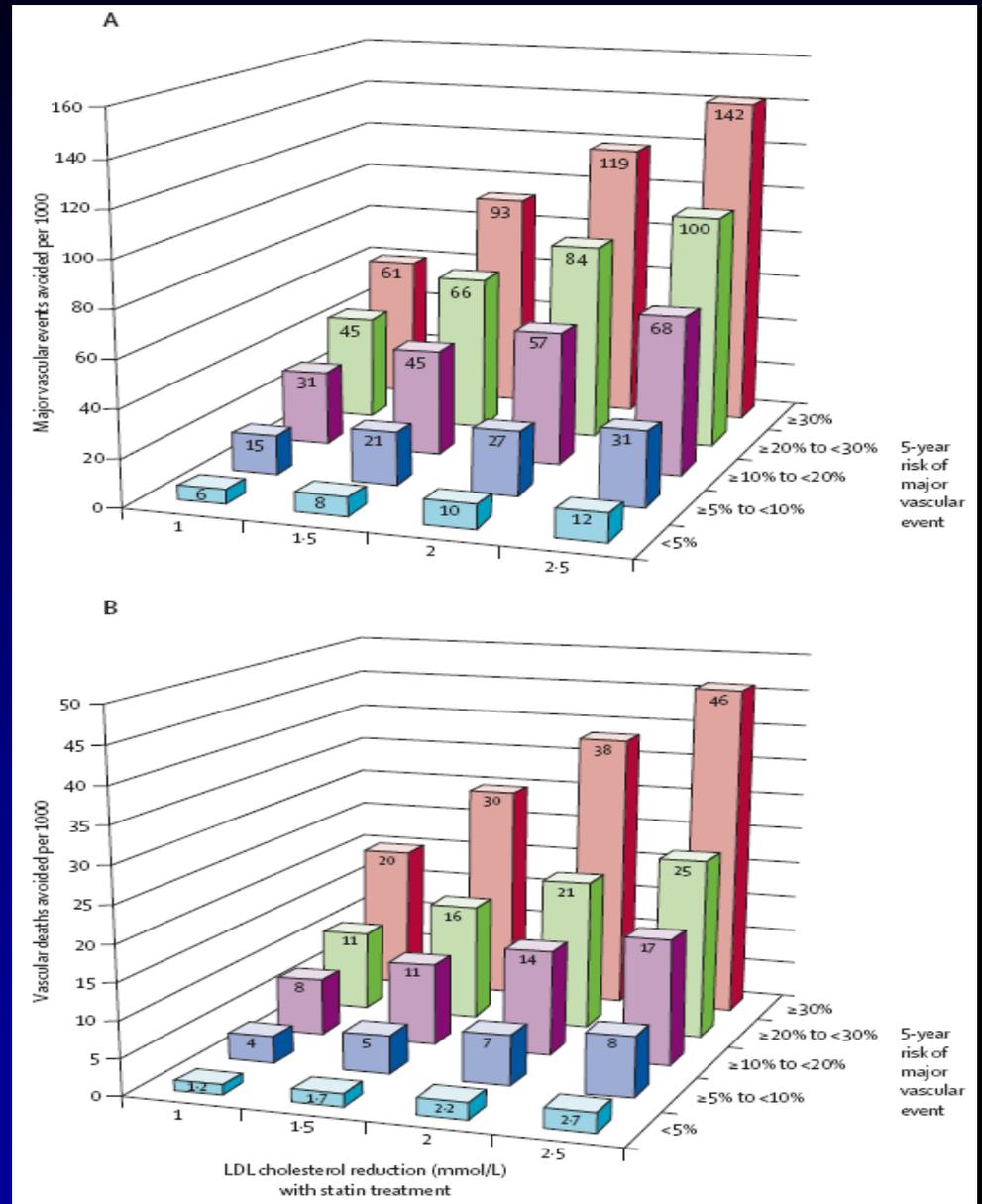
A low absolute 10 year risk in a younger person may conceal a high relative risk:

- Use relative risk chart
- Risk age
- Calculate lifetime risk ?

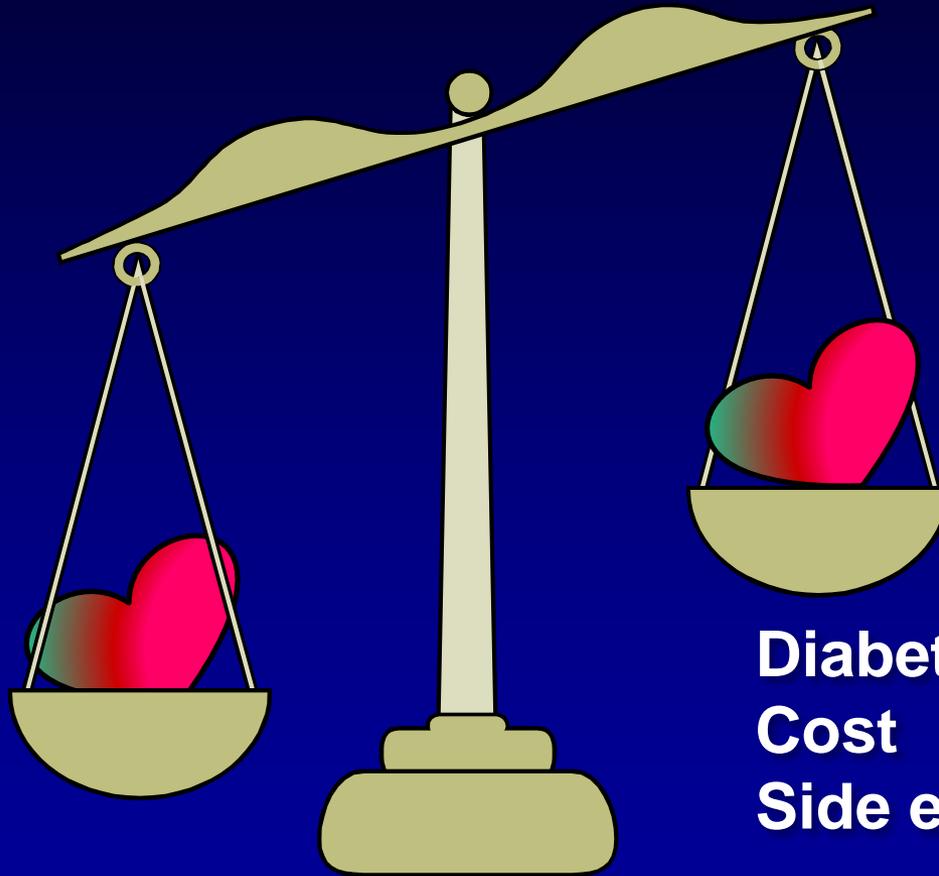


Low risk patients benefit from statins:

AFCAPS/TexCAPS
JUPITER
HOPE-3
CTT analysis



Prolonged use of statins in low risk



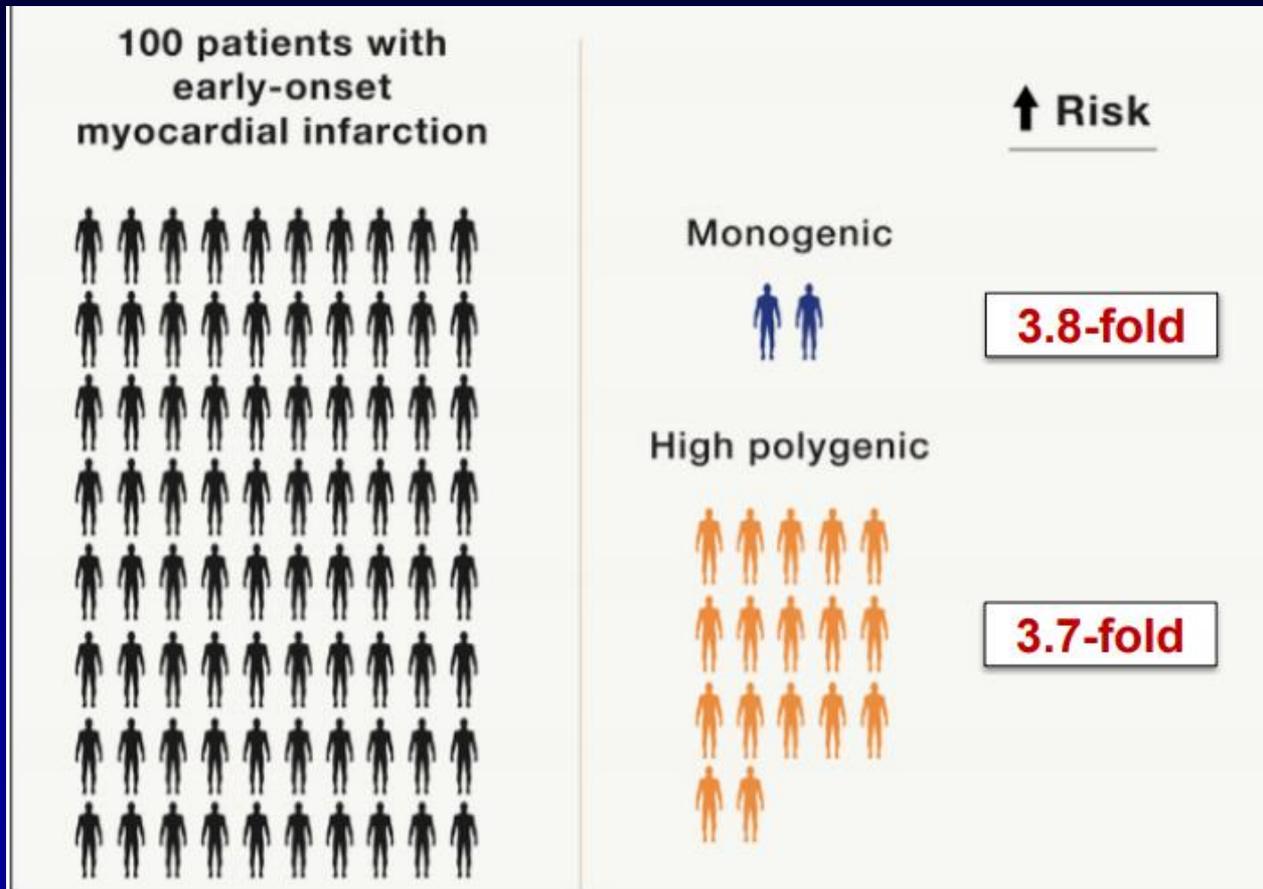
CV benefits

Diabetes risk
Cost
Side effects

What other parameter can help us decide to use statins in seemingly low short term risk patients?

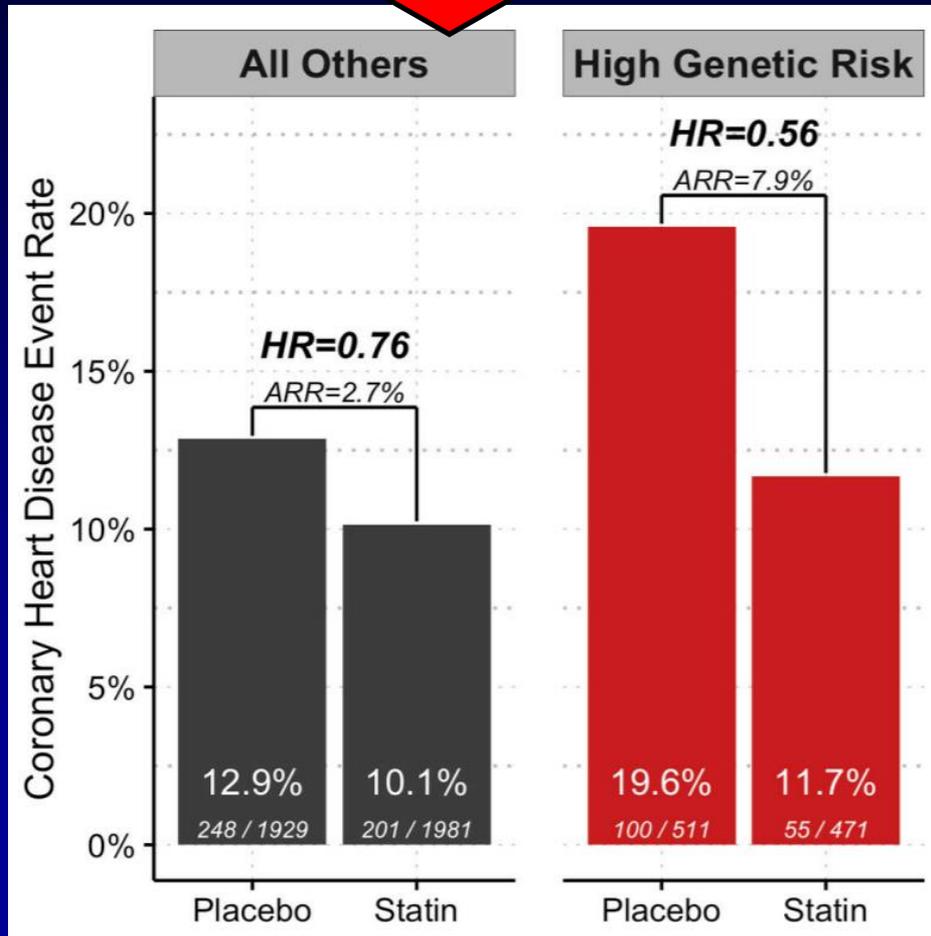
- ♥ **Genetics**
- ♥ **Biomarkers**
- ♥ **Imaging**

Rare monogenic mutations vs polygenic risk scores



Polygenic scores identify who will benefit most from statin despite similar LDL lowering:

RRR with statin 46 % at high risk, 26 % in others



Subjects with highest genetic score had highest risk reduction with statins

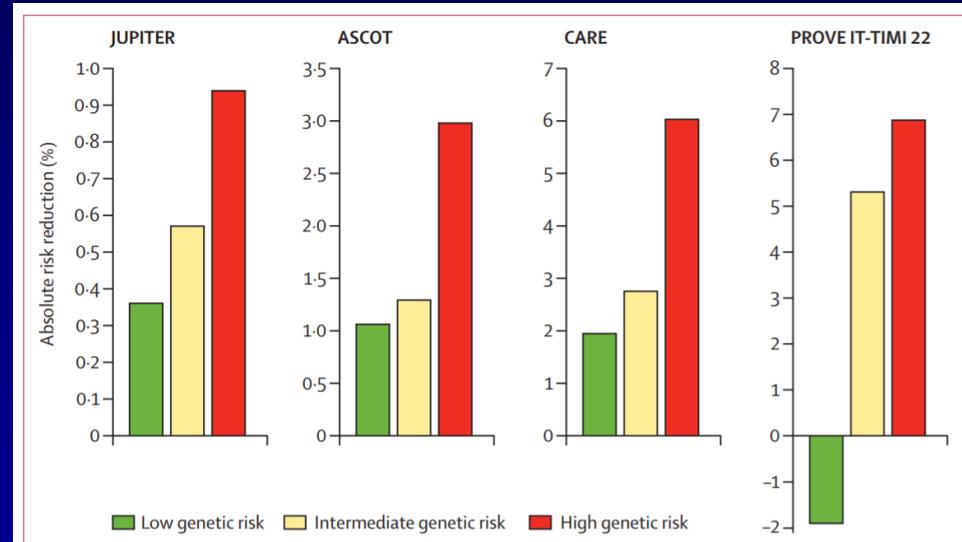


Figure 3: Absolute risk reductions of coronary heart disease events with statin therapy across genetic risk score categories

Mega et al Lancet (2015) 385:2264-71

Natarajan et al Circulation (2017) 135:2091-101

Can we improve risk prediction by adding more parameters-biomarkers ?

Inflammation:

hs CRP

GDF-15

Fibrinogen

Plaque

instability:

PAPP-A

MPO

MMPs

Neurohormonal

activation:

Copeptin

MR-proADM

Platelet

activation/thrombosis:

Lp-PLA₂

S-PLA₂

S CD40L

PAI-1

D-Dimer

Myocardial

necrosis:

hs-Tn

H-FABP

Lipidomics:

TAG

CE

PE

Myocardial

stress:

NT-proBNP

NT-proANP

ST 2

ET-1

Gal-3

NRG-1

Proteomics:

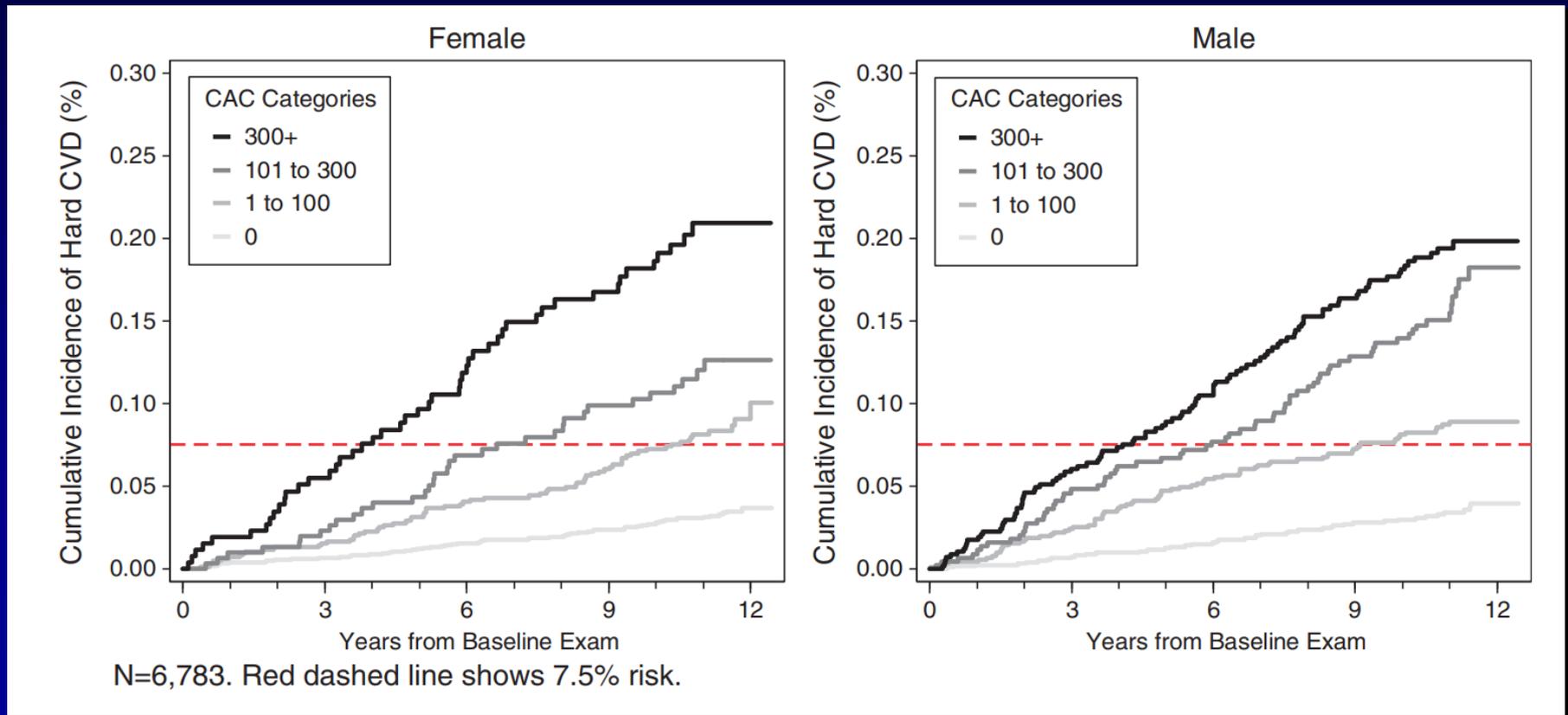
Brached chain
amino acids

Metabolomics:

Quartose IR

Micro RNAs

Ten-year association of coronary artery calcium with ASCVD events: MESA (n=6814, age 45-84)



Recommendations for cardiovascular imaging for risk assessment of atherosclerotic cardiovascular disease

Recommendations	Class	Level
Arterial (carotid and/or femoral) plaque burden on ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.	Ia	B
CAC score assessment with CT should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.	Ia	B

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STATINS: HIGHLY FAVOURABLE BENEFIT VS. RISK RATIO

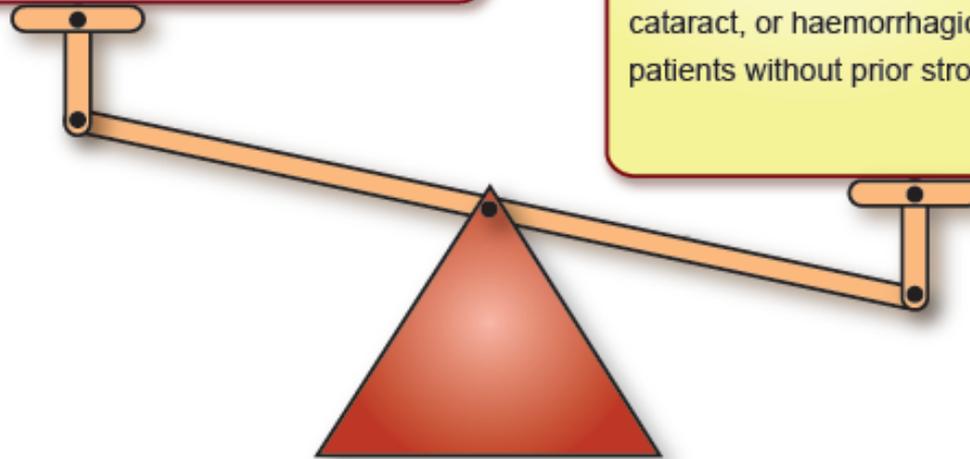
POTENTIAL RISKS

- Modest risk of new-onset diabetes (~0.1% annually), higher in those with the metabolic syndrome cluster
- Muscle symptoms, but be aware of the nocebo effect
- Very rarely, clinically relevant liver injury
- Possible increase in risk of haemorrhagic stroke in patients with a prior stroke suggested by SPARCL; not confirmed in the substantive evidence base of RCTs, cohort and case-control studies

BENEFITS

- Reduction in LDL-C levels
- Regression of coronary atheroma
- Reduction in ASCVD events

No evidence to support adverse effects of statins on cognitive function, clinically significant renal deterioration, or risk for cataract, or haemorrhagic stroke in patients without prior stroke



the established cardiovascular benefits of statin therapy far outweigh the risk of any such adverse effects ‘

Highest risk of adverse events:

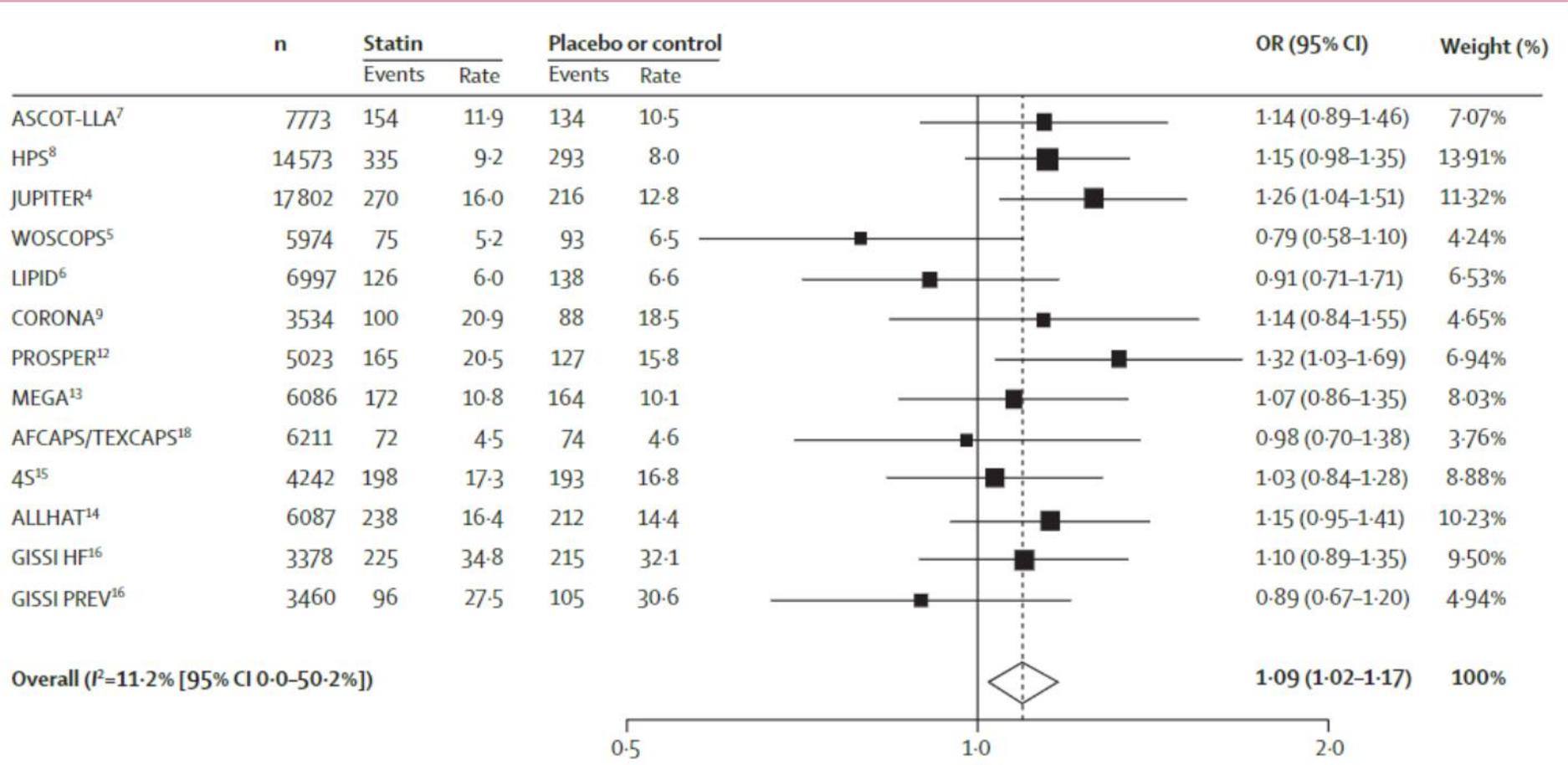
- ♥ Elderly sp after age 80
- ♥ Female
- ♥ Low BMI
- ♥ Hypothyroid
- ♥ Renal-hepatic impairment
- ♥ Recent surgery
- ♥ **Polypharmacy**
- ♥ Vit D deficient-for myalgia

Common drug interactions:

- ♥ Macrolide antibiotics
- ♥ Fibrates
- ♥ Cyclosporine
- ♥ Amiodarone
- ♥ Verapamil
- ♥ Antifungals
- ♥ HIV protease inhibitors
- ♥ CYP450 metabolism may be important



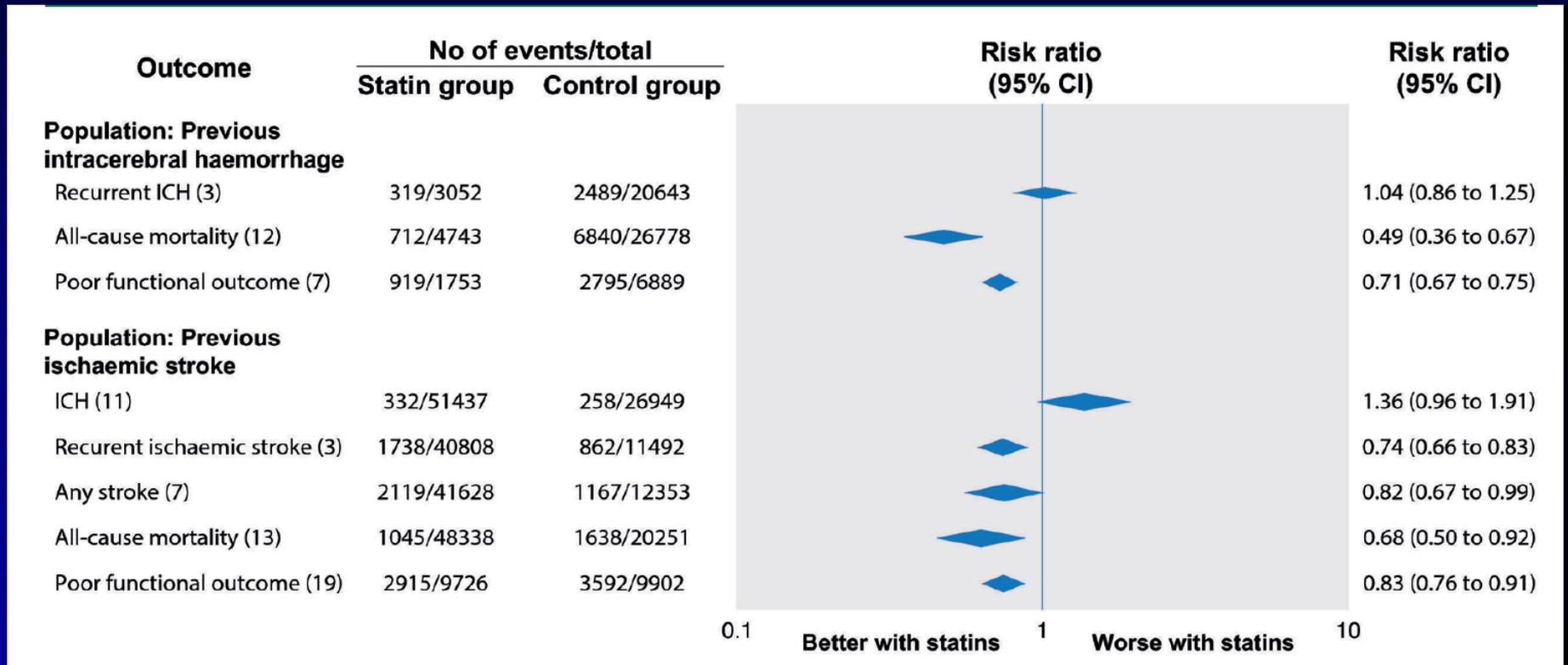
Statins and incident diabetes



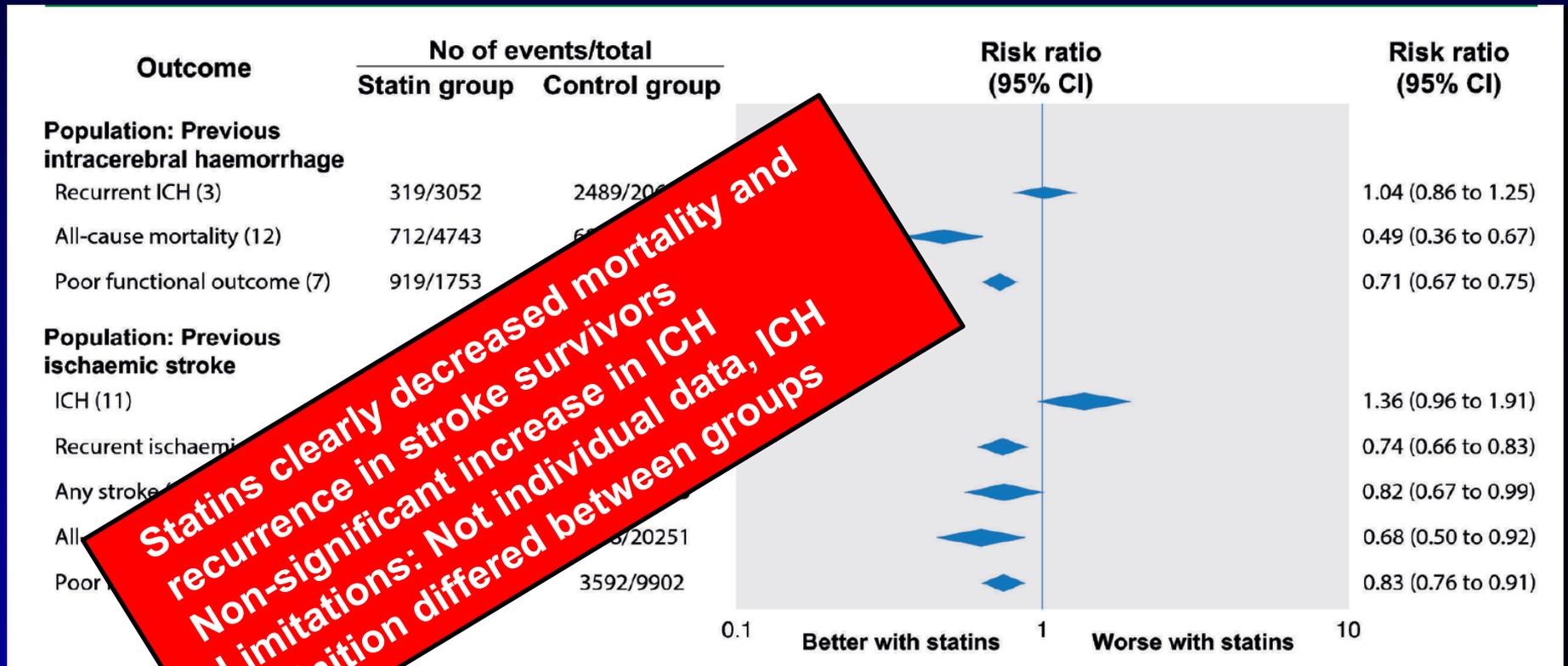
Statins and diabetes

- ♥ New onset DM seen in 1 case per 1000 patients per year of exposure while 5 CVD events prevented
- ♥ Higher dose of statins, elderly, patients with hypertension, multiple risk factors, obesity and metabolic syndrome
- ♥ Prava and pitava neutral on glycemc parameters
- ♥ DM diagnosed as HbA1c over 6.5 without symptoms, relevance for outcome?

Meta-analysis on statins in patients with previous stroke



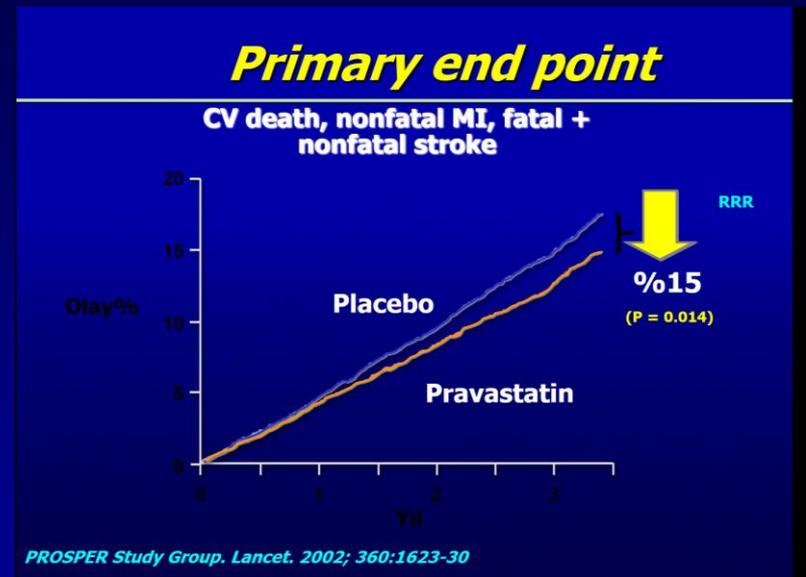
Meta-analysis on statins in patients with previous stroke



Statins and The Elderly

- In individuals 60 to 79 years of age:
 - 69.1% (men) and 67.9% (women) have CVD, heart failure, stroke, or hypertension
- In individuals ≥ 80 years of age:
 - In 84.7% of men and 85.9% of women CHD accounts for approximately 47.7% and stroke 16.4% of deaths attributable to CVD
- The average age of first heart attack is 65 in men and 71.8 in women
- Nearly 70% of first strokes occur in patients ≥ 65 years of age

PROSPER STUDY

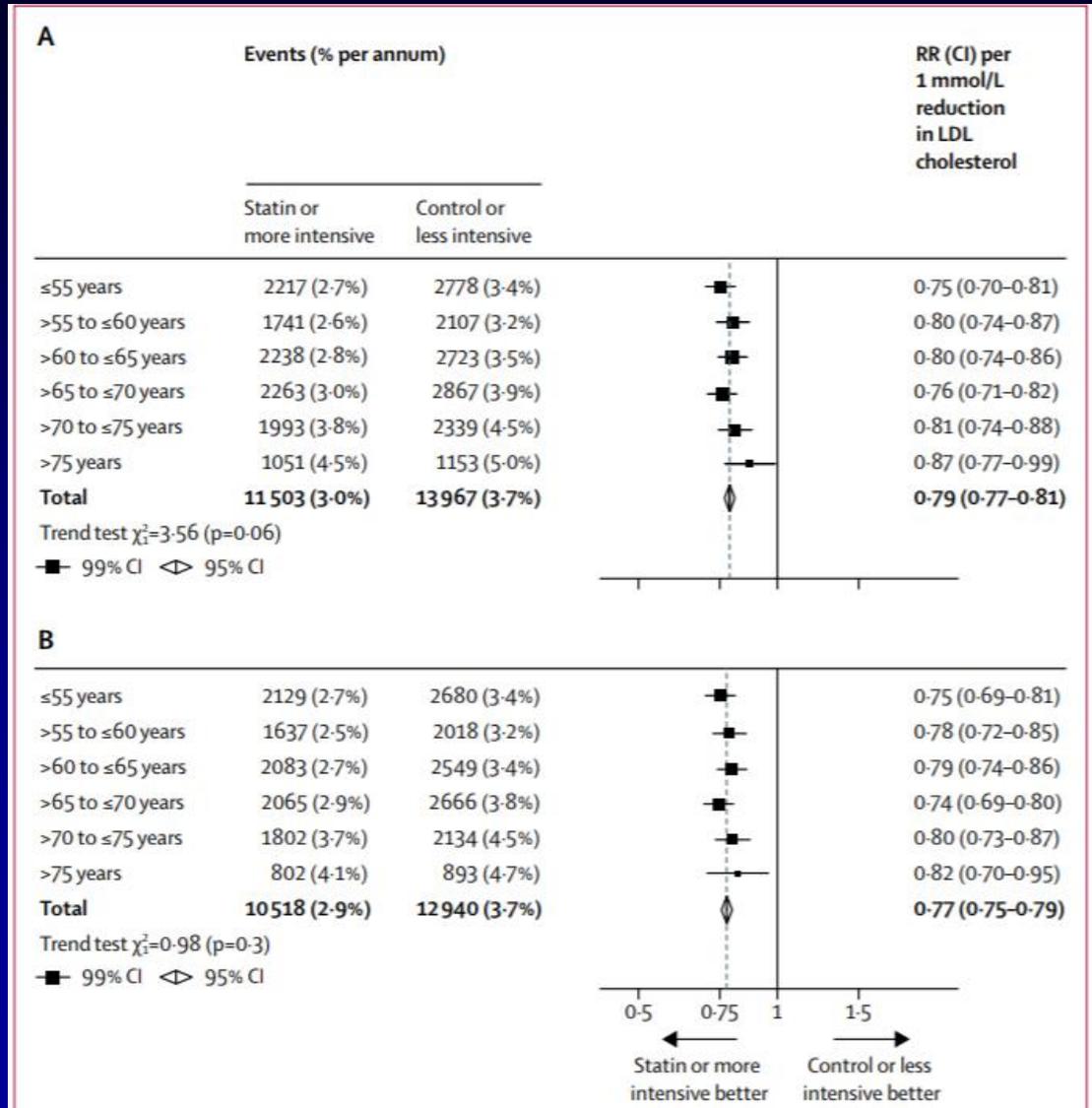


Effects on major vascular events per mmol/L reduction in LDL cholesterol by age at randomisation

RRR 21 % vs 13 %

ARR 0.5 % per year/mmol/L reduction in LDL

Never too old for Statins ?



Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

Recommendations	Class	Level
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged ≤ 75 .	I	A
Initiation of statin treatment for primary prevention in older people aged > 75 may be considered, if at high risk or above.	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

Statins in CKD:

- ♥ **Drugs mainly eliminated by hepatic route should be preferred: Atorvastatin, Fluvastatin, Pitavastatin**
- ♥ **Statins metabolized via CYP3A4 may lead to adverse events**
- ♥ **In stage 5 renal disease (GFR below 15 ml/min/1.73m²) decrease statin dose**

Recommendations for lipid management in patients with moderate to severe (KDOQI stages 3–5)* chronic kidney disease

Recommendations	Class	Level
It is recommended that patients with Kidney Disease Outcomes Quality Initiative stage 3–5 CKD are considered to be at high or very-high risk of ASCVD.	I	A
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.	I	A
In patients already on statins, ezetimibe or a statin/ ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.	IIa	C
In patients with dialysis-dependent CKD and free of ASCVD, commencing statin therapy is not recommended.	III	A

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Data not available

USAGE Study: Survey on 10.138 current and former statin users

Reason for stopping statin among former users:

- ♥ Side effect 62 % (mostly myalgia)
- ♥ Cost 17 %
- ♥ Efficacy 12 %
- ♥ One third stopped without consulting their doctor first !
- ♥ **Not satisfied with doctor discussion: 83 % of those who stopped, 65 % of those who continued !**

Consider if statin-attributed muscle symptoms favour statin continuation / reinitiation

Symptomatic & CK <4 X ULN

CK ≥4 X ULN +/- rhabdomyolysis

2-4 weeks washout of statin

6 week washout of statin until normalisation of CK/creatinine and symptoms

Symptoms persist:
statin re-challenge

Symptoms improve:
Second statin at usual or starting dose

Symptom-free:
Continue statin

Symptoms re-occur

- 1) Low dose third efficacious (potent)^a statin;
- 2) Efficacious^a statin with alternate day or once/twice weekly dosing regimen

- 1) Low dose second efficacious^a statin;
- 2) Efficacious^a statin with alternate day or once/twice weekly dosing regimen

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

Ezetimibe

A] + bile acid absorption inhibitor

B] + fibrate (not gemfibrozil)

A + B

If still not at goal: consider additional (future) novel therapies: PCSK9 monoclonal antibody therapy, CETP inhibitor

Rechallenge the patient

Most patients rechallenged can tolerate statins long-term

- Retrospective cohort study in 107,835 patients
- 18,778 (17.4%) patients had statin-related events.
Statin discontinued by 11,124 (56%) of these patients
- On re-challenge:
 - ✓ 92.2% were still on a statin >12 months later
 - ✓ 47.6% were still using the same statin

Conclusion:

- ♥ **Statins are the mainstay of lipid lowering therapy**
- ♥ **The benefit to risk ratio is highly favourable**
- ♥ **Compliance is a major challenge**