The Legacy Effect of Primary Prevention

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OUTLINE

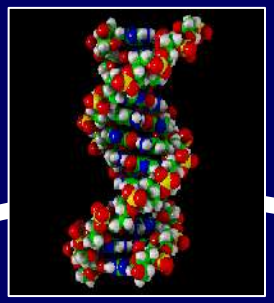
- **Role of LDL in Cardiovascular Disease**
- **Evidence Base for CVD Primary Prevention: Legacy Effect**
- **Strategies for Primary Prevention**

Role of LDL in Cardiovascular Disease

LDL as the primary causative factor and treatment target

LDL and atherosclerosis

A coalescence of evidence



Genomics
Genetics

Epidemiology

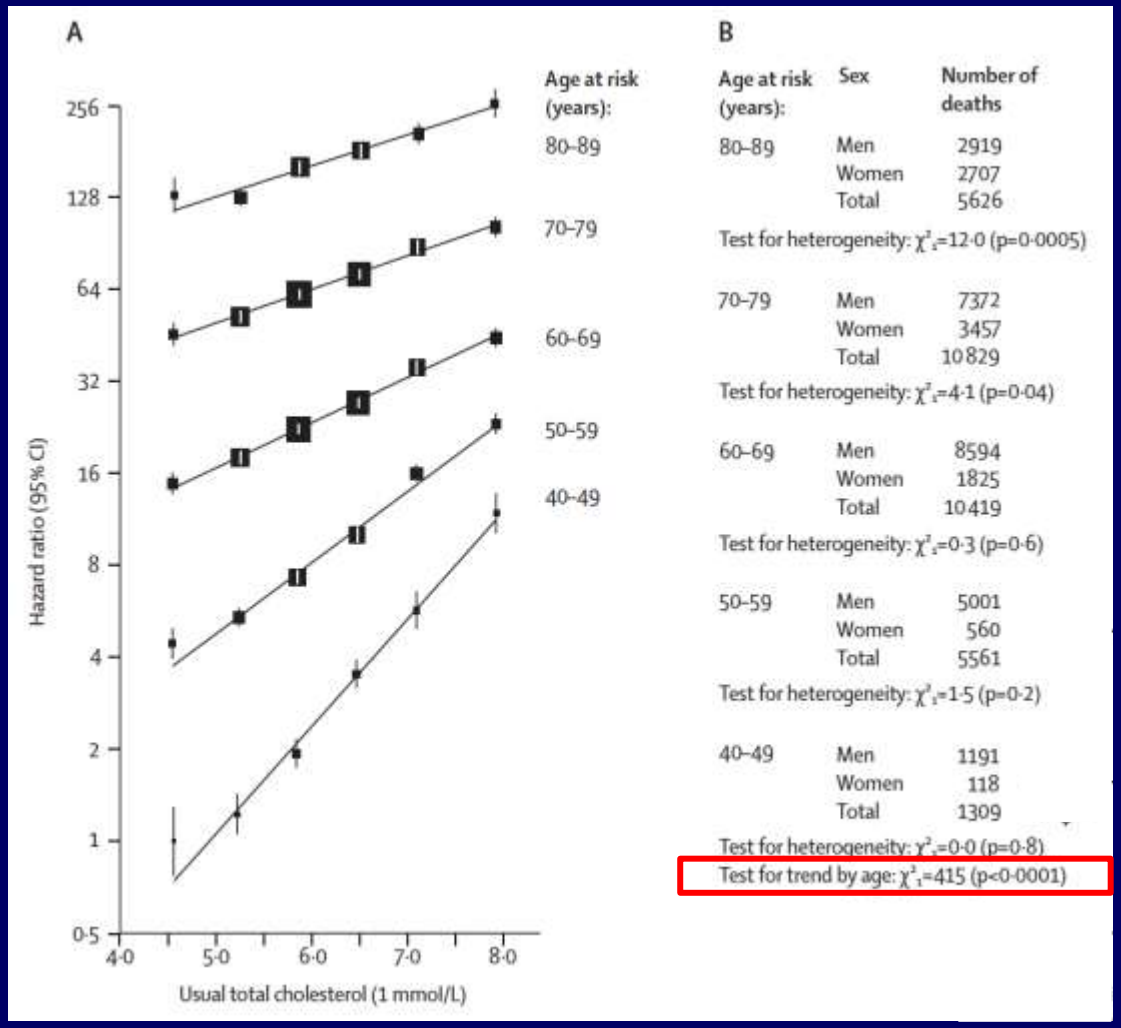
Pathology

Intervention
trials

Causal role of LDL in atherosclerosis

- Evidence from epidemiology and pathology.
- Evidence from intervention trials and genetic studies.

Age, cholesterol and CHD risk
Prospective Studies Collaboration



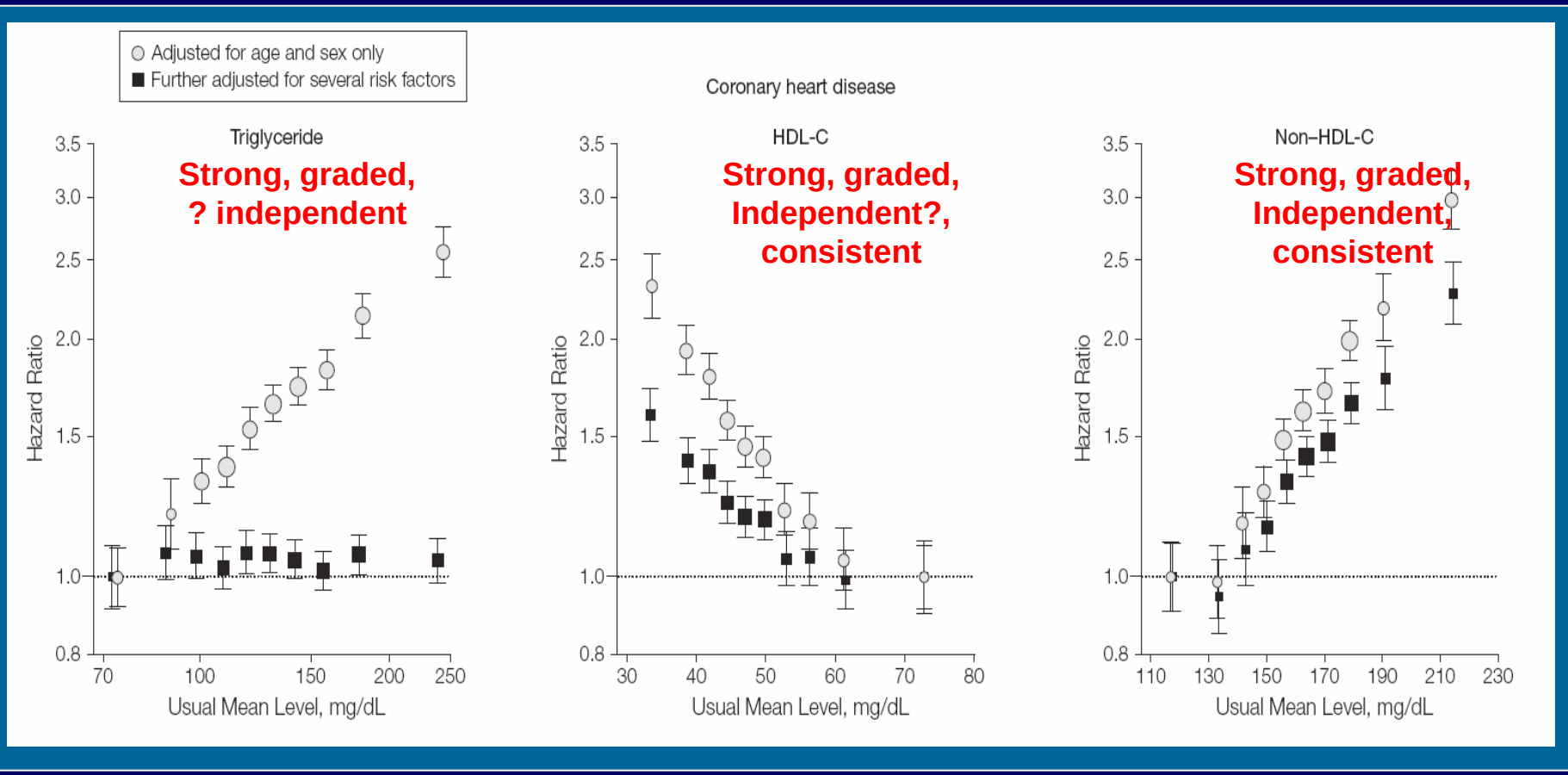
B

Age at risk (years):	Sex	Number of deaths
80–89	Men	2919
	Women	2707
	Total	5626
Test for heterogeneity: χ^2_1=12·0 (p=0·0005)		
70–79	Men	7372
	Women	3457
	Total	10829
Test for heterogeneity: χ^2_1=4·1 (p=0·04)		
60–69	Men	8594
	Women	1825
	Total	10419
Test for heterogeneity: χ^2_1=0·3 (p=0·6)		
50–59	Men	5001
	Women	560
	Total	5561
Test for heterogeneity: χ^2_1=1·5 (p=0·2)		
40–49	Men	1191
	Women	118
	Total	1309
Test for heterogeneity: χ^2_1=0·0 (p=0·8)		
Test for trend by age: χ^2_1=415 (p<0·0001)		

Prospective Studies Collaboration Lancet (2007) 370;1829-39

Emerging Risk Factors Collaboration
Plasma lipids and incident CHD

302,430 subjects; 2.79 million pt-yrs; 8857 MIs; 3928 strokes; 68 studies



Danesh et al (2009) JAMA 302:1993-2000

Role of LDL in atherogenesis

Pathological plausibility

Cellular remodelling

Release of bio-active lipids

Extracellular pathology

Lipoprotein retention
Deposits early micro- and later macro-cholesterol crystals.

Innate immunity

Initiates localised inflammation.
Macrophage recruitment.
Intracellular cholesterol accumulation.
Necrosis

Auto-immunity (apoB)
Adaptive immunity

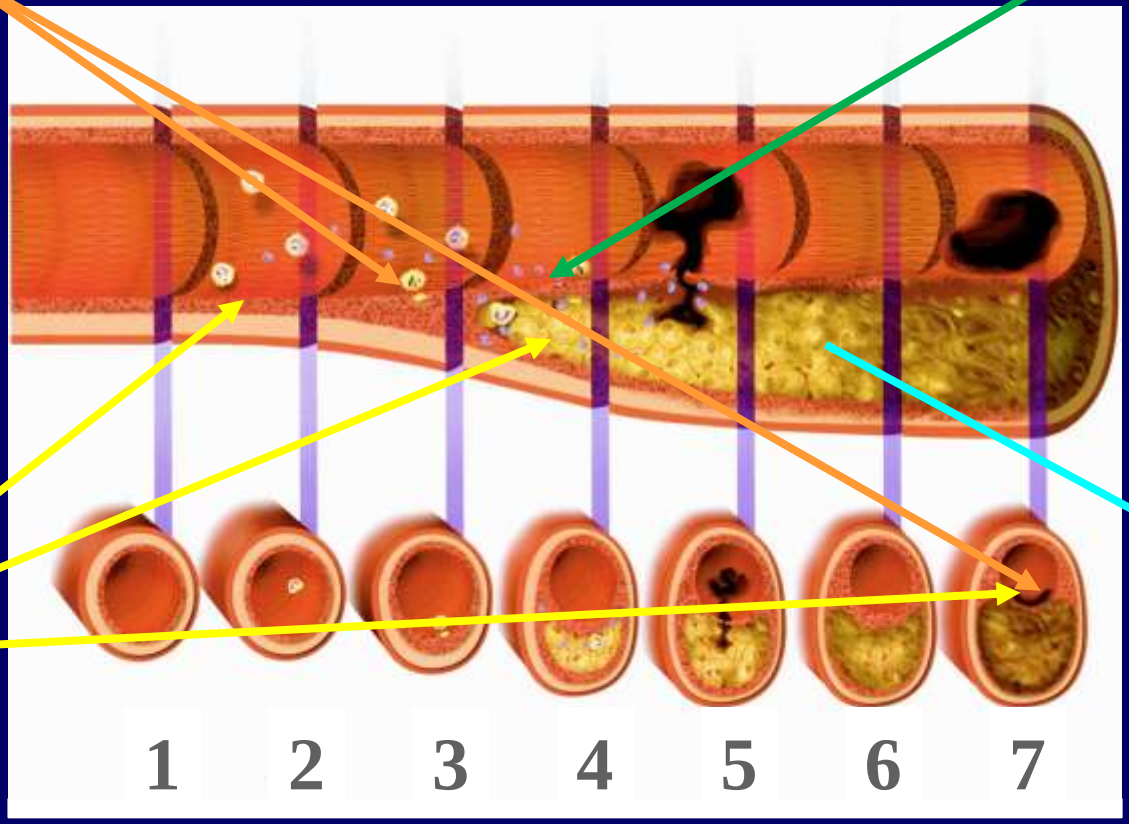
See Libby, Ridker, Hansson. Nature (2011); 473:317-325

Pathogenesis of atherosclerosis

A decades-long disease course

Inflammation
Selectins
ICAM
IL
M-CSF
CRP

Endothelial stress
BP
Smoking



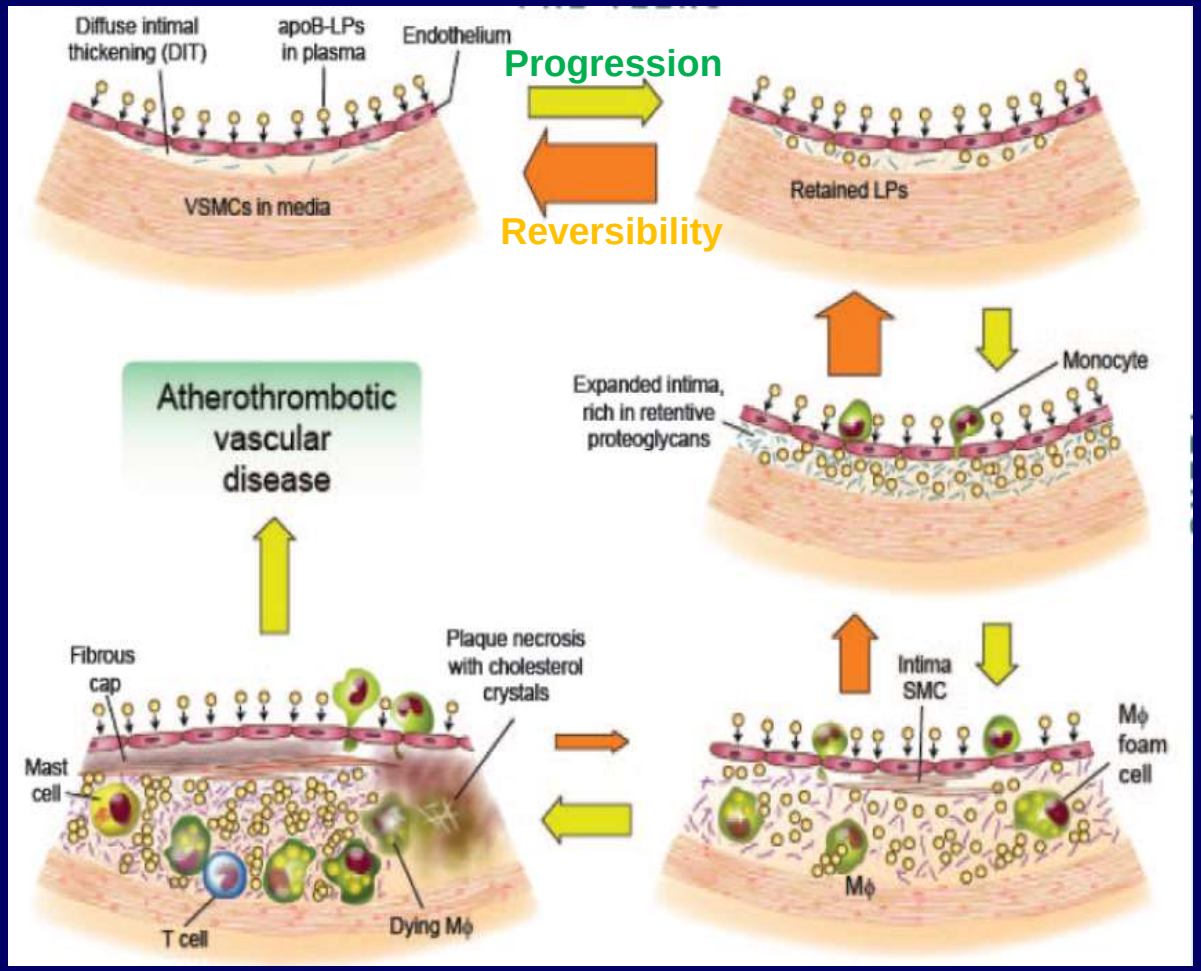
VLDL
LDL

HDL

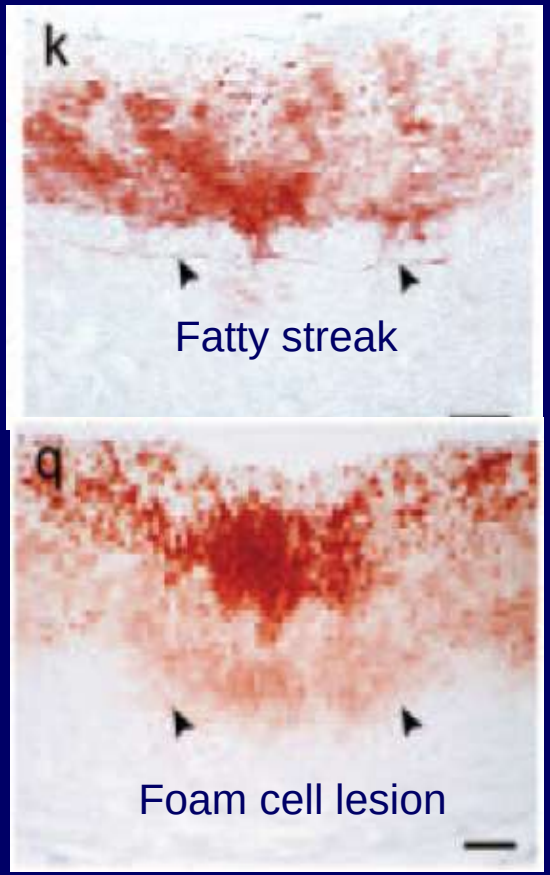
Age decade

Libby (2001) Circulation 104:365

Lipoprotein retention to foam cell formation

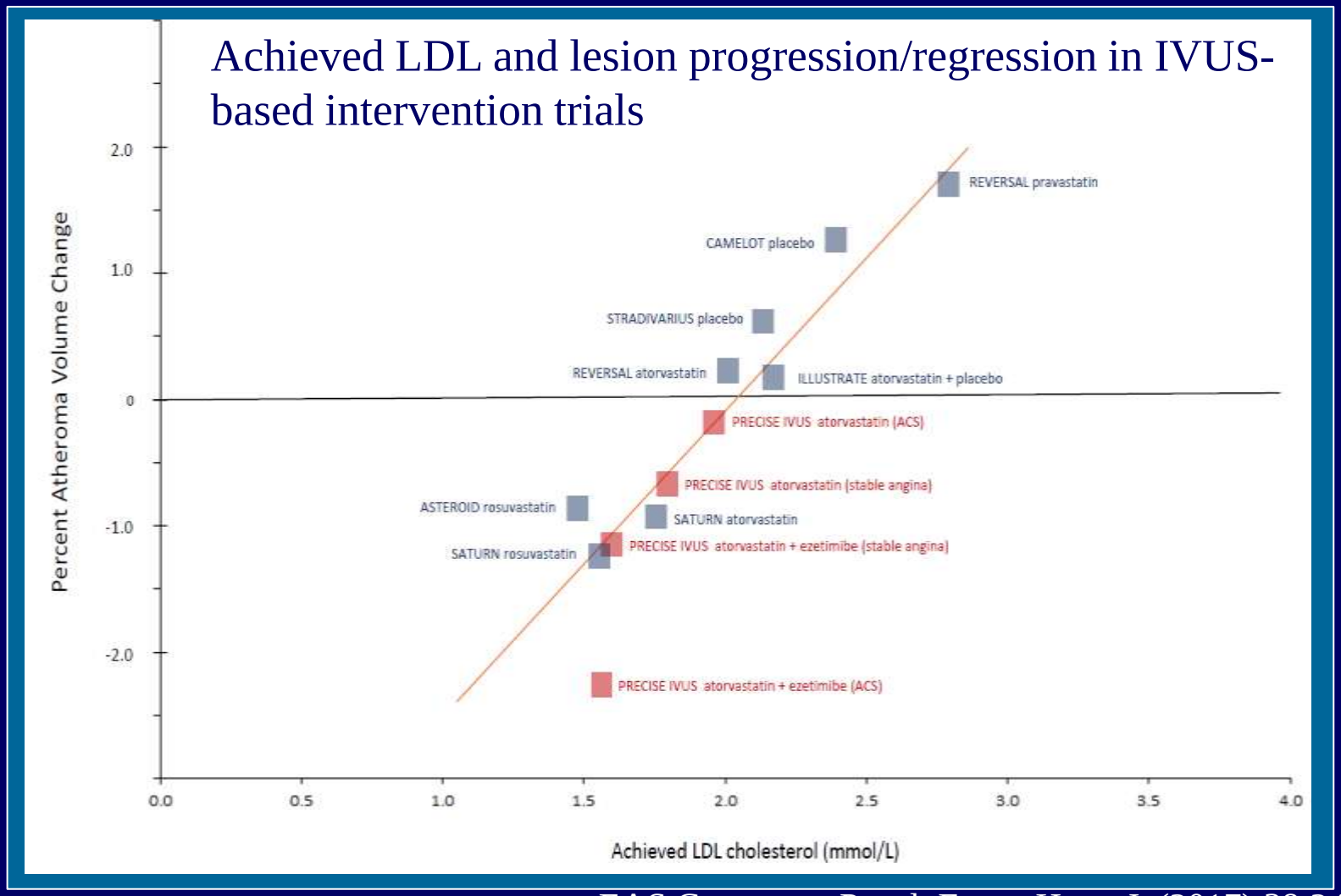


Tabas et al (2007) Circulation 116:1832-44



Nakashima et al (2007)
ATVB 27:1159-65

LDL and size of coronary lesions

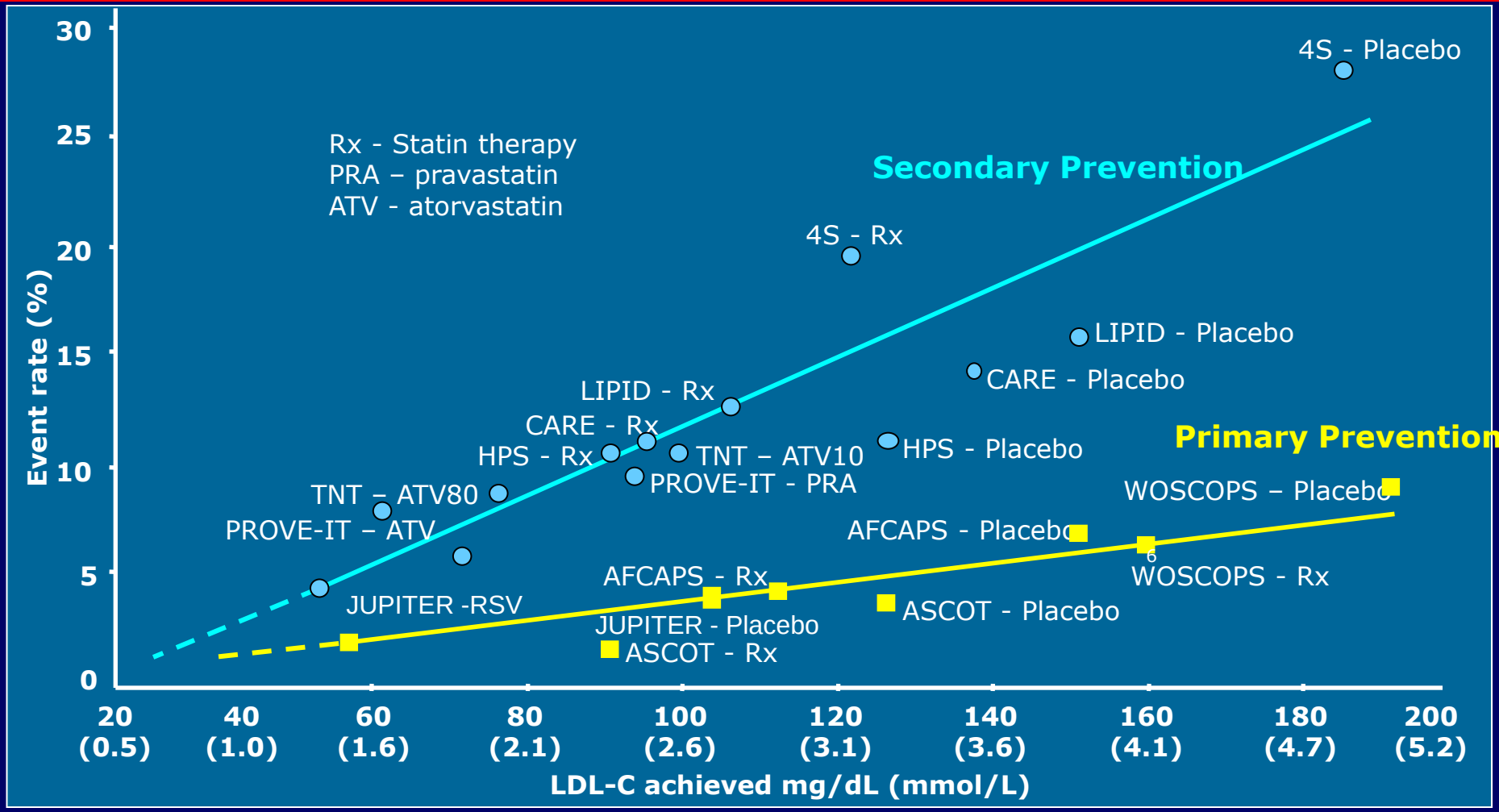


EAS Consensus Panel, Europ Heart J. (2017);38:2459-72

Causal role of LDL in atherosclerosis

- Evidence from epidemiology and pathology.
- Evidence from intervention trials and genetic studies.

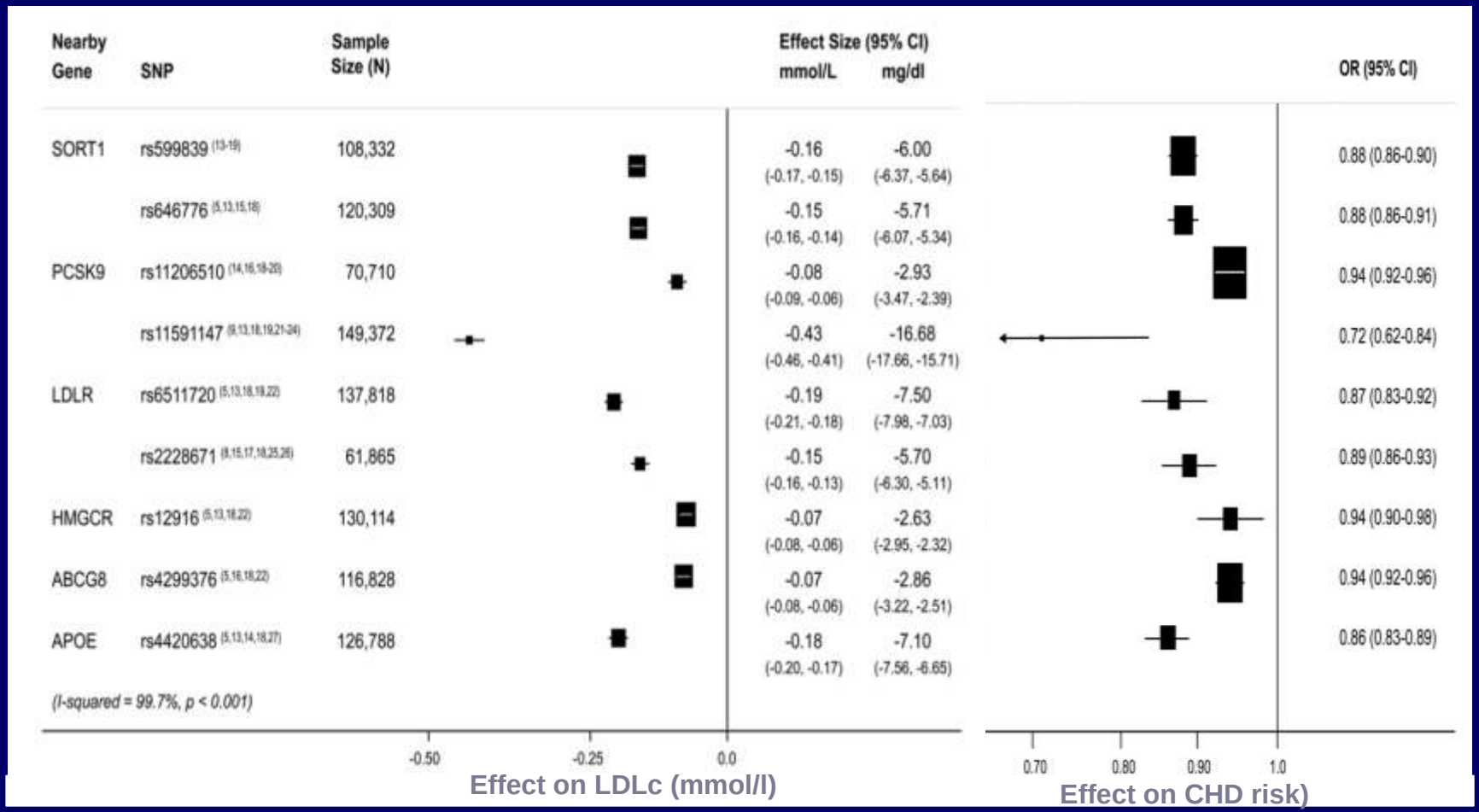
Association of LDL cholesterol with CHD risk in statin trials



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004;**9**(2):269-279 LaRosa JC *et al. N Engl J Med* 2005;**352**:e-version

Lessons from nature
Common genetic variation and CHD risk

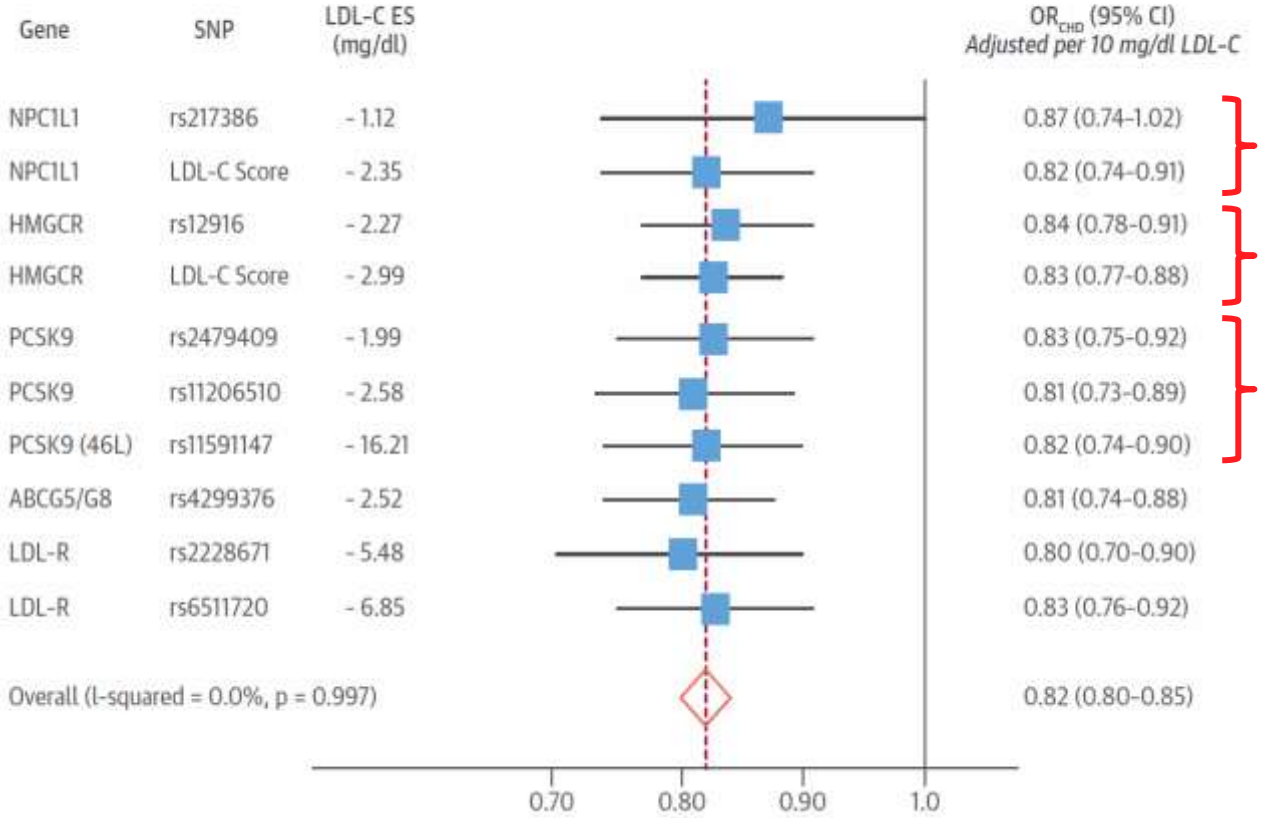
Analysis of genes regulating LDL cholesterol and association with CHD risk



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

Causal role of LDL – evidence from common inherited variants

FIGURE 4 Comparison of Effect of 10 mg/dl Lower LDL-C on Risk of CHD Mediated by Polymorphisms in the LDL-C Receptor Pathway in Up to 63,746 Cases of CHD and 130,681 Control Subjects



LDL lowering due to variation in:-

Cholesterol absorption

Cholesterol production

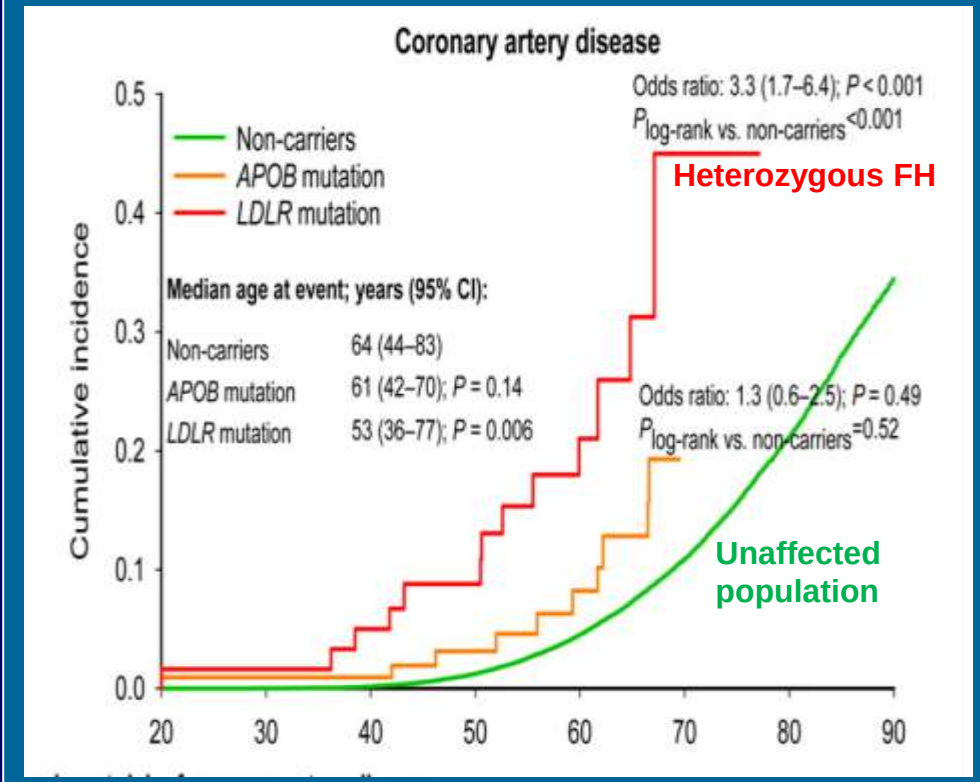
LDL receptor number

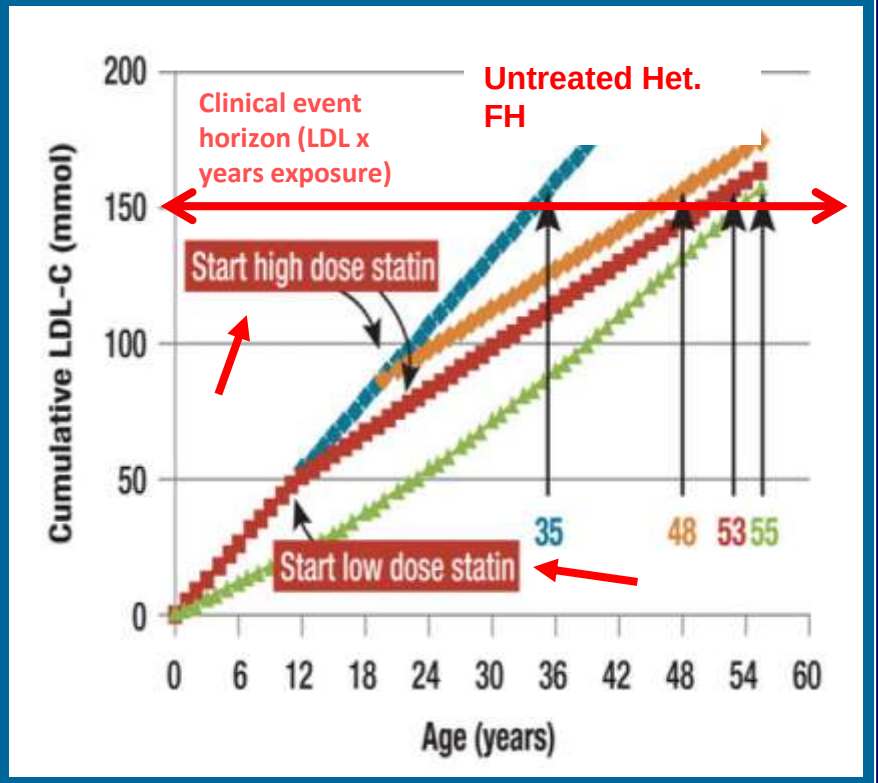
CHD risk reduction per unit LDL decrease is independent of underlying mechanism .

Ference et al JACC (2015) 65; 12552-61

Causal role of LDL – evidence from severe genetic variants

Cumulative LDL exposure and CHD risk in familial hypercholesterolemia





Benn et al. *Europ. Heart J.* 2016;37:1384-94

Weigman et al. *Europ. Heart J.* 2015;36:2425-37

Brief Summary #1

- LDL satisfies key criteria as the causative agent in atherosclerosis.
- LDL contributes to the pathogenesis of atherosclerosis over the decades long development of the disease
- LDL cholesterol is associated with the size of lesions and ongoing risk of CHD.
- Lifelong exposure – LDLc x years is an important determinant of risk. Exposure can be controlled most effectively by early intervention

Evidence Base for CVD Primary Prevention

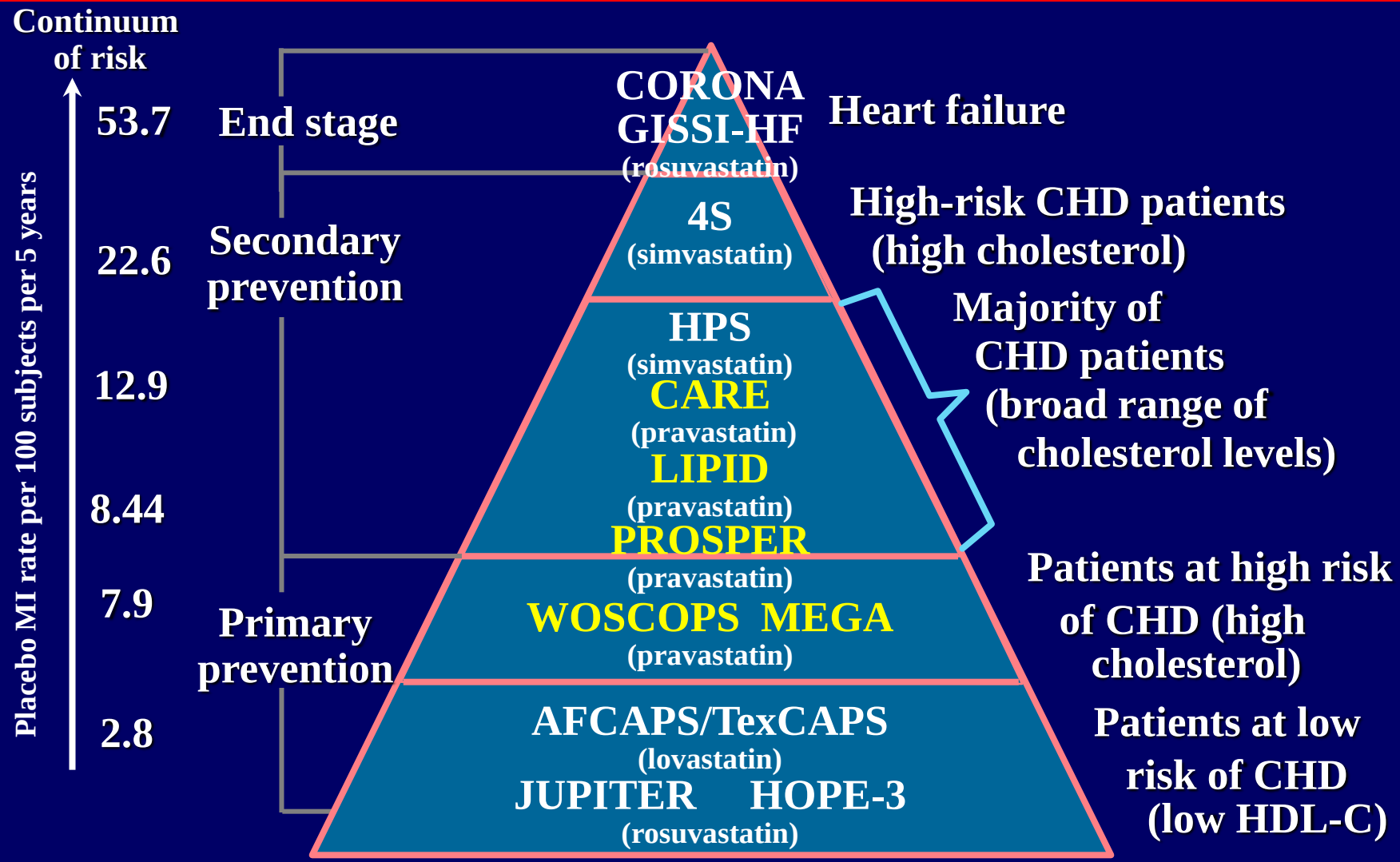
Understanding the Lifetime Benefits of LDL Lowering

Legacy Benefit

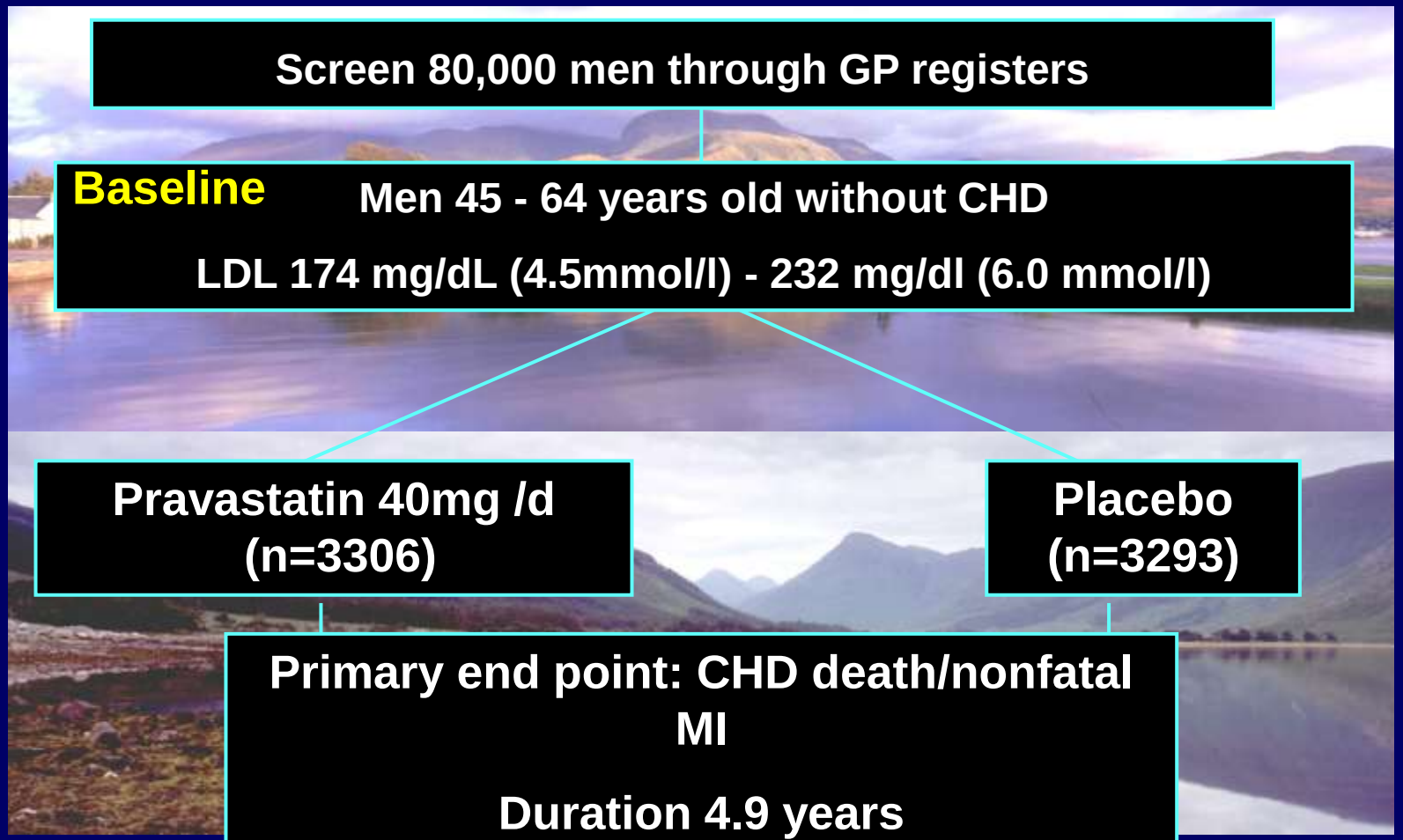
Understanding the lifetime benefits of statin treatment

- CVD primary prevention – key lessons from landmark trials.
- WOSCOPS 20-year experience with statin treatment.
- Adherence in primary prevention – efficacy, safety and tolerability.

Placebo - Statin outcome trials

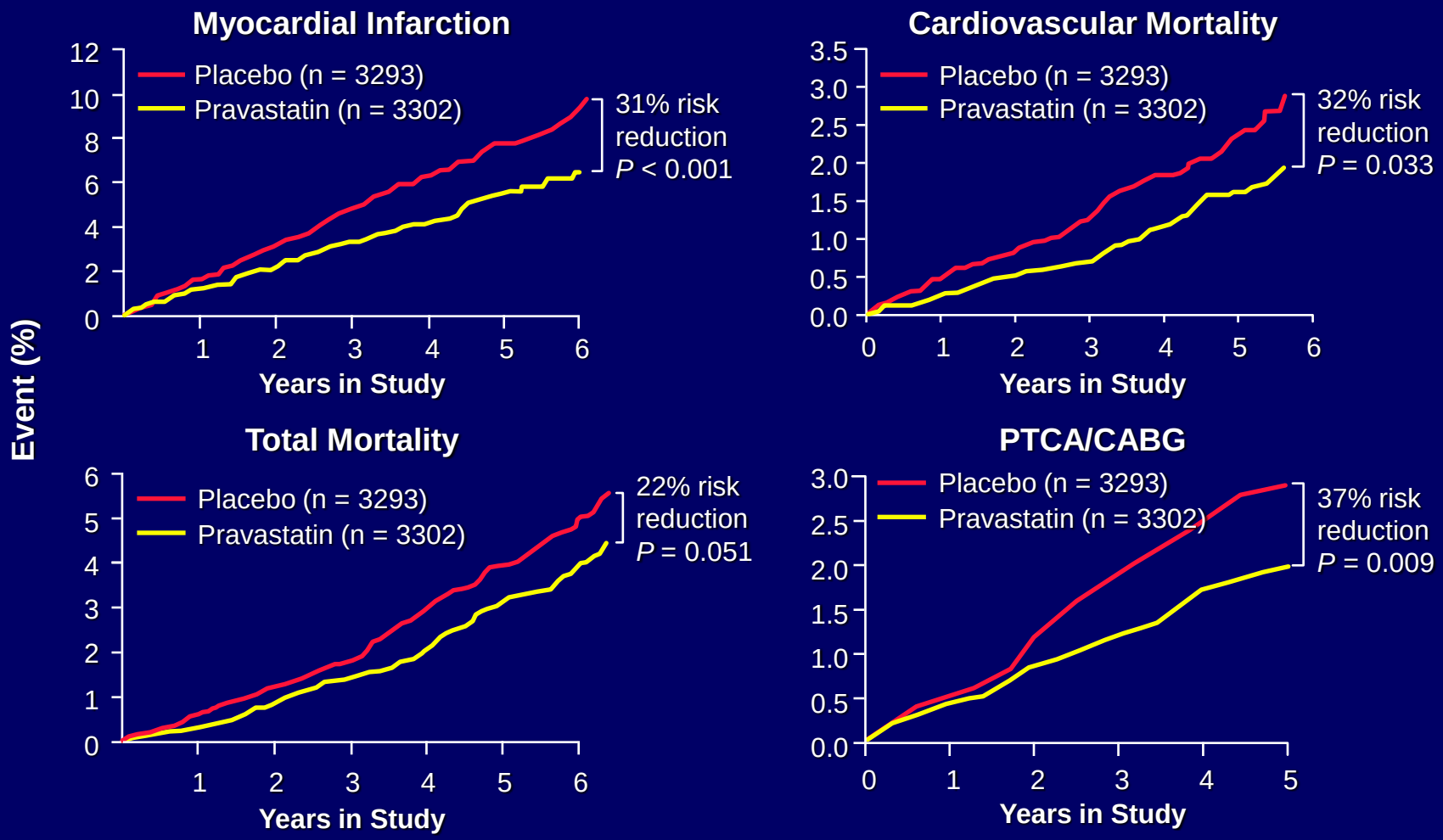


West of Scotland Coronary Prevention Study -Trial design



Shepherd et al. *N Engl J Med*. 1995;333:1301-7.

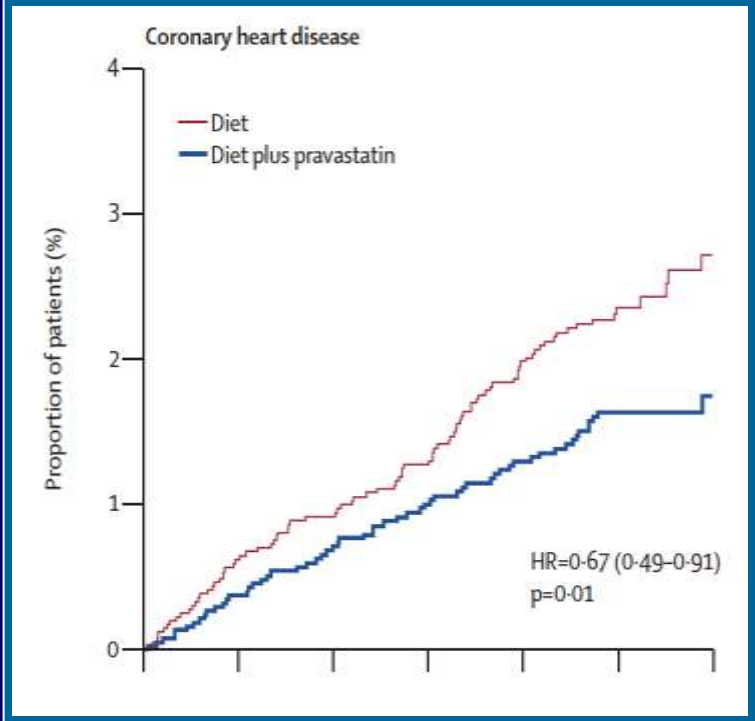
WOSCOPS: Early Event Reductions With Pravastatin



Shepherd et al. *N Engl J Med.* 1995;333:1301-1307.

Primary prevention of CVD with pravastatin in Japan – MEGA study

Impact of low dose statin therapy (10-20mg pravastatin) on CVD in asymptomatic Japanese subjects with raised cholesterol, 5.69– 6.08 mmol/l



Design – Prospective, randomized, open-label, blinded trial; 7832 subjects (69% women); baseline LDLc – 4.05mmol/l. LDL decrease in active treatment group was 18.0%

	5 years (35 962 person-years)				End of study (41 195 person-years)			
	Diet group	Diet plus pravastatin group	HR (95% CI)	p value	Diet group	Diet plus pravastatin group	HR (95% CI)	p value
Coronary heart disease	85 (4·8)	57 (3·3)	0·70 (0·50–0·97)	0·03	101 (5·0)	66 (3·3)	0·67 (0·49–0·91)	0·01
Number at risk*	2476	2434			223	249		
Coronary heart disease plus cerebral infarction	127 (7·1)	81 (4·7)	0·66 (0·50–0·87)	0·003	144 (7·1)	98 (5·0)	0·70 (0·54–0·90)	0·005
Number at risk*	2452	2422			223	243		
Stroke	61 (3·4)	38 (2·2)	0·65 (0·43–0·97)	0·03	62 (3·0)	50 (2·5)	0·83 (0·57–1·21)	0·33
Number at risk*	2489	2452			233	248		
Total mortality	66 (3·6)	43 (2·4)	0·68 (0·46–1·00)	0·048	79 (3·8)	55 (2·7)	0·72 (0·51–1·01)	0·055
Number at risk*	2604	2545			237	249		

*At 9 years for end of study. Data are number (cases per 1000 patient-years)

Table 3: Major endpoints at 5 years and end of study

Nakamura et al. Lancet (2006) 368;1155-63

Heart Outcome Prevention Evaluation-3
Study design

Primary prevention in subjects with intermediate risk

2 x 2 factorial design – Age >55y men; >65y (>60y) women + 1(2) risk factor

Dual placebo *n=3168* LDLc 128 mg/dl BP 138/82 mmHg	*Statin + BP placebo n= 3181* LDLc 26.5% ↓ vs placebo
BP Rx + statin placebo n= 3176 BP 6/3 mmHg ↓ vs placebo	*BP Rx + statin* *n= 3180* LDLc 26.5% ↓ vs placebo BP 6/3 mmHg ↓ vs placebo

Subject ethnicity – 29% Chinese, 27% Hispanic, 20% White, 14.6% South Asian
Age 65.8 y, 46.3% *female*

Yusuf et al New Eng J Med (2016) 374;2021-31

Lonn et al New Eng J Med (2016) 374;2009-20

HOPE -3 Primary prevention though cholesterol and BP lowering

LDLc lowering with statin in subjects with intermediate risk

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	235 (3.7)	304 (4.8)	0.76 (0.64–0.91)	0.002
Second coprimary outcome	277 (4.4)	363 (5.7)	0.75 (0.64–0.88)	<0.001

Blood pressure lowering

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Candesartan + Hydrochlorothiazide (N=6356)	Placebo (N=6349)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	260 (4.1)	279 (4.4)	0.93 (0.79–1.10)	0.40
Second coprimary outcome	312 (4.9)	328 (5.2)	0.95 (0.81–1.11)	0.51

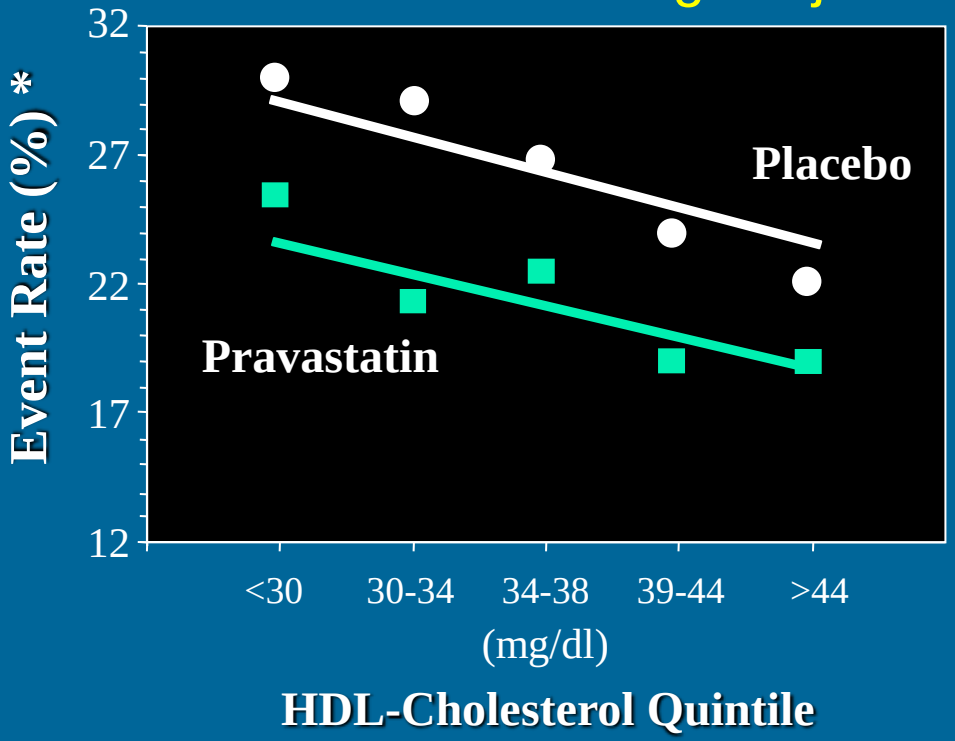
Yusuf et al New Eng J Med (2016) 374;2021-31

Lonn et al New Eng J Med (2016) 374;2009-20

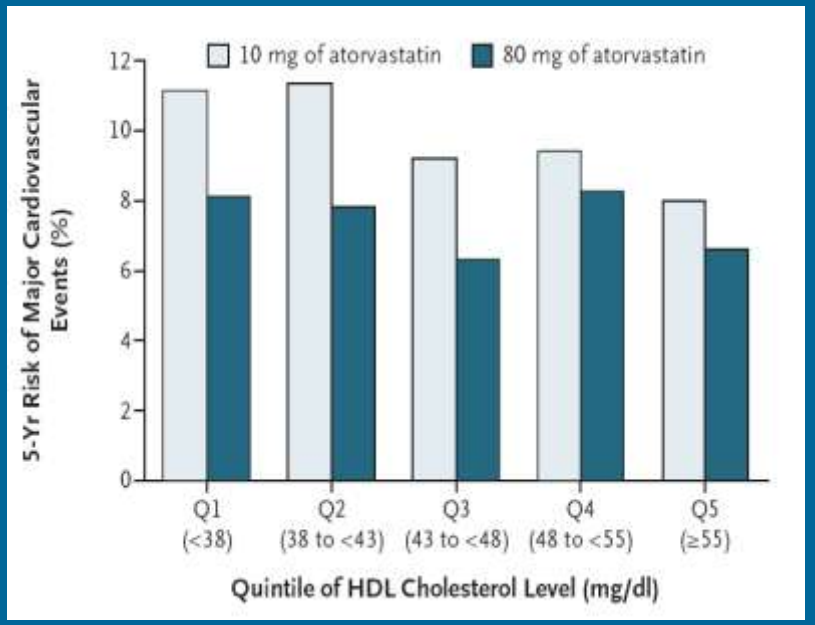
PPP and TNT

Baseline HDL Cholesterol and risk of CHD

Pravastatin Pooling Project



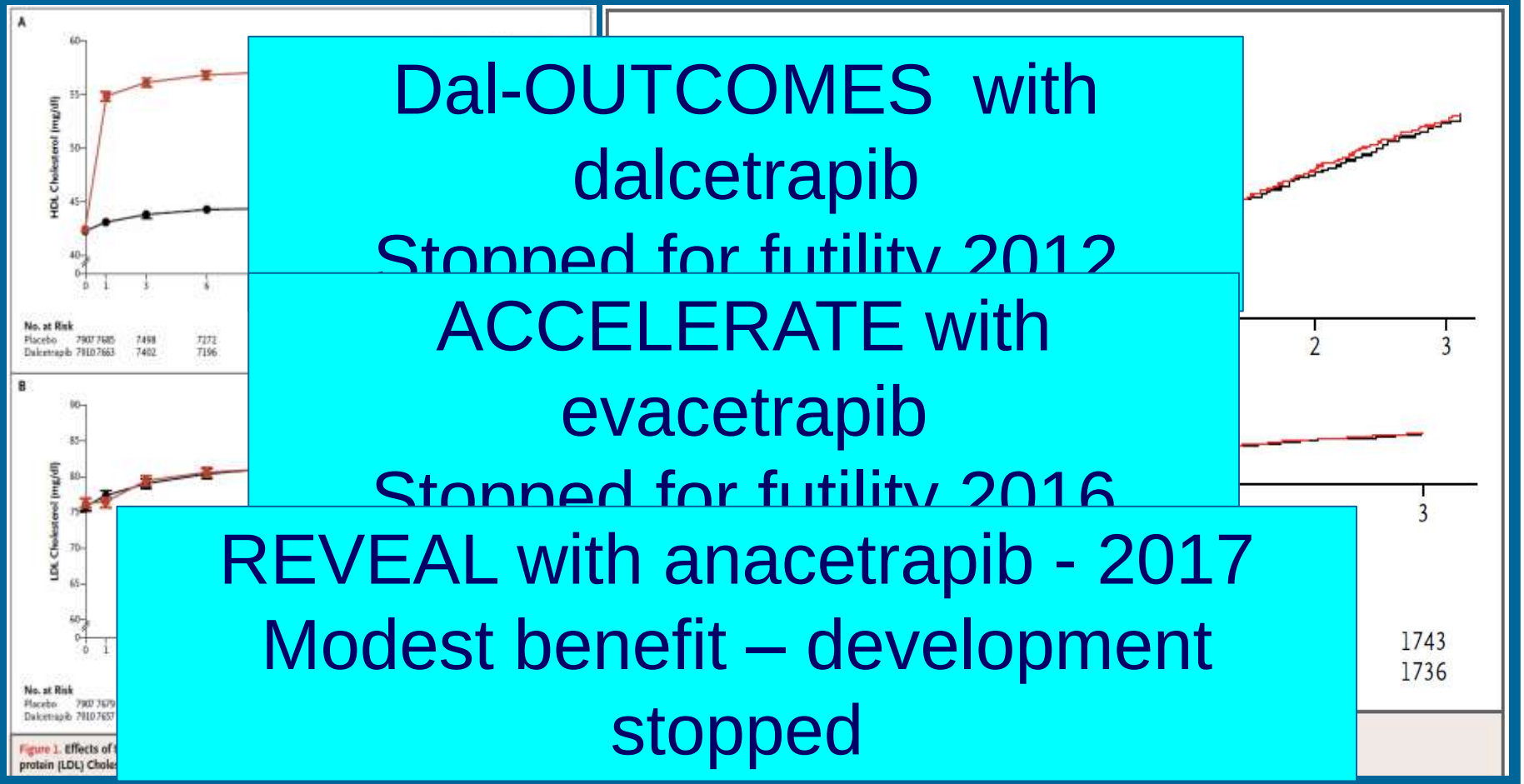
Treat to New Targets trial



Sacks et al. *Circulation*. 1999;100:I-739.

Barter et al. *New Eng J Med*. 2007;357:1301-1310

HDL raising with CETP inhibitors



Dal-OUTCOMES with dalcetrapib
Stopped for futility 2012

ACCELERATE with evacetrapib
Stopped for futility 2016

REVEAL with anacetrapib - 2017
Modest benefit – development stopped

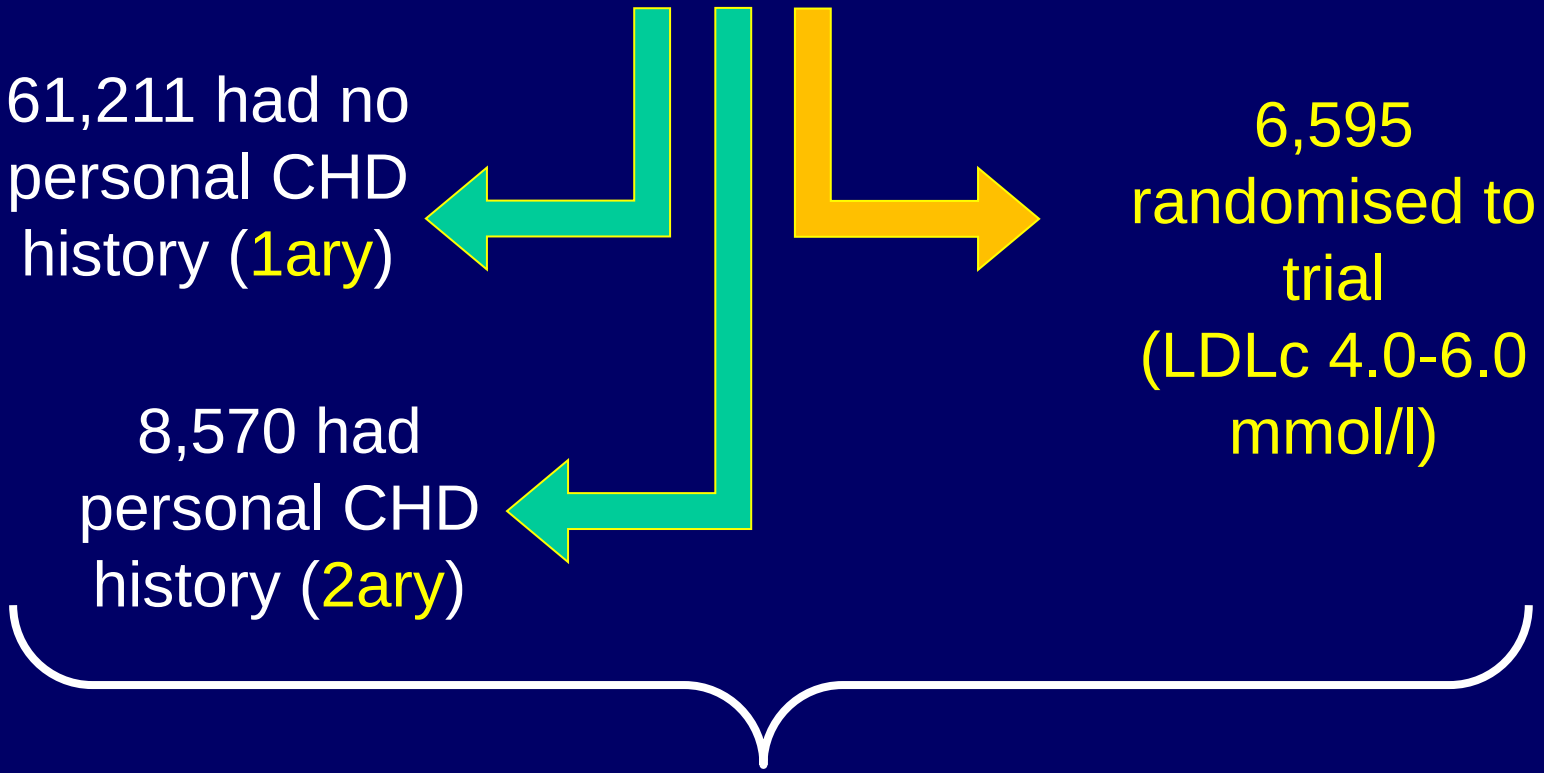
Schwartz et al. *New Engl J Med.* 2012;367:2089-99

Understanding the lifetime benefits of statin treatment

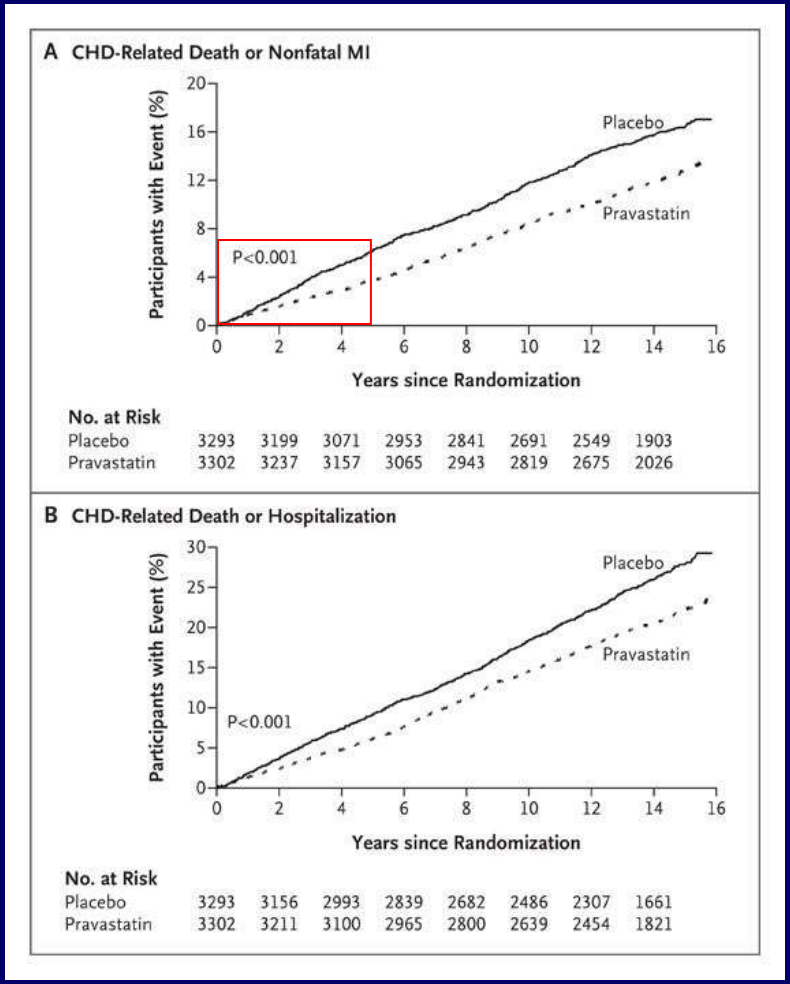
- CVD primary prevention – key lessons from landmark trials.
- WOSCOPS 20-year experience with statin treatment.
- Adherence in primary prevention – efficacy, safety and tolerability.

Long-term observational study of WOSCOPS

80,230 men attended Study Visit 1 for risk factor evaluation



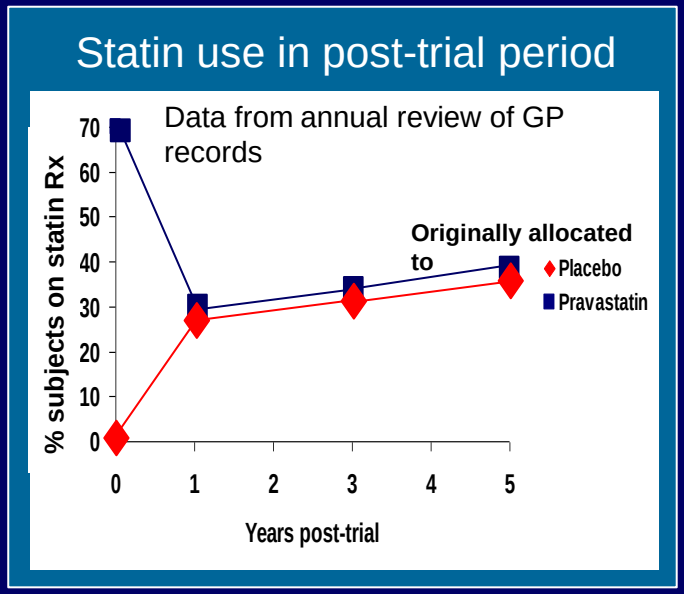
Long term safety of statins
WOSCOPS: 15 year follow up



K-M curves according to the originally assigned study group

CHD-related death or nonfatal MI
Risk reduction in statin group

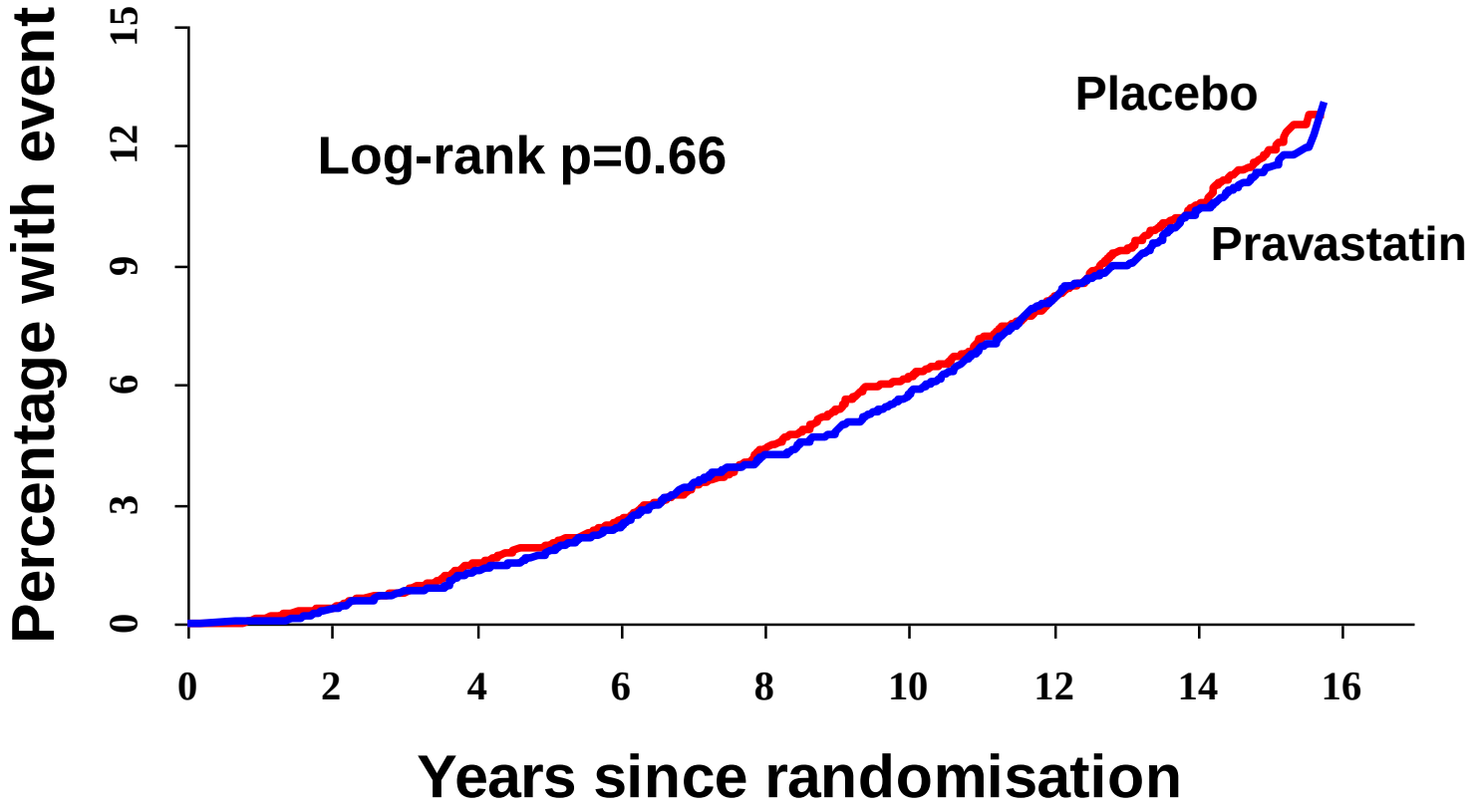
- 40% during trial (*P*<0.001)
- 18% post-trial (*P*=0.02)
- 27% overall follow-up (*P*<0.001)



Ford I et al. N Engl J Med 2007;357:1477-1486

WOSCOPS 15 year follow up

Long-term overall safety of pravastatin



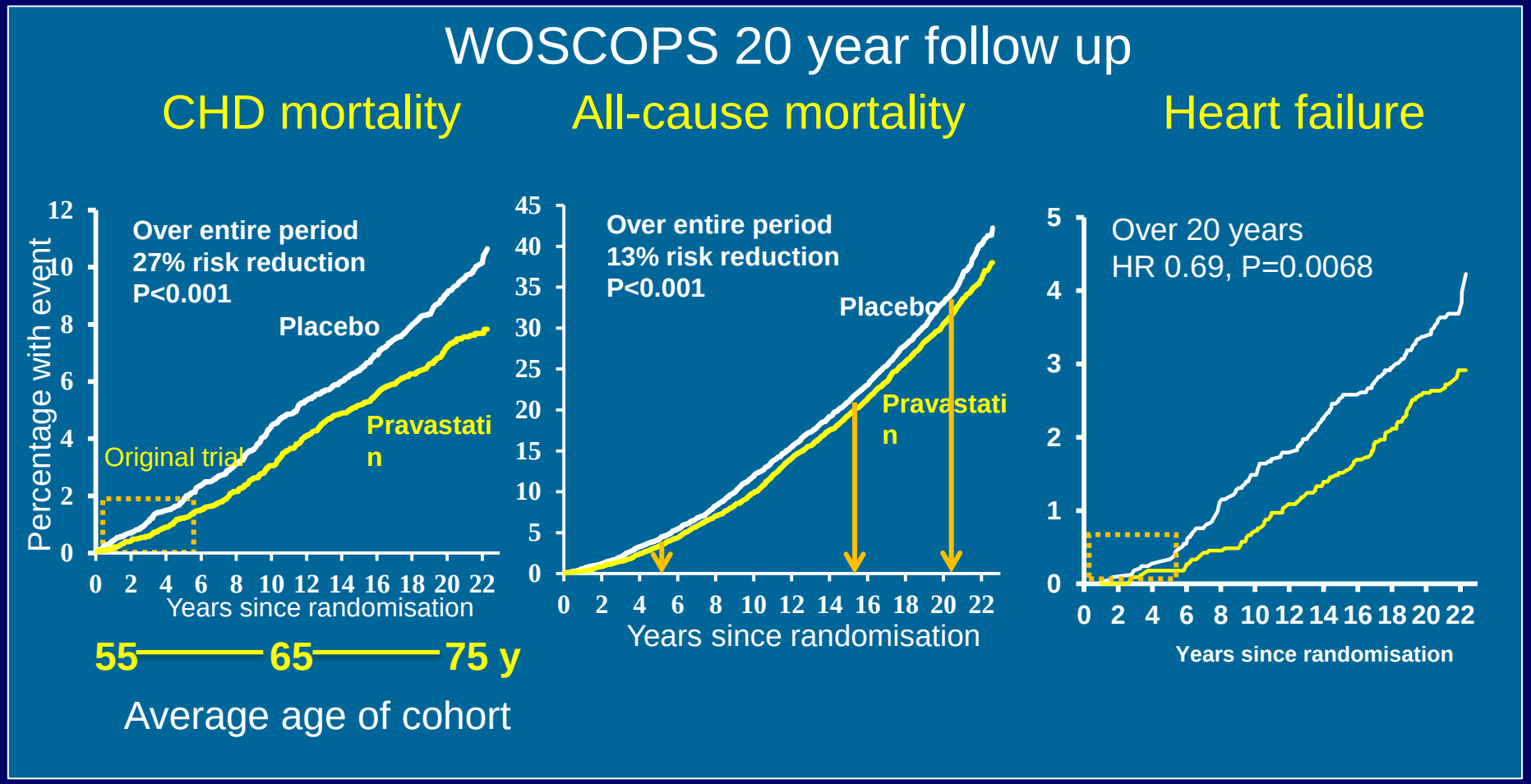
Ford et al, N Eng J Med (2007) 357 1477-86

Long term safety in statin studies
WOSCOPS 20 year experience

Endpoint	Placebo, number (%) with event Total n=3293	Pravastatin, number (%) with event Total n=3302	Adjusted Hazard Ratio (95% Confidence Interval)	P- Value
All cancers	816 (24.8%)	809 (24.5%)	0.96 (0.87, 1.06)	0.41
Colorectal cancer	140 (4.25%)	127 (3.85%)	0.87 (0.68, 1.10)	0.25
Lung cancer	202 (6.13%)	187 (5.66%)	0.89 (0.73, 1.08)	0.24
Prostate cancer	170 (5.16%)	186 (5.63%)	1.05 (0.85, 1.29)	0.65
Upper GI cancer	77 (2.34%)	87 (2.63%)	1.09 (0.80, 1.48)	0.60
Urinary tract cancer	97 (2.95%)	99 (3.00%)	0.99 (0.75, 1.31)	0.93
Other cancer	160 (4.86%)	157 (4.75%)	0.95 (0.76, 1.18)	0.62
All non-CVD deaths	757 (23.0%)	731 (22.1%)	0.92 (0.83, 1.02)	0.12

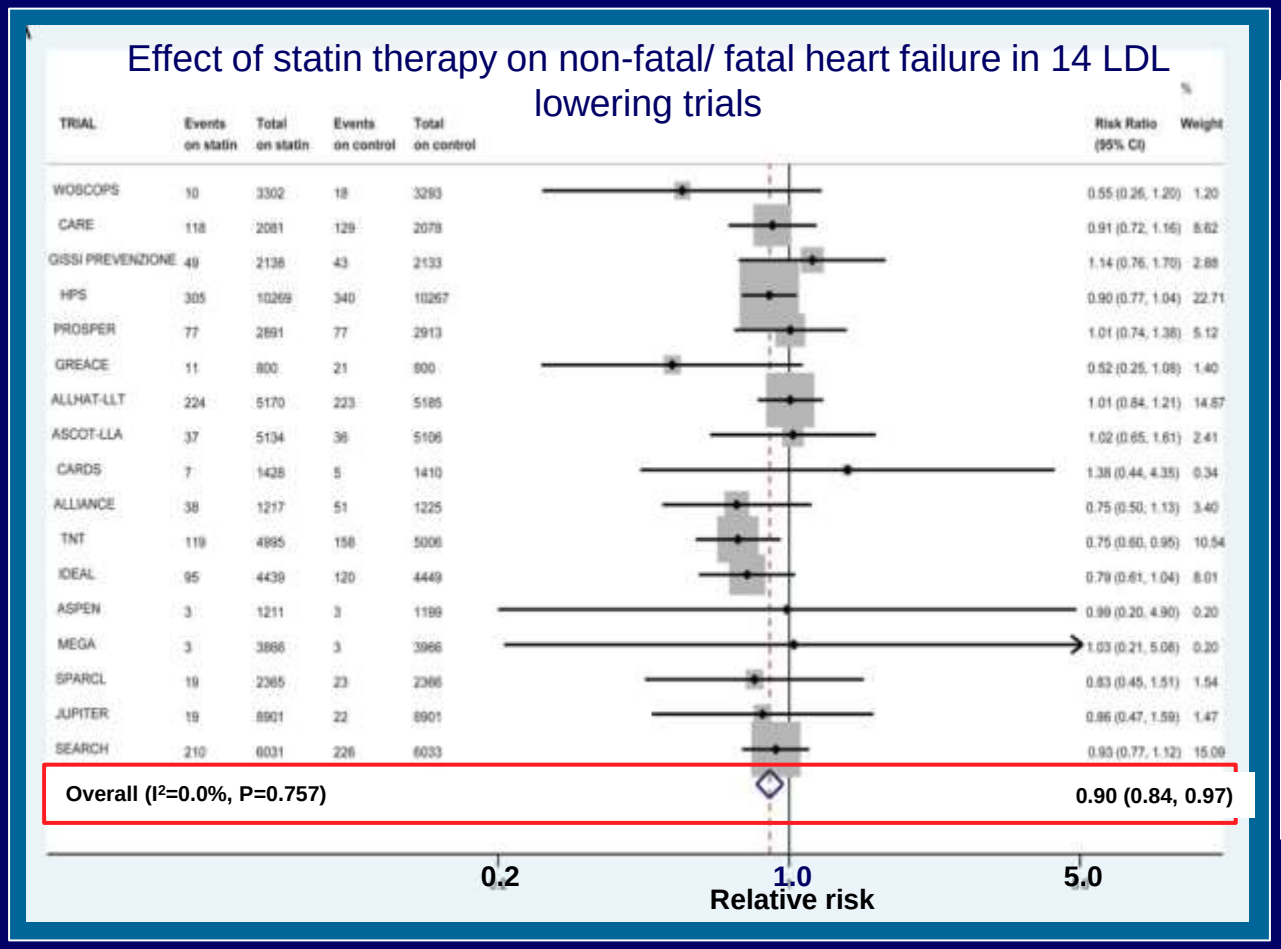
Ford I et al. Circulation. (2016); 133:1073-80

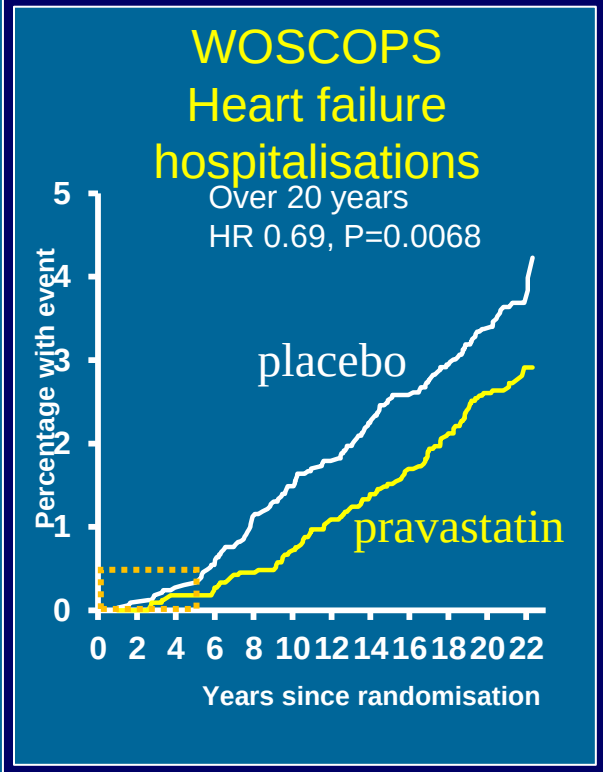
Assessing long term (lifetime) benefits of LDL lowering in WOSCOPS



Ford I et al. Circulation. (2016); 133:1073-80

Additional/ long term benefits of LDL lowering in heart failure





Preiss et. al Europ Heart J (2015) 36;1536-46

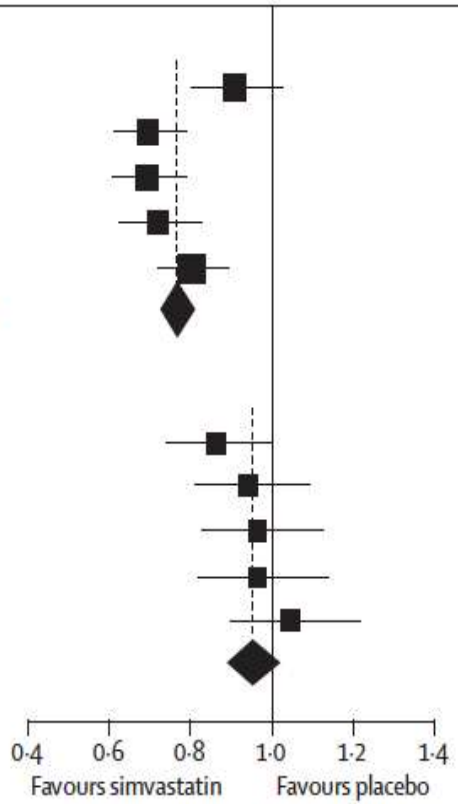
WOSCOPS - Legacy benefits during post-trial period

	In trial – 5 years			Post trial – 15 years		
Endpoint	Placebo, number (%) with event Total n = 3293	Pravastatin, number (%) with event Total n = 3302	Adjusted Hazard Ratio (95% CI) P-value*	Placebo, number (%) with event Total n = 3023	Pravastatin, number (%) with event Total n = 3118	Adjusted Hazard Ratio (95% CI) P-value*
Fatal or nonfatal MI	190 (5.77%)	115 (3.48%)	0.59 (0.47, 0.74) , <0.0001	427 (14.13%)	372 (11.93%)	0.82 (0.71, 0.94) , 0.0054
CHD related death or nonfatal MI	198 (6.01%)	119 (3.60%)	0.58 (0.47, 0.73) , <0.0001	480 (15.88%)	418 (13.41%)	0.82 (0.72, 0.93) , 0.0028
CHD related death or hospitalisation	273 (8.29%)	177 (5.36%)	0.58 (0.47, 0.72) , <0.0001	823 (27.92%)	739 (24.12%)	0.79 (0.70, 0.89) , 0.0002
CV related death or hospitalisation	415 (12.60%)	329 (9.96%)	0.62 (0.52, 0.73) , <0.0001	1301 (46.05%)	1215 (41.51%)	0.81 (0.73, 0.90) , <0.0001
Fatal or nonfatal stroke	40 (1.21%)	29 (0.88%)	0.56 (0.31, 1.03) , 0.0608	332 (10.61%)	329 (10.36%)	1.00 (0.82, 1.22) , 0.9856

Ford I et al. Circulation. (2016); 133:1073-80

Legacy benefit in statin trials - HPS

	Simvastatin allocation		Risk ratio (95% CI)	p value
	Simvastatin	Placebo		
In-trial				
Year 1	482/10269 (4·7%)	529/10267 (5·2%)	0·91 (0·80–1·03)	
Year 2	378/9744 (3·9%)	538/9681 (5·6%)	0·69 (0·61–0·79)	
Year 3	361/9286 (3·9%)	507/9053 (5·6%)	0·69 (0·61–0·79)	
Year 4	333/8814 (3·8%)	442/8463 (5·2%)	0·72 (0·62–0·83)	
Year 5+	599/8352 (7·2%)	696/7893 (8·8%)	0·80 (0·72–0·89)	
All in-trial	**2153/10269 (21·0%)**	**2712/10267 (26·4%)**	**0·77 (0·72–0·81)**	**p<0·0001**
Post-trial				
Year 1	320/7543 (4·2%)	341/6967 (4·9%)	0·86 (0·74–1·00)	
Year 2	343/7099 (4·8%)	333/6487 (5·1%)	0·94 (0·81–1·09)	
Year 3	332/6610 (5·0%)	313/6024 (5·2%)	0·96 (0·83–1·13)	
Year 4	291/6125 (4·8%)	274/5573 (4·9%)	0·96 (0·82–1·14)	
Year 5+	350/5677 (6·2%)	305/5156 (5·9%)	1·05 (0·90–1·22)	
All post-trial	**1636/7543 (21·7%)**	**1566/6967 (22·5%)**	**0·95 (0·89–1·02)**	**p=0·17**

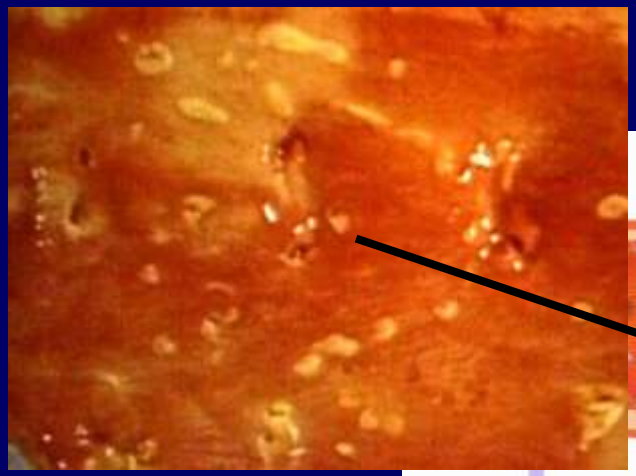


HPS Collaborative Group Lancet (2011) 378;2013-2020

Atherosclerosis over lifetime

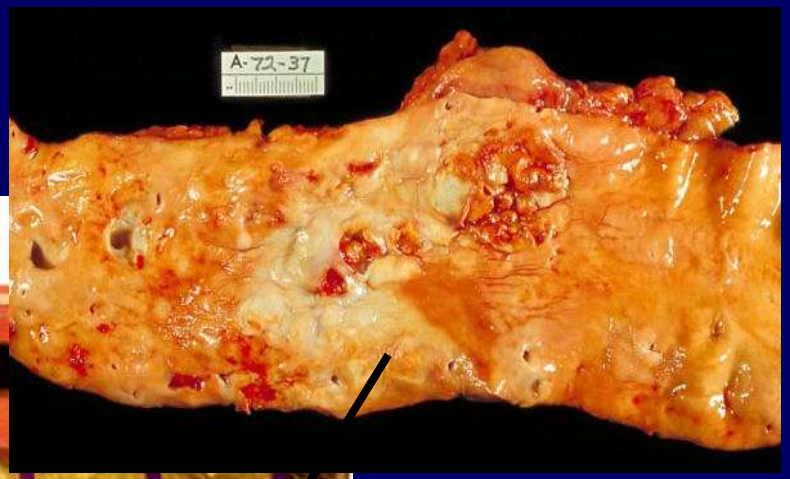
Changing nature of lesions

Asymptomatic early lesions

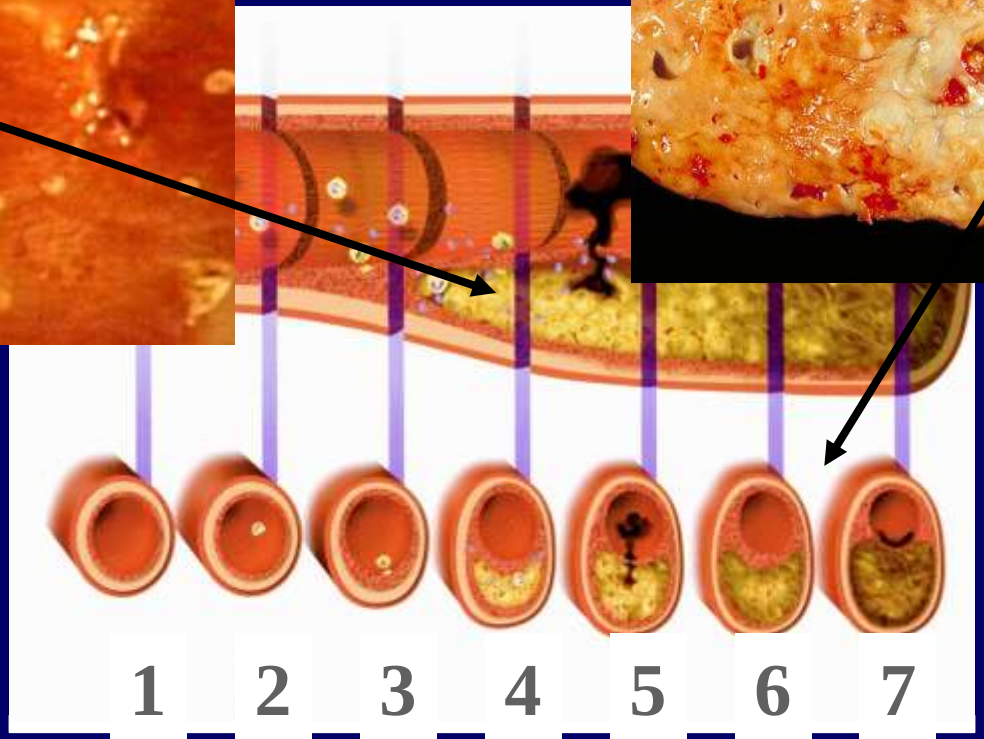


Raised fatty streaks

Clinically significant pathology

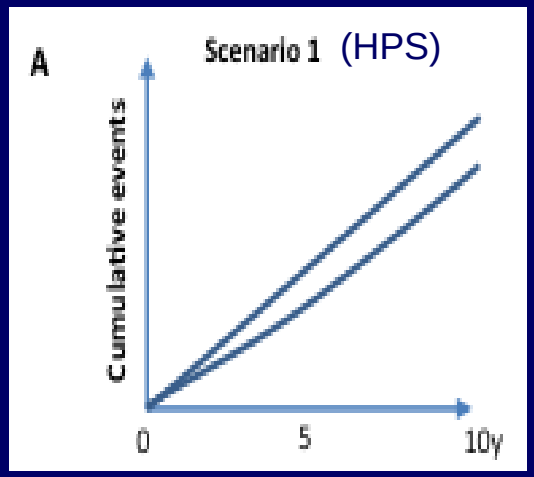


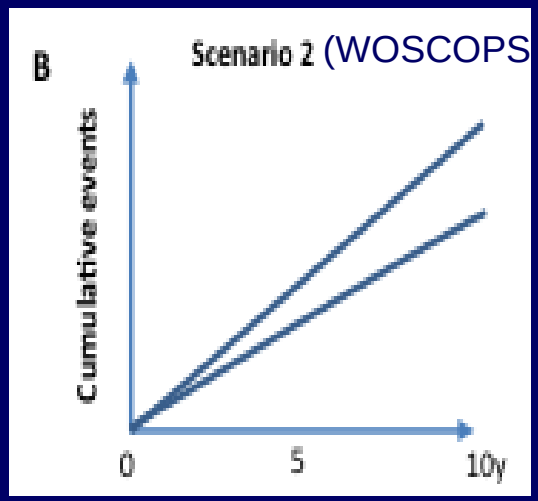
Complex/ ulcerated plaques

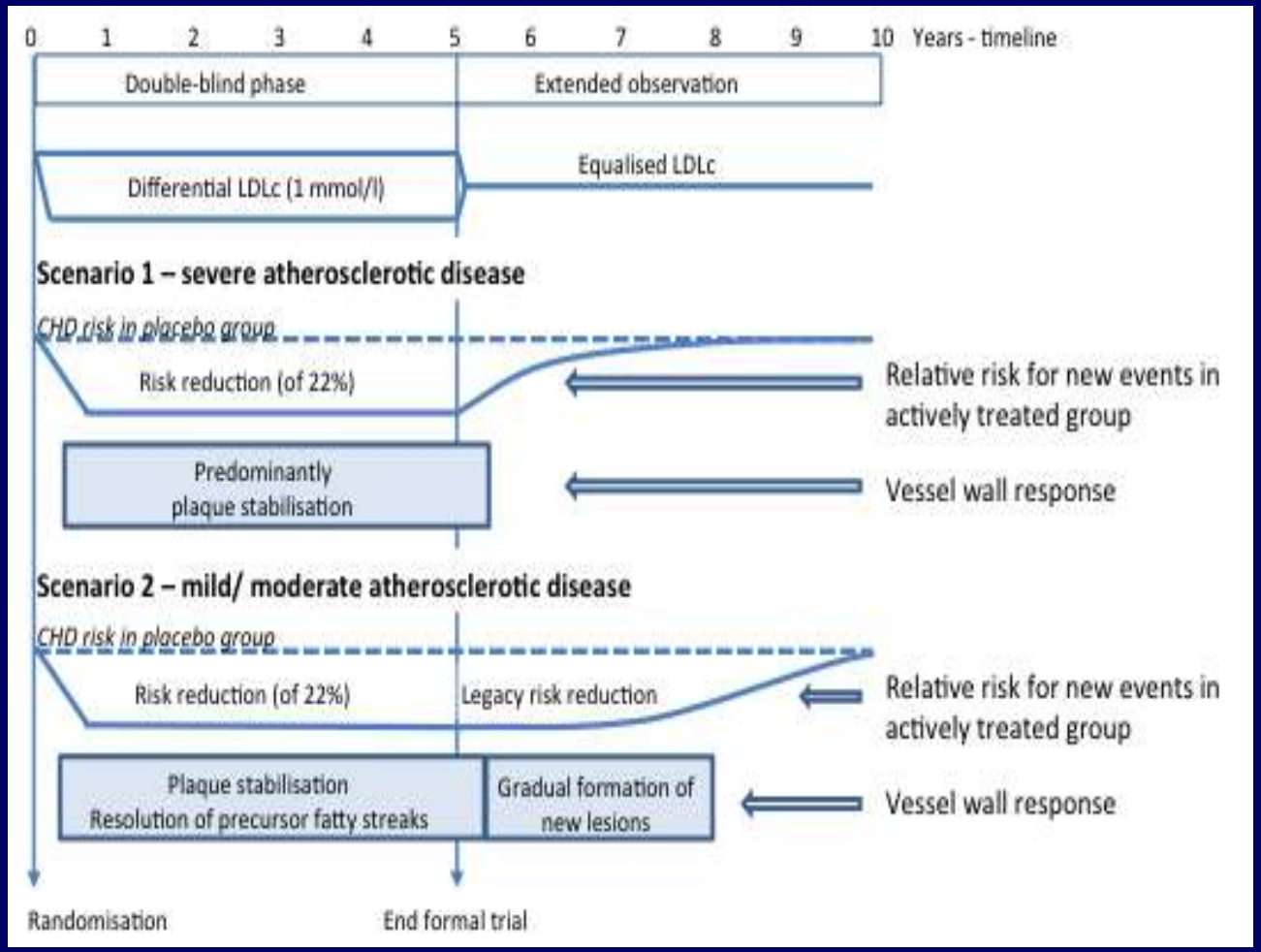


After Libby (2001) Circulation 104:365

Potential mechanism of a legacy effect in LDL lowering trials



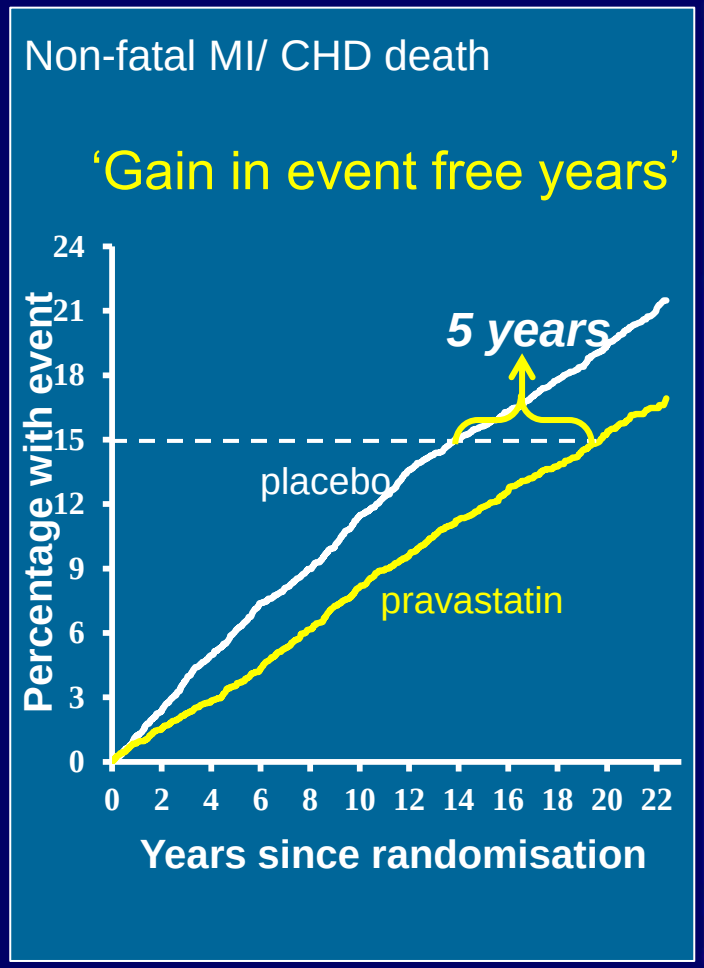


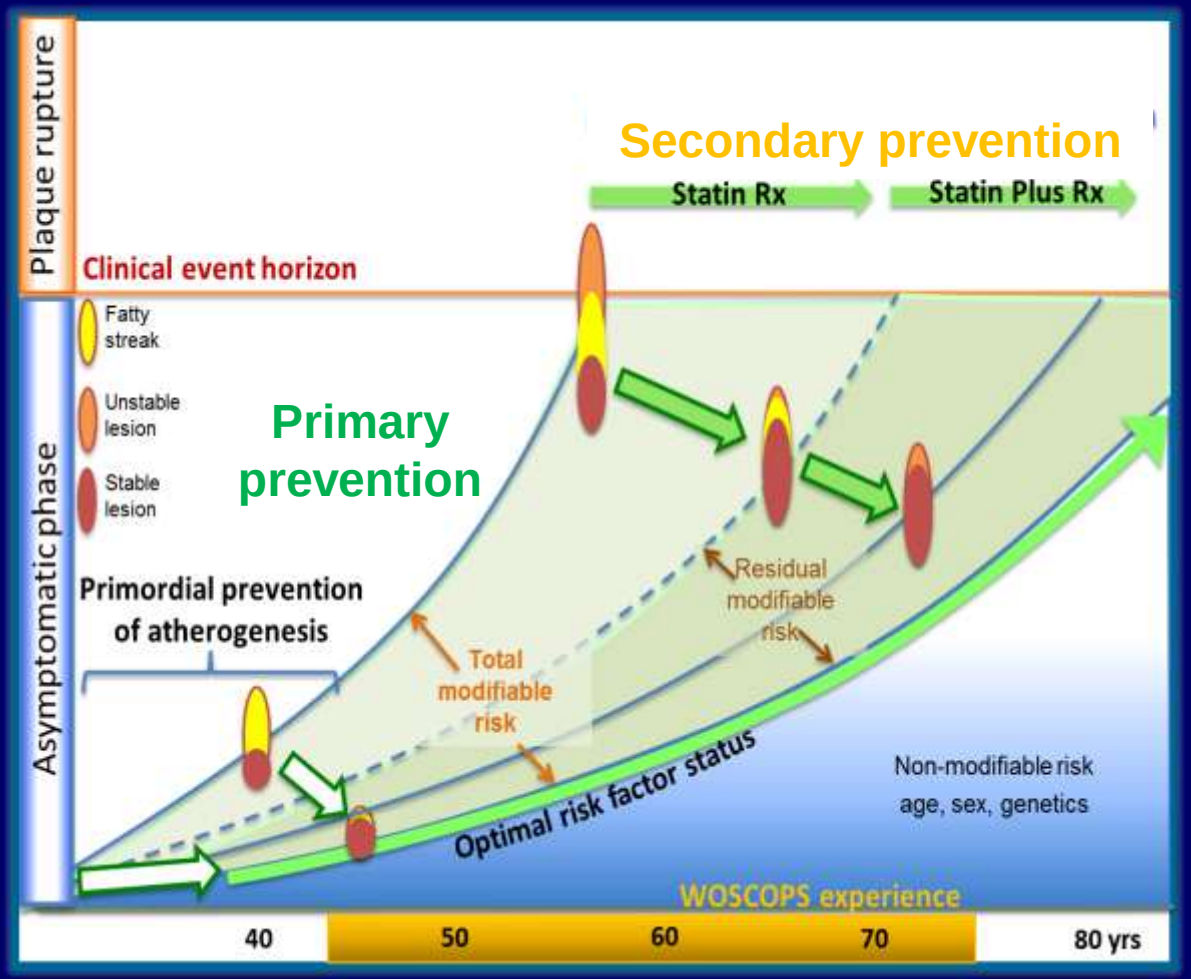


Packard, Ford Curr Opin Lipidol (2015) 26;572-9

Altering disease trajectories in CVD

Benefits of early intervention





Packard et al. Vasc Pharmacol (2015) 71;37-39

Economic benefits of primary prevention

Clinical benefit is evident in low risk populations

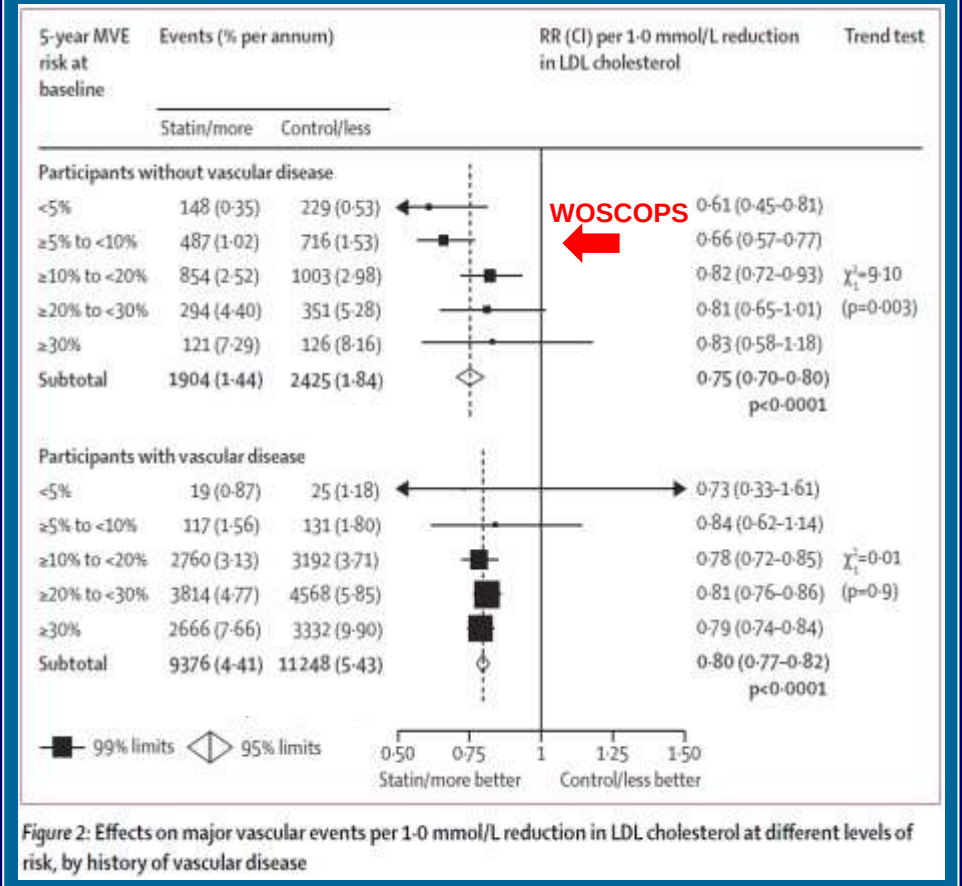
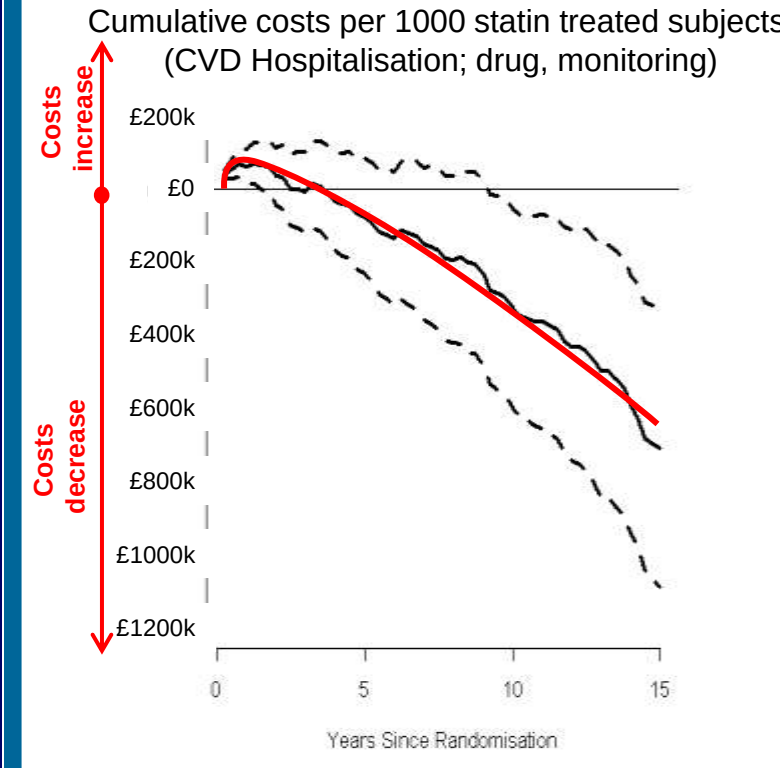


Figure 2: Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol at different levels of risk, by history of vascular disease

CTTC *Lancet* 2012:380:581-90

Statin therapy is 'cost-saving' over long term in primary prevention



McConnachie, Ford, Packard et al. 2013
(WOSCOPS,unpublished)

Understanding the lifetime benefits of statin treatment

- CVD primary prevention – key lessons from landmark trials.
- WOSCOPS 20-year experience with statin treatment.
- Adherence in primary prevention – efficacy, safety and tolerability.

Response to UK NICE widening of statin use in primary prevention – 2014/ 2016

21st March 2014

theguardian

• Statins for all: do the benefits outweigh the risks?

society

Doctors' fears over statins may cost lives, says top medical researcher

'I suffered terrible aching limbs'

Mail Online

May 15th 2016

But cardiologist Dr Aseem Malhotra said: 'I have no doubt millions of people taking statins in the UK will not benefit but are being put at risk of unnecessary harm.'

AE profile
High vs moderate intensity statin

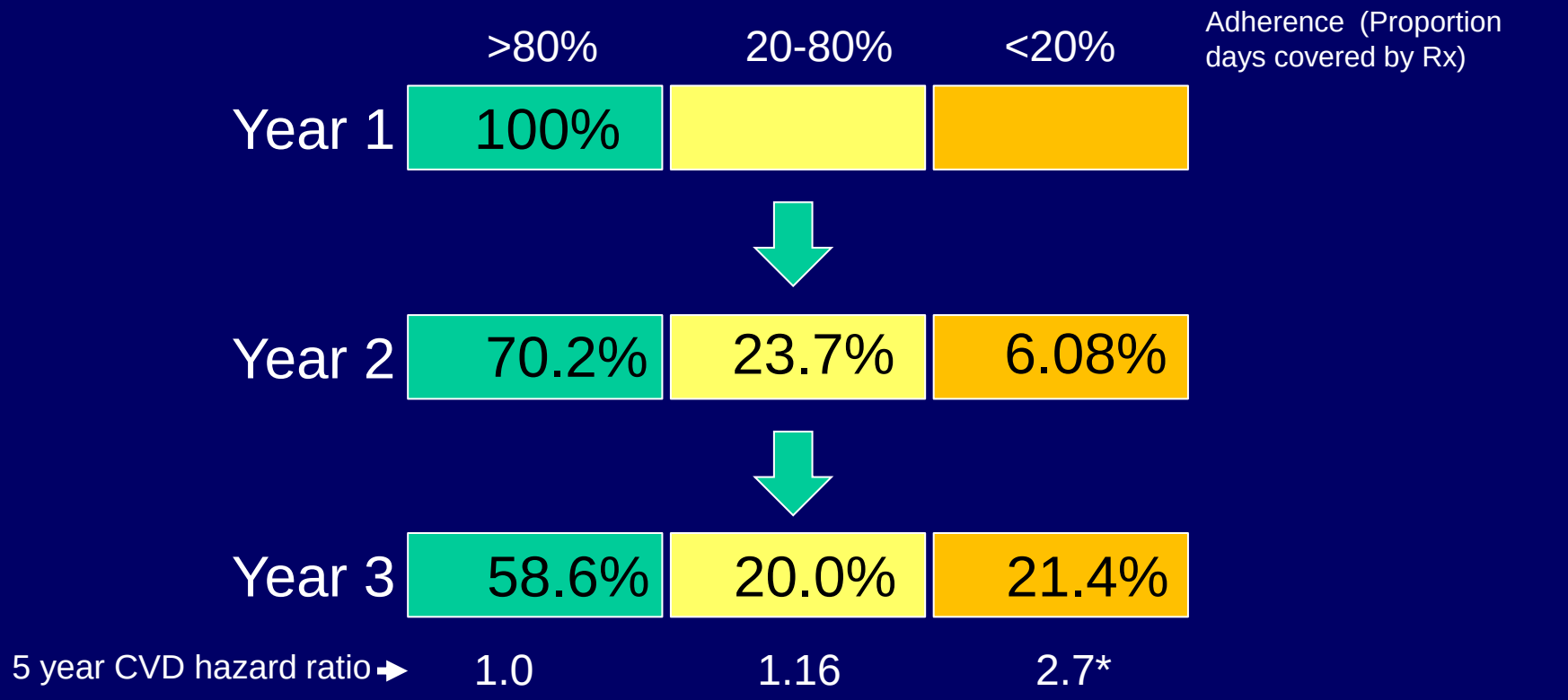
Event	Odds ratio(CI)
Any AE	1.44(1.33-1.55)
LFT abnormalities	4.48(3.27-6.16)
CK>10	9.97(1.28-77.9)
Rhabdomyolysis	1.66(0.60-4.57)

Silva et al (2007) Clin. Therap. 29:253-260

Adherence to statin therapy in primary prevention

US Prescription claims database - Asymptomatic patients prescribed statin n=11,126

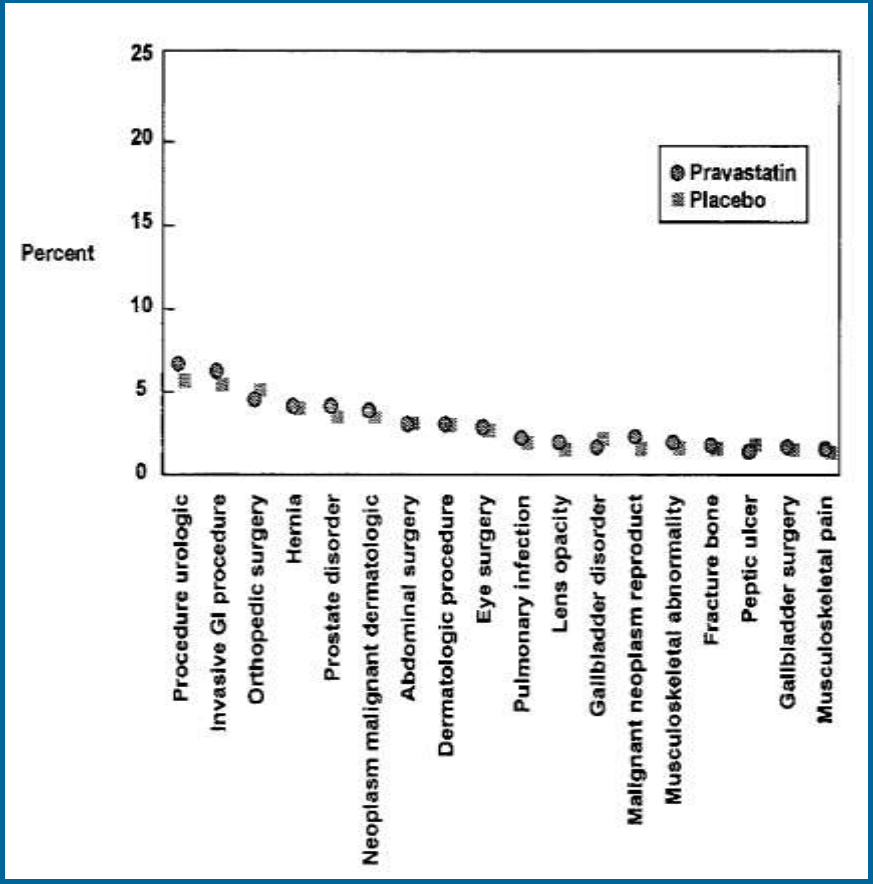
Yearly adherence changes in initially good compliers to statin



Sjelko et al (2014) JMCP 20:51-7

Pravastatin Pooling Project experience

Combined, individual subject level data from WOSCOPS, CARE and LIPID



- 19,592 Subjects randomised to placebo or pravastatin 40mg/d
- 5 years in-trial follow-up
- >112,000 patient-years exposure

TABLE 3. Serum Chemistry Abnormalities

	ALT Abnormalities			CPK Abnormalities		
	Pravastatin 40 mg (n=9185), n (%)	Placebo (n=9152), n (%)	95% CI of Difference	Pravastatin 40 mg (n=5245), n (%)	Placebo (n=5233), n (%)	95% CI of Difference
Any value >1.5×ULN	804 (8.8)	746 (8.2)	−0.21, 1.42	587 (11.2)	563 (10.8)	−0.78, 1.65
>1.5×ULN to ≤3×ULN	676 (7.4)	615 (6.7)	−0.11, 1.39	480 (9.2)	460 (8.8)	−0.75, 1.48
>3×ULN to ≤5×ULN	84 (0.9)	90 (1.0)	−0.36, 0.22	84 (1.6)	79 (1.5)	−0.40, 0.59
>5×ULN to ≤7×ULN	24 (0.3)	19 (0.2)	−0.10, 0.21	8 (0.2)	16 (0.3)	−0.36, 0.05
>7×ULN to ≤9×ULN	6 (<0.1)	9 (<0.1)	−0.13, 0.06	6 (0.1)	6 (0.1)	−0.15, 0.15
>9×ULN	14 (0.2)	13 (0.1)	−0.11, 0.13	9 (0.2)	2 (<0.1)	−0.02, 0.28

ULN=upper limit of normal.

Pfeffer et al (2002) Circulation 105:2341-6

Statin safety and tolerability in trials: Rankings of Statins

Comparative Tolerability and Harms of Individual Statins

A Study-Level Network Meta-Analysis of 246 955 Participants From 135 Randomized Controlled Trials

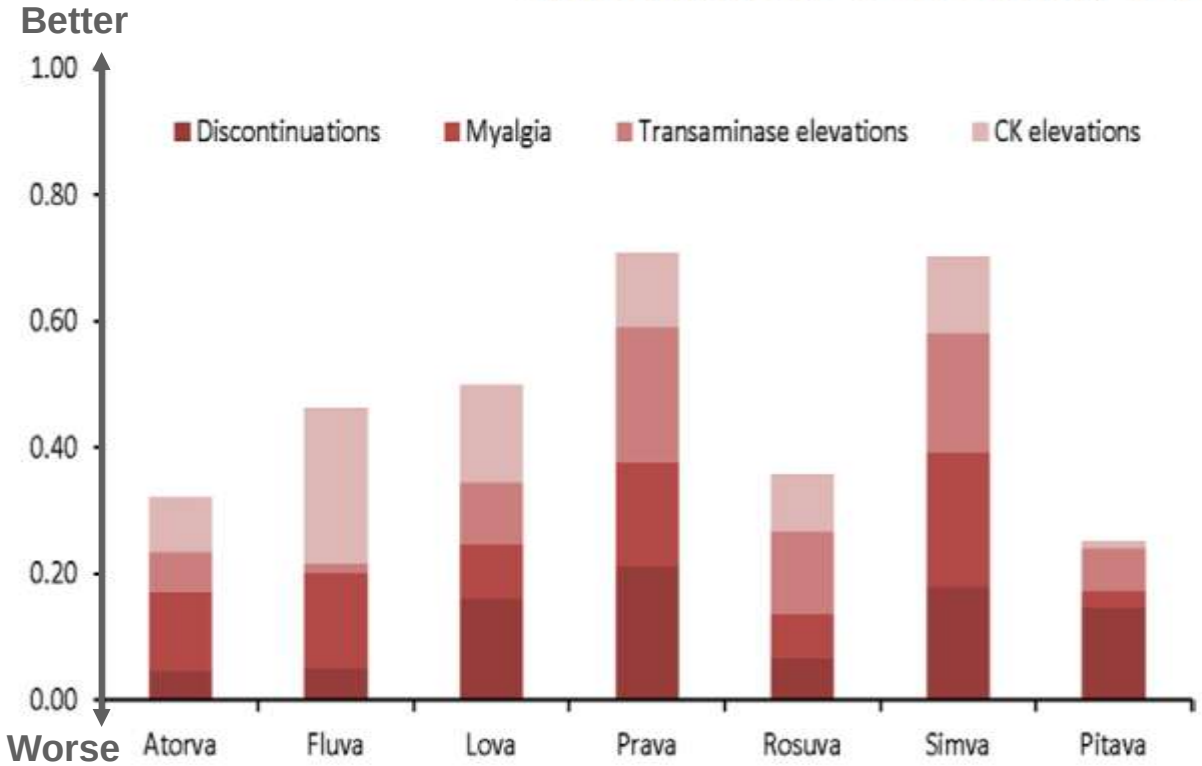


Figure 6. Overall ranking of individual statins in placebo-controlled and active-comparator trials of participants by their overall probability to be the best treatment in terms of discontinuations because of adverse events, myalgia, hepatic transaminase elevation, and CK elevation. In addition to the overall score for each statin, the relative contribution of each of the 4 outcomes to the overall score is also shown. Each statin was scored with points up to a maximum of 0.25 for each outcome (overall maximum score: 1.00). Higher scores indicate a better tolerability and safety profile. CK indicates creatine kinase.

Naci et al (2013) Circ Cardiovasc Qual Outcomes.6:390-9

Optimising adherence in primary prevention

When going beyond lifestyle and diet intervention, doctor and patient together need to:-

- Discuss risk of CVD event - use of charts and Apps.
- Be convinced of long-term benefits of medication – need for education.
- Review reassuring evidence of safety – comprehensive and long term data.
- Address tolerability – minimizes discontinuations.

Brief Summary #2

- Current therapeutic focus is on LDL as the primary target in CVD prevention.
- Long-term (lifelong) follow up of WOSCOPS provides extended safety and efficacy data – 'legacy' effect of statin therapy appears.
- Adherence is a major challenge in interventions in CVD primary prevention.
- Substantial evidence supports the concept of early intervention/ primary prevention to achieve maximum impact of LDL lowering.

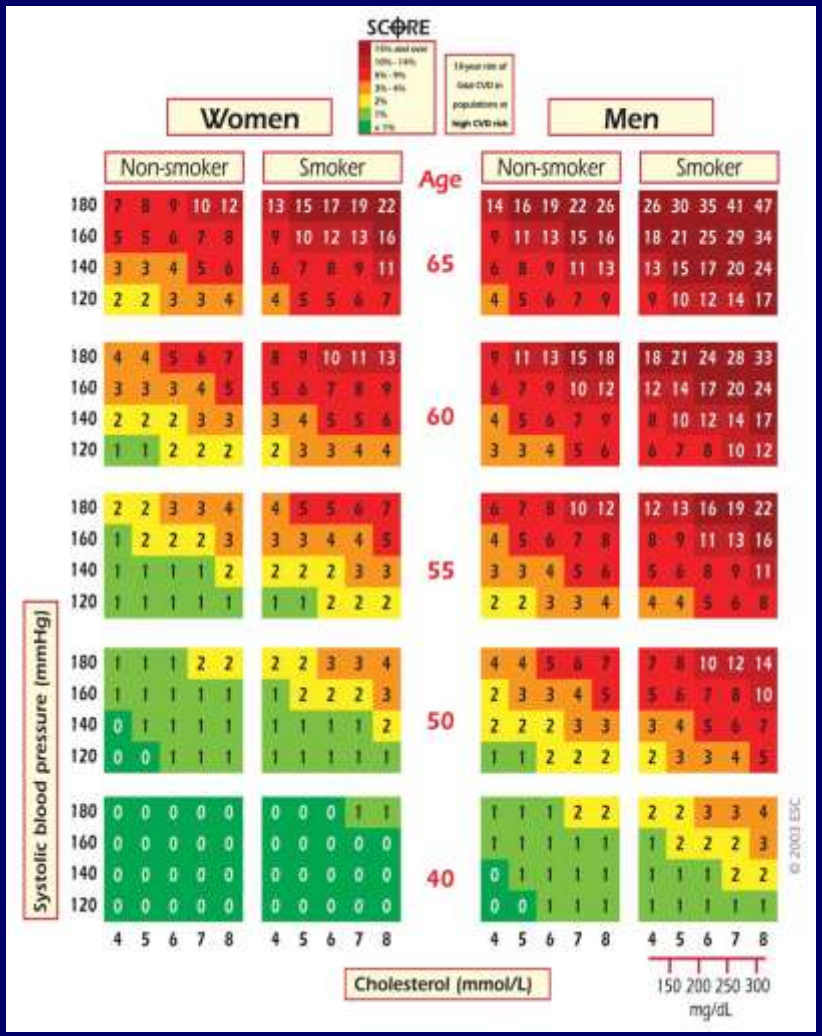
Strategies for Primary Prevention

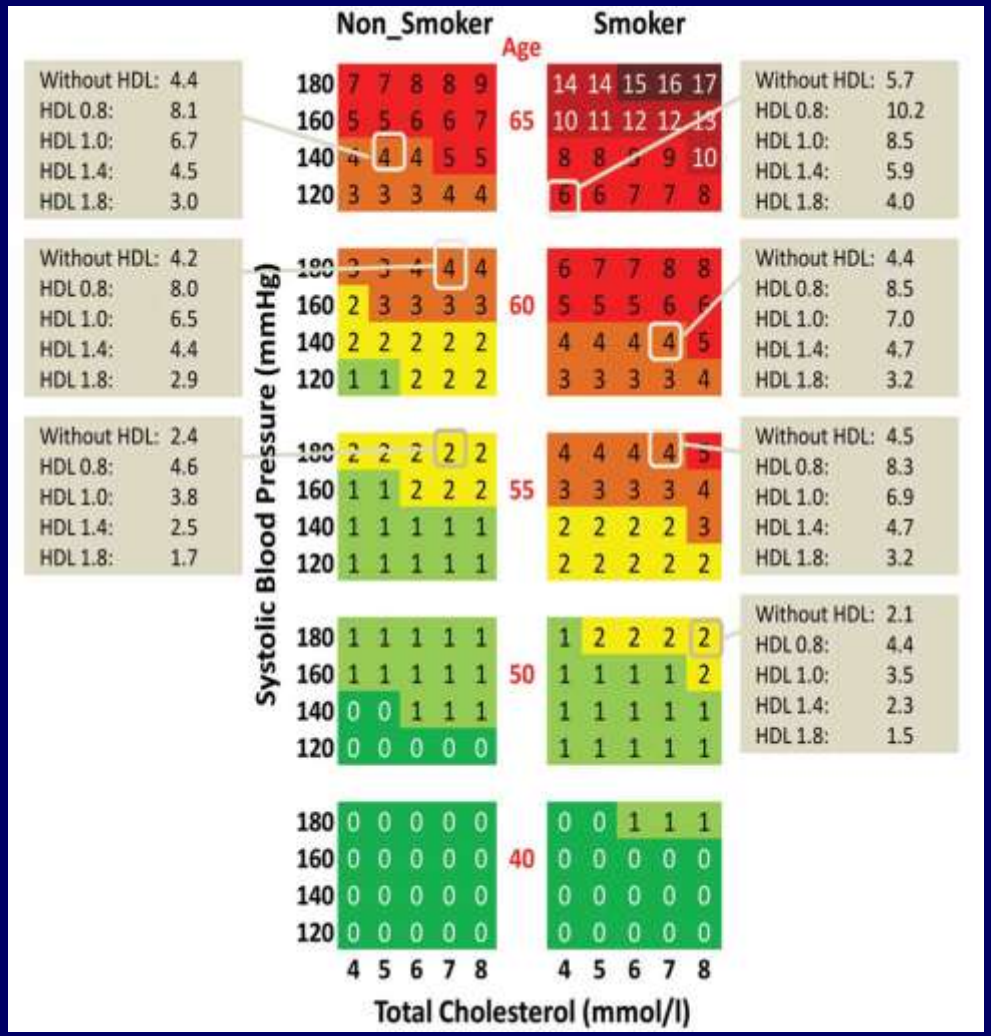
Early – safe - smart

Strategies for primary prevention

- Identification of individual at risk using of risk factor ‘score’ charts.
- Recognising advantages of early intervention.
- Use of biomarkers and gene scores – the future.

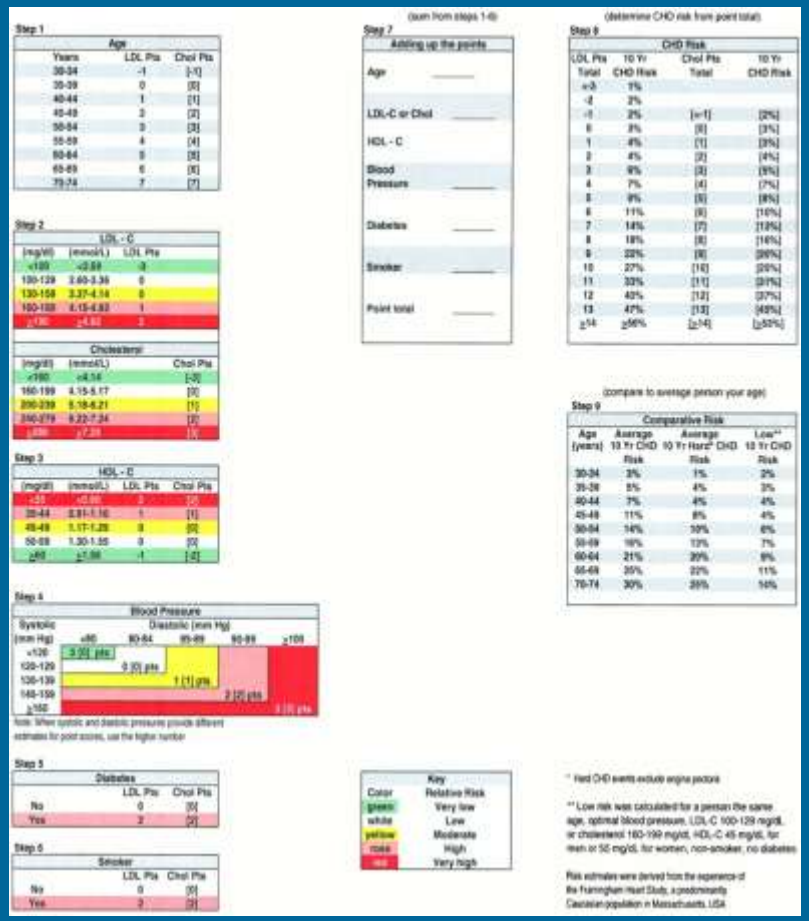
EAS/ ESC Guidelines 2011

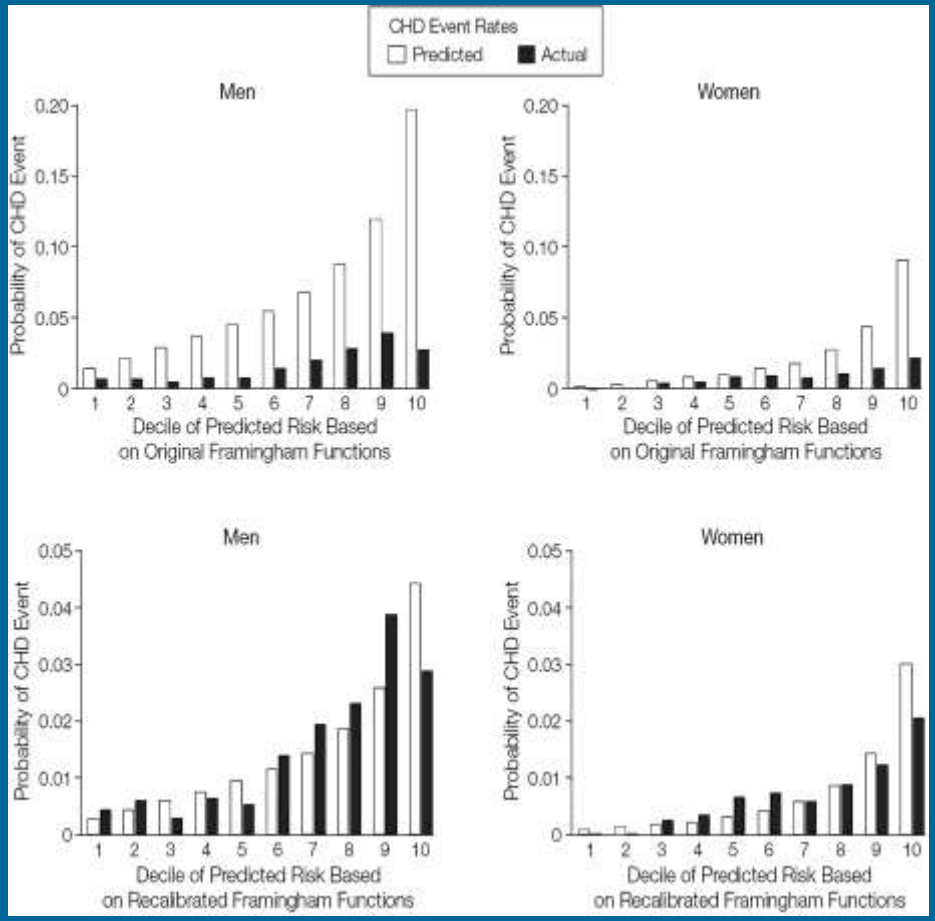




Catapano et al (2011) Atherosclerosis 217:3

International use of Framingham risk calculator after recalibration

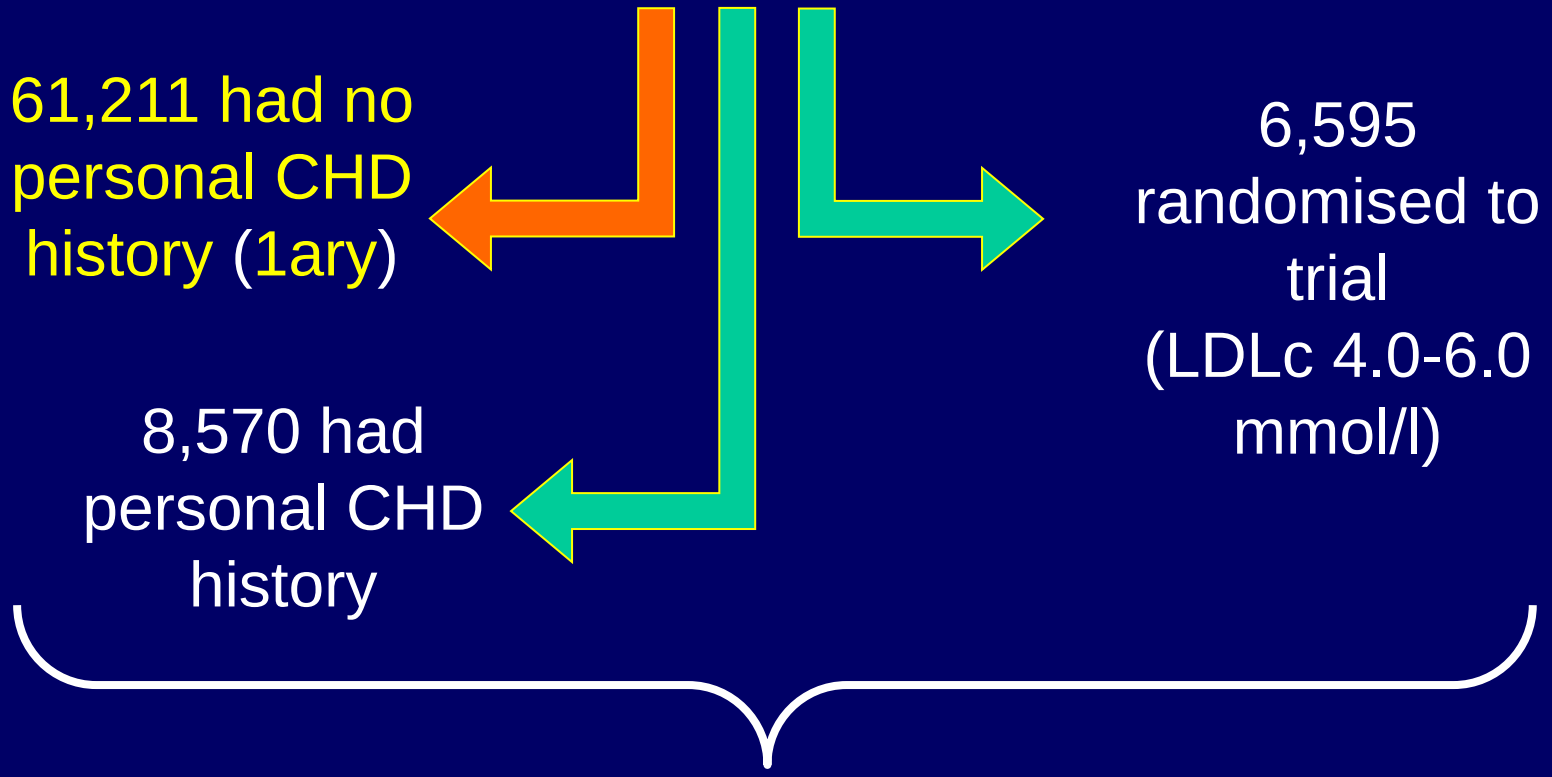




Review by Cooney, Dudina and Graham (2009) JACC 54:1209-27

Long-term observational survey of WOSCOPS screenees

80,230 men attended Study Visit 1 for risk factor evaluation



Packard et al. (2017) Europ Heart J Qual Care Clin Outcomes 3;281-288

Cumulative CHD burden

20 years in 61,211 WOSCOPS screened men

Long term observed clinical events in asymptomatic men

Group (n)	Mean cholesterol *[LDL]* (mmol/l)	Observed CHD hospitalisation events per 100 subjects over 20 years	Observed CHD hospital days per 100 subjects over 20 years	Adjusted hazard ratio [a] (95% CI)
		No CHD history – 'primary prevention'		
P4 (10767)	7.05 *[5.0]*	52.7	349.6	2.2(2.0-2.5)
P3 (22288)	5.98 *[4.0]*	42.4	288.3	1.8(1.7- 2.0)
P2 (18952)	5.06 *[3.1]*	33.6	232.2	1.5(1.3-1.6)
P1 (7414)	4.00 *[2.0]*	23.0	167.2	1.0(referent)

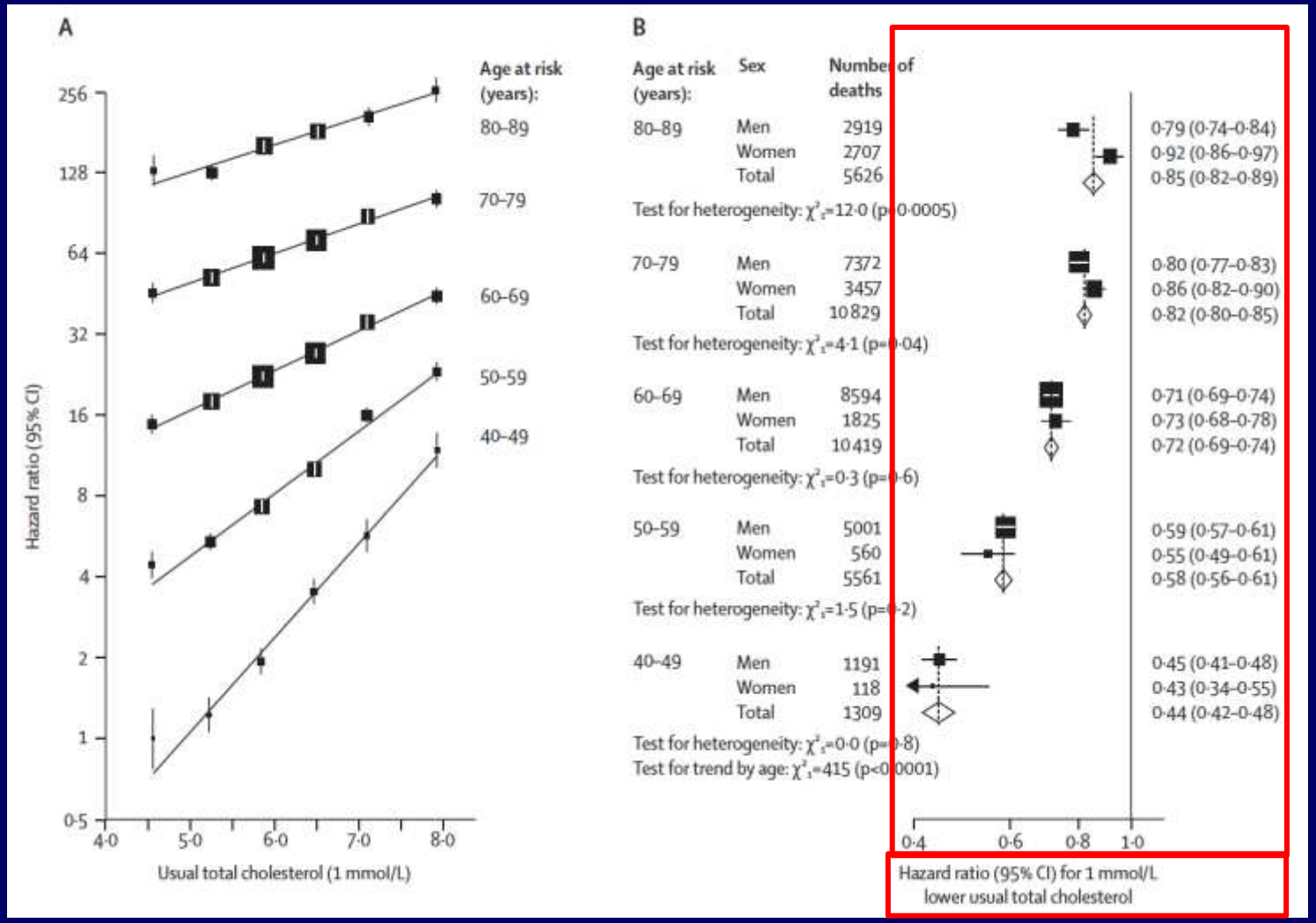
NNT = 3-4

Packard et al. (2017) Europ Heart J Qual Care Clin Outcomes 3;281-288

Strategies for primary prevention

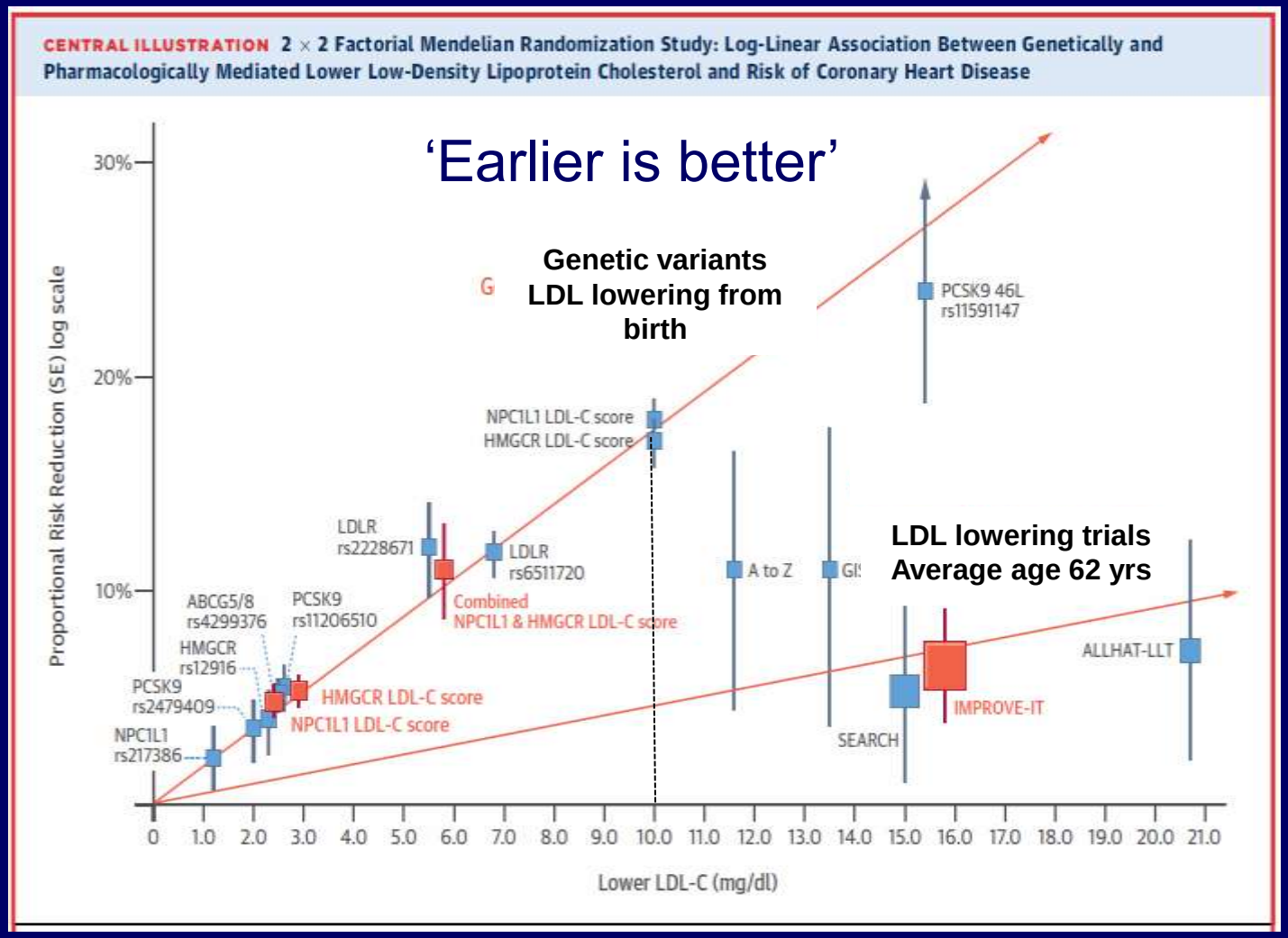
- Identification of individual at risk using of risk factor ‘score’ charts.
- Recognising advantages of early intervention.
- Use of biomarkers and gene scores – the future.

Age, cholesterol and CHD risk - Predicted greater relative risk reduction with early intervention



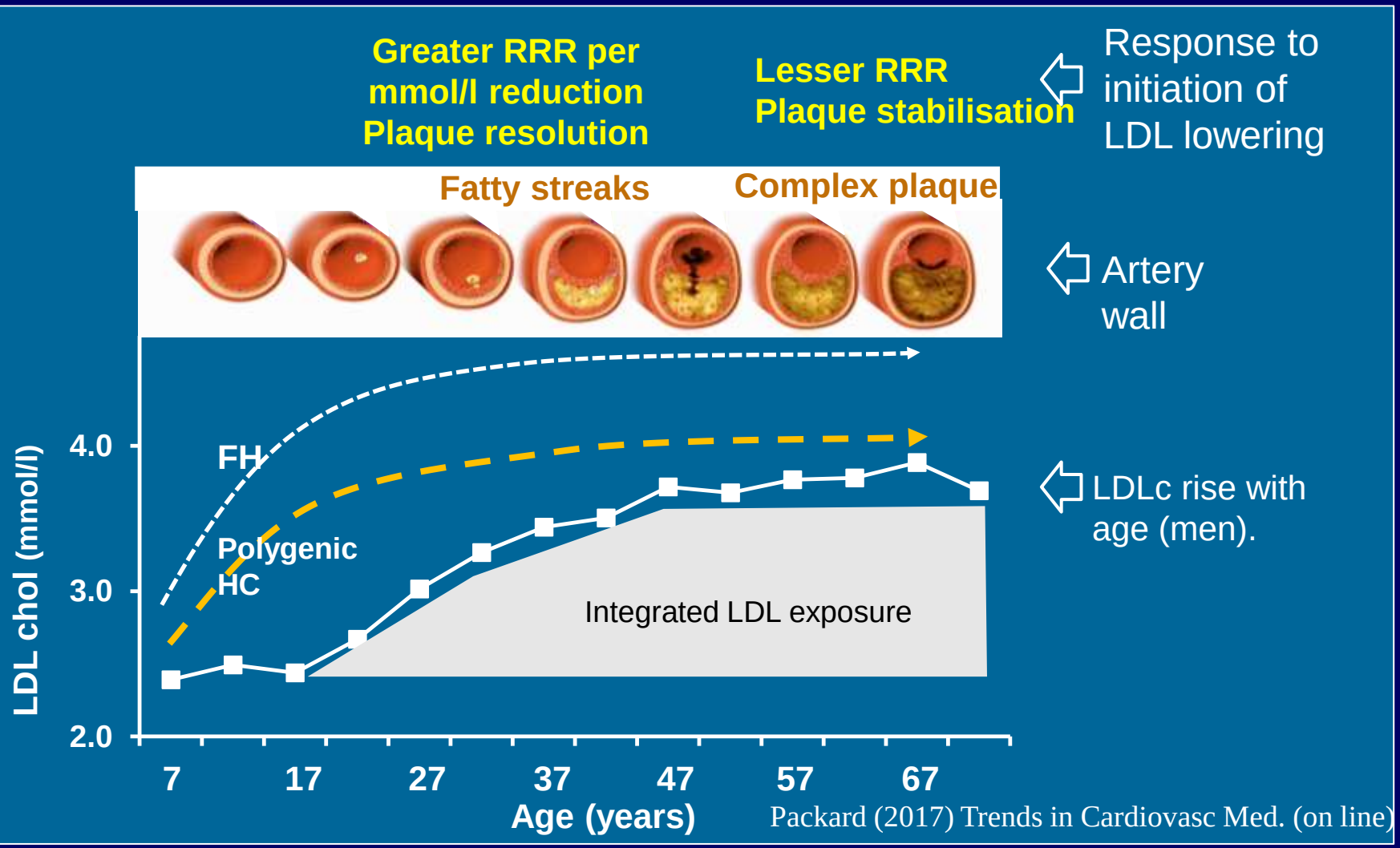
Prospective Studies Collaboration Lancet (2007) 370:1829-39

Inherited vs pharmacologically based LDL lowering



Ference et al JACC (2015) 65; 12552-61

Age and the impact of LDL on atherosclerosis



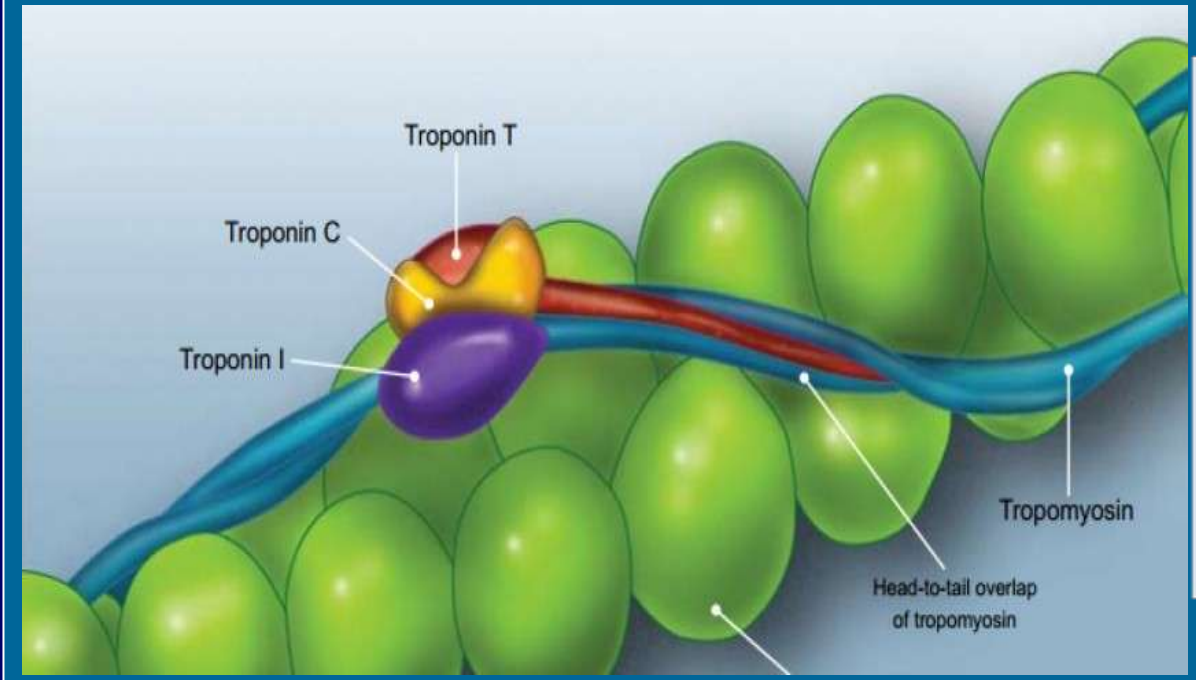
Packard (2017) Trends in Cardiovasc Med. (on line)

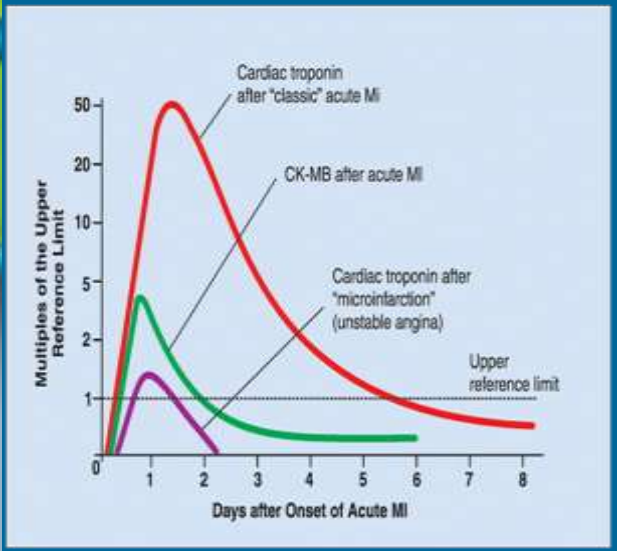
Strategies for primary prevention

- Identification of individual at risk using of risk factor ‘score’ charts.
- Recognising advantages of early intervention.
- Use of biomarkers and gene scores – the future.

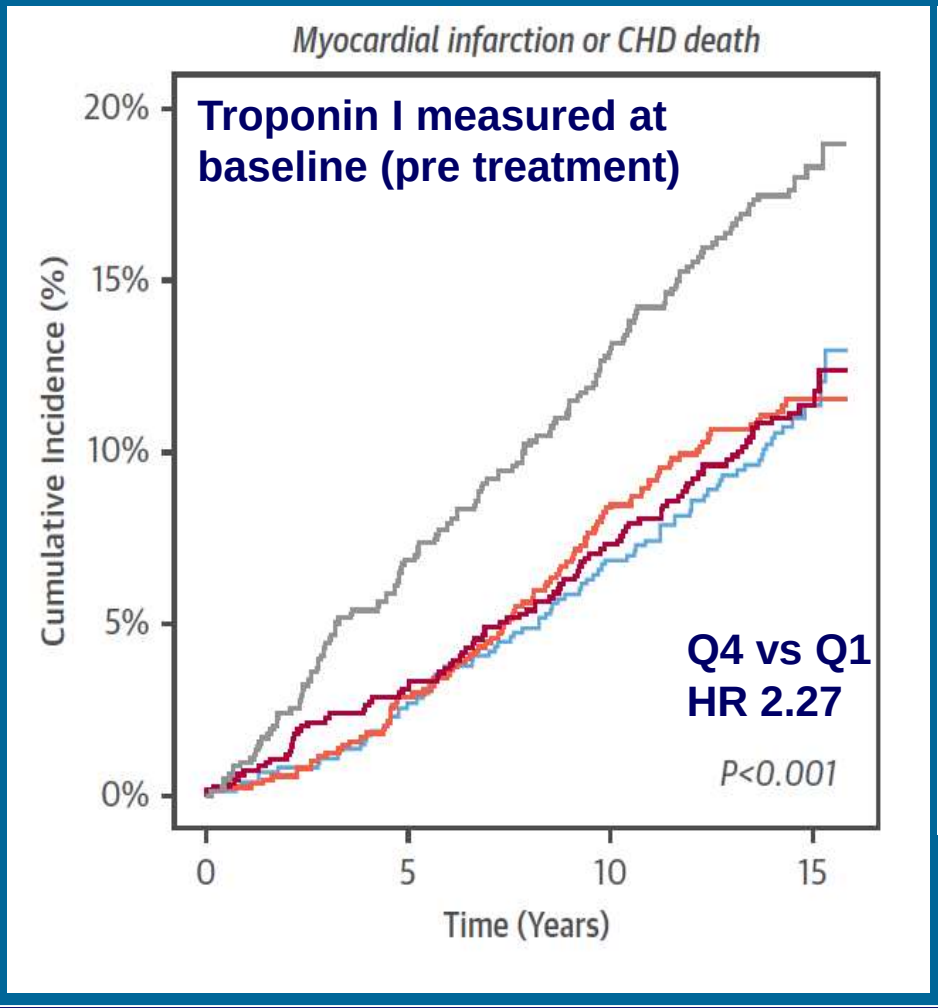
Troponin as an index of cardiomyocyte damage or stress

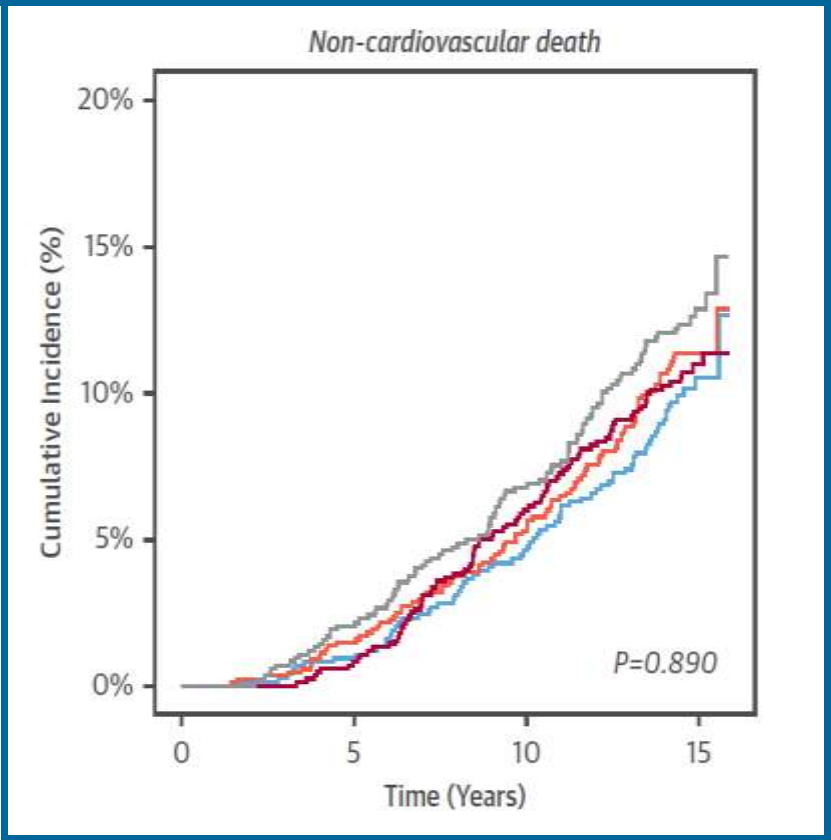
Troponin T, I, C complex with actino-myosin in cardiac muscle





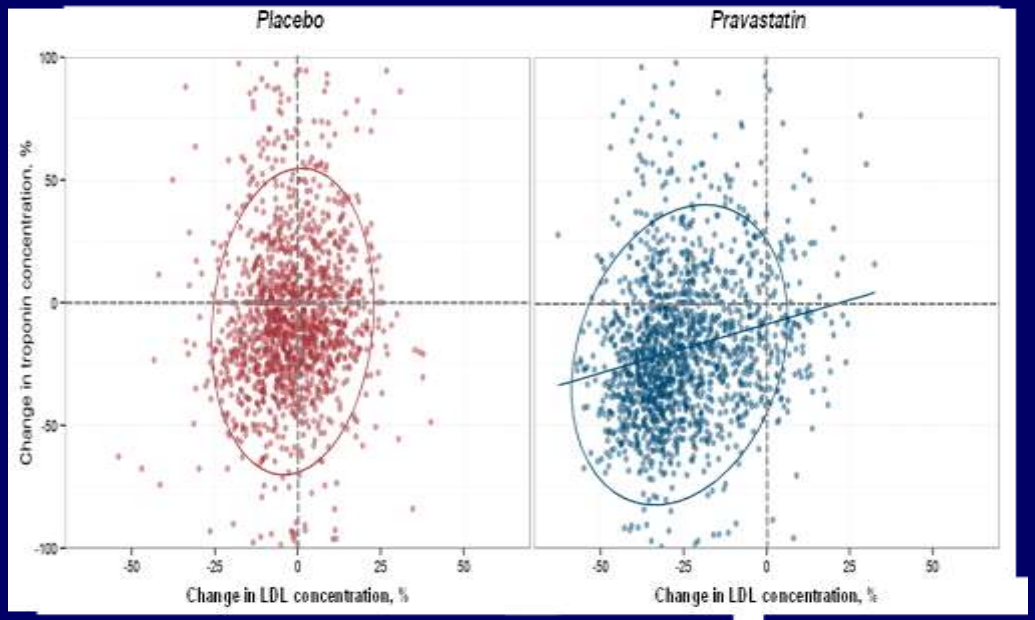
Troponin I and CVD risk in a primary prevention population - WOSCOPS

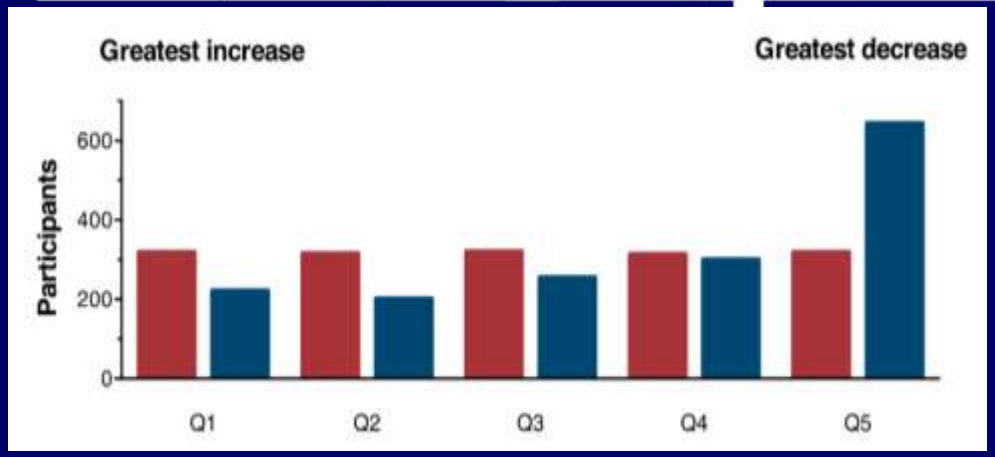




Ford et al JACC (2016) 68:2719-28

Troponin I is decreased by statins





LDL lowering with pravastatin moved subjects to lower quintiles of change in trop I.

? LDL lowering induced ‘net repair’.

? Change in trop I as biomarker of atherosclerosis progression.

Ford et al JACC (2016) 68:2719-28

LDL lowering in primary prevention

Targeting based on gene score

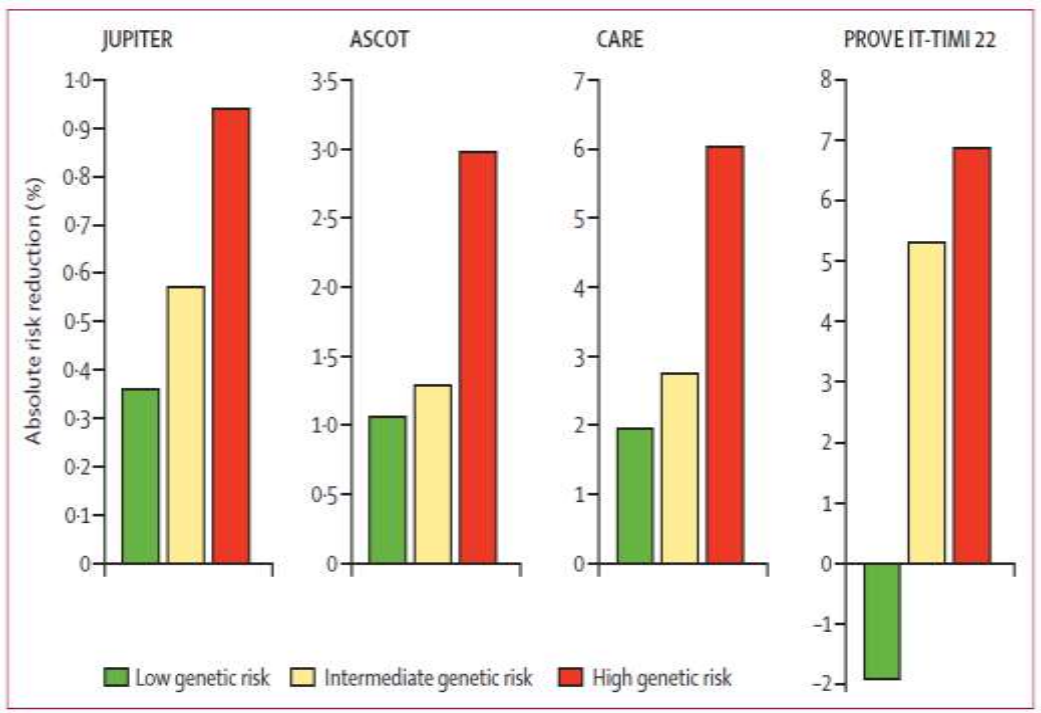
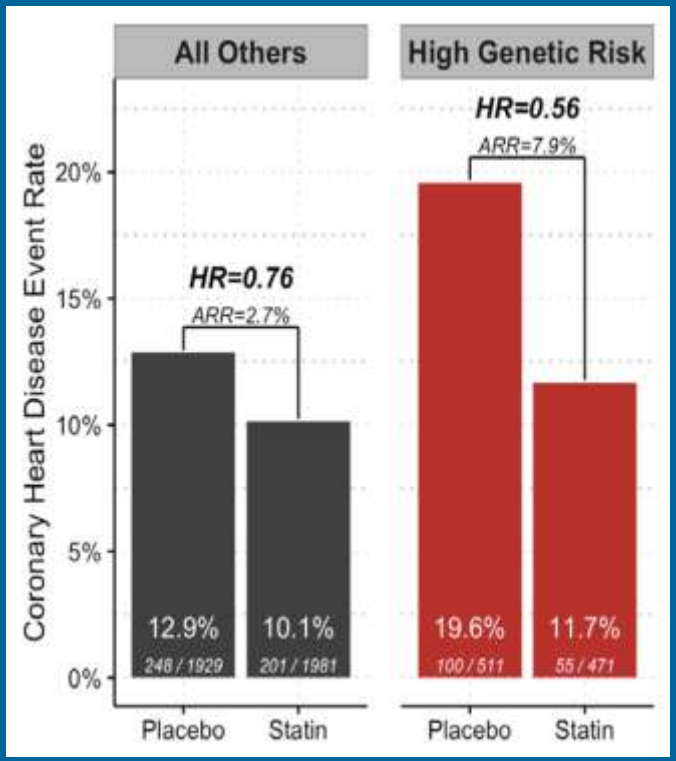


Figure 3: Absolute risk reductions of coronary heart disease events with statin therapy across genetic risk score categories

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

WOSCOPS



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

Conclusion

Conclusions

- Current therapeutic focus is on LDL as the causative agent in atherosclerosis.
- Effective primary prevention using moderate intensity statin therapy has a strong evidence base.
- Long-term (lifelong) follow up of WOSCOPS provides extended safety and efficacy data – **'legacy' effect** of pravastatin therapy appears.
- Challenge of adherence in primary prevention – need a combination of safety, efficacy, tolerability.
- Benefits of early LDLc lowering becoming apparent.