台灣血脂衛教協會
Taiwan Association of Lipid Educators

The legacy effect of primary prevention in hypercholesterolemia

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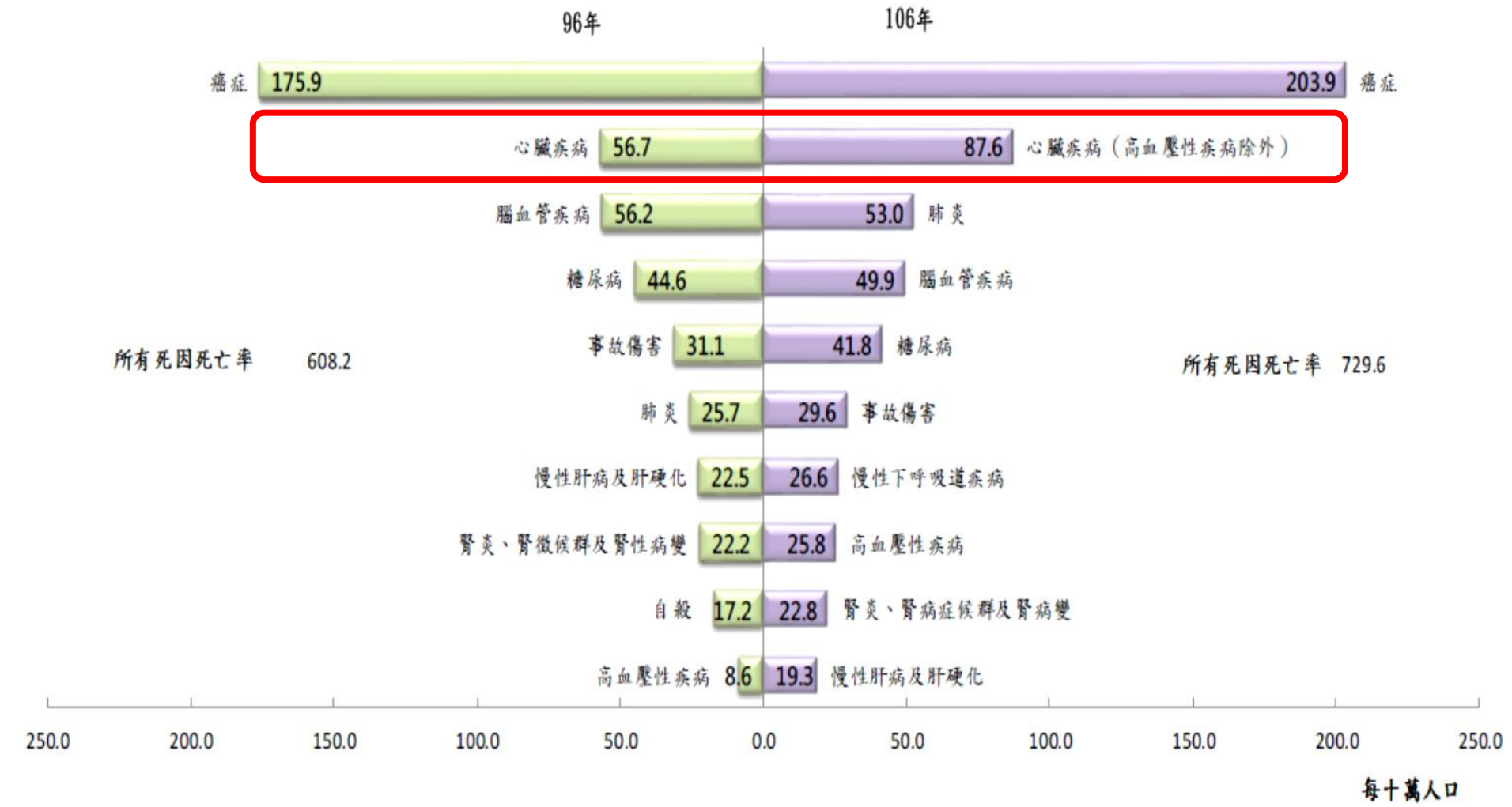
Taichung Veterans General Hospital 台中榮民總醫院

TOP 10 Cause of Death in Taiwan 2017

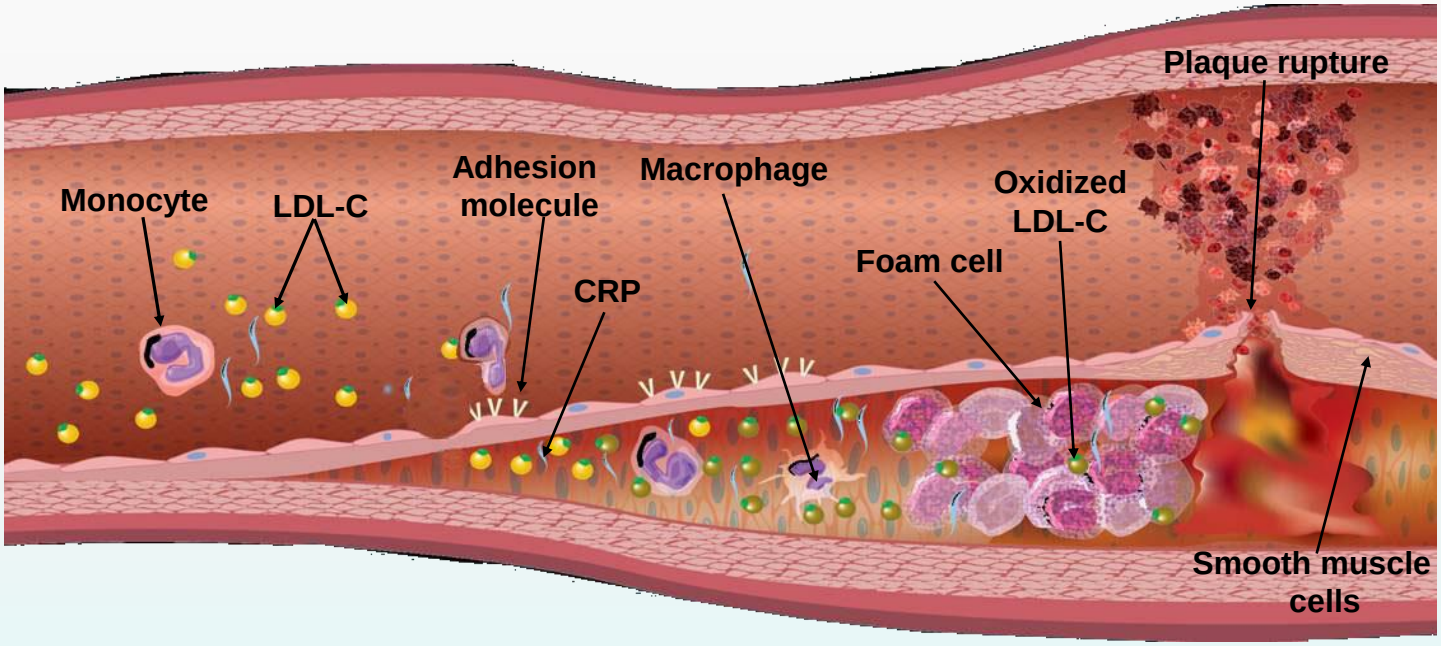
Cardiovascular disease is the secondary leading cause of death in Taiwan



衛福部 統計處 106年死因統計結果分析

Atherosclerosis: A decade-long disease process

Changing Nature of Lesions



Ischemic Stroke

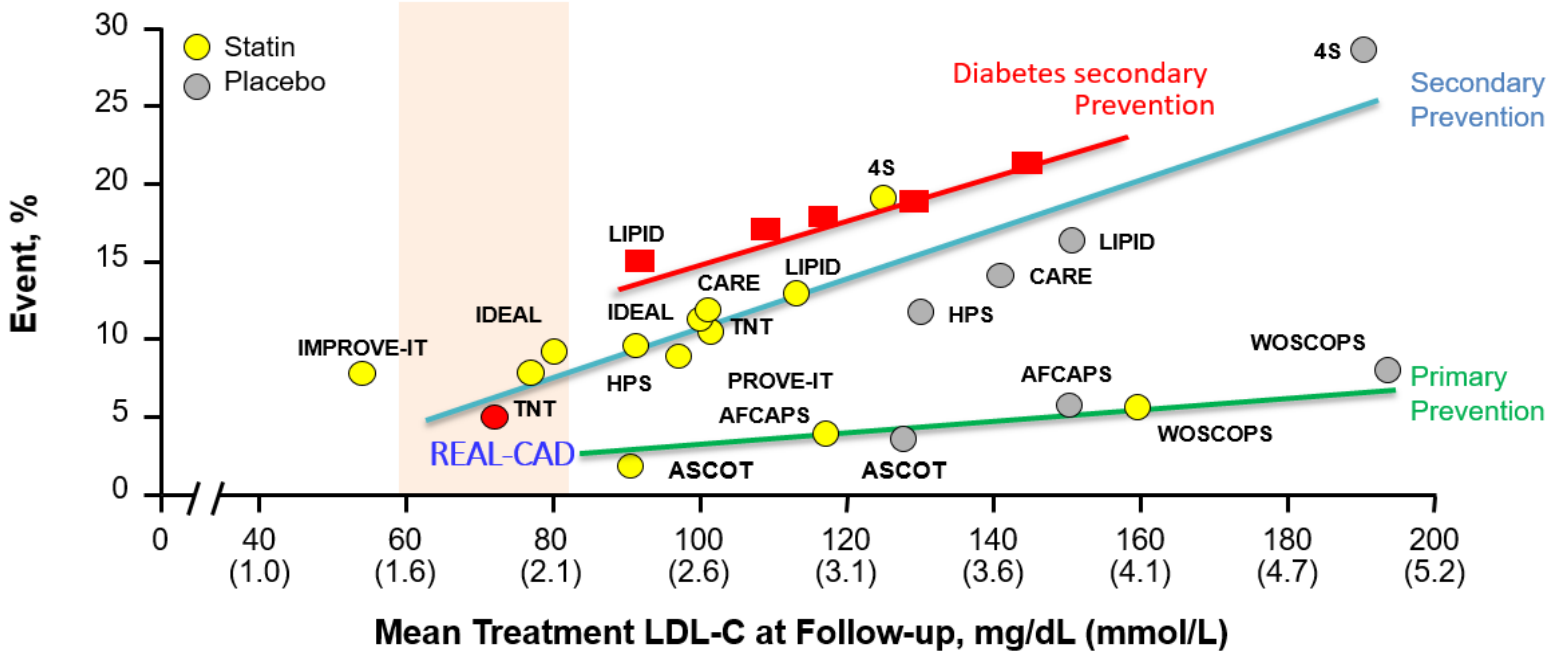
Myocardial Infarction

Cardiovascular Death

Endothelial dysfunction → Inflammation → Oxidation → Plaque instability and thrombus

Libby P. Circulation. 2001;104:365-372; Ross R. N Engl J Med. 1999;340:115-126

LDL-C Lowering and Decreased CHD Risk

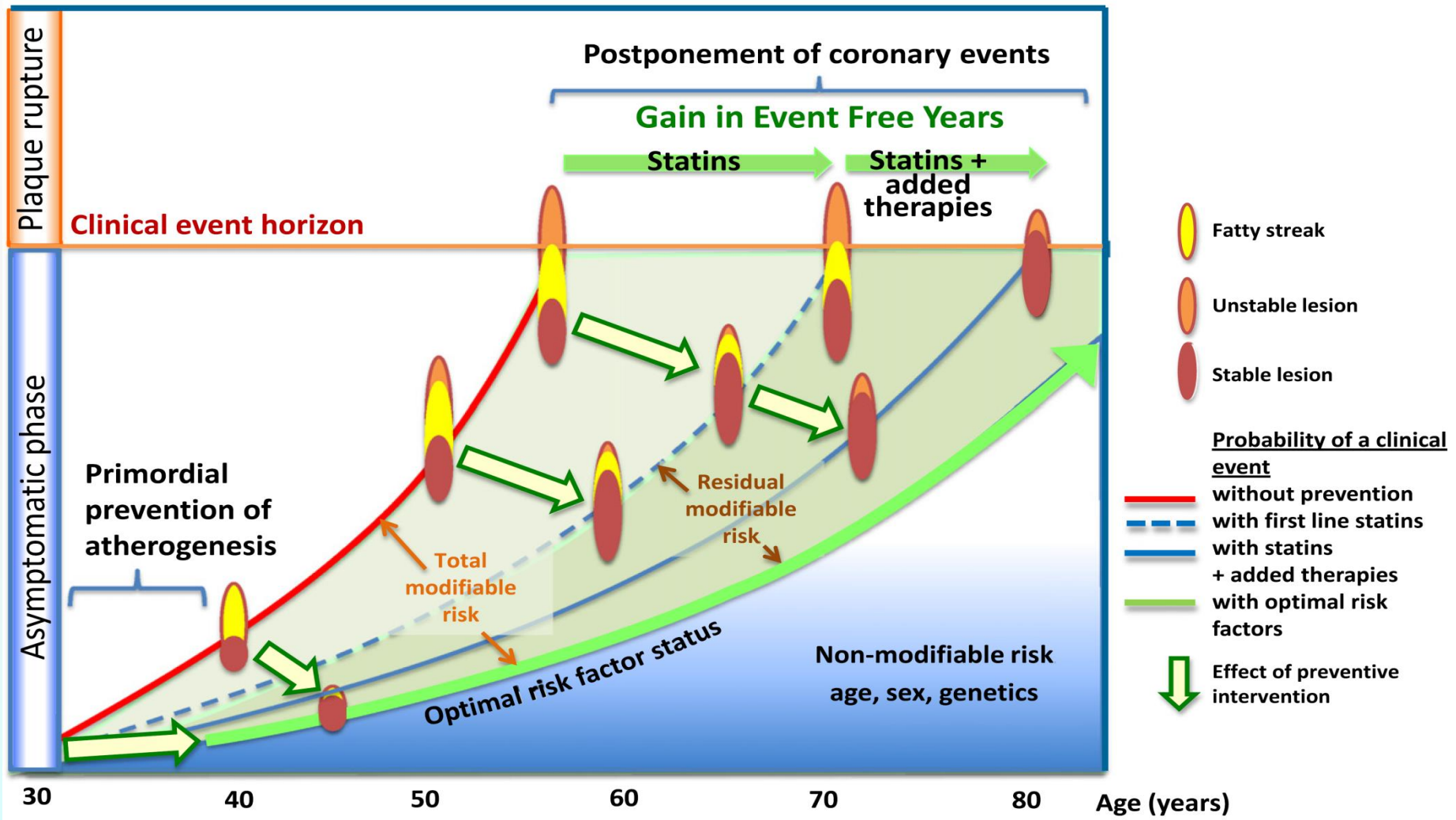


It is estimated that 1% reduction in LDL-C levels, the relative risk for major CHD events is reduced by approximately 1%

IDEAL=Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS=Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS=West of Scotland Coronary Prevention Study.

Adapted from Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9(2):269–279; LaRosa JC, et al. *N Engl J Med*. 2005;352(14):1425–1435; Pedersen TR, et al. *JAMA*. 2005;294(19):2437–2445.

Reversibility of Plaque Decreased along with Times



Vascul Pharmacol. 2015 Aug;71:37-9.

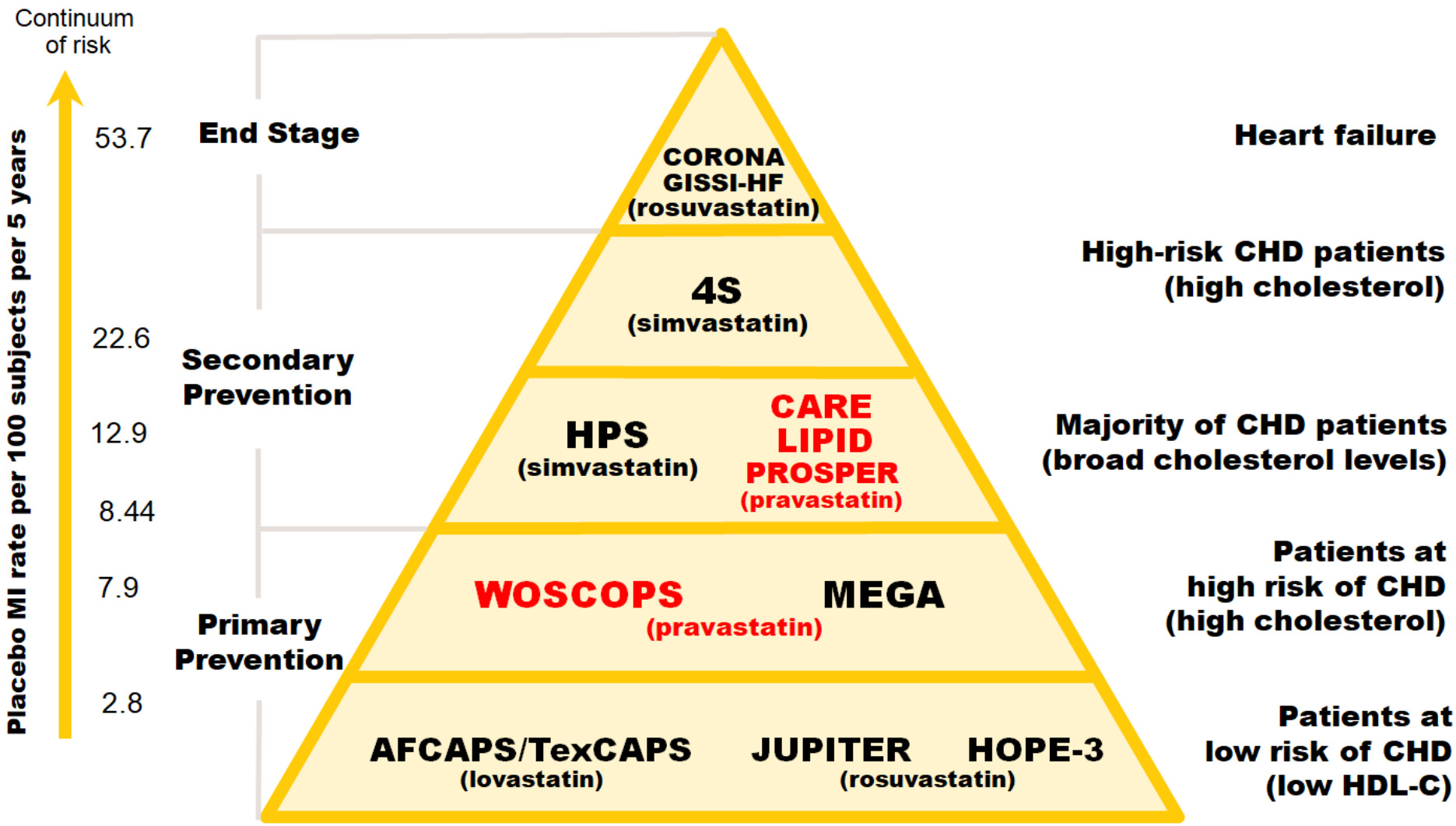
Legacy

- 'Legacy' in simple English means what one generation passes on to the next generation or past events affecting the present.

- A phenomenon of continuous beneficial effect of the intensive control on disease outcomes or even after a long duration of cessation of the intervention.

N Engl J Med. 2005;353:2643–2653.

Landmark Clinical CHD Event Trials



- Most of the statin trials have an average duration that is fairly short to study the long-term effects and safety of drugs that should be taken lifelong
- Longer followup of patients is important; need 20 year followup for development of solid tumors

Long-term followup of statin trials

Study	Populations	Age (yrs)	Baseline lipids	Followup lipids	Followup years	On statins	KM curves and treatment benefit
4S	MI or angina	35-70 (51% ≥60)	cholesterol 4.9 mmol/L, 190 mg/dl	cholesterol 5.1 mmol/L, 196 mg/dl	10	84%	Maintained for mortality
LIPID	MI or angina	Median 62	LDL 3.9 mmol/L, 150 mg/dl	LDL 3.9 mmol/L, 150 mg/dl	16	85%	Maintained for CHD mortality
HPS	CAD, occlusive arterial disease, diabetes	40-80 (27% ≥60)	LDL 3.4 mmol/L, 132 mg/dl	LDL 2.6 mmol/L, 100 mg/dl	11	59-84%	Diverged 14% first year, then parallel for major vascular events
ASCOT	Primary prevention, hypertension	40-70 Mean 63	LDL 4.4 mmol/L, 169 mg/dl	-	11	69%	Diverged for mortality and non CV mortality
PROSPER	Vascular disease or ↑ risk	70-82 Mean 75.3	3.8 mmol/L 147 mg/dl	-	8.6	-	Maintained for CHD mortality
WOSCOPS	**Primary prevention,** males	45-64 **Mean 55**	**LDL 4.9 mmol/L, 190 mg/dl**	-	20	**31%**	Diverged for CHD mortality

West of Scotland Coronary Prevention Study (WOSCOPS)

- Designed to determine whether the administration of pravastatin to men with hypercholesterolemia and no history of myocardial infarction reduced the combined incidence of nonfatal myocardial infarction and death from coronary heart disease

James Shepherd, et al, N Engl J Med 1995;333:1301-7

West of Scotland Coronary Prevention Study Group (WOS)

- Randomized, double-blind, placebo controlled
- 6595 men, 45 to 64 years of age
- Average follow-up of 4.9 years (seen at 3 month intervals)
- Pravastatin (40 mg each evening) vs. placebo

James Shepherd, et al, N Engl J Med 1995;333:1301-7

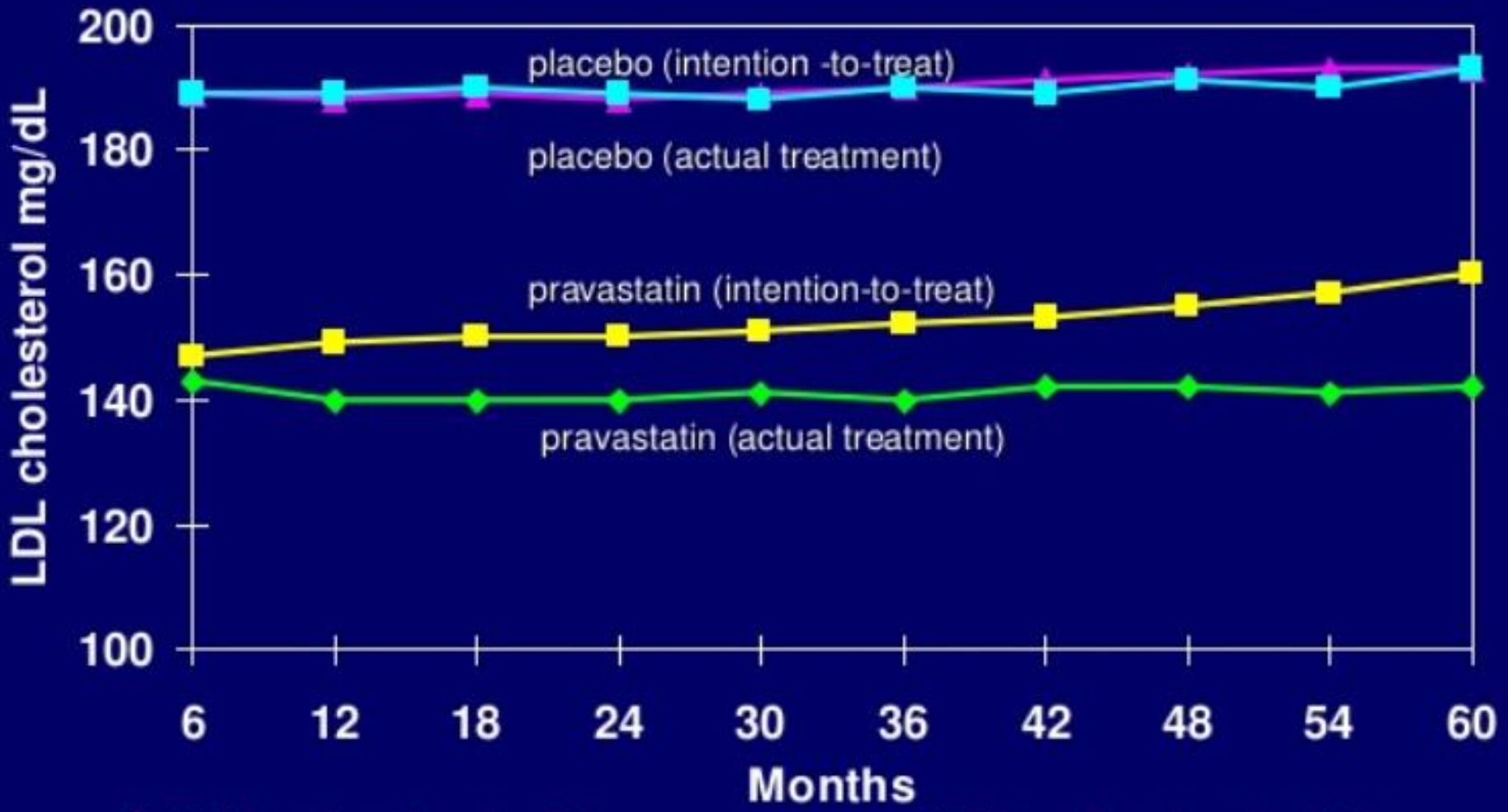
Baseline Characteristics (WOS)

Characteristic	Placebo (N = 3293)	Pravastatin (N = 3302)
Continuous variables		
Age — yr	55.1±5.5	55.3±5.5
Body-mass index†	26.0±3.1	26.0±3.2
Blood pressure — mm Hg		
Systolic	136±17	135±18
Diastolic	84±10	84±11
Cholesterol — mg/dl		
Total	272±22	272±23
LDL	192±17	192±17
HDL	44±10	44±9
Triglycerides — mg/dl	164±68	162±70
Alcohol consumption — units/wk‡	11±13	12±14
Categorical variables — no. of subjects (%)		
Angina§	174 (5)	164 (5)
Intermittent claudication§	96 (3)	97 (3)
Diabetes	35 (1)	41 (1)
Hypertension (self-reported)	506 (15)	531 (16)
Minor ECG abnormality	259 (8)	275 (8)
Smoking status		
Never smoked	705 (21)	717 (22)
Exsmoker	1127 (34)	1138 (34)
Current smoker	1460 (44)	1445 (44)
Employment status		
Employed	2324 (71)	2330 (71)
Unemployed	459 (14)	430 (13)
Retired	338 (10)	330 (10)
Disabled	171 (5)	210 (6)

WOSCOPS Endpoints

- **Primary**
  - Non-fatal MI or coronary heart disease death as a first event
- Secondary
  - Non-fatal MI
  - Coronary heart disease death
- Other Endpoints
  - Cardiovascular mortality
  - Total mortality
  - Coronary revascularization procedures

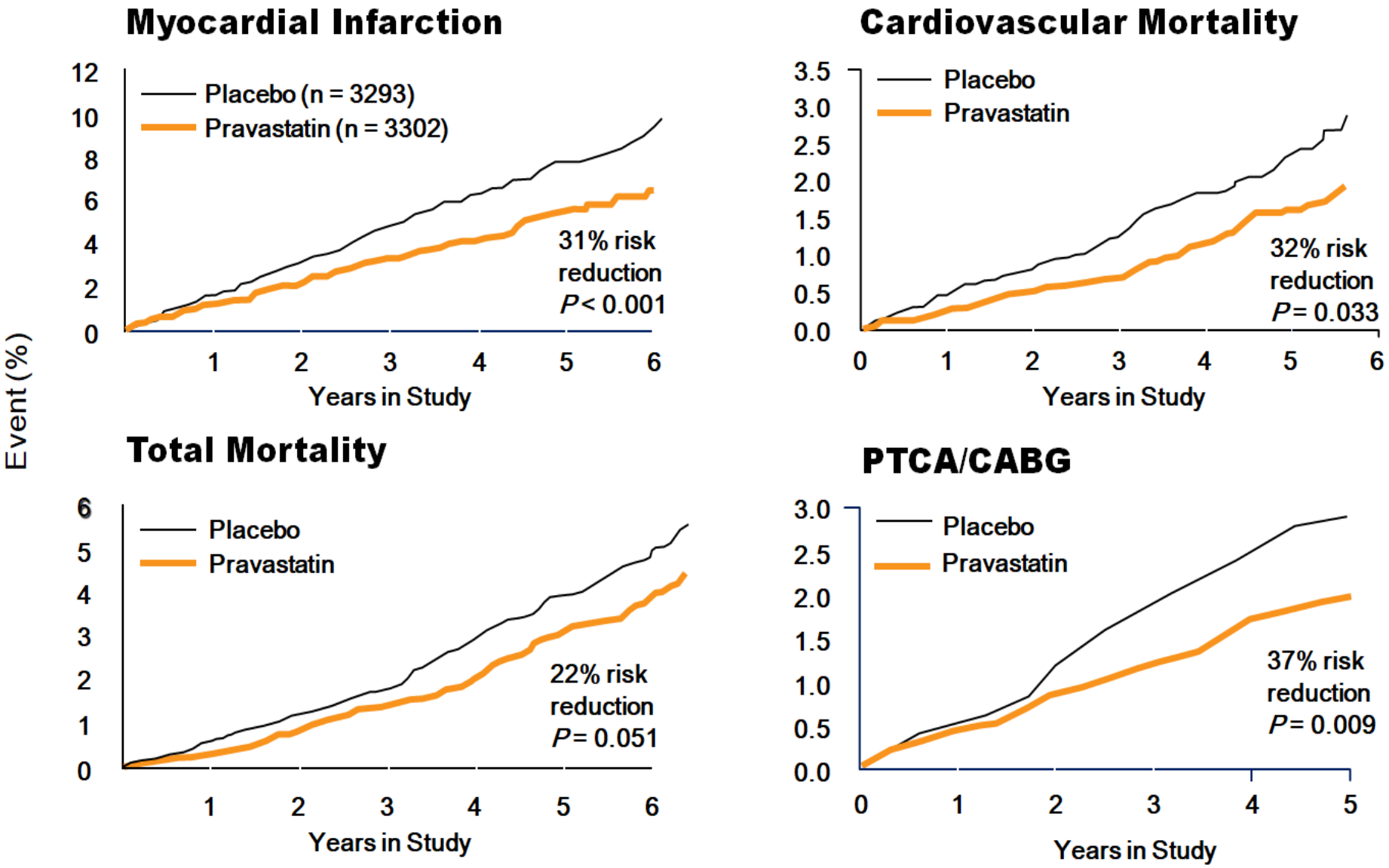
WOSCOPS Reduction in Lipids



- 20% reduction in TC
- 26% reduction in LDL
- 12% reduction in Trigs
- 5% increase in HDL

James Shepherd, et al, N Engl J Med 1995;333:1301-7

Early Event Reductions With Mevalotin



Legacy Effect of Mevalotin in Primary Prevention

Men without CHD

- **Mevalotin 40mg/D** (n=3306)
- **Placebo** (n=3293)

5-yr Outcome

降低LDL 26%
降低心血管死亡風險

The New England
Journal of Medicine

Volume 333 NOVEMBER 16, 1995 Number 20

PREVENTION OF CORONARY HEART DISEASE WITH PRAVASTATIN IN MEN WITH HYPERCHOLESTEROLEMIA

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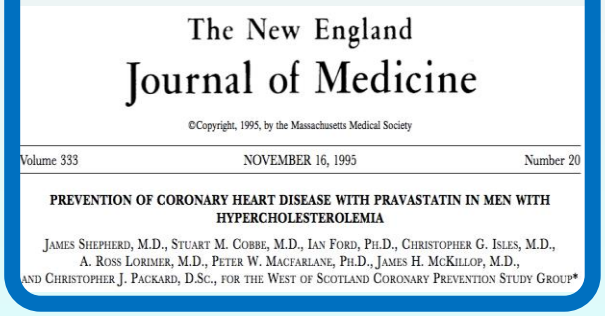

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1995 NEJM

15-yr Follow Up

持續降低心血管死亡風險

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 11, 2007 VOL. 357 NO. 15

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2007 NEJM

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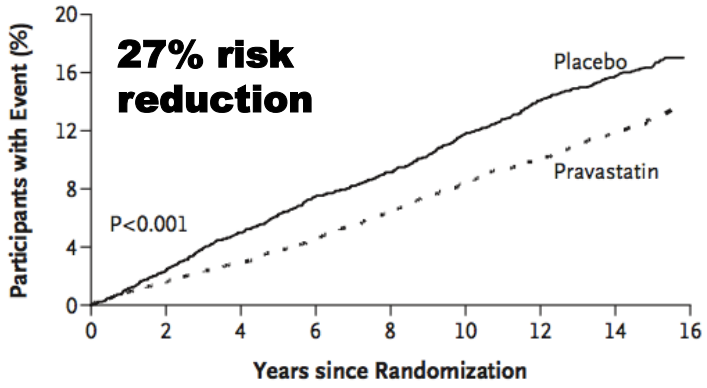
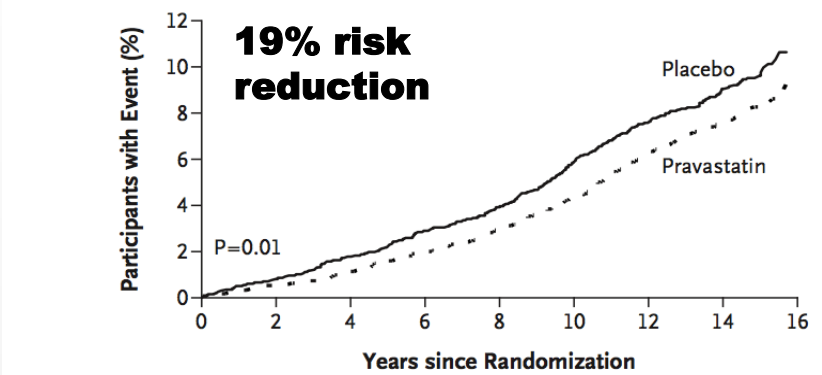
Mevalotin Still Provides Benefits 10 years After Trial End

CHD Mortality or Nonfatal MI



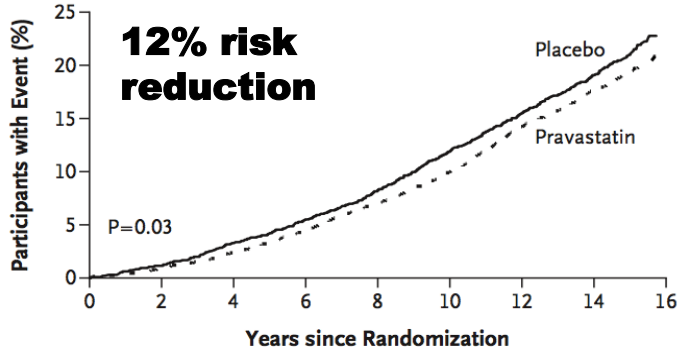
No. at Risk								
Placebo	3293	3199	3071	2953	2841	2691	2549	1903
Pravastatin	3302	3237	3157	3065	2943	2819	2675	2026

Cardiovascular Mortality



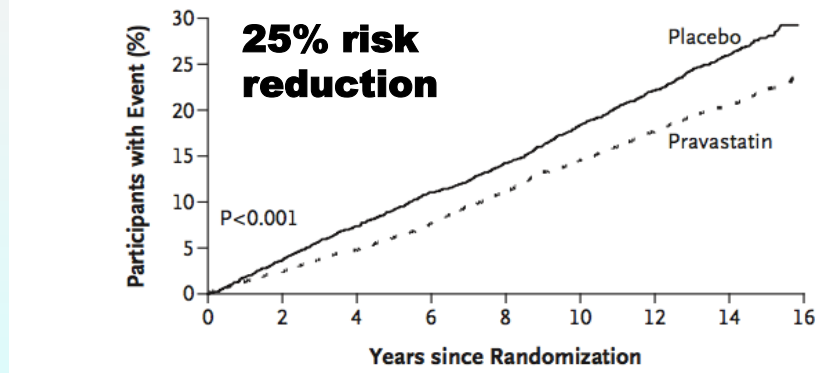
No. at Risk								
Placebo	3293	3254	3185	3113	3022	2902	2785	2114
Pravastatin	3302	3275	3223	3158	3068	2974	2835	2177

All Cause Mortality



No. at Risk								
Placebo	3293	3254	3185	3113	3022	2902	2785	2114
Pravastatin	3302	3275	3223	3158	3068	2974	2835	2177

CHD Mortality or Hospitalization



No. at Risk								
Placebo	3293	3156	2993	2839	2682	2486	2307	1661
Pravastatin	3302	3211	3100	2965	2800	2639	2454	1821

N Engl J Med. 2007 Oct 11;357(15):1477-86.

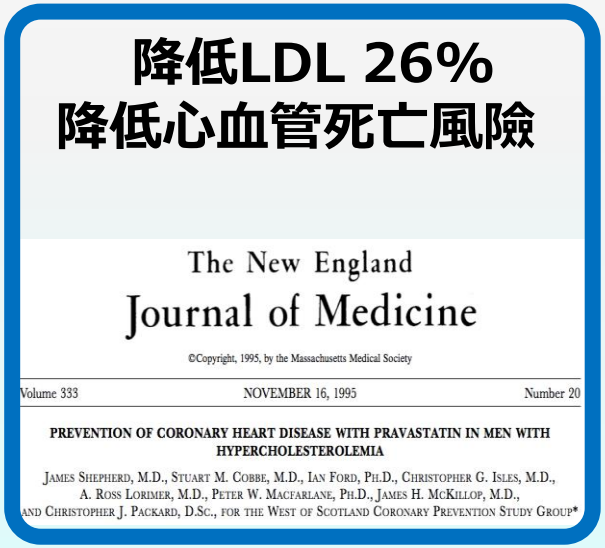
Legacy Effect of Mevalotin in Primary Prevention

WOSCOPS 20-year experience with statin treatment

Men without CHD

- **Mevalotin 40mg/D** (n=3306)
- **Placebo** (n=3293)

5-yr Outcome	15-yr Follow Up	20-yr Follow Up
降低LDL 26% 降低心血管死亡風險	持續降低心血管死亡風險	持續降低心血管死亡風險 長時間治療安全性
1995 NEJM	2007 NEJM	2016 CIRCULATION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Circulation

Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy

20-Year Follow-Up of West of Scotland Coronary Prevention Study

Ian Ford, PhD; Heather Murray, MSc; Colin McCowan, PhD; Chris J. Packard, DSc

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OPEN

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Ian Ford, PhD; Heather Murray, MSc; Colin McCowan, PhD; Chris J. Packard, DSc

- Extended follow-up of statin-based LDL-C lowering trials improves the understanding of statin safety and efficacy.

Circulation. 2016;133:1073-1080.

OPEN

Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy

20-Year Follow-Up of West of Scotland Coronary Prevention Study

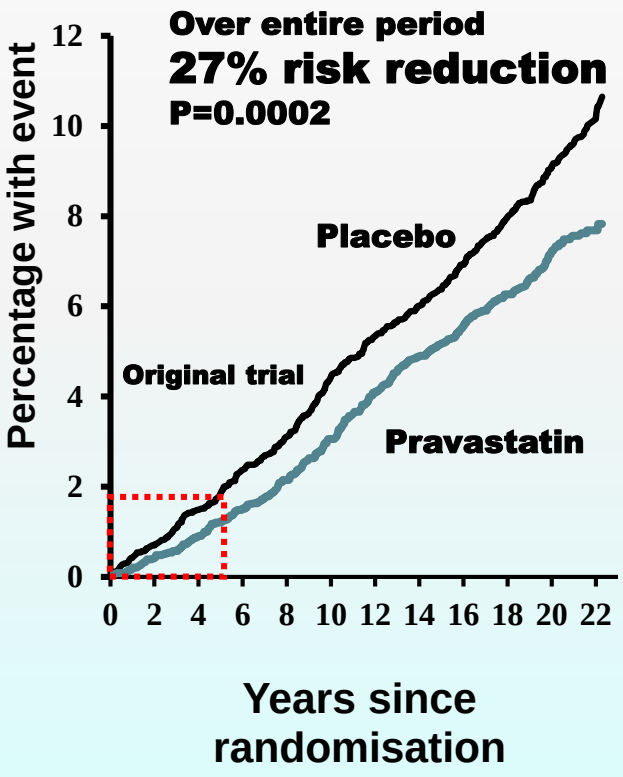
Ian Ford, PhD; Heather Murray, MSc; Colin McCowan, PhD; Chris J. Packard, DSc

- A total of 6,595 men were randomized to receive pravastatin 40 mg once daily or placebo for an average of 4.9 years.
- Subsequent linkage to HER permitted analysis of major incident events over 20 years.
- Post trial statin use was recorded for 5 years after the trial but not for the last 10 years.

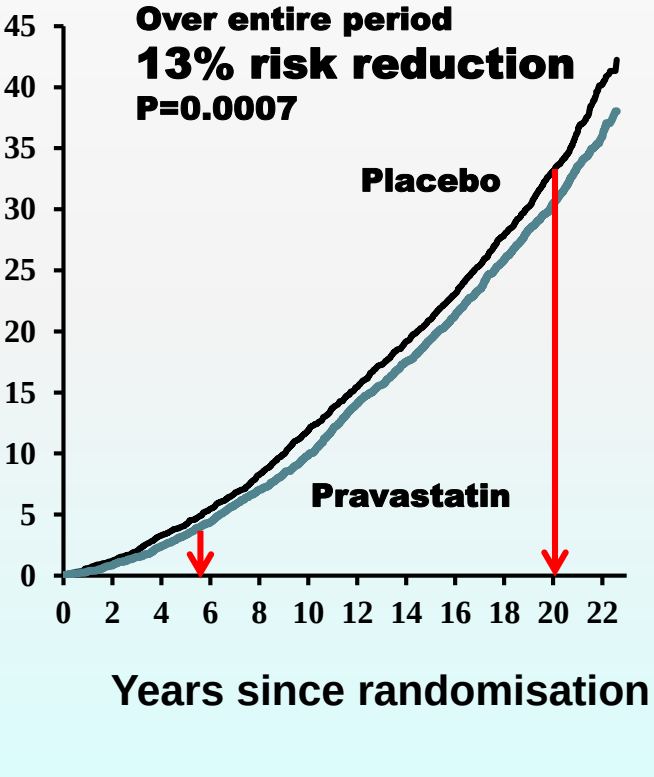
Circulation. 2016;133:1073-1080.

Long Term (Lifetime) Benefits of LDL Lowering with Mevalotin

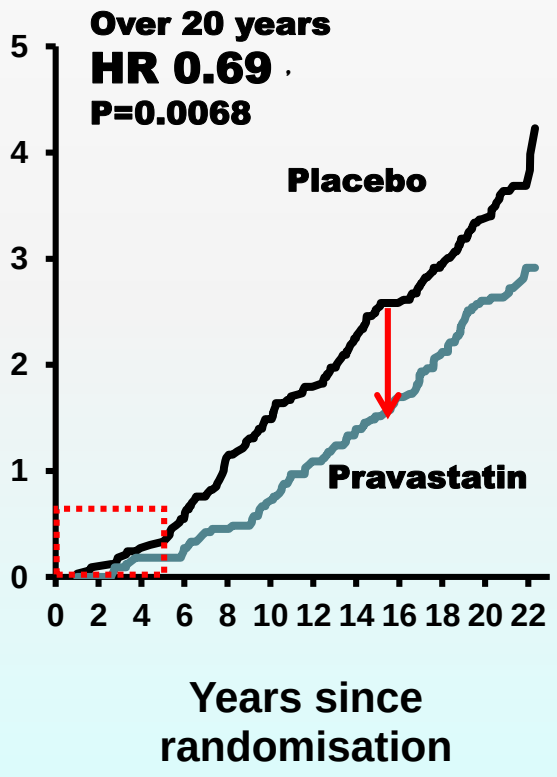
CHD mortality



All-cause mortality



Heart failure



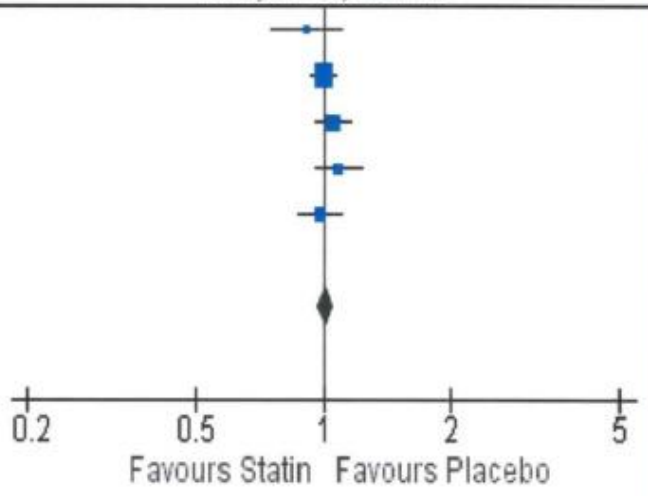
Circulation. (2016); 133:1073-80

Long term followup of statin trials:
Cancer incidence

Study or Subgroup	Statin Events	Statin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4S (10 years)	227	2221	248	2223	6.3%	0.91 [0.75, 1.10]
HPS (11 years)	1749	10269	1744	10267	41.2%	1.00 [0.93, 1.08]
LIPID (16 years)	1096	4512	1052	4502	22.7%	1.05 [0.95, 1.16]
PROSPER (8.6 years)	570	2891	537	2913	12.2%	1.09 [0.95, 1.24]
WOSCOPS (20 years)	809	3302	818	3293	17.6%	0.98 [0.88, 1.10]
Total (95% CI)		**23195**		**23198**	**100.0%**	**1.01 [0.97, 1.06]**
Total events	4451		4399			

Heterogeneity: $Chi^2 = 3.36$, $df = 4$ ($P = 0.50$); $I^2 = 0\%$

Test for overall effect: $Z = 0.61$ ($P = 0.54$)



20-year Followup of the West of Scotland Coronary Prevention Study

After 5 years of treatment the findings are remarkable

- 27% reduction in CHD mortality
- 13% reduction in all-cause mortality
- 19% reduction in CABG or PCI
- 31% reduction in heart failure admissions
- 21% reduction in length of stay, and cost saving
- No effect on stroke
- No decrease in non-CVD death
- No increase in cancer
- Gain of 5 event free years for primary endpoint of CHD death or MI; no age interaction

20-year Followup of the West of Scotland Coronary Prevention Study

Conclusions

- Important study showing the value of linkage of data sets and research
- Legacy effect with reduced mortality and gain in 5 event free years over 20 years attributable to 5 year treatment allocation
- No increase in cancer
- The investigators should be congratulated for performing 20 year follow-up of a landmark study

20-year Followup of the West of Scotland Coronary Prevention Study

Legacy Effect

Ongoing carry-over effect related to a slowing of the progression of the disease and/or stabilization of existing coronary artery plaque

Mechanism is unknown:

- ? Pleiotropic effects e.g. gene regulation[1]

Is “legacy effects” universally observed across different trials and statins?

Long-term followup of statin trials

Study	Populations	Age (yrs)	Baseline lipids	Followup lipids	Followup years	On statins	KM curves and treatment benefit
4S	MI or angina	35-70 (51% ≥60)	cholesterol 4.9 mmol/L, 190 mg/dl	cholesterol 5.1 mmol/L, 196 mg/dl	10	84%	Maintained for mortality
LIPID	MI or angina	Median 62	LDL 3.9 mmol/L, 150 mg/dl	LDL 3.9 mmol/L, 150 mg/dl	16	85%	Maintained for CHD mortality
HPS	CAD, occlusive arterial disease, diabetes	40-80 (27% ≥60)	LDL 3.4 mmol/L, 132 mg/dl	LDL 2.6 mmol/L, 100 mg/dl	11	59-84%	Diverged 14% first year, then parallel for major vascular events
ASCOT	Primary prevention, hypertension	40-70 Mean 63	LDL 4.4 mmol/L, 169 mg/dl	-	11	69%	Diverged for mortality and non CV mortality
PROSPER	Vascular disease or ↑ risk	70-82 Mean 75.3	3.8 mmol/L 147 mg/dl	-	8.6	-	Maintained for CHD mortality
WOSCOPS	**Primary prevention,** males	45-64 **Mean 55**	**LDL 4.9 mmol/L, 190 mg/dl**	-	20	**31%**	Diverged for CHD mortality

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial

*Heart Protection Study Collaborative Group**

- The aim of the extended follow-up of the HPS is to assess long-term efficacy and safety of lowering LDL cholesterol with statins (simvastatin).
- Mean in-trial follow-up was 5·3 years (SD 1·2), and post-trial follow-up of surviving patients yielded a mean total duration of 11·0 years (SD 0·6).

Lancet 2011; 378: 2013–20

HPS: Heart Protection Study

Purpose

To determine whether simvastatin reduces mortality and vascular events in patients with and without coronary disease, but all at high risk, and with a broad range of baseline cholesterol levels

Reference

HPS Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.

HPS: Heart Protection Study
- TRIAL DESIGN continued-

Baseline characteristics

	No.	% of total
All patients	20,536	
Men	15,454	75
Women	5082	25
History of coronary disease		
Previous MI	8510	41
Other	4876	24
Other risk factors in absence of coronary disease[a]	7150	35
Cerebrovascular disease	1820	9
Peripheral arterial disease	2701	13
Diabetes mellitus	3982	19

[a] Some patients had more than one of these conditions.

HPS Collaborative Group. *Lancet* 2002;**360**:7Ð22.

HPS: Heart Protection Study
- RESULTS continued -

First major vascular event

	Placebo (n=10,267) No. (%)	Simvastatin (n=10,269) No. (%)	Event rate ratio (95% CI)	P
Nonfatal MI or coronary death	1212 (11.8)	898 (8.7)	0.73 (0.67–0.79)	<0.0001
Fatal or nonfatal stroke	585 (5.7)	444 (4.3)	0.75 (0.66–0.85)	<0.0001
Revascularization	1205 (11.7)	939 (9.1)	0.76 (0.70–0.83)	<0.0001
Any major vascular event[a]	2585 (25.2)	2033 (19.8)	0.76 (0.72–0.81)	<0.0001

[a]Data are for patients having first event of each type, hence non-additivity

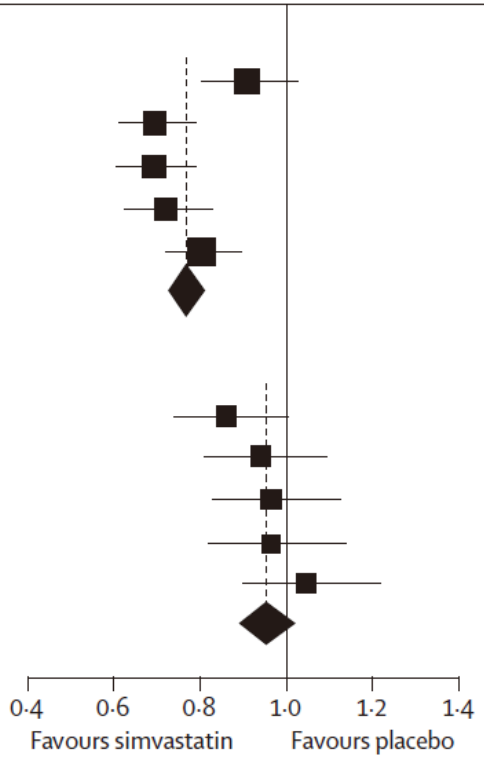
HPS: Heart Protection Study
- SUMMARY -

In high-risk patients with a broad range of baseline cholesterol values, simvastatin reduced:

- All-cause mortality
- Coronary deaths
- Major vascular events

First major vascular event by year during in-trial and post-trial follow-up

	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**



Lancet 2011; 378: 2013–20

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial

*Heart Protection Study Collaborative Group**

	Simvastatin-allocated	Placebo-allocated	Absolute difference
Total cholesterol (mmol/L)			
Baseline	5·9 (0·01)	5·9 (0·01)	0·0 (0·01)
In-trial	4·2 (0·01)	5·4 (0·01)	1·2 (0·02)
Post-trial	4·3 (0·04)	4·4 (0·04)	0·0 (0·06)
LDL cholesterol (mmol/L)			
Baseline	3·4 (0·01)	3·4 (0·01)	0·0 (0·01)
In-trial	2·3 (0·01)	3·3 (0·01)	1·0 (0·02)
Post-trial	2·6 (0·03)	2·6 (0·03)	0·0 (0·05)

Lancet 2011; 378: 2013–20

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial

*Heart Protection Study Collaborative Group**

	Simvastatin-allocated	Placebo-allocated
In-trial		
Year 1	8994/10 107 (89%)	389/10 088 (4%)
Year 2	8457/9909 (85%)	889/9826 (9%)
Year 3	8122/9664 (84%)	1608/9563 (17%)
Year 4	7764/9388 (83%)	2262/9241 (24%)
Year 5	6058/7370 (82%)	2345/7225 (32%)
Average	85%	17%
Post-trial		
Year 1	4163/7152 (58%)	4113/6845 (60%)
Year 2	4555/6525 (70%)	4381/6284 (70%)
Year 3	4665/6023 (77%)	4489/5821 (77%)
Year 4	5363/6651 (81%)	5136/6462 (79%)
Year 5	4527/5375 (84%)	4294/5165 (83%)
Average	74%	74%

Data show statin use/alive (in-trial) and statin use/completed forms (post-trial).

Lancet 2011; 378: 2013–20

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial

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- More prolonged LDL-lowering statin treatment produces larger absolute reductions in vascular events.

- Moreover, even after study treatment stopped in HPS, benefits persisted for at least 5 years without any evidence of emerging hazards.

Lancet 2011; 378: 2013–20

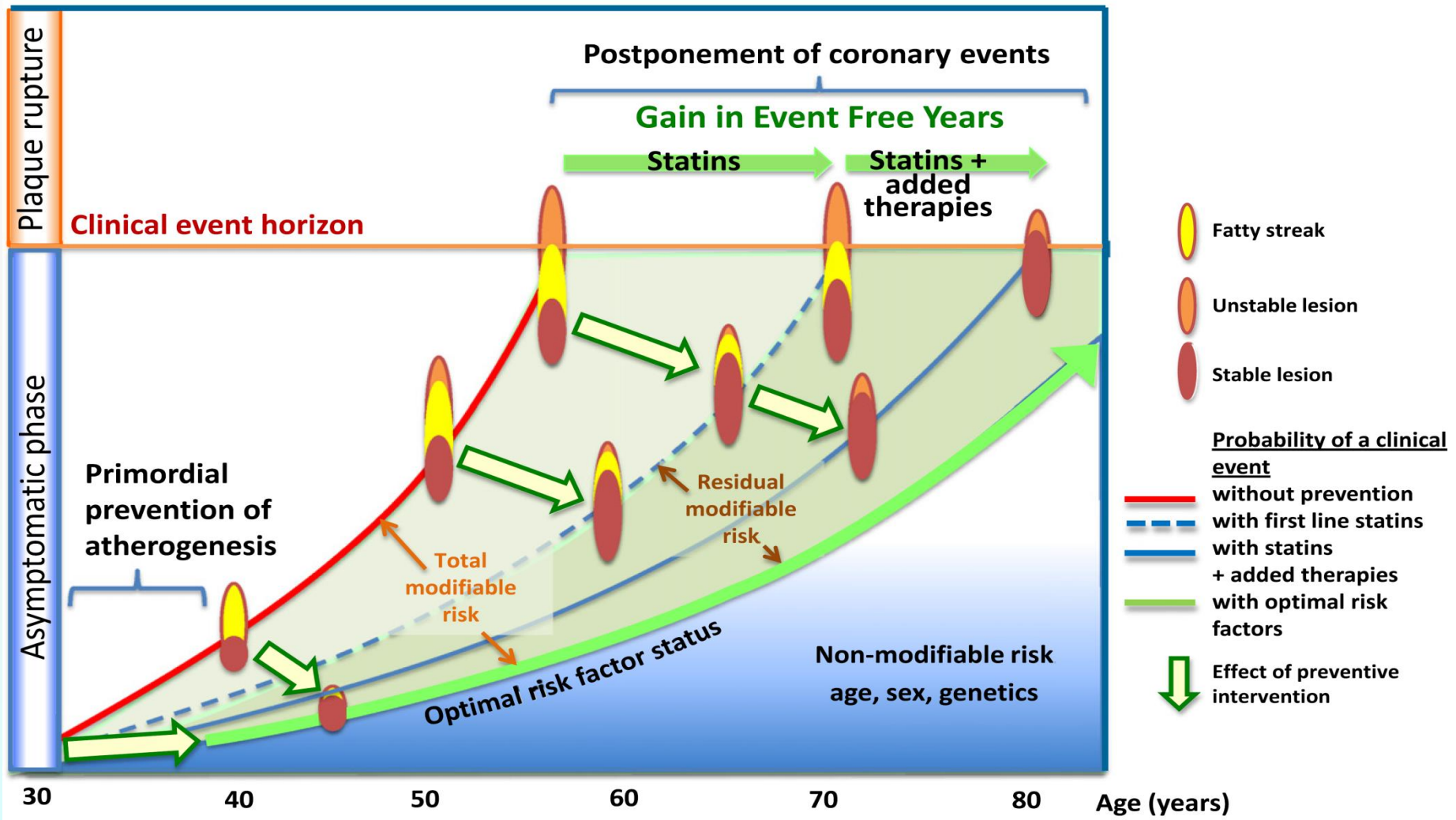
Long-term follow-up of lipid-lowering trials

Chris J. Packard[a] and Ian Ford[b]

- The current review brings together the findings of major trials that have conducted such long-term follow-up.
- Mechanisms of legacy effects with statin therapy.

Curr Opin Lipidol 2015, 26:572–579

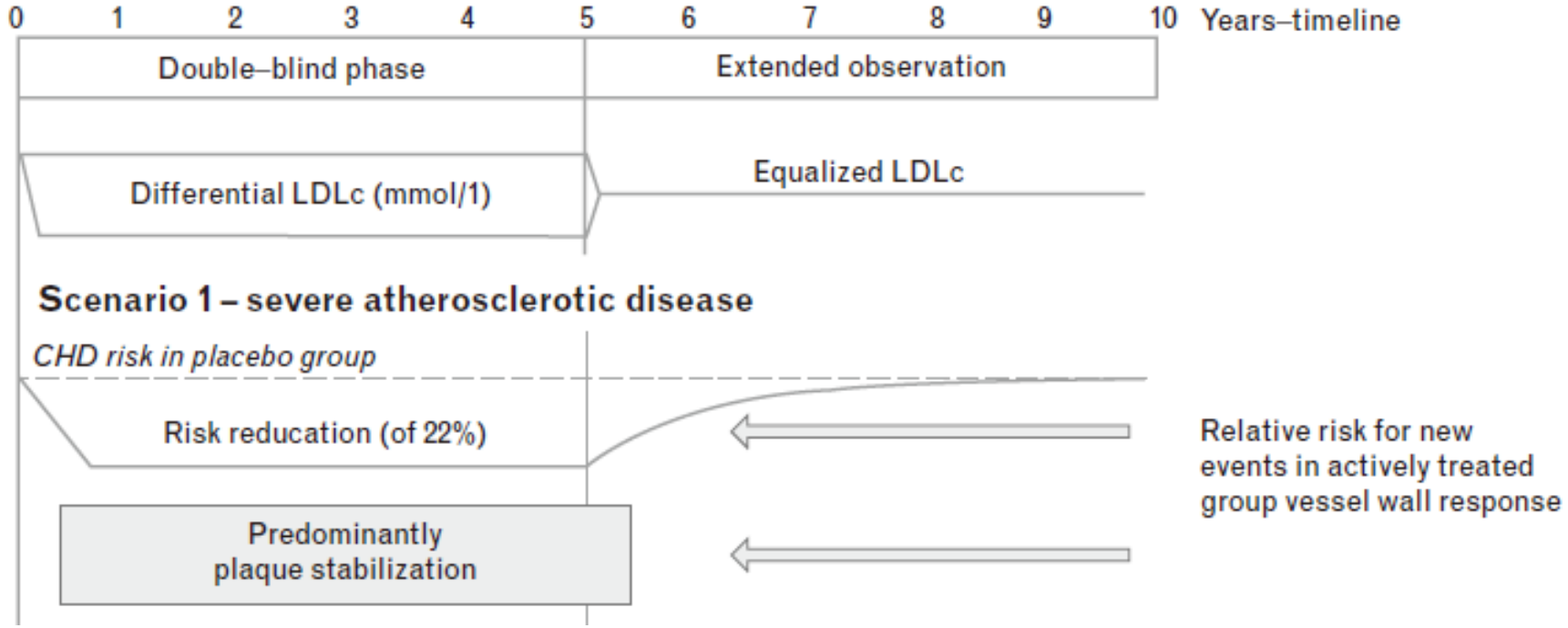
Reversibility of Plaque Decreased along with Times



Vascul Pharmacol. 2015 Aug;71:37-9.

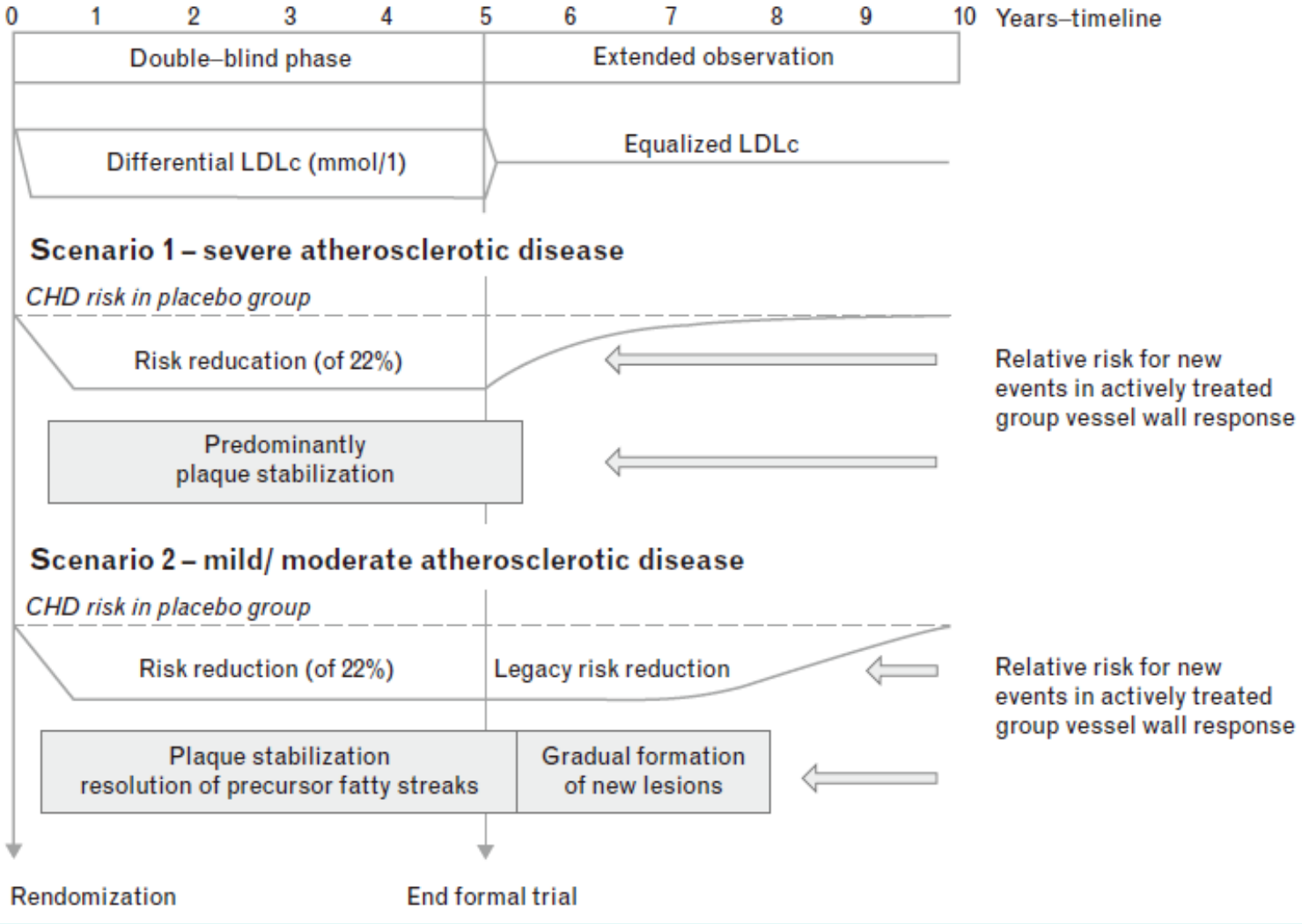
Long-term follow-up of lipid-lowering trials

Chris J. Packard[a] *and Ian Ford*[b]



In patients with ASCVD, there are a large number of complex lesions that are prone to rupture and the predominant effect of LDL lowering is to stabilize these.

The data from HPS suggest either that stabilization is rapidly reversed and relative protection from further clinical events is lost, or that post-trial statin use was so high that those originally on placebo caught up quickly with those originally on simvastatin.

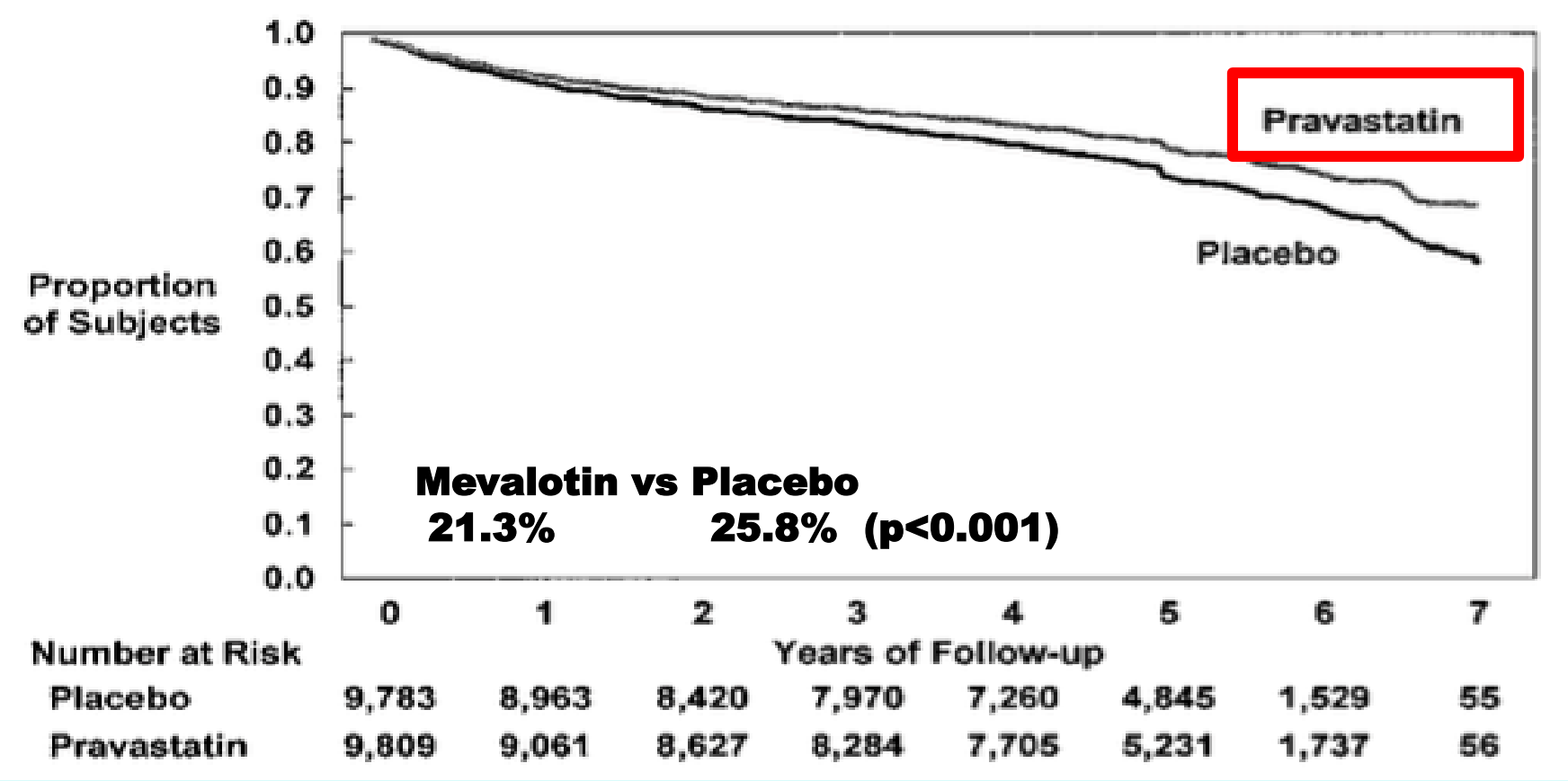


In patients with less severe disease – a mix of vulnerable plaque and precursor lesions such as fatty streaks – LDL-lowering therapy impacts on both pathological structures leading to stabilization of the plaque and regression/resolution of the lipid filled streaks.

It takes a number of years before the fatty streaks reform and so there is a prolonged legacy benefit manifest in a post-trial relative risk reduction that lasts for a considerable period.

Pravastatin Compliance

- After exclude CV event related discontinuation, the discontinuation rate of placebo is still higher than Mevalotin.



Circulation. 2002 May 21;105(20):2341-6.

Conclusions

- Statin treatment for 5 years was associated with a legacy benefit, with improved survival and a substantial reduction in CVD outcomes over a 20-year period, supporting the wider adoption of primary prevention strategies.

- More prolonged LDL-lowering statin treatment produces larger absolute reductions in vascular events.


OFFICE HOURS
Office Hours
Thank you !!