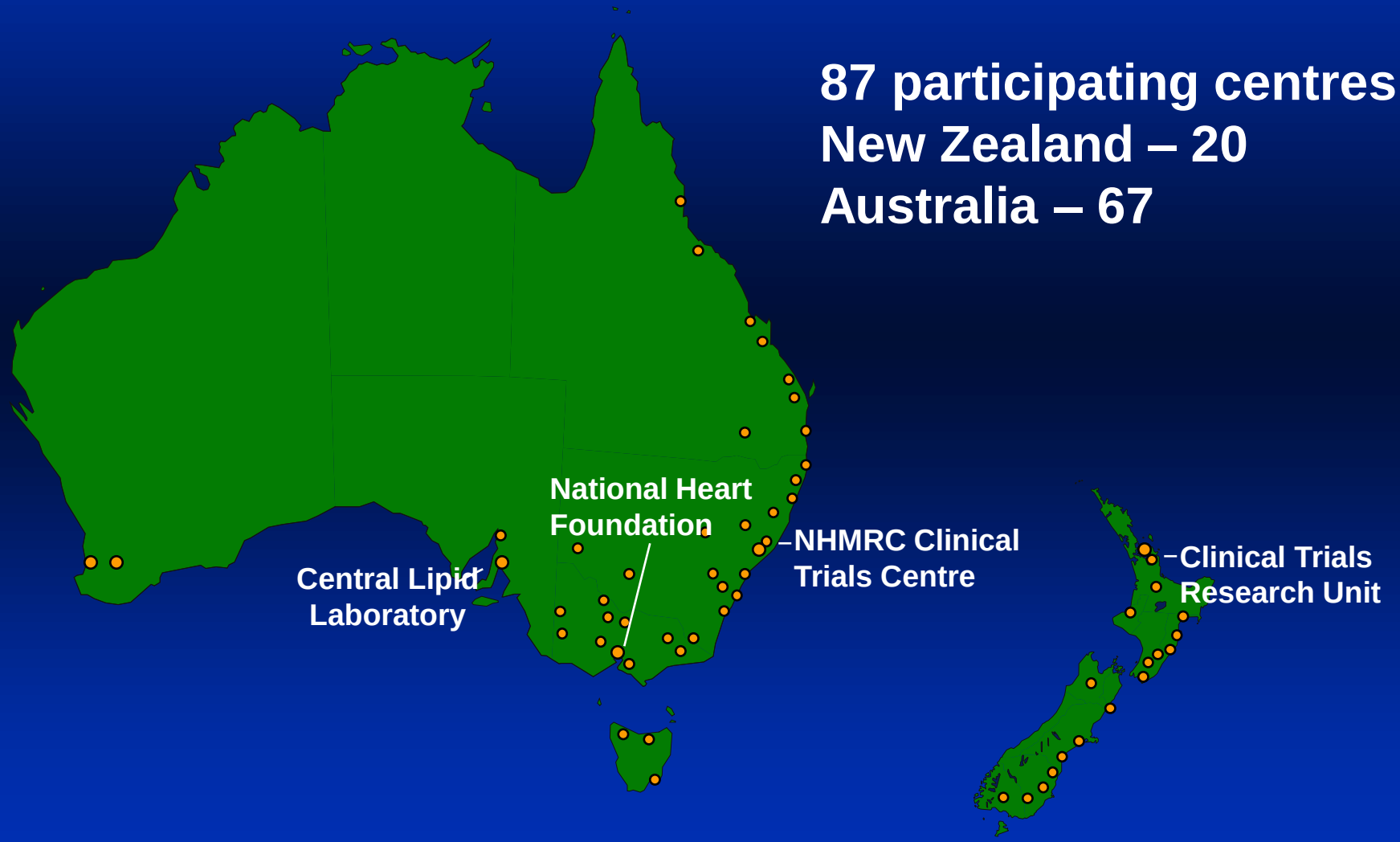
LIPID

Long-Term
Intervention with
Pravastatin in
Ischaemic
Disease

LIPID Study



87 participating centres
New Zealand – 20
Australia – 67

LIPID study design

11 106 patients registered

87 centres, 9014 patients (31–75 years), stratified by diagnosis, randomised, double-blind

Acute myocardial infarction or unstable angina pectoris

3 months to 3 years before study entry

Single-blind run-in phase (placebo + dietary advice)

8 weeks

TC 4.0–7.0 mmol/L (155–271 mg/dL)

Triglycerides 5.0 mmol/L (445 mg/dL)

Pravastatin + diet

Placebo + diet

Average follow-up 6 years

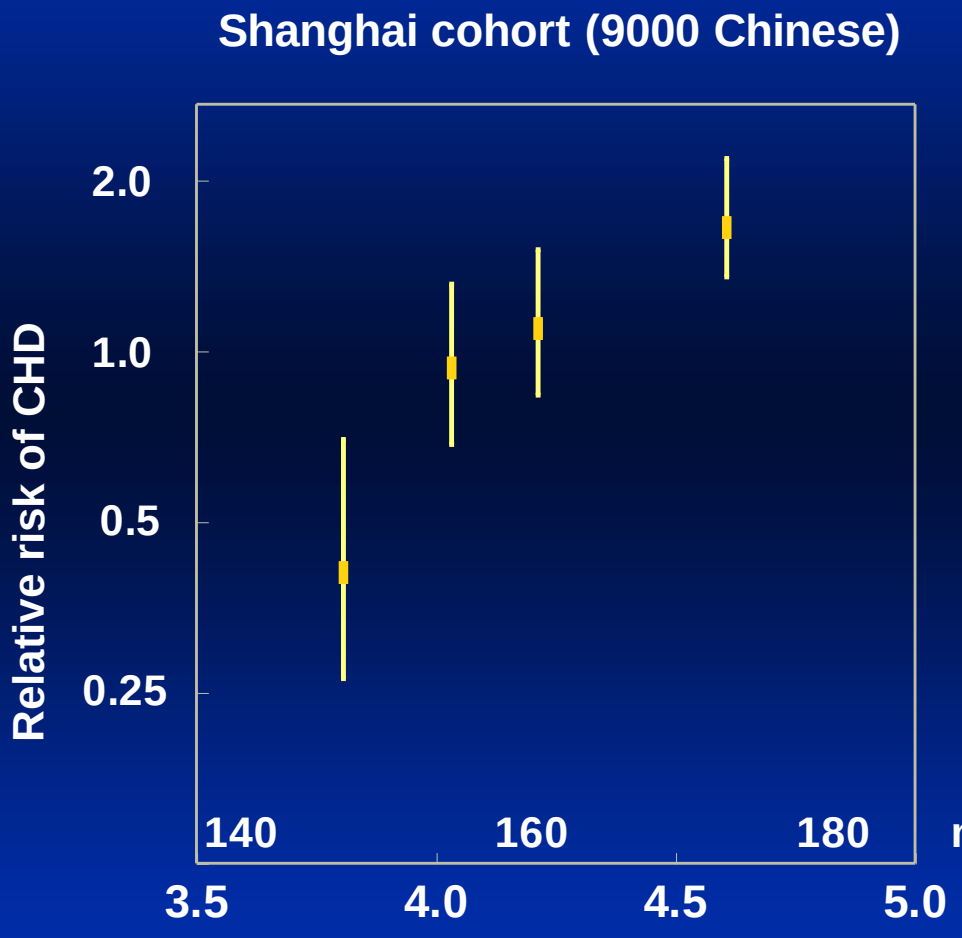
Background

- Compelling epidemiological data between usual cholesterol and subsequent risk of CHD events
- Apparent log-linear relationship between usual cholesterol and % reduction in CHD risk
  - about 50% less CHD risk per 1.0 mmol/L reduction in total cholesterol
  - relationship continues even for low cholesterol levels
- Epidemiological data provided a rationale for considering cholesterol-lowering treatment with pravastatin in a patient population at high risk for CHD events and with average cholesterol levels

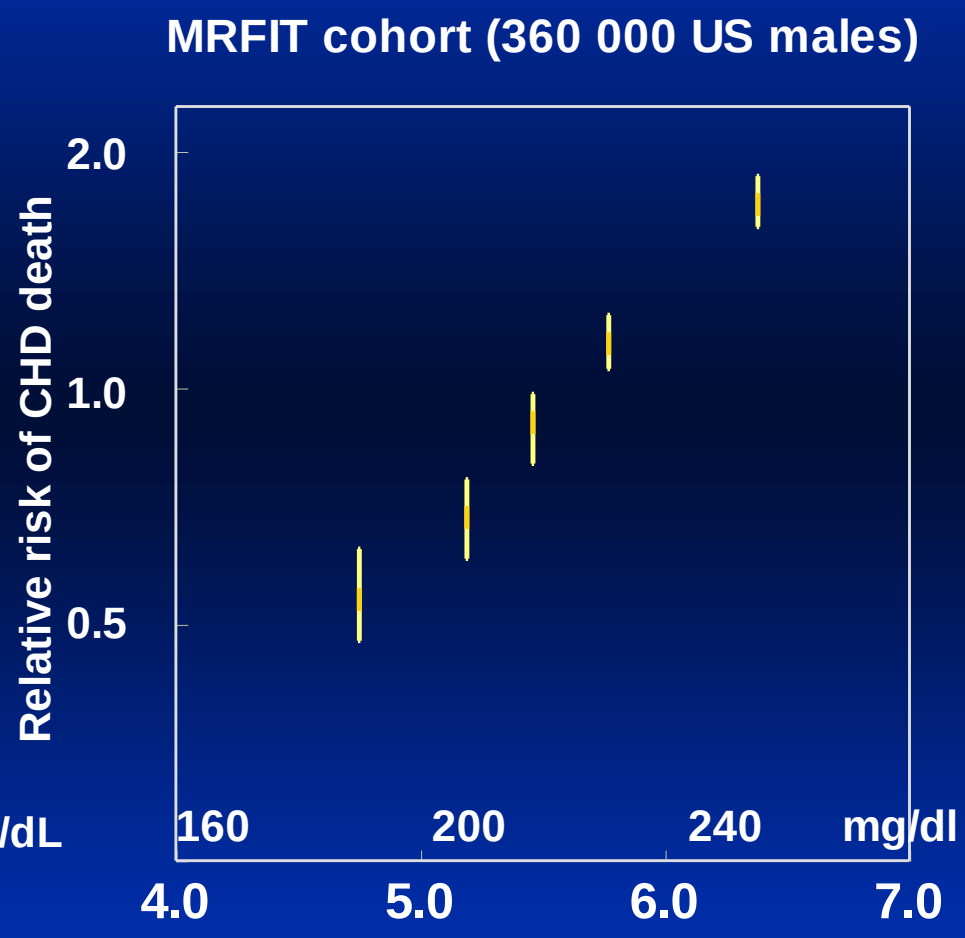
Baseline characteristics

Baseline lipid values	Placebo	Pravastatin
(mmol/L)	n = 4502	n = 4512
	median (25%, 75%)	median (25%, 75%)
Total cholesterol	5.65 (5.08, 6.20)	5.65 (5.07, 6.22)
LDL cholesterol	3.88 (3.38, 4.40)	3.87 (3.36, 4.39)
HDL cholesterol	0.92 (0.79, 1.09)	0.92 (0.79, 1.07)
Triglycerides	1.56 (1.18, 2.12)	1.60 (1.17, 2.21)
TC/HDL ratio	6.07 (5.12, 7.14)	6.11 (5.13, 7.15)

Relative risk of CHD by usual cholesterol

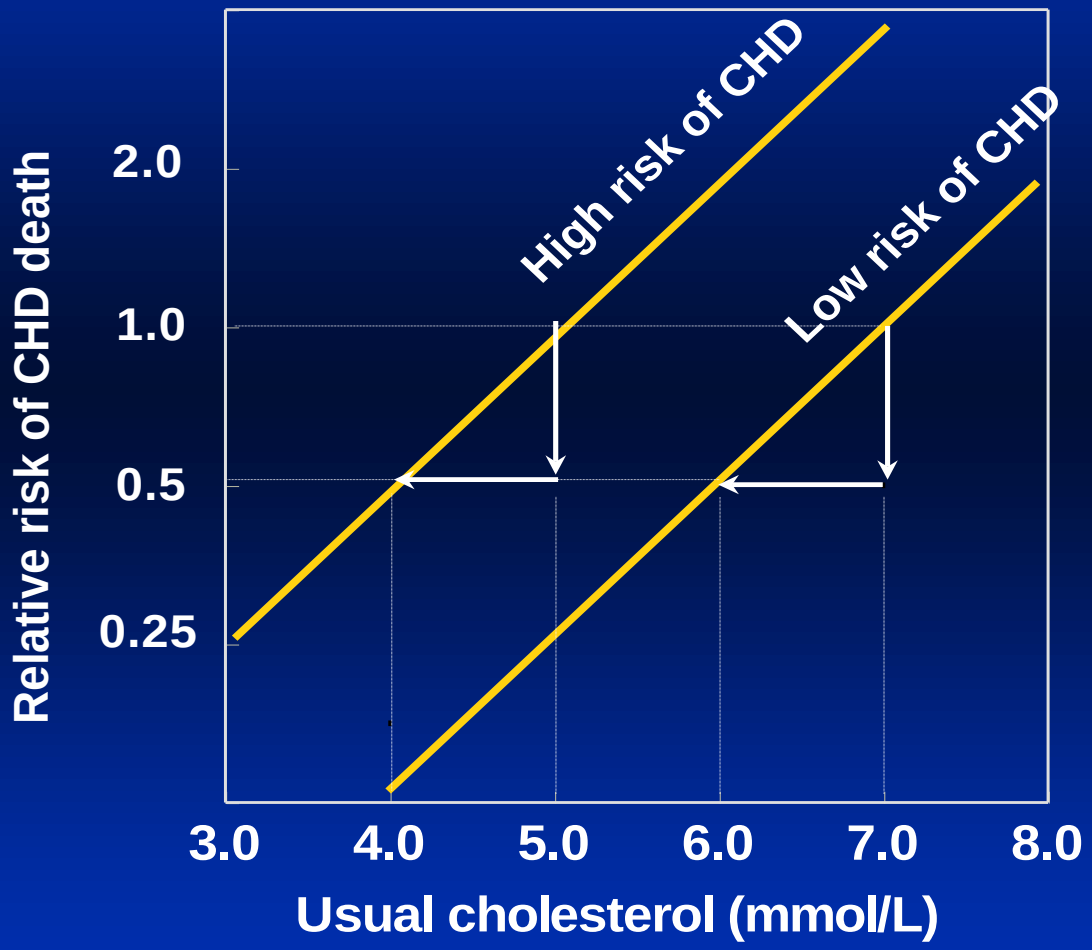


Chen Z, et al. *BMJ* 1991; 303: 276–82.



Neaton JD, et al. *Arch Intern Med* 1992; 152: 1490–1500.

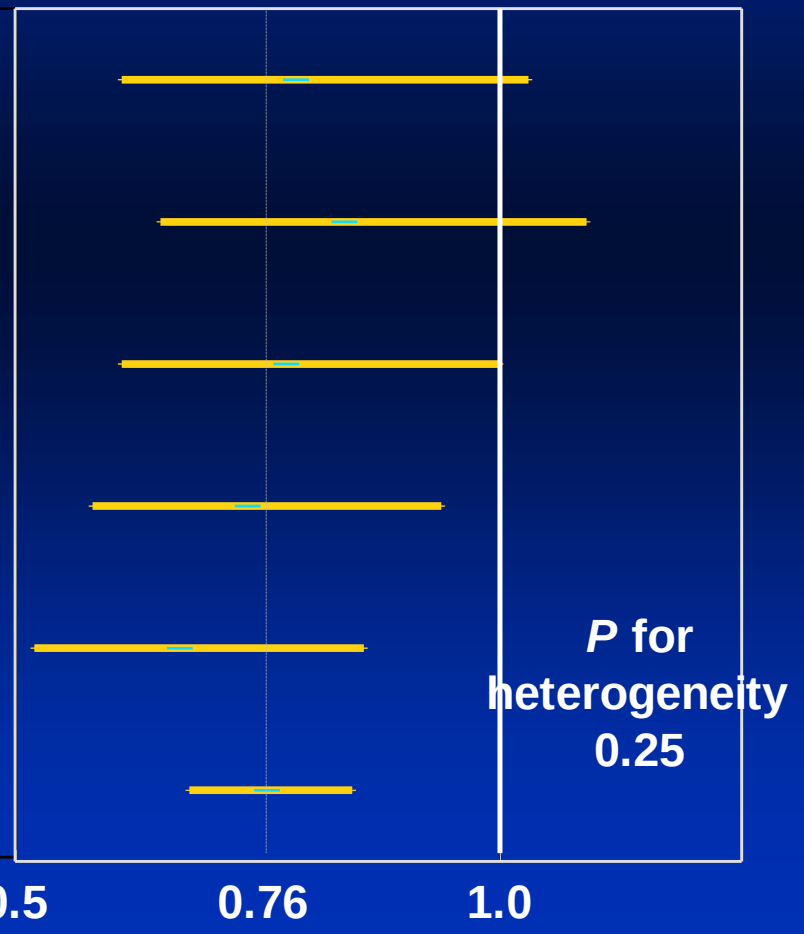
Relative risk of CHD by cholesterol level



Epidemiological model provided a rationale for assessing cholesterol-lowering treatment with pravastatin in a patient population at high risk for CHD death and with average cholesterol levels: the LIPID study

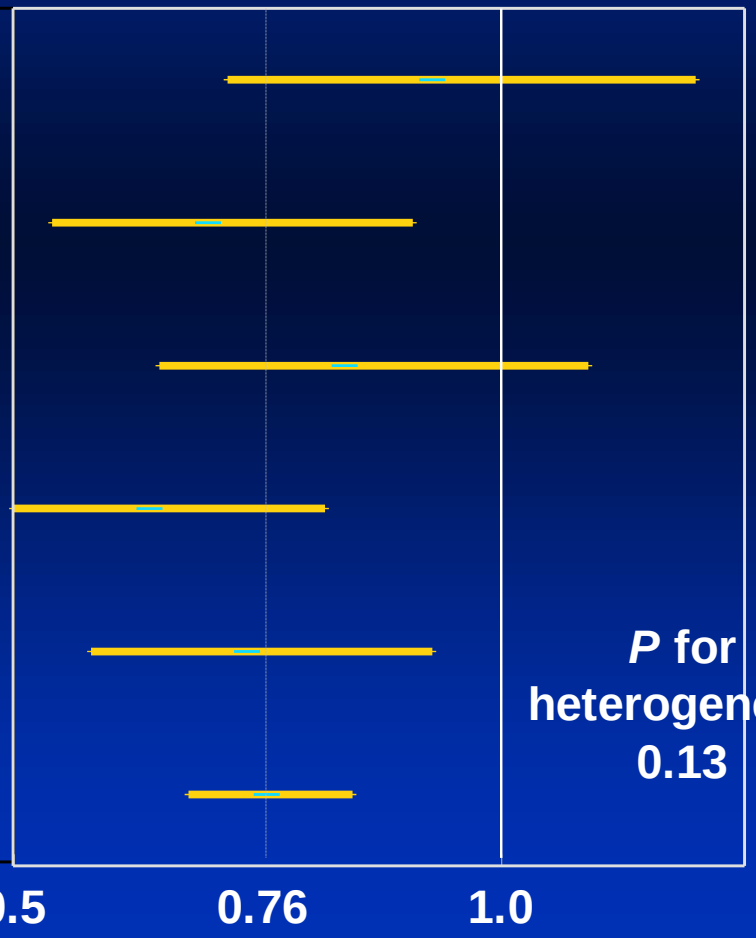
Relative risk of CHD events: by baseline total cholesterol

Baseline total cholesterol mmol/L	Baseline total cholesterol mg/dL	CHD events Plac %	CHD events Prav %
< 4.99	<193	14.3	11.5
4.99 – 5.46	193 – 211	14.4	12.0
5.46 – 5.86	211 – 227	16.2	12.8
5.86 – 6.32	227 – 245	17.5	13.5
> 6.32	> 245	17.0	11.9
Total		15.9	12.3



Relative risk of CHD events: by baseline LDL cholesterol

Baseline LDL cholesterol mmol/L	mg/dL	CHD events Plac %	Prav %
< 3.29	< 127	13.8	12.8
3.29 – 3.70	127 – 143	16.2	11.6
3.70 – 4.06	143 – 157	14.3	12.2
4.06 – 4.47	157 – 173	17.2	11.4
> 4.47	> 173	17.8	13.7
Total		15.9	12.3



Stroke adjudication

471 strokes reported

419 strokes confirmed

52 not strokes

309 ischaemic strokes*

79 unknown type

31 haemorrhagic

79 cardioembolic
55 large-artery
43 small-vessel
25 lacunar
18 other
132 unknown cause

24 intracerebral haemorrhage
7 subarachnoid haemorrhage

* 6 retinal artery occlusions were classified as ischaemic stroke

Stroke definitions

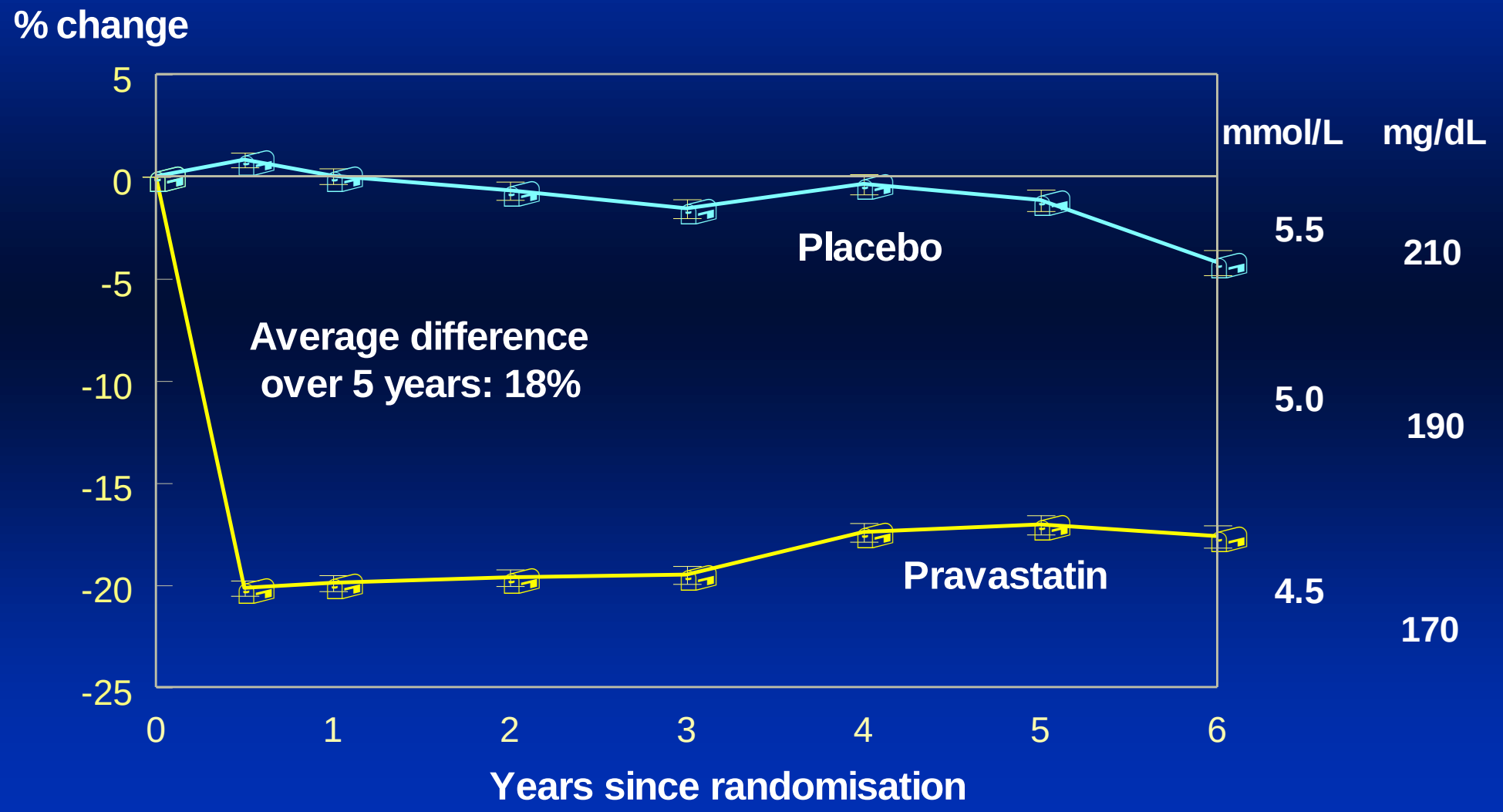
- Stroke: a sudden onset of focal neurological deficit lasting at least 24 hours or resulting in death

- Ischaemic stroke: a stroke with no evidence of intracranial haemorrhage on CT or MRI, done within 3 weeks of the event, or without evidence of haemorrhage at autopsy

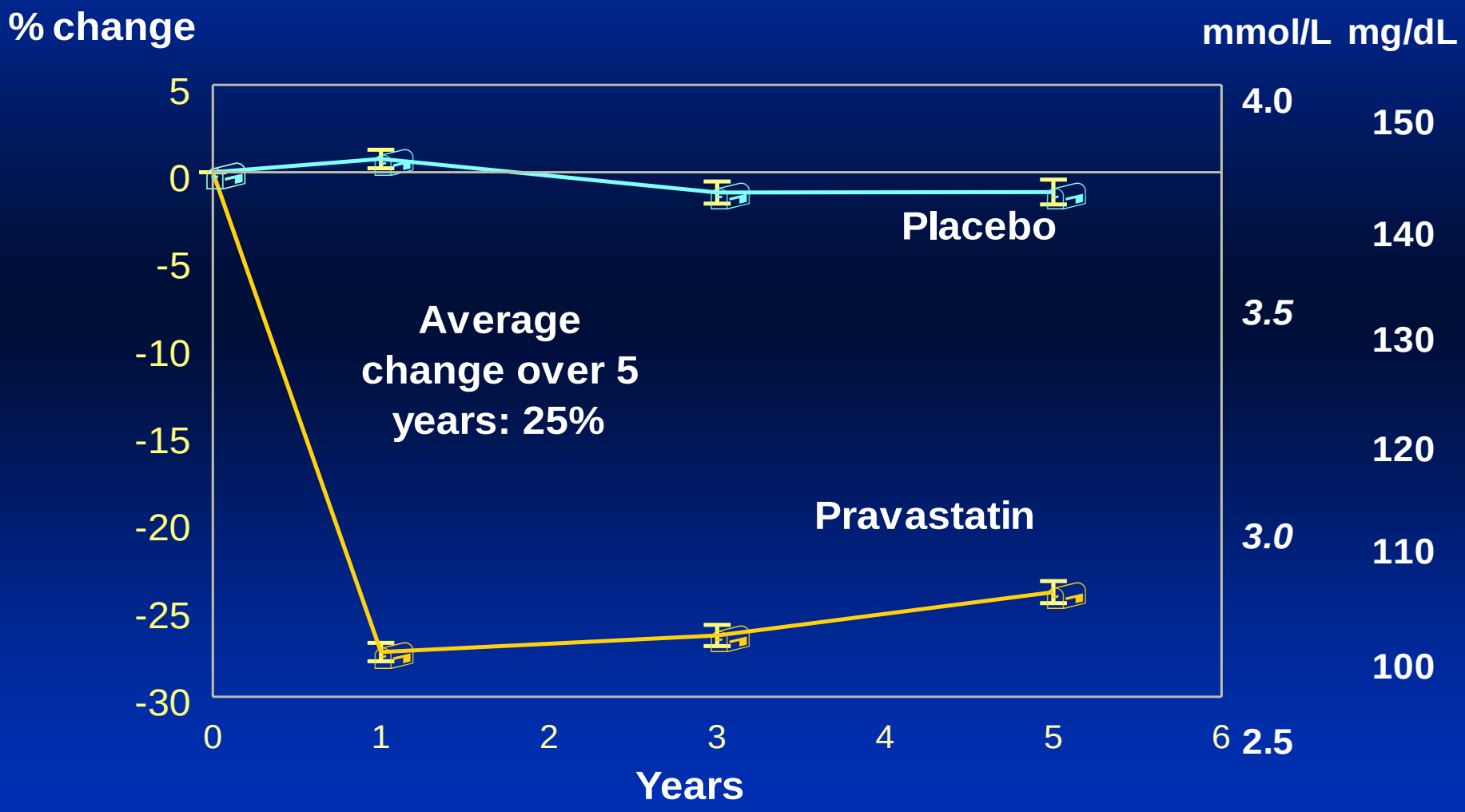
- Ischaemic strokes were further classified as
  - cardioembolic
  - larger-artery
  - lacunar
  - other small-vessel

Retinal artery infarction was classified as ischaemic stroke

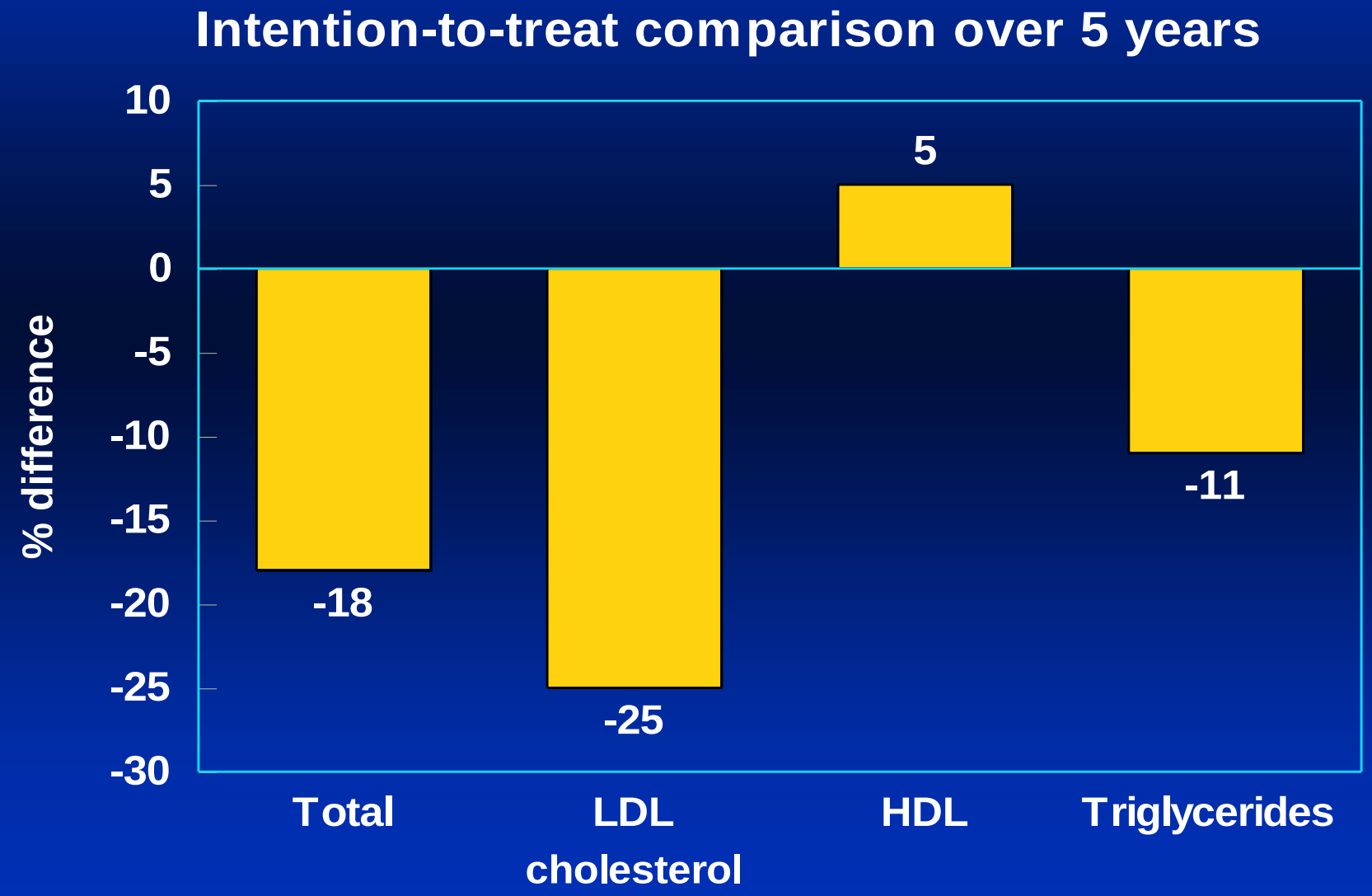
Change in total cholesterol



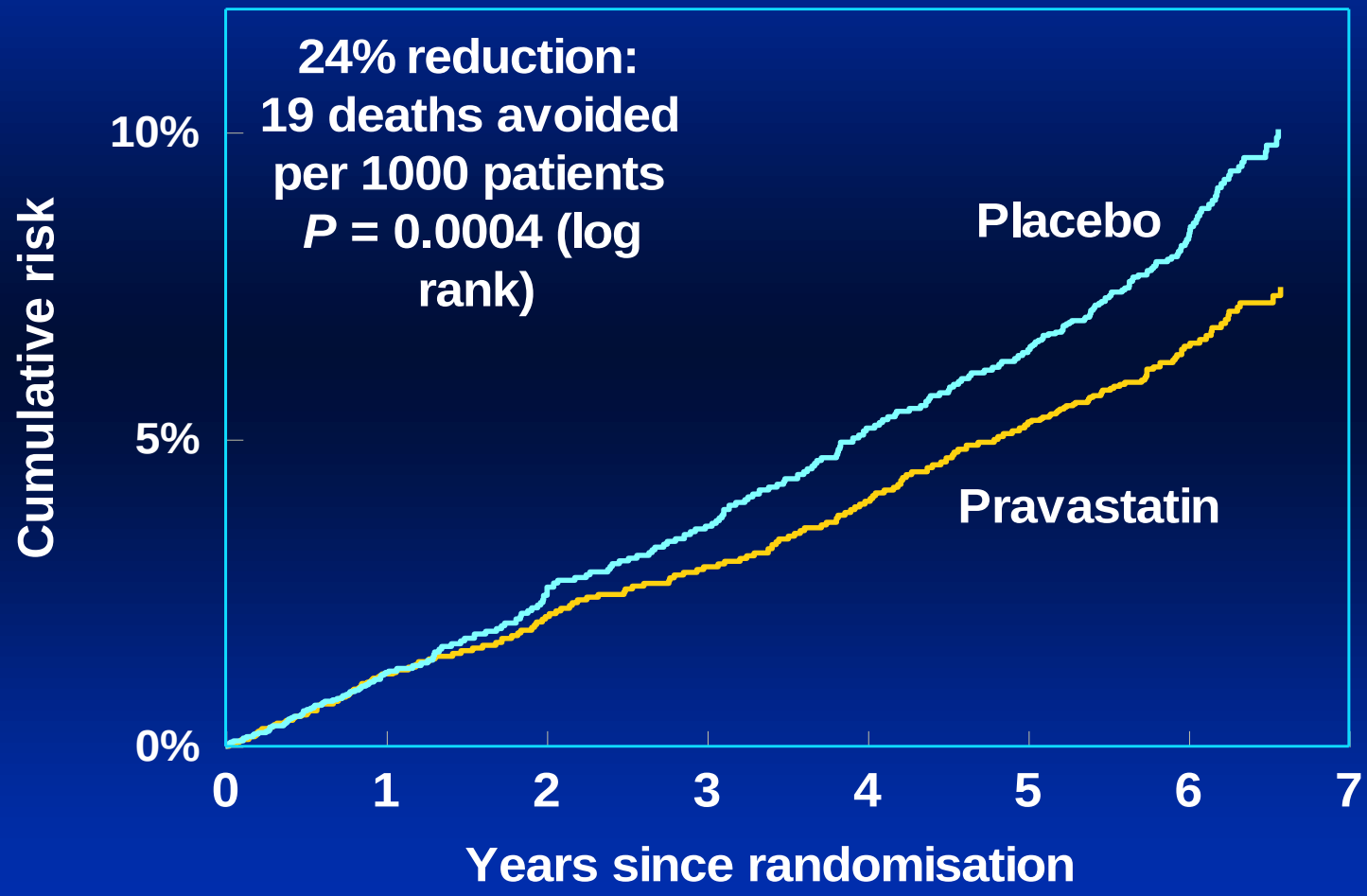
Change in LDL cholesterol



Average % differences in lipids

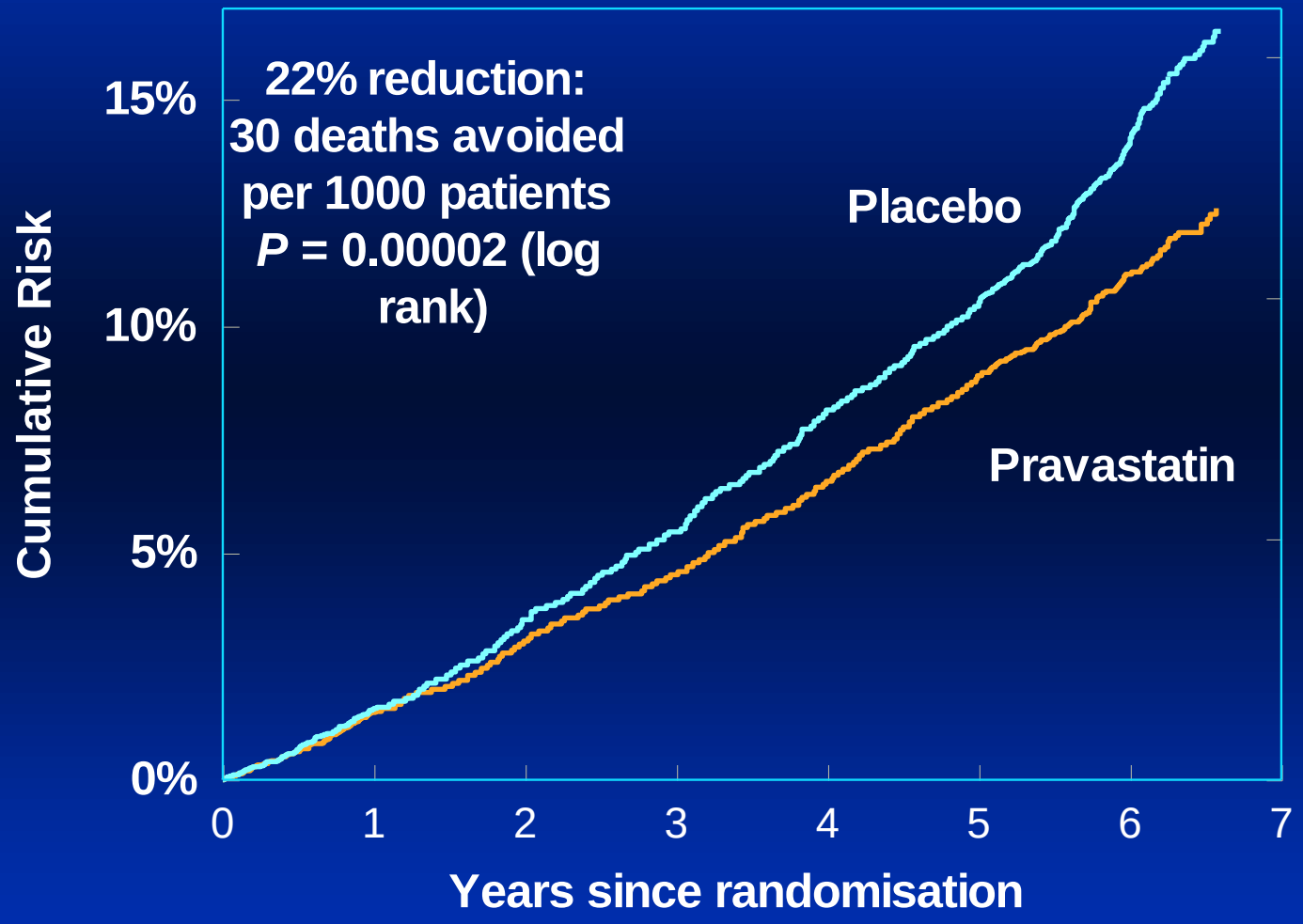


CHD mortality



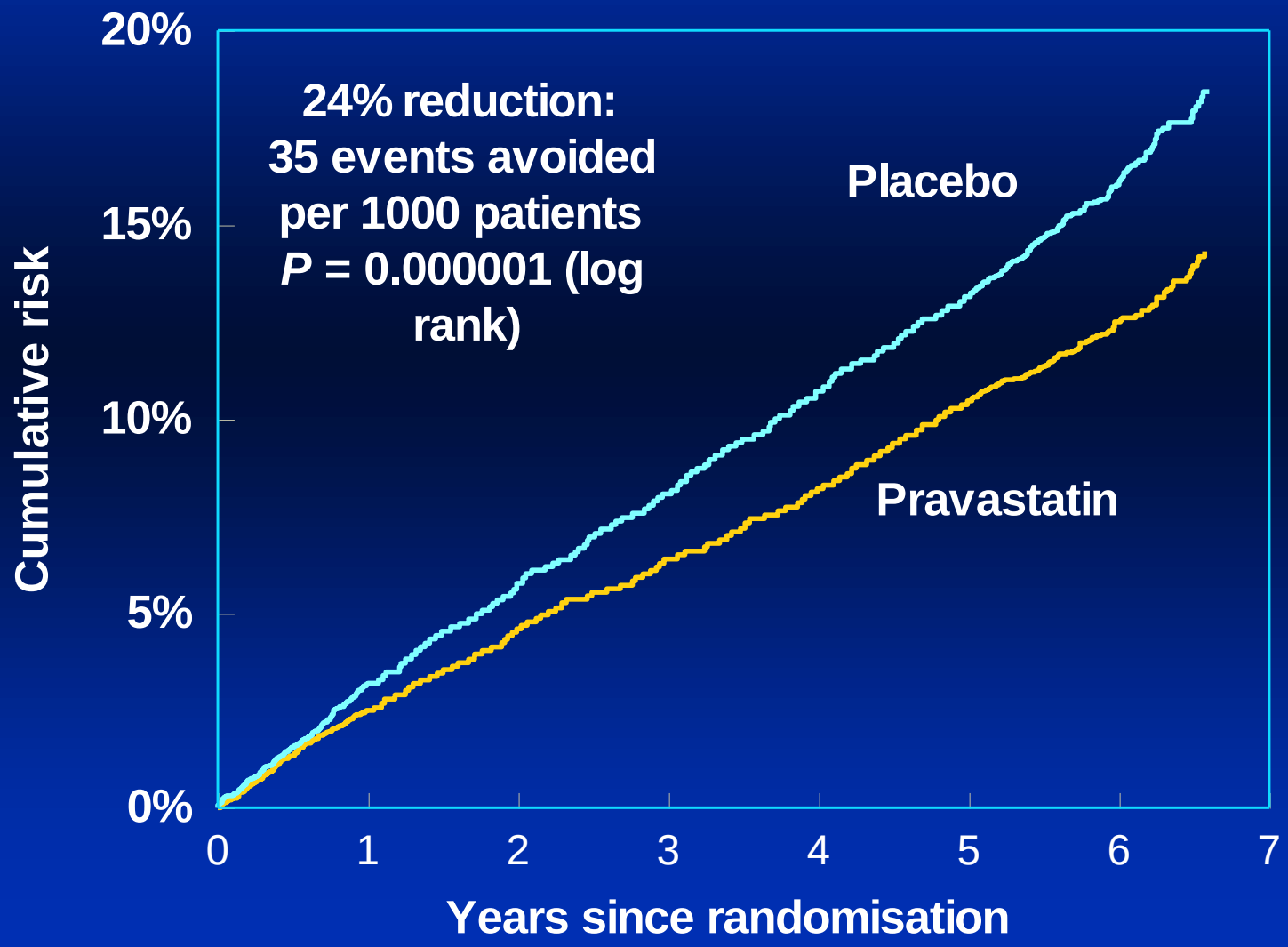
No. at risk	9014	8876	8712	8560	8350	7639	3544

Total mortality

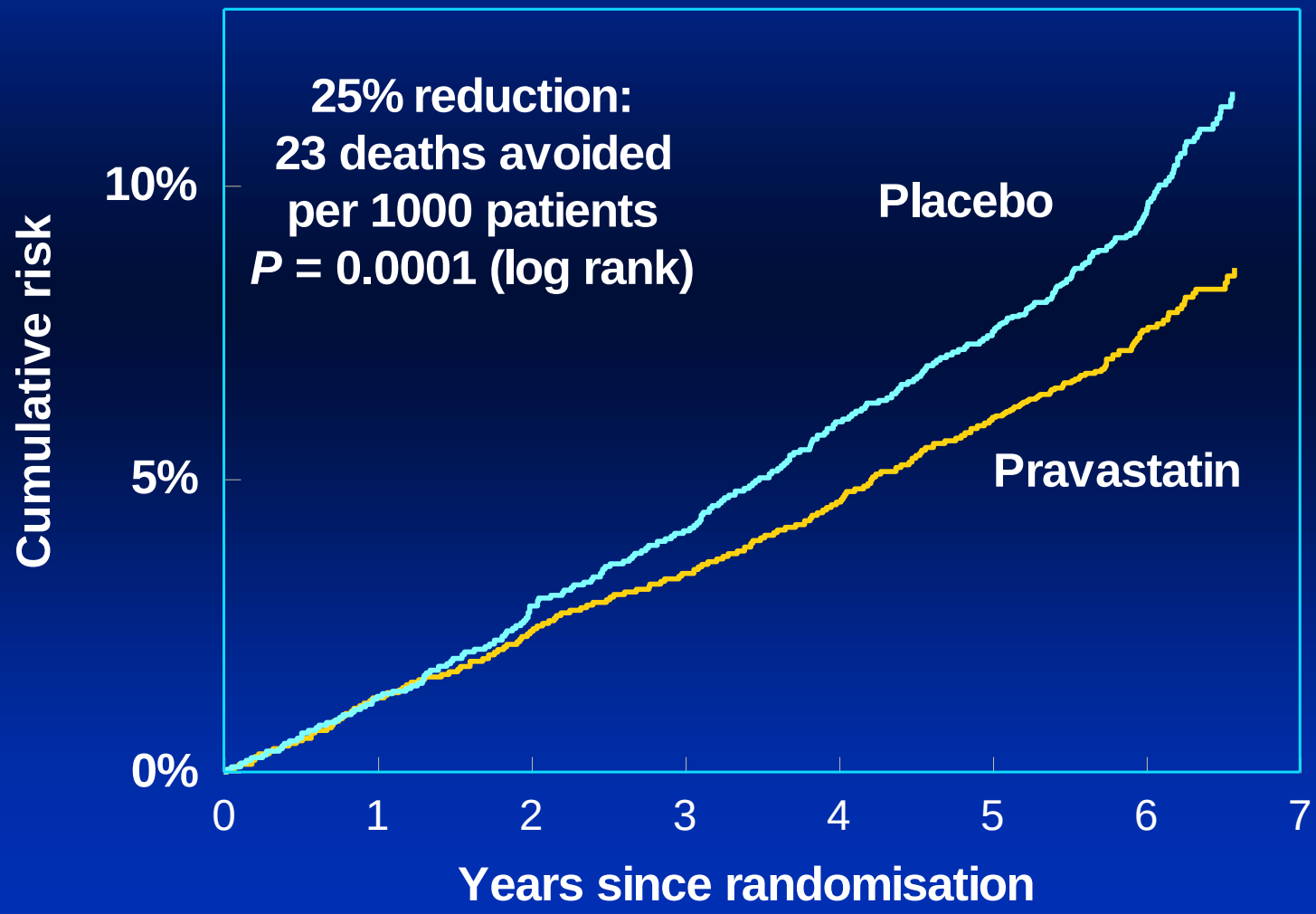


No. at risk	014	8876	8712	8560	8350	7639	3544

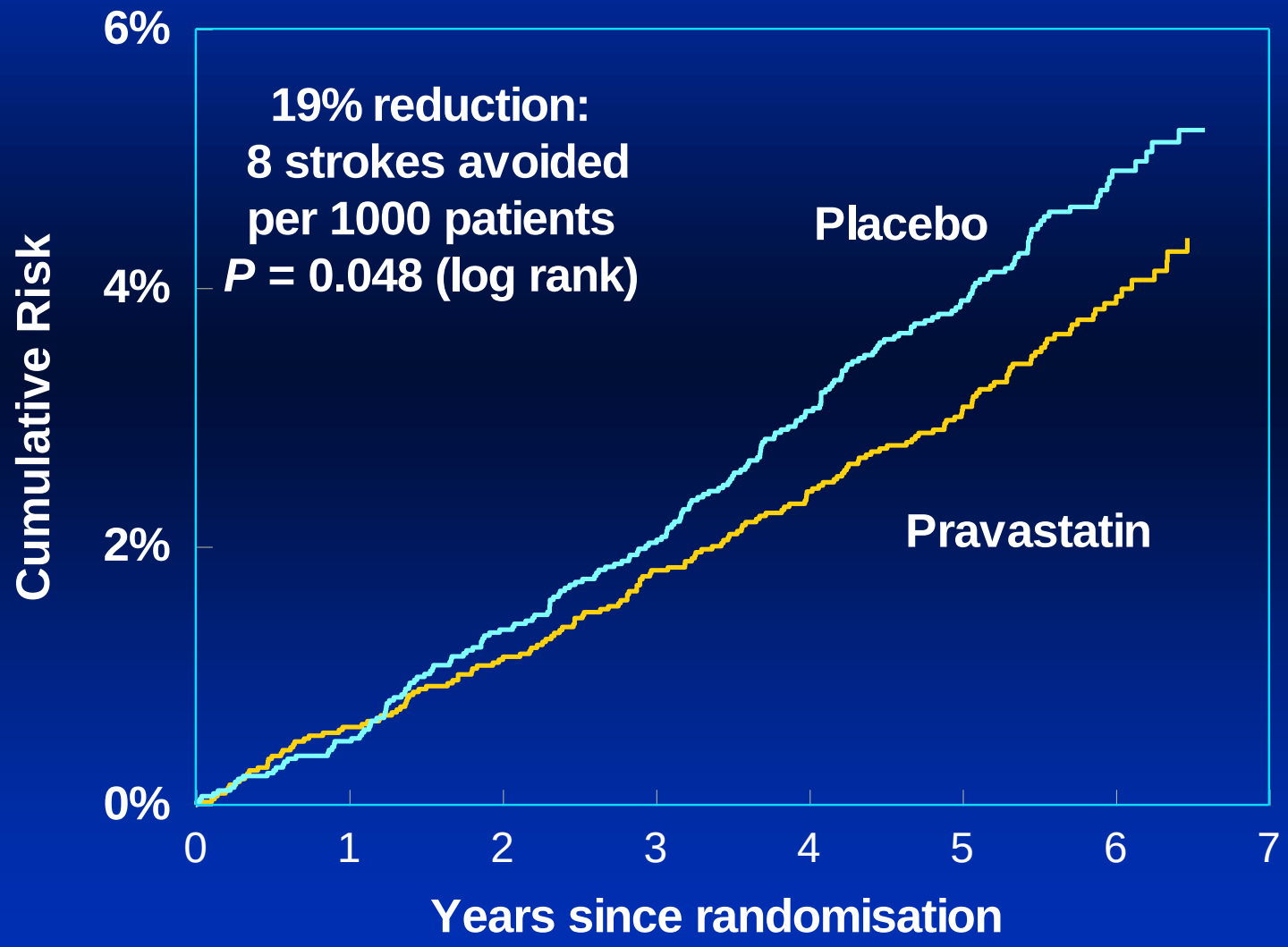
Fatal CHD + nonfatal MI



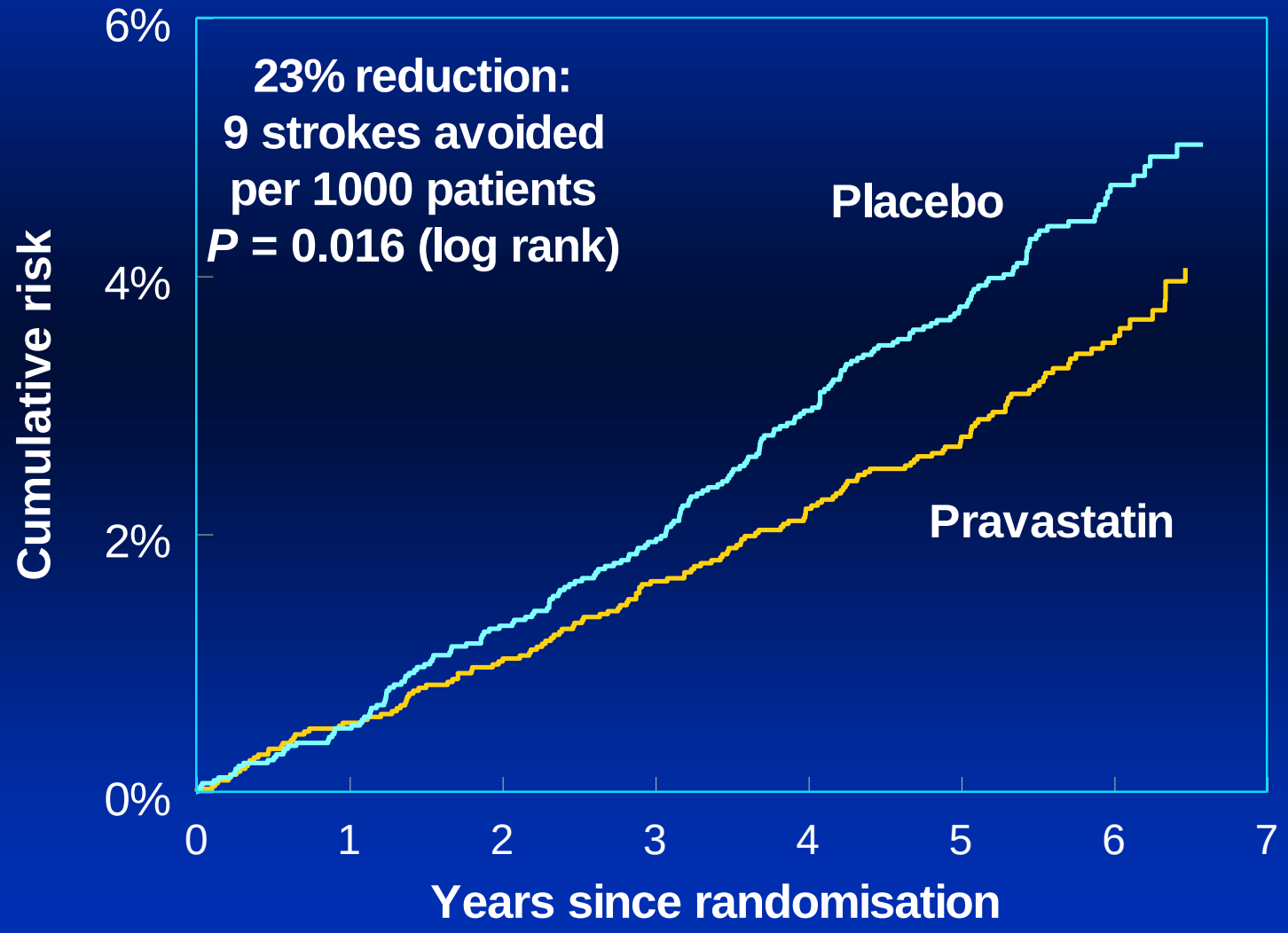
Cardiovascular mortality



Total stroke

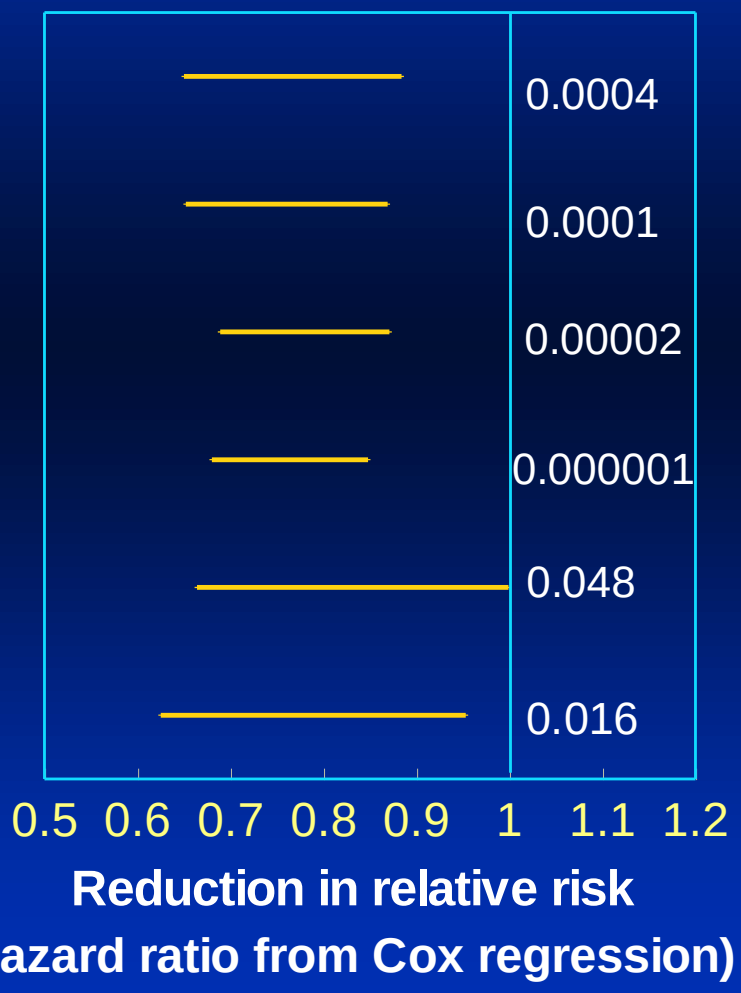


Nonhaemorrhagic stroke



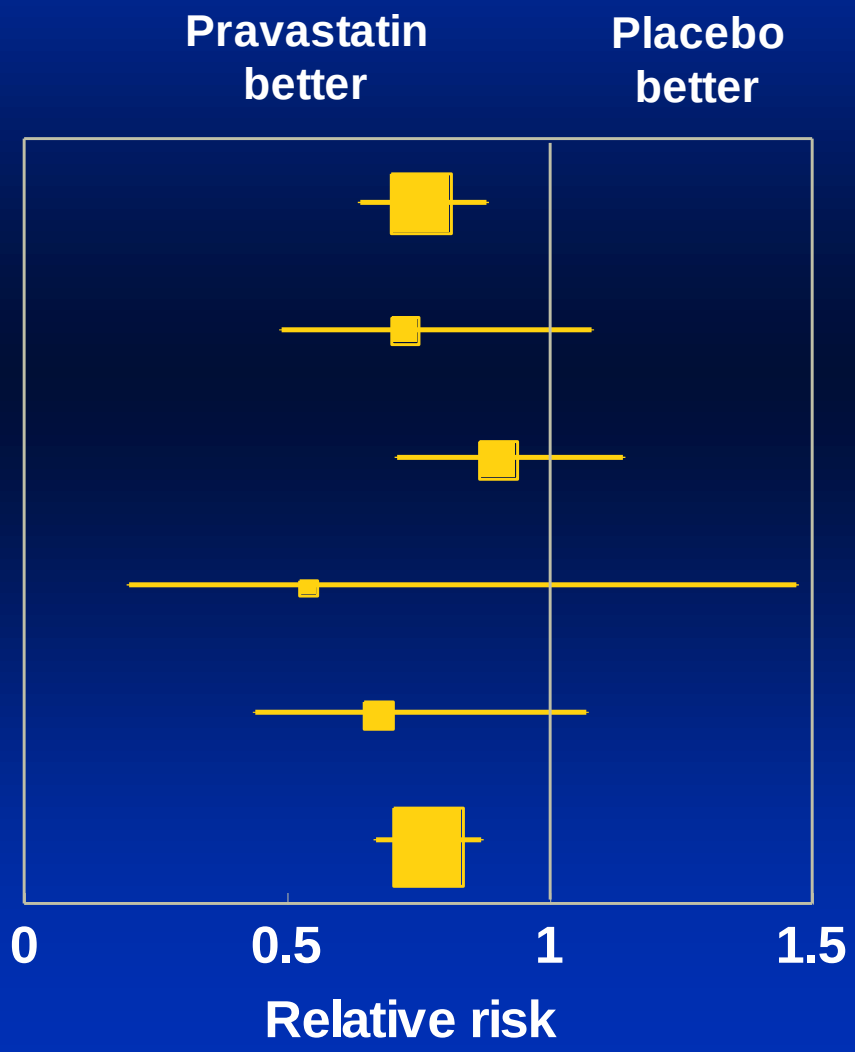
Major study outcomes: reduction in relative risk

	Plac %	Prav %	P
CHD mortality	8.3	6.4	0.0004
CVD mortality	9.6	7.3	0.0001
Total mortality	14.1	11.0	0.00002
CHD events	15.9	12.3	0.000001
Total stroke	4.5	3.7	0.048
Nonhaemorrhagic stroke	4.4	3.4	0.016

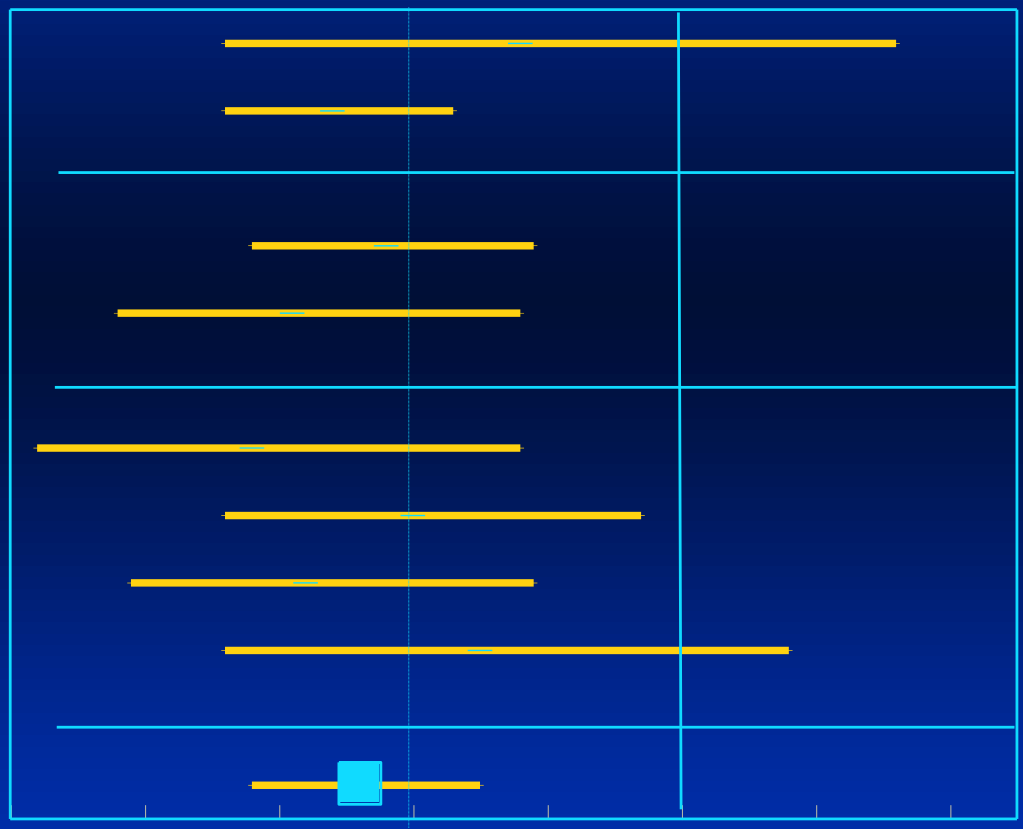


Cause-specific mortality

	Plac %	Prav %
CHD mortality	8.3	6.4
Other CVD	1.3	1.0
Cancer	3.1	2.8
Trauma or suicide	0.2	0.1
Other	1.1	0.7
Total	14.1	11.0



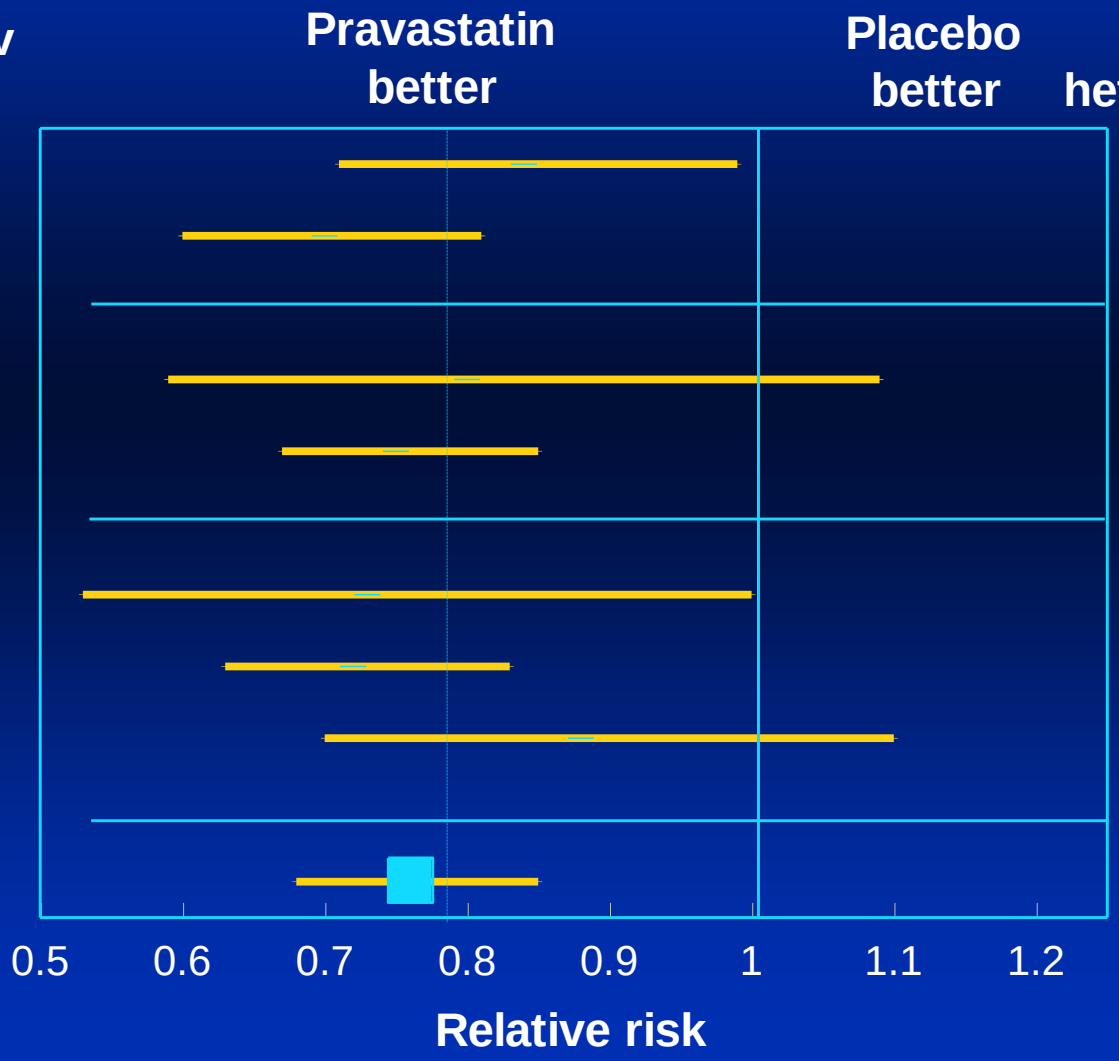
CHD death + nonfatal MI: major subgroups 1.



	Plac %	Prav %	*P* for heterogeneity
Female	14	12	
Male	16	12	0.28
MI	17	14	
UAP	13	10	0.47
< 55 yrs	13	9	
55 – 64	14	11	
65 – 69	19	14	0.59
70 yrs	21	18	
Total	16	12	

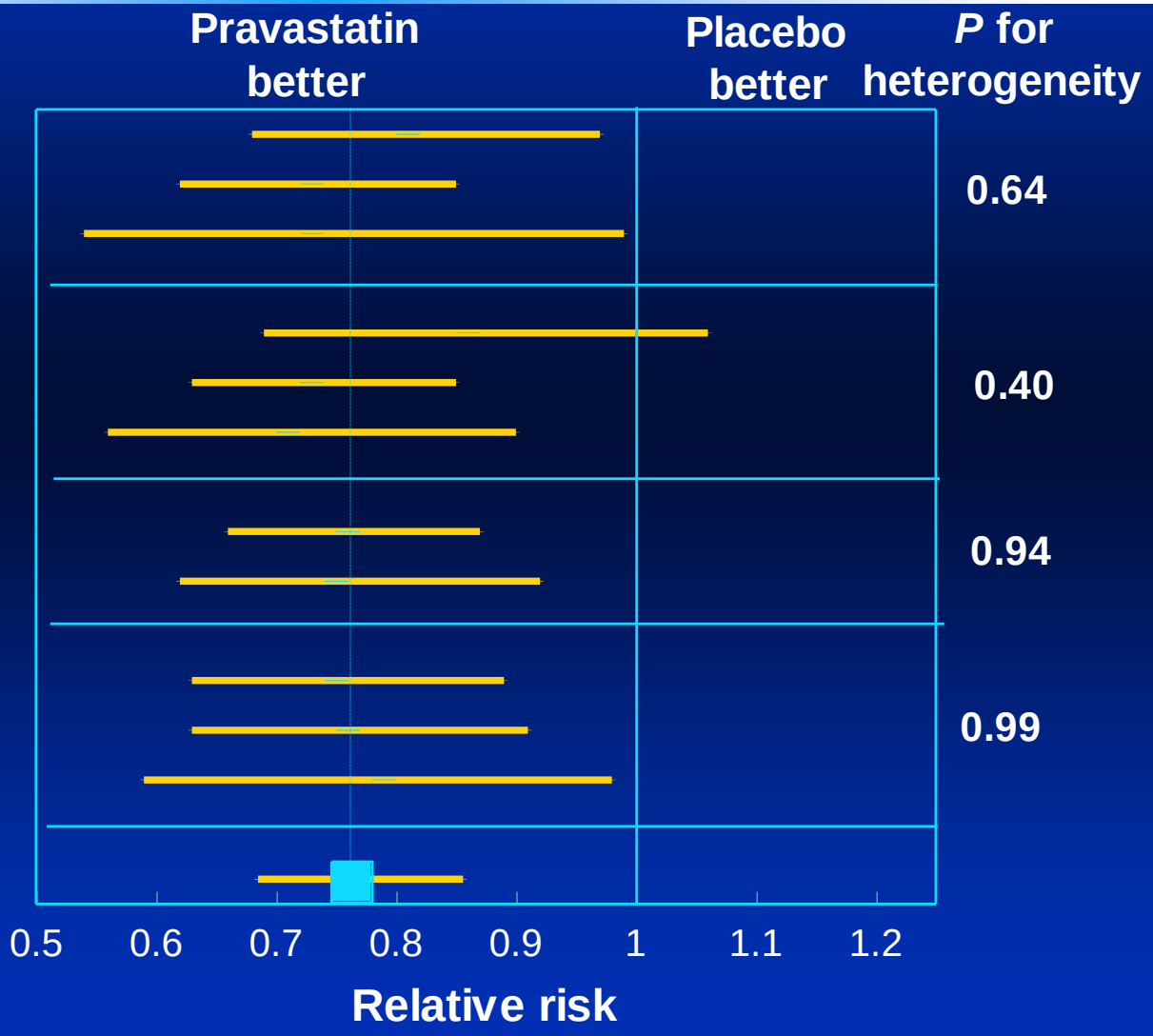
CHD death + nonfatal MI: major subgroups 2.

	Plac %	Prav %	*P* for heterogeneity
Hypertension	17	14	
No	15	11	0.10
Diabetes	23	19	
No	15	12	0.70
Smoker	21	16	
Ex-smoker	16	12	
Nonsmoker	13	12	0.33
Total	16	12	



CHD death + nonfatal MI: lipid subgroups

	(mmol/L)	Plac %	Prav %
Total cholesterol	< 5.5	14	12
	5.5 - 6.5	17	13
	≥ 6.5	16	12
LDL cholesterol	< 3.5	14	12
	3.5 - 4.5	16	12
	≥ 4.5	18	13
HDL cholesterol	< 1.0	17	13
	≥ 1.0	14	10
Triglycerides	< 1.5	16	12
	1.5 - 2.5	15	12
	≥ 2.5	18	14
Total		16	12

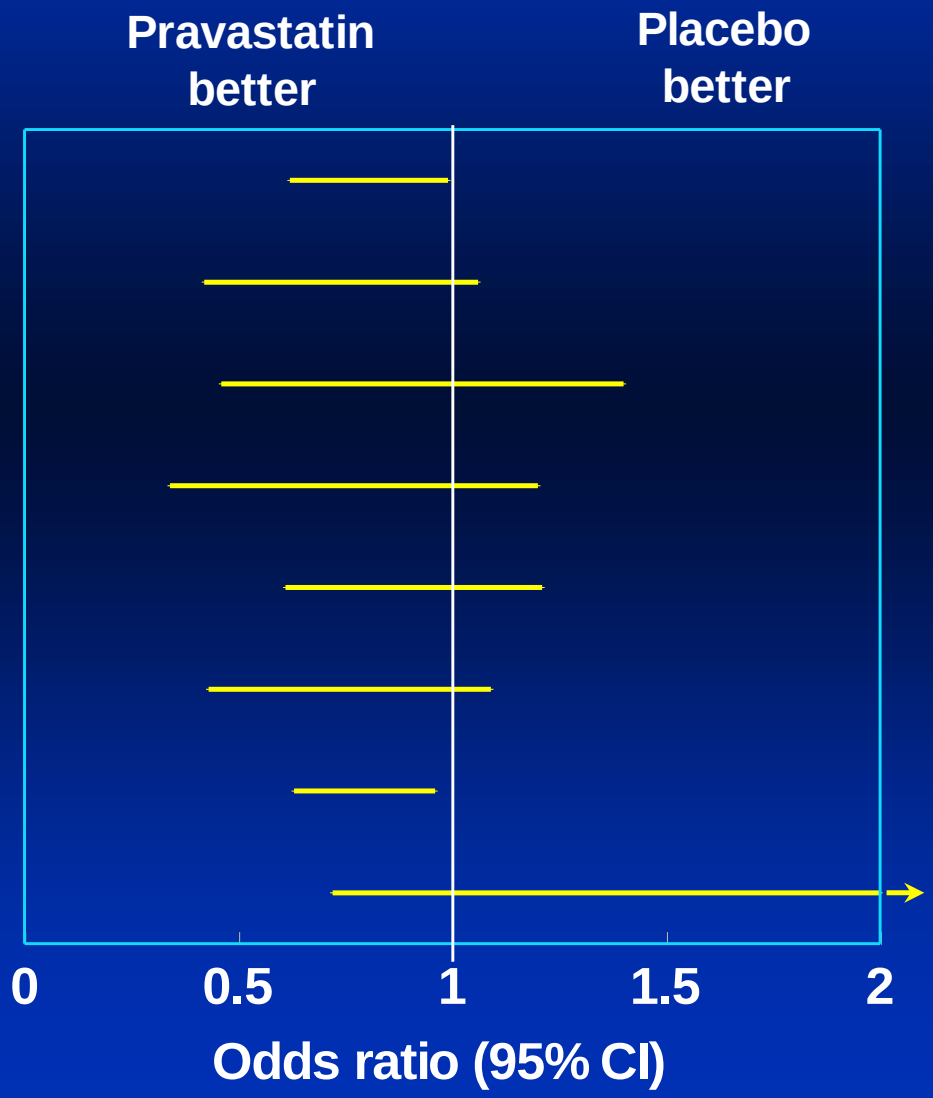


Stroke outcomes

Outcome	Placebo n = 4502	Pravastatin n = 4512	Total
No of patients with stroke	204	169	373
With single stroke	179	153	332 (89%)
With multiple strokes	25	16	41 (11%)
Fatal (< 30 days)	31	22	53 (14%)
Procedure-related stroke	20	14	34 (9%)
Total strokes	231	188	419

Stroke outcomes

	Plac %	Prav %
Ischaemic	3.6	2.8
Cardioembolic	1.0	0.7
Large-artery	0.6	0.5
Small-vessel	0.5	0.4
Unknown	1.6	1.4
Stroke of unknown type	1.0	0.7
Nonhaemorrhagic	4.4	3.4
Haemorrhagic	0.2	0.4



Cancer incidence

Cancer	Placebo	Pravastatin
Lung or pleura	62	49
Colorectal	60	57
Other GI	27	27
Prostate or testis	115	116
Renal or bladder	38	42
Melanoma	28	29
Breast	10	9
Head and neck	9	8
Liver	3	7
Leukaemia or lymphoma	33	27
Other	35	36
Total	399	379

Size of the benefit: CVD events prevented

Event	Events prevented per 1000 patients treated over 6 years
Fatal CHD	19
Nonfatal MI	16
CABG	24
PTCA	10
Unstable angina	23
All CHD events*	63
Stroke	8

* coronary events + CABG + PTCA + UAP

Hospital admissions

	Placebo group	Pravastatin group	Difference
Total admissions	12 784	11 709	1075
No. per patient	3.7	3.5	0.2
Average length of stay (days)	6.1	5.7	0.4
Total days per patient	17.3	14.7	2.6
Days per person-year	3.84	3.19	0.65

Conclusions

- The LIPID study provides clear evidence that cholesterol-lowering therapy with pravastatin reduces total mortality in patients with established CHD and average or below-average cholesterol levels

- Benefits of treatment were seen consistently for all cardiovascular outcomes, including:
  - MI
  - stroke
  - coronary revascularisation

Conclusions

- Effects of pravastatin treatment were similar for each of the prespecified subgroups and across the range of baseline lipid levels.
- Treatment was well tolerated and safe.
- Treatment was associated with significant cost offsets in terms of
  - fewer hospital admissions
  - less time in hospital per admission
  - less use of other drugs.
- Health-economic assessment suggests treatment is cost-effective and should be considered for most patients with established coronary heart disease.

Conclusions: stroke

- In patients with average cholesterol levels and established CHD, treatment with pravastatin significantly reduced the risk of stroke
- The risk of stroke was reduced by 19% (8 strokes prevented per 1000 patients treated over 6 years)
- The risk of nonhaemorrhagic stroke was reduced by 23% (9 strokes prevented per 1000 patients treated over 6 years)

Conclusions: stroke

- Reductions in the risk of stroke were seen consistently across all subtypes of ischaemic stroke
- No treatment effect was observed among the small number of haemorrhagic strokes
- The LIPID findings confirm the value of cholesterol-lowering treatment with pravastatin in reducing the risk of stroke

Conclusions: relationship with lipids

- Treatment benefits with pravastatin were seen across the full range of baseline lipid values. No significant variations were observed in treatment effects within prespecified subgroups or by quintiles of baseline cholesterol.

- There was no evidence of a threshold effect at low LDL cholesterol levels (a threshold effect is not excluded, owing to the small number of events).

Conclusions: relationship with lipids

- With a lower baseline total or LDL cholesterol level, the following may be expected:
  - smaller absolute risk of CHD events
  - slightly smaller change in cholesterol levels with treatment
  - a similar relative risk reduction, *and so*
  - a smaller absolute risk reduction with treatment

- About half of the epidemiological risk associated with a long-term difference of 1.0 mmol/L in usual cholesterol was eliminated with pravastatin treatment over 6 years