
**International Task Force for Prevention
Of Coronary Heart Disease**



*Clinical management of risk factors
of coronary heart disease and stroke*

Major recent drug trials

**MRC/BHF
Heart Protection Study**

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Slide 1:

Objective of the MRC/BHF Heart Protection Study



MRC/BHF Heart Protection Study Objective



- **Assessment of the effects of cholesterol-lowering therapy with simvastatin and of antioxidant vitamin supplementation on mortality and major morbidity in a wide range of different categories of high-risk patients**

Source: MRC/BHF Heart Protection Study Collaborative Group, *Eur Heart J* 1999;20:725-41



Objective of the MRC/BHF Heart Protection Study

This slide gives the objective of the Heart Protection Study (HPS) run by the British Medical Research Council (MRC) and the British Heart Foundation (BHF), known as the MRC/BHF Heart Protection Study.

Substantial uncertainty has existed about the long-term benefits of cholesterol-lowering drug therapy for particular types of high-risk patients irrespective of their initial cholesterol concentrations. Uncertainty as to the possible benefits or risks, of antioxidant vitamin supplementation is even greater. Evidence from observational studies suggests that people with higher intakes of these vitamins from their diets have lower rates of various diseases, including heart disease, cancer, Alzheimer's disease, diabetes and cataracts.

Slide 2:

Eligibility



ELIGIBILITY

- **Male or female, age 40-80 years**
- **High risk of CHD death over the next 5 years due to prior disease:**
 - Myocardial infarction or other coronary heart disease;**
 - occlusive disease of non-coronary arteries; or**
 - diabetes mellitus or treated hypertension**
- **No clear indication or contraindication for statin or vitamin treatment**
- **Total cholesterol >3.5 mmol/l (>135mg/dl)**



Source: MRC/BHF Heart Protection Study Collaborative Group, Eur Heart J 1999;20:725-41

Eligibility

This slide shows eligibility criteria of HPS.

Slide 3:

Patients characteristics at baseline

Patients Characteristics at Baseline

Baseline feature		Number	Percentage
Age (years)	< 70	14730	72
	≥ 70	5806	28
Gender	Male	15,454	75
	Female	5,082	25
Prior Disease	Previous MI	8,510	41
	Other CHD	4,876	24
	No CHD*	7,150	35
	cerebrovascular	1,820	9
	peripheral vascular	2,701	13
	Diabetes	3,982	19
Blood Lipid Levels** (mmol/L)	Total cholesterol	5.9	
	LDL cholesterol	3.4	
	HDL cholesterol	1.06	
	Triglycerides	2.1	

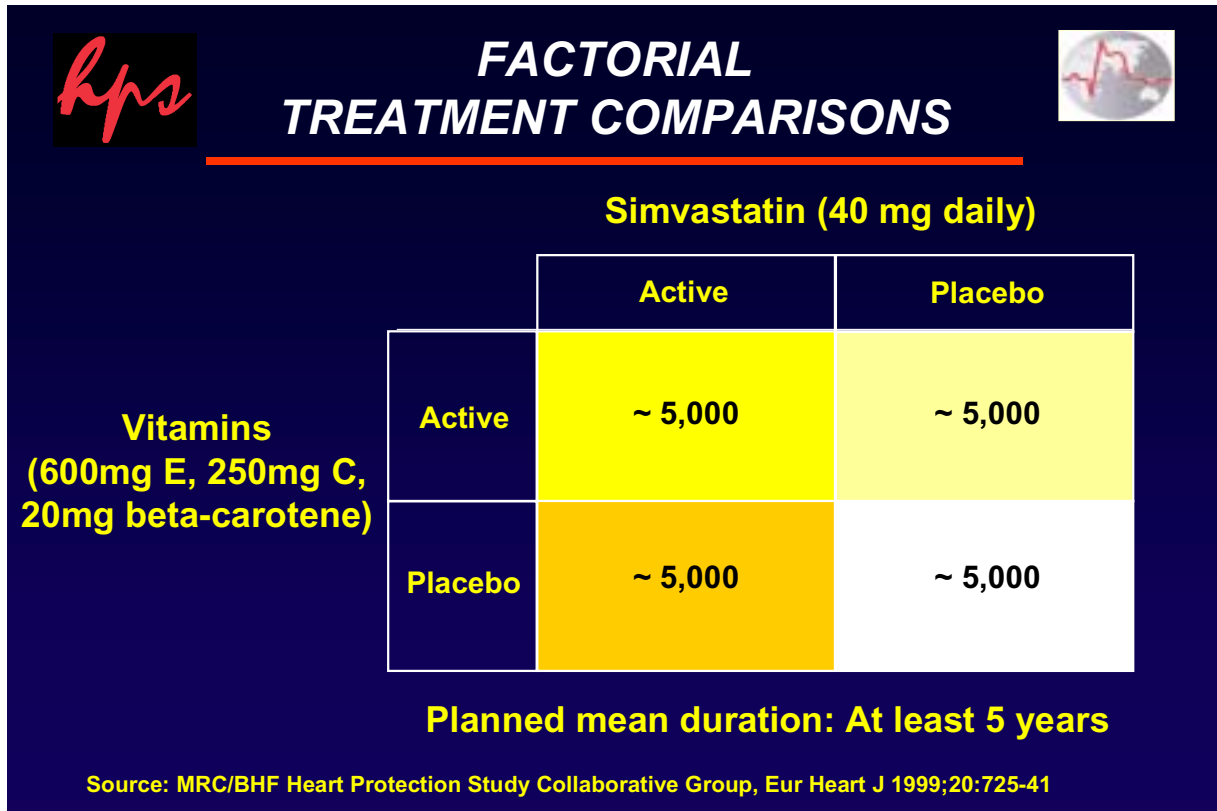
*Overlap between categories within "No CHD" group
 ** Data are mean
 Source: MRC/BHF Heart Protection Study Collaborative Group, Lancet 2002;360:7-22

Patients characteristics at baseline

Characteristics of the HPS participants at entry into the study. A total of 20,536 persons were included. The heterogeneous mixture of patients, all at a substantial 5-year risk of coronary heart disease death, comprised those in different prior disease categories, men and a substantial number of women, young and old, and those with varying blood cholesterol levels (especially with below-average cholesterol levels).

Slide 4:

Factorial treatment comparisons



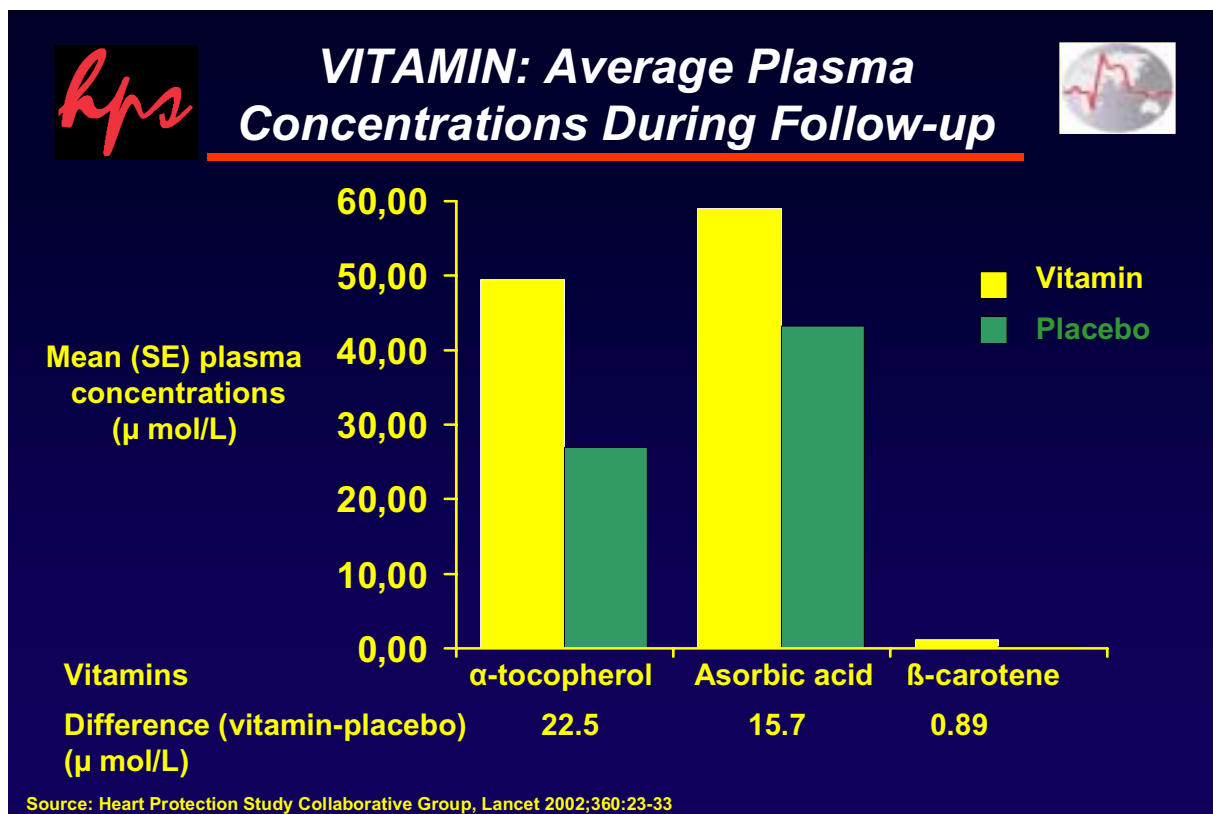
Factorial treatment comparisons

The factorial study design (2 x 2) of the Heart Protection Study is illustrated in this slide. Between July and April 1997, 20,536 individuals were assigned either to simvastatin vs placebo tablets, or to a cocktail of antioxidant vitamins vs placebo capsules, for a mean duration of at least 5 years.

5,000 were allocated to active statin and active vitamins, 5,000 were allocated to active statin and placebo vitamins, 5,000 were allocated placebo statin and active vitamins and 5,000 were allocated to placebo statin and placebo vitamins. Assessment of cholesterol-lowering therapy involves comparing the 10,000 allocated active statin versus the 10,000 allocated placebo statin. Likewise, the assessment of antioxidant vitamin supplementation involves comparisons of the 10,000 allocated active vitamins versus the 10,000 allocated placebo vitamins.

Slide 5:

Vitamin: Average plasma concentrations during follow-up



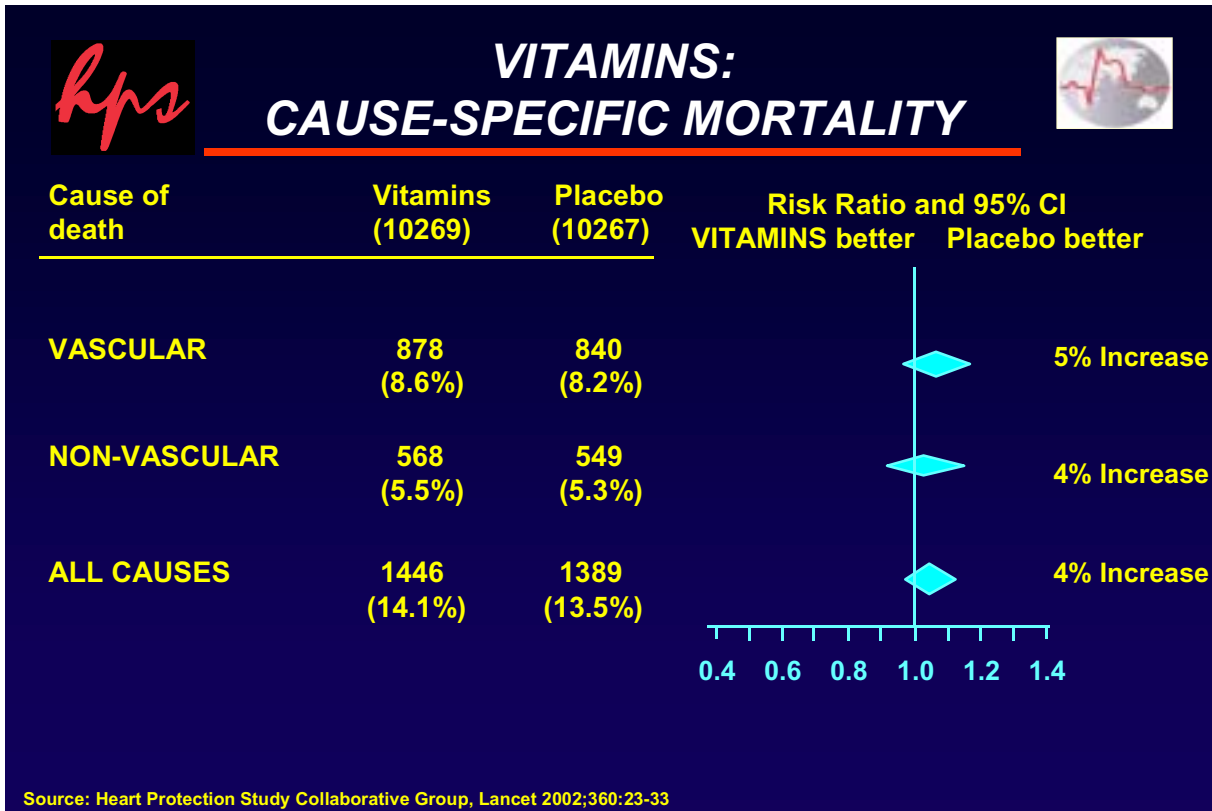
Vitamin: Average plasma concentrations during follow-up

The following four slides show the results for the vitamin arm of the Heart Protection Study. HPS volunteers were taking two vitamin pills a day or matching dummy "placebo" pills. The average compliance in each treatment group was 83%. The vitamin pills contain a total of 600 mg of vitamin E, 20 mg of beta-carotene and 250 mg of vitamin C.

This slide shows that compared with placebo, allocation to the study vitamins approximately doubled the average plasma concentration of alpha-tocopherol, increased that of vitamin C by about one-third, and quadrupled that of beta-carotene.

Slide 6:

Vitamin: cause-specific mortality

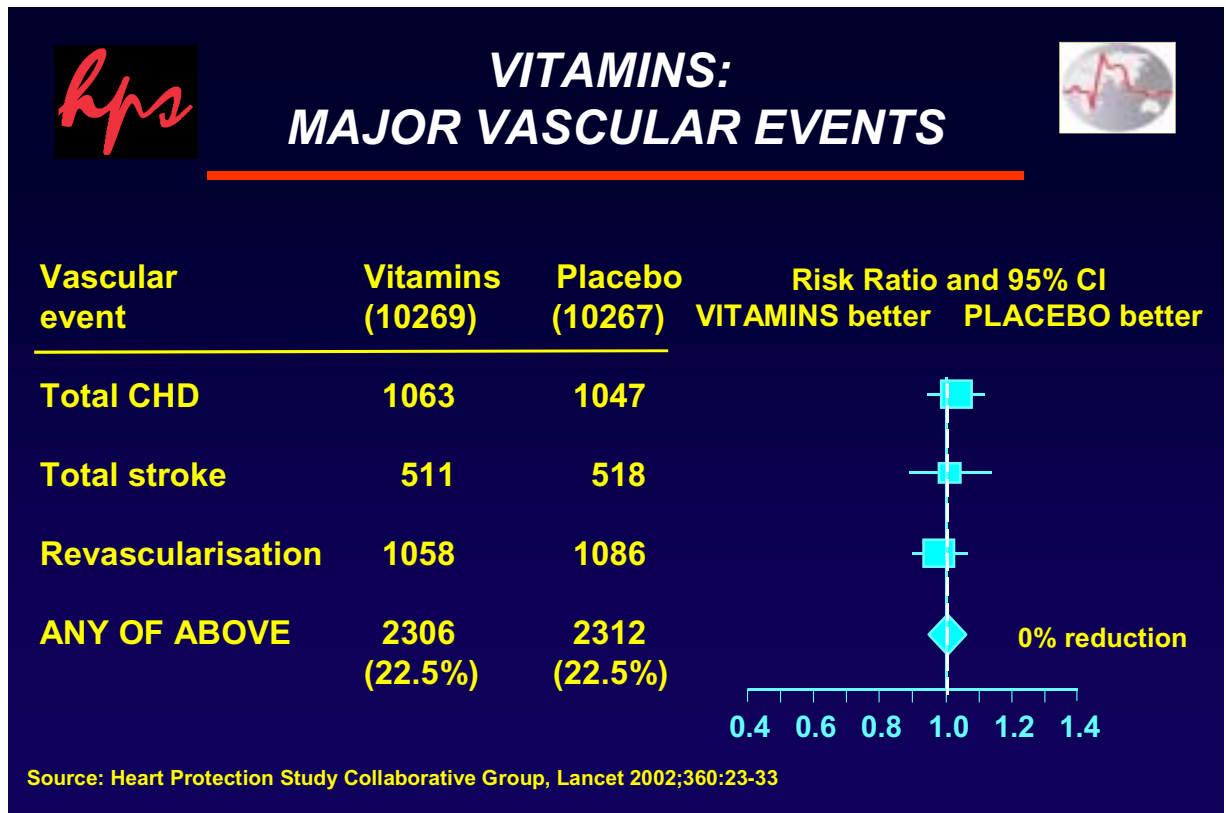


Vitamin: cause-specific mortality

Although this vitamin regimen increased blood vitamin concentrations substantially (see slide 5), it did not produce any significant reductions in the 5-year mortality from, or incidence of, any type of vascular disease, cancer, or other major outcome in this high-risk population.

Slide 7:

Vitamin: major vascular events



Vitamin: major vascular events

This slide illustrates that no significant effects of vitamin therapy on any specific major vascular event were observed.

Slide 8:

Vitamin: Summary of findings



VITAMIN: Summary of Findings



- **This antioxidant vitamin regimen (600 mg E, 250 mg C & 20 mg beta carotene daily) increased blood vitamin levels substantially**
- **These vitamins appeared to be safe, but did not reduce the 5-year risks of any type of vascular disease, cancer or other major outcome**
- **Given these results, continued recommendation of supplementation with such vitamins is difficult to justify**

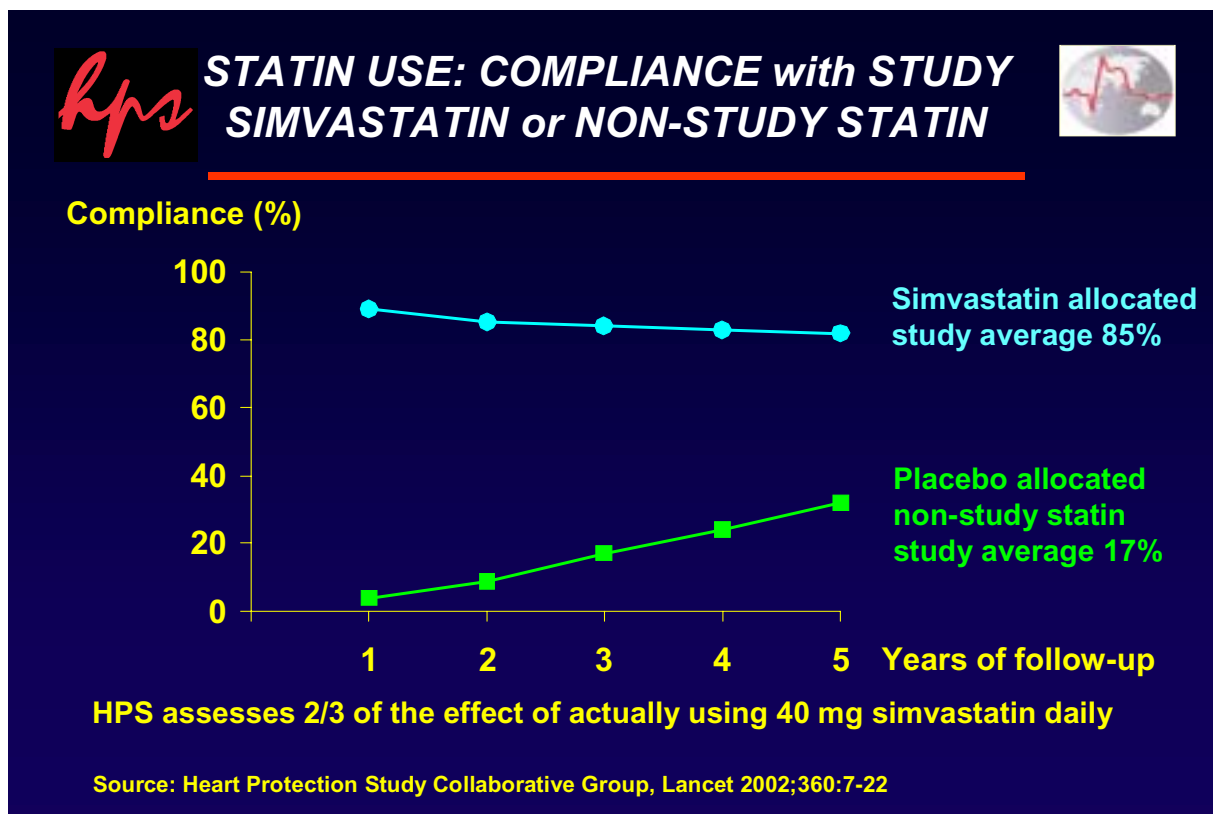
Source: Heart Protection Study Collaborative Group, Lancet 2002;360:23-33

Vitamin: Summary of findings

This slide shows the summary of findings of the vitamin arm of the Heart Protection Study.

Slide 9:

Statin Use: Compliance with study simvastatin or non-study statin

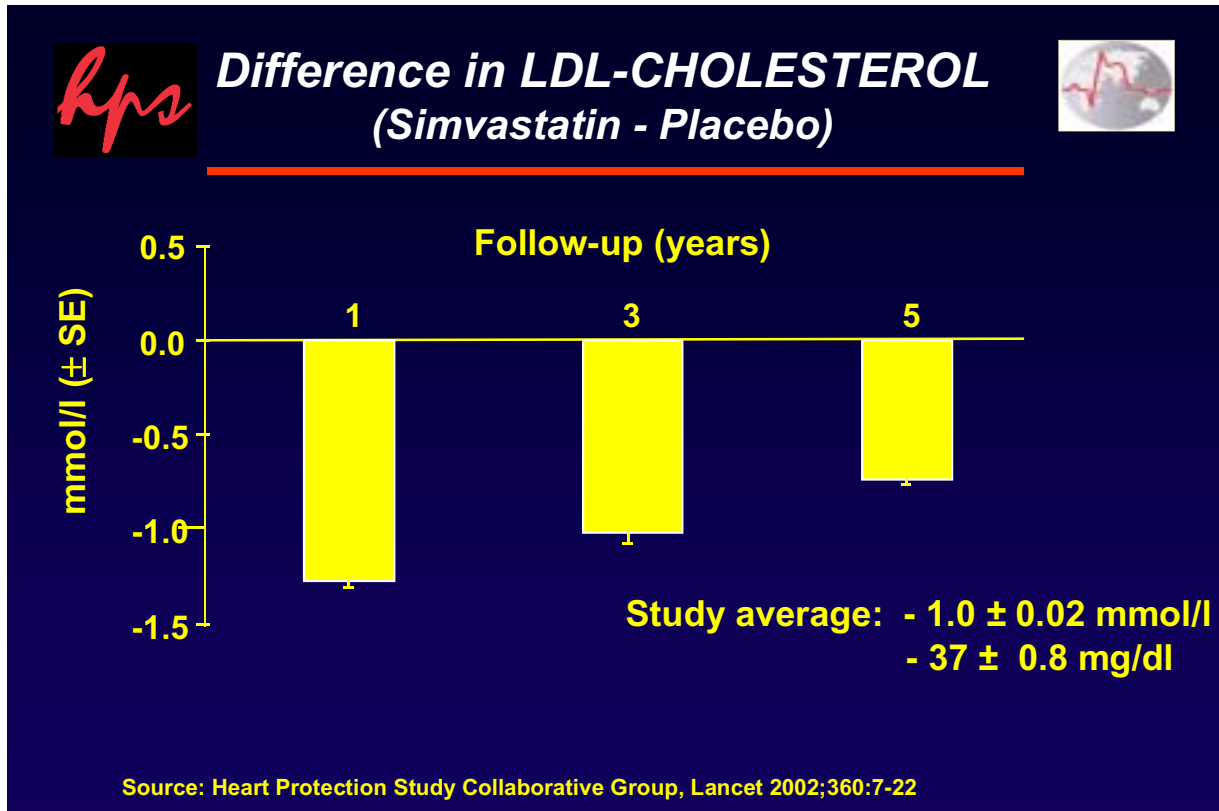


Statin Use: Compliance with study simvastatin or non-study statin

The average compliance of those allocated statins was 85%. Among those allocated to placebo on average 17% were taking a non-study statin. Hence, the average difference between these groups in the percentage actually taking a statin was about 67% (85% minus 17%). As a consequence, the intention-to-treat comparisons assessed the effects of about two-thirds of simvastatin-allocated participants actually taking 40 mg simvastatin daily.

Slide 10:

Difference in LDL-cholesterol (simvastatin - placebo)





Difference in LDL-cholesterol (simvastatin - placebo)

This slide shows the blood lipid differences between those allocated to simvastatin and those allocated to placebo, with an average difference in LDL cholesterol during the study of 1.0 mmol/L being produced by the average difference of two-thirds in statin use. It can be estimated that the average reduction in LDL cholesterol of about 1.0mmol/l (40mg/dl) seen in an intention-to-treat analysis represents a reduction of about 1.5mmol/l (i.e. $1.0 \times 3/2$) with actual use of 40 mg daily simvastatin.

Slide 11:

Simvastatin: average LDL difference (mmol/l ± se) by baseline LDL cholesterol

SIMVASTATIN:
Average LDL DIFFERENCE
(mmol/l) by BASELINE LDL-Cholesterol

LDL-cholesterol (mmol/L) at entry	SIMVASTATIN (n=10,269)	PLACEBO (n=10267)	Difference in LDL
< 3.0 (116 mg/dL)	1.8	2.7	-0.9
≥ 3.0 < 3.5	2.2	3.2	-1.0
≥ 3.5 (135 mg/dL)	2.7	3.7	-1.0
ALL PATIENTS	2.3	3.3	-1.0

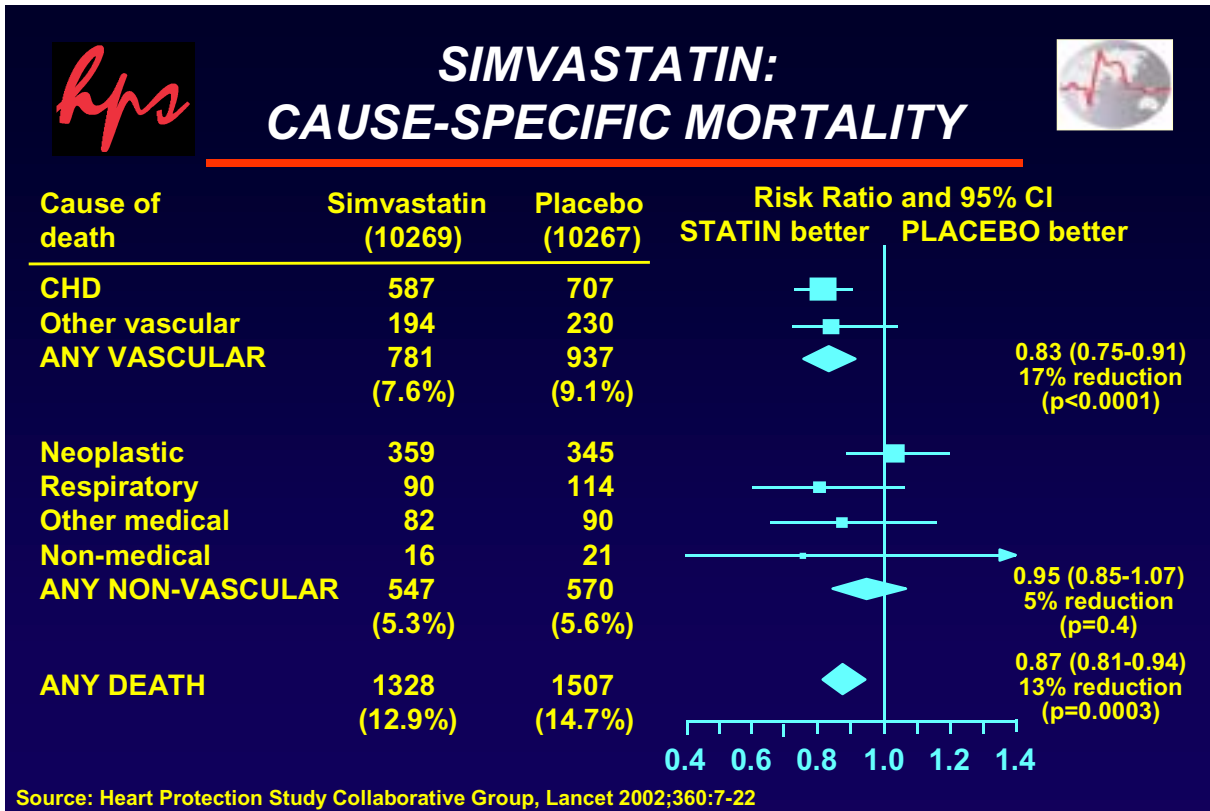
Source: Heart Protection Study Collaborative Group, Lancet 2002;360:7-22

Simvastatin: average LDL difference (mmol/l ± se) by baseline LDL cholesterol

This slide shows that the proportional reduction in LDL cholesterol produced by actual use of 40 mg simvastatin daily is approximately independent of the presenting cholesterol concentration.

Slide 12:

Simvastatin: cause-specific mortality

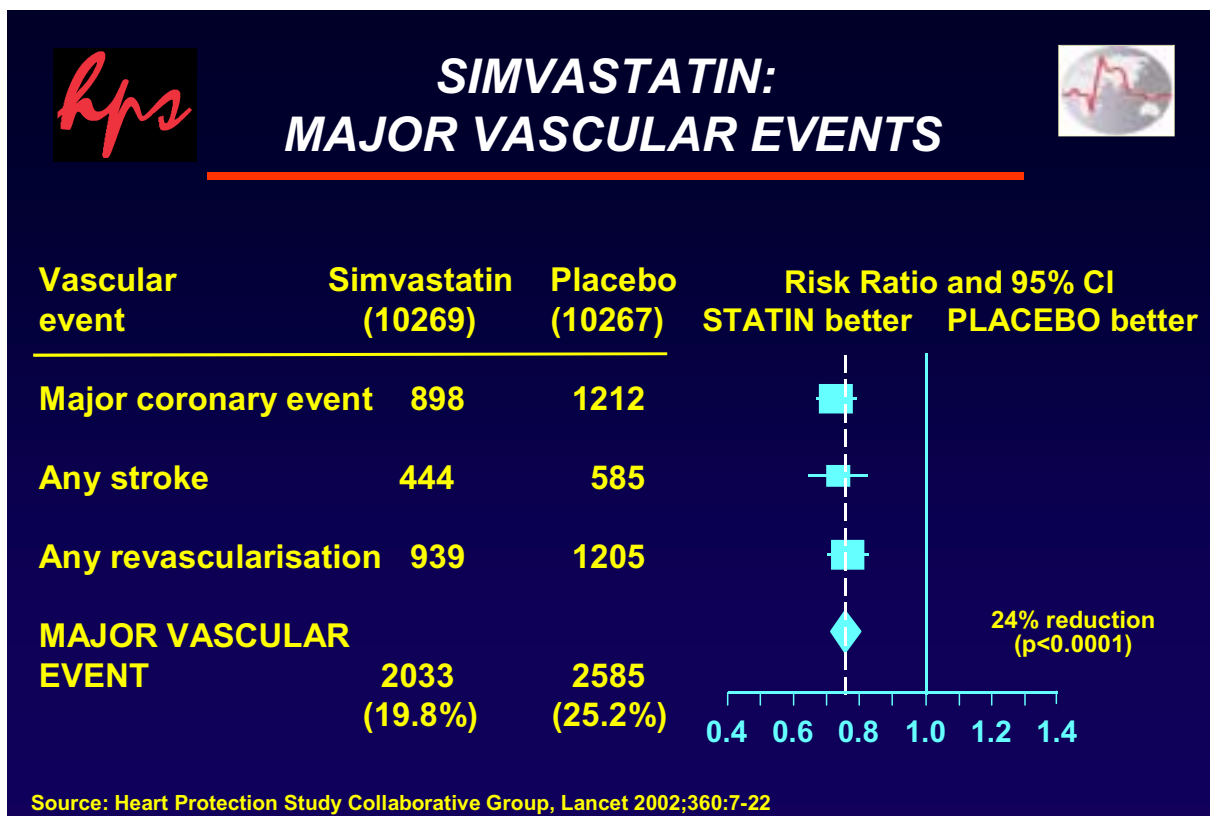


Simvastatin: cause-specific mortality

This slide shows the effect of simvastatin on cause-specific mortality compared to placebo. Simvastatin treatment reduced all cause mortality. This effect of simvastatin allocation on all-cause mortality is due chiefly to the definite 17% proportional reduction in the death rate from vascular causes, which consists of a highly significant 18% reduction in the coronary death rate and a marginally significant 16% reduction in the death rate from other vascular causes. There were no significant differences either in all non-vascular deaths considered together or in any of the prespecified categories of non-vascular deaths.

Slide 13:

Simvastatin: major vascular events

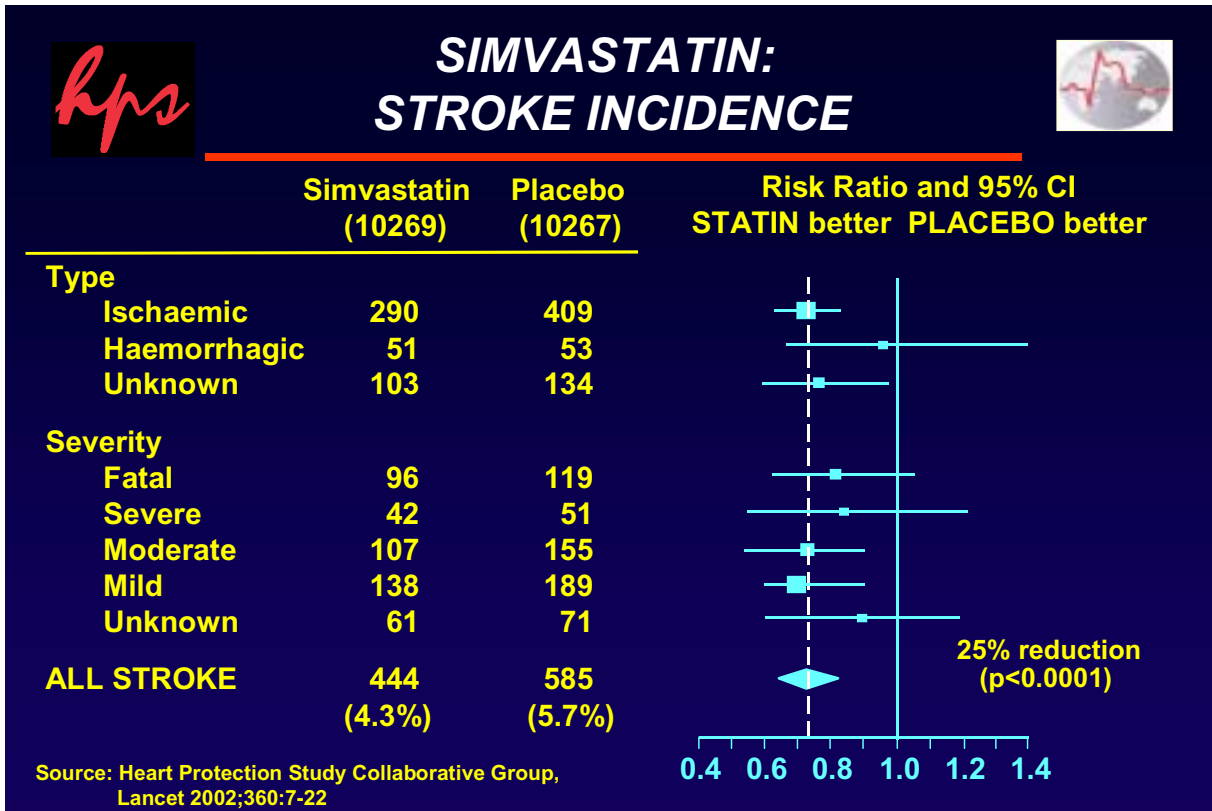


Simvastatin: major vascular events

Cholesterol-lowering with a statin reduced the risk not just of heart attacks but also of strokes and of both coronary and non-coronary revascularisation procedures. In HPS, about two-thirds of all participants complied with the therapy as prescribed within the study. Based on this level of compliance, these reductions in major vascular events of about one-quarter in intention-to treat analyses translate into reductions in vascular disease risk of at least one-third with full compliance to 40mg daily simvastatin. Cholesterol-lowering with statin treatment reduces the risk of heart attacks and of strokes by at least one-third, as well as reducing the need for arterial surgery, angioplasty and amputations. The stroke findings are particularly impressive. The epidemiological database prior to HPS had not suggested that total cholesterol levels were a strong predictor of stroke risk. In HPS however, statin therapy lowered the risk of subsequent stroke by almost 30%.

Slide 14:

Simvastatin: stroke incidence



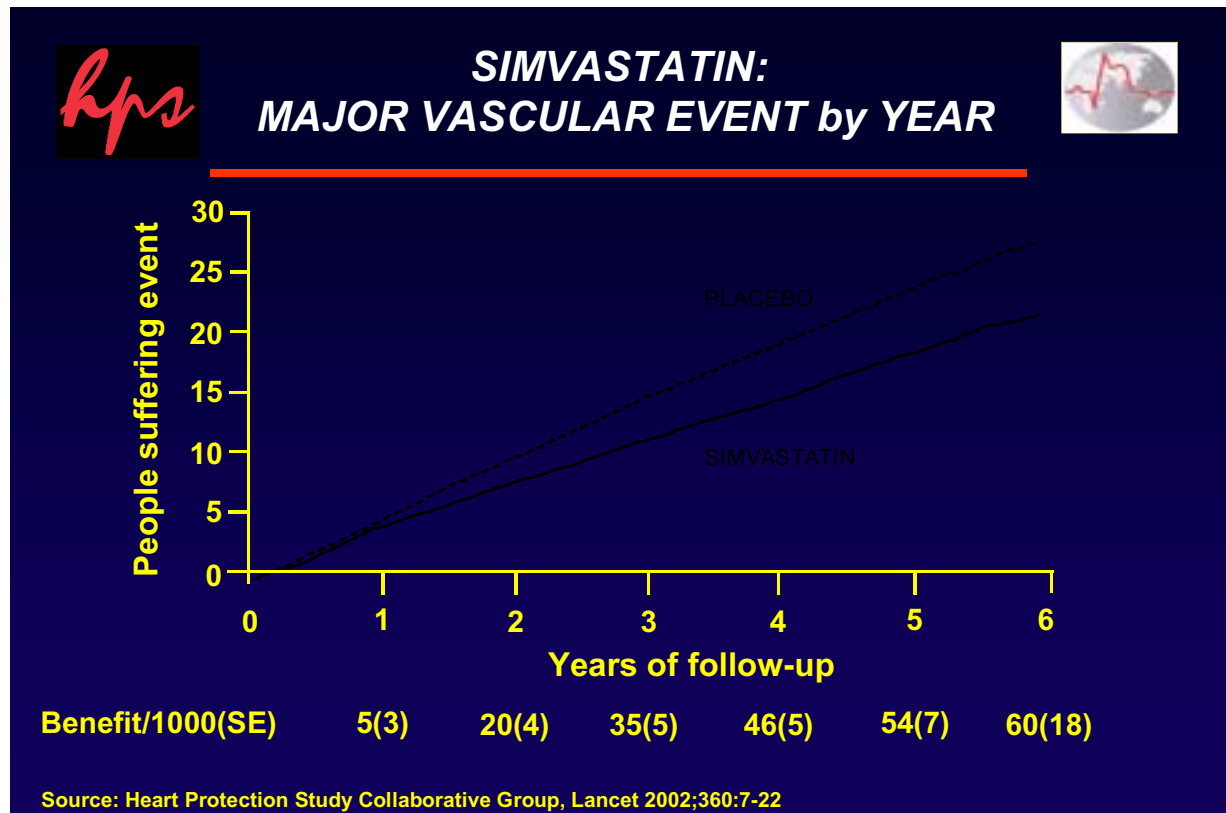
Simvastatin: stroke incidence

This slide shows the effect of simvastatin treatment compared to placebo on stroke incidence.

Overall, allocation to simvastatin produced a highly significant 25% proportional reduction in the incidence rate of first stroke following randomisation. This was due chiefly to a very definite 30% proportional reduction in the incidence rate of strokes attributed to ischaemia, the most prevalent type of stroke., with no apparent difference in strokes attributed to haemorrhage and a marginal significant reduction in stroke of unknown type. Considering the severity of stroke, significant reductions were observed in moderate and mild types of stroke.

Slide 15:

Simvastatin: vascular event by follow-up duration

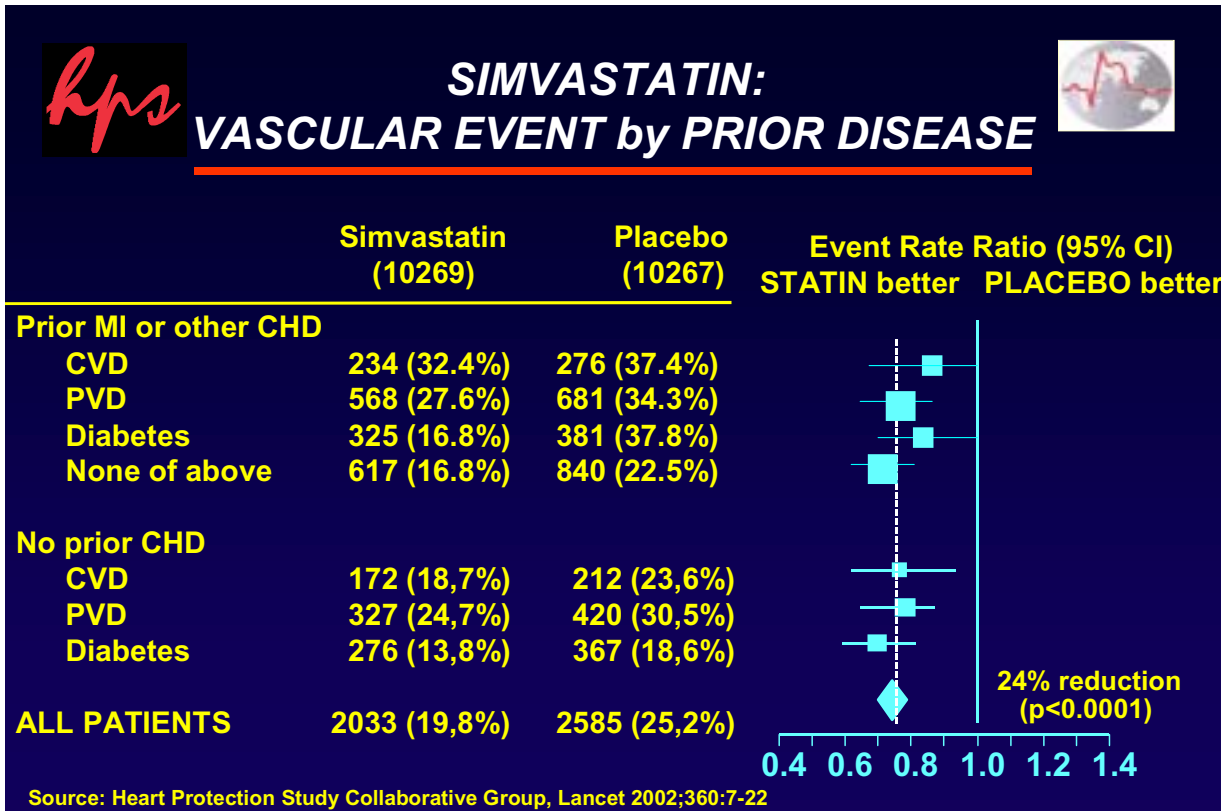


Simvastatin: vascular event by follow-up duration

This slide shows that in this high-risk population, about 5% of placebo-allocated participants had a first major vascular event during each year of follow-up. Among participants allocated to simvastatin, there was already a non-significant trend towards fewer major vascular events in the first year of follow-up after randomisation. Subsequently, during each year of follow-up, there were highly significant reductions of about one-quarter in the event rates even though, by the end of year 3, about one-sixth of the simvastatin-allocated participants had stopped their study treatment and about one-sixth of those allocated placebo had started statin therapy.

Slide 16:

Simvastatin: vascular event by prior disease

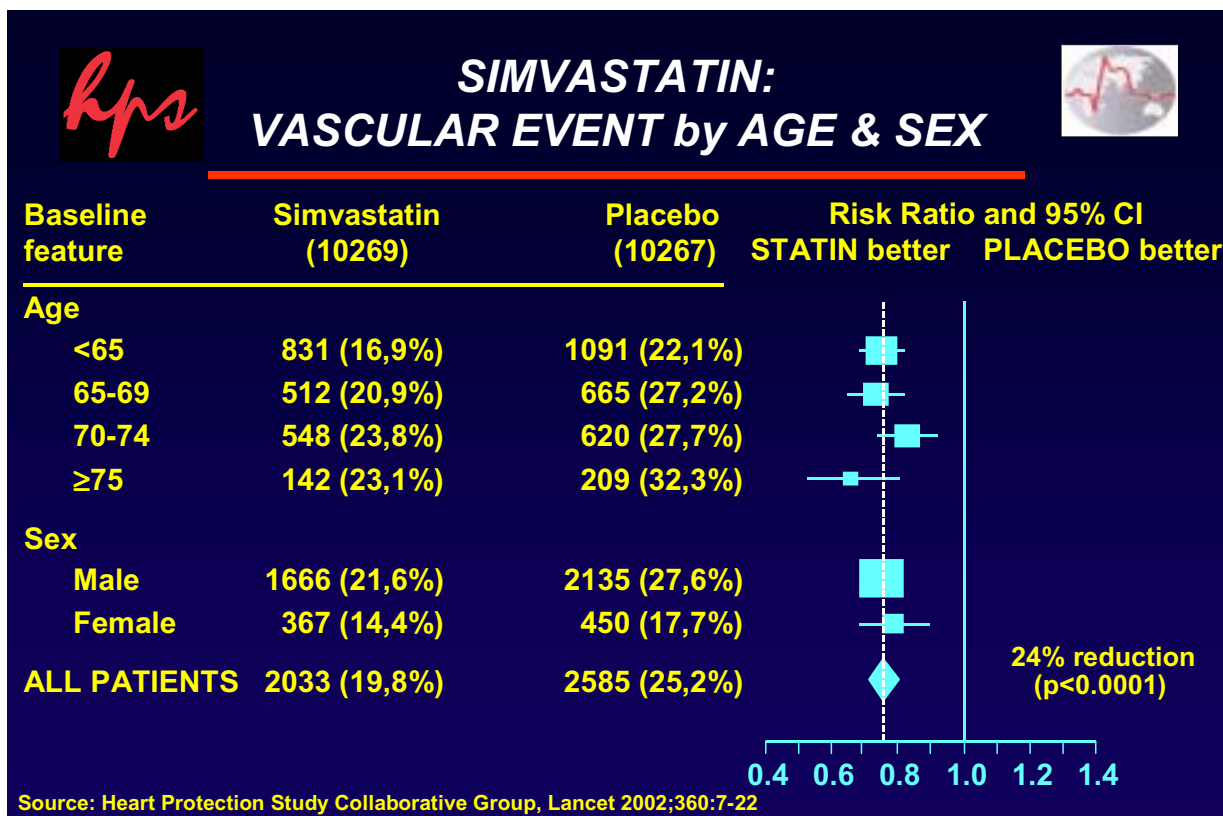


Simvastatin: vascular event by prior disease

This slide shows that the proportional reduction in the rate of major vascular events was about one-quarter in each subcategory of participants studied and especially high in the subgroup of patients with diabetes. HPS provides the first direct evidence that cholesterol-lowering therapy cuts the risk of heart attacks and strokes by at least one quarter not just in people who already have coronary disease but also in those who have diabetes, narrowing of arteries in their legs or a previous history of stroke.

Slide 17:

Simvastatin: vascular event by age & sex



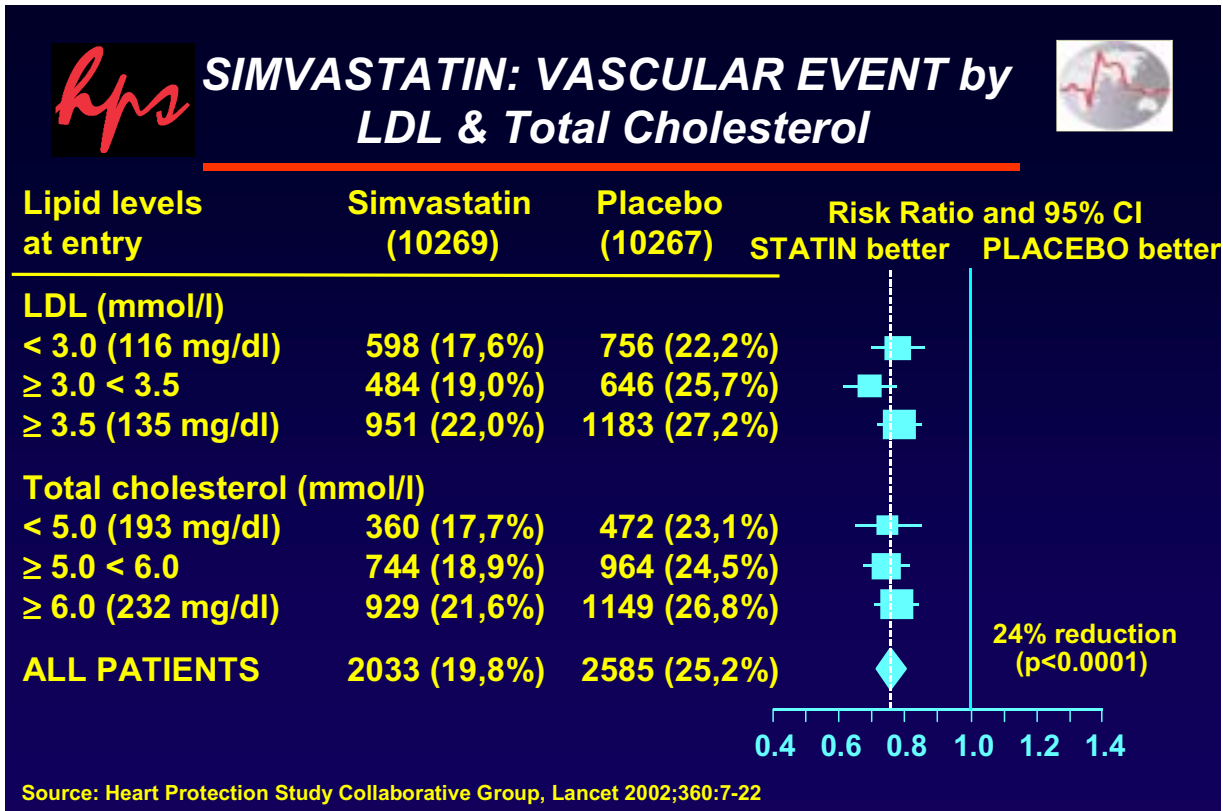
Simvastatin: vascular event by age & sex

This slide shows an about one-quarter proportional reduction in the rate of major vascular events with allocation to simvastatin irrespective of the sex or age of the participants compared with placebo.

Two subgroups are of major interest. This study includes the first definite evidence of benefit in older people (aged ≥70, n=5805) and in women (n=5082). Cholesterol-lowering has now been shown to reduce the risk of vascular disease to about the same extent in women as in men. Up to now the effects of cholesterol-lowering in women have been extrapolated from evidence in men. Women tend to develop vascular disease at older ages than men, so the evidence of benefit in this study among people aged over 70 is also of great relevance to improving the health of women.

Slide 18:

Simvastatin: vascular event by LDL & total cholesterol




Simvastatin: vascular event by LDL & total cholesterol


This slide illustrates that the proportional reduction in risk did not appear to be materially influenced by the pretreatment LDL or total cholesterol concentrations.

Slide 19:

Simvastatin: Main conclusions



SIMVASTATIN: Main conclusions



- **After allowance for non-compliance, 40mg daily simvastatin safely reduces the risk of heart attack, of stroke, and of revascularisation by at least one-third**
- **5 years of statin treatment typically prevents these “major vascular events” in about:**

100	of every 1000	with previous MI
80	“ “	other CHD
70	“ “	diabetes (age 40+)
70	“ “	previous stroke
70	“ “	other PVD

**irrespective of cholesterol level
(or age, or sex, or other treatments)**

Source: Heart Protection Study Collaborative Group, Lancet 2002;360:7-22 and Lancet 2002;360:23-33

Simvastatin: Main conclusions

This slide summarises the main conclusions of the MRC/BHF Heart Protection Study.