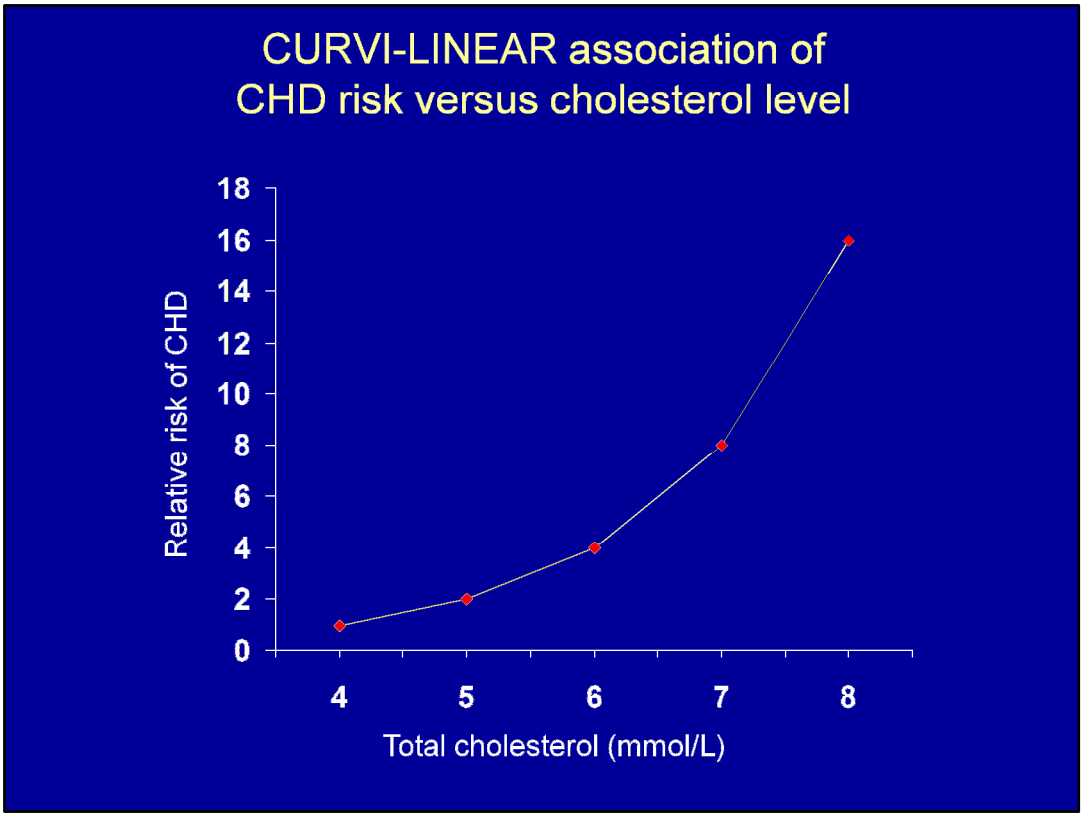
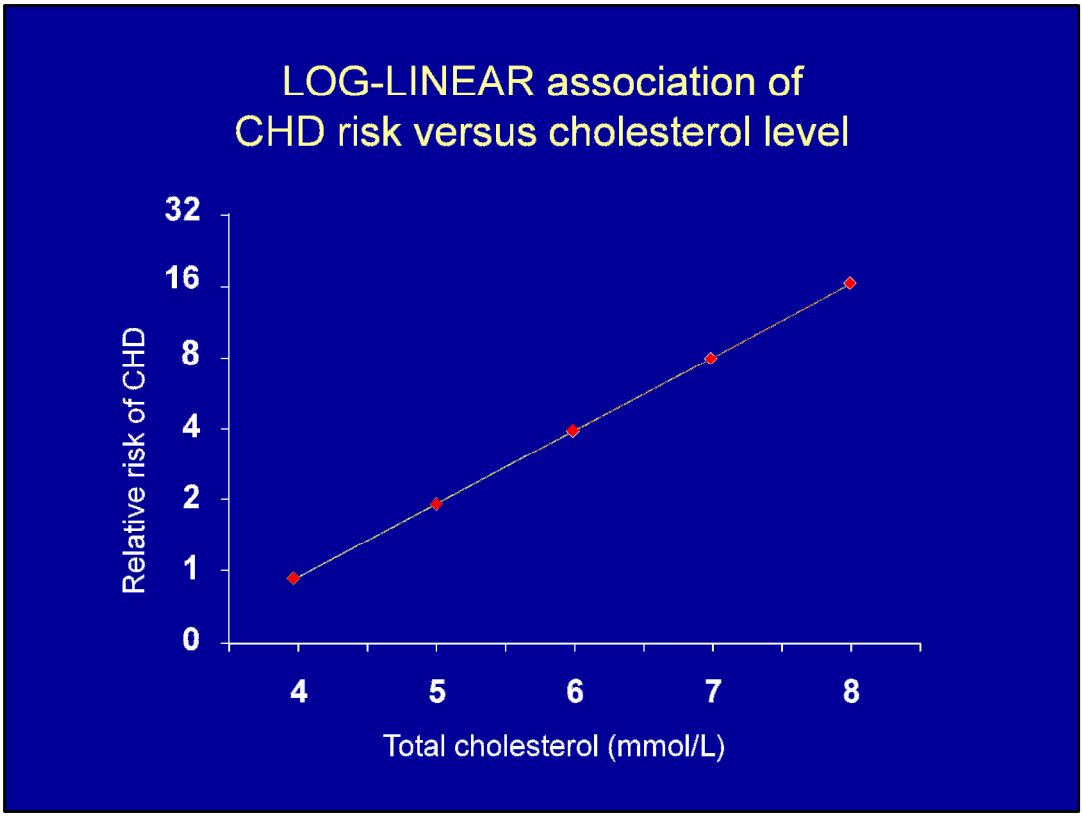
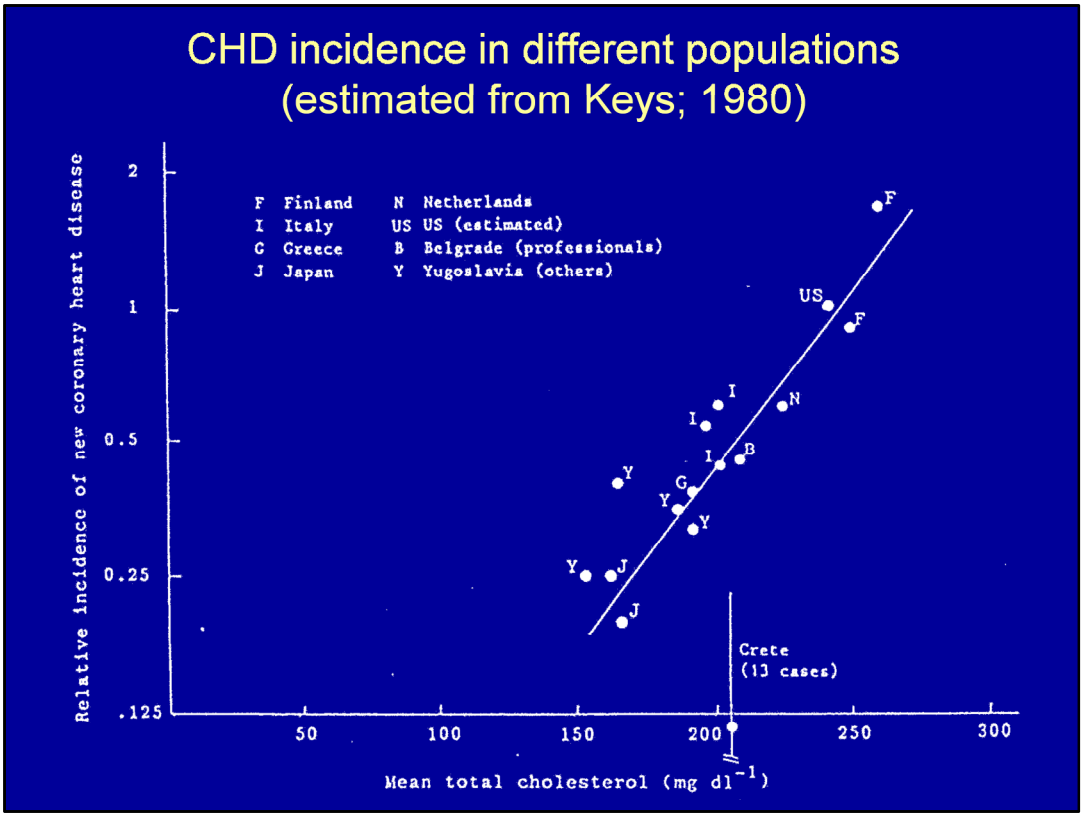


Slides 1 and 2:

These two "illustrative" slides (based on notional data) were used in my presentation to Dr Godlee at our meeting on 2 December 2013 to show that, if the risk of coronary disease (CHD) is plotted on a standard vertical axis (slide 1), there is an impression of a flat portion at lower cholesterol levels and then the curve gets steeper at higher levels, which might be mis-interpreted as cholesterol only being an important risk factor at higher levels. So, for example, Malhotra states in his article that *"75% of these patients [admitted with acute myocardial infarction] have normal total cholesterol concentrations"*

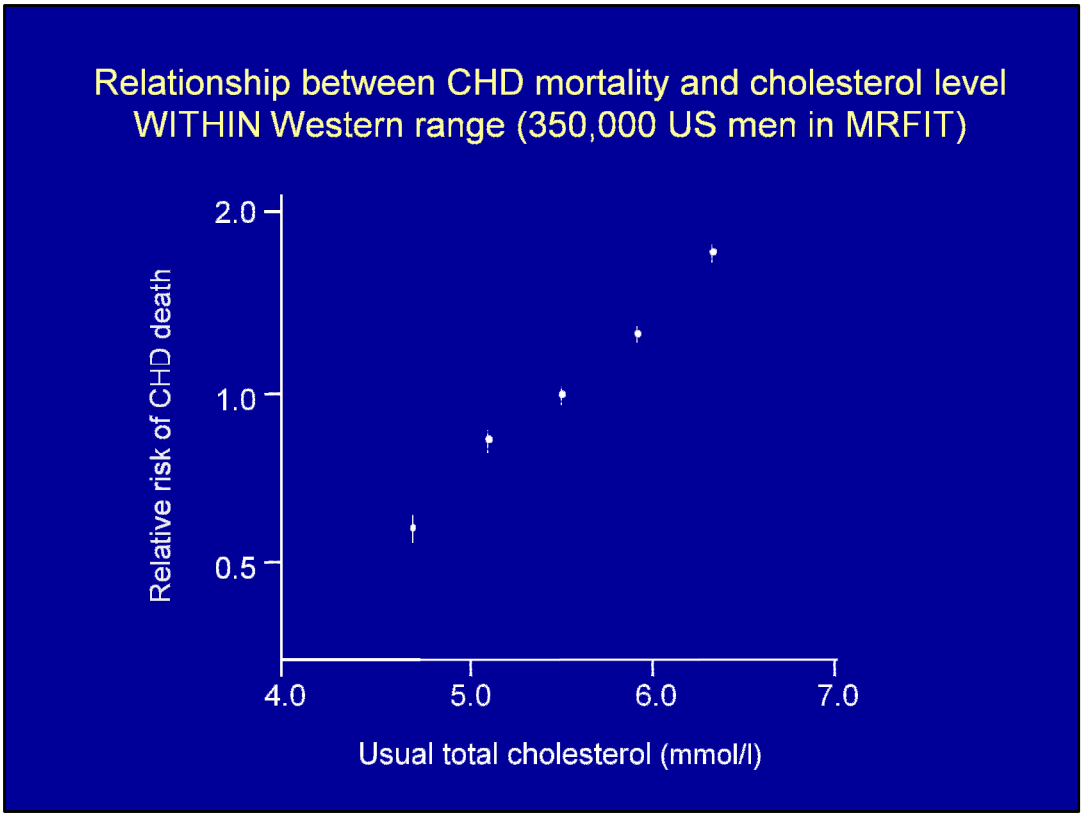


However, if instead, CHD risk is plotted on a doubling scale (as in slide 2) then there is a straight line "log-linear" relationship between risk and cholesterol level throughout the cholesterol range studied. The implications of this observation are that the same absolute difference in cholesterol is associated with the same proportional difference in CHD risk. That is, each 1 mmol/l lower total cholesterol is associated with about a halving in risk irrespective of whether the difference is, for example, between 8 and 7 mmol/l or between 5 and 4 mmol/l (and perhaps even lower: see subsequent slides).

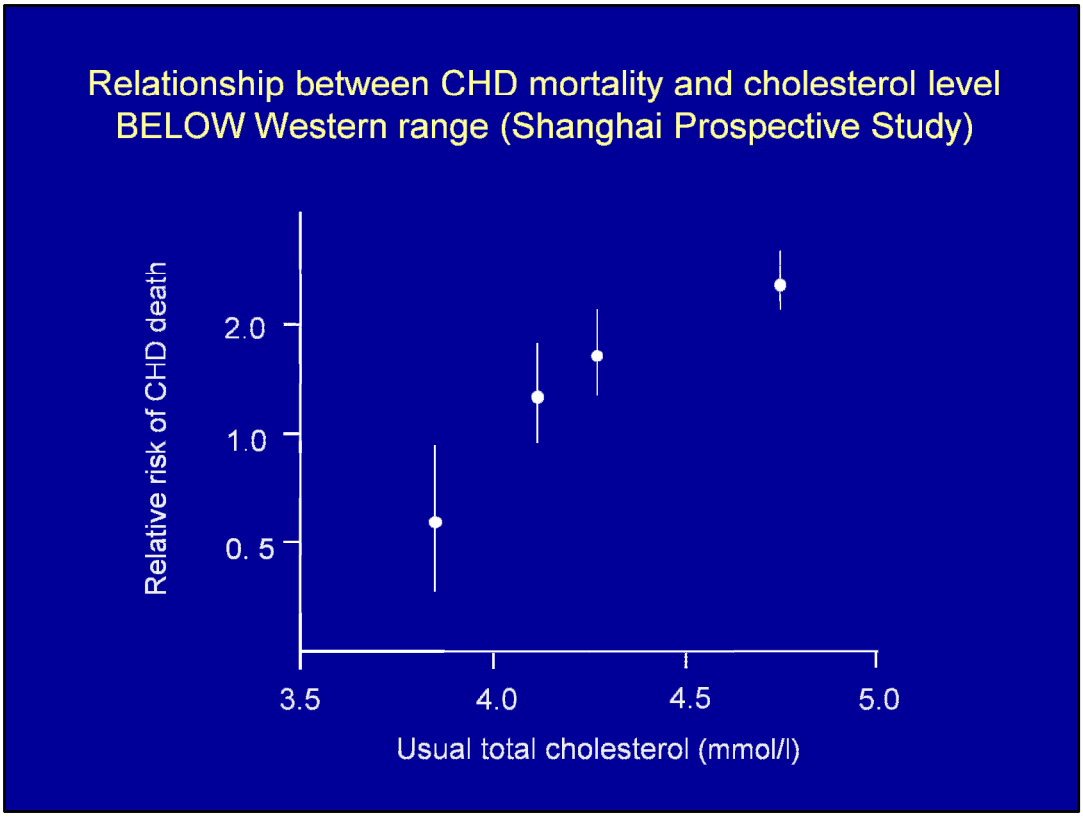


These are the Ancel Keys data referred to in the Malhotra paper, plotted with a doubling scale on the vertical axis for CHD mortality risk. As in the previous slide that used notional data, this figure indicates that there is an approximately log-linear association between the levels of CHD risk and total cholesterol in different countries. (Note that to convert mg/dl to mmol/l, the values should be divided by about 40; i.e. 160 mg/dl is about 4 mmol/l and 240 mg/dl is about 6 mmol/l.)

However, there are differences other than cholesterol levels between different populations which limit the inferences that can be drawn from such ecological comparisons. The results shown in the next two slides have the advantage that they relate to the risk/cholesterol associations within (rather than between) populations.

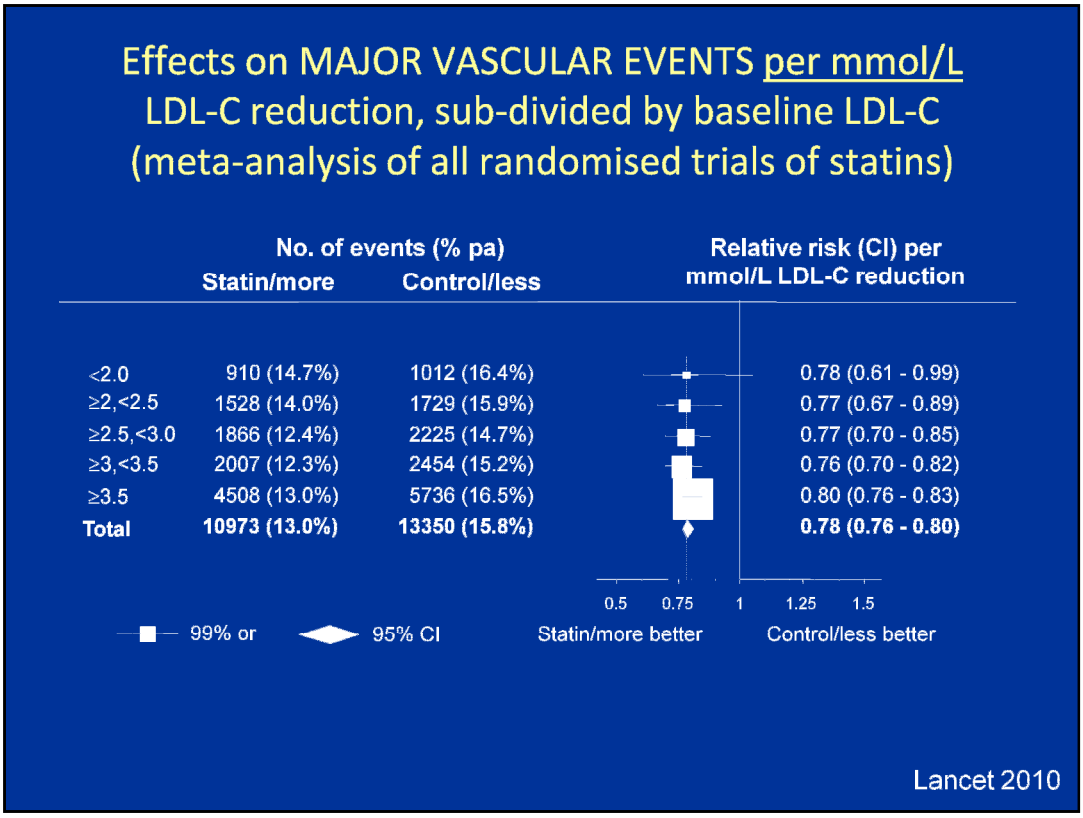


Among 1/3 of a million middle-aged US men, the MRFIT screening survey also demonstrates an approximately log-linear association between the risk of CHD death and total cholesterol level, with a 1 mmol/l difference associated with about a 2-fold difference in risk throughout the cholesterol range studied.



And the Shanghai Prospective Study shown on this slide indicates that this approximately log-linear association continues down below the Western range for cholesterol. These data, along with meta-analyses of observational studies of the associations of blood cholesterol with CHD conducted by the Prospective Studies Collaboration and the Emerging Risk Factors Collaboration, contradict the following strange claim in the paper by Malhotra:

"Despite the common belief that high cholesterol is a significant risk factor for coronary artery disease, several independent population studies in healthy adults have shown that low total cholesterol is associated with cardiovascular and non-cardiac mortality, indicating that high total cholesterol is not a risk factor in a healthy population."



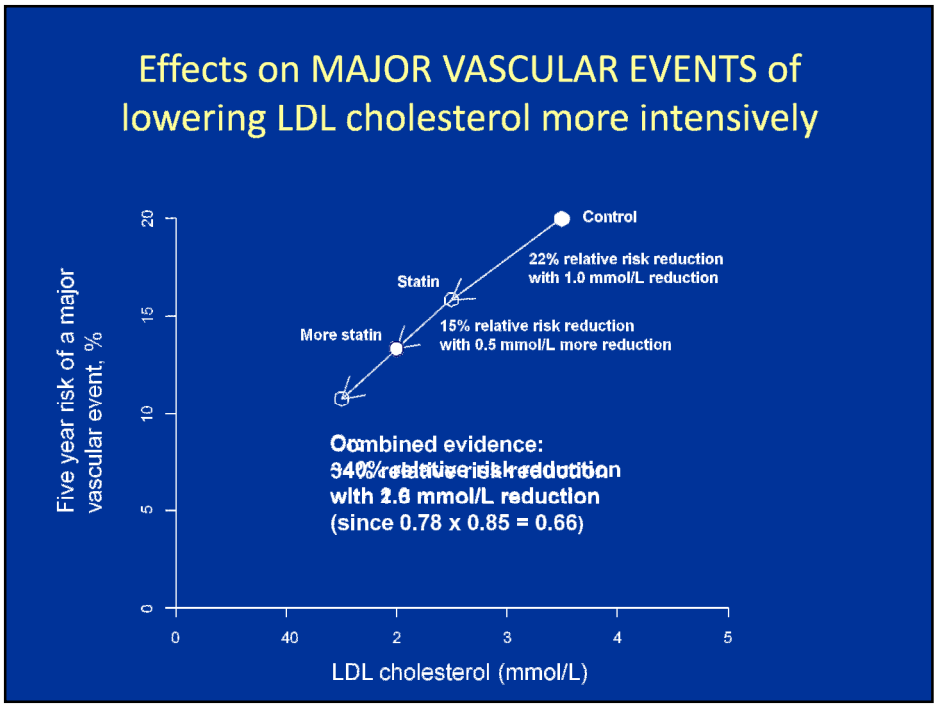
Consequently, based on the observational epidemiology (i.e. slides 3-5), it should be expected in randomised trials of cholesterol-lowering statin therapy that the same absolute reduction in LDL-cholesterol level would produce the same proportional reduction in risk irrespective of the starting cholesterol level.

Indeed, that was one of the pre-specified hypotheses of the MRC/BHF Heart Protection Study (HPS) randomised placebo-controlled trial of simvastatin 40mg daily versus placebo for an average of about 5 years in 20,000 UK patients with a history of occlusive vascular disease. HPS did find that there was a similar proportional reduction in the risk of major vascular events per mmol/l reduction in LDL cholesterol among patients with higher or lower starting cholesterol levels.

This slide shows that that HPS finding was reinforced by the results of the CTT meta-analysis published in The Lancet in 2010. The trials of statin versus control showed that lowering LDL-cholesterol lowered the risk of major vascular events irrespective of the starting LDL-cholesterol level (as had been anticipated from the observational epidemiology: see slides above) and the trials of more intensive statin therapy versus less intensive statin therapy showed that a further reduction in LDL-cholesterol was associated with a further reduction in vascular disease risk (again as anticipated from the observational epidemiology).

Hence, the statement in the paper by Malhotra, that *"all patients after a myocardial infarction are prescribed maximum dose treatment irrespective of total cholesterol, because of statin's anti-inflammatory or pleiotropic (coronary plaque stabilising) effects"* is thoroughly misleading.

So too is the subsequent statement *"The fact that no other cholesterol lowering drug has shown a benefit in terms of mortality supports the hypothesis that the benefits of statins are independent of their effects on cholesterol".* In fact, meta-analyses of the randomised

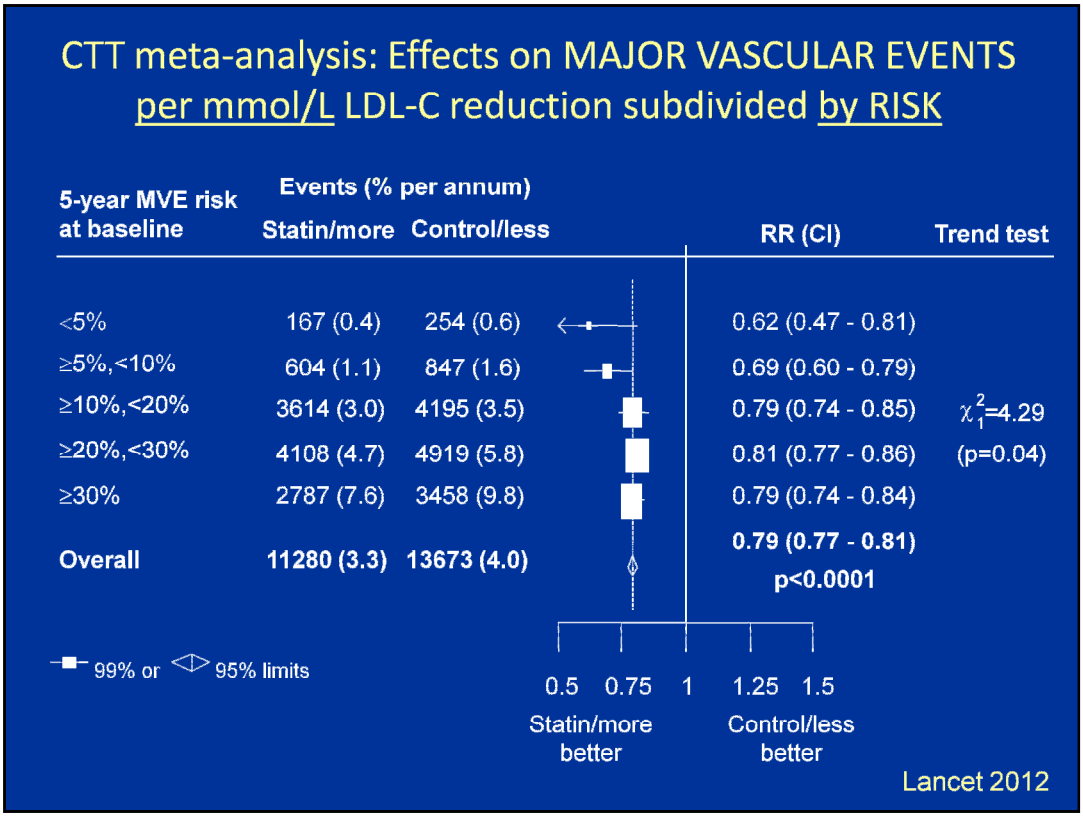


This slide summarises the average effects seen in the CTT meta-analysis of the randomised placebo-controlled trials of allocation to statin versus no statin therapy (22% reduction in risk with a 1.0 mmol/l reduction in LDL-cholesterol) and of allocation to more versus less intensive statin therapy (15% further reduction in risk with a 0.5 mmol/l further reduction in LDL-cholesterol).

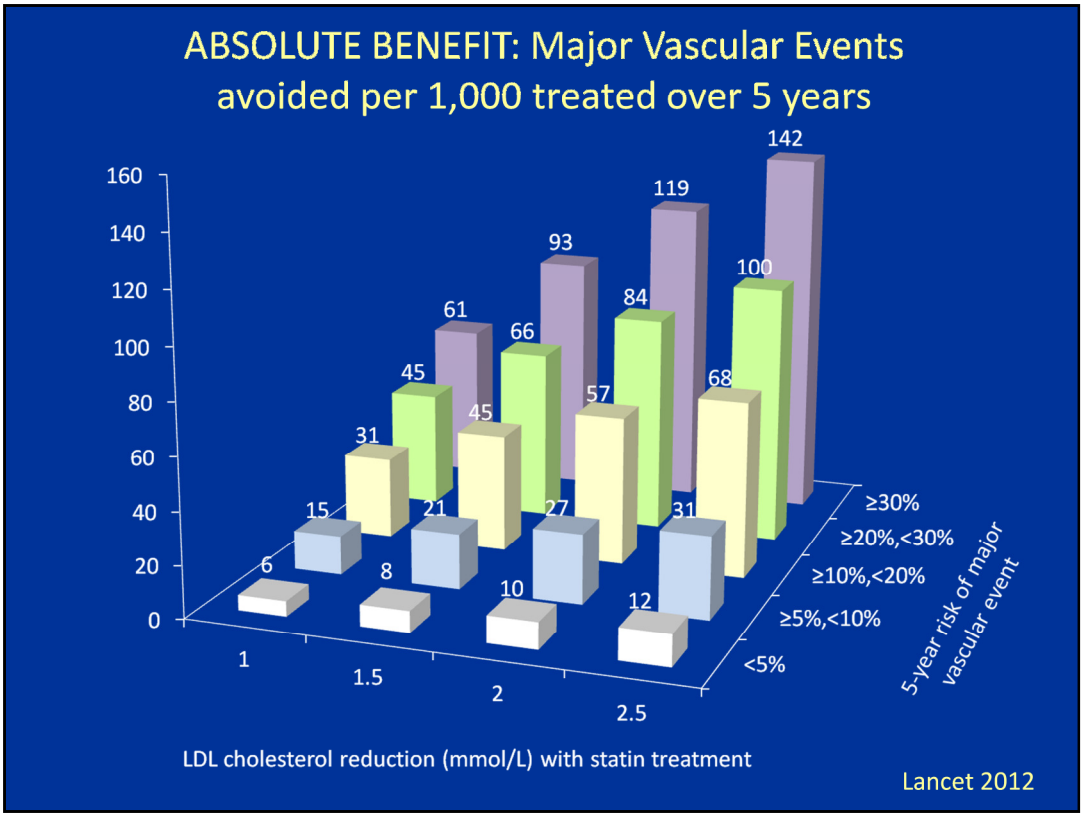
Given that these are multiplicative effects, the combined reduction is provided by the multiple of the odds ratios in each set of trials: i.e. odds ratio of 0.66 is a 33% reduction in risk with a 1.5 mmol/l reduction in LDL-cholesterol.

However, these “intention-to-treat” analyses of the differences in risk between all those patients allocated statin/more statin therapy (irrespective of whether they took it) versus all those allocated placebo/less statin (irrespective of whether they started non-study statin) tend to under-estimate both the reductions in LDL-cholesterol and the reductions in risk that can be achieved by actually taking the treatment allocated in the trial.

Consequently, if intensive statin therapy (e.g. generic atorvastatin 40mg daily) was taken and LDL-cholesterol was reduced by 2 mmol/l then the trials indicate that risk would be reduced by about 40% (as indicated in the Discussion of the 2010 and 2012 CTT Lancet papers).



This slide from the CTT Lancet 2012 paper (it is the bottom section of Figure 2) shows that the proportional reduction in the risk of major vascular events was at least as big among lower risk patients as among those at higher risk. The effects on major vascular events in various subgroups and on components of major vascular events were provided in the webfigures of that paper (but those results seem to have been overlooked – given the decision by Abramson et al to miscalculate the results for total mortality from Figure 3 despite them being provided in the web appendix – when commenting on the CTT report in their paper).



The results in the CTT Lancet 2012 paper are chiefly given as risk reductions per mmol/l reduction in LDL-cholesterol. However, this slide from the CTT Lancet 2012 paper (it is the top section of Figure 5) shows the absolute risk reductions predicted from the meta-analyses with different absolute reductions in LDL-cholesterol. As pointed out at the beginning of the Discussion of that paper (and in greater detail in the previous Lancet 2010 paper), *"Modern statin regimens, however, can often reduce LDL cholesterol by more than 1 mmol/L, which would yield even larger absolute reductions in major vascular events".* For example, the Lancet 2010 paper discusses the potential for reductions in LDL cholesterol of 2-3 mmol/l, which would yield absolute reductions at least twice as big as the risk reductions per mmol/l.

However, both Abramson et al and Malhotra misleadingly calculate the numbers needed to treat (NNT) to prevent one event based on the per mmol/l reductions. For example, in the 2nd paragraph of the second page of the Abramson et al paper, it is stated that *"140 low risk people must be treated with statin for five years to prevent one major coronary event or stroke"* (with a similar claim in the box). This is misleading as it is based on the effect per mmol/l rather than on the effect that can typically be achieved with standard statin regimens (and no related caveat is provided in the text).

HPS: Muscle symptoms in 5-year treatment period; ever or with treatment stopped

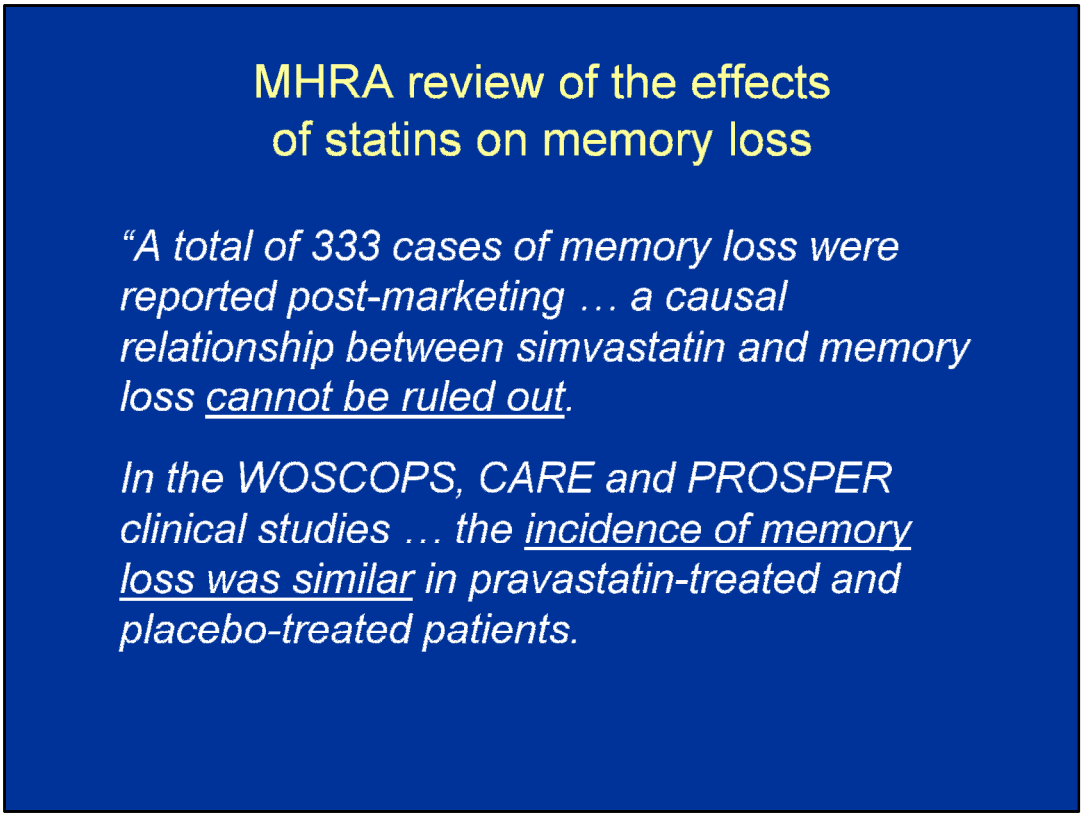
Muscle pain or weakness	SIMVASTATIN (10,269)	PLACEBO (10,267)	P-value
Ever reported	3380 (33%)	3410 (33%)	NS
Stopped tablets	49 (0.5%)	50 (0.5%)	NS

Both Abramson et al and Malhotra compare rates of myopathy as defined in the paper referenced (Armitage. Lancet 2007) in the CTT Lancet 2012 paper as muscle symptoms plus blood creatine kinase levels >10 x upper limit of normal versus reported rates from observational studies of musculoskeletal symptoms of any severity in Buettner et al (Abramson et al) or of statin-related adverse events, about 40% of which were myalgia, in Zhang et al (Malhotra). In doing so they conclude that:

Abramson et al: *"In absolute terms, this increase in muscle pain is 100 times greater that that reported in clinical trials…."*

Malhotra: *"unacceptable side effects… in 20% of participants… This is massively at odds with the major statin trials that report significant side effects of myopathy in only one in 10,000 "*.

In HPS, information was explicitly sought by the study nurses about all episodes of muscle pain or weakness that had occurred since the previous visit and, when such symptoms were reported, creatine kinase levels were measured. This slide was used to show that the reported rates of muscle pain of weakness were at least as high as in the observational studies, with about one third of patients reporting such symptoms at some time during the 5-year treatment period, but with no difference in rates between the patients allocated statin therapy and those allocated placebo tablets.



In 2009, the MHRA had issued a review of potential adverse events to add to the data sheet of the statins. This slide summarised some of the statements in that report for one category of adverse events being considered: memory loss.

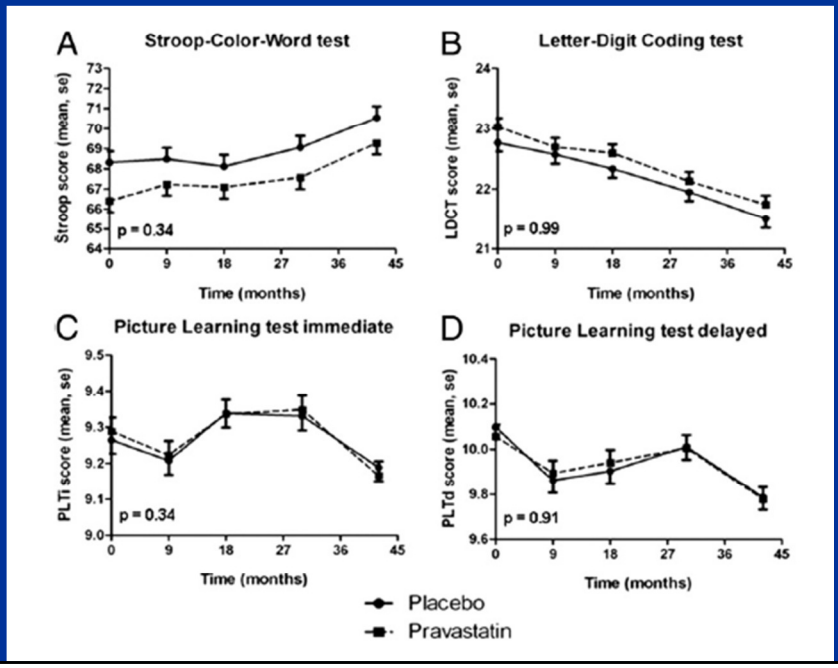
HPS: Cognitive impairment (TICS-m <22/39) at final follow-up visit (Lancet 2002)

Age (years) at randomisation	Simvastatin (8086)	Placebo (7834)
<65	17.1%	17.8%
65<70	25.8%	25.4%
70+	34.6%	36.2%
ALL PATIENTS	23.7%	24.2%

Comparing treatment groups: P-value = 0.4

This slide showed that, although the TICs-m test of cognitive function (which includes a memory component) was sensitive to changes associated with age in the HPS trial, there was no evidence of any difference between the patients allocated statin therapy and those allocated placebo tablets (even among the 6,000 who were aged 70+)

PROSPER: Effects of pravastatin on cognitive function in 5804 randomised participants aged 70-82 years (Trompet et al; J Neurol 2010)



The PROSPER trial was set up specifically to test statin therapy in the elderly and included similar numbers to HPS of patients aged over 70 at the start. It assessed cognitive function particularly carefully, with a battery of tests and repeated measures throughout the study, but it too found no adverse effects of statins (with the trends for the different measures shown in this slide generally in favour of active treatment). These results contradict the claims by Abramson et al that careful assessment of cognitive measures has not been conducted in randomised trials.

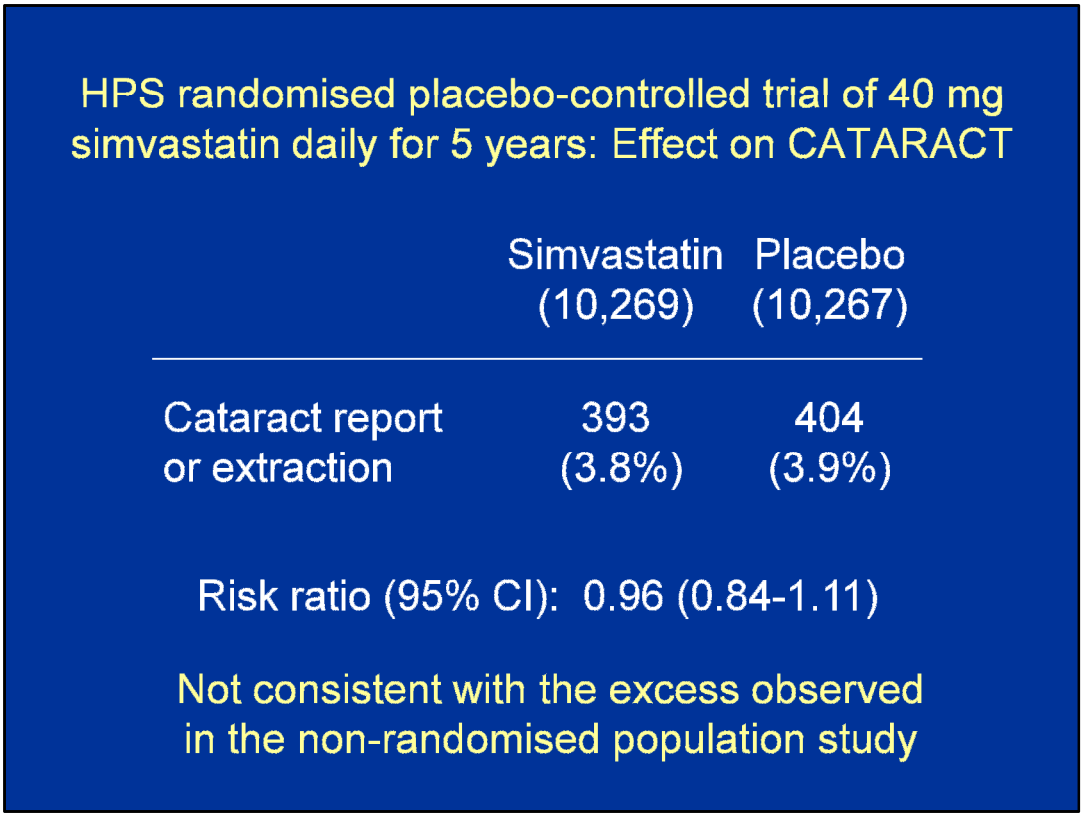
Non-randomised population study: Estimated effects of 5 years of statin therapy in men aged 35-74 with 10 year CV risk ≥20% (Hippisley-Cox; BMJ 2010)

Outcome	HR (95% CI)	NNT/NNH (95% CI)
CV events	0.76 (0.67 to 0.86)	-33 (-57 to -24)
Cataract	1.32 (1.26 to 1.37)	52 (44 to 63)
Myopathy	6.15 (5.19 to 7.30)	91 (74 to 112)
Liver dysfunction	1.53 (1.42 to 1.66)	142 (115 to 180)
Acute renal failure	1.61 (1.39 to 1.87)	346 (245 to 539)

Based on average of only 2.5 years of statin exposure and partial adjustment for potential confounders

The purpose of this slide was to consider some of the associations reported recently from non-randomised observational studies which had been referred to by Abramson et al (see section labelled “Known harms” and subsection “Others”, which references this study, and the box “What low risk patients need to know”).

In the observational study shown in this slide, the outcomes were identified through linkage to health records. The outcome of cataract was chosen for consideration because the reported “number needed to harm” (NNH) based on the association in that study was small and similar in magnitude to that of the NNT for CV events. A hazard ratio of 1.32 for cataract with 95% CI of 1.26 to 1.37 was reported in this hypothesis-generating non-randomised study.



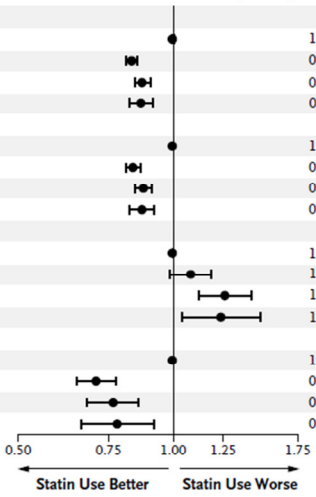
The HPS trial was then used to test the hypothesis that had been generated by the observational study shown in the previous slide. As can be seen, there was no excess of cataract reported among the patients allocated statin therapy for 5 years (i.e. twice as long as the exposure in the observational study), and the 95% confidence interval (CI) of 0.84 to 1.11 excluded an effect of the magnitude suggested by the association in the observational study.

This suggests that residual confounding, or other systematic differences between the patients taking a statin and those who were not, remained in the analyses of this observational study. The recently published meta-analysis of observational studies by Macedo et al (BMC Medicine 2014), which included this study, also found no excess of cataract associated with statin use.

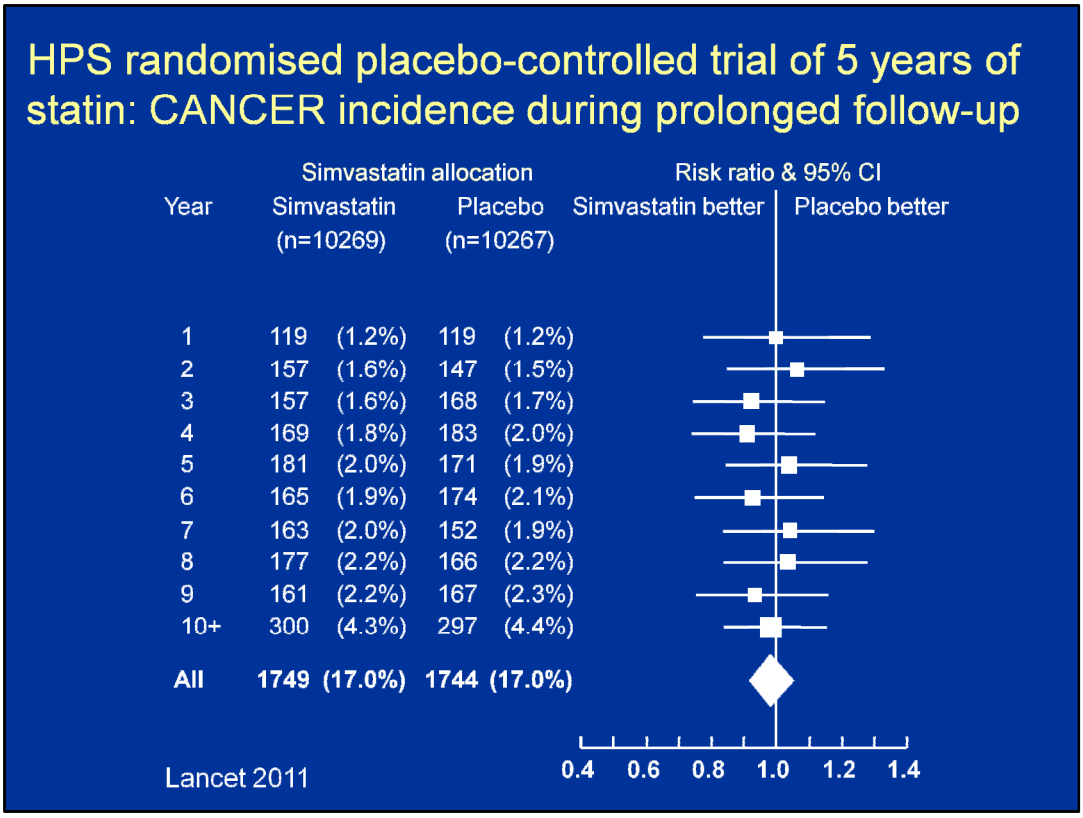
Danish population study: Statin use associated with reduced cancer-related mortality (Nielsen et al, NEJM 2012)

A Nationwide Study

Cause of Death and Statin Dose	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Any cause				
0.00	277,204	184,895	1.00	
0.01–0.75	9,780	5,730	0.82 (0.81–0.85)	<0.001
0.76–1.50	6,181	3,438	0.87 (0.83–0.89)	<0.001
>1.50	2,760	1,531	0.87 (0.81–0.91)	<0.001
Cancer				
0.00	277,204	153,327	1.00	
0.01–0.75	9,780	4,680	0.83 (0.81–0.86)	<0.001
0.76–1.50	6,181	2,810	0.87 (0.83–0.91)	<0.001
>1.50	2,760	1,250	0.87 (0.81–0.92)	<0.001
Cardiovascular cause				
0.00	277,204	13,512	1.00	
0.01–0.75	9,780	529	1.08 (0.99–1.19)	0.08
0.76–1.50	6,181	314	1.25 (1.21–1.41)	<0.001
>1.50	2,760	134	1.24 (1.03–1.48)	0.01
Other cause				
0.00	277,204	18,056	1.00	
0.01–0.75	9,780	521	0.70 (0.64–0.77)	<0.001
0.76–1.50	6,181	314	0.76 (0.68–0.86)	<0.001
>1.50	2,760	147	0.77 (0.66–0.92)	0.003

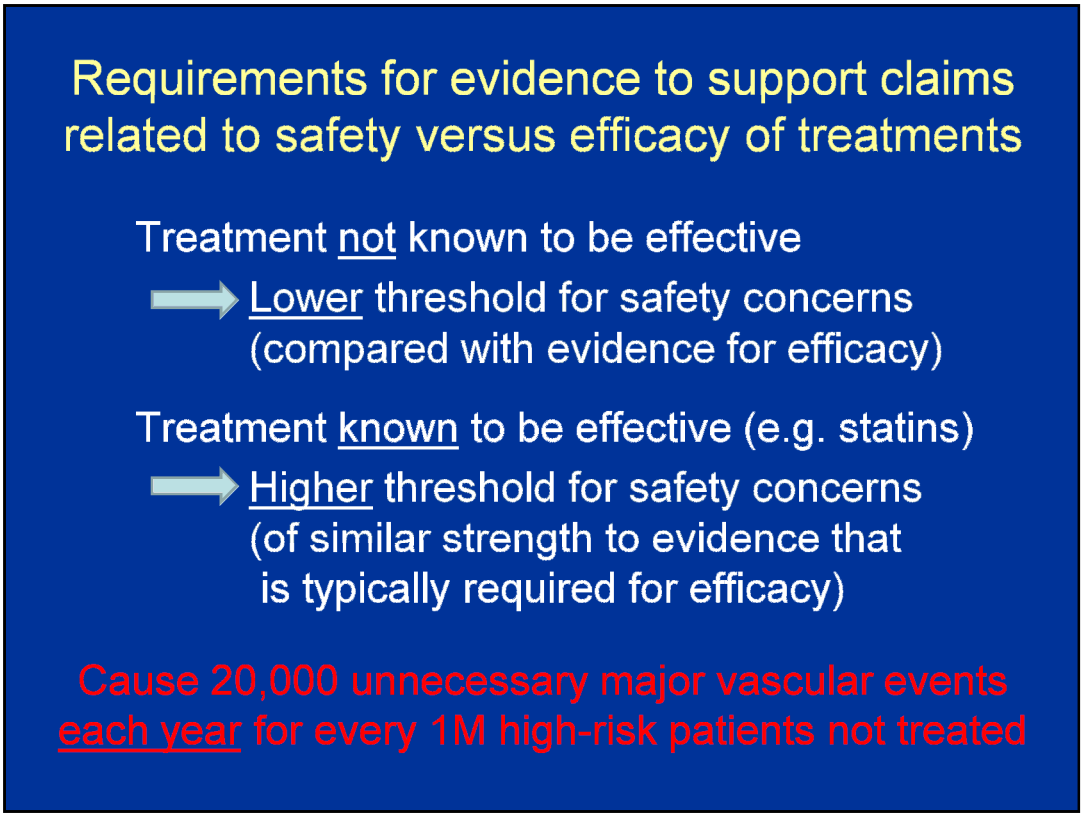


Another observational study was considered in which it had been observed that cancer-related mortality was lower among patients who were taking statin therapy than those who were not. By contrast, mortality from cardiovascular causes was higher among the patients taking a statin than among those who were not, which (given the reliable evidence for reductions in this outcome from large individual randomised trials and from extremely large meta-analyses of such trials) indicated that there was substantial confounding or some other sources of systematic differences between these two groups of patients or in their outcome assessment.



This slide then showed that the apparent reduction in cancer mortality in the observational study shown on the previous slide was not supported by the evidence for cancer incidence from extended follow-up through linkage to health records and direct follow-up with participants for more than 10 years (5-year treatment period plus 5-year post-treatment period) in the HPS trial.

Nor was there any effect on cancer mortality or site-specific cancer incidence, based on large numbers in the CTT meta-analysis of all of the randomised-controlled trials of statin versus control and more versus less statin included in the Lancet 2010 report (Figure 6).



The purpose of this final slide was to make the point that when it is not known that a treatment is effective at reducing the adverse outcomes at which it is targeted then it is reasonable to have a lower threshold for safety concerns than would be required to demonstrate efficacy.

However, when it is known reliably that a treatment does reduce the adverse outcomes at which it is targeted (as is the case with the definite evidence that statins lower the risk of heart attacks, ischaemic strokes, revascularisations and vascular deaths) then a higher threshold is required to demonstrate safety concerns (i.e. equivalent to that required for demonstrating efficacy) since misleadingly persuading patients to stop effective treatment, or not start it, would cause harm.

It was clear that such an approach had not been adopted either by Abramson et al or by Malhotra in their claims about the magnitude of the rate of side-effects caused by statins. If such misleading claims about side-effects were to result in 1M high-risk patients around the world not taking statin therapy, it was estimated (based on the evidence from the randomised trials) that this would cause about 20,000 major vascular events each year.