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Statins for the Prevention of Coronary Events

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Summary

Description of proposed service

The service evaluated in this review is the use of atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin for the prevention of cardivascular events.

Epidemiology and background

Cardiovascular disease is one of the major causes of premature death in the United Kingdom (UK), accounting for 35% of premature deaths in men and 27% in women. It is also a significant cause of morbidity.

The three major manifestations of cardiovascular disease are:

- coronary heart disease (CHD), including myocardial infarction (heart attack) and angina
- cerebrovascular disease (transient ischaemic attack and stroke)
- peripheral arterial disease (obstruction of the arteries carrying blood to the legs or, less commonly, the arms).

A number of risk factors for coronary heart disease have been identified; these include hyperlipidaemia. Some of these risk factors (e.g. smoking, obesity, and hypertension) can be modified, treated or controlled. Others (e.g. age, sex and ethnicity) cannot. Cholesterol lowering is only one of a number of methods of reducing the risk of coronary heart disease. CHD risk can also be reduced by changes in life style, such as smoking cessation, exercise and the use of cholesterol-lowering diets along with non-cholesterol drug treatments, including aspirin and anti-hypertensives. The cost-effectiveness of statins must be seen in the context of these other interventions.

Number and quality of studies, and direction of evidence

Thirty-one randomised studies were identified which compared a statin with placebo or with another statin, and which reported clinical outcomes. Meta-analysis of the available data from the placebo-controlled studies indicates that, in patients with or at risk of cardiovascular disease, statin therapy is associated with a reduced relative risk of all-cause mortality, cardiovascular mortality, CHD mortality and fatal myocardial infarction (MI), though not of fatal stroke. It is also associated with a reduced relative risk of morbidity (nonfatal stroke, nonfatal MI, transient ischaemic attack, unstable angina) and of coronary revascularisation. It is not possible, on the evidence available from the placebo-controlled trials, to differentiate between the clinical efficacy of atorvastatin, fluvastatin, pravastatin and simvastatin. There is, however, no evidence from randomised controlled trials (RCTs) for the effectiveness of the 10mg over the counter dose of simvastatin in preventing clinical events.

No relevant studies of rosuvastatin were identified which reported clinical outcomes. Thus, although there is RCT evidence to suggest that rosuvastatin is more effective than atorvastatin, pravastatin and simvastatin in reducing both total and LDL cholesterol, it is not possible to prove that these reductions translate into comparable reductions in clinical events.

There is limited evidence for the effectiveness of statins in different subgroups. There is no evidence that statins differ in their effectiveness in primary compared with secondary prevention,

in women compared with men at a similar level of cardiovascular risk, in people with diabetes compared with those without, or in people aged 65 and over compared with those younger than 65. In renal transplant patients, statin therapy is associated with a reduced risk of CHD death or nonfatal MI. However, no benefit has been demonstrated in cardiac transplant patients. For ethical reasons, no placebo-controlled trials have been carried out in patients with familial hypercholesterolaemia. The only randomised trial in this group therefore compared two statins, and found no significant difference between them. People from the Indian subcontinent are known to be at increased risk of cardiovascular disease. However, no placebo-controlled studies were found which studied the clinical effectiveness of statins in this population.

Safety

Although concerns have been raised about rosuvastatin, statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by post-marketing surveillance data. Although increases in creatine kinase and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a time-span remains unproven.

Summary of cost effectiveness evidence

Review of existing cost effectiveness literature

A review was undertaken to identify and evaluate studies exploring the cost effectiveness of statins in primary and secondary prevention of CHD and CVD in the UK. Electronic literature searches identified 206 potentially relevant publications. Of these only five UK studies satisfied all inclusion and exclusion criteria and formed the basis of the review. These studies were assessed for quality using components of the BMJ and Eddy checklists. All scored well on modelling methodologies and presentation of results. Twelve non-UK cost-effectiveness studies were retained to inform on methodological issues for use in the ScHARR cost-effectiveness model.

Comparison of the results of the UK was difficult due to the different objectives, populations and costings used. All studies reported on cost per Life Year gained (LYG) rather than cost per Quality-Adjusted life year (QALY). Four of the five studies had similar results in primary prevention treatment, results varied between £8,000 (k) and £30 k depending on baseline risk. One study estimated cost-effectiveness at £136 k which appears anomalous compared to the other studies. Cost-effectiveness in secondary treatment was estimated in two studies and ranged from £6 k to £40 k.

As part of their industry submissions to NICE, Pfizer, Novartis, Bristol-Myers Squibb and Astra Zeneca presented cost-effectiveness models. These were critiqued using the combined BMJ and Eddy framework. Of the four models submitted, two (Pfizer/Astra Zeneca) used the surrogate endpoint of cholesterol lowering for predicting reductions in clinical endpoints and two (Novartis/BMS) used trial evidence on reductions in clinical endpoints. The time horizon in the four models varied between 5 years and lifetime. Of the two models using surrogate outcomes the results are similar in primary treatment, with estimated cost per QALYs below £10k. In the Pfizer model (atorvastatin), the results suggest little difference in cost-effectiveness between primary and secondary treatment, whilst in the Astra Zeneca model (rosuvastatin) treatment is reported to be less cost-effective in secondary treatment. Novartis evaluate fluvastatin for the prevention of

cardiac events following PCI, with an estimated cost per QALY at £3.2k. BMS evaluate pravastatin in CHD/CVD prevention. In secondary treatment pravastatin dominates in the basecase and in primary prevention at an average baseline risk of 15% seen the cost per LYG is around £5k-£8k. The within trial economic analysis of simvastatin by MSD produced results in secondary prevention of a similar magnitude to the Novartis and Pfizer evaluations. Overall, considering the differences in techniques and objectives, the results could be considered to be of a similar order of magnitude for both primary and secondary prevention. The exception is perhaps the secondary prevention results for rosuvastatin which are markedly higher than the other evaluations.

ScHARR model

A Markov model has been developed to explore the costs and health outcomes associated with a lifetime of statin treatment using a UK NHS perspective. Data from UK epidemiological studies are used to inform event rates and are combined with results from the meta-analysis of RCT evidence on the effectiveness of statins to model the relative risk reductions of event rates for patients on statin therapy. Input parameters are assigned probability distributions to reflect their imprecision and Monte Carlo simulations are performed to reproduce this uncertainty in the results. Results are presented in terms of quality-adjusted life years (QALY) for both primary and secondary prevention of CHD/CVD events. Costs are at 2004 prices and discount rates of 6% and 1.5% are applied to costs and health benefits respectively.

The model utilises a cohort of 1,000 patients at a specified annual risk of a CHD event. The model is run separately for each age group, sex and risk level. Patients progress through the model from the chosen starting age until they either die or reach the age of 100 years.

For the primary prevention analyses, all patients commence the evaluation in the event free health state. During each annual cycle of the model, a proportion of patients enter one of the qualifying event health states: MI, stable angina, unstable angina, CHD death, TIA, stroke, CVD death or death through other causes while the remainder remain in the event free state. For the secondary prevention analyses all patients commence in either post MI, post stable angina, post unstable angina, post TIA or post stroke health states. In each subsequent cycle, patients in a non-fatal health state may move to a subsequent event state, die through CHD or CVD or other causes, or remain in the same state.

The probability of a patient moving between health states depends on both the current health state and age. The model cycles annually with patients moving between health states until all patients have entered a fatal health state or reached 100 years when it is assumed that all patients will die.

The basecase analysis considers the cost effectiveness of statins for a population with CHD or at risk of CHD, taking into account CHD outcomes only. This complies with the scope specifically requested by the Department of Health to only consider coronary heart disease. Two further scenarios were explored to take into account the growing evidence on the impact of statins on reducing stroke events. Scenario 1 is as the basecase but also takes into account the potential of statins to reduce stroke events in patients with a history of CHD. Scenario 2 explores the costs and benefits associated with statin treatment in reducing CVD events for patients with or at risk of CVD, with all patients entering the treatment arm of the model assumed to receive benefits associated with statin treatment.

Assumptions

UK specific incidence rates have been used to ensure patients entering the model match the likely distribution of events in the UK. Incident rates for primary CHD events are taken from the Bromley Coronary Heart Disease Register, TIA and stroke from the Oxfordshire Community Stroke Project.

The cohort of patients in each primary prevention analysis start at a selected annual CHD risk. As the ratio of CHD to CVD risk changes by age and sex, the corresponding CVD risk was calculated using published algorithms. The incidence rates were combined with the respective chosen CHD and corresponding calculated CVD annual risks to model the probability of a primary CHD or TIA/stroke event. In addition, as the risk of CHD and CVD increases naturally by age over time, for patients remaining in the event free state it was assumed that their risk and thus the probability of a primary event increased during the analyses.

Published UK prevalence rates are used to distribute patients to initial health states for the secondary prevention evaluations. For angina, MI and stroke these are taken from the British Heart Foundation Statistics Database while evidence from Bots et al is used to inform prevalence rates for TIA.

UK specific data is used wherever possible to ensure event rates match the likely distribution in the UK. Two main sources have been used: with the exception of stable angina, for patients with a primary CHD event, the occurrence of further MIs, strokes and vascular deaths are derived from patients on the Nottingham Heart Attack Register (NHAR) while the probabilities of subsequent strokes and vascular deaths for patients with a history of a stroke are derived from patients on the South London Stroke Register (SLSR). TIA transitions are taken from a study by Rothwell et al. Stable angina transitions were taken from Juul-Mohler et al, a double blind comparison of aspirin with placebo in patients with a history of chronic stable angina without a previous MI. To account for the proportion of patients dying from non-vascular causes, interim life tables published by the UK Government Actuary Department, were adjusted using the applicable deaths cited in the national mortality statistics for England and Wales.

The benefits associated with statin treatment are modelled by applying the relative risks observed from meta-analysis of statin RCTs to the events predicted in the model. Given that trials of rosuvastatin report only on the intermediate endpoint of cholesterol lowering and there is currently no direct trial evidence of the effect of rosuvastatin on morbidity and mortality, the ScHARR model has also been adapted to calculate the risk of CHD (morbidity and mortality) using a Framingham risk equation. There are, however a number of issues concerning the estimation of cost-effectiveness when using Framingham equations in modelling the link between cholesterol lowering and CHD risk.

Costs of health states were based on a review of published evidence to obtain the most recent and appropriate costs. First year costs and subsequent year costs are assigned for each of the different health states modelled. The annual cost of statins is a weighted average cost for all statins, (weighted by the trial evidence) for different statins at different dosage. The costs of liver function test, cholesterol tests and creatinine kinase test are included in the analysis. Given that statins have a good safety profile, and adverse events are rare, costs of managing adverse events are not modelled.

The utility of the general population is assumed to vary by age, based on data from Kind and Dolan using the EuroQol EQ-5D questionnaire. A literature review has been undertaken in order to identify utility estimates for health states within the model. These have been used as multipliers

to adjust the age-related utility of the general population following an event. It is assumed that there is no disutility for patients on statins.

Results- basecase analysis

The cost effectiveness of statins depends on the CHD risk in the population treated and the age and sex of the population under consideration. Cost effectiveness results are presented for males and females at ages 45 to 85 in 10 year age bands.

In secondary prevention the cost per QALY is estimated to vary between around £10 k and £17 k between age 45 and age 85, with ICERs increasing with age but with little difference between males and females. These results are sensitive to the modelling time frame and to the discount rates. The results of probabilistic sensitivity analysis show that, using a threshold of £20 k per QALY, statin therapy is cost effective for all patients with a history of CHD.

In primary prevention the estimated ICERs vary according to risk level and age. The estimated average ICER by risk level rises from around £20 k to £28 k for men between 3% and 0.5% CHD risk and between £21 k and £57 k for women. There is however significant variation by age within risk levels. At an annual CHD risk of 3%, the estimated cost per QALY ranges from £10 k to £37 k for males and from £14 k to £48 k for females between the ages of 45 and 85. At aged 85 the estimated cost per QALY rises from £37 k (£48 k) for males (females) at 3% CHD risk, to around £105 k (£111 k) for males (females) at 0.5% CHD risk.

Results - alternative scenarios

Alternative scenarios have also considered the cost effectiveness in statins in the wider context of CVD risk and outcomes. For scenario 1 (CHD analysis with CVD outcomes) the ICERs are similar to the basecase results (CHD analysis). For scenario 2 (CVD analysis) the ICERs are substantially lower than the basecase results due to the additional impact of exploring the effect of statin treatment on reducing stroke and TIA events for all patients.

Limitations of cost-utility estimates

One of the major limitations of the analyses is the requirement to extrapolate well beyond the timeframe of the trial period. This period of extrapolation will be longer for younger patients and therefore the results for the lower age bands are subject to greater uncertainty. In addition the analyses for primary prevention are extrapolating effectiveness results from higher risk primary prevention populations, to the treatment of populations at much lower risk and have to be treated with caution.

The analyses are sensitive to the cost of statin, and the future cost of statins is a key unknown. Therefore the cost effectiveness results will need to be reviewed in the light of any significant changes in the price of statins.

These analyses do not take in to account the costs of identifying and screening the relevant population. In primary prevention as the risk threshold gets lower the size of the population eligible for treatment increases. The number of patients who will require regular monitoring will expand, placing additional demands on staff and resources at GP surgeries.

Modelling clinical outcome on cholesterol lowering inherently favours drugs that are more potent at lowering cholesterol. In the absence of strong and conclusive evidence on the relationship between cholesterol lowering and clinical endpoints cost effectiveness results for rosuvastatin are subject to significant uncertainty. Evidence on clinical endpoints is therefore required.

The role of statins must be seen in the context of other interventions to reduce CHD risk, including smoking cessation, exercise and the use of diet, as well a range of drug treatments, such as anti-hypertensives, beta-blockers and aspirin. Several of these interventions have been shown to be more cost-effective than statins. Use of other interventions prior to statin prescribing to reduce CHD risk potentially has the effect of reducing an individual's risk to levels below which they would become eligible for statin treatment. Therefore significant efforts need to be made to ensure that use of other interventions of equivalent proven efficacy are optimised, to minimise the potential NHS impact of statin prescribing.

- Generalisability of the findings

The generalisability of the findings is limited by the exclusion, in some studies, of patients who were hypersensitive to or intolerant of statins, who were known to be unresponsive to statins, or who were not adequately compliant with study medication during a placebo run-in phase. A considerable proportion of patients with or at risk of CHD may have been excluded in this way. Consequently, the treatment effect may be reduced when statins are used in an unselected population.

There is a major question regarding the generalisability of the results of RCT evidence into routine clinical practice. Effectiveness of statins in routine clinical practice could well be lower than suggested by the trials due to a number of issues, particularly compliance and continuance. However sensitivity analysis on compliance and continuance assumptions shows that the impact on cost effectiveness results is not likely to be significant.

- Need for further research

Robust published evidence on quality of life, compliance and continuance is required to ensure that cost effectiveness results are as robust as possible.

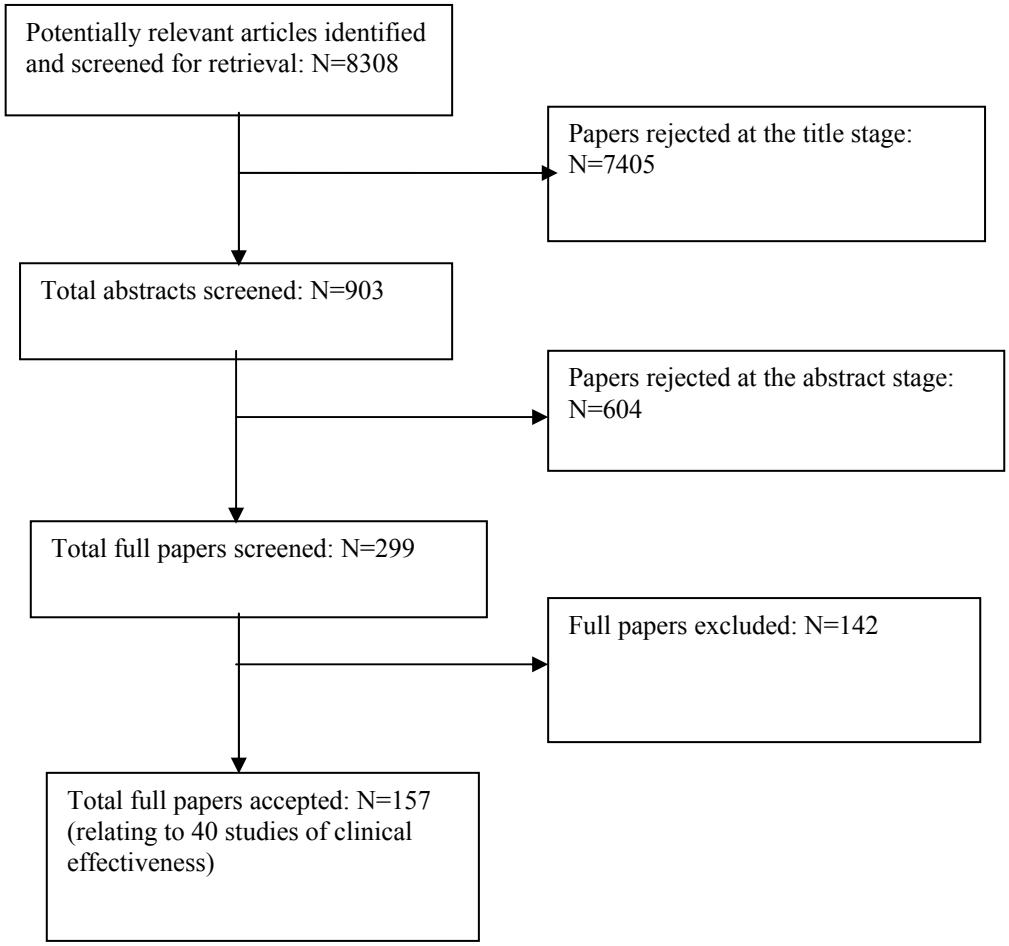
The current analyses are based on extrapolating results from much higher risk patients to the treatment of very normal people. Large outcome studies at lower CHD/CVD risk thresholds would be useful in order to determine if the relative risk reduction figures remain valid at lower risk levels and to determine to what extent potential disutility due to statins may become an issue as treatment is extended to a vast proportion of the "well" population.

Given the uncertainty of the results of the surrogate endpoint analysis clinical endpoint data for rosuvastatin is required.

Future service implementation research is important, particularly on effective policies for targeting low risk populations. Research on the attitudes of low risk patients and relatively healthy younger 45 year olds to taking lifetime medication is required, along with research into the optimal methods of explaining risks and benefits of treatment to patients so that they can make informed choices. Explanation will need to be valid across the social and ethnic spectrum of society.

The electronic literature searches identified 8308 potentially relevant articles. Of these, 157 articles were identified by the sifting process as relating to 40 randomised controlled trials which met the inclusion criteria (see Figure 1).

Figure 1 Summary of Study Selection and Exclusion: Electronic Literature Searches



A further five relevant studies (3T, [79] 4D, [80] ASAP, [81] DALI[82] and Sato 2001[83]), which were reported in articles identified by the electronic literature searches, had been rejected during the sifting process as their relevance was not apparent; they were subsequently identified from citations, as were three studies (the ALLIANCE, [84] ESTABLISH[85] and REVERSAL[86] studies) which were not picked up by the electronic searches.

3.2.1.2 Number and type of studies included

A total of 48 individual RCTs met the review inclusion criteria. A full list of these studies, with the identified papers relating to them, may be found in Appendix 2.

In addition, a further 13 potentially relevant studies were identified which are still ongoing, or for which the data are unavailable; these are listed in Appendix 3.

3.2.1.3 Number and type of studies excluded, with reasons

As may be seen from section 3.2.1.1 above, a very large number of studies which were identified by the electronic literature searches did not meet the inclusion criteria, and were therefore excluded as part of the sifting process. It is not practical to provide details of all these studies, and details are therefore given only of those studies which were excluded at the

full paper stage, and then only if the reason for exclusion is not immediately apparent from the full text. Such studies, and the reasons for their exclusion, are listed in Appendix 4. For clarity, this Appendix also lists all those clinical trials discussed in the company submissions which did not meet the inclusion criteria, together with at least one reason for their exclusion.

3.2.1.4 Tabulation of quality of studies

The quality of studies relating to each intervention is tabulated in Appendix 5.

It is only possible here to comment on the quality of those studies as reported in published articles. A surprising number of studies (19/48) did not provide enough information to allow the reader to judge whether the allocation of patients to treatment groups was truly random, even using generous criteria (ie assuming that randomisation which was said to be by minimisation or block randomisation was performed by computer or some other adequate technique, even if that was not specified). Even fewer studies (27/48) indicated whether allocation to treatment groups was adequately concealed.

Most studies were double-blind. However, only one (the LIPS study) assessed the success of the blinding process, and then only informally. In that study, anecdotal evidence suggested that many patients were aware of their total cholesterol levels, as these had been tested by their primary care physicians, and were therefore no longer blinded to the effects of treatment. [87] Clearly, this may also have occurred in other studies. If patients in the control group were aware of their cholesterol levels, they may have sought to reduce them either by modifying their behaviour or by seeking non-study lipid-lowering therapy, thus reducing the apparent effect of the study therapy.

Many studies reported the presence of cointerventions which were not equally distributed between treatment groups and which therefore potentially influenced the study outcome. Such cointerventions most commonly took the form of statin or other lipid-lowering therapy in the control group. The probable impact of such cointerventions is discussed in section 3.2.1.5.2.6 below. Of the studies which do not report such cointerventions, only two (FLARE, [88] LiSA[89]) specifically stated that the use of non-study lipid-lowering therapies was prohibited during the study. In a third study (Mehra 2002), no use appeared to have been made of non-study lipid-lowering therapies. [90]

3.2.1.5 Placebo-controlled studies

3.2.1.5.1 Quantity and quality of research available: placebo-controlled studies

28 RCTs were identified which compared a statin with placebo and which reported relevant outcomes: 4D, 4S, Aronow 2003, ASCOT-LLA, CAIUS, CARDS, CARE, CIS, DALI, FLARE, FLORIDA, HPS, KAPS, LIPID, LIPS, LiSA, MAAS, Mohler 2003, Mondillo 2003, Oxford Cholesterol Study, PLAC I, PLAC II, PMSG, PREDICT, PROSPER, REGRESS, SCAT, WOSCOPS. Of these, five used atorvastatin (4D, ASCOT-LLA, CARDS, DALI, Mohler 2003), four used fluvastatin (FLARE, FLORIDA, LIPS, LiSA), eleven pravastatin (CAIUS, CARE, KAPS, LIPID, PLAC I, PLAC II, PMSG, PREDICT, PROSPER, REGRESS, WOSCOPS) and eight simvastatin (4S, Aronow 2003, CIS, HPS, MAAS, Mondillo 2003, Oxford Cholesterol Study, SCAT) (for further details, see Appendix 6). These studies are set out by prevention category in Table 14.

Table 14: Placebo-controlled studies by prevention category

Primary CVD prevention	Primary CHD prevention	Secondary CHD prevention	Secondary CVD prevention	Mixed primary and secondary prevention
CAIUS CARDS	CAIUS CARDS ASCOT-LLA DALI	4S CARE CIS FLARE FLORIDA LIPID LIPS LiSA MAAS PLAC I PLAC II PREDICT REGRESS SCAT	4S CARE CIS FLARE FLORIDA LIPID LIPS LiSA MAAS PLAC I PLAC II PREDICT REGRESS SCAT Aronow 2003 Mohler 2003 Mondillo 2003	4D HPS KAPS Oxford Cholesterol Study PMSG PROSPER WOSCOPS

3.2.1.5.2 Assessment of effectiveness: placebo-controlled studies

As noted earlier, the evidence from all the placebo-controlled studies will be presented first. Evidence will then be presented in relation to the different prevention categories in turn, starting with primary CVD prevention (patients free of known CHD or CVD at baseline) followed by primary CHD prevention (patients free of known CHD at baseline), and then by secondary CHD prevention (patients with CHD at baseline) and finally secondary CVD prevention (patients with CVD (including CHD) at baseline)

3.2.1.5.2.1 Assessment of effectiveness of statins : all placebo-controlled trials

Many of the studies which report mortality data are too small to show a statistically significant effect. However, meta-analysis of data from all the studies which provided such data in usable form indicates that statins are associated with a reduction in the risk of all-cause mortality, cardiovascular mortality, CHD mortality and fatal MI, but not of stroke mortality (see Figures 2-4). (Only forest plots for key outcomes are included here; those for other outcomes may be found in Appendix 7.) Studies which were excluded from any meta-analysis of clinical outcomes because they had not published such data in usable form were 4D, for which only preliminary data were available, indicating a nonsignificant reduction in the primary endpoint of combined cardiac death, nonfatal MI and stroke, [91] and the Oxford Cholesterol Study, which collected data on the number of patients who suffered all-cause, CHD and other vascular mortality, non-fatal MI and stroke, but only published these data in an interim report which did not attribute such outcomes to treatment groups. [92] Mondillo 2003 did not report any clinical outcomes other than walking distances. [93]

Figure 2: Placebo-controlled studies: effect of statins on all-cause mortality

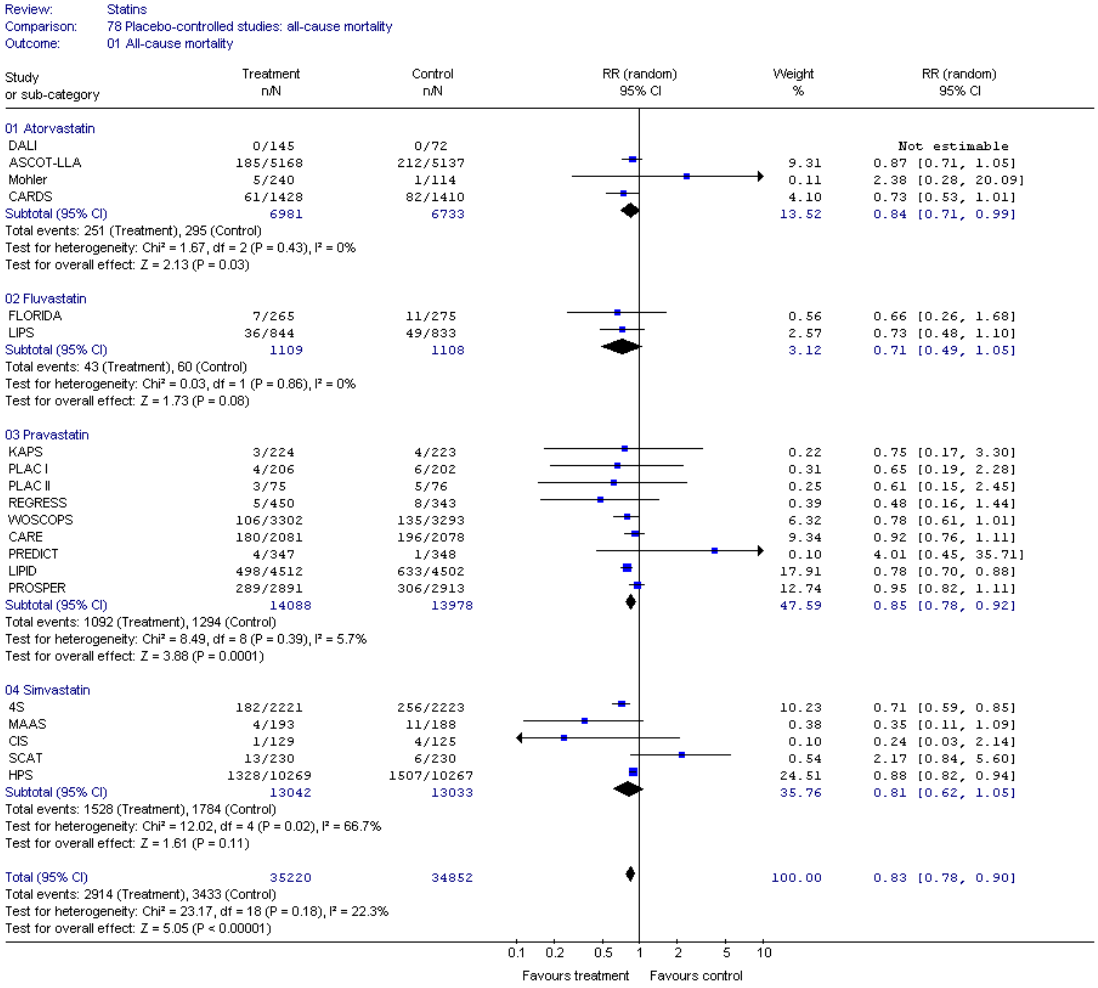


Figure 3: Placebo-controlled studies: effect of statins on CHD mortality

Review: Statins
Comparison: 80 Placebo-controlled studies: CHD mortality
Outcome: 01 CHD mortality

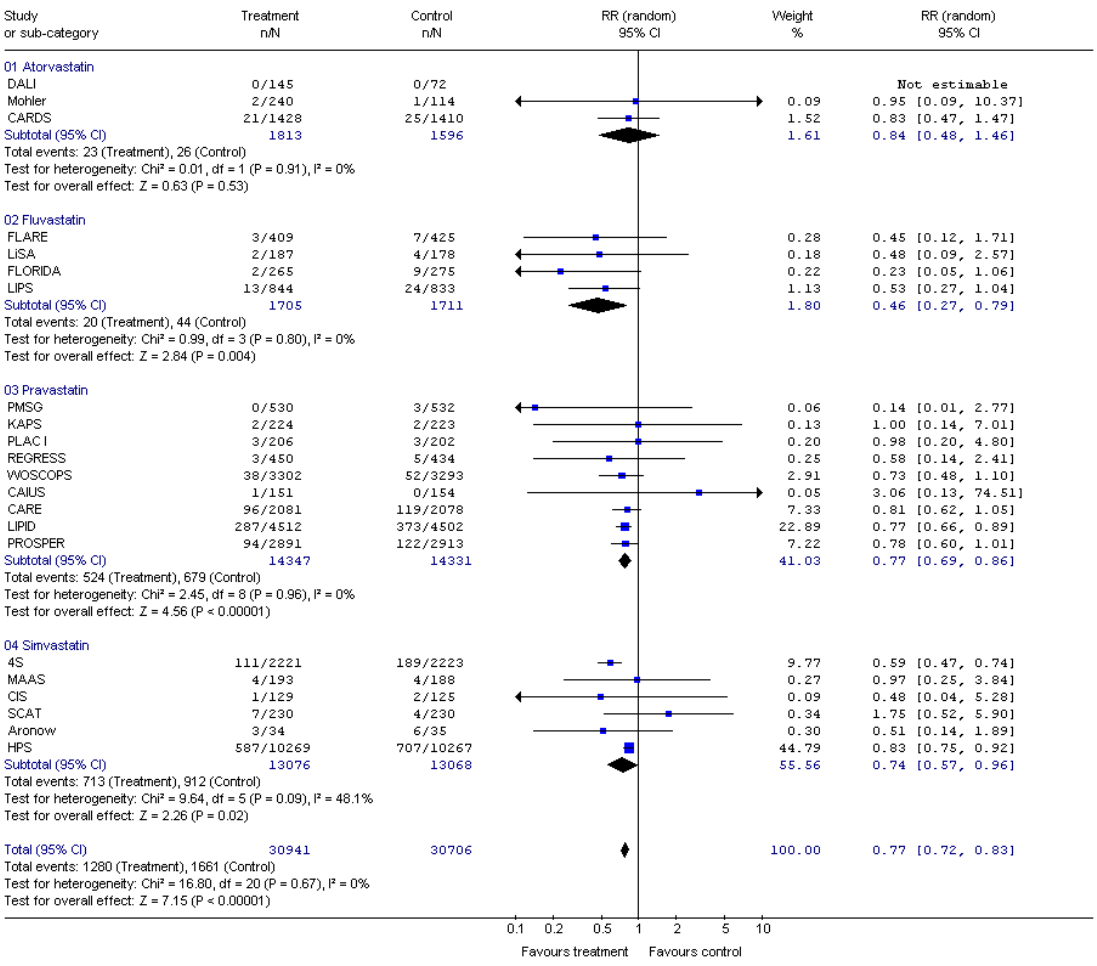
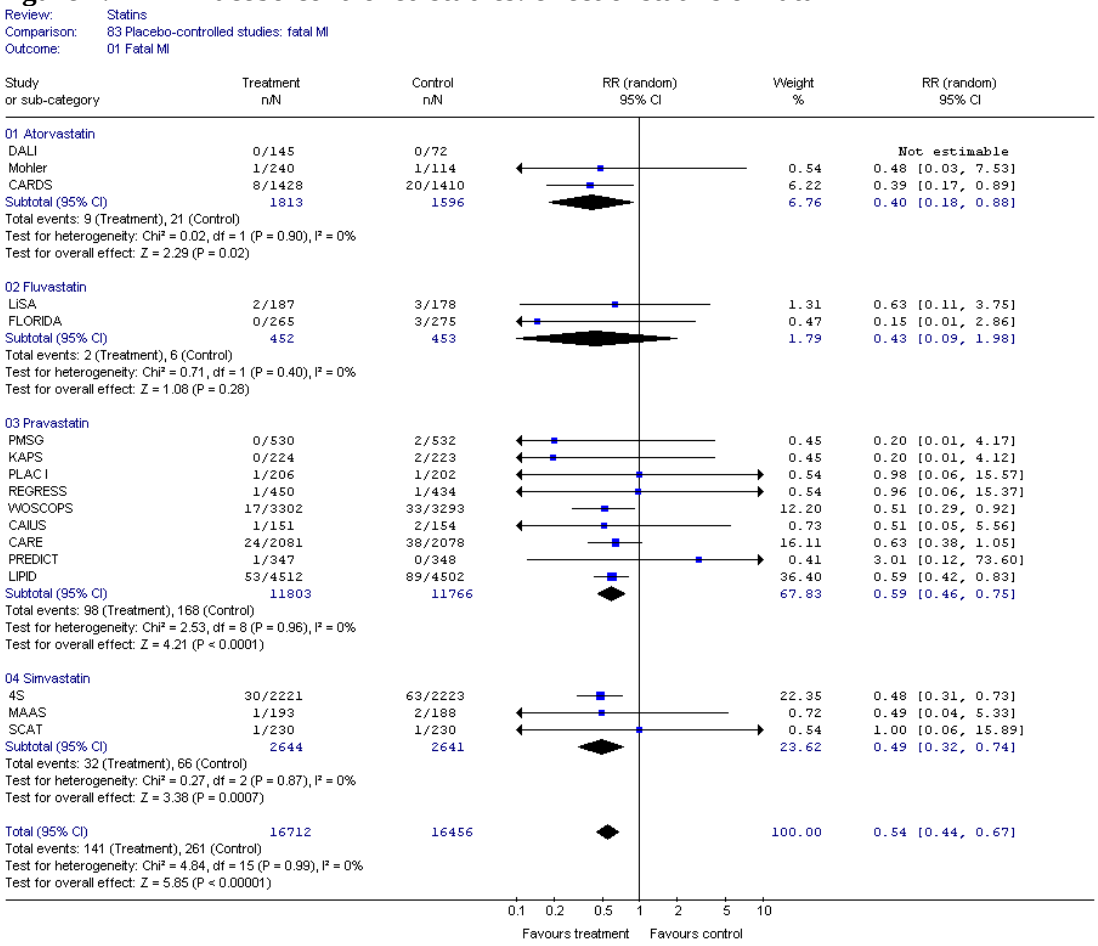
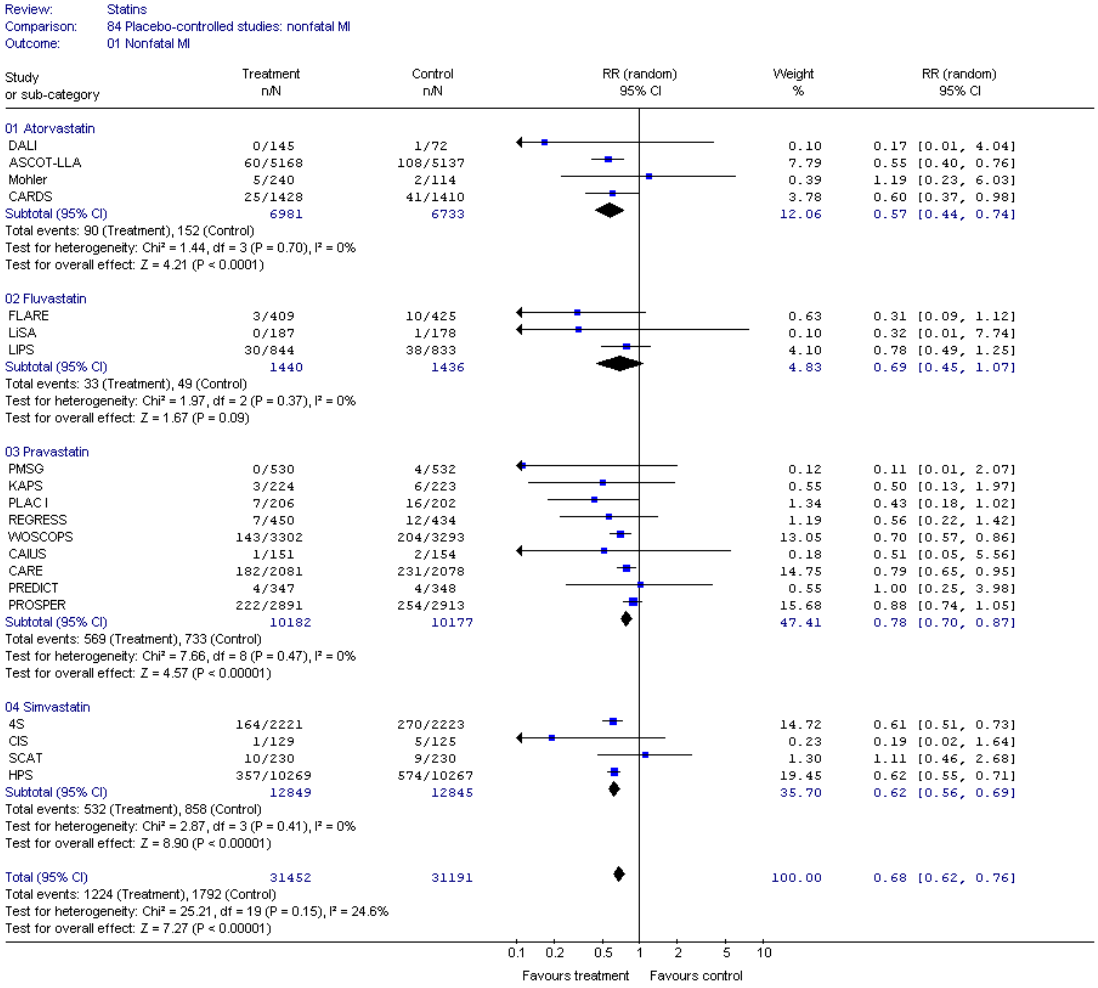


Figure 4: Placebo-controlled studies: effect of statins on fatal MI



Many studies were also too small to show a statistically significant effect in relation to nonfatal outcomes. However, meta-analysis of data from all the studies which provided such data in usable form indicates that statins are associated with a reduction in the risk of nonfatal stroke, TIA, nonfatal MI (see Figure 5), unstable angina, and hospitalisations for unstable angina. In the only study which reported this outcome,[94] statin treatment was also found to be associated with a reduction in relative risk of chronic stable angina (RR 0.59, 95% CI 0.38-0.90).

Figure 5: Placebo-controlled studies: effect of statins on nonfatal MI

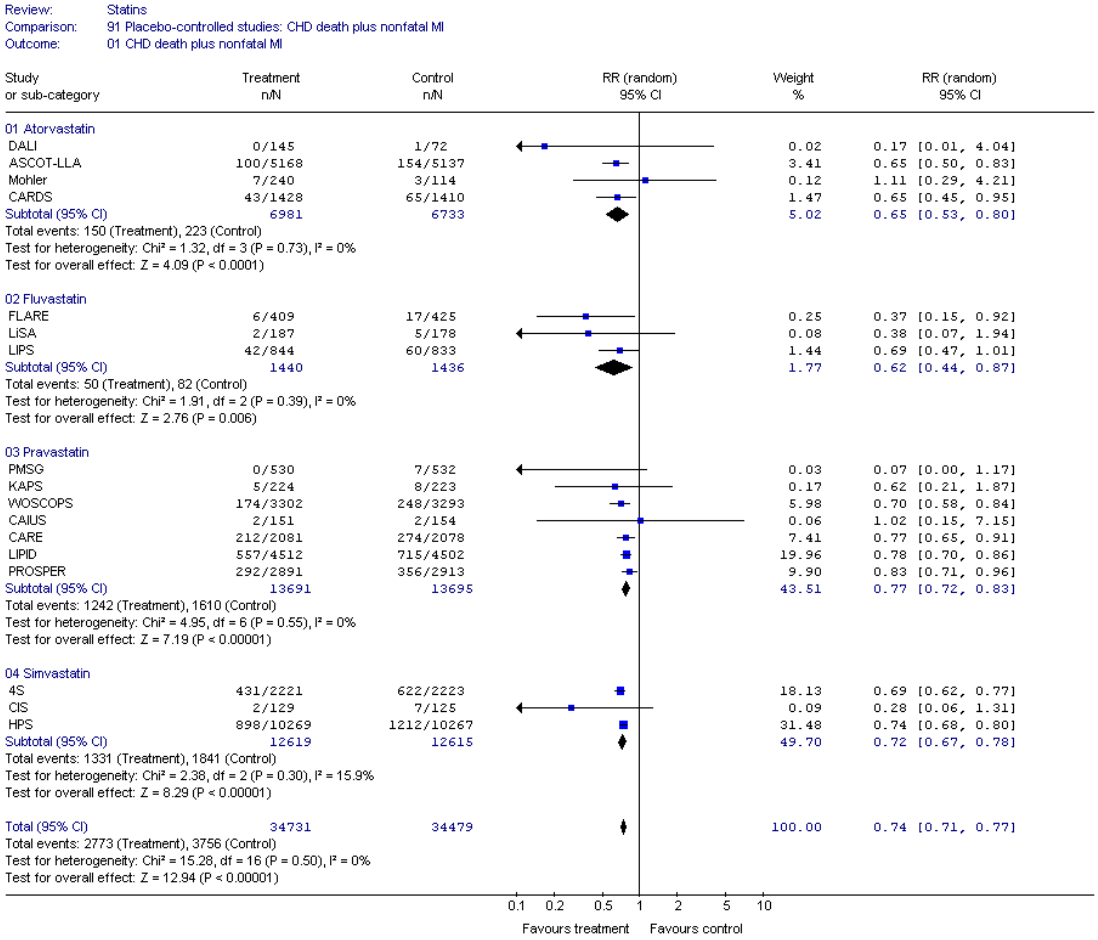


Because few studies reported the effect of statins on peripheral arterial disease, the results were not statistically significant even when combined. However, one of the studies included in the meta-analysis was carried out in patients with stable intermittent claudication. [22] This found that statin therapy was associated with a significant reduction in the incidence of peripheral arterial events (worsening claudication, development of rest ischaemia, peripheral revascularisation and limb amputation), suggesting that statins may have a beneficial effect on PAD at least in this patient group.

Statin treatment was also found to be associated with a reduction in both CABG and PTCA.

The most robust results are demonstrated in relation to the composite endpoint of CHD mortality plus nonfatal MI (see Figure 6).

Figure 6: Placebo-controlled studies: effect of statins on CHD mortality plus nonfatal MI



The fact that statin therapy is associated with a statistically significant reduction in the risk of nonfatal stroke, but not of fatal stroke, may be due to a differential effect on haemorrhagic and nonhaemorrhagic stroke. Only three studies differentiated between types of stroke. Two of these provided data in a form which enabled them to be combined in a meta-analysis. [95,71] The results show that, whilst statin therapy was not shown to have an effect on haemorrhagic stroke, it reduced the risk of non-haemorrhagic stroke (see Figures 7 and 8).

Figure 7: Placebo-controlled studies: effect of statins on haemorrhagic stroke

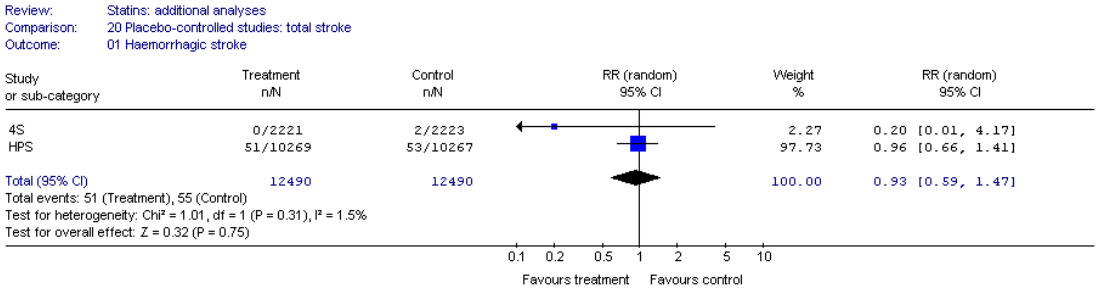
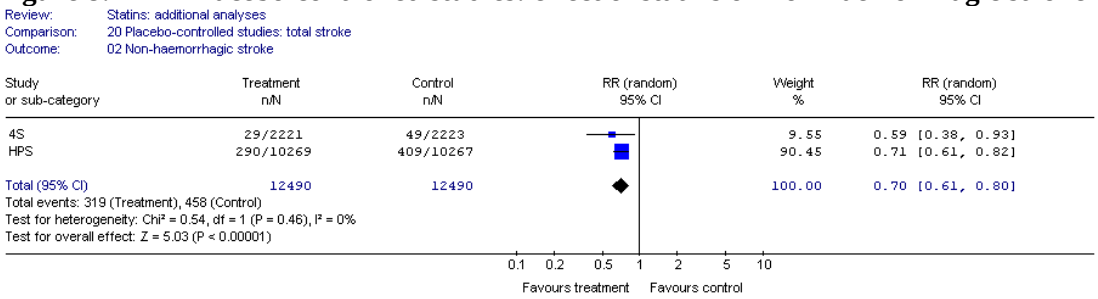


Figure 8: Placebo-controlled studies: effect of statins on non-haemorrhagic stroke



These results are supported by those of the third study, the LIPID study[96] in which statin therapy was associated with a significant reduction in the risk of non-haemorrhagic stroke but not of haemorrhagic stroke (see Table 15). Thus, statin therapy appears to be associated with a reduced risk of the more common, non-haemorrhagic, stroke and has not been shown to increase the risk of haemorrhagic stroke.

Table 15: Effect of statin therapy on types of stroke: the LIPID study[96]

Outcome	% of patients		Risk reduction (%)	95% CI	P value
	Pravastatin (N=4512)	Placebo (N=4502)			
Haemorrhagic stroke	0.4	0.2	Not reported		0.28
Non-haemorrhagic stroke	3.4	4.4	23	5-38	0.02

Overall, therefore, the evidence indicates that statins are associated with a reduction in the risk of all-cause, cardiovascular and CHD mortality, and of a number of nonfatal outcomes (nonfatal MI, nonfatal stroke, TIA, angina and coronary revascularisation). No effect has been demonstrated in respect of stroke mortality.

On the evidence available from the placebo-controlled trials, it is not possible to differentiate between the different statins in relation to any outcome: although the point estimates of their effect sizes may vary, in each case the confidence intervals overlap. Head-to-head comparisons of one statin with another are reviewed in section 3.2.1.6 below.

3.2.1.5.2.2 Assessment of effectiveness of statins in patients free of CVD at baseline (primary CVD prevention)

The evidence for the effectiveness of statins in primary CVD prevention rests on two placebo-controlled RCTs (CAIUS, [97] CARDS[98]), and on subgroup analyses in three placebo-controlled studies of CHD prevention (ASCOT-LLA[94]) or populations with mixed CVD status (PROSPER, [77] WOSCOPS[78]). However, these latter studies only presented data relating to patients without CVD at study entry in relation to the following composite endpoints:

- fatal CHD and non-fatal MI (ASCOT-LLA, WOSCOPS)
- fatal CHD, nonfatal MI and fatal or non-fatal stroke (PROSPER)

Moreover, two of these studies (PROSPER and WOSCOPS) did not stratify randomisation to take into account prior disease status. In the ASCOT-LLA study, randomisation was by minimisation, and it is not specified whether this took prior disease status into account. Consequently, the subgroup analyses from the PROSPER and WOSCOPS studies are not, and those from the ASCOT-LLA study may not be, true randomised comparisons.

The two studies which were carried out specifically in patients without CVD differed in their populations: CARDS recruited patients with type 2 diabetes from the UK and Republic of Ireland (a high-risk primary prevention population), while CAIUS was conducted in a Mediterranean population with ultrasonographic evidence of early carotid artery atherosclerosis. The ASCOT-LLA study was a factorial study evaluating atorvastatin in hypertensive patients without a history of CHD who were also receiving aggressive antihypertensive treatment with either a beta-blocker or a calcium antagonist[94] (again, a high-risk primary prevention population; for further details, see Appendix 6). Of the studies with mixed populations, the PROSPER study was specifically carried out in elderly patients, [77] and the WOSCOPS study in men. [78]

Meta-analysis indicates that, in patients without clinical CVD, statins are associated with a statistically significant reduction in the risk of fatal MI, nonfatal MI, and CHD death plus nonfatal MI. There was also a statistically significant reduction in the composite endpoint of CHD death, nonfatal MI, any stroke or coronary revascularisation. However, the studies were too small to demonstrate statistically significant effects in relation to other clinical outcomes (see Appendix 8, Table 1 and Figures 1-6).

Two of the studies which provided subgroup data relating to patients without prior CVD reported combined data on CHD death plus nonfatal MI in a form which did not allow them to be included in a meta-analysis. The ASCOT-LLA investigators calculated that, in patients without prior CVD, statin treatment was associated with an unadjusted hazard ratio in relation to this outcome of 0.61 (95% CI 0.46-0.81), [94] while the WOSCOPS investigators calculated that, in such patients, statin treatment was associated with a risk reduction of 33% (95% CI 15-46%).[78] These figures are not incompatible with the results of the meta-analysis presented in Table 16 below.

The WOSCOPS investigators also calculated a risk reduction of 33% (95% CI 15-46%) for a composite endpoint of CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularisation in patients without CVD at baseline. [78] This is again not incompatible with the relative risk of that same endpoint of 0.64 (95% CI 0.48-0.84) calculated from data presented in the CARDS study relating to the number of patients who had CHD death, nonfatal MI, fatal or nonfatal stroke, or CABG or other surgery as their primary endpoint.

3.2.1.5.2.3 Assessment of effectiveness of statins in patients free of CHD at baseline (primary CHD prevention)

The evidence for the effectiveness of statins in patients without prior CHD rests on the CAIUS and CARDS studies discussed above, the DALI study which compared two doses of atorvastatin with placebo in patients with type 2 diabetes (a high-risk primary prevention population), [82] and the full ASCOT-LLA study. In addition, the subgroup data from the PROSPER[77] and WOSCOPS[78] studies, noted above, relating to patients without CVD at study entry, are also relevant here. In addition, the HPS study, [71] a factorial study evaluating both simvastatin and antioxidant vitamins[71] (for further details, see Appendix 6), presented subgroup data relating to patients without CHD at study entry, although only in relation to the first major vascular event (coronary death, non-fatal MI, fatal or non-fatal stroke or any revascularisation).

Meta-analysis indicates that, in patients without clinical CHD, statin therapy is associated with a statistically significant reduction in the risk of all-cause mortality, fatal and nonfatal MI, stable angina, CHD death plus nonfatal MI, and a composite of coronary death, non-fatal MI, fatal or non-fatal stroke or any revascularisation (see Figures 9-14). However, the studies were again too small to demonstrate significant results in relation to other fatal events,

nonfatal stroke, PAD, unstable angina, or coronary revascularisation (see Appendix 9, Table 1 and Figures 1-7).

Figure 9: Placebo-controlled studies: statins in primary CHD prevention: all-cause mortality

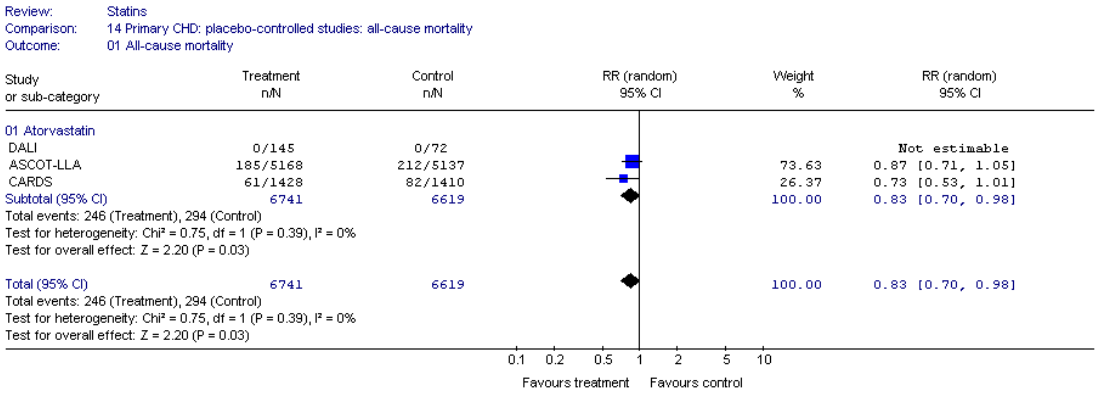


Figure 10: Placebo-controlled studies: statins in primary CHD prevention: fatal MI

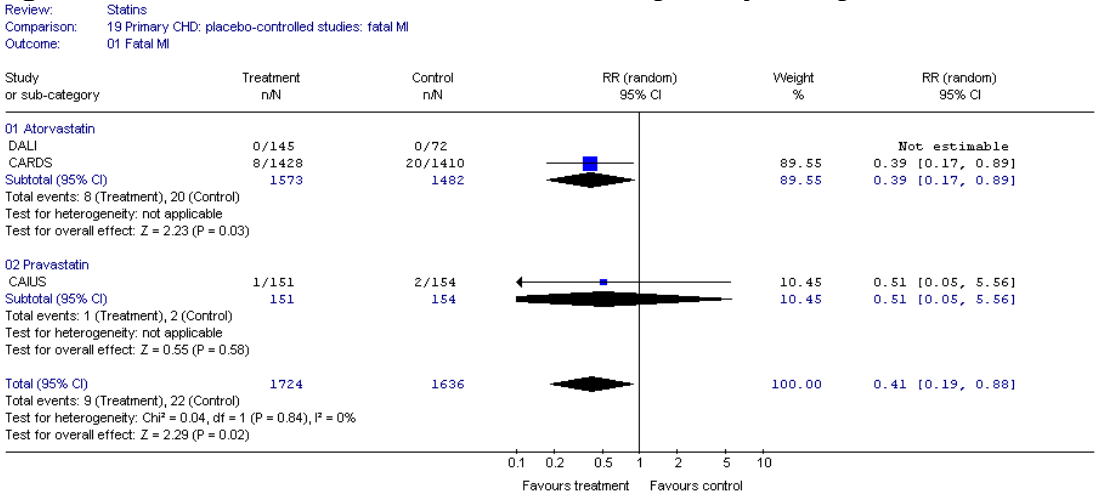


Figure 11: Placebo-controlled studies: statins in primary CHD prevention: nonfatal MI

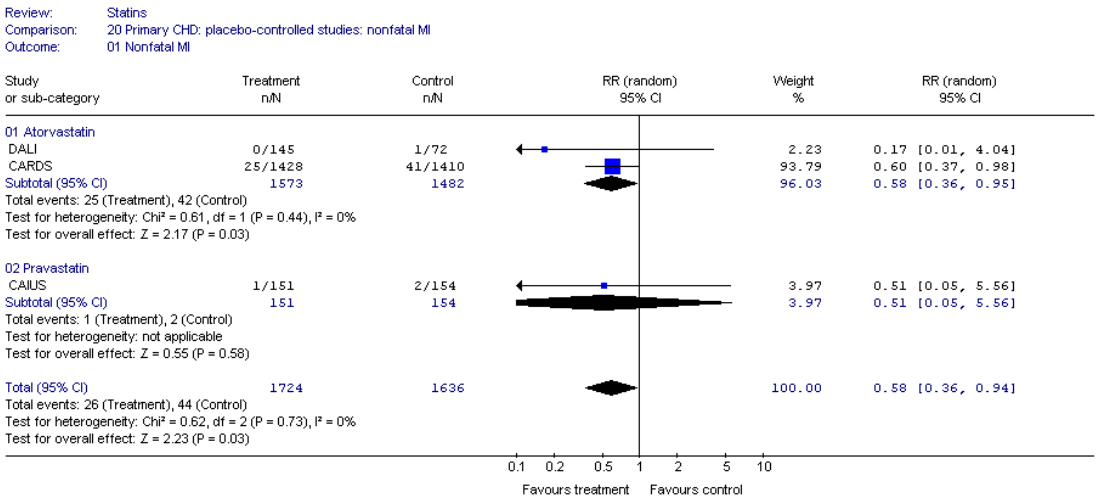


Figure 12: Placebo-controlled studies: statins in primary CHD prevention: chronic stable angina

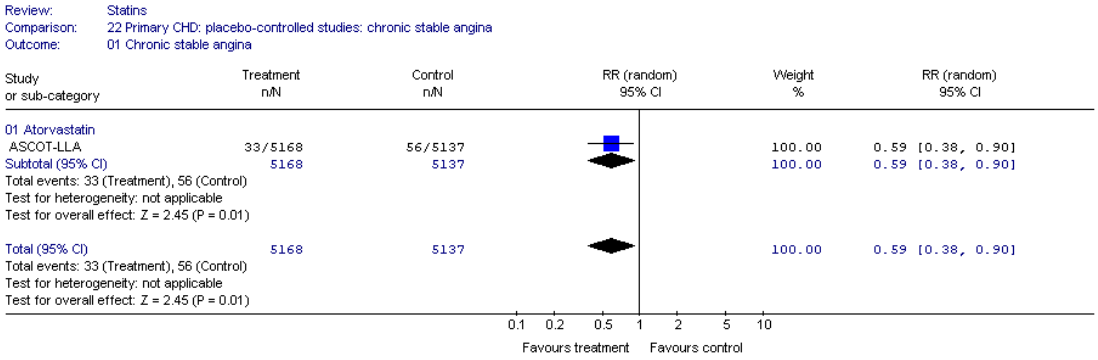


Figure 13: Placebo-controlled studies: statins in primary CHD prevention: CHD death plus nonfatal MI

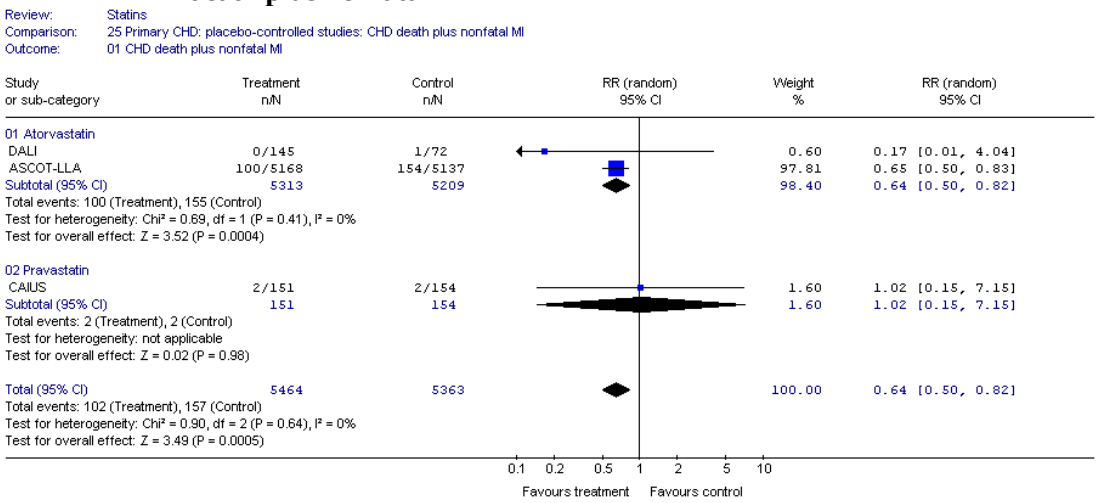
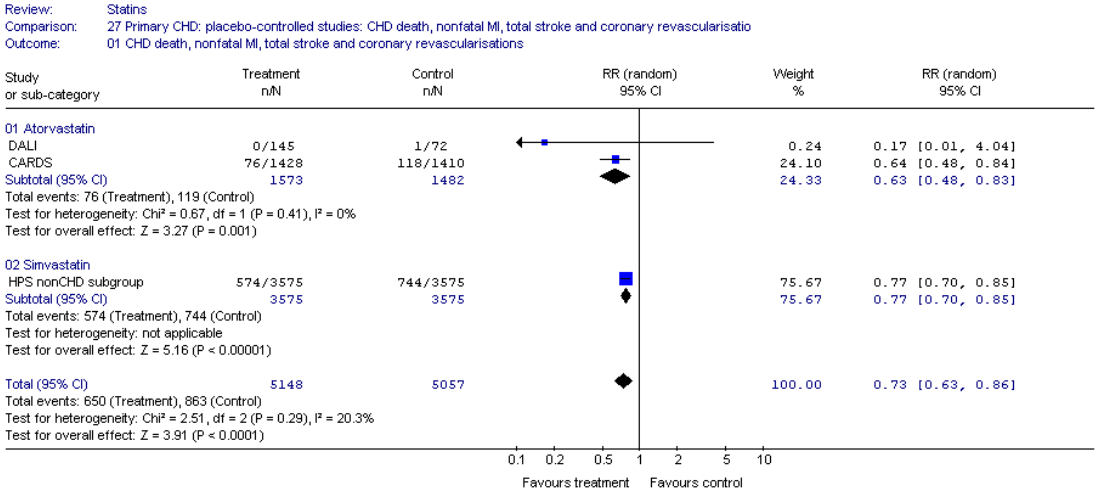


Figure 14: Placebo-controlled studies: statins in primary CHD prevention: CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularisation



3.2.1.5.2.4 Assessment of effectiveness of statins in patients with CHD at baseline (secondary CHD prevention)

There is a larger body of evidence relating to the use of statins in patients with symptomatic CHD. 14 placebo-controlled studies were identified which were carried out in this patient

group and which reported relevant clinical outcomes: LiSA, [89] FLARE, [99] FLORIDA, [100] LIPS, [101] CARE, [102] LIPID, [103] PLAC I, [104] PLAC II, [105] PREDICT, [106] REGRESS, [107] MAAS, [108] 4S, [95] CIS, [109] and SCAT. [110] In addition, one study in a mixed population (HPS) presented data relating to a subgroup of patients with prior CHD, although only in relation to a composite endpoint, first major vascular event (ie coronary death, non-fatal MI, fatal or non-fatal stroke or any revascularisation). [71]

Meta-analysis of the relevant data indicated that, in patients with clinical CHD, statin treatment was associated with a statistically significant reduction in the risk of all-cause mortality, cardiovascular mortality and CHD mortality, fatal and nonfatal MI, unstable angina and hospitalisation for unstable angina, nonfatal stroke, PAD, coronary revascularisation and a composite of CHD death and nonfatal MI (see figures 15-25). For other analyses, see Appendix 10, Table 1 and figures 1-4.

Figure 15: Placebo-controlled studies: statins in secondary CHD prevention: all-cause mortality

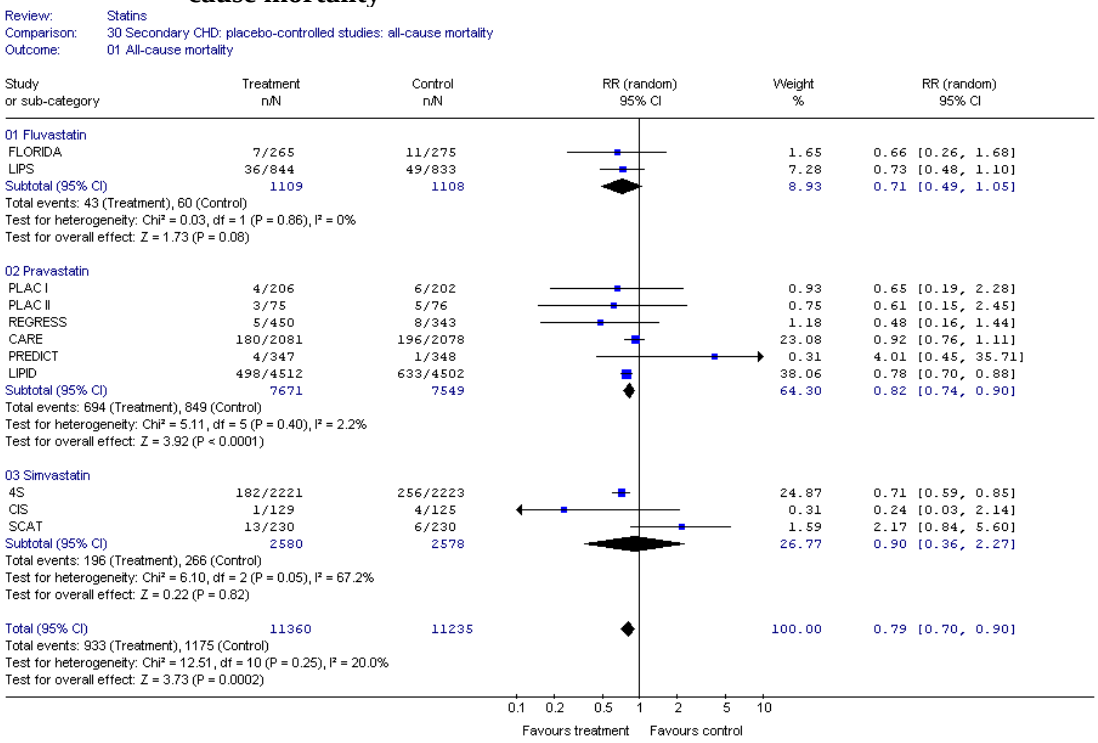


Figure 16: Placebo-controlled studies: statins in secondary CHD prevention: CVD mortality

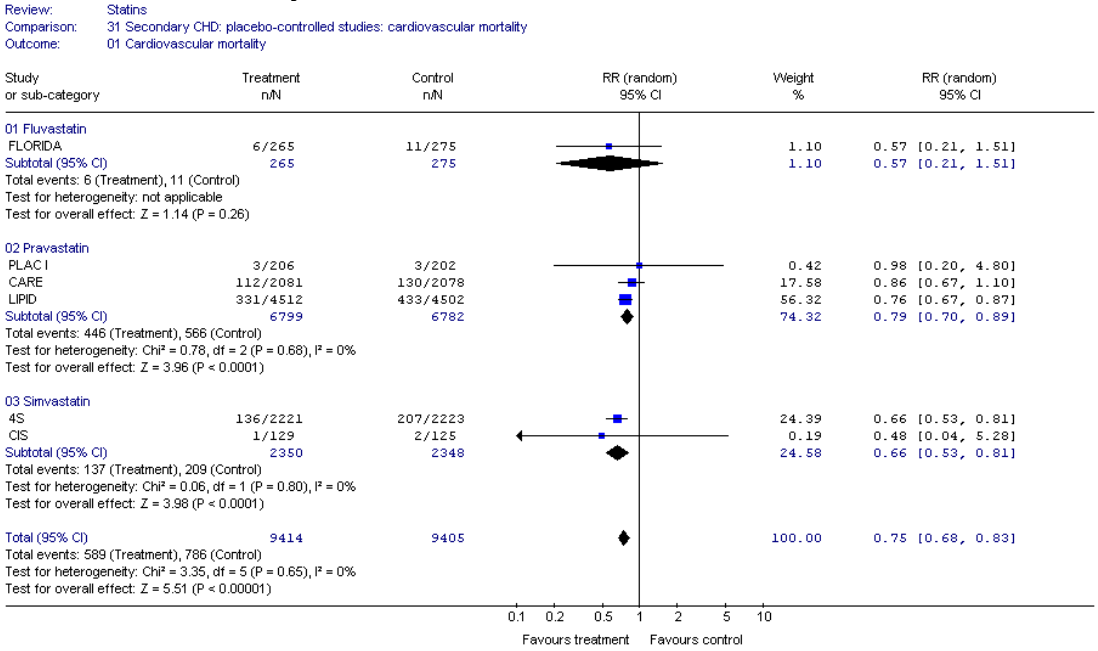


Figure 17: Placebo-controlled studies: statins in secondary CHD prevention: CHD mortality

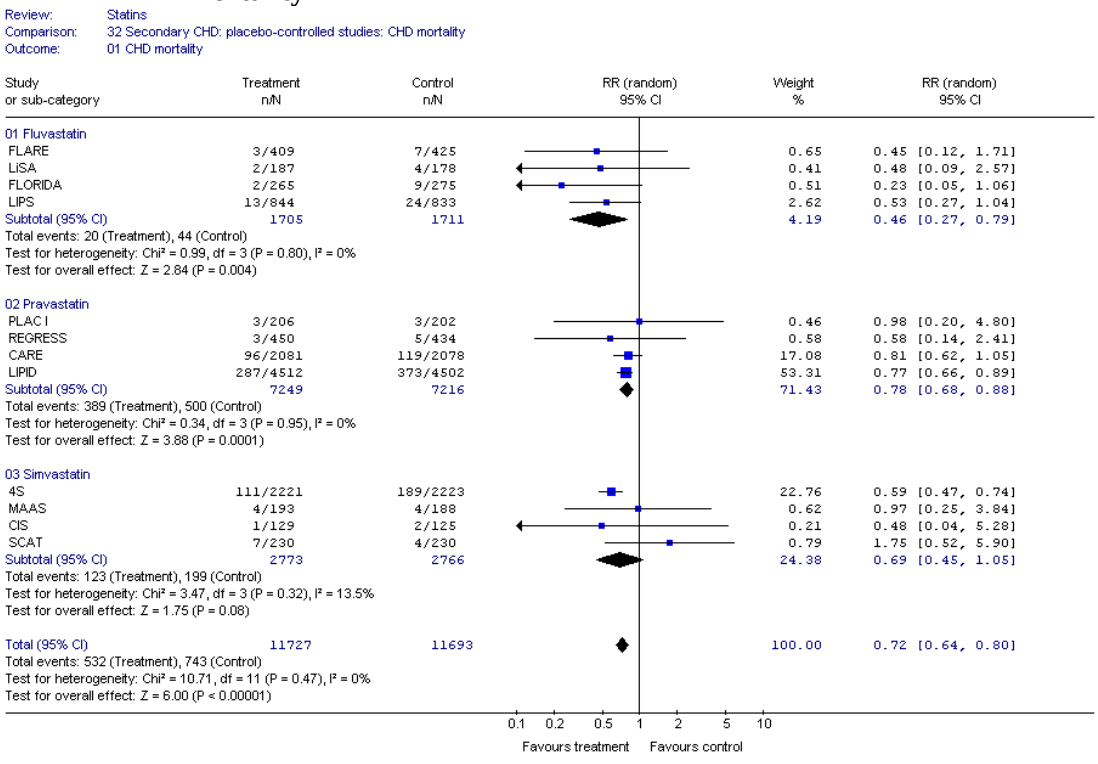


Figure 18: Placebo-controlled studies: statins in secondary CHD prevention: fatal MI

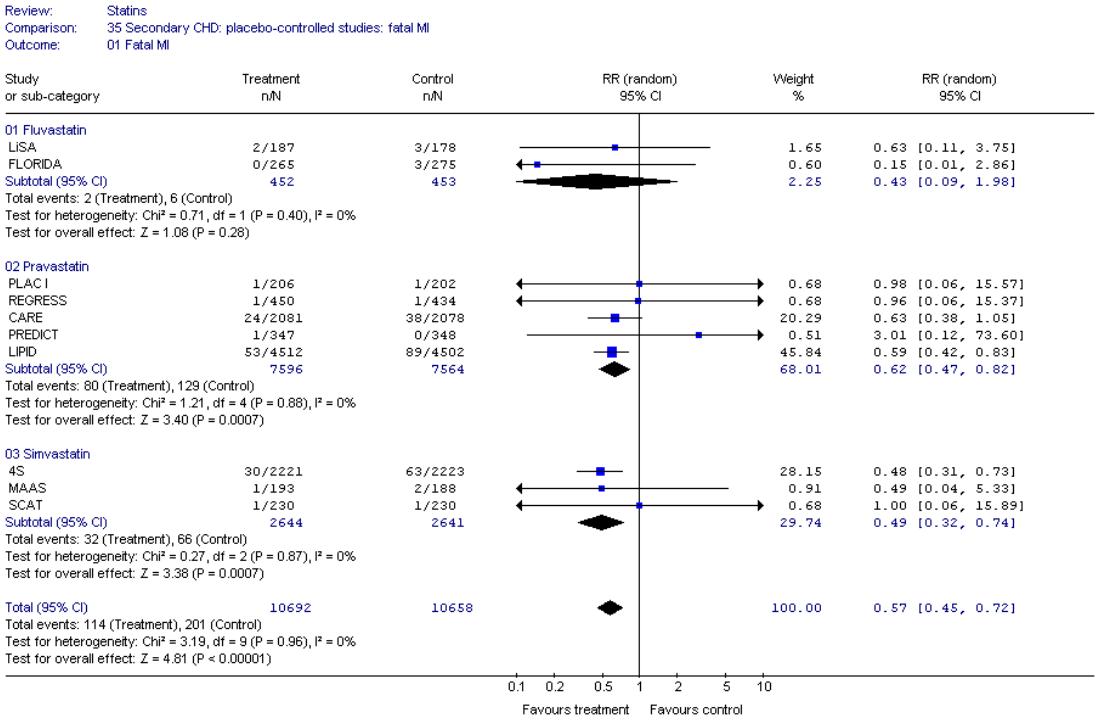


Figure 19: Placebo-controlled studies: statins in secondary CHD prevention: nonfatal MI

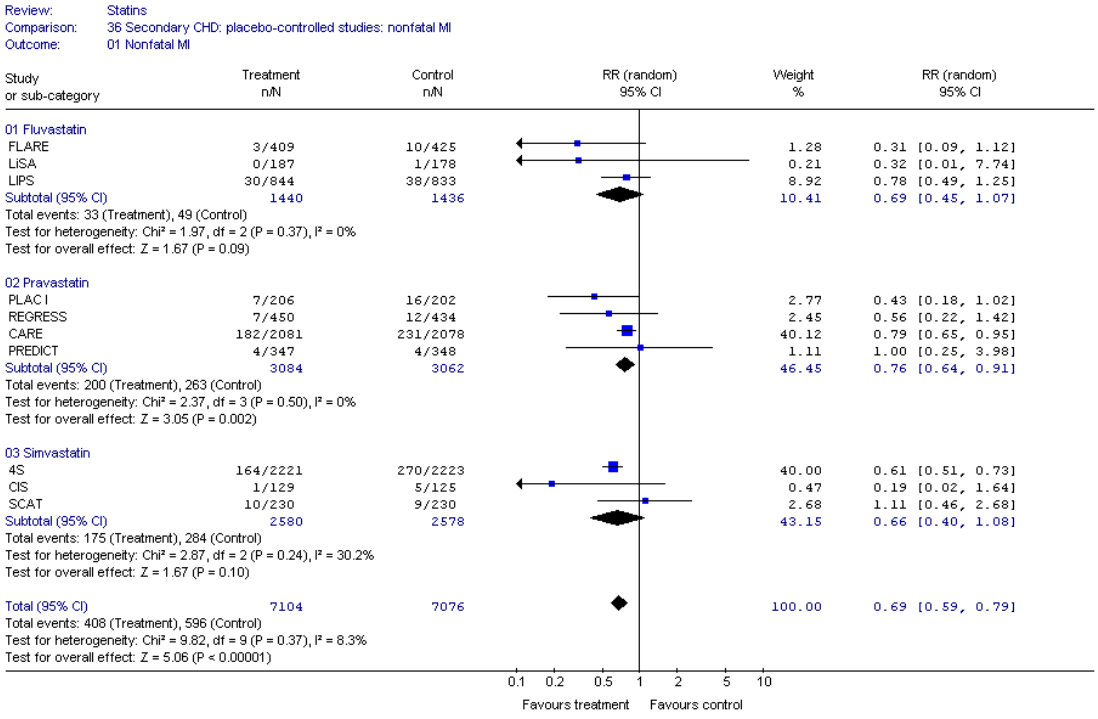


Figure 20: Placebo-controlled studies: statins in secondary CHD prevention: unstable angina

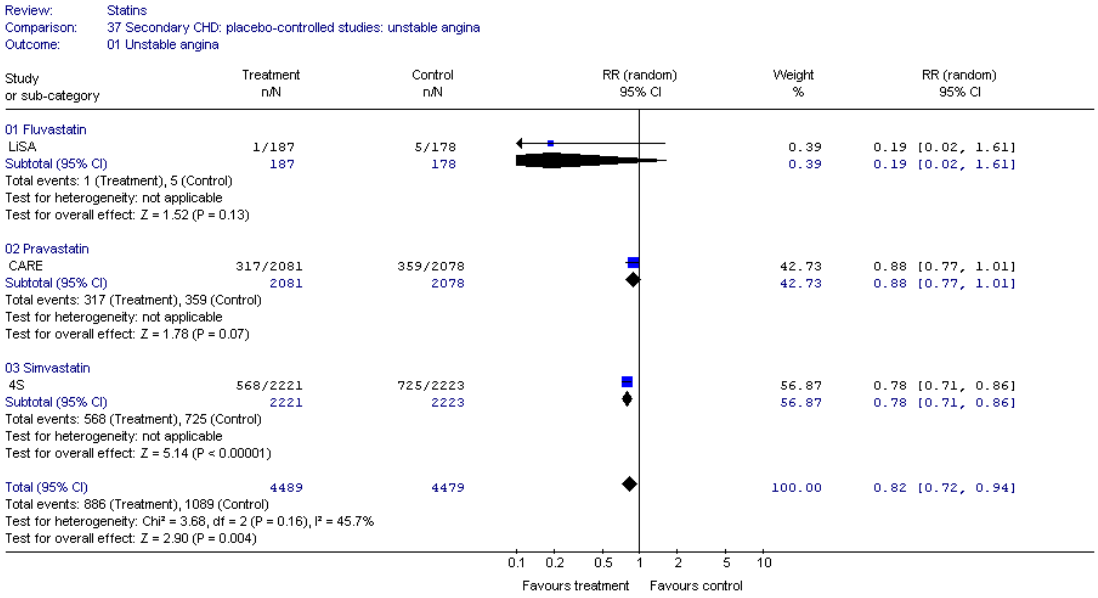


Figure 21: Placebo-controlled studies: statins in secondary CHD prevention: hospitalisation for unstable angina

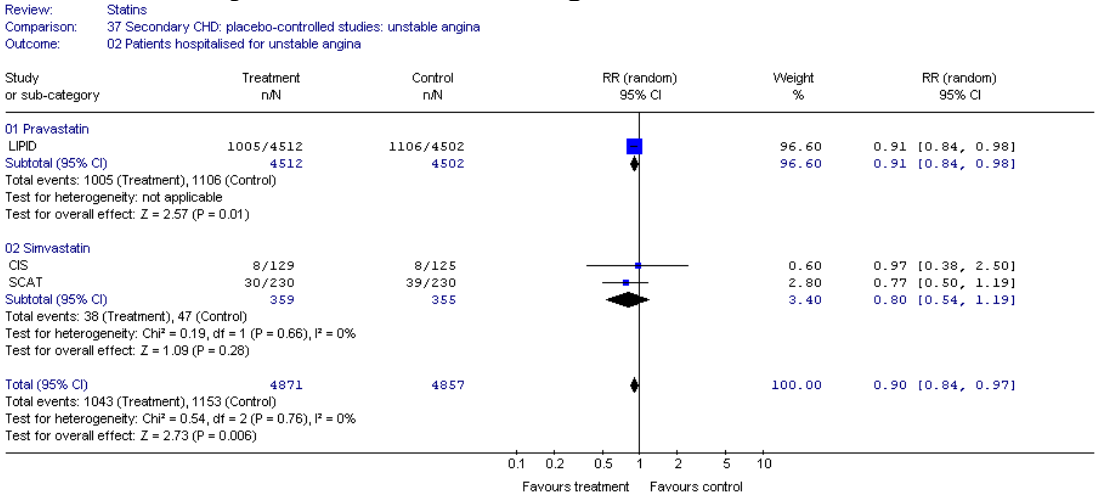


Figure 22: Placebo-controlled studies: statins in secondary CHD prevention: nonfatal stroke

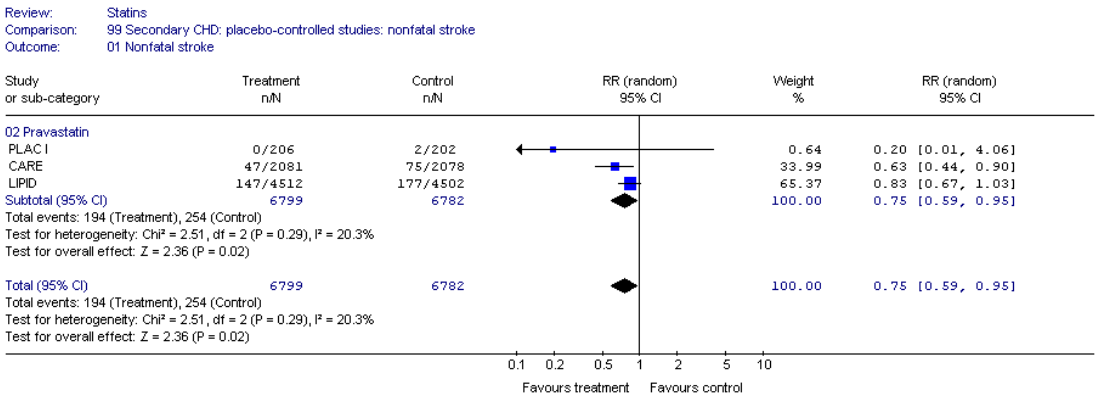


Figure 23: Placebo-controlled studies: statins in secondary CHD prevention: new or worsening intermittent claudication

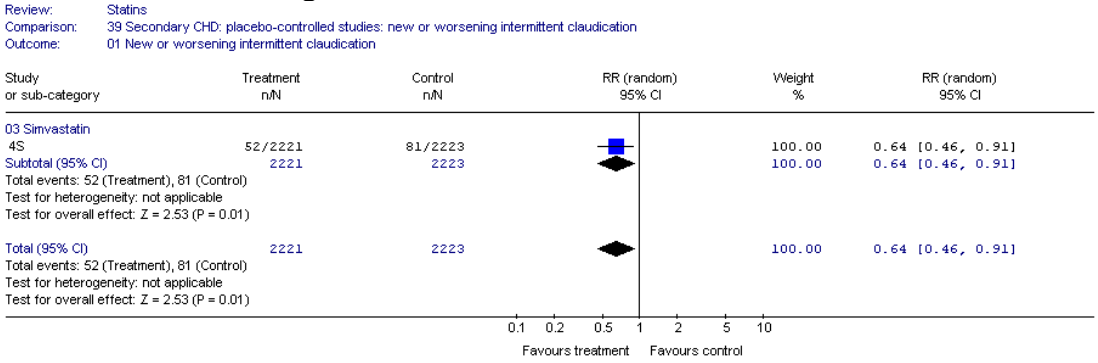


Figure 24: Placebo-controlled studies: statins in secondary CHD prevention: coronary revascularisation

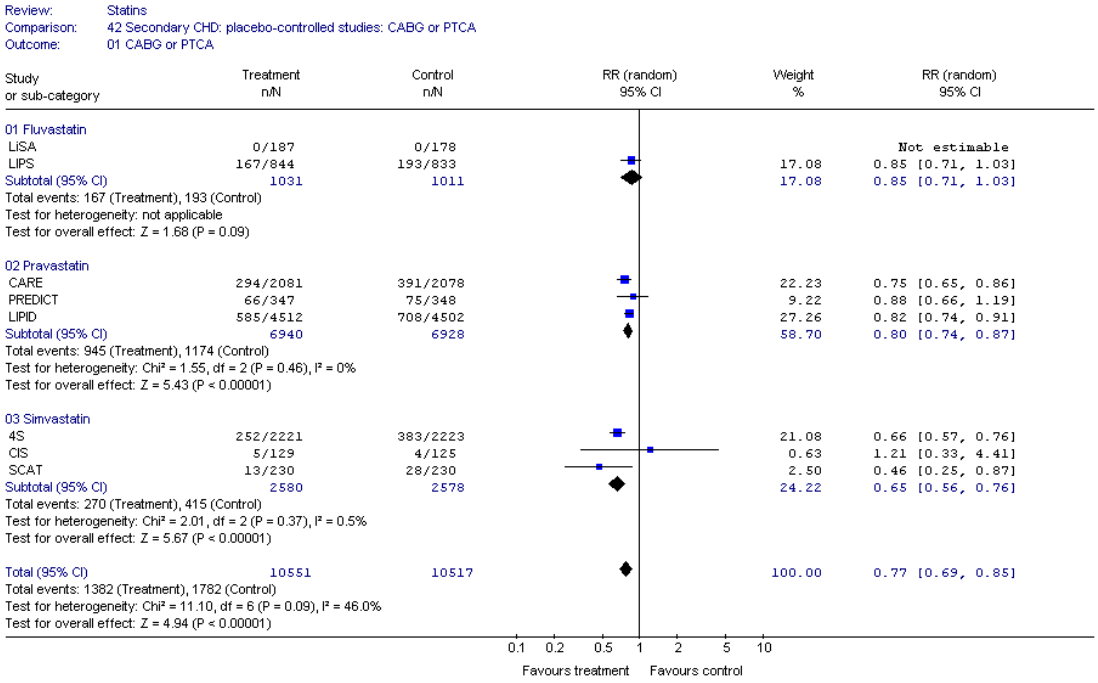
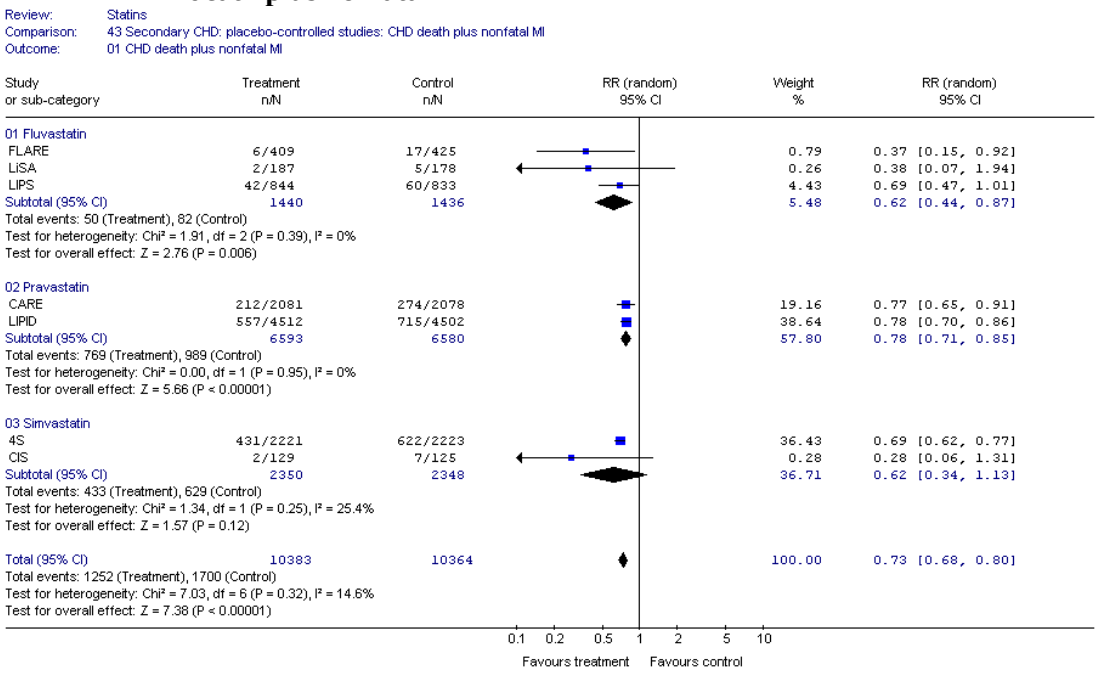


Figure 25: Placebo-controlled studies: statins in secondary CHD prevention: CHD death plus nonfatal MI



After the conclusion of the placebo-controlled phase of the 4S trial, which lasted for a median of 5.4 years, patients were followed up for a further 5 years. During that 5-year period, when more than 80% of patients in each group were treated with lipid-lowering drugs, the relative risks of mortality were close to unity. However, over the whole 10.4-year period, the original simvastatin group had a reduced risk of all-cause and CHD mortality relative to the original placebo group, [111] suggesting that benefit may be gained from earlier rather than deferred statin therapy.

3.2.1.5.2.5 Assessment of effectiveness of statins in patients with CVD (including CHD) at baseline (secondary CVD prevention)

The evidence for the effectiveness of statins in patients with prior CVD is derived primarily from the studies of statins in secondary CHD prevention discussed in section 3.2.1.5.2.3 above. However, it also draws on the findings of three relatively small studies (Mohler 2003, [22] Aronow 2003, [112] and Mondillo 2003[93]) in patients with intermittent claudication. In addition, the ASCOT-LLA and WOSCOPS studies reported data relating to subgroups with vascular disease at baseline; however, these results should be treated with caution because, as noted above, the subgroup analysis from the WOSCOPS study is not, and that from the ASCOT-LLA study may not be, a true randomised comparison.

It might be argued that the two of the three studies in patients with intermittent claudication[22,93] might be classified as primary CHD prevention, as they do not specify whether any participants had CHD at baseline. However, since all the participants in these studies had symptomatic CVD at baseline, it seemed more appropriate to categorise them as secondary CVD prevention.

As the additional studies are small, and do not report data relating to all endpoints, the changes to the tabulation of the effects of statins in secondary CHD prevention are few and so small as to be barely worth mentioning (see Appendix 11).

The two studies which reported subgroup data did so in a form which did not allow them to be included in the meta-analysis. Both provided data relating to the effect of statins on the

composite endpoint of CHD death plus nonfatal MI: in the ASCOT-LLA CVD subgroup, the investigators calculated the unadjusted hazard ratio to be 0.80 (0.45 to 1.42, p=0.4376), while in the WOSCOPS study the risk reduction was calculated to be 29% (-4 to 51%, p=0.075). Both results are broadly similar to the relative risk of 0.74 (95% CI 0.68-0.79) calculated in our meta-analysis.

3.2.1.5.2.6 Placebo-controlled studies: summary of results

The results reported above, and summarised in Table 16 below, suggest that, relative to placebo, in both primary and secondary prevention, statin therapy is associated with a statistically significant reduction in the risk of all-cause mortality, fatal and nonfatal MI, and of a composite endpoint of CHD death plus nonfatal MI; in primary prevention, it is also associated with a reduction in the risk of stable angina. In secondary prevention, statin therapy is associated with a statistically significant reduction in the risk of cardiovascular mortality, CHD mortality, nonfatal stroke, PAD, unstable angina, and coronary revascularisation. As the confidence intervals for each outcome in each prevention category overlap, it is not possible to differentiate, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention.

Table 16: Placebo-controlled trials of statin therapy: relative risk of event by prevention category (95% CI) (statistically significant results in bold)

Outcome	All studies	Primary CVD prevention	Primary CHD prevention	Secondary CHD prevention	Secondary CVD prevention
All-cause mortality	**0.83 (0.78-0.90)**	0.73 (0.53-1.01)	**0.83 (0.70-0.98)**	**0.79 (0.70-0.90)**	**0.80 (0.71-0.90)**
Cardiovascular mortality	**0.79 (0.74-0.85)**	0.67 (0.40-1.10)	0.83 (0.63-1.08)	**0.75 (0.68-0.83)**	**0.75 (0.68-0.83)**
CHD mortality	**0.77 (0.72-0.83)**	0.86 (0.49-1.52)	0.86 (0.49-1.52)	**0.72 (0.64-0.80)**	**0.72 (0.64-0.80)**
Stroke mortality	0.92 (0.74-1.14)	0.20 (0.02-1.69)	0.20 (0.02-1.69)	1.07 (0.67-1.71)	1.08 (0.67-1.72)
Nonfatal stroke	0.75 (0.63-0.90)	0.66 (0.38-1.15)	0.66 (0.38-1.15)	0.75 (0.59-0.95)	0.75 (0.59-0.95)
TIA	0.79 (0.68-0.91)	No data	No data	0.66 (0.37-1.17)	0.66 (0.37-1.17)
PAD	0.61 (0.13-2.78)	No data	0.59 (0.66-1.56)	0.64 (0.46-0.91)	**0.58 (0.42-0.80)**
Fatal MI	**0.54 (0.44-0.67)**	**0.41 (0.19-0.88)**	**0.41 (0.19-0.88)**	**0.57 (0.45-0.72)**	**0.57 (0.45-0.72)**
Nonfatal MI	**0.70 (0.63-0.77)**	**0.60 (0.37-0.97)**	**0.58 (0.36-0.94)**	**0.69 (0.59-0.79)**	**0.69 (0.61-0.78)**
Stable angina	**0.59 (0.38-0.90)**	No data	**0.59 (0.38-0.90)**	No data	No data
Unstable angina	**0.82 (0.74-0.90)**	0.77 (0.29-2.06)	0.87 (0.53-1.43)	**0.82 (0.72-0.94)**	**0.82 (0.72-0.94)**
Patients hospitalised for unstable angina	**0.88 (0.84-0.94)**	No data	No data	**0.90 (0.84-0.97)**	**0.90 (0.84-0.97)**
CABG	**0.74 (0.67-0.82)**	No data	No data	**0.76 (0.66-0.87)**	**0.76 (0.66-0.87)**
PTCA	**0.78 (0.67-0.90)**	No data	No data	**0.79 (0.67-0.94)**	**0.79 (0.67-0.94)**
CABG + PTCA	**0.75 (0.70-0.81)**	0.72 (0.49-1.21)	0.72 (0.43-1.21)	**0.77 (0.69-0.85)**	**0.77 (0.69-0.85)**
CHD death plus nonfatal MI	**0.74 (0.71-0.77)**	**0.66 (0.46-0.96)**	**0.64 (0.50-0.82)**	**0.73 (0.68-0.80)**	**0.74 (0.69-0.79)**

Although there is no significant difference, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention, there is a difference in terms of absolute risk reduction, and therefore in terms of the number needed to treat to avoid an event. Because, as noted in section 3.1.5 above, both absolute risk and numbers needed to treat include a time dimension, it is not possible to base those estimates on data from all the studies which have been combined in the meta-analyses of relative risk, as these vary in length. Therefore, for primary CHD prevention, absolute risk and numbers needed to treat have been derived from the largest study of primary CHD prevention, the ASCOT-LLA study, which has a median follow-up of 3.3 years (see Table 17).

Table 17: Primary CHD prevention: absolute risk reduction and numbers needed to treat

ASCOT-LLA study	Risk of event in placebo arm	Absolute risk reduction (95% CI)	Number needed to treat for approximately 3 years to avoid an event (95% CI)
All-cause mortality	4.13%	0.55% (-0.20 to 1.29)	183*
CHD mortality	Not reported		
Total stroke	2.36%	0.63% (0.09 to 1.18)	158 (84.8 to 1141.4)
CHD mortality + nonfatal MI	3.00%	1.06% (0.46 to 1.66)	95 (60.2 to 215.5)

*Not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial)

Numbers needed to treat to avoid key outcomes have also been calculated for the three largest studies of secondary CHD prevention: 4S, CARE and LIPID (see Table 18). The length of time to which the treatment effect applies is 5.0 years for the CARE study, 5.4 years for 4S, and 6.1 years for the LIPID study.

Table 18: Secondary CHD prevention: absolute risk reduction and numbers needed to treat

Study/outcome	Risk of event in placebo arm	Absolute risk reduction (95% CI)	Number needed to treat to avoid an event (95% CI)
4S			
All-cause mortality	11.52%	3.32% (1.57 to 5.07)	31 (19.7 to 63.6)
CHD mortality	8.50%	3.50% (2.03 to 4.98)	29 (20.1 to 49.2)
Total stroke	Not reported		
CHD mortality + nonfatal MI	27.98%	8.57% (6.09 to 11.06)	12 (9.0 to 16.4)
CARE			
All-cause mortality	9.43%	0.78% (-0.96 to 2.53)	128*
CHD mortality	5.73%	1.11% (-0.23 to 2.46)	90*
Total stroke	3.66%	1.16% (0.11 to 2.21)	87 (45.3 to 915.6)
CHD mortality + nonfatal MI	13.19%	3.00% (1.05 to 4.95)	34 (20.2 to 95.5)
LIPID			
All-cause mortality	14.06%	3.02% (1.66 to 4.39)	34 (22.8 to 60.4)
CHD mortality	8.29%	1.92% (0.85 to 3.00)	52 (33.3 to 117.7)
Total stroke	4.53%	0.79% (-0.04 to 1.61)	128*
CHD mortality + nonfatal MI	15.88%	3.54% (2.10 to 4.97)	29 (20.1 to 47.6)

*Not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial)

Unfortunately, the studies included in Tables 17 and 18 do not provide data on the number of patients suffering CHD mortality, nonfatal MI or any stroke, so the number needed to treat to avoid any of these three outcomes cannot be calculated, as the addition of the figures relating to patients who had suffered a stroke to the total of patients who had suffered CHD death or a nonfatal MI would incur the risk of double-counting.

Because the studies differ in length, the absolute risk reduction and numbers needed to treat relate to different lengths of time. Nonetheless, it is clear that the number of people needed to treat to avoid an event is lower in secondary prevention than in primary prevention, even though the ASCOT-LLA population was a primary prevention population which was at relatively high risk of a cardiovascular event. At first sight, it seems surprising that the absolute risk of CHD mortality or nonfatal MI is so much higher, and the number needed to treat to avoid such an event consequently considerably smaller, in the 4S study compared with the CARE and LIPID trials. This does not seem due to differences in the study populations, and is more likely to be due to the level of crossover in those trials: fewer than 1% of patients in the 4S study who were randomised to placebo received lipid-lowering drugs, [95] compared with 8% in the CARE study[102] and 24% in the LIPID study. [103]

It is important that patients with CHD risk factors other than, or additional to, elevated cholesterol levels should receive appropriate treatment for those risk factors, both because of their potential contribution to CHD risk and because they may also be associated with other health problems (as in the case of smoking and lung cancer, or diabetes and diabetic retinopathy and neuropathy). However, it is not clear to what extent optimising the treatment of CHD risk factors other than cholesterol impacts on the effectiveness of statins. One placebo-controlled trial, ASCOT-LLA, recruited hypertensive patients with total cholesterol concentrations $\leq$ 6.5 mmol/L; these patients received aggressive antihypertensive therapy. [94] In that study, the relative risk of CHD death plus nonfatal MI (0.65, 95% CI 0.50-0.83) was comparable with the overall result of the meta-analysis (RR 0.74, 95% CI 0.71-0.77, see Figure 7).

3.2.1.5.2.7 Placebo-controlled studies: results from Bayesian meta-analysis

A Bayesian meta-analysis has been undertaken in addition to the classical meta-analysis reported in sections 3.2.1.5.2.1 to 3.2.1.5.2.6 above. The Bayesian evidence synthesis provides the same inputs to the model as the classical meta-analysis i.e. the relative risk (RR) of the effect of statins for the event states in the model. The Bayesian method has the important benefit of being able to incorpoate correlations between outcomes in the subsequent economic analysis.

Since some of the five events are mutually exclusive, conditional relative risks were considered as shown in Table 19.

Table 19 : Relative risks (RR) from Bayesian meta-analysis

	No of trials	Mean	2.5th percentile	Median	97.5th percentile
RR of CHD death	27	0.740	0.640	0.741	0.824
RR of CVD death, conditional on no CHD death	12	0.854	0.601	0.851	1.106
RR of unstable angina, conditional on no death	7	0.716	0.293	0.754	0.990
RR of non-fatal MI, conditional on no death	24	0.656	0.553	0.657	0.746
RR of non-fatal stroke, conditional on no death	11	0.769	0.634	0.769	0.906

The relative risks from the Bayesian analysis are generally similar to those from the standard meta-analysis, given in the first column of Table 16. In the case of RR of CVD death in table 18 this is the risk of CVD death having excluded CHD death and is therefore most comparable with stroke mortality from Table 16. In both cases the confidence interval cross 1, indicating the impact is non significant

3.2.1.5.2.8 Placebo-controlled studies: discussion of results

The results from the placebo-controlled trials are likely to be conservative as a result of the degree of crossover (use of lipid-lowering therapies, in particular statins, in the placebo arm, and non-compliance with study therapy in the statin arm) reported in many studies. In some studies, the use of lipid-lowering therapy in the placebo arm was pre-planned. For example, in ASCOT-LLA, patients whose dyslipidaemia was judged by their physician to require additional lipid-lowering therapy could receive open-label treatment in addition to trial treatment: after 3 years of follow-up, 9% of the placebo group had been prescribed open-label statins. [94] Similarly, in the LIPS study, patients whose total cholesterol exceeded 7.2 mmol/L for 3 months or longer could discontinue study therapy at the investigator's discretion and receive an open-label statin or other lipid-lowering therapy. As a result, 10.7% of patients in the treatment arm and 24% in the placebo arm started taking other lipid-lowering medications (mainly statins) before their first major adverse cardiac event or completion of follow-up. [101] In the LIPID study, although study personnel and patients remained unaware of lipid results from the core laboratory, [113] the patient's general care was at the discretion of the patient's own doctor, and this allowed changes in lipid treatment to be made in the light of local cholesterol results. [114] The investigators recognised that the difference in the incidence of events between treatment groups was likely to have been reduced by the large numbers of patients in the placebo group who ultimately received cholesterol-lowering therapy outside the study combined with those in the pravastatin group who discontinued treatment. [103]

In other studies, the use of lipid-lowering drugs in the placebo arm was not pre-planned. When the results of the 4S study were published in 1994 (less than half way through the SCAT trial), the SCAT investigators deemed it unethical to keep on placebo patients whose total cholesterol persistently exceeded 5.5 mmol/L. Consequently, the protocol was modified to permit such patients to be identified and reallocated, in a double-blind fashion, to simvastatin. It is not stated how many patients this affected. [110] In addition, in the LIPS study, there was anecdotal evidence that many patients were aware of their total cholesterol levels as these had been tested by primary care physicians who were not involved in LIPS; as a result these patients were no longer blinded to their treatment allocation. [87]

Only two studies reported mean statin use in both the placebo and treatment arms, enabling an estimate of the extent to which the intention-to-treat analysis might underestimate the full potential effect of statin treatment. In the HPS study, average statin use during the scheduled treatment period was said to be 85% in the simvastatin-allocated group and 17% in the placebo-allocated group; thus, the average absolute difference in statin use between all those randomised to simvastatin and all those randomised to placebo was 67% (85% minus 17%), suggesting that the intention-to-treat analyses represent the effects of about two-thirds of the statin group taking 40 mg/d simvastatin. [71] However, non-study statin use in the placebo arm was not random, but was more common in patients with diagnosed CHD at entry, in younger participants and, particularly, in those with higher baseline total cholesterol or LDL-C, and therefore the reduction in the apparent effect of therapy in the statin arm may be even greater than suggested. In the CARDS study, mean noncompliance in the study arm was 15% and mean statin use in the placebo arm 9%,[98] suggesting a potential reduction of 24% in the treatment effect.

The generalisability of the results reported above is limited by the exclusion, in some studies, of patients who were hypersensitive to or intolerant of statins, [115,89,116] who were known to be unresponsive to statins, [71,117,116,107] or who were not adequately compliant with study medication during a placebo run-in phase. [114,115] A considerable proportion of potential participants may have been excluded in this way: in the HPS study, around 30% of those who entered the run-in phase either chose not to continue in the study or were deemed unlikely to be compliant long-term. [115]

3.2.1.6.1 Direct statin:statin comparisons

3.2.1.6.2 Quantity and quality of research available: direct statin:statin comparisons

Three studies were identified which directly compared two different statins and which reported clinical outcomes. All three were in patients with symptomatic CHD. The 3T study compared atorvastatin with simvastatin in adults with CHD and dyslipidaemia. [79] PROVE IT-TIMI compared atorvastatin with pravastatin in patients who had been hospitalised with acute coronary syndrome (either acute MI or high-risk unstable angina) in the previous 10 days. [118] The REVERSAL study compared atorvastatin with pravastatin in patients requiring coronary angiography for a clinical indication. [86] (For further details of these studies, see Appendix 12.)

A further two studies of 6 months or longer were identified which compared the LDL-C-lowering efficacy of rosuvastatin (5mg and 10mg) with that of atorvastatin in patients with hypercholesterolaemia in Northern Europe (Study 452II/0026[119]) and with that of pravastatin or simvastatin in similar patients in the USA (Study 452II/0028[120]). These studies did not report clinical outcomes. In both studies, each statin was started at the lowest stated dose, and this dose was maintained for a 12-week period. During the following 40-week period, the dose could be sequentially doubled at weeks 12, 20, 28, 36 and 44 in study 45211/0026, [119] and at weeks 20, 28, 36 and 44 in study 45211/0028, [120] up to the maximum stated dose (for details, see Appendix 12).

In Study 452II/0026, mean doses over the 40-week titration period were as follows:

- Group 1: 9.3 mg/day rosuvastatin
- Group 2: 13.4 mg/day rosuvastatin
- Group 3: 20.8 mg/day atorvastatin. [119]

In Study 452II/0028, mean doses over the 40-week titration period were as follows:

- Group 1: not reported
- Group 2: 13.8 mg/day rosuvastatin

- Group 3: 32.6 mg/day pravavastatin
- Group 4: 36.3 mg/day simvavastatin. [120]

3.2.1.6.2 Assessment of effectiveness: direct statin:statin comparisons

Although the PROVE IT-TIMI and REVERSAL studies compared the same interventions, it was not possible to combine their results in a meta-analysis because PROVE IT-TIMI only reported the percentage of patients in each arm, rather than the number, who experienced an event. The results of the individual studies are therefore summarised in Table 20 below.

Table 20: Direct statin: statin comparisons: statins in secondary CHD prevention: relative risk, or relative risk reduction, of event with atorvastatin compared with pravastatin or simvastatin

Outcome	**3T atorvastatin 20-40 mg/d vs simvastatin 20-40 mg/d**	**PROVE IT-TIMI atorvastatin 80 mg/d vs pravastatin 40 mg/d (risk reductions calculated by investigators)**	**REVERSAL atorvastatin 80 mg/d vs pravastatin 40 mg/d**
All-cause mortality	Not reported	28%, p=0.07	1.00 (0.06-15.92)
Total stroke	2.90 (0.12-70.97)	-9%, NS	1.00 (0.06-15.92)
Total MI	0.32 (0.01-7.89)	13%, NS	0.57 (0.17-1.93)
Hospitalisation for unstable angina	Not reported	29%, p=0.02	Not reported
Coronary revascularisations	Not reported	14%, p=0.04	Not reported
CHD death or nonfatal MI	Not reported	18%, p=0.06	Not reported
CHD death, nonfatal MI, or coronary revascularisation	Not reported	14%, p=0.029	Not reported
All-cause mortality, MI, hospitalisation for documented unstable angina, revascularisation (performed at least 30 days after randomisation), stroke	Not reported	16% (95% CI 5-26%) p=0.005	Not reported

Rosuvastatin appeared to be more effective than atorvastatin, pravastatin and simvastatin in reducing total and LDL cholesterol (see Table 21).

Table 21: Mean percent change in lipid variables from baseline at 52 weeks (standard error)

	Rosuvastatin 5-80 mg/d	Rosuvastatin 10-80 mg/d	Atorvastatin 10-80 mg/d	Pravastatin 20-40 mg/d	Simvastatin 20-80 mg/d
Study 45211/0026[119]					
Total cholesterol	-34 (0.9)	-38 (1.0)	-33 (0.9)	N/A	N/A
LDL-C	-47(1.2)	-53 (1.2)	-44 (1.1)	N/A	N/A
HDL-C	+2 (1.3)	+3 (1.4)	-1 (1.3)	N/A	N/A
Triglycerides	-20 (2.4)	-21 (2.6)	-19 (2.4)	N/A	N/A
LDL-C/HDL-C	-48 (1.3)	-54 (1.4)	-43 (1.3)	N/A	N/A
Total-C/HDL-C	-35 (1.1)	-40 (1.1)	-32 (1.0)	N/A	N/A
Study 45211/0028[120]					
Total cholesterol	-30.1 (1.1)	-34.2 (1.1)	N/A	-22.8 (1.1)	-27.0 (1.1)
LDL-C	-41.6 (1.4)	-48.0 (1.4)	N/A	-31.6 (1.4)	-37.9 (1.4)
HDL-C	+4.5 (1.3)	+7.6 (1.3)	N/A	+4.5 (1.4)	+6.2 (1.3)
Triglycerides	-15.8 (2.6)	-18.0 (2.7)	N/A	-9.3 (2.7)	-14.1 (2.6)
LDL-C/HDL-C	-43.3 (1.5)	-51.1 (1.6)	N/A	-34.1 (1.6)	-40.8 (1.5)
Total-C/HDL-C	-32.3 (1.3)	-38.2 (1.3)	N/A	-25.6 (1.3)	-30.4 (1.3)

3.2.1.6.3 Direct statin:statin comparisons: discussion

As may be seen, the only statistically significant results are those reported by the PROVE IT-TIMI investigators for hospitalisations for unstable angina, coronary revascularisations, and for two composite endpoints: in each case, the results favour atorvastatin. However, no significant difference was found between atorvastatin and pravastatin in terms of the most important composite endpoint, CHD mortality plus nonfatal MI. The investigators found the results of the PROVE IT-TIMI study difficult to interpret because of the difficulty, if not impossibility, of determining whether any benefit seen in the atorvastatin group was due solely to the aggressive reduction in LDL-cholesterol, compared with the moderate reduction achieved with the lower dose of pravastatin (median LDL-C fell from 2.74 mmol/L in each group to 2.46 mmol/L in the pravastatin group and 1.60 mmol/L in the atorvastatin group, $p<0.001$), or to individual or inherent differences in the statins themselves. [118] In practice, however, this seems to be of little relevance as both statins were used at their maximum licensed dose.

In the absence of any direct evidence relating to the effect of treatment with rosuvastatin on clinical outcomes, some indication of the possible impact of treatment may perhaps be obtained by comparing the lipid-lowering effects of rosuvastatin with the lipid-lowering and clinical effects of statin therapy in the major placebo-controlled trials which report these outcomes. The effects of therapy on LDL-C and CHD death plus nonfatal MI are summarised in Table 22 below. It should be noted that the 4S study did not use simvastatin at its maximum licensed dose of 80 mg/d.

Table 22: Results from major placebo-controlled studies

Study	Mean baseline LDL-C (mmol/L)	Length of follow-up	Intervention	Mean change from baseline in LDL-C		Change in LDL-C in treatment group relative to placebo group	CHD death + nonfatal MI: relative risk (95% CI)
				Treatment group	Placebo group		
ASCOT-LLA	3.4	3.3 years	Atorvastatin 10 mg/d	Not reported	Not reported	-29%	0.65 (0.50-0.83)
LIPS	3.4	3.9 years	Fluvastatin 80 mg/d	-27%	+11%	-38%	0.69 (0.47-1.01)
CARE	3.6	5 years	Pravastatin 40 mg/d	-32%	Not reported	-28%	0.77 (0.65-0.91)
LIPID	3.9	5 years	Pravastatin 40 mg/d	Not reported	Not reported	-25%	0.78 (0.70-0.86)
PROSPER	3.8	3.2 years	Pravastatin 40 mg/d	Not reported	Not reported	-27% at 2 years	0.83 (0.71-0.96)
4S	4.9	5.4 years	Simvastatin 20-40 mg/d	-35%	+1%	-36%	0.69 (0.62-0.77)

These results suggest that studies which achieve a reduction in LDL-C relative to placebo of 25-29% achieve a 17-35% reduction in the risk of CHD death plus nonfatal MI, while studies which achieve a 36-38% reduction in LDL-C achieve a 31% reduction in the risk of CHD death plus nonfatal MI. The data summarised in Table 21 above indicate that rosuvastatin is capable of achieving a reduction in LDL-C of up to approximately 50% in patients with a mean baseline LDL-C of 4.9 mmol/L (noticeably higher than in the studies summarised in Table 22 above, with the exception of the 4S study). However, it is not clear how this reduction in LDL-C would translate into a reduction in clinical events given that, in Table 22, the largest relative reduction in clinical events does not occur in the study with the largest relative reduction in LDL-C. In support of this, preliminary results from the 4D study indicate that atorvastatin was associated with a mean reduction of 41% in LDL-C, but only with a non-significant reduction of 8% in the primary endpoint, the combined incidence of cardiac death, nonfatal MI, and stroke. [91]

3.2.1.7 Comparisons with 'usual care'

3.2.1.7.1 Quantity and quality of research available: comparisons with 'usual care'

Four open-label studies compared a statin with 'usual care': ALLHAT-LLT, [121] ALLIANCE, [84] ESTABLISH, [85] and GREACE. [122] Three of these studies (ALLIANCE, ESTABLISH and GREACE) used atorvastatin in patients with a history of CHD. The fourth study, ALLHAT-LLT, studied pravastatin in moderately hypercholesterolaemic patients aged >55 years with well-controlled hypertension with and without CHD. For further details, see Appendix 13.

3.2.1.7.2 Assessment of effectiveness: comparisons with 'usual care'

When meta-analysed, the results of these studies suggest that, in comparison with 'usual care', statins are associated with statistically significant reductions in the risk of nonfatal MI (RR 0.51, 95% CI 0.39-0.67), and of a composite of CHD death and nonfatal MI (RR 0.65, 95% CI 0.44-0.96); they were not associated with a significant reduction in the risk of any other event (for full details, see Appendix 14). These results should be treated with caution. The study whose results are most favourable to statin therapy, the GREACE study, is flawed. Patients who received atorvastatin also received hospital-based structured care designed to achieve a specified target LDL-C level, while the control group only received community-based 'usual care'. As a result, it is difficult to determine the extent to which the better outcomes seen in the atorvastatin arm are due to the use of atorvastatin, and the extent to which they are due to other components of the package of care which differed from those experienced by patients in the control arm. Certainly, although the use of both aspirin and beta-blockers was virtually identical in both groups, only 14% of patients in the 'usual care' arm are said to have received hypolipidaemic drug therapy of any sort throughout the study, compared with 98% in the atorvastatin arm. [122] By comparison, by the end of the ALLHAT-LLT study 26% of the 'usual care' arm were receiving a statin, and 2.4% another lipid-lowering drug, while only 70% of the pravastatin arm were receiving pravastatin at the planned dose of 40 mg/d (another 7% were taking pravastatin at a lower dose, 6% were taking a non-study statin, 0.6% were taking another lipid-lowering drug, and 16% were not taking any lipid-lowering drug). [121] Similarly, in the ALLIANCE study, patients in the 'usual care' arm were maintained on their original lipid-lowering therapy (which included diet, behaviour modification, and anti-hyperlipidaemic medication, including atorvastatin), with adjustments made entirely at the discretion of their regular physicians: 66% were receiving lipid-lowering therapy at baseline. [84] It therefore seems plausible that the particularly favourable results seen in the GREACE study compared with ALLIANCE and ALLHAT-LLT are attributable to a lower standard of 'usual care' in the former study. However, it should be noted that, despite substantial use of lipid-lowering therapies in the control arm, the ALLIANCE study also found that atorvastatin was associated with a statistically significant reduction in the risk of nonfatal MI and CHD death plus nonfatal MI.

3.2.1.8 Comparisons with 'no statin'

3.2.1.8.1 Quantity and quality of research available: comparisons with 'no statin'

Three open-label studies compared a statin with no statin treatment in patients with CHD: Colivicchi 2002, [123] Sato 2001[83] and GISSI-P. [124] One of these was a very small study of the effect of adding atorvastatin to conventional medical treatment in patients with end-stage CAD who were already receiving conventional combination therapy. [123] Another studied the use of low-dose pravastatin in patients with a recent myocardial infarction in a Mediterranean population. [124] The third used pravastatin in normocholesterolaemic Japanese patients with coronary atherosclerosis. [83] For further details of these studies, see Appendix 15.

3.2.1.8.2 Assessment of effectiveness: comparisons with 'no statin'

Meta-analysis of the data from the studies which compared statins with no statin therapy yielded a statistically significant result only in relation to one endpoint, CHD mortality (RR 0.64, 95% CI 0.42-0.98) (for full details, see Appendix 16). This general failure to demonstrate a treatment effect other than for this one outcome seems due in part to the small size of the Colivicchi and Sato studies, and in part to crossover. In the Colivicchi study, all patients in the control arm who were already receiving statins or other lipid-lowering drugs before inclusion in the study continued to use these after randomisation, with the dosage titrated to reach LDL-C levels below 2.59 mmol/L. Any patients in the control arm who failed

to achieve LDL-C levels lower than 2.59 mmol/L could receive atorvastatin (initiated at 20 mg/d). Thus, 83% of patients in the control arm received statins, and 10% received fibrates, although no lipid-lowering drug other than atorvastatin was allowed in the intervention arm. [123] In the GISSI-P study, 19% of the control group started lipid-lowering treatment (mainly with pravastatin) during the course of the study, mainly as a result of a protocol modification following publication of the results of the 4S study, while 2% of patients in the pravastatin arm were prescribed an adjunctive cholesterol-lowering drug. [124] The third study did not provide any information on the use of non-study statins or other lipid-lowering drugs. [83]

3.2.1.8.3 Summary: comparisons with 'usual care' and 'no statin'

The results of the studies which compare a statin with 'usual care' and 'no statin' are difficult to interpret, largely because of lack of clarity about the interventions used in the control groups. As a result, they appear to add little to our understanding of the benefits of statin therapy.

3.2.1.9 Dose comparisons

3.2.1.9.1 Quantity and quality of research available: dose comparisons

Two studies were identified which compared two doses of the same statin. The A-to-Z study compared the early use of an aggressive dose of simvastatin (40 mg/d for 30 days, then 80 mg/d) with 4 months' placebo treatment followed by a lower dose of simvastatin (20 mg/d) in patients with acute coronary syndrome and total cholesterol $\leq$6.5 mmol/L. [125] The PATE study compared low-dose pravastatin (5 mg/d) with the standard Japanese dose of 10-20 mg/d in a population of elderly Japanese patients with hypercholesterolaemia with and without previous cardiovascular disease[126] (for details see Appendix 17).

3.2.1.9.2 Assessment of effectiveness: dose comparisons

In the A-to-Z study, the use of an aggressive dose of simvastatin was associated with a statistically significant reduction in the risk of cardiovascular mortality (RR 0.75, 95% CI 0.57-0.99), although not of any other clinical outcomes. [125] The PATE study did not show a statistically significant result in relation to any clinical endpoint, even when all fatal and nonfatal cardiovascular events were pooled[126] (for details see Appendix 18).

3.2.1.10Subgroups

Particular interest has been expressed in the effectiveness of statins in specific subgroups, especially women, people with diabetes, the elderly (defined here as people aged 65 and over), cardiac and renal transplant recipients, people with familial hypercholesterolaemia, and those with relatively low serum cholesterol. The evidence from placebo-controlled studies relating to each of these subgroups is discussed in turn below.

3.2.1.10.1 Women

Although several of the included placebo-controlled studies were carried out specifically in men, [127,107,78] none were carried out specifically in women. Consequently, the results for women are derived from subgroup analyses from studies carried out in mixed populations. This is problematic as none of those studies stratified randomisation by sex (with the possible exceptions of the ASCOT-LLA and HPS studies which randomised using minimisation and did not state which characteristics informed the minimisation algorithm). As a result, none of the data relating to women are known to represent true randomised comparisons, nor are those

data relating to men which are not derived from the KAPS, REGRESS and WOSCOPS studies.

Such data as were available in suitable form were combined by meta-analysis. The LIPID and LIPS studies presented data in a form which did not allow them to be included in the meta-analyses, and therefore their results are summarised separately. Although the results of the meta-analyses should be treated with caution, they suggest that statin treatment in women is associated with a statistically significant reduction in the relative risk of nonfatal MI, coronary revascularisation, and CHD death plus nonfatal MI. Failure to achieve significant results in relation to other outcomes is likely to be due to the small numbers involved. When the results are divided into primary and secondary prevention, statin therapy in women is associated with a significant reduction in risk of CHD death plus nonfatal MI in secondary prevention (RR 0.75, 95% CI 0.61-0.92) but not in primary prevention (RR 1.10, 95% CI 0.57-2.10), whereas in men statin therapy was associated with a statistically significant reduction in risk in both secondary and primary prevention (RR 0.77 (95% CI 0.70-0.85) and 0.59 (95% CI 0.45-0.77) respectively); again, this failure to achieve a statistically significant result in primary prevention in women may be due to the small numbers involved. Thus, although the incidence of CHD is lower in women than in men, there is no evidence that the effectiveness of statins differs in women relative to men at the same level of cardiovascular risk as, for each outcome, although the point estimates of effect may vary, the confidence intervals overlap (for data, see Appendix 19).

3.2.1.10.2 People with diabetes

Two of the included placebo-controlled studies were carried out specifically in people with diabetes, [98,82] but none were carried out specifically in people without diabetes. Consequently, the results for people without diabetes which are presented below are derived entirely from subgroup analyses from studies carried out in mixed populations. As noted above in relation to women, this is problematic as randomisation was not stratified by diabetes status in any of the studies, with the possible exceptions of the ASCOT-LLA and HPS studies which randomised using minimisation, and did not state which characteristics were utilised. As a result, only those data relating to people without diabetes, and those data relating to people with diabetes which are derived from the CARDS or DALI studies, definitely represent true randomised comparisons.

For comparability with the CARDS and DALI studies, which recruited patients who had been diagnosed with type 2 diabetes at least 6 months[98] and a year[82] respectively before study entry, the data used from the 4S and LIPID studies are those relating to patients with and without a clinical history of diabetes at study entry[95,128] rather than those relating to patients who either had known diabetes at study entry or were found to have impaired fasting glucose.[129,130]

Where data were available in suitable form, they were combined by meta-analysis. As the HPS study presented data in a form which did not allow them to be included in the meta-analyses, its results are summarised separately (see Appendix 19). Although these results should again be treated with caution, statin therapy in people with diabetes appears to be associated with a statistically significant reduction in the relative risk of all-cause mortality, fatal and nonfatal MI, PTCA, and a composite of CHD death, nonfatal MI and coronary revascularisation. Failure to achieve significant results in relation to other outcomes is again probably due to the small numbers involved. There is no evidence that statins are either more or less effective in people with diabetes than in those without as, although for some outcomes the point estimates of effect may vary, in all cases the confidence intervals overlap. Although the incidence of CHD is higher in people with diabetes than in those without, the numbers of

people with diabetes are too small to indicate any difference in the effect of statins when used for primary or secondary prevention in diabetic patients.

It is difficult to compare the effect of statins in people with and without diabetes in terms of absolute risk reduction and numbers needed to treat. The best evidence for people with diabetes comes from the CARDS study, a large study conducted entirely in people with diabetes but without either raised cholesterol levels or a clinical history of cardiovascular disease. [131] Not surprisingly, in this population the numbers needed to treat to avoid an event are relatively large (see Table 23).

Table 23: People with diabetes: absolute risk reduction and numbers needed to treat

CARDS	**Risk of event in placebo arm**	**Absolute risk reduction (95% CI)**	**Number needed to treat for approximately 4 years to avoid an event (95% CI)**
All-cause mortality	5.82%	1.70% (0.11 to 3.29)	59 (30.4 to 880.5)
CHD mortality	1.77%	0.36% (-0.56 to 1.27)	281*
Total stroke	2.77%	1.35% (0.30 to 2.40)	75 (41.7 to 330.5)
CHD mortality + nonfatal MI	Not reported		

*Not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial)

As most of the data relating to people without diabetes are derived from studies of secondary prevention (4S, CARE, LIPID), no direct comparison can be made with the CARDS study. It is possible to compare subgroup data for CHD death plus nonfatal MI from the ASCOT-LLA study of primary CHD prevention and the CARE study of secondary CHD prevention (see Table 24) but, although in both primary and secondary prevention the risk of an event in the placebo arm is higher in patients with diabetes than in those without, the studies are not able to demonstrate that, as a result, the number needed to treat to avoid an event is smaller in people with diabetes than in those without.

Table 24: CHD death plus nonfatal MI: people with and without diabetes: absolute risk reduction and numbers needed to treat

	Risk of event in placebo arm	**Absolute risk reduction (95% CI)**	**Number needed to treat to avoid an event (95% CI)**
Primary CHD prevention (ASCOT-LLA)			**Treatment period approximately 3.3 years**
People with diabetes	3.61%	0.59% (-0.80 to 1.98)	170*
People without diabetes	2.80%	1.21% (0.56 to 1.86)	83 (53.7 to 178.8)
Secondary CHD prevention (CARE)			**Treatment period approximately 5 years**
People with diabetes	20.39%	2.66% (-3.69 to 9.02)	38*
People without diabetes	11.95%	2.95% (0.94 to 4.95)	34 (20.2 to 106.6)

*Not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial)

3.2.1.5.10.3 Elderly patients

One of the included placebo-controlled studies, the PROSPER study, was carried out specifically in elderly people (aged 70-82). [77] The 4S and CARE studies presented subgroup data relating to people aged under 65, and those aged 65 and over, but in these studies randomisation was not stratified by age, and therefore such subgroup data do not represent true randomised comparisons.

Although the results should again be treated with caution, in people aged 65 and over statin treatment appears to be associated with a statistically significant reduction in the relative risk of CHD mortality, total stroke, nonfatal MI, coronary revascularisation, and CHD death plus nonfatal MI. Failure to achieve significant results in relation to other outcomes is again probably due to the small numbers involved. Again, there is no evidence that statins are more or less effective in older people and in those aged under 65 as, although the point estimates of effect vary, the confidence intervals overlap.

It is again difficult to compare the effect of statins in people aged under 65 and in those aged 65 and over in terms of absolute risk reduction and numbers needed to treat. As the PROSPER study was a mixture of primary and secondary prevention, [77] whereas the 4S and CARE studies were both of secondary CHD prevention, they are not directly comparable; moreover, all were of different length. However, subgroup analysis of the CARE study indicates that, in secondary CHD prevention, the number needed to treat to prevent CHD death or nonfatal MI is substantially lower in patients aged 65 and over than in younger patients (see Table 25).

Table 25: CHD death plus nonfatal MI: people aged <65 and ≥65 years: secondary CHD prevention: absolute risk reduction and numbers needed to treat

CARE study	Risk of event in placebo arm	Absolute risk reduction (95% CI)	Number needed to treat for approximately 5 years to avoid an event (95% CI)
People aged <65	11.36%	1.44% (-0.82 to 3.69)	70*
People aged ≥65	17.26%	6.48% (2.70 to 10.26)	16 (9.7 to 37.0)

*Not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial)

3.2.1.10.4 Cardiac transplant recipients

Only one placebo-controlled statin study was identified in cardiac transplant patients. This was a small study of 40 mg/d fluvastatin in patients with hyperlipidaemia 3 months to 12 years after cardiac transplant. [132] In addition, one very small study directly compared two statins (pravastatin 20 mg/d and simvastatin 10 mg/d) in adults undergoing cardiac transplant. [90] A further two studies compared statin therapy with no statin in patients who had received cardiac transplants either 1-2 weeks[133] or 4 days[134] previously (for further details, see Appendix 20).

None of these studies had statistically significant results in relation to clinical outcomes (for further details, see Appendix 21.)

3.2.1.10.5 Renal transplant recipients

Only one study was identified which studied the use of a statin (fluvastatin 40-80 mg/d) in renal transplant recipients. In this study, 15% of participants had previously experienced a cardiac, cerebrovascular or other vascular event[135] (for further details, see Appendix 22).

Treatment with fluvastatin reduced the risk of CHD death plus nonfatal MI (RR 0.67, 95% CI 0.50-0.90). None of the other clinical outcomes yielded statistically significant results (for further details, see Appendix 23). However, the power of the study will have been reduced by the fact that 14% of the placebo group took non-study lipid-lowering drugs (mainly statins), as did 7% of the fluvastatin group.

3.2.1.10.6 People with familial hypercholesterolaemia

No placebo-controlled studies were identified relating to this patient group. This is not surprising: these patients are at very high risk of cardiac events, and the current medical consensus is therefore that the benefits of statin therapy in this group are undeniable, making a placebo-controlled study unethical.

One relevant study, [81] a direct statin:statin comparison, was identified. This was carried out in patients with known heterozygous familial hypercholesterolaemia, 31% of whom had known cardiovascular disease at study entry (for details, see Appendix 24). The study compared atorvastatin 80 mg/d with simvastatin 40 mg/d. As its primary endpoint was atherosclerosis progression as measured by carotid intima media thickness, it was underpowered to demonstrate an effect in terms of clinical outcomes. Moreover, the difference in outcomes between the two groups was potentially reduced as, in accordance with the study protocol, any participant whose serum cholesterol concentrations remained higher than 8.0 mmol/L on two consecutive visits was given a resin in addition to the study medication. 15% of those in

the simvastatin group required this treatment, compared with only 2.5% of those in the atorvastatin group.

In this study, clinical outcomes were reported only as reasons for withdrawal from the study. In the case of nonfatal outcomes, it is not clear whether other participants with those outcomes might have remained in the study: as clarification on this point could not be obtained from the study investigators, only mortality data are reported here. No significant difference was demonstrated between the two interventions (for details, see Appendix 25).

3.2.1.10.7 Ethnic minorities

No studies were identified which provided information relating to populations from the Indian subcontinent, and the only study to present subgroup analyses of black and non-black ethnic groups was the ALLHAT-LLT study of pravastatin versus 'usual care', in which nearly 40% of participants were black. However, as the study was carried out in north America, Puerto Rico and the US Virgin Islands, [121] the ethnic mix of that black population would differ considerably from that of the black population of England and Wales.

The results of subgroup analyses for black and non-black participants are summarised in Appendix 26. Interestingly, although there appears no difference between the subgroups in terms of all-cause mortality, pravastatin reduced the risk of CHD death plus nonfatal MI significantly in black but not in non-black populations. However, too much weight should not be put upon this finding, for two reasons. First, randomisation was not stratified by ethnic group, and therefore the subgroup findings are not true randomised comparisons. Secondly, the comparator in this study was 'usual care', and it is possible that the 'usual care' given to black ethnic groups may have differed from that given to non-black groups, and that this may have had the effect of enhancing the apparent efficacy of pravastatin in black patients.

3.2.1.10.8 Patients with different baseline LDL-C

Logically, one might expect the relative reduction in risk of CHD death and nonfatal MI associated with statin therapy to be greatest in those populations with the highest serum cholesterol levels at baseline. However, there is no clear evidence to support this suggestion. Only one study, PLAC I, stratified randomisation by baseline LDL-C; this reported the effect of statin therapy in patients with baseline LDL-C <4.14 mmol/L, but did not provide the equivalent data for those with baseline LDL-C ≥4.14 mmol/L for comparison. [104] A further two placebo-controlled studies which had not stratified randomisation by baseline cholesterol nonetheless analysed the effects of statin therapy in subgroups with higher and lower baseline LDL-C levels; these are therefore not true randomised comparisons. In the CARDS study, the hazard ratio for a composite endpoint of a major coronary event, revascularisation, unstable angina, resuscitated cardiac arrest, or stroke was virtually identical in those with baseline LDL-C < and ≥3.1 mmol/L. [98] In the WOSCOPS study, the point estimate of the relative reduction in the risk of CHD death or nonfatal MI associated with statin therapy in fact appeared greater, at 37% (95% CI 15-53%), in patients whose baseline LDL-C was less than 4.9 mmol/L than in those with baseline LDL-C ≥4.9 (risk reduction 27%, 95% CI 6-43%), although the confidence intervals overlapped. [78]

Table 26 summarises data from those placebo-controlled studies whose participants had the highest and lowest mean baseline LDL-C. Again, the confidence intervals overlap, and the point estimates are often very similar, again suggesting that statins are no less effective in reducing the risk of CHD death and nonfatal MI in people with relatively low baseline LDL-C than in those with higher cholesterol levels.

Table 26: Statin therapy: relative risk of CHD death and nonfatal MI, by mean baseline LDL-C

Study	Mean baseline LDL-C	Relative risk	95% CI
CARDS	3.0	0.65	0.45-0.95
ASCOT-LLA	3.4	0.65	0.50-0.83
HPS	3.4	0.74	0.68-0.80
LIPS	3.4	0.69	0.47-1.01
CARE	3.6	0.77	0.65-0.91
CIS	4.3	0.28	0.06-1.31
CAIUS	4.7	1.02	0.15-7.15
4S	4.9	0.69	0.62-0.77
KAPS	4.9	0.62	0.21-1.87
WOSCOPS	5.0	0.70	0.58-0.84
LiSA	5.1	0.38	0.07-1.94

3.2.1.11Quality of life

Four studies were identified which reported results related to quality of life. These were the Aronow, Mohler and Mondillo studies in patients with intermittent claudication[112,22,93] and the Oxford Cholesterol Study in patients at increased risk of CHD because of a history of MI, angina pectoris, stroke, TIA, PAD, treated diabetes mellitus or treated hypertension. [92]

The Mohler study specifically measured quality of life, using the SF-36; it did not find any significant difference between treatment groups. [22] This study also used the Walking Impairment Questionnaire (WIQ) and the Low Level Physical Activity Recall (LOPAR) questionnaire. Although no significant differnce was seen in the WIQ, the LOPAR questionnaire indicated an improvement in physical activity compared with placebo in patients receiving both 10 mg (p=0.032) and 80 mg atorvastatin (p=0.02), and in the combined atorvastatin group (p=0.011). The Mondillo study used a claudication self-assessment questionnaire, and found that patients receiving simvastatin displayed improvements in all four subjective parameters compared with those receiving placebo. [93]

All three studies in patients with intermittent claudication found that statin treatment was associated with an improvement in mean total walking time[22] or distance, [93] and in mean pain-free walking time[112] or distance. [93]

The Oxford Cholesterol Study found that simvastatin therapy did not affect either sleep[136] or mood. [137]

3.2.1.12Adverse effects

Despite their potential benefits, most if not all drugs have the potential to cause adverse effects. It is vitally important to understand these risks. This is particularly true in the case of statins, because of the very large number of people who may take these drugs, the fact that many of these individuals do not have symptomatic disease, and the fact that they may take those drugs for life.

The most common adverse reactions caused by statins are relatively minor and transient: they include headache, dizziness, rash, diarrhoea, abdominal pain, constipation and flatulence. [138] However, some of the adverse effects associated with statins are potentially very serious. Rare but clinically important adverse effects are elevations in hepatic transaminases, peripheral neuropathy, and myopathy. If statin therapy is not discontinued, myopathy (defined as creatine kinase increase to $\geq$10 times the upper limit of normal accompanied by muscle pain

or weakness) may result in rhabdomyolysis (severe muscle damage) and acute renal failure. [139] Although the exact mechanism by which statins cause rhabdomyolysis remains unclear, the risk appears to be dose-related. [53]

There is increasing evidence that the different statins differ both in their potential for interacting with other drugs, and in their rates of adverse events. In August 2001, cerivastatin, a synthetic statin, was withdrawn from the world market after the occurrence of 52 unexpected deaths from drug-related rhabdomyolysis (31 in the USA and a further 21 worldwide). [140,141] In addition, 385 nonfatal cases were reported among the estimated 700,000 cerivastatin users in the USA, and most of these required hospitalisation. Many of the fatalities had either received the full dose of cerivastatin (0.8 mg/day) or were using the drug concomitantly with gemfibrozil: this drug-drug interaction was implicated in 12 of the 31 US fatalities. [140]

3.2.1.12.1 Sources of evidence

A systematic literature review of the adverse effects of statins is beyond the scope of this review. Instead, the aim of this section is to provide a summary of the important adverse effects reported by the clinical trials included in this review, and then discuss other important evidence – in particular, where available, post-marketing surveillance data.

3.2.1.12.1.1 *Randomised controlled trials*

Serious adverse events are potentially the most important outcomes measured in RCTs. Regulatory bodies require all clinical trials to collect data on serious adverse events, including any adverse experiences which result in any of the following outcomes: death, a life-threatening experience, inpatient hospitalisation or prolongation of existing hospitalisation, or persistent or significant disability. [142] As many events which might generally be regarded as serious adverse events (all-cause mortality, cardiovascular events) have already been discussed as outcome measures in the review of clinical effectiveness, this section focuses on those events which have not already been reviewed.

Although RCTs are considered to provide the highest level of evidence for assessing the therapeutic efficacy of drugs, they can only provide limited data for assessing their safety. Premarketing trials are generally not powered to reliably detect rare adverse drug reactions, nor is their follow-up long enough to permit the detection either of adverse drug reactions which are widely separated in time from the original use of the drug or of delayed consequences associated with long-term administration. [143] Moreover, trials often exclude special populations who may be at risk of unique adverse drug reactions or of an increased frequency of adverse drug reactions compared with the general population. [143] Participants in clinical trials are less likely than non-selected patients to be receiving potentially interacting medications; they may also be monitored more carefully than in real-life situations.

3.2.1.12.1.2 *Post-marketing surveillance*

By contrast with experimental studies, post-marketing surveillance monitors the safety of medicines under their usual conditions of use. Its aim is to identify any safety concerns which emerge when new products are in widespread use. However, post-marketing surveillance systems also have limitations, including under-reporting due to reliance on voluntary reporting, the poor quality of submitted reports, and the presence of confounders which prohibit the definitive establishment of causality to drug exposure. [144]

3.2.1.12.2 Trial evidence

3.2.1.12.2.1 Atorvastatin, fluvastatin, pravastatin and simvastatin

Although, the first statin became available in the mid 1980s, the effects of lifetime use are still unknown. The best clinical trial evidence of long-term safety comes from large-scale trials of

simvastatin and pravastatin. By comparison, the trial evidence for the long-term safety of atorvastatin and fluvastatin is weak, and that for rosuvastatin is non-existent.

The clinical trial results suggest that the incidence of severe muscle problems with statin therapy is low (see Table 27). Aggregation of data from all the RCTs included in the review of clinical effectiveness indicates that there were only 6 non-fatal cases of rhabdomyolysis among 47,637 patients randomly assigned to statin treatment versus 3 cases among 47,180 patients randomised to control (placebo, 'usual care' or no statin treatment). Excluding data from the LIPID trial, which did not differentiate between myosotis and myalgia, there were 22 cases of myositis in 43,125 patients randomised to statin treatment and 25 cases in 42,678 patients randomised to the control group. Not all studies reported the number of patients suffering myalgia. However, in the largest study, the Heart Protection Study, [71] 20,536 patients were randomised to 40mg simvastatin per day or placebo, and creatine kinase levels were measured in patients who either reported unexplained muscle complaints or used a non-study statin in addition to study therapy. Over the mean 5 years of the study, similar numbers of patients in each group (3,379 (32.9%) in the simvastatin group and 3,409 (33.2%) in the placebo group) complained of unexplained muscle pain or weakness, and only 49 (0.48%) statin patients and 50 (0.49%) control patients discontinued because of muscle symptoms.

Although the RCT results indicate a low incidence of serious muscle problems in study participants who were followed up by researchers, they are likely to underestimate the incidence of such problems if statins are used in unselected populations. [145] In addition to the general issues relating to RCT evidence noted above, the generalisability of the statin RCT findings is further limited by the fact that some of the large, long-term studies such as 4S, [95] ASCOT-LLA, [94] CARDS, [131] CARE, [102] ALLHAT-LLT, [121] and the Heart Protection Study[71] excluded patients known to be hypersensitive to, or intolerant of, statins.

Details of other clinical adverse events and withdrawals or discontinuation of study medication due to adverse events are summarised in Appendix 27.

Table 27: Summary of adverse events (rhabdomyolysis, myositis, creatine kinase elevations and myalgia) in randomised controlled trials of statin therapy

Study	Duration	Statin dosage (mg/d)	No. of patients		No. with rhabdomyolysis[a]		No. with myositis [b]		No. with CK elevation [c]		No with myalgia [d]		Additional information reported by authors (no. with myopathy)[e]	
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Atorvastatin														
Control arm: Placebo														
ASCOT-LLA[94]	3.3 years (median)	10	5168	5137	1	0	NR	NR	NR	NR	NR	NR	-	-
CARDS[131]	4 years (median)	10	1428	1410	0	0	2	10	2	10	61	72	1	1
DALI[82]	30 weeks	10 80	73 72	72	NR	NR	NR	NR	NR	NR	NR	NR	10 7	9
Mohler et al[22]	1 year	10 80	120 120	114	NR	NR	NR	NR	NR	NR	NR	NR	-	-
Control arm: Usual care or no treatment														
ALLIANCE[146]	52 months (mean)	10-80 (median 40.5)	1217	1225	0	0	0	NR	NR	NR	NR	NR	0	0
Colivicchi[123]	1 year	80	40	41	NR	NR	NR	NR	1	NR	NR	NR	-	-
ESTABLISH[85]	6 months	20	35	35	NR	NR	NR	NR	NR	-	NR	NR	-	-
GREACE[122]	3 years (mean)	10-80 (mean 24)	800	800	NR	NR	NR	NR	NR	NR	0	0	0	0
Sub-total	-	-	**9073**	**8834**	**1**	**0**	**2**	**10**	**3**	**10**	**61**	**72**	**18**	**10**

Continued

Study	Duration	Statin dosage (mg/d)	No. of patients		No. with rhabdomyolysis[a]		No. with myositis [b]		No. with CK elevation [c]		No with myalgia [d]		Additional information reported by authors (no. with myopathy)[e]	
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Fluvastatin														
Control arm: Placebo														
ALERT[135]	5.4 years (median)	40-80	1050	1052	0	0	3	1	6	5	NR	NR	-	-
FLARE[99]	40 weeks	80	409	425	NR	NR	0	0	NR	NR	7	3	-	-
FLORIDA[100]	1 year	80	265	275	NR	NR	NR	NR	NR	NR	NR	NR	-	-
LIPS[101]	3.9 years (median)	80	844	833	0	NR	0	3	NR	NR	NR	NR	-	
LiSA[89]	1 year	40-80	187	178	NR	NR	NR	NR	0	1	NR	NR	-	-
O'Rourke et al[132]	1 year	40	52	27	0	0	NR	NR	7	1	6	2	-	-
Sub-total	**-**	**-**	**2807**	**2790**	**0**	**0**	**3**	**4**	**13**	**7**	**13**	**5**	**-**	**-**

Continued

Study	Duration	Statin dosage (mg/d)	No. of patients		No. with rhabdomyolysis[a]		No. with myositis [b]		No. with CK elevation [c]		No with myalgia [d]		Additional information reported by authors (no. with myopathy)[e]	
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Pravastatin														
Control arm: Placebo														
CAIUS[97]	3 years	40	151	154	NR	NR	NR	NR	NR	NR	NR	NR	-	-
CARE[102]	5 years (median)	40	2081	2078	0	0	0	4	12	7	NR	NR	-	-
KAPS[127]	3 years	40	224	223	NR	NR	NR	NR	NR	NR	NR	NR	-	-
LIPID[103]	6.1 years (mean)	40	4512	4502	0	0	NR (myositis or myalgias, n=60)	NR (myositis or myalgias, n=71)	NR	NR	NR (myositis or myalgias, n=60)	NR (myositis or myalgias, n=71)	8	10
PLAC I[104]	3 years	40	206	202	NR	NR	NR	NR	NR	NR	NR	NR	0	0
PLAC II[105]	3 years	10-40	75	76	NR	NR	NR	NR	NR	NR	NR	NR	-	-
PMSG[147]	26 weeks	20-40	530	532	NR	NR	NR	NR	14	8	NR	NR	0	0
PREDICT[106]	6 months	40	347	348	NR	NR	NR	NR	NR	NR	NR	NR	-	-
PROSPER[77]	3.2 years (mean)	40	2891	2913	0	0	NR	NR	NR	NR	36	32	-	-
REGRESS[107]	2 years	40	450	434	NR	NR	NR	NR	NR	NR	1	0	-	-
WOSCOPS[78]	4.9 years (mean)	40	3302	3293	NR	NR	NR	NR	3	1	20	19	-	-
Control arm: Usual care or no treatment														
ALLHAT-LLT[121]	4.8 years (mean)	40	5170	5185	NR	NR	NR	NR	NR	NR	NR		-	-
GISSI-P[124]	24.3 months (median)	20-40	2138	2133	0	0	NR	NR	NR	NR	NR		-	-
Kobashigawa et al[133]	1 year	20-40	47	50	0	0	0	0	0	0	0	0	-	-
Sato et al[83]	21.7 months (mean)	10	54	66	NR	NR	NR	NR	NR	NR	NR		-	-
Sub-total	**-**	**-**	**22178**	**22189**	**0**	**0**	**0†**	**4†**	**29**	**16**	**57†**	**51†**	**8**	**10**

Continued

Study	Duration	Statin dosage (mg/d)	No. of patients		No. with rhabdomyolysis[a]		No. with myositis [b]		No. with CK elevation [c]		No with myalgia [d]		Additional information reported by authors (no. with myopathy)[e]	
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Rosuvastatin (No placebo controlled, treatment or usual care trials)														
Simvastatin														
Control arm: Placebo														
4S[95]	7.4 years (median)	20-40	2221	2223	0	0	6	1	NR	NR	NR	NR	1	0
Aronow et al[112]	1 year	40	34	35	NR	NR	NR	NR	NR	NR	NR	NR	-	-
CIS[109]	2.3 years (mean)	20-40	129	125	NR	NR	NR	NR	NR	NR	NR	NR	-	-
HPS[71]	5 years (mean)	40	10269	10267	5	3	11	6	30	19	3379	3409	10	4
MAAS[108]	4 years	20	204	200	NR	NR	NR	NR	NR	NR	NR	NR	0	-
Mondillo et al[93]	6 months	40	43	43	NR	NR	NR	NR	NR	NR	NR	NR	-	-
Oxford Cholesterol Study	3.4 years (median)	20 40	206 208	207	NR NR	NR	NR NR	NR	7 9	8	2 4	2		
SCAT[110]	47.8 months (mean)	20-40	230	230	NR	NR	NR	NR	NR	NR	NR	NR	-	-
Control arm: Usual care or no treatment														
Wenke et al[134]	4 years	5-20	35	37	NR	NR	0	0	0	0	NR	NR	-	-
Sub-total	**-**	**-**	**13576**	**13367**	**5**	**3**	**17**	**7**	**46**	**27**	**3385**	**3411**	**11**	**4**
Total for all statins	**-**	**-**	**47637**	**47180**	**6**	**3**	**22†**	**25†**	**91**	**60**	**3516†**	**3539†**	**37**	**24**

CK, creatine kinase; NR, not reported

[a] Rhabomyolysis defined by study investigators (fatal or non fatal)

[b] Myositis defined by study investigators or as a CK elevation greater than 10 times the upper limit of normal

[c] Number with CK elevations defined by study investigators

[d] Myalgia defined by study investigators or muscle complaints without serum CK elevations

[e] Myopathy defined by study investigators

† Data from the LIPID study not included as numbers with myositis or myalgias could not be differentiated

3.2.1.12.2.2 Rosuvastatin

Rosuvastatin is currently marketed at a dose range of 5 to 40 mg; the 80mg dose was withdrawn because of safety concerns. [141] There are no large and or long-term (>6 months) placebo-controlled trials which examine adverse effects related to its use. Both studies included in the review, which have 52-week follow-ups, compare rosuvastatin with other statins. One reported that 10 of 268 patients receiving rosuvastatin (3.5%) withdrew because of adverse events which were considered to be related to trial medication, compared with 8 of 140 patients receiving atorvastatin (5.7%). Only two of the events associated with rosuvastatin were considered serious (rectal haemorrhage, serum creatinine elevation). [119] In the other study, no serious adverse events were reported in patients receiving rosuvastatin. [120]

3.2.1.12.3 Post-marketing surveillance data

3.2.1.12.3.1 Atorvastatin, fluvastatin, pravastatin and simvastatin

No published post-marketing surveillance data for the UK are available for atorvastatin, fluvastatin, pravastatin or simvastatin. An epidemiological study using data from the UK General Practice Research Database for the years 1991-1997 found that current statin therapy was associated with an eightfold increase in the risk of myopathy. However, this equated to approximately one case per 10,000 person-years of statin therapy. [148]

The non-UK data suggest that, between product approval and 26 June 2001, fatal cases of rhabdomyolysis associated with statin therapy were rare, with reporting rates lower than 1 death per million prescriptions, with the exception of cerivastatin, which has been withdrawn from world markets (see Table 28). [149] However, these figures are likely to underestimate the risk both because they are based on voluntary reporting by health care professionals, and because they use as the denominator the number of prescriptions, not the number of individuals using the medication. [145]

Table 28: Reported cases of fatal rhabdomyolysis and numbers of prescriptions for statins dispensed in the United States[149]

Variable	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Cerivastatin ‡	Total
Date approved in United States	31/10/91	23/12/91	31/12/93	17/12/96	26/6/97	-
Cases of fatal rhabdomyolysis*	3	14	0	6	31	54
No. of prescriptions dispensed since marketing began†	81,364,000	116,145,000	37,392,000	140,360,000	9,815,000	385,076,000
Reporting rate (per 1 million prescriptions) ††	0.04	0.12	0.00	0.04	3.16	0.14

* US cases reported to the Food and Drug Administration (FDA) before 26 June 2001 and which met the following criteria: the report included a clinical diagnosis of rhabdomyolysis, a temporal association between rhabdomyolysis and the use of a statin could be identified from the report, and death resulted either directly or indirectly from rhabdomyolysis.
†Data up to and including May 2001, derived from the US National Prescription Audit Plus, excluding the Long Term Care Channel.
††The FDA does not recommend rigorous comparisons between drugs based on these data since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. They emphasise that reporting rates are not incidence rates.
‡ Withdrawn from world market in August 2001

Rates of fatal and non-fatal rhabdomyolysis reported to the United States Food and Drug Administration's (FDA) post-marketing database were also similar, at less than 1 case per million prescriptions, for all statins except cerivastatin[150] (see Table 28). More than 80% of cases reported for each drug when taken as monotherapy resulted in hospitalization for renal failure and dialysis, and 10% resulted in death. [150] This demonstrates that, although rhabdomyolysis is a rare event, it presents a significant safety issue for statin drugs even when taken as monotherapy; the risk is increased when statins are used in combination with gemfibrozil (see Table 29).

Table 29: Reporting rates per million prescriptions for all US cases of rhabdomyolysis associated with statins through 31 July, 2001[150]

Variable	Pravastatin 1992 to 2001	Simvastatin 1992 to 2001	Fluvastatin 1994 to 2001	Atorvastatin 1997 to 2001	Cerivastatin‡ 1998 to 2001	Total
Monotherapy						
Cases of rhabdomyolysis*	17	99	1	45	200	482
Estimated Prescriptions†	82,000,000	118,986,000	38,791,000	147,610,000	11,038,000	495,761,000
Crude rate per 1 million prescriptions	0.21	0.83	0.03	0.30	18.12	0.97
Combination therapy with gemfibrozil						
Cases of rhabdomyolysis*	2	37	0	6	279	324
Estimated Prescriptions††	1,422,000	962,000	316,000	1,198,000	22,000	3,920,000
Crude rate per 1 million prescriptions	1.41	38.46	0.00	5.01	12681.82	82.65

* Cases identified in the Food and Drug Administration (FDA) Adverse Event Reporting System database with creatine phosphokinase >10,000 IU/L, signs and symptoms (myalgia, myopathy, gait disturbance) and clinical diagnosis of rhabdomyolysis.
† Estimates of prescriptions for statin therapy, with or without concomitant gemfibrozil therapy, based on percentage of mentions (IMS HEALTH NDTI™) summed across all years of marketing for each drug and applied to prescriptions for all years drug was marketed (IMS HEALTH NPA*Plus*™).
†† All dispensed prescriptions for all years the drug was marketed between 1988 and July 2001 (IMS HEALTH NPA*Plus*™, excluding Long Term CARE)
‡ Withdrawn from world market in August 2001
NOTE: Analysis does not include concomitant therapy with fenofibrate, which was prevalent in 0-1% of mentions across statins. Few cases of rhabdomyolysis were reported for any statin plus fenofibrate or clofibrate, however, these were not included in the analysis

A more accurate estimate of the incidence of rhabdomyolysis attributed to statins, alone or in combination with fibrates, may be obtained from a recently published major analysis. [151] Prescription data were used to identify a cohort of 252,460 lipid-lowering drug users from 11 health plans across the US between January 1998 and June 2001. Hospital data were then used to establish how many of that cohort were admitted to hospital with a diagnosis of rhabdomyolysis. There were 21 cases, all associated with statin intake (i.e. none occurred during non-exposed time); a further 7 cases were excluded from the analysis because, according to automated claims data, they were not exposed to a lipid-lowering drug at the time when they developed rhabdomyolysis, although in each case their hospital record explicitly stated that they had been taking a statin at the time of the event. All patients with rhabdomyolysis were taking statins at half or less of the recommended maximum dose. The incidence rate of hospitalised rhabdomyolysis with monotherapy of atorvastatin, pravastatin and simvastatin was 0.44 (95% CI, 0.20-0.84) cases per 10,000 person-years exposure; there was no statistically significant difference between those statins (average incidence of rhabdomyolysis for atorvastatin 0.54 (95% CI 0.22-1.12), for pravastatin 0.0 (95% CI 0-1.11), and for simvastatin 0.49 (95% CI 0.22-1.12)). By comparison, the incidence rate for cerivastatin was 5.34 (95% CI 1.46-13.68). Inclusion of the 7 excluded cases resulted in an

incidence rate for atorvastatin, pravastatin and simvastatin of 0.68 (95% CI0.38-1.15); again, the individual incidence rates remained indistinguishable. However, when atorvastatin and simvastatin were used in combined statin-fibrate therapy, the risk increased considerably, to 5.98 (95% CI, 0.72-216). The risk was also increased in patients aged 65 or older, and in those with diabetes mellitus. [151]

3.2.1.12.3.2 Rosuvastatin

Rosuvastatin was licensed and launched in the UK in March 2003. By the end of July 2004, it had been used by over 190,000 patients in the UK. By mid August 2004, over 8.5 million prescriptions had been written and approximately 3 million patients worldwide had received rosuvastatin. [55] During this period, the most frequently reported adverse events were myalgia, headache, nausea, dizziness and arthralgia. However, by October 2004 the UK Committee on Safety of Medicines[53] had received 10 reports of suspected rhabdomyolysis associated with rosuvastatin. The majority of these cases involved patients who started on high doses of rosuvastatin; some had pre-existing risk factors for myopathy.

In a recent letter in the Lancet, Wolfe expressed concern about the safety of rosuvastatin, based on both pre-marketing and post-marketing data. [152] The pre-marketing data indicated that, at 80 mg/day, rosuvastatin was associated with a higher frequency of creatine kinase elevations, and a higher incidence of myopathy and rhabdomyolysis, than any other currently approved statin; as a result, the 80 mg dose was discontinued, but the FDA approved rosuvastatin in the belief that doses lower than 80 mg would be much safer. Subsequently, 18 additional cases of rhabdomyolysis were reported between the beginning of marketing and 13th April 2004, including 11 cases in 7 months in the USA. Two of the 18 patients were using a 40 mg dose, 5 were using 20 mg and 11 were using 10 mg, as was one of the pre-marketing cases (the remaining 7 cases of rhabdomyolysis reported in pre-marketing data occurred in patients receiving the 80 mg dose). Rosuvastatin thus appears to have a higher rate of rhabdomyolysis than any other currently marketed statin. [152] By 26th August 2004, the number of cases of rhabdomyolysis associated with rosuvastatin had risen to 65 in the USA alone. [153]

Rosuvastatin has also been associated with instances of acute renal failure and renal insufficiency which were not secondary to rhabdomyolysis. Pre-marketing data indicated that a small proportion of patients taking rosuvastatin (primarily at the 80 mg dose) displayed persistent proteinuria and haematuria, in some cases associated with an increase in serum creatinine. This was dose-related, affecting 1.3% of patients receiving a 40 mg dose, and concern was expressed that it might progress to renal failure in a small number of patients. By 13th April 2004, post-marketing data record 8 cases of acute renal failure and four of renal insufficiency in patients using rosuvastatin. Nine of these patients were taking a 10 mg dose, one 40 mg and one 80 mg. [152]

In response to Wolfe, AstraZeneca claimed, on the basis of data from their clinical trial programme and ongoing pharmocovigilance assessments, that rosuvastatin was no more likely to cause adverse muscle effects than the other marketed statins. They concluded that rosuvastatin's safety profile was similar to those of the marketed statins, and stated that "This view of the benefit-risk profile of rosuvastatin is shared by regulatory authorities in the 64 countries where rosuvastatin is approved". [154] However, as a result of post-marketing reports of adverse events in patients receiving rosuvastatin, labelling changes were made within the European Union, reflecting those already in use in the USA. These changes highlight the patient populations who may be at increased risk of myopathy, particularly at the highest approved dose (40 mg). Patients at risk include those aged over 65, those with hypothyroidism and/or renal insufficiency, and also some Asian populations, and people concomitantly using cyclosporine and gemfibrozil. [155]

3.2.1.12.4 Other evidence

Concerns about the long-term safety of statins were originally raised by a review of the carcinogenicity of lipid-lowering drugs in animal studies. [52] However, other studies suggest that statins have an inhibitory effect on cancer cell proliferation. [156] A recent meta-analysis of data from six large studies found no evidence to suggest that statin therapy affected the overall rates of fatal or non-fatal cancer (see Table 30). However, the reviewers cautioned that none of the trials reported all of the outcomes, most reported cancer in different ways, and reporting of site-specific cancers in the trials was incomplete; moreover, it is not possible, on the basis of trials averaging 5 years' duration, to exclude the possibility of cancer risk resulting from longer exposure or after a longer latency period. [157]

Table 30: Risk of fatal and non-fatal cancer with statin therapy*[157]

Event	Number of trials	Number of patients	No. of events /total		Relative risk (95% CI)
			Statin	Placebo	
Non-fatal cancer					
Excluding non-melanoma skin cancer	3†	31575	583/15792	576/15783	1.01 (0.90-1.13)
Including non-melanoma skin cancer	2††	13173	374/6593	374/6580	1.00 (0.87-1.15)
Fatal cancer					
Excluding non-melanoma skin cancer	3†	31575	436/15792	429/15783	1.02 (0.89-1.16)
Including non-melanoma skin cancer	2††	13173	177/6593	186/6580	0.95 (0.78-1.16)
All cancers					
Excluding non-melanoma skin cancer	4‡	38198	1271/19114	1264/19084	1.00 (0.93-1.08)
Including non-melanoma skin cancer	4‡‡	40314	2110/20166	2067/20148	1.02 (0.96-1.08)

* WOSCOP, CARE and LIPID used pravastatin, 4S and HPS used simvastatin, and AFCAPS used lovastatin (not reviewed in this appraisal)
† Data from 4S, WOSCOPS, HPS
†† Data from CARE, LIPID
‡ Data from 4S, WOSCOPS, AFCAPS, HPS
‡‡ Data from CARE, LIPID, AFCAPS, HPS

One large randomised placebo-controlled trial, the PROSPER trial, [77]specifically studied the efficacy of pravastatin in patients aged between 70 and 82 years with pre-existing cardiovascular disease or significant risk of developing this condition. This study found a statistically significant 25% increase in incident cancer with pravastatin relative to placebo. In view of these findings, the authors performed a meta-analysis of pravastatin trials, including PROSPER: this revealed no significant effect of the drug on cancer rates. The authors concluded that the imbalance in cancer rates in the PROSPER study was a chance finding, which could in part have been driven by the recruitment of individuals with occult disease. [77]

Evidence from a case-control study conducted in Denmark suggest that statin use is associated with a 4- to 14-fold increase in the risk of developing idiopathic polyneuropathy, corresponding to one excess case for every 2,200 (95% CI 880-7,300) person-years of statin use. The risk increased in patients treated with statins for two or more years. [158] This evidence supports that of a cohort study undertaken by the same researchers in the UK, which found an elevated risk of idiopathic peripheral neuropathy in current statin users compared both with patients with hyperlipidaemia who had not been prescribed a lipid-lowering drug, and with an age- and sex-matched cohort drawn from the general population. [159]

3.2.1.12.5 Summary

Although concerns have been raised about rosuvastatin, statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by post-marketing surveillance data. Although increases in creatine kinase and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a time-span remains unproven.

3.2.1.13Continuance and compliance

The efficacy of an intervention is clearly related to the length of time for which it is taken and the extent to which it is taken in accordance with the intended dosing regimen. It has been claimed that a level of compliance of >80%, with only trivial deviations, in relation to both the prescribed total dose and the prescribed timing of that dose will provide an adequate therapeutic effect in most drugs. [66] Although most of the studies included in this review report continuance, in some studies it is not clear whether the authors are reporting continuance or

compliance. Moreover, some do not report compliance with statin therapy even in terms of total dose, and none report compliance in terms of timing. However, the WOSCOPS study found a significant reduction in risk of definite CHD death or nonfatal MI, relative to placebo, in patients who took 75% or more of the prescribed statin (RR 0.62, 95% CI 0.50-0.76), but not in those taking less than 75% (RR 1.01, 95% CI 0.66-1.55). This result should be treated with caution as analyses conditional on compliance are no longer truly randomised. However, the investigators recalculated this result in the high-compliance group using the Cox proportional-hazards model, adjusting for baseline risk factors which had previously been identified as being of prognostic value (smoking status, diabetes, taking nitrates, minor ECG abnormality, positive Rose questionnaire for angina, family history of CHD, age, history of hypertension, diastolic BP, LDL/HDL cholesterol ratio), and still found a 38% reduction (95% CI 23-50%) in the risk of definite CHD death or nonfatal MI in the high-compliance group relative to placebo, compared with a 31% reduction (95% CI 17-43%) in the entire cohort. [160] This result suggests that long-term compliance is probably required to achieve optimum benefits from statin therapy.

Because of the importance of continuance and compliance in relation to the effects of treatment, data drawn from the studies included in the review will be supplemented with data from other relevant studies.

3.2.1.13.1 Evidence from included studies

3.2.1.13.1.1 Continuance

The evidence relating to continuance with statin therapy is summarised in Table 31 below. Where available, information is provided by year of treatment. The WOSCOPS study is included under primary CHD prevention as, although it was undertaken in a mixed population, only 5% of participants were reported as having CHD at baseline.

Table 31: Studies reporting continuance: percentage of patients in statin group still taking statin therapy

Study	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Primary CHD prevention						
ASCOT-LLA[94]	NR	NR	87			
CARDS[131]	90	87	86	78		
WOSCOPS[160]	85	NR	NR	NR	70	
Secondary CHD prevention						
4S[95]	NR	NR	NR	NR	90	
CARE[102]	NR	NR	NR	NR	94	NR
LIPID[103]	94	NR	89	NR	NR	81
LIPS[87]	NR	NR	NR	73		
MAAS[108]	NR	NR	NR	75		
Mixed primary and secondary CHD prevention						
ALLHAT-LLT[121]	NR	87	NR	80	NR	77

As would be expected, all studies which report continuance at more than one point in time demonstrate a gradual decrease in continuance over time (see Table 31). As noted earlier, compliance with drug therapy is generally higher in patients with symptomatic disease than in those without. It is therefore perhaps not surprising that, at one year, the highest continuance is reported by a secondary prevention study, the LIPID study, nor that, by year 5, continuance is substantially lower in the WOSCOPS study, which is predominantly of primary prevention, than in the 4S and CARE studies of secondary prevention. It is also perhaps not surprising that, of the primary prevention studies which present data at one year, continuance is lower in

the WOSCOPS study than in the CARDS study, since the latter was carried out in diabetic patients, 80% of whom were already taking medication for their diabetes. However, the issue is not straightforward: within studies of statins in secondary prevention, it is not clear why the LIPS and MAAS studies report much lower continuance rates at four years than 4S and CARE do at five.

Most studies did not provide information on the reasons why participants specifically discontinued study medication rather than why they withdrew from the study. However, the 4S study stated that just over half of those who discontinued statin therapy did so because of adverse events; the reason given by the remainder was mainly patient reluctance to continue. [95]

3.2.1.13.1.2 Compliance

As noted above, very few studies report compliance, and not all of those who do specify how it was measured. In the only study of primary prevention which reported compliance, the DALI study in diabetic patients, compliance was said to be over 95% in all three treatment groups, but no indication was given as to how it was measured;. [82]

There is a more evidence relating to studies of statins in secondary prevention. The 3T study assessed compliance by questioning the patient and by counting tablets at each clinic visit; patients taking ≥85% of the correct doses were considered compliant. 88% of patients in the atorvastatin group were at least 85% compliant throughout, as were 86% in the simvastatin group. [79] In PLAC I, mean compliance, assessed by pill count, was 95%.[104] The SCAT trial also assessed compliance by pill count at each visit. As an attempt had been made to exclude potentially noncompliant patients during the placebo run-in phase, average compliance with statin therapy was approximately 95% throughout the trial. [110]

The fullest information on compliance with statin therapy comes from the HPS study, which was carried out in a mixed population. This study assessed compliance by reviewing the calendar-packed tablets remaining; compliance was defined as consumption of at least 80% of the study medication since the previous follow-up visit. An average of 85% of patients allocated to statin therapy were compliant with therapy throughout the study; this figure fell from 89% at the end of the first year to 82% at 5 years. Most of the non-compliant patients appear to have discontinued therapy: only about 2% of patients overall were reported to be taking some, but less than 80%, of their allocated treatment. [71] In another mixed study, the KAPS study, compliance, assessed by tablet count, was 92% in the pravastatin group, [127] while another mixed study, the PROSPER study, achieved 94% compliance, again assessed by tablet count; however, in this study potential participants who were less than 75% compliant had been screened out in the placebo run-in phase. [161] In another mixed study, ALLHAT-LLT, which did not seem to screen participants for compliance, only 70-75% of patients reported taking 80% or more of their assigned pravastatin. [121]

In the WOSCOPS study, although continuance was relatively low, compliance was very high once patients were established on medication. At the first trial visit, mean compliance with statin therapy was approximately 85%, but it rose to approximately 95% at the end of the first year and remained stable until study end. A history of taking regular medication (for angina, diabetes or hypertension) increased the likelihood of being 100% compliant with study medication, while current smokers were less likely to be compliant. [160]

3.2.1.13.2 Evidence from other studies

It is generally accepted that continuance and compliance with medication is higher in RCTs than in general clinical practice. A number of studies have explored continuance and

compliance with lipid-lowering therapies in real life. However, because of the possibility that economic and cultural factors may influence continuance and compliance, only the evidence from UK studies is reviewed here.

A study carried out in Tayside, Scotland, studied patients who experienced their first MI between Jan 1990 and November 1995. Adherence with statin therapy was calculated on the basis of prescriptions dispensed after discharge from hospital, dividing the number of days with statin supply by the total number of days from the first prescription for a statin to the end of the study; [162] this may combine elements of continuance and compliance. 64% of patients had greater than 80% adherence, as did 69% of patients aged over 65 years. Adherence was not associated with deprivation. After adjusting for prior lipid-lowering therapy, dose, and other risk factors, only patients with $\geq$80% adherence to statin therapy had significantly lower risks of further MI and of all-cause mortality. [162]

A retrospective cohort study was undertaken in a large general practice in Liverpool to investigate true patient compliance with statin therapy in primary care. Electronic medical records were used to identify any patient prescribed a statin between 31 December 1991 and 26 January 2003. 869 patients met the study inclusion criteria. Of these, 74 (8.5%) had discontinued therapy: 44 did so within the first 6 months, and 27 did not take the statin for longer than a month. In 54 cases (73%), no reason for discontinuation was recorded, but 10 patients (14%) were recorded as discontinuing because of side effects (for comparison, 14% of compliant patients had their statin prescription changed because of side effects). Compliance was defined as taking <80% of therapy: overall, 25% of patients were non-compliant. Cholesterol monitoring was found to be a significant predictor of patient compliance ($P<0.001$). [70]

Tolmie et al undertook a study in an area of high social deprivation in the West of Scotland in patients prescribed statin therapy for at least 3 months. 86% of patients appeared to be good compliers, taking 70-100% of their statins. 8% were moderate compliers (taking 41-69%) and 6% were poor compliers (taking <41%). In-depth interviews with patients who were good, moderate and poor compliers indicated the importance, for compliance, of the credence patients attached to the prescriber, and of their perceptions of the primary purpose of the consultation at which the drug was initiated. [163]

3.2.1.13.3 Continuance and compliance: summary

Not all patients who are prescribed statins will take them for any length of time. Between 5 and 15% are likely to discontinue therapy within the first year, and at the end of five years as many as 30% are likely to have discontinued. Although the proportion of people who discontinue treatment is likely to be higher in those receiving statins for primary prevention, the issue is complicated, with a likelihood of greater continuance in patients with conditions such as diabetes or hypertension, regardless of whether they have suffered a prior cardiovascular event. Compliance appears to be good in patients who do not discontinue therapy.

3.2.1.14Summary of clinical effectiveness

There is evidence from placebo-controlled studies to suggest that statin therapy is associated with a statistically significant reduction in the risk of:

- all-cause mortality, fatal and nonfatal MI, and a composite endpoint of CHD death plus nonfatal MI, in both primary and secondary prevention
- stable angina in primary prevention
- cardiovascular mortality, CHD mortality, nonfatal stroke, PAD, unstable angina, and coronary revascularisation in secondary prevention.

As the confidence intervals for each outcome in each prevention category overlap, it is not possible to differentiate, in terms of relative risk, between the effectiveness of statins in primary and secondary prevention. However, the absolute risk of CHD death or nonfatal MI is higher, and the number needed to treat to avoid such an event is consequently lower, in secondary than in primary prevention.

There is no evidence that the effectiveness of statins differs in women relative to men at the same level of cardiovascular risk, in patients with diabetes compared with those without, or in older patients compared with those under 65 years of age, nor is there evidence that statins differ in effectiveness in patients with lower or higher cholesterol levels at baseline.

Because of poor study design, it is difficult to interpret the results of the studies which compare a statin with 'usual care', while those which compared a statin with no statin therapy very largely failed to achieve statistically significant results in relation to clinical outcomes.

It is not possible to differentiate between the different statins on the basis of the evidence from the placebo-controlled trials: although the point estimates of their effect sizes may vary, in each case the confidence intervals overlap. Only three head-to-head comparisons of one statin with another have reported clinical outcomes, and only one of these, the PROVE IT-TIMI trial, reported statistically significant results. These suggest that aggressive reduction in LDL-cholesterol with atorvastatin is more effective than moderate LDL-C reduction using pravastatin in reducing the risk of hospitalisation for unstable angina, and of coronary revascularisation; however, these results cannot be considered conclusive as there was no statistically significant difference between the two statins in terms of the key composite endpoint of CHD death or nonfatal MI.

It should, however, be noted that the different statins vary in terms of the volume of evidence available from placebo-controlled studies which report clinical outcomes. As noted earlier, there is no such evidence relating to rosuvastatin. Of the remaining four statins, there is least evidence for fluvastatin, with four studies of secondary CHD prevention in a total of 3,416 patients (see Table 32). There are five studies of atorvastatin, involving 14,969 patients; three of these studies were of primary prevention, but all of these were in patients who, because of their pre-existing medical conditions, were at relatively high risk of cardiovascular events. The eight studies of simvastatin, involving 26,851 patients, were all of secondary or mixed prevention. All of the eleven studies of pravastatin, involving 29,524 patients, were all of secondary or mixed prevention with the exception of the CAIUS study, which recruited patients with ultrasonographically identified early atherosclerosis but without symptomatic CVD. [97] Each statin is represented both by studies which appear to be of good quality, and others whose quality cannot be assessed in that it is not clear from published sources whether the method used to assign participants to the treatment group was really random or the allocation of treatment was concealed (see Table 32).

Table 32: Strength of evidence from placebo-controlled studies reporting clinical outcomes for different statins (excluding studies in transplant patients)

Statin/study	Prevention	Patient group	No	Study

	category		randomised	quality*
Atorvastatin				
4D	Mixed	Diabetic + renal failure	1255	Good
ASCOT-LLA	Primary CHD	Hypertensive	10305	Good
CARDS	Primary CVD	Diabetic	2838	Good
DALI	Primary CHD	Diabetic	217	?
Mohler 2003	Secondary CVD	Intermittent claudication	354	?
Total			**14,969**	
Fluvastatin				
FLARE	Secondary CHD	PTCA	834	?
FLORIDA	Secondary CHD	Acute MI	540	?
LIPS	Secondary CHD	Angina or silent ischaemia	1677	Good
LiSA	Secondary CHD	Stable symptomatic CHD	365	?
Total			**3,416**	
Pravastatin				
CAIUS	Primary CVD	Ultrasonographically identified early atherosclerosis	305	Good
CARE	Secondary CHD	MI	4159	Good
KAPS	Mixed	Hypercholesterolaemia, with and without CVD	447	Good
LIPID	Secondary CHD	MI or unstable angina	9014	?
PLAC I	Secondary CHD	CHD	408	?
PLAC II	Secondary CHD	CHD	151	?
PMSG	Mixed	Primary hypercholesterolaemia and ≥2 additional CHD risk factors	1062	?
PREDICT	Secondary CHD	CHD (successful PTCA)	695	?
PROSPER	Mixed	Elderly, with or at significant risk of CVD	5804	Good
REGRESS	Secondary CHD	CHD	884	?
WOSCOPS	Mixed	Moderate hypercholesterolaemia	6595	?
Total			**29,524**	
Simvastatin				
4S	Secondary CHD	CHD	4444	Good
Aronow 2003	Secondary CVD	Intermittent claudication	69	?
CIS	Secondary CHD	CHD	254	?
HPS	Mixed	Substantial risk of death from CHD	20536	Good
MAAS	Secondary CHD	CHD	381	?
Mondillo 2003	Secondary CVD	PAD	86	?
Oxford Cholesterol Study	Mixed	Increased risk of CHD	621	Good
SCAT	Secondary CHD	CHD	460	Good
Total			**26,851**	

* This is said to be good if it was clear from the report both that the method used to assign participants to the treatment group was really random and that the allocation of treatment was concealed

Statins are generally considered to be well tolerated and to have a good safety profile. . This view is generally supported both by the evidence of the trials included in this review and by post-marketing surveillance data. Although increases in creatine kinase and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a time-span remains unproven.

10 References

1. Petersen, S., Peto, V., and Rayner, M. Coronary heart disease statistics 2004 edition. 2004.

2. Grundy, S. M., Balady, G. J., Criqui, M. H., Fletcher, G., Greenland, P., Hiratzka, L. F., Houston-Miller, N., Kris-Etherton, P., Krumholz, H. M., LaRosa, J., Pearson, T. A., Reed, J., Washington, R., and Smith, S. C., Jr. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association.[see comment]. *Circulation* 1998; **97** 1876-1887.

3. Cairns, J. A. Medical management of unstable angina. *Lancet* 1995; **346** 1464-1465.

4. Anonymous Key health statistics from general practice 1998. 2000.

5. Anonymous British Heart Foundation statistics website. *British Heart Foundation* 2004.

6. Sproston, K. and Primatesta, P. Health Survey for England 2003. Vol 1. Cardiovascular disease. 2004.

7. Sutcliffe, S. J., Fox, K. F., Wood, D. A., Sutcliffe, A., Stock, K., Wright, M., Akhras, F., and Langford, E. Incidence of coronary heart disease in a health authority in London: review of a community register. *BMJ* 2003; **326** 20-20.

8. Albers, G. W., Caplan, L. R., Easton, J. D., Fayad, P. B., Mohr, J. P., Saver, J. L., and Sherman, D. G. Transient ischemic attack - proposal for a new definition. *New England Journal of Medicine* 2002; **347** 1713-1716.

9. Fisher, C. M. Transient ischemic attacks. *New England Journal of Medicine* 2002; **347** 1642-1643.

10. Johnston, S. C. Transient ischaemic attack. *New England Journal of Medicine* 2002; **347** 1687-1692.

11. Gibbs, R. G. J., Newson, R., Lawrenson, R., Greenhalgh, R. M., and Davies, A. H. Diagnosis and initial management of stroke and transient ischemic attack across UK health regions from 1992 to 1996: experience of a national primary care database. *Stroke* 2001; **32** 1085-1090.

12. The Stroke Association TIA fact sheet. *The Stroke Association* 2004.

13. Corvol, J. C., Bouzamondo, A., Sirol, M., Hulot, J. S., Sanchez, P., and Lechat, P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. [Review] [68 refs]. *Archives of Internal Medicine.* 24-3-2003; **163** 669-676.

14. Gaziano, J. M., Hebert, P. R., and Hennekens, C. H. Cholesterol reduction: Weighing the benefits and risks. *Annals of Internal Medicine* 1996; **124** 914-918.

15. Bamford, J., Sandercock, P., Dennis, M., Warlow, C., Jones, L., McPherson, K., Vessey, M., Fowler, G., Molyneux, A., Hughes, T., and et al A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. I. Methodology, demography and incident cases of first-ever stroke. *Journal of Neurology, Neurosurgery & Psychiatry.* 1988; **51** 1373-1380.

16. Du, X., Sourbutts, J., Cruickshank, K., Summers, A., Roberts, N., Walton, E., and Holmes, S. A community based stroke register in a high risk area for stroke in north west England. *Journal of Epidemiology & Community Health* 1997; **51** 472-478.

17. Al Inany, H., Aboulghar, M., Mansour, R., and Serour, G. Meta-analysis of recombinant versus urinary-derived FSH: an update.[see comment]. *Human Reproduction* 2003; **18** 305-313.

18. British Heart Foundation statistics website. *Internet* 2004.

19. Wolfe, C. D. A., Rudd, A. G., Howard, R., Coshall, C., Stewart, J., Lawrence, E., Hajat, C., and Hillen, T. Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *Journal of Neurology, Neurosurgery & Psychiatry.* 2002; **72** 211-216.

20. Burns, P., Gough, S., and Bradbury, A. W. Management of peripheral arterial disease in primary care.[see comment]. [Review] [22 refs]. *BMJ.* 15-3-2003; **326** 584-588.

21. Golledge, J. Lower-limb arterial disease. *Lancet* 1997; **350** 1459-1465.

22. Mohler, E. R., III, Hiatt, W. R., and Creager, M. A. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation.* 23-9-2003; **108** 1481-1486.

23. Anon Cholesterol and coronary heart disease: screening and treatment. *Effective Health Care* 1998; **4** 1-16.

24. Ebrahim, S., Davey, Smith G., McCabe, C., Payne, N., Pickin, M., Sheldon, T. A., Lampe, F., Sampson, F., Ward, S., and Wannamethee, G. What role for statins? A review and economic model. [Review] [157 refs]. *Health Technology Assessment (Winchester, England).* 1999; **3** i-iv.

25. Meads, C., Cummins, C., Jolly, K., Stevens, A., Burls, A., and Hyde, C. Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review. *Health Technology Assessment* 2000; **4.**

26. Anonymous Mortality statistics: cause. Review of the Registrar General on deaths by cause, sex and age, in England and Wales, 2001. 2003; **DH2 no.28.**

27. Lawlor, D. A., Ebrahim, S., and Davey Smith, G. Sex matters: secular and geographical trends in sex differences in coronary heart disease mortality. *British Medical Journal* 2001; **323** 541-545.

28. Beery, T. A. Gender bias in the diagnosis and treatment of coronary artery disease. *Heart & Lung: Journal of Acute & Critical Care.* 1995; **24** 427-435.

29. de Belder, M. BCIS Audit Returns of Interventional Procedures 2001. *citation* 2002.

30. Hackett, M. L., Duncan, J. R., Anderson, C. S., Broad, J. B., and Bonita, R. Health-related quality of life among long-term survivors of stroke: results from the Auckland Stroke Study, 1991-1992. *Stroke* 2000; **31** 440-447.

31. Dennis, M., Bamford, J., Sandercock, P., and Warlow, C. Prognosis of transient ischemic attacks in the Oxfordshire Communiyt Stroke Project. *Stroke* 1990; **21** 848-853.

32. Lovett, J. K., Dennis, M. S., Sandercock, P. A. G., Bamford, J., Warlow, C. P., and Rothwell, P. M. Very early risk of stroke after a first transient ischemic attack. *Stroke* 2003; **34** e138-e140.

33. Johnston, S. C., Gress, D. R., Browner, W. S., and Sidney, S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000; **284** 2901-2906.

34. Lichtman, J. H., Krumholz, H. M., Wang, Y., Radford, M. J., and Brass, L. M. Risk and predictors of stroke after myocardial infarction among the elderly. *Circulation* 2002; **105** 1082-1087.

35. Criqui, M. H., Langer, R. D., Fronek, A., Feigelson, H. S., Klauber, M. R., McCann, T. J., and Browner, D. Mortality over a period of 10 years in patients with peripheral arterial disease. *New England Journal of Medicine* 1992; **326** 381-386.

36. Hiatt, W. R. Quality of life assessment in peripheral arterial disease. *Atherosclerosis* 1997; **131** S35-S36.

37. Mark, D. B., Naylor, C. D., Hlatky, M. A., Califf, R. M., Topol, E. J., Granger, C. B., Knight, J. D., Nelson, C. L., Lee, K. L., Clapp-Channing, N. E., Sutherland, W., Pilote, L., and Armstrong, P. W. Use of medical resources and quality of life after acute myocardial infarction in Canada and the United States.[see comment]. *New England Journal of Medicine* 1994; **331** 1130-1135.

38. Lukkarinen, H. and Hentinen, M. Assessment of quality of life with the Nottingham Health Profile among patients with coronary heart disease. *Journal of Advanced Nursing* 1997; **26** 73-84.

39. Roebuck, A., Furze, G., and Thompson, D. R. Health-related quality of life after myocardial infarction: an interview study. *Journal of Advanced Nursing* 2001; **34** 787-794.

40. Department of Health Heart drug available without a prescription. 2004; **2004/0186.**

41. Goyder, E., McBeath, S., Sims, A., Ashwell, S., and Sherry, R. Quantifying the gap between policy and practice in cardiovascular risk reduction. A review of the evidence from recent cardiovascular and diabetes audits in the UK. 2003.

42. Department of Health Department of Health Statistics website. *http://www.publications.doh.gov.uk/stats/pca2003.xls* 2003.

43. Dr Foster's case notes: Prescribing of lipid regulating drugs and admissions for myocardial infarction in England. *BMJ* 2004; **329** 645-645.

44. Prescription Pricing Authority Electronic drug tariff. *Internet* 2004.

45. Thompson, A. Patent expiries — how should they affect prescribing advice? *The Pharmaceutical Journal* 2003; **271** 587-589.

46. Department of Health Reimbursement prices for four generic medicines. 2003.

47. Department of Health National Service Framework for Coronary Heart Disease. 2000.

48. Williams, B, Poulter, NR, Brown, MJ, and et al British Hypertension Society Guidelines. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004 - BHS IV. *J Hum Hypertens* 2004; **18** 139-185.

49. Anonymous Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106** 3143-3421.

50. Joint Formulary Committee British National Formulary. *Internet* 2004.

51. Anon Cholesterol lowering medicines: statins. *Internet* 2003.

52. Newman, T. B. and Hulley, S. B. Carcinogenicity of lipid-lowering drugs.[see comment]. [Review] [54 refs]. *JAMA* 3-1-1996; **275** 55-60.

53. Committee on Safety of Medicines Statins and cytochrome P450 interactions. *Current Problems in Pharmacovigilance* 30-10-2004;1-2.

54. Wan, Y Generic pravastatin available in UK. *Drug Infozone* 2005.

55. AstraZeneca Statins for the prevention of coronary events: the clinical and cost effectiveness of rosuvastatin. 2004.

56. EMEA Press release: European Medicines Agency Committee for Medicinal Products for Human Use 15-18 November 2004. *Internet* 2004.

57. Merck Sharp and Dohme Limited Simvastatin (ZOCOR(R)). The use of statins in the management of patients at increased risk of death or other cardiovascular events from coronary heart disease (CHD). A submission to the National Institute for Clinical Excellence. 2004.

58. Royal Pharmaceutical Society of Great Britain Practice guidance on: sale of over-the-counter simvastatin. 2004.

59. Kedward, J and Dakin, L A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *British Journal of General Practice* 2003; **53** 684-689.

60. Anon Statins and the law of unintended consequences. *Bandolier* 2003; **113.**

61. Prospective Studies Collaboration Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995; **346** 1647-1653.

62. Davey Smith, G. Low blood cholesterol and non-atherosclerotic disease mortality: where do we stand? *European Heart Journal.* 1997; **18** 6-9.

63. Crouse, J. R., III, Byington, R. P., Hoen, H. M., and Furberg, C. D. Reductase inhibitor monotherapy and stroke prevention.[see comment]. *Archives of Internal Medicine.* 23-6-1997; **157** 1305-1310.

64. Cranney, A, Tugwell, P, Wells, G, and Guyatt, G Systematic reviews of randomized trials in osteoporosis: introduction and methodology. *Endocrine Reviews* 2002; **23** 497-507.

65. Cramer, J. A. Effect of partial compliance on cardiovascular medication effectiveness. *Heart* 2002; **88** 203-206.

66. Insull, W., Troendle, A., Silvers, A., and Dunne, C. W. Substantial non-compliance to dose and time prescriptions for medications treating hypercholesterolemia. *Atherosclerosis* 1995; **115** S93-S93.

67. Stephenson, B. J., Rowe, B. H., Haynes, R. B., Macharia, W. M., and Leon, G. Is this patient taking the treatment as prescribed? *JAMA* 1993; **269** 2779-2781.

68. Voss, S, Quail, D, Dawson, A, Backstrom, T, Aguas, F, Erenus, M, Bonnar, HS, De Geyter, C, Hunter, M, and Nickelsen, T A randonised, double-blind trial comparing raloxifene HCI and continuous combined hormone replacement therapy in postmenopausal women: effects on compliance and quality of life. *BJOG* 2002; **109** 874-885.

69. McDonald, H. P., Garg, A. X., and Haynes, R. B. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA* 2002; **288** 2868-2879.

70. Howell, N., Trotter, R., Mottram, D. R., and Rowe, P. H. Compliance with statins in primary care. *Pharmaceutical Journal* 2004; **272** 23-26.

71. Heart Protection Study 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.

72. Centre for Reviews and Dissemination Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews. 2001; **4 (2nd Edition).**

73. Windeler, J and Lange, S Events per person year -- a dubious concept. *BMJ* 1995; **310** 454-456.

74. Review Manager (RevMan). *Revman* 2000.

75. GraphPad Software, Inc. GraphPad QuickCalcs. *Google* 2004.

76. Smith, G. D., Song, F., and Sheldon, T. A. Cholesterol lowering and mortality: the importance of considering initial level of risk. *British Medical Journal* 1993; **306** 1367-1373.

77. Shepherd, J., Blauw, G. J., Murphy, M. B., Bollen, E. L., Buckley, B. M., Cobbe, S. M., Ford, I., Gaw, A., Hyland, M., Jukema, J. W., Kamper, A. M., Macfarlane, P. W., Meinders, A. E., Norrie, J., Packard, C. J., Perry, I. J., Stott, D. J., Sweeney, B. J., Twomey, C., Westendorp, R. G., and PROSPER study group.PROspective Study of Pravastatin in the Elderly at Risk Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 23-11-2002; **360** 1623-1630.

78. Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Lorimer, A. R., Macfarlane, P. W., McKillop, J. H., Packard, C. J., and The West of Scotland Coronary Prevention Study Group Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *New England Journal of Medicine.* 1995; **333** 1301-1307.

79. Olsson, A. G., Eriksson, M., Johnson, O., Kjellstrom, T., Lanke, J., Larsen, M. L., Pedersen, T., Tikkanen, M. J., Wiklund, O., and Investigators, T. Study A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: the treat-to-target (3T) study. *Clinical Therapeutics.* 2003; **25** 119-138.

80. Wanner, C., Krane, V., Ruf, G., Marz, W., and Ritz, E. Rationale and design of a trial improving outcome of type 2 diabetics on hemodialysis. *Kidney International.* 1999; **56** S222-S226.

81. Smilde, T. J., van Wissen, S., Wollersheim, H., Trip, M. D., Kastelein, J. J., and Stalenhoef, A. F. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet.* 24-2-2001; **357** 577-581.

82. Kastelein, J. J. P., Isaacsohn, J. L., Ose, L., Hunninghake, D. B., Frohlich, J., and et al Comparison of effects of simvastatin versus atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I levels. *American Journal of Cardiology* 15-7-2000; **86** 221-223.

83. Sato, S., Kobayashi, T., Awata, N., Reiber, J. H. C., Nakagawa, Y., Hiraoka, H., Katoh, O., Kirino, M., Shibata, Nobuhiko, Kobayashi, T., Itoh, T., and Shibata, N. Randomized, controlled trial of secondary prevention of coronary sclerosis in normocholesterolemic patients using pravastatin: Two-

year follow-up of the prevention of coronary sclerosis study. *Current Therapeutic Research, Clinical & Experimental* 2001; **62** 473-485.

84. Koren, M. J. and Hunninghake, D. B. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics. *Journal of the American College of Cardiology.* 2004; **44** 1772-1779.

85. Okazaki, S., Yokoyama, T., Miyauchi, K., Shimada, K., Kurata, T., Sato, H., and Daida, H. Early statin treatment in patients with acute coronary syndrome. Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH study. *Circulation* 2004; **110** 1061-1068.

86. Nissen, S. E., Tuzcu, E. M., Schoenhagen, P., Brown, B. G., Ganz, P., Vogel, R. A., Crowe, T., Howard, G., Cooper, C. J., Brodie, B., Grines, C. L., and DeMaria, A. N. Effect of intensive compared wiht moderate lipid-lowering therapy on progression of coronary atherosclerosis. A randomized controlled trial. *JAMA* 2004; **291** 1071-1080.

87. Lesaffre, E., Kocmanova, D., Lemos, P. A., Disco, C. M., and Serruys, P. W. A retrospective analysis of the effect of noncompliance on time to first major adverse cardiac event in LIPS. *Clinical Therapeutics.* 2003; **25** 2431-2447.

88. Foley, D. P., Bonnier, H., Jackson, G., Macaya, C., Shepherd, J., Vrolix, M., and Serruys, P. W. Prevention of restenosis after coronary balloon angioplasty: rationale and design of the Fluvastatin Angioplasty Restenosis (FLARE) Trial. The FLARE Study Group. *American Journal of Cardiology.* 26-5-1994; **73** 50D-61D.

89. Riegger, G., Abletshauser, C., Ludwig, M., Schwandt, P., Widimsky, J., Weidinger, G., and Welzel, D. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis* 1999; **144** 263-270.

90. Mehra, M. R., Uber, P. A., Vivekananthan, K., Solis, S., Scott, R. L., Park, M. H., Milani, R. V., and Lavie, C. J. Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. *Journal of the American College of Cardiology.* 6-11-2002; **40** 1609-1614.

91. Rauscher, M. Atorvastatin lowers LDL but not risk of CV events in diabetics with ESRD. *Google* 2004.

92. Keech, A., Collins, R., MacMahon, S., Armitage, J., Lawson, A., Wallendszus, K., Fatemian, M., Kearney, E., Lyon, V., Mindell, J., and et al Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *European Heart Journal.* 1994; **15** 255-269.

93. Mondillo, S., Ballo, P., Barbati, R., Guerrini, F., Ammaturo, T., Agricola, E., Pastore, M., Borrello, F., Belcastro, M., Picchi, A., and Nami, R. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *American Journal of Medicine.* 1-4-2003; **114** 359-364.

94. Sever, P. S., Dahlof, B., Poulter, N. R., Wedel, H., Beevers, G., Caulfield, M., Collins, R., Kjeldsen, S. E., Kristinsson, A., McInnes, G. T., Mehlsen, J., Nieminen, M., O'Brien, E., Ostergren, J., and ASCOT, investigators Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 5-4-2003; **361** 1149-1158.

95. Pedersen, T. R. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344** 1383-1389.

96. White, H. D., Simes, R. J., Anderson, N. E., Hankey, G. J., Watson, J. D. G., Hunt, D., Colquhoun, D. M., Glasziou, P., MacMahon, S., Kirby, A. C., West, M. J., and Tonkin, A. M. Pravastatin therapy and the risk of stroke. *New England Journal of Medicine.* 2000; **343** 317-326.

97. Mercuri, M., Bond, M. G., Sirtori, C. R., Veglia, F., Crepaldi, G., Feruglio, F. S., Descovich, G., Ricci, G., Rubba, P., Mancini, M., Gallus, G., Bianchi, G., D'Alo, G., and Ventura, A. Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. *American Journal of Medicine.* 1996; **101** 627-634.

98. Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A. W., Livingstone, S. J., Thomason, M. J., Mackness, M. I, Charlton-Menys, V., and Fuller, J. H. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364** 685-698.

99. Serruys, P. W., Foley, D. P., Jackson, G., Bonnier, H., Macaya, C., Vrolix, M., Branzi, A., Shepherd, J., Suryapranata, H., de Feyter, P. J., Melkert, R., van Es, G. A., and Pfister, P. J. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. *European Heart Journal.* 1999; **20** 58-69.

100. Liem, A. H., Van Boven, A. J., Veeger, N. J. G. M., Withagen, A. J., Robles de Medina, R. M., Tijssen, J. G. P., and van Veldhuisen, D. J. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. *European Heart Journal.* 2002; **23** 1931-1937.

101. Serruys, P. W. J. C., de Feyter, P., Macaya, C., Kokott, N., Puel, J., Vrolix, M., Branzi, A., Bertolami, M. C., Jackson, G., Strauss, B., and Meier, B. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **287** 3215-3222.

102. Sacks, F. M., Pfeffer, M. A., Moye, L. A., Rouleau, J. L., Rutherford, J. D., Cole, T. G., Brown, L., Warnica, J. W., Arnold, J. M. O., Wun, C-C., Davis, B. R., and Braunwald, E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *New England Journal of Medicine.* 1996; **335** 1001-1009.

103. The LIPID Study Group Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *New England Journal of Medicine.* 1998; **339** 1349-1357.

104. Pitt, B., Mancini, G. B., Ellis, S. G., Rosman, H. S., Park, J. S., and McGovern, M. E. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. *Journal of the American College of Cardiology.* 1995; **26** 1133-1139.

105. Crouse, J. R., III, Byington, R. P., Bond, M. G., Espeland, M. A., Craven, T. E., Sprinkle, J. W., McGovern, M. E., and Furberg, C. D. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology.* 1995; **75** 455-459.

106. Bertrand, M. E., McFadden, E. P., Fruchart, J. C., Van Belle, E., Commeau, P., Grollier, G., Bassand, J. P., Machecourt, J., Cassagnes, J., Mossard, J. M., Vacheron, A., Castaigne, A., Danchin,

N., and Lablanche, J. M. Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. The PREDICT Trial Investigators. Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty. *Journal of the American College of Cardiology.* 1997; **30** 863-869.

107. Jukema, J. W., Bruschke, A. V. G., Van Boven, J. A., Reiber, J. H. C., Bal, E. T., Zwinderman, A. H., Jansen, H., Boerma, G. J. M., van Rappard, F. M., and Lie, K. I. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995; **91** 2528-2540.

108. Anonymous Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (**MAAS**). *Lancet* 1994; **344** 633-638.

109. Bestehorn, H. P., Rensing, U. F., Roskamm, H., Betz, P., Benesch, L., Schemeitat, K., Blumchen, G., Claus, J., Mathes, P., Kappenberger, L., Wieland, H., and Neiss, A. The effect of simvastatin on progression of coronary artery disease. The Multicenter coronary Intervention Study (CIS). *European Heart Journal.* 1997; **18** 226-234.

110. Teo, K. K., Burton, J. R., Buller, C. E., Plante, S., Catellier, D., Tymchak, W., Dzavik, V., Taylor, D., Yokoyama, S., and Montague, T. J. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation.* 10-10-2000; **102** 1748-1754.

111. Strandberg, T. E., Pyorala, K., Cook, T. J., Wilhelmsen, L., Faergeman, O., Thorgeirsson, G., Pedersen, T. R., and Kjekshus, J. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004; **364** 771-777.

112. Aronow, W. S., Nayak, D., Woodworth, S., and Ahn, C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *American Journal of Cardiology.* 15-9-2003; **92** 711-712.

113. Tonkin, A. M., Colquhoun, D., Emberson, J., Hague, W., Keech, A., Lane, G., MacMahon, S., Shaw, J., Simes, R. J., Thompson, P. L., White, H. D., and Hunt, D. Effects of pravastatin in 3260 patients with unstable angina: results from the LIPID study. *Lancet.* 2-12-2000; **356** 1871-1875.

114. Tonkin, A., Aylward, P., Colquhoun, D., Glasziou, P., Harris, P., Hunt, D., MacMahon, S., Nesel, P., Sharpe, N., Simes, J., Thompson, P., Thopmson, A., West, M., White, H., Shaw, J., Nestel, P., Ablett, M., MacAskill, M., Turner, R., and et, al Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) Study: a randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. *American Journal of Cardiology.* 1995; **76** 474-479.

115. Anonymous MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. *European Heart Journal.* 1999; **20** 725-741.

116. Sacks, F. M., Pfeffer, M. A., Moye, L., Brown, L. E., Hamm, P., Cole, T. G., Hawkins, C. M., and Braunwald, E. Rationale and design of a secondary prevention trial of lowering normal plasma cholesterol levels after acute myocardial infarction: the Cholesterol and Recurrent Events trial (CARE). *American Journal of Cardiology.* 1991; **68** 1436-1446.

117. Anon The lescol in severe atherosclerosis (LiSA) trial. *British Journal of Cardiology.* 1998; **5** 1-2.

118. Cannon, C. P., Braunwald, E., McCabe, C. H., Rader, D. J., Rouleau, J. L., Belder, R., Joyal, S. V., Hill, K. A., Pfeffer, M. A., and Skene, A. M. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *New England Journal of Medicine.* 2004; **350** 1495-1504.

119. Olsson, A. G., Istad, H., Luurila, O., Ose, L., Stender, S., Tuomilehto, J., Wiklund, O., Southworth, H., Pears, J., Wilpshaar, J. W., and Rosuvastatin Investigators Group Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *American Heart Journal.* 2002; **144** 1044-1051.

120. Brown, W. V., Bays, H. E., Hassman, D. R., McKenney, J., Chitra, R., Hutchinson, H., and Miller, E. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *American Heart Journal.* 2002; **144** 1036-1043.

121. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA.* 18-12-2002; **288** 2998-3007.

122. Athyros, V. G., Papageorgiou, A. A., Mercouris, B. R., Athyrou, V. V., Symeonidis, A. N., Basayannis, E. O., Demitriadis, D. S., and Kontopoulos, A. G. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Current Medical Research & Opinion* 2002; **18** 220-228.

123. Colivicchi, F., Guido, V., Tubaro, M., Ammirati, F., Montefoschi, N., Varveri, A., and Santini, M. Effects of atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave myocardial infarction. *American Journal of Cardiology.* 15-10-2002; **90** 872-874.

124. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? *Italian Heart Journal: Official Journal of the Italian Federation of Cardiology.* 2000; **1** 810-820.

125. Blazing, M. A., De Lemos, J. A., Dyke, C. K., Califf, R. M., Bilheimer, D., and Braunwald, E. The A-to-Z Trial: Methods and rationale for a single trial investigating combined use of low-molecular-weight heparin with the glycoprotein IIb/IIIa inhibitor tirofiban and defining the efficacy of early aggressive simvastatin therapy. *American Heart Journal.* 2001; **142** 211-217.

126. Ito, H. A comparison of low versus standard dose pravastatin therapy for the prevention of cardiovascular events in the elderly: the pravastatin anti-atherosclerosis trial in the elderly (PATE). *Journal of Atherosclerosis & Thrombosis* 2001; **8** 33-44.

127. Salonen, R., Nyyssonen, K., Porkkala-Sarataho, E., and Salonen, J. T. The Kuopio Atherosclerosis Prevention Study (KAPS): effect of pravastatin treatment on lipids, oxidation resistance of lipoproteins, and atherosclerotic progression. *American Journal of Cardiology.* 1995; **76** 34C-39C.

128. Keech, A., Colquhoun, D., Baker, J., Simes, R. J., Bradfield, R., Best, J., and Tonkin, A. Benefits of long term cholesterol lowering therapy using pravastatin among patients with diabetes in the Lipid Study. *Australian & New Zealand Journal of Medicine* 2000; **30** 172.

129. Haffner, S. M., Alexander, C. M., Cook, T. J., Boccuzzi, S. J., Musliner, T. A., Pedersen, T. R., Kjekshus, J., and Pyorala, K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Archives of Internal Medicine.* 1999; **159** 2661-2667.

130. Keech, A., Colquhoun, D., Best, J., Kirby, A., Simes, R. J., Hunt, D., Hague, W., Beller, E., Arulchelvam, M., Baker, J., Tonkin, A., and for the LIPID Study Group Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose. *Diabetes Care* 2003; **26** 2713-2721.

131. Colhoun, H. M., Thomason, M. J., Mackness, M. I., Maton, S. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A. W., Fuller, J. H., Reckless, J. P. D., Jennings, P., Fisher, B. M., Stephens, W. P., Beer, S. F., Bhatnagar, D., Vora, J. P., Leatherdale, B., Wiles, P. G., O'Connell, N., Borthwick, L. J., Dayan, C. M., Speirs, C., Winocour, P. H., Young, R. J., Dean, J. D., Kerr, D., Harvey, J. N., Clements, M. R., Paterson, K. R., Gray, R. S., Patel, V., Singh, B. M., Matthews, D. R., Walker, J. D., Lawrence, J. R., Reith, S. B. M., Page, M. D., Hayes, J. R., Brown, M. J., Johnston, C. L. W., Broom, J., Dodson, P. M., Barron, J. L., Tindall, H., Gallacher, S. J., Sands, K. A., Weaver, J. U., Fleming, S., Burden, A. C., Press, M., Hammond, P. J., MacLeod, A., Shaw, K. M., Kemp, T. M., MacMahon, M., MacRury, S., O'Brien, I. A. D., Collier, A., Kesson, C. M., Robertson, D. A., Martin, U., Scobie, I. N., Wheatley, T., Waise, A., Seed, M., O'Hare, J. P., Burr, W. A., Nolan, J. J., McCance, D. R., Jowett, N. I., Morris, A. D., Scott, A. R., Cowie, A., McKenna, M. J., Hillhouse, E. W., Neleman, I., Lennon, C. H., Cahill, T. E., Tilley, J., Heffer, J. S., Duckworth, M. J. B., Middleton, A., Gray, N. I. D. B., Garrod, G. D., Cook, R. C., Ryan, J. F., Evans, P. W. G., Hampton, J., Orpen, I. M., Edwards, R., Dorn, horst A., Marshall, B. S. M., Parfitt, V. J., Benbow, S. J., Oelbaum, R. S., Bullen, K. R., Harris, T. J., Ellery, A., Mansell, P. I., and et, al Design of the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with Type 2 diabetes. *Diabetic Medicine.* 2002; **19** 201-211.

132. O'Rourke, B., Barbir, M., Mitchell, A. G., Yacoub, M. H., and Banner, N. R. Efficacy and safety of fluvastatin therapy for hypercholesterolaemia after heart transplantation. Results of a randomised double blind placebo controlled study. *International Journal of Cardiology.* 2004; **94** 235-240.

133. Kobashigawa, J. A., Katznelson, S., Laks, H., Johnson, J. A., Yeatman, L., Wang, X. M., Chia, D., Terasaki, P. I., Sabad, A., Cogert, G. A., Trosian, K., Hamilton, M. A., Moriguchi, J. D., Kawata, N., Hage, A., Drinkwater, D. C., and Stevenson, L. W. Effect of pravastatin on outcomes after cardiac transplantation. *New England Journal of Medicine.* 1995; **333** 621-627.

134. Wenke, K., Meiser, B., Thiery, J., Nagel, D., von Scheidt, W., Steinbeck, G., Seidel, D., and Reichart, B. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. *Circulation* 2-9-1997; **96** 1398-1402.

135. Holdaas, H., Fellstrom, B., Jardine, A. G., Holme, I., Nyberg, G., Fauchald, P., Gronhagen-Riska, C., Madsen, S., Neumayer, H. H., Cole, E., Maes, B., Ambuhl, P., Olsson, A. G., Hartmann, A., Solbu, D. O., Pedersen, T. R., and Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet.* 14-6-2003; **361** 2024-2031.

136. Keech, A. C., Armitage, J. M., Wallendszus, K. R., Lawson, A., Hauer, A. J., Parish, S. E., and Collins, R. Absence of effects of prolonged simvastatin therapy on nocturnal sleep in a large randomized placebo-controlled study. Oxford Cholesterol Study Group. *British Journal of Clinical Pharmacology.* 1996; **42** 483-490.

137. Wardle, J., Armitage, J., Collins, R., Wallendszus, K., Keech, A., and Lawson, A. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. Oxford Cholesterol Study Group. *BMJ* 13-7-1996; **313** 75-78.

138. Ho, C. Rosuvastatin: do we need another statin? *Issues in Emerging Health Technologies.* 2001;1-4.

139. Benghozi, R., Bortolini, M., Jia, Y., Isaacsohn, J. L., Troendle, A. J., and Gonasun, L. Frequency of creatine kinase elevation during treatment with fluvastatin. *American Journal of Cardiology* 2002; **89** 231-233.

140. Furberg, C. D. and Pitt, B. Withdrawal of cerivastatin from the world market. *Current Controlled Trials in Cardiovascular Medicine* 2001; **2** 205-207.

141. Anon The statin wars: why AstraZeneca must retreat. *Lancet* 2003; **362** 1341-1341.

142. Therapeutics Initiative Serious adverse event analysis: Lipid lowering therapy revisited. *Therapeutics Letter* 2001; **42** 1-2.

143. Brewer, T and Colditz, G. A. Postmarketing surveillance and adverse drug reactions: Current perspectives and future needs. *JAMA* 1999; **281** 824-829.

144. Fontanarosa, P. B., Rennie, D., and DeAngelis, C. D. Postmarketing surveillance -lack of vigilance, lack of trust. *JAMA* 2004; **292** 2647-2650.

145. Thompson, P. D., Clarkson, P., and Karas, R. H. Statin-associated myopathy.[see comment]. [Review] [100 refs]. *JAMA* 2-4-2003; **289** 1681-1690.

146. Hunninghake, D. B., Koren, M., and on behalf of the ALLIANCE Investigators Comparison of clinical outcomes in managed care patients with CHD treated in aggressive lipid lowering programs using atorvastatin versus usual care. The ALLIANCE Study. *Program and abstracts from the American College of Cardiology 53rd Annual Scientific Session; March 7-10, 2004; New Orleans, Louisiana.Late-Breaking Clinical Trials I* 2004.

147. The Pravastatin Multinational Study Group for Cardiac Risk Patients Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. *American Journal of Cardiology.* 1993; **72** 1031-1037.

148. Gaist, D., Rodriguez, L. A. G., Huerta, C., Hallas, J., and Sindrup, S. H. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001; **12** 565-569.

149. Staffa, JA, Chang, J., and Green, L. Cerivastatin and reports of fatal rhabdomyolysis. *New England Journal of Medicine* 2002; **346** 539-540.

150. Chang, JT, Staffa, JA, Parks, M, and Green, L Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf.* 2004; **137417426**

151. Graham, D. J., Staffa, JA, Shatin, D., Andrade, S. E., Schech, S. D., La Grenade, L., Gurwitz, J. H., Chan, K. A., Goodman, M. J., and Platt, R. Incidence of hospitalised rhabdomyolysis in patients treated with lipid lowering drugs. *JAMA* 2004; **292** 2585-2590.

152. Wolfe, S. M. Dangers of rosuvastatin identified before and after FDA approval. *Lancet* 2004; **363** 2189-2190.

153. Wolfe, S. M. Author's reply. *Lancet* 2004; **364** 1578-1579.

154. Olsson, G. O. and Fox, J. C. Correspondence: Should rosuvastatin be withdrawn from the market. *Lancet* 2004; **364** 1579-1580.

155. Waknine, Y. Rosuvastatin label change in EU indicates risk of myopathy. *Medscape* 2004.

156. Rao, S., Porter, D. C., Chen, X., Herliczek, T., Lowe, M., and Keyomarsi, K. Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent pf hydroxymethyl glutaryl-Co-A reductase. *Proceedings of the National Academy of Sciences of the United States of America* 1999; **96** 7797-7802.

157. Statins and cancer. *http://www.jr2.ox.ac.uk/bandolier/booth/cardiac/ statcanc.html (accessed 1st December 2004)* 2004.

158. Gaist, D., Jeppesen, U., Andersen, M., Garcia-Rodriguez, L. A., Hallas, J., and Sindrup, S. H. Statins and risk of polyneuropathy: A case-control study. *Neurology* 14-5-2002; **58(9): 1333-1337** 9-1337.

159. Gaist, D., Rodriguez, L. A., Huerta, C., Hallas, J., and Sindrup, S. H. Are users of lipid-lowering drugs at increased risk of peripheral neuropathy? *European Journal of Clinical Pharmacology* 2001; **56** 931-933.

160. Shepherd, J., Cobbe, S. M., Lorimer, A. R., McKillop, J. H., Ford, I., Packard, C. J., Macfarlane, P. W., and Isles, C. Compliance and adverse event withdrawal: their impact on the West of Scotland Coronary Prevention Study. *European Heart Journal.* 1997; **18** 1718-1724.

161. Shepherd, J., Blauw, G. J., Murphy, M. B., Cobbe, S. M., Bollen, E. L. E. M., Buckley, B. M., Ford, I., Jukema, J. W., Hyland, M., Gaw, A., Lagaay, A. M., Perry, I. J., Macfarlane, P. W., Meinders, A. E., Sweeney, B. J., Packard, C. J., Westendorp, R. G. J., Twomey, C., and Stott, D. J. The design of a prospective study of pravastatin in the elderly at risk (PROSPER). *American Journal of Cardiology.* 1999; **84** 1192-1197.

162. Wei, L., Wang, J., Thompson, P., Wong, S., Struthers, A. D., and MacDonald, T. M. Adherence to statin treatment and readmission of patients after myocardial infarction: A six year follow up study. *Heart* 2002; **88(3): 229-233** 3-233.

163. Tolmie, E. P., Lindsay, G. M., Kerr, S. M., Brown, M. R., Ford, I., and Gaw, A. Patients' perspectives on statin therapy for treatment of hypercholesterolaemia: a qualitative study. *European Journal of Cardiovascular Nursing* 2003; **2** 141-149.

164. Drummond, M. Jefferson T. O. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996; **313** 275-283.

165. Eddy, DM Technology assessment: The role of mathematical modeling. in Assessing medical technology. *Washington DC: National Academy Press* 1985;144-154.

166. Marshall, T. Coronary heart disease prevention: insights from modelling incremental cost effectiveness.[see comment]. *BMJ.* 29-11-2003; **327** 1264.

167. Marshall, T. and Rouse, A. Resource implications and health benefits of primary prevention strategies for cardiovascular disease in people aged 30 to 74: Mathematical modelling study. *British Medical Journal* 27-7-2002; **325** 197-199.

168. Grover, S. A., Coupal, L., Zowall, H., and Dorais, M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes : who should be treated? *Circulation.* 15-8-2000; **102** 722-727.

169. Caro, J., Klittich, W., McGuire, A., Ford, I., Norrie, J., Pettitt, D., McMurray, J., and Shepherd, J. The West of Scotland coronary prevention study: Economic benefit analysis of primary prevention with pravastatin. *British Medical Journal* 1997; **315** 1577-1582.

170. Glick, H., Heyse, J. F., Thompson, D., Epstein, R. S., Smith, M. E., and Oster, G. A model for evaluating the cost-effectiveness of cholesterol-lowering treatment. *International Journal of Technology Assessment in Health Care* 1992; **8** 719-734.

171. Pharoah, P. D. and Hollingworth, W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population.[see comment]. *BMJ* 8-6-1996; **312** 1443-1448.

172. Pickin, D. M., McCabe, C. J., Ramsay, L. E., Payne, N., Haq, I. U., Yeo, W. W., and Jackson, P. R. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment.[see comment]. *Heart (British Cardiac Society).* 1999; **82** 325-332.

173. Pickin, D. M., Payne, J. N., Haq, I. U., McCabe, C., Ward, S., Jackson, P. R., Yeo, WW, and Ramsay, L. E. Statin therapy/HMG CO-A reductase treatment in the prevention of coronary heart disease. 1996.

174. Elliott, W. J. and Weir, D. R. Comparative cost-effectiveness of HMG-CoA reductase inhibitors in secondary prevention of acute myocardial infarction.[see comment]. *American Journal of Health-System Pharmacy.* 1-9-1999; **56** 1726-1732.

175. Barry, M. and Heerey, A. Cost effectiveness of statins for the secondary prevention of coronary heart disease in Ireland. *Irish Medical Journal.* 2002; **95** 133-135.

176. Muls, E., Van Ganse, E., and Closon, M. C. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: Comparison between Belgium and the United States of a projected risk model. *Atherosclerosis* 1998; **137** S111-S116.

177. Ashraf, T., Hay, J. W., Pitt, B., Wittels, E., Crouse, J., Davidson, M., Furberg, C. D., and Radican, L. Cost-effectiveness of pravastatin in secondary prevention of coronary artery disease.[see comment]. *American Journal of Cardiology* 15-8-1996; **78** 409-414.

178. van Hout, B. A. and Simoons, M. L. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat?[see comment]. *European Heart Journal.* 2001; **22** 751-761.

179. Glasziou, P. P., Eckermann, S. D., Mulray, S. E., Simes, R. J., Martin, A. J., Kirby, A. C., Hall, J. P., Caleo, S., White, H. D., and Tonkin, A. M. Cholesterol-lowering therapy with pravastatin in patients with average cholesterol levels and established ischaemic heart disease: is it cost-effective? *Medical Journal of Australia.* 21-10-2002; **177** 428-434.

180. Lim, S. S., Vos, T., Peeters, A., Liew, D., and McNeil, J. J. Cost-effectiveness of prescribing statins according to pharmaceutical benefits scheme criteria. *Medical Journal of Australia.* 5-11-2001; **175** 459-464.

181. Riviere, M., Wang, S., Leclerc, C., Fitzsimon, C., and Tretiak, R. Cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease in Canada.[see comment]. *CMAJ Canadian Medical Association Journal.* 1-4-1997; **156** 991-997.

182. McAlister, F. A. and Teo, K. K. Antiarrhythmic therapies for the prevention of sudden cardiac death. [Review] [115 refs]. *Drugs.* 1997; **54** 235-252.

183. Grover, S. A., Coupal, L., Paquet, S., and Zowall, H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Archives of Internal Medicine.* 22-3-1999; **159** 593-600.

184. Johannesson, M. At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? *European Heart Journal* 2001; **22** 919-925.

185. D'Agostino, R. B., Russell, M. W., Huse, D. M., Ellison, R. C., Silbershatz, H., Wilson, P. W. F., and Hartz, S. C. Primary and subsequent coronary risk appraisal: New results from the Framingham study. *Am Heart J* 2000; **139** 272-281.

186. Stevens, RJ, Kotari, V, Adler, AI, and Stratton, IM The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (London)* 2001; **101** 671-679.

187. DOH Publications and statistics. *Department of Health* 2005.

188. ONS Mortality Statistics: cause. England and Wales. *London: Office for National Statistics, Stationery Office* 2001.

189. Consultative document from Department of Health: Reimbursement prices for four generic medicines. *DoH* 2005.

190. Clarke, P, Gray, A, Legood, R, Briggs, A, and Holman, R The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med* 2003; **20** 442-450.

191. Chambers, M, Hutton, J, and Gladman, J Cost-effectiveness Analysis of Antiplatelet Therapy in the Prevention of Recurrent Stroke in the UK. Aspirin, Dipyridamole and Aspirin Dipyridamole. *Pharmacoeconomics* 1999; **16** 577-593.

192. Youman, P., Wilson, K., Harraf, F., and Kalra, L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003; **Suppl 1** 43-50.

193. Health Survey for England 1998: Cardiovascular disease. *London: The Stationary Office* 1998.

194. Clarke, P, Gray, A, and Holman, R Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Med Decis Making* 2002; **22** 340-349.

195. Serruys, P., Unger, F, Sousa, JE, Jatene A, Bonnier, HJRM, and Schonberger, JPAM Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *European Heart Journal* 2001; **344** 1117-1124.

196. National Institute for Clinical Excellence Health Technology Appraisal:Review of coronary stents and appraisal of drug-eluting stents. 2003.

197. Meslop, K, Boothroyd, DB, and Hlatky, MA Quality of life and time trade-off utility measures in patients with coronary artery disease. *Am Heart J* 2003; **145** 36-41.

198. Jones, P. H., Davidson, M. H., Stein, E. A., Bays, H. E., McKenney, J. M., and et al Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *American Journal of Cardiology* 15-7-2003; **92** 152-160.

199. Ballantyne, C. M., McKenney, J., and Trippe, B. S. Efficacy and safety of an extended-release formulation of fluvastatin for once-daily treatment of primary hypercholesterolemia. *American Journal of Cardiology* 1-10-2000; **86** 759-763.

200. Wilson, K., Marriott, J., Fuller, S., Lacey, L., and Gillen, D. A model to assess the cost effectiveness of statins in achieving the UK National Service Framework target cholesterol levels. *Pharmacoeconomics.* 2003; **21** 1-11.

201. Brindle, P. Emberson Lampe F. Walker M. Whincup P Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ* 2003; **327** 1267.

202. Frolkis, JP. Pearce GL Nambi, V Statins do not meet expectations fro lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med* 2002; **113** 625-629.

203. Palmer, S and et al A cost-effectiveness model comparing alternative management strategies for the use of glycoprotein IIb/IIIa antagonists in non- st-elevation acute coronary syndrome. Report to the National Institute for Clinical Excellence. { HYPERLINK "http://www.nice.org.uk/Docref.asp?d=32030" }http://www.nice.org.uk/Docref.asp?d=32030. *NICE* 2002.

204. Mant and et al HCNA. *HCNA* 2004.

205. Lacey, EA. Walters SJ Continuing inequality: gender and social class influences on self perceived health after a heart attack. *Journal of Epidemiology and Community Health* 2003; **57** 622-627.

206. Sandercock, P. Berge E. Dennis M. Forbes J. Hand P. Kwan J. Lewis S. Lindley R. Neilson A. Wardlaw J. Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. *Stroke* 2004; **35** 1490-1497.

207. Bosch, JL. Hunink MG. Comparison of the Health Utilities Index Mark 3 (HUI3) and the EuroQol EQ-5D in patients treated for intermittent claudication. *Qual Life Res* 2000; **9** 591-601.

208. Jonsson, B, Johannesson, M, Kjekshus, J, Olsson, AG, Pedersen, TR, and Wedel, H Cost-effectiveness of cholesterol lowering. Results from the Scandinavian Simvastatin Survival Study (4S). *European Heart Journal* 1996; **17** 1001-1007.

209. Morris, S. A comparison of economic modelling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. *Health Economics.* 1997; **6** 589-601.

210. Sonnenberg, FA and Beck, JR Markov models in medical decision making: a practical guide. *Med Decision Making* 1993; **13** 322-339.

211. Mueck, A. O. and Seeger, H. Statins and menopausal health. *Journal of the British Menopause Society* 2002; **8(4): 141-146** 4-146.

212. National Institute for Clinical Excellence (NICE) Guidance for manufacturers and sponsors. *NICE* 2001.

213. National Institute for Clinical Excellence (NICE) Guide to the Methods of Technology Appraisal. *NICE* 2004.

214. Dennis, M. S., Bamford, J. M., Sandercock, P. A., and Warlow, C. P. Incidence of transient ischemic attacks in Oxfordshire, England. *Stroke* 1989; **20** 333-339.

215. Yeo, WW and Yeo, KR Coronary risk versus cardiovascular risk for treatment decisions in mild hypertension. *J Cardiovascular Risk* 2000; **9** 275-280.

216. British Heart Foundation statistics database. *BHF* 2004.

217. Bots, ML, van der Wilk, EC, Koudstaal, PJ, and et al Transient neurological attacks in the general population: prevalence, risk factors and clinical relevance. *Stroke* 1997; **28** 768-773.

218. Gray, D, Hampton, JR, and Nottingham Heart Attack Register. Twenty years' experience of myocardial infarction: the value of a heart attack register. *British Journal of Clinical Pharmacology* 1993; **47** 292-295.

219. Wolfe, CDA, Rudd, AG, Howard, R, Coshall, C, Stewart, J, Lawrence, E, and et al Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *J Neurol Neurosurg Psychiatry* 2002; **72** 211-216.

220. Juul-Moller, S, Edvardsson, N, Jahnmatz, B, Rosen, A, Sorenson, S, and Omblus, R Double blind trial of aspirin in primary prevention of MI in patients with stable chronic angine pecoris. *Lancet* 1992; **340** 1421-1425.

221. Rehnqvist, N., Hjemdahl, P., Billing, E., Bjorkander, I., Eriksson, S. V., Forslund, L., Held, C., Nasman, P., and Wallen, N. H. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS)[erratum appears in Eur Heart J 1996 Mar;17(3):483]. *European Heart Journal* 1996; **17** 76-81.

222. Dargie, HJ, Ford, I, and Fox, KM Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. Total Ischaemic Burden European Trial (TIBET). *European Heart Journal* 1996; **17** 104-112.

223. Pepine, CJ, Cohn, PF, Deedwania, PC, Gibson, RS, Handberg, E, Hill, JA, Miller, E, Marks, RG, and Thadani, U Effects of treatment on outcome in midly symptomatic patients with ischaemia during daily life. The Atenolol Silent Ischaemai Study (ASIST). *Circulation* 1994; **90** 762-768.

224. Haq, IU, Ramsey, LE, Yeo, WW, Jackson, PR, and Wallis, EJ Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. *Heart* 1999; **81** 40-46.

225. Maron, D. J., Fazio, Sergio, and Linton, MacRae F. Current perspectives on statins. *Circulation* 2000; **101** 207-213.

226. Anderson, K. M., Odell, P. M., Wilson, P. W. F., and Kannel, W. B. Cardiovascular disease risk profiles. *Am Heart J* 1990; **121** 293-298.

227. Curtis, L. Netten A Unit Costs of Health and Social Care 2004. *PSSRU* 2004.

228. Kind.P, Dolan, P, Gudex, C, and Williams, A Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998; **316** 736-741.

229. Brazier JE, Deverill M Harper R Booth A A review of the use of Health Status measures in economic evaluation. *Health Technology Assessment* 1999; **3.**

230. Brazier, JE, Green, C, and Kanis, JA A systematic review of health state utility values for osteoporosis related conditions. *Osteoporosis Int* 2002; **13** 768-776.

231. Van Exel, NJA Assessment of post-stroke quality of life in cost-effectiveness studies: the usefulness of the Barthel Index and the EuroQol-5D, Qyuality of life research. *Quality of Life Research* 2004; **13** 427-433.

232. Tengs, TO and Lin, TH A meta-analysis of quality of life estimates for stroke. *Pharmacoeconomics* 2003; **21** 191-200.

233. BARI Investigators Protocol for the Bypass Angioplasty Revascularization Investigation. *Circulation* 1991; **84** 1-27.

234. Goodacre, S, Nicholl, J, Dixon, S, Cross, E, Angelina, K, Arnold, J, Revill, S, Locker, T, Capewell, SJ, Quinney, D, Campbell, S, and Morris, F Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004; **328** 254-254.

235. Bradley, CJ, Kroll, J, and Holmes-Rover, M The health and activities limitation index in patients with acute myocardial infarction. *J Clin Epid* 2000; **53** 55-562.

236. Jacobs, D, Blackburn, H, Higgins, M, and et al Report of the conference on low blood cholesterol: mortality associations. *Circulation* 1992; **86** 1046-1060.

237. Neaton, JD, Blackburn, H, Jacobs, D, and et al Serum cholesterol and mortality findings for men screened in the multiple risk factor intervention trial. *Archives of Internal Medicine* 1992; **152** 1490-1500.

238. Zureik, M, Courbon, D, and Ducimetiere, P Serum cholesterol concentration and death from suicide in men: Paris prospective study. *BMJ* 1996; **313** 649-651.

239. Muldoon, M. F., Manuck, S. B., and Matthews, K. A. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials.[see comment]. *BMJ* 11-8-1990; **301** 309-314.

240. Davey Smith, GD. and Pekkanen, J Should there be a moratorium onthe use of cholesterol lowering drugs? *BMJ* 2004.

241. Davey Smith, GD., Song, F, and Sheldon, TA Cholesterol lowering and mortality: importance of considering initial level of risk. *BMJ* 1993; **306** 1367-1373.

242. Carlsson, C. M. and Papcke-Benson, K. Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. *Drugs & Aging* 2002; **19** 793-805.

243. Tsevat, J., Kuntz, K. M., Orav, E. J., Weinstein, M. C., Sacks, F. M., and Goldman, L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *American Heart Journal.* 2001; **141** 727-734.

244. Prosser, L. A., Stinnett, A. A., Goldman, P. A., Williams, L. W., Hunink, M. G., Goldman, L., and Weinstein, M. C. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics.[see comment]. *Annals of Internal Medicine.* 16-5-2000; **132** 769-779.

245. Berto, P., Munro, V., Gaddi, A., Negrini, C., Hutton, J., and Mast, O. Cost-effectiveness analysis for statin therapies in the primary prevention of coronary heart disease in Italy. *Clinical Drug Investigation* 2000; **20** 109-121.

246. Huse, D. M., Russell, M. W., Miller, J. D., Kraemer, D. F., D'Agostino, R. B., Ellison, R. C., and Hartz, S. C. Cost-effectiveness of statins. *American Journal of Cardiology.* 1-12-1998; **82** 1357-1363.

247. Russell, M. W., Huse, D. M., Miller, J. D., Kraemer, D. F., and Hartz, S. C. Cost effectiveness of HMG-CoA reductase inhibition in Canada. *Canadian Journal of Clinical Pharmacology.* 2001; **8** 9-16.

248. Yeo, KR and Yeo, WW Lipid lowering in patients with diabetes mellitus: what coronary heart disease risk threshold should be used? *Heart* 2002; **87** 423-427.

249. Yeo, WW and Yeo, KR Predicting CHd risk in patients with diabetes mellitus. *Diabetes UK, Diabetes Medicine* 2001; **18** 341-344.

250. National Statistics Online. *National Statistics Online* 2001.

251. Jones, A. F., Walker, J., and Jewkes, c Comparative accuracy of cardiovascular risk prediction methods in primary care patients. *Heart* 2001; **85** 37-43.

252. Durrington, P. N., Prais, H., and Bhatnagar, D. Indications for cholesterol-lowering medication: comparison of risk assessment methods. *Lancet* 1999; **353** 278-81.

253. McManus, RJ, Mant, J, and Meulendijks, CF Comparison of estimates and calculations of risk of coronary heart disease by doctors and nurses using different calculation tools in general practice. *BMJ* 2002; **324** 459-64.

254. Wierzbicki, A. S., Reynolds, T. M., Gill, K., Alg, S., and Crook, M. A. A comparison of algorithms for initiation of lipid lowering therapy in primary prevention of coronary heart disease. *Journal of Cardiovascular Risk.* 2000; **7** 63-71.

255. Sheridan, S, Pignone, M., and Mulrow, C. Framingham-based tools to calculate the global risk of coronary heart disease. *Journal of General Internal Medicine* 2003; **18** 1039-1052.

256. Haq, I. U., Ramsay, L. E., Jackson, P. R., and Wallis, E. J. Prediction of coronary risk for primary prevention of coronary heart disease: a comparison of methods. *Qjm.* 1999; **92** 379-385.

257. Thompson, A Patent expiries-how should they affect prescribing advice. *The Pharmaceutical Journal* 2003; **271** 587-589.

258. Belsey, J. Lipid-lowering in coronary heart disease. 1998; **1** 1-8.

259. Furnham, A Overcoming the obstacles-the outsider's view. *Arteriosclerosis* 1999; **147(Suppl 1)** S53-S56.

260. Dunbar, Jacob J. and Stunkard, AJ Adherence to diet and drug regimens. 1979;391-417.

261. Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. *BMJ* 2000; **320** 705-708.

262. Guidelines Committee. 2003 European Society of Hypertension Eauropean Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21** 1053.

263. OTC Statins: a bad decision for public health. *The Lancet* 2004; **363** 1659-1659.

264. *MHRA* 2004.

265. Do statins have a role in primary prevention? *Therapeutics Letter 48 April, May & June* 2003.

266. Packham, C., Robinson, J., Morris, J., Richards, C., Marks, P., and Gray, D. Statin prescribing in Nottingham general practices: a cross-sectional study. *Journal of Public Health Medicine* 1999; **21** 60-64.

267. Packham, C., Pearson, J., Robinson, J., and Gray, D. Use of statins in general practices, 1996-8: cross sectional study. *British Medical Journal* 2000; **320** 1583-1584.

268. Diaz, C., Aristegui, R., and Hernandez, G. Primary prevention in patients with non-insulin dependent diabetes mellitus (NIDDM) and albuminuria: AIDA study ("Atorvastatin in diabetes with albuminuria"). *Atherosclerosis* 1997; **134** 46.

269. Anon ASPEN Atorvastatin as Prevention of CHD Endpoints in patients with Non-insulin dependent diabetes mellitus. *Google* 2005.

270. Fellstrom, B., Zannad, F., Schmieder, R., Holdaas, H., Jardine, A., Armstrong, J., and Siewert-Delle, A. A study to evaluate the use of rosuvastatin in subjects on regular haemodialysis: an assessment of survival and cardiovascular events - the aurora study. *Nephrology Dialysis Transplantation.* 2003; **18** 713.

271. Von Haehling, S. and Anker, S. D. Statins for heart failure: at the crossroads between cholesterol reduction and pleiotropism? *Heart* 2005; **91** 1-2.

272. Novartis Lescol® following angioplasty sharply reduces risk of cardiac events in patients with advanced coronary artery disease down to that of patients with early stage disease. *Google* 31-3-2003.

273. Pedersen TR, Faergeman O. Effect of greater LDL-C reductions on prognosis - the incremental decrease in endpoints through aggressive lipid lowering (ideal) trial. *Atherosclerosis* 1999; **144** 38.

274. Waters, D. D., Guyton, J. R., Herrington, D. M., McGowan, M. P., Wenger, N. K., and Shear, C. Treating to New Targets (TNT) study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *American Journal of Cardiology* 2004; **93** 154-158.

275. Nakamura, H. The design and background characteristics of the study on the primary prevention of coronary events with pravastatin among Japanese with mildly elevated cholesterol levels (Japanese Mega Study). *Atherosclerosis* 2000; **151** 136.

276. Ridker, P. M. and on behalf of the JUPITER study group Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Circulation* 2003; **108** 2292-2297.

277. Anon Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). *Google* 2005.

278. Amarenco, P., Bogousslavsky, J., Callahan, A. S., Goldstein, L., Hennerici, M., Sillsen, H., Welch, M. A., Zivin, J., and SPARCL, Investigators Design and baseline characteristics of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study. *Cerebrovascular Diseases.* 2003; **16** 389-395.

279. Stegmayr, B. G., Nasstrom, B. G., Brannstrom, M., Bucht, S., Dimeny, E., Gosch, J., Granroth, B., Ingman, B., Isaksson, B., Johansson, G., Lundberg, L., Mikaelsson, L., Olausson, E., Wirell, M. P., Svensson, M., and Wikdahl, A. M. Safety and efficacy of atorvastatin in patients with severe renal dysfunction. *Journal of the American Society of Nephrology* 1998; **9** 161A.

280. Herd, J. A., Ballantyne, C. M., Farmer, J. A., Ferguson, J. J. III, Jones, P. H., West, M. S., Gould, K. L., and Gotto, A. M., Jr. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *American Journal of Cardiology.* 1997; **80** 278-286.

281. Sawayama, Y., Shimizu, C., Maeda, N., Tatsukawa, M., Kinukawa, N., Koyanagi, S., Kashiwagi, S., and Hayashi, J. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). *Journal of the American College of Cardiology.* 2002; **39** 610-616.

282. Betteridge, D. and Gibson, M. Effect of rosuvastatin and atorvastatin on LDL-C and CRP levels in patients with type 2 diabetes: results of the ANDROMEDA study. *Atherosclerosis Supplements.* 2004; **5** 107-Abstract M.464.

283. Franken, A., Wolffenbuttel, B., and Vincent, H. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes. *Atherosclerosis Supplements.* 2004; **5** 118-Abstract M.513.

284. Schuster, H., Barter, P. J., Stender, S., Cheung, R. C., Bonnet, J., Morrell, J. M., Watkins, C., Kallend, D., and Raza, A. Effect of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *American Heart Journal.* 2004; **147** 705-712.

285. Jukema, J., Liem, A., Dunselman, P., van der Sloot, J., Lok, D., and Zwinderman, A. LDL-C/HDL-C ratio in patients with coronary artery disease and low HDL-C: the RADAR study. *Atherosclerosis Supplements.* 2004; **5** 125-Abstract M.542.

286. Davidson, M., Ma, P., Stein, E. A., Gotto Jr, A. M., Raza, A., and et al Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *American Journal of Cardiology* 1-2-2002; **89** 268-275.

287. Schwartz, G. G. and et al Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial. *American Heart Journal.* 2004; **148** H1-H9.

288. Paoletti, R. Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study. *Journal of Cardiovascular Risk* 2001; **8** 383-390.

289. Stein, E. A., Strutt, K., Southworth, H., Diggle, P. J., Miller, E., and HeFH Study Group Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. *American Journal of Cardiology.* 1-12-2003; **92** 1287-1293.

290. Schneck, D. W., Knopp, R. H., Ballantyne, C. M., McPherson, R., Chitra, R. R., and Simonson, S. G. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia and without active arterial disease. *American Journal of Cardiology.* 1-1-2003; **91** 33-41.

291. Berne, C. and Siewert-Delle, A. Use of rosuvastatin versus atorvastatin in type 2 diabetes mellitus subjects: results of the URANUS study. *Atherosclerosis Supplements.* 2004; **5** 107-Abstract M.463.

292. Wiegman, A., Hutten, B. A., de Groot, E., Rodenburg, J., Bakker, H. D., Buller, H. R., Sijbrands, E. J. G., and Kastelein, J. J. P. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; **292** 331-337.

293. Baggio, G., De Candia, O., Forte, P. L., Mello, F., Andriolli, A., Donazzan, S., Valerio, G., Milani, M., and Crepaldi, G. Efficacy and safety of fluvastatin, a new HMG CoA reductase inhibitor, in elderly hypercholesterolaemic women. *Drugs* 1994; **47 Suppl 2** 59-63.

294. Bruckert, E., Lievre, M., Giral, P., and et al Short-term efficacy and safety of extended-release fluvastatin in a large cohort of elderly patients. *American Journal of Geriatric Cardiology.* 2004; **12** 225-231.

295. Buzzi, A. P. and Pastore, M. Argentine multicenter evaluation of fluvastatin in the treatment of patients with hypercholesterolemia. *Current Therapeutic Research.* 1997; **58** 1013-1028.

296. Farnier, M. Effect of combined fluvastatin-fenofibrate therapy compared with fenofibrate monotherapy in severe primary hypercholesterolemia. *American Journal of Cardiology* 2000; **85** 53-57.

297. Farnier, M., Salko, T., Isaacsohn, J. L., and et al Effects of baseline level of triglycerides on changes in lipid levels from combined fluvastatin + fibrate (bezafibrate, fenofibrate, or gemfibrozil). *American Journal of Cardiology.* 2003; **92** 794-797.

298. Davidson, M. H. Fluvastatin Long-Term Extension Trial (FLUENT): summary of efficacy and safety. *American Journal of Medicine* 6-6-1994; **96** 41S-44S.

299. Marcus, A. Fluvastatin titrate-to-goal clinical practice study: interim results. *Clinical Cardiology.* 1994; **17** IV16-IV20.

300. Hunninghake, D. B., Davidson, M. H., Knapp, H. R., and et al Extended-release fluvastatin 80 mg shows greater efficacy, with comparable tolerability, versus immediate-release fluvastatin 40 mg for once daily treatment of primary hypercholesterolaemia. *British Journal of Cardiology.* 2002; **9** 469-475.

301. Insull, W., Jr., Black, D., Dujovne, C., Hosking, J. D., Hunninghake, D., Keilson, L., Knopp, R., McKenney, J., Stein, E., and Troendle, A. J. Efficacy and safety of once-daily vs twice-daily dosing with fluvastatin, a synthetic reductase inhibitor, in primary hypercholesterolemia. *Archives of Internal Medicine* 14-11-1994; **154** 2449-2455.

302. Insull, W., Marais, A. D., Aronson, R., and et al Efficacy and safety of fluvastatin ER 80 mg compared with fluvastatin IR 40 mg in the treatment of primary hypercholesterolaemia. *British Journal of Cardiology.* 2004; **11** 148-155.

303. Isaacsohn, J. L., LaSalle, J., Chao, G., and Gonasun, L. Comparison of treatment with fluvastatin extended-release 80-mg tablets and immediate-release 40-mg capsules in patients with primary hypercholesterolemia. *Clinical Therapeutics.* 2003; **25** 904-918.

304. Jacotot, B., Banga, J. D., Pfister, P., and Mehra, M. Efficacy of a low dose-range of fluvastatin (XU 62-320) in the treatment of primary hypercholesterolaemia. A dose-response study in 431 patients. The French-Dutch Fluvastatin Study Group. *British Journal of Clinical Pharmacology* 1994; **38** 257-263.

305. Leitersdorf, E., Muratti, E. N., Eliav, O., and Peters, T. K. Efficacy and safety of triple therapy (fluvastatin-bezafibrate-cholestyramine) for severe familial hypercholesterolemia. *American Journal of Cardiology* 13-7-1995; **76** 84A-88A.

306. Lye, M. Elderly patients with hypercholesterolaemia: results with fluvastatin. *Atherosclerosis* 1997; **130** S29.

307. Olsson, A. G., Pauciullo, P., Soska, V., and et al Comparison of the efficacy and tolerability of fluvastatin extended-release and immediate-release formulations in the treatment of primary hypercholesterolemia: a randomized trial. *Clinical Therapeutics.* 2001; **23** 45-61.

308. Pauciullo, P., Borgnino, C., Paoletti, R., and et al Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidaemia (FACT study).[comment]. *Atherosclerosis* 2000; **150** 429-436.

309. Peters, T. K., Muratti, E. N., and Mehra, M. Efficacy and safety of fluvastatin in women with primary hypercholesterolaemia. *Drugs* 1994; **47 Suppl 2** 64-72.

310. Teramoto, T., Goto, Y., Kurokawa, K., Nakamura, H., Yoshida, S., Saito, Y., Nakaya, N., Itakura, H., Takaku, F., and Yamada, N. Clinical efficacy of fluvastatin for hyperlipidemia in Japanese patients. *American Journal of Cardiology* 13-7-1995; **76** 33A-36A.

311. Tomlinson, B., Mak, T. W., Tsui, J. Y., Woo, J., Shek, C. C., Critchley, J. A., and Masarei, J. R. Effects of fluvastatin on lipid profile and apolipoproteins in Chinese patients with hypercholesterolemia. *American Journal of Cardiology* 13-7-1995; **76** 136A-139A.

312. Winkler, K. Effect of fluvastatin slow-release on low density lipoprotein (LDL) subfractions in patients with type 2 diabetes mellitus: baseline LDL profile determines specific mode of action. *Journal of Clinical Endocrinology & Metabolism* 2002; **87** 5485-5490.

313. Andrews TC, Ballantyne CM Hsia JA Kramer JH Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. *American Journal of Medicine* 15-8-2001; **111** 185-191.

314. Bays, H. E., Dujovne, C. A., McGovern, M. E., White, T. E., Kashyap, M. L., Hutcheson, A. G., Crouse, J. R., and ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *American Journal of Cardiology.* 15-3-2003; **91** 667-672.

315. Taylor, A. J., Kent, S. M., Flaherty, P. J., Coyle, L. C., Markwood, T. T., and Vernalis, M. N. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness.[see comment]. *Circulation.* 15-10-2002; **106** 2055-2060.

316. Insull, W., Kafonek, S., Goldner, D., and Zieve, F. Comparison of efficacy and safety of atorvastatin (10 mg) with simvastatin (10 mg) at six weeks. *American Journal of Cardiology* 2001; **87** 554-559.

317. Assmann, G., Huwel, D., Schussman, K-M., Smilde, J. G., Kosling, M., Withagen, A. J. A. M., Wunderlich, J., Stoel, I, Van Dormaal, J. J., Neuss, J., Oldenbroek, C., Cuppers, M. C., von Eckardstein, A., Schulte, H., Wagner, B., McLain, R., and Black, D. M. Efficacy and safety of atorvastatin and pravastatin in patients with hypercholesterolemia. *European Journal of Internal Medicine* 1999; **10** 33-39.

318. Athyros, V. G., Papageorgiou, A. A., Hatzikonstandinou, H. A., Athyrou, V. V., and Kontopoulos, A. G. Effect of atorvastatin versus simvastatin on lipid profile and plasma fibrinogen in patients with hypercholesterolaemia. *Clinical Drug Investigation.* 1998; **16** 219-227.

319. Cortellaro, M. Atorvastatin and thrombogenicity of the carotid atherosclerotic plaque: the ATROCAP study. *Thrombosis & Haemostasis* 2002; **88** 41-47.

320. Bakker-Arkema, R. G., Davidson, M. H., Goldstein, R. J., Davignon, J., Isaacsohn, J. L., Weiss, S. R., Keilson, L. M., Brown, W. V., Miller, V. T., Shurzinske, L. J., and Black, D. M. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA* 10-1-1996; **275** 128-133.

321. Ballantyne, C. M., Houri, J., Notarbartolo, A., Melani, L., Lipka, L. J., Suresh, R., Sun, S., LeBeaut, A. P., Sager, P. T., and Veltri, E. P. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 20-5-2003; **107** 2409-2415.

322. Raggi, P., Callister, T. Q., Davidson, M., Welty, F. K., Bachmann, G. A., Laskey, R., Pittman, D., Kafonek, S., and Scott, R. Aggressive versus moderate lipid-lowering therapy in postmenopausal women with hypercholesterolemia: Rationale and design of the Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES) trial. *American Heart Journal.* 2001; **141** 722-726.

323. Bertolami, M. C., Ramires, J. A. F., Nicolau, J. C., Novazzi, J. P., and Bodanese, L. C. Open, randomized, comparative study of atorvastatin and simvastatin, after 12 weeks treatment, in patients with hypercholesterolemia alone or with combined hypertriglyceridemia. *Revista Brasileira de Medicina* 2002; **59** 577-584.

324. Bertolini, S., Bittolo, B. G., Malcolm, C. L., Farnier, M., Langan, J., and et al Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis* 1997; **130** 191-197.

325. Best, J. D., Nicholson, G. C., O'Neal, D. N., Kotowicz, M. A., Tebbutt, N. C., Chan, K. W., and Sanders, K. M. Atorvastatin and simvastatin reduce elevated cholesterol in non- insulin dependent diabetes. *Diabetes, Nutrition & Metabolism - Clinical & Experimental* 1996; **9** 74-80.

326. Bo, M., Nicolello, M. T., Fiandra, U., Mercadante, G., Piliego, T., and Fabris, F. Treatment of heterozygous familial hypercholesterolemia: atorvastatin vs simvastatin. *Nutrition Metabolism & Cardiovascular Diseases.* 2001; **11** 17-24.

327. Boquist, S., Karpe, F., Danell-Toverud, K., and Hamsten, A. Effects of atorvastatin on postprandial plasma lipoproteins in postinfarction patients with combined hyperlipidaemia. *Atherosclerosis* 2002; **162** 163-170.

328. Branchi, A., Fiorenza, A. M., Torri, A., Muzio, F., Rovellini, A., and et al Effects of atorvastatin 10 mg and simvastatin 20 mg on serum triglyceride levels in patients with hypercholesterolemia. *Current Therapeutic Research, Clinical & Experimental* 2001; **62** 408-415.

329. Soedamah-Muthu, S. S., Colhoun, H. M., Thomason, M. J., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Fuller, J. H., Julier, K., Mackness, M. I., Neil, H. A., and CARDS, Investigators The effect of atorvastatin on serum lipids, lipoproteins and NMR spectroscopy defined lipoprotein subclasses in type 2 diabetic patients with ischaemic heart disease. *Atherosclerosis.* 2003; **167** 243-255.

330. Ma, P. CAVEAT: A randomised, double-blind, parallel group evaluation of cerivastatin 0.4 mg and 0.8 mg compared to atorvastatin 10 mg and 20 mg once daily in patients with combined (type IIb) dyslipidaemia. *British Journal of Cardiology* 2000; **7** 780-786.

331. Chan, D. C., Watts, G. F., Mori, T. A., Barrett, P. H. R., Beilin, L. J., and Redgrave, T. G. Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. *European Journal of Clinical Investigation* 2002; **32** 429-436.

332. Jones, P., Kafonek, S., Laurora, I., and Hunninghake, D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *American Journal of Cardiology* 1998; **81** 582-587.

333. Dalla Nora, E., Passaro, A., Zamboni, P. F., Calzoni, F., Fellin, R., and Solini, A. Atorvastatin improves metabolic control and endothelial function in type 2 diabetic patients: a placebo-controlled study. *Journal of Endocrinological Investigation* 2003; **26** 73-78.

334. Dallongeville, J., Fruchart, J. C., Maigret, P., Bertolini, S., Bon, G. B., Campbell, M. M., Farnier, M., Langan, J., Mahla, G., Pauciullo, P., and Sirtori, C. Double-blind comparison of apolipoprotein and lipoprotein particle lowering effects of atorvastatin and pravastatin monotherapy in patients with primary hypercholesterolemia. *Journal of Cardiovascular Pharmacology & Therapeutics* 1998; **3** 103-110.

335. Dart, A. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia.[comment]. *American Journal of Cardiology* 1-7-1997; **80** 39-44.

336. Davidson, M., McKenney, J., Stein, E., Schrott, H., Bakker-Arkema, R., and et al Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. *American Journal of Cardiology* 1997; **79** 1475-1481.

337. Farnier, M., Portal, J. J., and Maigret, P. Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia. *Journal of Cardiovascular Pharmacology & Therapeutics* 2000; **5** 27-32.

338. Ferrier, K. E., Muhlmann, M. H., Baguet, J. P., Cameron, J. D., Jennings, G. L., and et al Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *Journal of the American College of Cardiology* 20-3-2002; **39** 1020-1025.

339. Gentile, S., Turco, S., Guarino, G., Sasso, C. F., Amodio, M., and et al Comparative efficacy study of atorvastatin vs simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia. *Diabetes, Obesity & Metabolism* 2000; **2** 355-362.

340. Harris, K. P. G., Wheeler, D. C., and Chong, C. C. A placebo-controlled trial examining atorvastatin in dyslipidemic patients undergoing CAPD. *Kidney International* 2002; **61** 1469-1474.

341. Heinonen, T. M., Stein, E., Weiss, S. R., McKenney, J. M., Davidson, M., Shurzinske, L., and Black, D. M. The lipid-lowering effects of atorvastatin, a new HMG-CoA reductase inhibitor: results of a randomized, double-masked study. *Clinical Therapeutics* 1996; **18** 853-863.

342. Hunninghake, D., Insull, W., Jr., Toth, P., Davidson, D., Donovan, J. M., and Burke, S. K. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis.* 2001; **158** 407-416.

343. Hunninghake, D., Insull, W., Knopp, R., Davidson, M., Lohrbauer, L., and et al Comparison of the efficacy of atorvastatin versus cerivastatin in primary hypercholesterolemia. *American Journal of Cardiology* 15-9-2001; **88** 635-639.

344. Illingworth, D. R., Crouse, J. R., Hunninghake, D. B., Davidson, M. H., Escobar, I. D., and et al A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Current Medical Research & Opinion* 2001; **17** 43-50.

345. Nakamura, H., Ohashi, Y., Maruhama, Y., Ninomiya, K., Toyota, T., and et al Efficacy of atorvastatin in primary hypercholesterolemia. *American Journal of Cardiology* 1997; **79** 1248-1252.

346. Jialal, I., Stein, D., Balis, D., Grundy, S. M., Adams-Huet, B., and Devaraj, S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation.* 17-4-2001; **103** 1933-1935.

347. Jilma, B., Joukhadar, C., Derhaschnig, U., Rassoul, F., Richter, V., et al, and e Levels of adhesion molecules do not decrease after 3 months of statin therapy in moderate hypercholesterolaemia. *Clinical Science* 2003; **104** 189-193.

348. Joukhadar, C., Klein, N., Prinz, M., Schrolnberger, C., Vukovich, T., and et al Similar effects of atorvastatin, simvastatin and pravastatin on thrombogenic and inflammatory parameters in patients with hypercholesterolemia. *Thrombosis & Haemostasis* 2001; **85** 47-51.

349. Kadikoylu, G., Yukselen, V., Yavasoglu, I., Bolaman, Z., Lugo, S. I., and et al Hemostatic effects of atorvastatin versus simvastatin. *Annals of Pharmacotherapy.* 2003; **37** 478-484.

350. Karalis, D. G., Ross, A. M., Vacari, R. M., Zarren, H., and Scott, R. Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslipidemia with and without coronary heart disease. *American Journal of Cardiology* 15-3-2002; **89** 667-671.

351. Ebrahim, S. and Smith, G. D. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease.[see comment]. *BMJ.* 7-6-1997; **314** 1666-1674.

352. McCrindle, B. W., Ose, L., and Marais, A. D. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *Journal of Pediatrics* 2003; **143** 74-80.

353. Magnani, G., Carinci, V., Magelli, C., Potena, L., Reggiani, L. B., et al, and . Role of statins in the management of dyslipidemia after cardiac transplant: randomized controlled trial comparing the efficacy and the safety of atorvastatin with pravastatin. *Journal of Heart & Lung Transplantation* 2000; **19** 710-715.

354. Mullen, M. J., Wright, D., Donald, A. E., Thorne, S., Thomson, H., and et al Atorvastatin but not L-arginine improves endothelial function in type I diabetes mellitus: a double-blind study. *Journal of the American College of Cardiology* 2000; **36** 410-416.

355. Muscari, A., Bastagli, L., Poggiopollini, G., Tomassetti, V., Massarelli, G., and et al Short term effect of atorvastatin and vitamin E on serum levels of C3, a sensitive marker of the risk of myocardial infarction in men. *Cardiovascular Drugs & Therapy* 2001; **15** 453-458.

356. Nawawi, H., Osman, N. S., Yusoff, K., and Khalid, B. A. K. Reduction in serum levels of adhesion molecules, interleukin-6 and C-reactive protein following short-term low-dose atorvastatin treatment in patients with non-familial hypercholesterolemia. *Hormone & Metabolic Research* 2003; **35** 479-485.

357. Nawrocki, J. W., Weiss, S. R., Davidson, M. H., Sprecher, D. L., Schwartz, S. L., Lupien, P. J., Jones, P. H., Haber, H. E., and Black, D. M. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arteriosclerosis, Thrombosis & Vascular Biology* 1995; **15** 678-682.

358. Olsson, A. G., Pears, J., McKellar, J., Mizan, J., and Raza, A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *American Journal of Cardiology* 1-9-2001; **88** 504-508.

359. Oranje WA, Sels JP Rondas-Colbers GJ Lemmens PJ Wolffenbuttel BH Effect of atorvastatin on LDL oxidation and antioxidants in normocholesterolemic type 2 diabetic patients. *Clinica Chimica Acta* 25-9-2001; **311** 91-94.

360. Paiva, H., Laakso, J., Lehtimaki, T., Isomustajarvi, M., Ruokonen, I., and Laaksonen, R. Effect of high-dose statin treatment on plasma concentrations of endogenous nitric oxide synthase inhibitors. *Journal of Cardiovascular Pharmacology.* 2003; **41** 219-222.

361. Pontrelli, L., Parris, W., Adeli, K., and Cheung, R. C. Atorvastatin treatment beneficially alters the lipoprotein profile and increases low-density lipoprotein particle diameter in patients with combined dyslipidemia and impaired fasting glucose/type 2 diabetes. *Metabolism: Clinical & Experimental* 2002; **51** 334-342.

362. Raison, J., Rudnichi, A., and Safar, M. E. Effects of atorvastatin on aortic pulse wave velocity in patients with hypertension and hypercholesterolaemia: A preliminary study. *Journal of Human Hypertension* 2002; **16** 705-710.

363. Recto, C. S., Acosta, S., and Dobs, A. Comparison of the efficacy and tolerability of simvastatin and atorvastatin in the treatment of hypercholesterolemia. *Clinical Cardiology* 2000; **23** 682-688.

364. Renders, L., Mayer-Kadner, I, Koch, C., Scharffe, S., Burkhardt, K., Veelken, R., Schmieder, R. E., and Hauser, I. A. Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated transplant recipients. *Nephrology Dialysis Transplantation.* 2001; **16** 141-146.

365. Sardo, M. A., Castaldo, M., Cinquegrani, M., Bonaiuto, M., Maesano, A., Versace, A., Spadaro, M., Campo, S., Nicocia, G., Altavilla, D., and Saitta, A. Effects of atorvastatin treatment on sICAM-1 and plasma nitric oxide levels in hypercholesterolemic subjects. *Clinical & Applied Thrombosis/Hemostasis.* 2002; **8** 257-263.

366. Schrott, H., Fereshetian, A. G., Knopp, R. H., Bays, H., Jones, P. H., and et al A multicenter, placebo-controlled, dose-ranging study of atorvastatin. *Journal of Cardiovascular Pharmacology & Therapeutics* 1998; **3** 119-124.

367. Schuster, H., Berger, J., and Luft, F. C. Randomised, double-blind, parallel-group trial of atorvastatin and fluvastatin on plasma lipid levels in patients with untreated hyperlipidaemia. *British Journal of Cardiology.* 1998; **5** 597-602.

368. Sposito, A. C., Santos, R. D., Amancio, R. F., Ramires, J. A., Chapman, M. J., and Maranhao, R. C. Atorvastatin enhances the plasma clearance of chylomicron-like emulsions in subjects with atherogenic dyslipidemia: relevance to the in vivo metabolism of triglyceride-rich lipoproteins. *Atherosclerosis.* 2003; **166** 311-321.

369. Stein, D. T., Devaraj, S., Balis, D., Adams-Huet, B., and Jialal, I. Effect of statin therapy on remnant lipoprotein cholesterol levels in patients with combined hyperlipidemia. *Arteriosclerosis, Thrombosis & Vascular Biology* 2001; **21** 2026-2031.

370. Stein EA, Strutt KL and Miller ZD4522 is superior to atorvastatin in the treatment of patients with ozygous familial hypercholesterolemia. *Atherosclerosis* 2001; **.159, pp.248, 2001.**

371. Tan, K. C. B., Chow, W. S., Tam, S. C. F., Ai, V. H. G., Lam, C. H. L., and Lam, K. S. L. Atorvastatin lowers C-reactive protein and improves endothelium-dependent vasodilation in type 2 diabetes mellitus. *Journal of Clinical Endocrinology & Metabolism* 2002; **87** 563-568.

372. Tanaka, A., Yamada, N., Saito, Y., Kawakami, M., Ohashi, Y., and Akanuma, Y. A double-blind trial on the effects of atorvastatin on glycemic control in Japanese diabetic patients with hypercholesterolemia. *Clinica Chimica Acta.* 2001; **312** 41-47.

373. Tannous, M., Cheung, R., Vignini, A., and Mutus, B. Atorvastatin increases ecNOS levels in human platelets of hyperlipidemic subjects. *Thrombosis & Haemostasis* 1999; **82** 1390-1394.

374. Marz, W., Wollschlaeger, H., Klein, G., Neiss, A., and Wehling, M. Safety of low-density lipoprotein cholesterol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the target tangible trial). *American Journal of Cardiology* 1999; **84** 7-13.

375. van den Akker, J. M., Bredie, S. J., Diepenveen, S. H., van Tits, L. J., Stalenhoef, A. F., and et al Atorvastatin and simvastatin in patients on hemodialysis: effects on lipoproteins, C-reactive protein and in vivo oxidized LDL. *Journal of Nephrology* 2003; **16** 238-244.

376. Vansant, G., Mertens, A., and Muls, E. The effect of atorvastatin on postprandial lipaemia in overweight or obese women homozygous for apo E3. *Acta Cardiologica* 2001; **56** 149-154.

377. Wang, K-Y. and Ting, C-T. A randomized, double-blind, placebo-controlled, 8-week study to evaluate the efficacy and safety of once daily atorvastatin (10 mg) in patients with elevated LDL-cholesterol. *Japanese Heart Journal* 2001; **42** 725-738.

378. Watts, G. F., Chan, D. C., Barrett, P. H. R., O'Neill, F. H., and Thompson, G. R. Effect of a statin on hepatic apolipoprotein B-100 secretion and plasma campesterol levels in the metabolic syndrome. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity* 2003; **27** 862-865.

379. Wierzbicki, A. S., Lumb, P. J., Chik, G., and Crook, M. A. Comparison of therapy with simvastatin 80 mg and atorvastatin 80 mg in patients with familial hypercholesterolaemia. *International Journal of Clinical Practice* 1999; **53** 609-611.

380. Wolffenbuttel, B. H. R., Mahla, G., Muller, D., Pentrup, A., and Black, D. M. Efficacy and safety of a new cholesterol synthesis inhibitor, atorvastatin, in comparison with simvastatin and pravastatin, in subjects with hypercholesterolemia. *Netherlands Journal of Medicine.* 1998; **52** 131-137.

381. Wu, C-C., Sy, R., Tanphaichitr, V., Hin, A. T. T., Suyono, S., and et al Comparing the efficacy and safety of atorvastatin and simvastatin in Asians with elevated low-density lipoprotein-cholesterol--a multinational, multicenter, double-blind study. *Taiwan i Hsueh Hui Tsa Chih - Journal of the Formosan Medical Association* 2002; **101** 478-487.

382. Colhoun, H., Betteridge, J., Durrington, P., Hitman, G., Neil, A., Livingstone, S., Thomason, M., Mackness, M., Menys, V., and Fuller, J. Collaborative Atorvastatin Diabetes Study. CARDS. *www.cardstrial.org* 2004.

383. Pedersen, T. R., Kjekshus, J., Pyorala, K., Olsson, A. G., Cook, T. J., Musliner, T. A., Tobert, J. A., and Haghfelt, T. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian simvastatin survival study (4S). *American Journal of Cardiology.* 1998; **81** 333-335.

384. De Lemos, J. A., Blazing, M. A., Wiviott, S. D., Lewis, E. F., Fox, K. A. A., White, H. D., Rouleau, J-L., Pedersen, T. R., Gardner, L. H., Mukherjee, R., Ramsey, K. E., Palmisano, J., Bilheimer, D. W., Pfeffer, M. A., Califf, R. M., Braunwald, E., and for the A to Z Investigators Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. Phase Z of the A to Z trial. *JAMA* 2004; **292** 1307-1316.

385. Freeman, D. J., Norrie, J., Sattar, N., Neely, R. D., Cobbe, S. M., Ford, I., Isles, C., Lorimer, A. R., Macfarlane, P. W., McKillop, J. H., Packard, C. J., Shepherd, J., and Gaw, A. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation.* 23-1-2001; **103** 357-362.

386. Pedersen, T. R., Berg, K., Cook, T. J., Faergerman, O., Haghfelt, T., Kjekshus, J., Miettinen, T., Musliner, T. A., Olsson, A. G., Pyorala, K., Thorgeirsson, G., Tobert, J. A., Wedel, H., and Wilhelmsen, L. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Archives of Internal Medicine.* 1996; **156** 2085-2092.

387. Collins, R., Armitage, J., Parish, S., Sleigh, P., Peto, R., and Heart Protection Study Collaborative Group MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 14-6-2003; **361** 2005-2016.

388. Yeo, WW and Yeo, KR Coronary risk versus cardiovascular risk for treatment decisions in mild hypertension. *J Cardiovascular Risk* 2002; **9** 275-280.

389. NICE Guide to Methods of Technology Appraisal. *NICE* 2004.