Interpretation of the evidence for the efficacy and safety of statin therapy

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Summary

This review is intended to help clinicians, patients and the public make informed decisions about statin therapy for the prevention of heart attacks and strokes. It explains how the evidence that is available from randomized controlled trials yields reliable information about both the efficacy and safety of statin therapy. In addition, it discusses how claims that statins commonly cause adverse effects reflect a failure to recognise the limitations of other sources of evidence about the effects of treatment.

Large-scale randomized trial evidence shows that statin therapy reduces the risk of heart attacks, ischaemic strokes and coronary revascularization procedures ("major vascular events") by about one quarter for each mmol/L reduction in low density lipoprotein (LDL) cholesterol during each year (after the first) that it continues to be taken. The absolute benefits of statin therapy depend on an individual's absolute risk of occlusive vascular events and the absolute reduction in LDL cholesterol that is achieved. For example, lowering LDL cholesterol by 2 mmol/L (77 mg/dL) with an effective low-cost statin regimen (e.g. atorvastatin 40 mg daily, costing about £2 per month) for 5 years in 10,000 patients would typically prevent major vascular events from occurring in about 1000 patients (i.e. 10% absolute benefit) with pre-existing occlusive vascular disease ("secondary prevention") and in 500 patients (i.e. 5% absolute benefit) who are at increased risk but have not yet had a vascular event ("primary prevention"). Statin therapy has been shown to reduce vascular disease risk during each year it continues to be taken, so larger absolute benefits would accrue with more prolonged therapy, and these benefits persist long-term.

The only serious adverse events that have been shown by large-scale randomized trials to be caused by long-term statin therapy – that is, are adverse effects of the

statin – are myopathy (defined as muscle pain or weakness combined with large increases in blood levels of creatine kinase), new onset diabetes mellitus and, probably, haemorrhagic stroke. Typically, treatment of 10,000 patients for 5 years with an effective regimen (e.g. atorvastatin 40 mg daily) would cause about 5 cases of myopathy (1 of which might progress, if the statin therapy is not stopped, to the more severe condition of rhabdomyolysis), 50-100 new cases of diabetes, and 5 haemorrhagic strokes. However, any adverse impact of these side-effects on major vascular events has already been taken into account in the estimates of the absolute benefits. Statin therapy may cause symptomatic adverse events (e.g. muscle pain or weakness) in up to about 50-100 (i.e. 0.5-1.0%) patients per 10,000 treated for 5 years. However, placebo-controlled randomized trials have shown definitively that almost all of the symptomatic adverse events that are attributed to statin therapy in routine practice are not actually caused by it (that is, they represent mis-attribution).

The available large-scale randomized trial evidence also indicates that it is unlikely that large absolute excesses in other serious adverse events still await discovery. Consequently, any further findings that emerge about the effects of statin therapy would not be expected to alter materially the balance of benefits and harms. It is, therefore, of concern that exaggerated claims about side-effect rates with statin therapy may be responsible for its under-use among individuals at increased risk of cardiovascular events. For, whereas the rare cases of myopathy and any muscle-related symptoms that are attributed to statin therapy generally resolve rapidly when it is stopped, the heart attacks or strokes that may occur if statin therapy is stopped unnecessarily can be devastating.

Introduction

Used appropriately, modern medical therapies have the potential to prevent a large proportion of the burden of cardiovascular disease. However, their appropriate use relies on the availability of robust data on safety and efficacy, as well as on a sound understanding of the interpretation and application of such evidence.

Randomized controlled trials of adequate size are needed to be confident that any moderate benefits and any moderate harms of a treatment have been assessed sufficiently reliably.[1,2] In certain circumstances, available evidence from randomized trials about the effects of a treatment may be limited (perhaps because it is deemed not possible or too difficult to do them).[2] However, the particular context that this paper addresses is the appropriate interpretation of evidence about the safety and efficacy of a treatment when large randomized trials of it have been conducted in many different types of patient (as is the case for statin therapy), as well as the additional value of information from observational studies based on cohorts, health care databases or other sources.[3-5] Not only have the limitations of observational studies[4,6-9] often been under-estimated when attributing adverse effects to treatment (such as misleading claims that statins cause side-effects in one-fifth of patients[10-12]), but so too have the strengths of randomized trials with blinded treatment allocation and systematic ascertainment of many different types of adverse event been under-estimated for the reliable assessment of the safety and efficacy of treatment.[3,9,13-15]

This paper first considers the generic strengths and limitations of randomized trials and observational studies for assessing the effects of treatment, and then considers the specific evidence that is available on the efficacy and safety of statin therapy. It concludes by considering the public health implications of the failure to recognise the

full benefits of using statin therapy and of the exaggerated claims that have been made about the rates of side-effects.

Randomized controlled trials: strengths and weaknesses for assessing the benefits and harms of treatment

Insert Panel 1

Like-with-like comparisons within randomized trials

The key strength of randomized controlled trials is that the process of randomization results in groups of patients who differ from each other only by the play of chance with respect to their risks of suffering all types of health outcome (i.e. the randomized treatment groups are balanced with respect to both known and unknown risk factors, irrespective of whether or not these have been assessed).[3,7,9,14-16] In addition, blinding assignment of study treatment with a placebo minimises the differential assessment of adverse events between the study treatment groups following randomization.[17,18] Continued follow-up of all randomized patients (even if some stop taking their assigned treatment) maintains the "like-with-like" comparison produced by the randomization process (since, for example, the patients who stop may differ between the randomized groups).[3,7,9,14-16] Consequently, subject to statistical tests of the likely impact of chance, the observed differences in the rates of health outcomes between the randomly assigned patient groups within a trial (i.e. "intention-to-treat" comparisons) can be attributed causally to differences in the study treatment.

Information about a health outcome does not need to be obtained in the same way in the different randomized trials of an intervention (e.g. different statin trials recorded muscle-related outcomes differently: see webtable) for the comparisons of the rates of the outcome between the randomly allocated groups within each separate trial to

provide unbiased assessments of any real effects of the treatment. However, biases can be introduced by making non-randomized comparisons between rates of events across different trials, not only because the outcome definitions may differ but also because the types of patient studied and the duration of follow-up may differ. Such between-trial comparisons may be seriously misleading,[19] which is the reason why meta-analysis of randomized trials involve statistical methods that are based on the within-trial differences in a particular outcome.[20,21]

Robustness for detecting real treatment effects

It has been suggested that ascertainment of adverse events in randomized trials may not be sufficiently specific or sensitive to detect adverse effects of treatment reliably.[11,12,22-24] However, comparisons within randomized trials with unbiased ascertainment of outcomes between the treatment groups are robust against both over- and under-ascertainment.[25] For example, if the study treatment produced a 20% proportional decrease (or increase) in the rate of an outcome that occurred in 10% of control patients, then (as shown in Table 1) the ability to detect such an effect in a randomized trial of 20,000 patients would not be much altered by the random addition of reported events that were not actually the outcome of interest (i.e. “false positives”) in 10-20% of patients. Likewise, similar amounts of under-ascertainment (i.e. “false negatives”), would not materially affect the ability to detect such effects in a trial. Moreover, these false positives would have little or no impact on estimates of the absolute effects, and the false negatives would have limited impact. The robustness of these within-trial randomized comparisons applies not only to the detection of beneficial effects, but also to the detection of harms that a treatment might cause (such as any muscle-related symptoms with statin therapy).

It has been suggested that, when data for some types of health outcome are not available from all of the relevant randomized trials of a treatment, this will bias the assessment of its effects.[11,26,27] However, while some of these trials may have recorded all types of health outcome reported by the participating patients, others may have only recorded those outcomes that were considered "serious" (typically defined as resulting in hospitalisation or death), perhaps because previous trials had ruled out material differences in less serious outcomes. If information on a particular outcome is not available from a randomized trial because it was not recorded that would not bias assessment of the effects of the treatment based on trials that did record the outcome. Also, if randomized trials have already reported results based on large numbers of occurrences of a particular outcome then the inclusion of any unpublished data from other trials that did record such outcomes is not likely to materially alter the assessment of the effect of the treatment on that outcome.

"Intention-to-treat" analyses based on comparisons between all randomized patients, irrespective of whether they are adherent to their assigned study treatment (i.e. stop taking the active drug or, if assigned to the control group, start taking it), will tend to underestimate the effects produced by actually taking the treatment. However, rather than using potentially biased "on treatment" comparisons among only those patients who took their assigned study treatment, more appropriate allowance can be made by applying an approximate estimate of the level of adherence to the estimate of the treatment effect provided by the intention-to-treat comparison.[28] For example, if the average adherence to treatment assignment is two-thirds and the observed relative risk reduction (or increase) is 20%, then the adjusted estimate of the effect of actual use of the treatment would be a 30% proportional reduction (or increase).

Specificity versus sensitivity of composite outcomes

When there is clear evidence that a treatment produces effects on the incidence of different types of outcome that are in the same direction and of similar magnitude (for example, the reductions in coronary events, ischaemic strokes and coronary revascularisations produced by statin therapy[29-33]), combination of these outcomes in a composite outcome (such as "major vascular events" in the statin trials) may well provide more robust assessments of the effects of the treatment because they involve larger numbers of events than for any of the constituent outcomes. That does not necessarily mean that – when deciding whether the absolute benefits of the treatment outweigh the harms for any particular type of patient (e.g. offering statin therapy to individuals at lower versus higher risk of cardiovascular events) – equal weight should be given to the different components of such composite outcomes. Instead, such analyses of composite outcomes may allow more reliable evidence to emerge about the effects of the treatment in different circumstances (for example, the similar proportional reductions in major vascular events that have been found with statin therapy among many different types of patient: Figure 1[29-33]).

However, when a treatment has effects on different outcomes that differ in direction, then their combination in a composite outcome will reduce the ability to detect these outcome-specific effects and limit generalizability of the analyses.[34-37] For example, if a treatment reduces the incidence of ischaemic strokes but increases the incidence of haemorrhagic strokes (as appears to be the case for statin therapy[31,38]) then the adverse effect on haemorrhagic strokes may be missed by an assessment based on the composite of all stroke types since ischaemic strokes occur more commonly in most circumstances. By contrast, the assessment of the effects of the treatment on ischaemic and haemorrhagic strokes considered separately would not only be more

sensitive to any benefits and harms, but it would also yield findings that are more readily generalized to different settings.[39]

Equally, if treatment produced similar proportional reductions in vascular mortality and increases in non-vascular mortality, then the effect on the composite outcome of all-cause mortality would depend on the ratio of vascular to non-vascular deaths in a particular setting: the treatment would appear to be beneficial when vascular deaths predominated, but harmful when non-vascular deaths predominated. Instead, the application of the proportional reductions and increases in the separate causes of death (or other relevant outcomes) to the expected rates of these outcomes in the population of interest would yield estimates of the absolute effects of treatment on each type of death and, hence, of the net effect on survival for particular types of individual (as is discussed later in the context of statin therapy).[4,40]

The lack of sensitivity and generalizability of composite outcomes can be even more problematic when they involve very disparate outcomes. It has been suggested that the assessment of statin therapy should be based on the composite outcome of all serious adverse events of any kind (e.g. mixing vascular outcomes that are known to be prevented by statin therapy with outcomes in gastro-intestinal, genito-urinary, neuropsychiatric, and other systems that may not be affected).[11] A key problem with such an approach is that it can prevent the identification of both specific benefits and specific hazards of treatment. For example, analyses of specific outcomes among the 25,673 randomized patients in the THRIVE trial were able to detect unexpected hazards of niacin therapy (i.e. increases in serious infections and bleeding)[41] that would have been missed by analyses based on the composite of all serious adverse events (as in the original report of the AIM-HIGH trial of niacin[42]). Consideration of

the effects of treatment on specific outcomes allows any differences in its effects to be determined, and its use can then be appropriately targeted at those who are likely to get more benefit than harm.

Value of meta-analyses of randomized trials

Meta-analyses of randomized trials may be required when the effects of a treatment on some particular outcome are likely to be moderate and too few cases of it have occurred in any individual trial to assess the effects sufficiently reliably.[3,20,43-46] For example, Table 2 shows that a meta-analysis of 100,000 randomized patients (as is available for statin therapy[33]) would have 90% statistical power at p=0.01 to detect a an absolute excess of 0.5% in the incidence of events that have a control rate of 5% (i.e. a 10% proportional increase) and an absolute excess of 1% for events that have a 20% control rate (i.e. a 5% proportional increase). Meta-analysis can also reduce the impact of selective emphasis on effects observed in particular trials that may over-estimate the real effects [20,45] (e.g. the excess of diabetes cases with statin therapy first noticed in the JUPITER trial[47] was found to be smaller in the other statin trials[48]) or may not even be real (e.g. the small excesses of incident cancer cases in the CARE and PROSPER trials[49,50] were not confirmed by the much larger numbers of cases in the other statin trials[51,52]).

However, meta-analyses of randomized trials are not typically required to detect large effects of a treatment on common outcomes. Instead, individual trials will suffice if they have recorded large enough numbers of cases of the outcome of interest: for example, a trial of 2,500 patients allocated to active treatment versus 2,500 allocated matched placebo would have at least a 90% chance at p=0.01 of detecting a 20% versus 15% event rate difference if it existed; and a trial of 20,000

patients would have similar statistical power to detect (or refute) reliably an absolute difference as small as about 2% (i.e. 20% vs 18%: Table 2). In such circumstances, it may be more informative to consider the separate within-trial comparisons in each of the relevant randomized trials in order to determine whether (when considered in the context of the other trials) any of them do provide compelling evidence that there are any relevant effects on any specific outcomes (for example, see the webtable of muscle-related outcomes reported in the large randomized placebo-controlled trials of prolonged exposure to statin therapy).

In addition, an individual trial that has been specifically designed to assess the effects of a treatment on some particular outcome especially carefully (for example, serial assessments of cognitive function[53-55] and of lens opacities[56-58] in statin trials) may be more sensitive to any real effects of treatment than would be a meta-analysis based on the less specific assessment of the outcome in all of the other randomized trials – or, to an even greater extent, on non-randomized comparisons involving data recorded for entirely different purposes in observational studies (see below).

Generalizability of evidence on efficacy from randomized trials

It has been suggested that, because of the exclusion criteria in randomized trials, results from observational studies based on use of a treatment in routine practice (sometimes referred to, misleadingly, as "real world" evidence[10,22,24,59]) are more widely generalizable about its effects.[11,22,24,60,61] However, meta-analyses of randomized trials with different eligibility criteria that have included large numbers of different types of patient (e.g. although some statin trials excluded people who were older or who had particular conditions, other statin trials did not) may be able to address this putative limitation by yielding unbiased information based on sufficient

numbers of individuals with different characteristics that can then be widely generalized (for example, with the statin trials,[31-33,62] older and younger people, women and men, individuals with and without pre-existing vascular disease or other conditions).[36,63] Such analyses would not, of course, provide direct evidence among those types of patient who were excluded largely or wholly from randomized trials because the treatment was considered to be contraindicated. However, if the treatment is not used routinely in such patients, neither would observational studies provide such evidence – and, in most cases, the effects in such circumstances would be of limited clinical relevance.

The risk ratio for a particular outcome in a randomized controlled trial is the ratio of the proportion of the treated and control patients who develop the specific outcome. As a result, only those individuals who have the outcome contribute information on the risk ratio. Moreover, inclusion of individuals who will not have the outcome (such as most of those in a primary prevention population) would not change the effect of treatment in individuals who will have it.[36,64] In general, therefore, any proportional reductions or increases in the rate of a specific outcome should be expected to be similar in different circumstances. Consequently, when a treatment has been shown unequivocally to affect the rate of a particular outcome, definite evidence of an effect in each separate type of person is not generally required. Instead, it may be more appropriate to conclude that the treatment produces similar proportional effects on that outcome among different patient types (as has been found generally with statin therapy[31-33,62]), unless compelling evidence emerges that the effect in a particular group of patients differs from the overall risk ratio.[3,65-69]

This feature of similar proportional effects of treatment on specific outcomes is useful for generalizing results from randomized trials. It is, of course, the absolute – not the proportional – effects on outcome that matter for an individual when considering the use of a treatment. However, application of the proportional effects of a treatment on specific outcomes from randomized trials to the absolute rates of these outcomes derived from observational studies in some particular population of interest (e.g. for secondary prevention in patients at high-risk of recurrent vascular events versus primary prevention in lower-risk individuals in the general population) can yield generalizable estimates of both the absolute benefits and the absolute harms of a treatment.[4,40] Combination of these separate estimates then allows the net effect of using the treatment to be estimated for particular types of individual.

Generalizability of evidence on side-effects from randomized trials

It has been suggested that randomized trials yield under-estimates of side-effect rates because they exclude patients in whom the treatment being studied is known to cause adverse effects (e.g. so-called "statin-intolerant" patients).[11,12,22-24,61,70-73] However, for treatments that are not yet on the market or that have not yet been widely adopted into routine practice (as was the case during the recruitment phase of many of the large clinical outcome trials of statins[62,74]), few patients will have previously been exposed to the treatment and excluded because of having had problems with it.

Some trials use a pre-randomization "run-in" phase to improve the subsequent adherence to the randomly assigned treatment (whether active drug or placebo). Run-in phases involving the use of a placebo (as in about half of the large trials of statin versus control: see webtable) would not lead to under-estimates of the rates of

side-effects. Indeed, by improving post-randomization adherence, the sensitivity of randomized comparisons to detect any effects of treatment would be expected to be improved.[75] Less commonly, trials have used run-in phases with the active drug (as in a few of the large statin trials: see webtable), which may exclude some patients in whom the treatment would cause adverse effects soon after starting it (although, in one of the large statin trials, no differences in reasons for stopping treatment were observed between placebo and active phases of run-in[76]). However, it is less likely that use of an active run-in would prevent the emergence of genuine side-effects during the later years of such trials. For example, it was the SEARCH randomized trial with an active run-in phase that identified a substantial increase in the risk of myopathy with simvastatin 80mg daily (a regimen recommended for routine care[77]) compared to simvastatin 20 mg daily (see webtable).[78]

For all of these reasons, evidence about side-effects from randomized trials is likely to be far more widely generalizable to routine practice than is often asserted.[79-81]

Observational studies: limited additional value for assessing the effects of treatment when large-scale randomized controlled evidence exists

Observational epidemiologic studies have been extremely valuable for identifying associations of risk factors with disease (for example, smoking with lung cancer; blood pressure and cholesterol with cardiovascular disease), but their value for the assessment of the effects of treatment is more limited.

Insert Panel 2

Potential to detect large effects on rare outcomes

Case reports to regulatory authorities or studies based on health care databases often involve the exposure of large numbers of individuals to a treatment that is being used in routine practice. Consequently, they do have the potential to detect large adverse effects on health outcomes that would not normally be expected to occur (e.g. Reye's syndrome with aspirin use in children; tendon disorders with fluoroquinolones; myopathy with statin therapy).[1,2,4,82] Such studies are also able to detect large beneficial effects of a treatment when a good outcome would otherwise not be expected (e.g. insulin for diabetic ketoacidosis; penicillin for lobar pneumonia; ganciclovir for cytomegalovirus retinitis).[2,82] However, due to the potential biases that are inherent in observational studies, they cannot be relied on for demonstrating the causal nature of treatment-related associations when the relative risks are both not large (e.g. less than 3- to 4-fold[7,82,83]) and do not relate to health outcomes that are rare in the types of patient studied.[4,6,7,9,83-85]

This limitation is not confined to the assessment of beneficial treatment effects, but applies equally to the detection of harmful effects. For, although unintended adverse effects may be more plausible than are any unintended beneficial effects,[86] the potential impact of the biases in observational studies is similar irrespective of the direction of the associations. Consequently, when large-scale randomized controlled evidence does exist (as it does for statin therapy), the additional value of information from non-randomized observational studies about treatment effects is very limited.

Potential to assess prolonged exposure to treatment

An oft-cited advantage of observational studies is that they may involve prolonged exposure to the treatment of interest. However, adequate data about the use of a treatment in health care databases may not involve a duration of exposure that is

longer than in randomized trials. For example, in several prominently reported health care database studies of statin therapy, the average treatment exposure ranged between 2 and 5 years[87-90] (compared with about 4 to 5 years in the randomized trials designed to assess clinical efficacy and safety[33]). Moreover, information about the duration and dose of the treatment may be importantly incomplete in databases (e.g. based on limited prescription data without information about actual use) that have not been compiled specifically for the purpose of assessing the effects of that specific treatment (e.g. primary care or hospital data that are being used for patient care or administrative purposes).[91-95]

In addition, whereas randomized trials assess the effects of a specific exposure (i.e. a particular dose of a particular drug with information about adherence) on outcomes that are sought systematically, observational studies often only assess more general associations (e.g. prescription of many different doses of a drug, or a class of drug, on ill-defined outcomes) which may prevent the detection of effects that are specific (e.g. the higher rate of myopathy with simvastatin 80 mg daily than with 20-40 mg daily[78]). Combination of precise information about the treatment that is received during a specific period in a randomized trial and prolonged follow-up of outcomes after the trial has ended (perhaps through linkage to electronic health records[96]) may also allow the reliable assessment of the later effects of the treatment (as has been done for statin therapy[97-104]) while still avoiding the potential biases that are inherent in observational studies.

Biases due to differences in underlying risks of health outcomes

The magnitude of the potential biases inherent in observational studies of treatment is often under-estimated in the interpretation of associations that are found with

health outcomes.[4,6,7,9,16,84] Confounding by indication, or contraindication, occurs when the treatment being considered tends to be provided more, or less, frequently to individuals with medical conditions or other characteristics that are associated with increased, or decreased, risks of various health outcomes (which is, of course, what would be expected to occur in clinical practice[105]). Bias may also be introduced by other differences in the underlying risks of developing health outcomes among the individuals who have received a particular treatment and the individuals with whom they are compared who have not received that treatment. Even when associations between the treatment and health outcomes remain after statistical adjustment for observed differences between these different groups of individuals, the adjusted associations may still reflect residual confounding due to differences in factors that were assessed incompletely or not at all (and so would not necessarily have been taken fully into account in adjusted analyses) or due to other inadequacies in the approach to adjustment (e.g. using the wrong statistical model).[6,7,93,106-108]

Consequently, relying on evidence from observational studies about the effects of treatment on common outcomes – rather than considering it to be "hypothesis-generating" – may well have adverse consequences for patients and public health. For example, in observational studies, the use of hormone replacement therapy by post-menopausal women was associated with about 50% less coronary disease than among those who did not use it.[109-111] This apparent protective effect was considered by many to be biologically plausible because of the marked differences in coronary heart disease rates between men and women before the menopause, as well as the known effects of oestrogens on lipid profiles.[111-113] As a result, hormone replacement therapy was widely prescribed to prevent coronary disease (even though it was not

licensed for that purpose),[114] becoming one of the most commonly used medications in industrialized countries.

However, despite the widespread belief that this association was causal, large randomized trials of hormone replacement therapy were conducted which showed that it did not protect against coronary heart disease.[115-118] A range of retrospective "explanations" were proposed for this apparent discrepancy with the results in the observational studies (e.g. that the wrong type of adjustment had been used or the timing of initiating treatment mattered),[119,120] but these were eventually refuted.[121,122] Likewise, randomized trials have not confirmed the 30% increased risk of breast cancer found in observational studies of estrogen-alone preparations, although the results for combined estrogen-progestin preparations appear similar.[123-125] Despite these discrepancies, the similarity of the direction – but not the size[126,127] – of the differences in the rates of stroke and pulmonary embolism in observational studies and in randomized trials of hormone replacement therapy has been used to justify continued reliance on observational evidence,[2] rather than as an illustration of the difficulty of determining which – if any – associations with treatment in observational studies provide a reliable basis for safe and effective care of patients and the public.

A number of reviews have been conducted to compare the estimates of treatment effects from observational studies and randomized trials, but their methods have been criticized (chiefly because of concerns about the methods used to select the studies and compare the results) and their findings have been inconsistent.[106] It has been concluded that these reviews identified many examples where the results of the same intervention were on average the same, but also many examples where the results differed. For example, there have been many claims about the benefits of

various vitamin supplements based on observational studies[128,129] that have been reliably refuted by large-scale randomized trials.[130-132] Similarly, when compared with the results from randomized trials of the effects of treatments for several different cancers, observational studies have generated improbable results despite controlling for comorbidity, extent of disease and many other characteristics that were recorded in detailed databases[133-135] (as is also the case for reported associations of statins with lower rates of cancer[90,136-138]). These findings are consistent with empirical studies in which biases in observational studies were shown to be large enough to conclude falsely that treatment produced benefit or harm, with none of a range of statistical strategies (such as regression analysis or propensity matching) capable of adjusting adequately or predictably for bias.[93,106-108]

Biases due to differences in the ascertainment of health outcomes

Observational studies of treatment effects are often based on health outcome data that have been recorded without consistent coding or validation.[92-95] Moreover, by contrast with the situation in randomized controlled trials with blinded treatment assignment (i.e. when patients and their doctors do not know whether they are taking the active treatment or a matching placebo), patients being treated in routine practice know that they are taking a particular drug, as do their doctors. Indeed, the patients may have been specifically told that the treatment has potential side-effects[139,140] (e.g. patients given statin therapy are typically advised that serious muscle problems can occur, albeit rarely, and to advise their doctors if they develop muscle pain or weakness[141-144]), and they may be more closely monitored by their doctors. Such biases may be exacerbated by concomitant changes in lifestyle recommended by the patients' doctors (for example, the "prescription" of physical activity as well as statin therapy may lead to exercise-induced muscle pain being attributed to the

drug). Consequently, assessment of the effects of a treatment in observational studies may be biased by differences in the reporting and detection of health outcomes between the patients who are taking it and those who are not.[139,145,146]

However, despite it having been shown that randomized controlled trials without blinded treatment assignment can produce misleading estimates of treatment effects (particularly for subjective outcomes),[17,18,146] the inability to make allowances for such ascertainment biases is rarely acknowledged adequately in the interpretation of observational studies[147,148] (including for statin therapy[87,89,149,150]). The magnitude of these biases can be large:[140,151] for example, in a blinded randomized trial among patients considered to be "statin-intolerant" due to a history of muscle pain on statin therapy, myalgia was reported by about 25% of patients irrespective of whether they were taking atorvastatin 20 mg daily or placebo for 24 weeks, but the rates fell below 5% immediately after stopping either the active or placebo tablets.[152,153] These results indicate the extent to which mis-attribution of adverse events can bias assessments of treatment in observational studies which, necessarily, do not involve blinded ascertainment of outcomes.

Potential benefits and harms of lowering LDL cholesterol concentrations

Associations between LDL cholesterol and vascular disease

By contrast with observational studies of treatment, observational epidemiologic studies are valuable for the assessment of causal risk factors. In particular, such studies have shown that there is a continuous positive association between blood concentrations of LDL cholesterol and the rates of coronary heart disease events in different populations, without any suggestion within the range that has been studied of a "threshold" below which a lower concentration is not associated with a lower

risk.[154,155] The absolute difference in coronary disease risk associated with a given absolute difference in LDL cholesterol is greater at higher concentrations (Figure 2a), which helps to explain the emphasis in previous treatment guidelines on individuals with “hypercholesterolaemia”. However, if risk is plotted on a logarithmic scale then the proportional difference in risk associated with a given absolute difference in LDL cholesterol concentration is similar throughout the range (Figure 2b).

Consequently, with a treatment that acts through LDL-lowering, the proportional reduction in cardiovascular disease risk per mmol/L reduction in LDL cholesterol should be expected to be similar irrespective of the starting cholesterol levels (rather than, as has been suggested for statin therapy,[10] being evidence that the effects are not related to cholesterol lowering). Moreover, the absolute reduction in vascular risk per mmol/L reduction in LDL cholesterol would also be expected to be similar for individuals who are at comparable levels of risk but present with different cholesterol concentrations. The results of randomized controlled trials of statin therapy support these epidemiological expectations (see below),[31-33,156,157] and treatment guidelines now tend to focus on an individual’s risk of having atherosclerosis-related events as well as on their LDL cholesterol level.[158,159]

Lower concentrations of cholesterol have been associated in observational studies with higher rates of all-cause mortality, particularly in older people.[160-162] However, such associations can be shown not to be causal. For example, using the Mendelian randomization approach, lower genetically-determined LDL cholesterol levels are associated with lower all-cause mortality even among individuals aged over 90.[163] It appears that pre-existing disease causes lower cholesterol concentrations (so-called

"reverse causality"); spurious associations can be largely avoided in analyses of observational epidemiologic studies by censoring the first few years of follow-up.[164]

Causal relationship between LDL cholesterol and vascular disease

Observational studies can provide evidence about associations of risk factors with health outcomes, but they do not necessarily suffice to confirm the causal nature of such associations. In the case of LDL cholesterol, a number of additional sources of evidence have helped to show that the continuous association with atherosclerotic disease is causal. These include experimental studies of atherosclerosis in animals, monogenetic and polygenic associations in humans, and randomized trials of LDL-lowering therapy (which also assess the extent of risk reversibility and its timescale).

Experimental studies in animals have shown that diets that raise LDL cholesterol concentrations increase the extent of atherosclerosis in the arterial wall, and that lowering LDL cholesterol concentrations with either diet or drugs (including statins) can reduce atherosclerosis.[165,166] Genetic disorders in humans that cause large elevations of LDL cholesterol concentrations (in particular, LDL receptor mutations) are associated with substantially elevated rates of atherosclerotic disease.[167,168] Moreover, these disorders (i.e. familial hypercholesterolaemia) provide compelling evidence of "dose" effects, whereby individuals in Western populations who inherit the abnormal genetic variant from both parents typically have LDL cholesterol levels above 12 mmol/L and coronary events before the age of 20 years,[167] while those who inherit the abnormal variant from one parent typically have levels above 8 mmol/L and events in early middle-age.[168] In addition, a number of common genetic variants have been identified that cause much smaller increases in LDL cholesterol

levels and these are associated with correspondingly smaller increases in the risk of coronary events, providing further evidence in support of a causal association.[169]

Proven beneficial effects of lowering LDL cholesterol with statin therapy

In the pre-statin era, meta-analyses of randomized controlled trials of cholesterol-lowering diets, drugs and ileal bypass surgery did show that, within a few years of reducing blood cholesterol concentrations, rates of non-fatal myocardial infarction and coronary death are reduced.[170] In addition, the randomized trials that involved larger and more prolonged cholesterol reductions yielded larger reductions in the rates of coronary events. However, it was suggested that these beneficial effects might be offset by excesses in non-coronary deaths and cancers, which generated uncertainty about the overall benefits of lowering cholesterol.[171-173] The development of the statins, which can lower LDL cholesterol to a greater extent than any of the previously available treatments, provided an opportunity to obtain clear evidence about the beneficial effects of LDL-lowering on atherosclerotic events and deaths, as well as to determine whether it produces adverse effects on other causes of major morbidity and mortality.[174] For, although it may not always be possible to distinguish between adverse effects caused by lowering LDL cholesterol and those due to off-target effects of statins (such as myopathy), reliable evidence of a lack of adverse effects should be generalizable about the safety of lowering LDL cholesterol.

Effects of statin therapy on LDL cholesterol concentrations

During the past 20 years, the increasingly widespread use of statin therapy among individuals who are known to have occlusive vascular disease or are considered to be at increased risk of cardiovascular events for other reasons (e.g. having high cholesterol concentrations or other risk factors, such as older age, hypertension or

diabetes) has been associated with downward shifts in the distributions of LDL and total cholesterol concentrations in many populations.[175,176] In addition, due to the tendency for statin therapy to be prescribed more commonly to individuals with elevated LDL cholesterol concentrations, the proportions with high levels have been preferentially reduced.[175,176] Representative data from population-based studies conducted before evidence of beneficial effects of statin therapy on fatal and non-fatal vascular events emerged from large randomized trials indicate that average LDL cholesterol concentrations in Western populations among people in middle and old age are about 4 mmol/L (or more) in the absence of statin therapy.[177,178]

The proportional reductions in LDL cholesterol achieved with statin therapy are not materially affected by the starting LDL cholesterol concentration or by other patient characteristics (such as age, sex, vascular risk, genetic markers).[30-33,179] Different statins have different potency on a “mmol/L-per-mg” basis, with the newer agents (e.g. atorvastatin and rosuvastatin) able to produce larger LDL-reductions than the older agents (e.g. simvastatin and pravastatin: Table 3).[159] Irrespective of the statin used, each doubling of the dose produces an extra reduction of about 6 percentage points in LDL cholesterol (e.g. 43% versus 49% reductions with atorvastatin 20 mg versus 40 mg daily). The ACC/AHA 2013 Blood Cholesterol Guideline classified statin regimens as being “low-intensity” (e.g. <30% LDL-reduction with simvastatin 10 mg daily), “moderate-intensity” (e.g. 30% to <50% reduction with simvastatin 20-40 mg, atorvastatin 10-20 mg, or rosuvastatin 5-10 mg daily) and “high-intensity” (e.g. ≥50% reduction with atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily).[158] Use of high-intensity statin therapy would be expected to reduce LDL cholesterol by at least 2 mmol/L in individuals who present with concentrations of 4 mmol/L or more (i.e. about half of the population in the absence of statin therapy[177,178]), but by only

about 1 mmol/L in those with concentrations of 2 mmol/L. Consequently, since the proportional reductions in vascular event rates with statin therapy are related to the absolute reductions in LDL cholesterol that are achieved (see below), intensive statin therapy should be focused on patients at higher risk of vascular events rather than just those with high cholesterol concentrations.[158,159,180]

The Cholesterol Treatment Trialists' (CTT) collaboration was established to conduct meta-analyses of individual patient data from all of the randomized controlled trials of statin therapy that were scheduled to involve at least 2 years of treatment in at least 1,000 patients.[181] Pre-specification of the inclusion of a defined set of large trials and of the approach to their analysis before the results of any of the trials were available was intended to avoid selection bias. During the scheduled study treatment periods (which were typically about 5 years), the average reduction in LDL cholesterol was about 1.0 mmol/L in the trials that compared the effects of allocating routine statin therapy versus no routine statin therapy, and it was further reduced by about 0.5 mmol/L in the trials that compared allocation to more versus less intensive statin regimens.[31] That is, based on combination of the "intention-to-treat" analyses of these two sets of trials, allocation to an intensive statin regimen versus no routine statin therapy reduced LDL cholesterol concentrations by 1.5 mmol/L. However, such comparisons under-estimate the LDL-reductions that can be achieved by actually taking a particular regimen, since some of the patients did not take their assigned statin therapy or more intensive statin therapy throughout the scheduled study treatment period, whereas some of the patients in the control groups started to take a statin or a more intensive regimen.[29] Instead, based on the LDL-reductions that can be achieved (Table 3), the use of more intensive statin therapy would have been expected to reduce LDL cholesterol by about 2 mmol/L in such patients.

Insert Panel 3

Reductions in rates of major vascular events

The pre-specified purpose of the CTT meta-analyses was to assess the effects of lowering LDL cholesterol on atherosclerotic events in different types of patient more reliably than would be possible in any of the separate randomized trials and (given previous concerns about cholesterol-lowering therapy) to determine whether there were adverse effects on non-vascular causes of death and site-specific cancers.[181] Consequently, data were sought for each of the eligible trials about the baseline characteristics of each patient and about myocardial infarctions, strokes, coronary revascularizations, cancers and causes of death that occurred during the scheduled treatment period (but not any other adverse events, which is the subject of an on-going project[182]). Follow-up of outcomes in the trials was reported to be about 99% complete. It was pre-specified that results of the meta-analyses would be presented as risk reductions per mmol/L reduction in LDL cholesterol.[29,181]

In total in the CTT meta-analyses, there were about 25,000 “major vascular events” (defined as the composite of coronary deaths or non-fatal myocardial infarctions, strokes of any type, and coronary revascularisation procedures) during an average of about 5 years of scheduled study treatment. The proportional reductions in these major vascular event rates were related to the absolute reductions in LDL cholesterol that were achieved (Figure 3). Overall, in the trials of routine statin therapy versus no routine use, there was a 20% proportional reduction in the major vascular event rate per mmol/L LDL-reduction (Figure 4).[32] The proportional risk reduction was smaller during the first year after starting treatment, whereas it was 24% (i.e. a risk ratio of 0.76) during each subsequent year that allocation to statin therapy was continued

(p<0.0001 for difference between effects in first versus later years).[31] In the trials of more versus less intensive statin regimens, the average 0.5 mmol/L further reduction in LDL cholesterol yielded a 15% further proportional reduction in the rate of major vascular events (Figure 3), corresponding to a 28% reduction (i.e. a risk ratio of 0.72) per mmol/l further LDL-reduction during each year of treatment (with no apparent delay after increasing the intensity of statin therapy).[32]

Consequently, the proportional reduction in the risk of major vascular events per mmol/l was about one-quarter in the trials of statin versus no statin (after an initial delay) and of more versus less intensive therapy. Based on the combined findings from these two sets of trials, it can be estimated that reducing LDL cholesterol levels by 2 mmol/L would reduce the risk of major vascular events by about 45% (derived as [1.0 – (0.75 x 0.75)] x 100) during each year treatment is continued. In principle, even larger reductions in LDL cholesterol would be expected to produce even larger risk reductions (e.g. 60-70% with 3-4 mmol/L LDL-reductions); however, this is likely only to be clinically relevant in limited circumstances (e.g. for individuals with familial hypercholesterolaemia who have very high LDL cholesterol levels).

In these meta-analyses, statin therapy produced similar proportional reductions per mmol/L LDL-reduction in the risks of each of the main components of the composite outcome of major vascular events (i.e. myocardial infarctions and coronary deaths; strokes of any type; or coronary revascularisations).[32] The proportional reductions in major vascular events were also similar among different types of patient.[31-33,183] For example, as would be expected from the log-linear associations in observational epidemiological studies between coronary disease risk and cholesterol concentration (Figure 2b), the proportional reductions in risk per mmol/L reduction were about the

same irrespective of the presenting levels of cholesterol (Figure 1). The proportional risk reductions appeared to be smaller among individuals aged over 75 who were included in these trials, but they had a higher prevalence of severe heart failure and end-stage renal disease (conditions associated with non-atherosclerotic vascular outcomes not much influenced by lowering LDL cholesterol).[184] Moreover, since the absolute risks of major vascular events were higher among older individuals, the absolute benefits were of similar size to those among the younger individuals. The proportional risk reductions also appeared to be slightly smaller among the women included in these trials. However, this apparent difference could be accounted for largely by differences in non-sex-related characteristics, and the relative effects were similar for men and women at equivalent risk of cardiovascular events.[33] The risks of major vascular events were reduced in secondary prevention as well as in primary prevention (including among individuals with diabetes or hypertension),[29,31] but the proportional reductions were somewhat larger among lower-risk individuals. This finding is consistent with results from "Mendelian randomization" studies,[185] which indicate that genetically-determined exposure to lower LDL cholesterol levels before atherosclerosis has developed may produce larger risk reductions.[169]

In general, the absolute benefits of using statin therapy depend on an individual's absolute risk of atherosclerotic events and the absolute reduction in LDL cholesterol that can be achieved. For example, 5 years of treatment with a statin regimen that lowers LDL cholesterol by 2 mmol/L would be expected to prevent major vascular events in about 1000 (10%) higher-risk patients per 10,000 treated and in about 500 (5%) lower-risk patients per 10,000 treated (Figure 5; which also provides estimates of the absolute benefits with 1.5 and 1.0 mmol/L LDL-reductions).[32] The continued follow-up of patients beyond the end of the trials has found that the benefits of statin

therapy persist[97-102] (and may even become larger[96,103,104]) for many years after the differences in statin use between the randomized groups have ceased. However, of more relevance for a treatment that is intended to be continued life-long once it has been started, the meta-analyses show that statin therapy reduces the risk of major vascular events during each year that it is continued (Figure 4). Consequently, even larger absolute benefits would be expected with statin therapy that is continued for longer than the average of about 5 years in these randomized trials.

Reductions in coronary mortality

Overall in the CTT meta-analyses, there was a statistically robust 12% proportional reduction in vascular mortality per mmol/L LDL-reduction (Figure 6), attributable chiefly to a 20% proportional reduction in coronary deaths (with, as was seen for major vascular events, a greater proportional effect after the first year of treatment), along with a 8% reduction in other cardiac deaths (some of which, such as those due to arrhythmias or heart failure, may not be due to atherosclerotic causes and so not amenable to LDL-lowering therapy).[32] Both for the aggregate of all vascular deaths and for coronary and non-coronary causes considered separately, the proportional reductions in risk per mmol/L LDL-reduction appear to be similar in patients with and without pre-existing vascular disease, and in those who present at different levels of baseline vascular risk, as well as in other subgroups that have been considered.[31-33]

As discussed above, when there is compelling evidence of an effect of a treatment on a particular outcome (i.e. vascular mortality) and this is supported by the effects on related outcomes (i.e. the even more statistically robust reductions in non-fatal major vascular events with statin therapy), then the appropriate question to ask is whether there is good evidence that the treatment does not reduce that outcome in

different circumstances[3,68,69] (rather than whether there is direct evidence of benefit in every circumstance). Even in the aggregate of all of the trials in the CTT meta-analyses, too few vascular deaths occurred among lower-risk participants for direct assessment of the effects of statin therapy in such individuals considered in isolation (as has been proposed by some commentators[11,12,186]). However, the proportional risk reduction was statistically compatible with the reduction observed in higher-risk patients (trend p=0·7) and it was supported by the clear reduction in major vascular events among lower-risk patients.[32] Similarly, although there were too few women in these trials to assess the effects on vascular mortality directly (which has been the basis of assertions that statin therapy is not beneficial for women[187-191]), the proportional reductions were similar among women and men (interaction p=0·8) and were reinforced by definite reductions in major vascular events among women.[33]

Consequently, it is reasonable to conclude that statin therapy produces proportional reductions of at least 20% in coronary mortality per mmol/L LDL-reduction among people at different levels of occlusive vascular risk irrespective of their gender and, assuming that the proportions of vascular deaths due to coronary and non-coronary causes are similar, of 12% in deaths from all vascular causes. The availability of additional evidence from large-scale trials (such as the recently reported HOPE-3 trial in primary prevention[192] and on-going STAREE trial in people aged over 70[193]) will provide more direct evidence about the effects in particular circumstances.

Lack of effects on non-vascular mortality and cancer

The CTT meta-analyses involved over 6,000 non-vascular deaths, and there was no suggestion that lowering LDL cholesterol with statin therapy had an effect on any non-vascular cause of death, including cancer (Figure 6).[31,51] In a large database

analysis, a few years of statin therapy was associated with a 15% proportionally lower rate of cancer-related mortality after adjustment for the potential confounding factors that had been recorded[90] and, in some other observational studies,[136] with as much as a halving in colon cancer incidence and in prostate cancer mortality.[137,138] By contrast, there were small excesses of incident breast cancer in the CARE trial[49] and of incident cancer at all sites in the PROSPER trial among patients who were randomized to receive statin therapy.[50] However, based on more than 10,000 cases of incident cancer in the CTT meta-analyses (including CARE and PROSPER), there were no apparent effects – either overall or at any particular site – during an average of 5 years of statin therapy (Figure 7). Nor were there any effects on incident cancer among any particular type of patient,[51] including older individuals (by contrast with claims of hazards[194]). Some of these trials have extended follow-up for up to 15 years beyond the scheduled study treatment period (after which the use of statin treatment in the randomized groups was similar), with no evidence that any effects on non-vascular mortality or on incident cancer were emerging subsequently.[96-103]

All-cause mortality was reduced by statin therapy in both secondary and primary prevention settings[32] in the CTT meta-analyses of the randomized trials. However, separate assessments of the effects of statin therapy on vascular mortality and on non-vascular mortality (supplemented by analyses of more specific causes of death and of the even more definite effects on related non-fatal outcomes[3]) are likely to be more sensitive to the beneficial effects, and the absence of adverse effects, of statin therapy on mortality than are analyses of the composite outcome of death from all causes combined (i.e. all-cause mortality). In addition, such cause-specific analyses are more readily generalized to different circumstances: given the lack of any effect on non-vascular mortality, the overall effects on all-cause mortality of LDL-lowering

with statin therapy reflect the observed reductions in vascular mortality or, perhaps even more specifically, in coronary mortality (Figure 6).

Other beneficial effects that have been attributed to statin therapy

In addition to the proven benefits of lowering LDL cholesterol with statin therapy on non-fatal atherosclerotic events and vascular mortality, it has been suggested that statins might produce beneficial effects on other health outcomes (perhaps by effects that are not related to lowering cholesterol).[195,196] For example, statin therapy was found to be associated with about a halving in cases of deep vein thrombosis and pulmonary embolism in some large randomized trials,[192,197,198] but this result has not been confirmed in other trials.[199] Similarly, the rate of post-operative atrial fibrillation was halved by perioperative statin therapy in some small randomized trials, but not in larger trials that assessed this outcome systematically.[200] Use of statin therapy has also been associated in observational studies with lower rates of several other conditions (e.g. infections,[201-203] chronic obstructive lung disease,[204-206] and acute respiratory distress syndrome[207]), but those claims have been reliably refuted by randomized trials of adequate size.[208-212] These findings reinforce concerns about basing inference about treatment effects on relatively small numbers of events in randomized trials or on observational studies irrespective of their size.[3,4,213,214]

In summary, lowering LDL cholesterol with statin therapy has been shown to prevent both non-fatal and fatal major vascular events in a wide range of circumstances, and the absolute benefits depend chiefly on an individual's absolute risk of such events and on the magnitude of the LDL-reduction that is achieved (as well as the duration of treatment). Although statin therapy does not increase the risk of death from non-

vascular causes or the incidence of cancer, other potential adverse effects of statin therapy do still need to be considered when deciding whether to use statin therapy.

Proven adverse effects of statin therapy

The only excesses of adverse events that have been reliably demonstrated to be caused by statin therapy are myopathy and diabetes mellitus, along with a probable excess of haemorrhagic stroke. These excesses are larger in certain circumstances, but the absolute risks remain small by comparison with the absolute benefits.

Insert Panel 4

Increases in rates of myopathy

Myopathy (sometimes referred to as myositis) is typically defined as muscle pain, tenderness, or weakness that is accompanied by substantial increases in blood creatine kinase (CK) levels (e.g. greater than 10 times the laboratory upper limit of normal).[141,215] Rhabdomyolysis is a severe form of myopathy involving muscle breakdown (usually identified by even larger increases in CK concentrations), with myoglobin released into the circulation and, in some cases, leading to acute renal failure or worsened renal function.[141] Myopathy is rare in normal circumstances. Approved statin regimens have been associated both in observational studies and in randomized trials with large relative risks for myopathy,[141,150,216] but typically with small absolute excesses (about 1 case per 10,000 people treated per year) and even smaller excesses in the incidence of rhabdomyolysis (about 2-3 cases per 100,000 treated per year).[31,217] It usually resolves rapidly when statin therapy is stopped.[141]

The underlying mechanisms for statin-related myopathy are not well understood. The risk of myopathy is dose-related and it appears to depend on the levels of the statin

in the circulation (as indicated by its association with a *SLCO1B1* gene variant that reduces the transport of all statins from the blood into the liver).[78,216,219] Cerivastatin was withdrawn from use because the myopathy rate observed in post-marketing surveillance with approved doses was much higher than with other statins.[220] In the SEARCH randomized trial, simvastatin 80 mg daily produced a more than 10-fold higher rate (at least 1 myopathy case per 1,000 patients treated annually) than 20-40 mg daily (about 1 case per 10,000 annually),[78,221] so the high-dose regimen is no longer recommended routinely.[222] The rates of reports of myopathy in regulatory databases are also higher with higher doses of atorvastatin, although such spontaneous reports may be biased and the absolute risks are still small even with the highest approved dose.[216] The rate of myopathy can be increased substantially when statins are used in combination with other drugs that affect their metabolism (in particular, inhibitors of cytochrome P450 or the P-glycoprotein, such as cyclosporine and azole antifungals) [141,174,217] and in certain types of patient (e.g. people of Asian origin and those who have functional variation in the SLCO1B1 gene).[223] More moderate increases (e.g. risk ratios of about 1.5 to 2) in the rate of myopathy are also seen in other circumstances (e.g. in combination with certain antihypertensive drugs and in women, people aged over 80, and those with diabetes).[78]

Despite this causal association with myopathy, the randomized controlled evidence indicates that statin therapy has little effect on less severe muscle pain (i.e. myalgia) or weakness, although such symptoms are commonly attributed to statins in routine practice (see below). Indeed, an excess of muscle-related symptoms has generally only been seen in trials when it occurs in combination with increased CK levels, with bigger relative risks observed with larger CK increases.[37] For example, in the Heart Protection Study of simvastatin 40 mg daily versus placebo, the relative risk for any

myalgia irrespective of increased CK levels was 0.99 (95% CI 0.95-1.03), whereas it was 1.7 (0.9-3.1) for myalgia with CK>4 times the upper limit of normal and 2.5 (0.8-8.0) with CK>10 times the upper limit of normal.[37,221] This result provides another illustration of the value of using specific outcomes to detect treatment effects, rather than composites of outcomes that are affected by treatment and those that are not.

Increases in rates of diabetes mellitus

In the JUPITER randomized trial among 17,802 patients without a history of vascular disease, glycated haemoglobin levels were slightly higher after about 2 years among the patients allocated rosuvastatin 20 mg daily than among those allocated placebo (5.9% vs 5.8%; p=0.001).[47,224] There was also a small excess of newly diagnosed diabetes (3.0% vs 2.4%; p=0.01), which corresponds to a 25% (95% CI 5%-49%) proportional increase. In subsequent meta-analyses of the available results from the randomized trials, standard statin dose regimens were associated with a proportional increase of about 10% in reported diabetes, and more intensive statin regimens (as used in JUPITER) with about a 10% further increase.[48,225] This excess of diabetes diagnoses appeared soon after the statin therapy started, chiefly among patients who had risk factors for diabetes (e.g. elevated BMI or HbA1c, or impaired fasting glucose), and did not appear to get larger as treatment continued.[47,224,226,227] Prior to these reports from randomized trials, adverse associations had not been reported between statin therapy and diabetes incidence in observational studies, although several reports of such associations have been published subsequently.[228,229]

Recently, it has been found that genetic variants that reduce the activity of HMGCoA reductase (which is analogous to inhibiting this enzyme with a statin) are associated with increased incidence of diabetes.[230] On the other hand, individuals with familial

hypercholesterolaemia – in whom the numbers and function of LDL-receptors on cell surfaces are reduced (by contrast with the increase in receptors produced by statins) – had been diagnosed with diabetes less frequently than their unaffected relatives.[231] These genetic "experiments of nature" provide support for the association of statin therapy with an excess of diabetes being causal. The mechanism is not known: it could be that it is directly related to LDL-lowering, but it has also been hypothesised that increasing the numbers of LDL-receptors (e.g. with treatments like statins and PCSK9 inhibitors) may cause diabetes by allowing more cholesterol to enter and damage pancreatic cells.[231]

However, the clinical relevance of this excess of diabetes is less clear; in particular, the cardiovascular benefits of statin therapy are substantial despite any increase in diabetes-related morbidity. The underlying incidence of new onset diabetes in the primary prevention trials was about 1% per year, so the absolute excess with statin therapy was about 10-20 per 10,000 per year (with this range reflecting the intensity of the statin regimen). If it is assumed that this statin-related diabetes is associated with as much as a doubling of cardiovascular risk (as is the case for spontaneously-occurring diabetes[232]) then it might result in major vascular events among about 5-10 of 10,000 primary prevention individuals with an underlying 5-year risk of 5-10% who are treated for 5 years. However, despite this potential adverse impact, lowering LDL cholesterol by 1-2 mmol/L with statin therapy prevents major vascular events among about 150-300 per 10,000 such primary prevention individuals who are treated for 5 years (Figure 5). The absolute benefits are even larger among higher-risk patients (including those who already have diabetes: Figures 1 and 5)[32] and, again despite any adverse impact of the diabetes excess, increase while statin therapy continues

to be taken (Figure 4). As is discussed later, there is also no good evidence of an excess of microvascular complications related to diabetes with statin therapy.

Probable increases in rates of haemorrhagic stroke

In observational studies, blood cholesterol levels have been found to be negatively associated with haemorrhagic stroke rates, particularly at low levels of cholesterol in people with high blood pressure.[154,233,234] In the randomized SPARCL trial among 4700 patients with prior cerebrovascular disease, allocation to atorvastatin 80 mg daily produced a definite reduction in ischaemic stroke (218 [9.2%] vs 274 [11.6%]; p=0·008), but there was also a possible increase in haemorrhagic stroke (55 [2.3%] vs 33 [1.4%]; p=0·02).[38] When these results were combined with those from the other trials included in the CTT meta-analysis, there was a 21% (95% CI 5%-41%; p=0·01) proportional increase in the incidence of haemorrhagic stroke per mmol/L reduction in LDL cholesterol.[31,32]

In Western populations, this would typically translate into an absolute excess of about 5-10 haemorrhagic strokes per 10,000 patients in whom LDL cholesterol is reduced by 1-2 mmol/L for 5 years with statin therapy. The absolute excess would be expected to be bigger in individuals with pre-existing cerebrovascular disease[38] and in populations (such as Asia) where the underlying rates of haemorrhagic stroke are higher.[235] However, statin therapy has been found to reduce the overall risk of stroke in many different settings (including in people who have already had a stroke[38] or have hypertension[103]) irrespective of the underlying risk of vascular disease.[32] For example, the increase in haemorrhagic stroke is outweighed by the reduction in the risk of ischaemic stroke, as well as in other occlusive vascular events and deaths, even among individuals with a 5-year risk of major vascular events below 10%.

Other adverse events that have been attributed to statin therapy

It has been suggested that statin therapy causes increased rates of other types of adverse health outcome, as well as of symptomatic side-effects (chiefly muscle pain and weakness) that prevent a large proportion of patients from continuing to take statin therapy long-term, often now referred to as "statin intolerance".[10-12,22,61,71-73] These claims have been based chiefly on reports to regulatory authorities of adverse events that have been attributed to a statin and on non-randomized observational studies based on health care databases. However, they are not supported by the randomized controlled trial evidence: in particular, statin therapy has been found to be no less well tolerated than placebo (see below and webtable).[52,62,236-239]

As is discussed above, the potential biases inherent in studies without both randomly assigned control groups and blinded ascertainment of outcomes limit their ability to demonstrate causal associations (except for large effects on rare outcomes). This is particularly the case for symptomatic adverse events that are attributed to statin use, especially if such reports have been prompted by guidance from clinicians to their patients or from patient information leaflets and other sources.[142-144,240,241] By contrast, the inclusion of large numbers of different patient types in randomized controlled trials of prolonged statin therapy with different eligibility criteria provides unbiased evidence about adverse effects of treatment that are relevant to routine clinical practice.

Muscle-related outcomes (other than myopathy)

The adverse events most commonly attributed to statin therapy relate to muscle pain (i.e. myalgia) or other muscle-related symptoms. For example, based on the National Health and Nutrition Examination Survey (NHANES), it was reported that 23% of 671

statin users who did not have arthritis recalled having episodes of musculoskeletal pain (not muscle pain specifically) during the previous month compared with 18% of 4499 individuals who were not taking a statin.[242] After statistical adjustment for the recorded differences (which were substantial) between the characteristics of the patients using and not using a statin, a prevalence ratio of 1.33 (95% CI 1.06-1.67; p=0.02) was reported with statin use. In another observational study of statin use based on health care data, musculoskeletal pain was reported by 73.4% of 6967 statin users compared with 71.6% of 6967 non-users during a median of 4.7 years, yielding an odds ratio of 1.09 (95% CI 1.02-1.18; p=0.02) after attempting to match patients with propensity scores based on recorded characteristics (which, again, differed substantially).[89]

Both of these reports discussed the inability of such non-randomized studies to assess causality due to the potential for residual differences between patients who had used statins and those who had not (despite statistical adjustment for recorded characteristics). They also mentioned the potential for ascertainment bias due to patients who were taking statins being examined more frequently. However, neither report commented on the inherent lack of “blinding” of treatment in such studies and the consequent potential for bias due to patients prescribed statins being advised by their doctors that they may cause muscle pain (whereas such advice is, of course, not given to patients not prescribed a statin)[243]. In addition, the analysis of NHANES excluded the 3,058 individuals with arthritis in whom statin use was not associated with any excess of musculoskeletal pain (0.96; 95% CI 0.81-1.15).[242] Such data-dependent selection of which patients to exclude introduces yet another potential source of bias into this assessment of the effects of statin therapy.[3]

In general, the data available for observational studies based on health care records do not derive from a systematic approach to seeking and recording information about symptoms or about the use of statin therapy. The Prédiction du Risque Musculaire en Observationnel (PRIMO) survey tried to overcome this limitation by systematically seeking information about the muscle symptoms that were reported.[244] Among 7924 hyperlipidaemic patients receiving high-dose statin therapy, 10.5% reported muscle symptoms at a median of about 1 month after starting it. However, those patients were required to give informed consent, which presumably involved advising them that statins can cause muscle problems and that the aim was to assess this outcome specifically, increasing the likelihood of prompting reports of muscle symptoms. In any case, since there was no control group in that study, it is not able to provide any useful information as to whether statins cause an increase in such symptoms.

It has been asserted that the rates of muscle-related symptoms caused by statins may be under-estimated in randomized trials due to exclusion of patients at risk of these problems (such as those with a history of muscle problems or CK elevations with statin therapy) and a perceived lack of systematic questioning and standardised definitions.[11,12,22-24,72,245] However, as is discussed above, few patients would have been exposed to statin therapy prior to recruitment into many of the large clinical outcome trials and use of a pre-randomization placebo “run-in” phase in about half of the trials (see webtable) would tend to increase the sensitivity of the subsequent randomized comparisons to detect any effects.[75] The inclusion of large numbers of different types of patient in different randomized trials with different eligibility criteria also makes the evidence about any side-effects of statin therapy far more widely generalizable[63] to routine practice than is often asserted.[2,11,12,22-24]

In addition, as is also discussed above, use of blinded control groups ensures that health outcomes are ascertained in the same way in the different treatment groups within any particular trial.[17,18,243] Consequently, even though different randomized trials of statin therapy did not always use the same methods to identify or classify muscle symptoms (and may even have failed to detect some relevant events: see Table 1), each within-trial blinded comparison should still provide a reliable assessment of the effects of statin therapy on muscle-related problems (and, indeed, on other adverse events).[19] Moreover, even though some of the trials did not seek information about muscle-related problems, this would not introduce bias into the assessment of the effects of statin therapy based on the trials that did record them. In principle, the failure of some trials that did record such outcomes to publish their results does have the potential to introduce bias. However, muscle-related problems are common, and the large numbers of such outcomes that have been reported from many different trials makes it unlikely that material bias in the published literature exists.

Consequently, the general lack of differences between the randomized treatment groups in the rates of the different muscle-related outcomes recorded in the large blinded trials that are eligible for the CTT meta-analysis (some of which assessed such symptoms particularly carefully: see webtable) provides strong evidence against statin therapy causing much effect on muscle-related symptoms. In the JUPITER and HOPE-3 trials of rosuvastatin 20 mg and 10 mg daily, respectively, there were small excesses in some muscle-related outcomes[47,192,246]. However, no excesses of muscle-related outcomes were observed among the large numbers of patients in the other large randomized blinded trials of long-term statin therapy. Nor

were there excesses in those trials that sought information about the severity of any muscle symptoms or about stopping study treatment due to muscle symptoms.[243]

The STOMP trial was specifically designed to assess the effects of statin therapy on a number of pre-specified muscle-related measures.[245] Compared with 236 patients allocated placebo, there were no apparent effects on muscle strength or endurance, aerobic performance or physical activity among 232 statin-naïve patients randomly allocated atorvastatin 80 mg daily for 6 months. Cases of unexplained muscle pain (23 [9.9%] vs 14 [5.9%]; p=0.1) and the subset of those cases defined as myalgia (19 [8.2%] vs 10 [4.2%]; p=0.08) were reported more commonly among patients allocated atorvastatin, but these differences in the pre-specified intention-to-treat comparisons were compatible with chance. In a meta-analysis of 26 blinded trials (including STOMP) that involved at least 6 months of statin therapy,[247] there was little difference in the reported rates of muscle problems during an average treatment duration of 3 years: 12.7% among 59,237 participants allocated statin versus 12.4% among 54,458 allocated placebo; an absolute excess of 0.3% (95% CI 0% to 0.7%; p=0.06) or, alternatively, a range of 0 to 20 cases per 10,000 years of treatment. Similarly, combination of the results for myalgia in the large placebo-controlled trials that were eligible for the CTT meta-analyses (see webtable) yields similar results: 5162 (11.7%) cases allocated statin therapy versus 5015 (11.4%) allocated placebo control during an average of 5 years of treatment (p=0.10). Moreover, the difference is even smaller in the numbers of cases of muscle problems that resulted in study treatment being stopped: 210 (0.65%) versus 182 (0.59%); p=0.83.

Cross-over trials in which active and placebo treatment are allocated in a random sequence to each patient may be particularly sensitive for detecting adverse effects

that emerge rapidly after treatment starts and resolve soon after stopping treatment. No differences in myalgia or other pain measures were observed in a randomized re-challenge trial with 3 statin/placebo paired cross-over comparisons among 8 patients with prior statin-related myalgia (with or without CK elevations), and 5 of the patients resumed statin therapy.[248]In another trial, 86 patients were assigned simvastatin 40 mg daily (combined with amlodipine, losartan and hydrochlorthiazide) or a matching placebo in a random sequence; muscle pain was reported more commonly on the active polypill (9 vs 1 cases), but it was not considered sufficiently troublesome to stop treatment.[249] Among 491 patients with a history of not tolerating two or more statin regimens who were randomized to receive atorvastatin 20 mg daily then placebo or placebo then atorvastatin,[250] muscle-related symptoms were reported by 43% of the patients when on atorvastatin but not on placebo versus 27% of them when on placebo but not on atorvastatin; yielding a risk ratio of 1.5 (although it has been suggested that this trial may not have been properly blinded[243]). In a similar cross-over trial among 120 patients with a history of muscle complaints who were randomized to simvastatin 20 mg daily then placebo or placebo then simvastatin, muscle pain was reported by 36% of the patients when on simvastatin but not on placebo versus 29% of them when on placebo but not on simvastatin.[251,252] These results indicate that, even among highly selected patients who have repeatedly attributed intolerable symptoms to statin therapy, some of the reported muscle-related intolerance may be due to the statin but most of it is not.

In summary, given the 0.3% absolute excess of muscle problems based on more than 10,000 reported cases in meta-analyses of randomized trials during 3-5 years of treatment (webtable),[247] the excess rate of symptomatic muscle pain and other muscle-related problems due to statin therapy would appear to be no more than

about 10-20 cases annually per 10,000 treated individuals, with only about 1 of those cases associated with substantial elevations in CK concentrations (i.e. myopathy) and requiring statin therapy to be stopped.

Memory and other aspects of cognition

Another adverse event that is commonly attributed to statin therapy is memory loss. Following a review of potential side-effects, the UK Medicines & Healthcare products Regulatory Agency (MHRA) decided in 2009 that memory loss should be listed as a side-effect in the product information for all statins.[253] The stated rationale was that the evidence from re-challenge studies for cases of memory loss reported with statin therapy was not sufficient to rule out causality. Similarly, in 2012, the US Food and Drug Administration (FDA) required a statement to be added to the drug label for all statins that there was a potential for cognitive side-effects (such as memory loss and confusion).[254] The basis for this decision was post-marketing event reports from individuals of ill-defined memory loss or impairment that appeared to be reversible after discontinuing statin therapy, and not because there was high quality evidence for a causal link. Indeed, a subsequent assessment of FDA surveillance databases found the rates of cognition-associated adverse event reporting rates for statins to be similar to those of other drugs used in patients with atherosclerotic disease.[255]

Moreover, large-scale randomized trials with blinded control groups have provided evidence that allocation to statin therapy is <u>not</u> associated with an excess of memory loss or adverse effects on other aspects of cognitive function. In particular, cognitive measures were carefully assessed among the 5804 patients aged 70-82 years who were randomly allocated pravastatin 40 mg daily or placebo for an average of 3.2 years in the PROSPER trial.[53,54] At baseline and then annually, the mini mental state

examination and a battery of psychometric tests (i.e. picture-word learning test, Stroop colour word test, and letter digit coding test) were administered. This elderly population might be expected to be especially sensitive to effects of treatment on cognition. However, these specific measures of cognitive function declined at the same rate in the statin and placebo groups, with no apparent differences between the randomized treatment groups.

Effects on memory were also systematically assessed among the 20,536 patients randomly allocated simvastatin 40 mg daily or placebo for an average of 5 years in the Heart Protection Study.[221] At the end of the scheduled treatment period, the well-validated modified Telephone Interview for Cognitive Status (TICS-m) questionnaire was administered to participants. A TICS-m score below 22 was pre-specified as indicative of cognitive impairment and, as would be expected, was more common among older individuals. However, despite this discriminatory ability, there were no apparent differences between the statin and placebo groups in the percentages of participants classified as cognitively impaired, either overall (23·7% simvastatin vs 24·2% placebo) or among the 5806 patients aged 75-85 years when assessed (34·6% vs 36·2%). Nor were there differences between the treatment groups in the numbers of participants reported to have developed dementia during follow-up (31 [0·3%] vs 31 [0·3%]), albeit that the numbers of events were small.

In addition, a randomized placebo-controlled trial among 1016 individuals without cardiovascular disease or diabetes has been conducted specifically to assess the effects of statin therapy on cognition (as well as on several outcomes related to mood and behaviour).[256] In that trial, the patients were allocated simvastatin 20 mg daily, pravastatin 40 mg daily or placebo for 6 months, with the administration of a

battery of tests of cognition (i.e. recurrent words, Elithorm maze, digital vigilance and grooved pegboard) at baseline and at 1, 3, 6 and 8 months. Although the trial was completed in 2004, results for the primary outcome of cognition have not yet been published in full (although selected results for some of the other outcomes were published recently[257]); however, the results reported in a meeting abstract indicate that the statin regimens tested were not associated with adverse effects on cognitive function, albeit the duration of exposure was comparatively short.[258] Qualitative and quantitative systematic reviews of available evidence from randomized trials have also not found evidence of any adverse effects of exposure to statin therapy on a wide range of different cognitive measures.[255,259]

In a particularly rigorous assessment of effects on cognitive function, 640 patients aged 50-90 with mild-to-moderate Alzheimer's disease were randomized to receive atorvastatin 80 mg daily or placebo for 72 weeks.[55] The co-primary outcomes were Alzheimer's Disease Assessment Scale-cognitive subscale and Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, which were assessed at 3 monthly intervals for 18 months, along with several other measures of cognition at 6 monthly intervals. The results for both of these scores were slightly in favour of statin therapy, with no apparent differences between the treatment groups in any of the other cognitive outcomes assessed, which provides further reassurance.

Consequently, given the weight of evidence against adverse effects of statin therapy on memory or other aspects of cognition, it would now be appropriate for regulatory authorities to consider their removal from lists of potential adverse effects in the drug labels so that patients are not inappropriately deterred from using statin therapy.

Quality of life related measures

Few of the large long-term randomized placebo-controlled trials of statin therapy specifically assessed quality of life, but there was no evidence of any adverse effect in those that did. For example, in the AFCAPS trial in primary prevention, an adapted version of the Medical Outcomes Study Short-Form General Health Survey was administered in 1126 patients between lovastatin 20 mg daily versus placebo. Mean scores at baseline for emotional well-being and health perception measures were 84 and 83 respectively (range = 0 to 100; higher score representing better quality of life) and differences of ±1.2 points and ±1.5 points at 1 year were excluded.[260] In the LIPID trial among patients with coronary disease, an enhanced version of the utility-based quality-of-life questionnaire was administered at baseline and 1, 3 and 5 years later in a sub-cohort of 1112 randomized patients.[261] The summary utility score was 0.98 (where 0 = dead and 1 = normal good health) at baseline, with a slight decline over time but no apparent difference in scores among survivors at 5 years between the pravastatin and placebo groups (0.978 vs 0.976).

The CRISP trial was conducted specifically to assess the effects of statin therapy on health-related quality of life in 431 men and women aged over 65 years of age.[262] At 6 and 12 months, there were no apparent differences between patients allocated lovastatin 40 or 20 mg daily versus placebo in terms of a battery of tests related to physical functioning, sleep, social support, depression, cognitive function and health perception. Nor were there any apparent differences in reported symptoms, including worsening muscle pain (15.0% vs 14.5% vs 15.0%) at 6 months. Measures related to quality of life have also been assessed in randomized controlled trials of statin therapy in specific types of patient (e.g. those with rheumatoid arthritis, systemic lupus erythematosus, peripheral arterial disease, and erectile dysfunction),[263-266] with no good evidence of any adverse effects on any of these measures. Nor was there

evidence for an adverse effect of statin therapy in a meta-analysis of randomized trials that assessed psychological outcomes.[267]

Cataract and other vision-related outcomes

It has been claimed, based on an observational study of the records of more than 2 million people in general practice databases, that statin therapy produces absolute increases in the risk of developing cataract that are of about the same magnitude as the absolute reductions in major coronary events and cerebrovascular events when used in primary prevention for people with a 10 year risk of cardiovascular events of at least 20%.[87] The report of that study does mention that observational studies have potential biases and that it was not designed to show causality. However, it goes on to describe the observed associations with cataract as *"effects"* of statin therapy (as does a related website[268]) and refers to *"numbers-needed-to-harm"*, which implies that there is a causal association.

In the report of that observational study, it was stated that it had advantages over the available randomized controlled trials of statin therapy because they lack sufficient detail about health outcomes, duration of follow-up and statistical power.[87] However, with respect to data quality, information obtained from retrospective interrogation of databases created for other purposes (primary care records in this case) are not likely to be more reliable than information about adverse events sought prospectively and systematically in randomized trials. In addition, the ability to blind the treatment assignment in randomized trials helps to ensure that outcomes are ascertained and reported in the same way (within any particular randomized trial) both among the patients who are allocated to statin therapy and among those who are not, which helps to avoid biased ascertainment (by contrast with observational studies). With

regard to the duration of exposure to statin therapy, this was not reported explicitly for that observational study, but the person-years of follow-up[87] indicate that it was not longer than several randomized trials of the effects of statin therapy on clinical outcomes.[33] Consequently, any real effects would be expected to have emerged in those trials, particularly since the risk of cataract was reported in this observational study to have been increased within a year of starting a statin.

With respect to statistical power, it is the case that this very large observational study does involve more cases of different health outcomes than even the meta-analyses of the randomized trials of statin therapy. However, some of the larger trials involved sufficient numbers of cases of various outcomes to be able to confirm or refute quite moderate effects reliably. The relative risk of cataract in the observational study that was used to estimate the stated “number-needed-to harm” with statin therapy was about 1.30 (with a narrow 95% CI of 1.26-1.35).[87] Two large randomized trials have reported information on cataract: in the Heart Protection Study of simvastatin 40 mg daily and HOPE-3 trial of rosuvastatin 10 mg daily, cataracts were recorded among a total of 634 (3.8%) patients assigned 5-6 years of statin therapy versus 598 (3.6%) who had been assigned placebo,[192,269] corresponding to an odds ratio of 1.06 (95% CI 0.95-1.19) which excludes the effect size that had been claimed.

Moreover, as was the case for cognition, some of the randomized controlled trials of statin therapy were designed specifically to detect effects on lens opacities and on other outcomes related to vision. For example, the Expanded Clinical Evaluation of Lovastatin (EXCEL) trial involved pupil dilation and slit lamp examination at baseline and after 48 weeks of lovastatin (20 mg or 40 mg daily) or matching placebo in 8032 patients.[56] Despite using such sensitive measures in large numbers of patients, there

were no apparent differences between the statin and placebo groups in the rates of ocular opacities after 48 weeks of exposure. Nor did detailed ophthalmic examination at 6 and 18 months in the Oxford Cholesterol Study find any differences in lens opacities between the 539 patients randomly assigned simvastatin (20 or 40 mg daily) or placebo.[58] In the 4S placebo-controlled trial of simvastatin (20-40 mg daily) among 4443 patients, slit lamp examination conducted at baseline, 1 year and 5-6 years also did not identify any excesses in lens opacities with prolonged exposure to statin therapy, and nor was there an excess of cataract: 53 (2.4%) cases among patients allocated simvastatin vs 66 cases (3.0%) among those allocated placebo (odds ratio 0.80; 95% CI 0.55-1.17).[57]

In addition, there is no good evidence of eye-related microvascular complications due to statin therapy. For example, despite careful assessment of more than 12,000 patients in EXCEL and 4S, no adverse effects on visual acuity were detected [56,57]. Annual fundoscopy in the on-going EMPATHY randomized trial comparing 4.5 years of more versus less intensive statin therapy among about 6,000 patients who have diabetic retinopathy will provide more information about the retinopathy outcome.[270] Statin therapy has been associated with lower rates of progression of age-related macular degeneration in observational studies, but there is limited evidence from randomized trials to support this apparent protective effect.[271]

The refutation of the claims of large effects of statin therapy on cataract, reinforced by the clear lack of effects on more sensitive measures of lens opacities, provides another illustration of how the combination of large size and the inherent biases of non-randomized studies can lead to associations of a treatment with an outcome that may be precise (i.e. involve small random errors) but not causal.

Kidney-related outcomes

In light of the increased incidence of diabetes with statin therapy, it is appropriate to consider whether there are any excesses of microvascular complications related to the kidney. In a meta-analysis of 57 randomized controlled trials involving a total of about 140,000 patients treated for at least 6 months, statin therapy slowed the rate of decline of the estimated glomerular filtration rate (eGFR) by 0.41 (95% CI 0.11 to 0.70) mL/min/1.73 m^2 per year.[272] In addition, compared with control, statin therapy produced a standardized mean smaller increase in albuminuria or proteinuria of 0.65 (95% CI 0.94 to 0.37) among about 5,000 patients in 29 trials that had reported such data. Despite these beneficial trends, statin therapy did not appear to have an effect on progression to end-stage renal disease in randomized trials: 1261 (13.5%) cases on statin versus 1282 (13.6%) cases on control (odds ratio 0.98; 95% CI 0.90-1.07).

It has been variously reported from observational studies that use of a statin is associated with increases, decreases and no change in rates of kidney injury or failure.[87] Short-term peri-operative statin therapy increased blood levels of creatinine consistent with acute kidney injury in some randomized trials in cardiac surgery.[273,274] However, in large randomized controlled trials of long-term statin-based therapy, excesses of renal failure were not observed: for example, acute-on-chronic renal failure in the SHARP trial among people who already had chronic kidney disease when randomized: 209 (6.7%) cases on simvastatin 20 mg plus ezetimibe 10 mg daily versus 231 (7.4%) cases on placebo (risk ratio 0.91; 95% CI 0.75-1.09);[275] renal failure or impairment in the Heart Protection Study among people with pre-existing cardiovascular disease or diabetes: 65 (0.6%) cases on simvastatin 40mg daily versus 60 (0.6%) cases on placebo (risk ratio 1.07; 95% CI 0.76-1.52); [276] and renal failure in the JUPITER trial in the primary prevention setting: 71 (0.9%)

cases on rosuvastatin 20mg daily versus 70 (0.9%) cases on placebo (risk ratio 1.01; 95% CI 0.73-1.41).[246]

Consequently, as with differences in the rates of other outcomes that have been associated with statin use in observational studies, the randomized controlled trial evidence does not provide support for an adverse effect of statin therapy on the kidney (except perhaps in the peri-operative setting) and, instead, indicates that it may slow the progression of renal impairment (although the clinical significance of the small effect that has been observed is uncertain). If, however, statin therapy is not stopped when statin-related myopathy occurs this may lead to renal failure, so doctors and patients do need to be alert to the possibility of this rare complication (while, at the same time, not attributing muscle symptoms to statin therapy without confirmatory evidence and stopping it unnecessarily).

Evidence against adverse effects on other outcomes

In addition to the proven and refuted adverse effects described above, it has also been suggested that statin therapy might produce adverse effects on several other health outcomes (for example, liver disease, sleep disturbance, aggression, suicidal behaviour, erectile dysfunction, neuropathy).[253] These claims have typically derived from case reports or observational studies of statin use and, in most cases, reliable evidence exists that refutes them.[52] For example, although statin therapy can lead to increases in liver enzyme levels, it is associated with very low rates of serious liver injury (about 1 case per 100,000 users)[277] in post-marketing surveillance data and it is uncertain that this association is causal.[254] On the other hand, the National Lipid Association's Liver Expert Panel concluded that routine liver function monitoring might motivate doctors to discontinue statin therapy inappropriately when liver

enzyme elevations are detected and, by so doing, put patients at increased risk of cardiovascular events.[278] Statin therapy has also been associated with increased rates of pancreatitis in observational studies, whereas a meta-analysis of the available evidence from randomized trials indicates that it may reduce the risk (although more evidence is required to confirm that finding).

Even when not all the adverse events that were recorded in randomized trials have been reported publicly, they are likely to have been reviewed in detail by regulatory authorities.[62] Moreover, the data that are publicly available from large randomized trials are often sufficient to rule out excesses of the magnitude claimed from non-randomized and uncontrolled studies (as with the examples of myalgia and cataract discussed above and, similarly, with the refutation[246,280] of case reports[281] suggesting a 3-fold risk of peripheral neuropathy with statin therapy). In many cases, the lack of availability of recorded data reflects restrictions that used to exist on the amount of information that could be included in a journal paper, with the emphasis being on reporting observed differences in outcome between the treatment groups (which tended to result in bias against reporting null findings). That limitation can now be avoided by linking web-tabulations of all recorded adverse events to the journal article, as was done recently for the THRIVE trial of niacin[41] and HOPE-3 trial of rosuvastatin 10 mg daily.[192] Such tabulations have also been provided for the Heart Protection Study of simvastatin 40 mg daily versus placebo [276] and for the SEARCH trial of simvastatin 20 mg versus 80 mg daily,[282] and it is anticipated that they will become available for other statin trials.

Although meta-analyses based on all of the adverse events recorded in all of the major trials of statin therapy – as are now being conducted by the CTT Collaborative

Group[182] – may identify some small additional adverse or beneficial effects, it is not likely that large absolute effects on any outcome will emerge. Consequently, their findings are not likely to alter the balance of benefit and harm materially for any particular type of patient (even those at low risk of cardiovascular events).

CONCLUSIONS

There is an important need for greater recognition of the limitations of observational studies and case reports as a source of reliable information about the effects of a treatment on health outcomes (except in the special circumstances where both the effects are large and the outcome would not normally be expected to occur). By contrast, a better understanding is needed of the strengths of randomized controlled trials of adequate size with systematic assessment of adverse health outcomes and, particularly for symptomatic side-effects, blinded assignment of treatment for the identification of any moderate beneficial and adverse effects on common outcomes that may exist.

Proven benefits of lowering LDL cholesterol with effective statin regimens

Large-scale evidence from randomized controlled trials demonstrates clearly that, after a somewhat smaller risk reduction in the first year of treatment, statin therapy reduces the risk of major vascular events during each subsequent year by about one quarter for <u>each</u> mmol/L reduction in LDL cholesterol.[32] The failure to recognise that the reported risk reductions with statin therapy related specifically to 1 mmol/L LDL-reductions led some commentators to under-estimate substantially the benefits of actually taking statin therapy.[10-12,22,70,186] For, whereas lowering LDL cholesterol by 1 mmol/L would reduce risk by about one quarter during each year after the first, the

effective statin regimens now available that can reduce LDL cholesterol by 2 mmol/L in many patients would approximately halve their risk of heart attacks and strokes.

Statins have been shown to produce similar proportional reductions per mmol/L LDL-reduction in the risks of major vascular events in many different types of patient (e.g. lower and higher risk, women and men, older and younger), irrespective of their presenting cholesterol levels.[32,33] Consequently, the absolute benefits of lowering LDL cholesterol by a given amount depend on the absolute risk of the individuals being treated rather than their presenting cholesterol levels (or other characteristics). For that reason, treatment guidelines now focus on an individual's risk of vascular events rather than on their LDL cholesterol concentrations alone.[158,159] Lowering LDL cholesterol by 2 mmol/L with an effective low-cost statin regimen (e.g. atorvastatin 40 mg daily, which costs less than £2 per month[283]) for 5 years in 10,000 patients would typically prevent major vascular events from occurring in about 1000 high-risk patients (i.e. 10% absolute benefit) with pre-existing occlusive vascular disease ("secondary prevention") and in 500 patients (i.e. 5% absolute benefit) who are at increased risk but have not yet had a vascular event ("primary prevention").[32] Moreover, since statin therapy reduces vascular event risk further during each year it is taken, more prolonged therapy would produce even larger absolute benefits.[169,284]

The proportional reduction in LDL cholesterol produced by a given statin regimen is similar irrespective of the starting cholesterol level. As a consequence, and perhaps somewhat counter-intuitively, more potent statin regimens are required to produce the same absolute LDL-reduction and, hence, the same proportional risk reduction among individuals presenting with lower rather than higher LDL cholesterol levels.[180] This finding is reflected in the recent ACC/AHA guidelines,[158] with the "high-intensity"

statin regimens considered to be warranted for patients at elevated risk of vascular events even if they present with average or below average LDL cholesterol levels (i.e. a change in emphasis towards treating high risk levels and away from treating high cholesterol levels). Adoption of this strategy should help avoid under-treatment of higher-risk patients who have LDL cholesterol levels close to the values that were recommended in previous guidelines as “targets” for dose titration of statin therapy.

Proven harms of statin therapy, but minimal symptomatic side-effects

The only adverse events shown definitely to be caused by statin therapy – that is, are *adverse “effects*” of it – are myopathy (specifically defined as muscle pain or weakness combined with large increases in blood levels of creatine kinase) and diabetes, although it is likely that the risk of haemorrhagic stroke is also increased. Typically, treatment of 10,000 patients for 5 years with an effective statin regimen (e.g. atorvastatin 40 mg daily) would be expected to cause about 5 extra cases of myopathy (1 of which might progress to rhabdomyolysis), 50-100 cases of diabetes, and 5 haemorrhagic strokes. Statin therapy may also cause symptomatic adverse events (e.g. muscle pain or weakness) in up to about 50-100 patients per 10,000 treated for 5 years. The absolute excesses of adverse events with statin therapy are increased in certain circumstances (e.g. with higher statin doses and in combination with certain drugs, or in particular types of patient or population), but they are still small by comparison with the beneficial effects. Moreover, any adverse impact on major vascular events that is caused by the excesses of diabetes and haemorrhagic stroke has already been taken into account in the estimates of the overall benefits.

Even so, because statins are taken by so many people, substantial numbers will still suffer adverse effects of statin therapy. For example, it is to be expected that about

100 myopathy cases would be caused each year among each million people who are prescribed statin therapy. However, whereas these adverse events are readily attributed to the statin (along with many other events that are not causally related[285]), it is not possible to identify those individuals in whom statin therapy has prevented a heart attack or stroke, even though these absolute benefits are much larger. For example, among each million secondary prevention patients, it can be estimated that about 20,000 people would avoid major vascular events each year that statin therapy continues.[32] In addition, whereas many of the adverse effects (such as myopathy) can be reversed with no residual effects by stopping the statin therapy, the effects of a heart attack or stroke are often irreversible.

As discussed above, it has been claimed – based chiefly on case series (e.g. reports to regulatory authorities of adverse events attributed to a statin) and non-randomized observational studies (e.g. analyses of health care databases)[10-12] – that statin therapy causes increased rates of many other types of adverse event, including symptomatic side-effects (in particular, muscle pain and weakness) that prevent a large proportion of patients from continuing statin therapy long-term. This idea that so-called “statin intolerance” is a common problem is being widely promulgated, not just in the medical literature[10-12,22,61,71-73,286] but also in the public media.[186,240,287,288] In addition, the focus of new LDL-lowering agents in development (such as PCSK9 inhibitors) is shifting towards their use in patients classified as statin intolerant[152,250] in whom the reductions in LDL cholesterol would, in the absence of any background statin therapy, be larger (and, hence, their value might be perceived to be greater).

It is worth noting that, whereas statins are now generic and low-cost, the newer agents are costly and there may be commercial pressures to create a market (with,

for example, the drafting of some reports about statin intolerance being funded by manufacturers of the new agents[61,73,289]). Of most relevance, however, claims that statin intolerance occurs in up to one-fifth of treated patients[10-12] are not supported by the large-scale randomized evidence that exists: in particular, statin therapy has generally been found to be no less well tolerated than placebo. For example, there was no excess of discontinuations related to adverse events with statin therapy, and any excesses of muscle-related symptoms due to statin therapy occur in only about 0.1-0.2% of patients during each year of treatment.[52,150,236,237,243]

Public health consequences of misleading claims about the safety of statins

There is a serious cost to public health of making misleading claims about the safety and efficacy of statin therapy.[10,11,70,186,241,287,290,291] Following publication of reports of exaggerated side-effect rates,[10-12,70] and related media coverage, the Picker Institute conducted in-depth interviews and focus groups with patients, general practitioners, and cardiologists, along with online surveys, in 2015.[292] They found that the adverse media coverage was linked to increased reticence among the doctors to discuss and prescribe statins, and reduced compliance by the patients (including those with pre-existing cardiovascular disease) due to raised awareness of perceived side-effects.

There is already evidence that lipid-lowering therapy is substantially under-used by people at high risk of heart attacks and strokes. For example, in the Prospective Urban Rural Epidemiological (PURE) study across 22 countries in 2016, 66% of individuals aged 35-70 years with cardiovascular disease were using statin therapy in high income countries (e.g. Sweden or Canada), but only 27% in upper middle-income countries (e.g. Poland, Turkey or Brazil) and about 5% in lower income countries (e.g. China or India).[293] Across mainland Europe, in the Study of Health

and Retirement in Europe (SHARE), 42% of individuals aged at least 50 years with prior cardiovascular disease were taking any form of lipid-lowering therapy in 2013, with large variations between different countries (e.g. 55-56% in Belgium, Denmark or Netherlands versus 27-29% in Estonia or Slovenia).[294] There was also evidence of substantial levels of drug discontinuation, particularly among people who had not had recent cardiovascular events. In a cross-sectional study based on the Australian National Health Measures Survey in 2011-12, lipid-lowering therapy was being taken by 56% of people aged 45-74 years who had pre-existing cardiovascular disease and by 33% of those considered to have a “high” 5-year risk (>15%) of a primary cardiovascular event.[295] Similarly, in the US Medical Expenditure Survey, statin therapy was being used in 2010 by 58% of people aged 30-79 years with coronary artery disease and by 52% of those aged over 40 years with diabetes.[296] In the UK, analyses of the Clinical Practice Research Datalink in 2014-15 indicated that statin therapy had been started by only about 60% of patients who had recently had a first cardiovascular event and by about 25% of patients in whom a 10 year cardiovascular risk ≥20% had been recorded by the General Practitioner within the past month.[297]

A study in Denmark found that negative statin-related news stories were repeatedly followed by average proportional increases of about 10% in the likelihood of stopping statin therapy.[298] An Australian television programme that was withdrawn after being broadcast because it misrepresented the evidence about statins [287,299] was followed during the subsequent year by a reduction in the numbers of prescriptions of statin therapy for patients at elevated risk of heart attacks and strokes.[300] The researchers estimated that about 60,000 fewer Australians had statins dispensed than predicted from previous rates and that, if those patients continue to avoid statin therapy during the next 5 years, between 1,500 and 3,000 potentially fatal heart attacks and strokes

will occur that would otherwise have been avoided. Similarly following publication of claims that statins cause side-effects in about one-fifth of patients,[10-12] analyses of prescription data from the UK Clinical Practice Research Datalink indicate that there was a 12% proportional increase in patients stopping statin therapy for secondary and primary prevention (as well as reductions in the numbers of patients who had their cardiovascular risk assessed to determine their eligibility for statin therapy).[301] The researchers estimated that more than 200,000 UK patients had stopped taking their statin therapy and that (depending on what proportion resume treatment) this will result in between 2,000 and 6,000 cardiovascular events during the subsequent decade that would have been avoided.

In such circumstances, much greater caution is warranted than has sometimes been the case when making claims about possible side-effects, since otherwise patients at high-risk of heart attacks, strokes and related deaths, and their doctors, may well be inappropriately dissuaded from using statin therapy despite the proven benefits .

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Summary Panels

Panel 1: Contribution of randomized trials for assessing treatment effects

- ***Like-with-like patient comparisons:*** randomization results in groups of patients that differ from each other only by the play of chance with respect to their risks of suffering all types of health outcome, so observed differences in rates of health outcomes can generally be attributed causally to differences in study treatment
- ***Like-with-like outcome comparisons:*** non-differential outcome ascertainment between the randomized treatment groups within a trial helps to minimise bias in the assessment of treatment effects. It can be enhanced by blinding, which is likely to be of most value for symptomatic adverse events that are subjective
- ***Robustness for detecting effects:*** comparisons within randomized trials with unbiased ascertainment of outcomes between treatment groups are robust for the detection of both beneficial and harmful effects of treatment
- ***Generalizability of evidence:*** randomized trials with different eligibility criteria that involve large numbers of many different types of patient (ideally combined in meta-analyses of individual patient data) can provide reliable information about treatment effects that can be widely generalized to different circumstances

Panel 2: Contribution of observational studies for assessing treatment effects

- ***Detect large effects on rare outcomes:*** exposure to treatment in large numbers of individuals in observational studies based on health care databases or on post-marketing case reports allows large effects (adverse or beneficial) to be detected on outcomes that would otherwise not be expected to occur (i.e. are usually rare)
- ***Assess effects of prolonged exposure:*** observational studies may involve data on prolonged exposure to a treatment that can allow long-term effects to emerge, although the available information about duration and dose may be importantly incomplete in available databases, limiting the inferences that can be drawn
- ***Biases due to differences in risks:*** even when associations between treatment and health outcomes remain after statistical adjustment for observed differences between different groups of individuals, the associations may still reflect residual confounding due to differences that were assessed incompletely or not at all
- ***Biases due to differences in ascertainment:*** patients treated in routine practice know they are taking a particular drug and, indeed, may be told it has side-effects and be monitored more closely. Consequently, any associations with a treatment in observational studies may be biased by differences in reporting and detection of health outcomes between patients who are taking it and those who are not.

- ***Generalizability of evidence:*** application of the proportional effects of treatment on specific outcomes derived from randomized trials to the absolute rates of the outcomes derived from observational studies in the population of interest can be used to yield generalizable estimates of its absolute benefits and harms

Panel 3: Proven beneficial effects of statin therapy

- Effective low-cost statin regimens (e.g. generic atorvastatin 40 mg daily costs about £2 per month) reduce LDL cholesterol by more than 50% (i.e. at least 2 mmol/L in individuals with LDL cholesterol concentrations of 4 mmol/L or more)
- Large-scale randomized evidence shows that each 1 mmol/L LDL-reduction with statin therapy produces a proportional reduction of about 25% in the rate of major vascular events (coronary deaths, myocardial infarctions, strokes and coronary revascularisations) during each year (after the first) that it continues to be taken. Consequently, lowering LDL cholesterol by 2 mmol/L reduces risk by about 45%
- Lowering LDL cholesterol by 2 mmol/L with an effective statin regimen for about 5 years in 10,000 patients would typically prevent major vascular events in about 1000 (10%) patients at high risk of heart attacks and strokes (e.g. “secondary prevention”) and 500 (5%) patients at lower-risk (e.g. “primary prevention”)
- Despite reports based largely on non-randomized observational studies, there is not good evidence that statin therapy produces beneficial effects on other health outcomes (e.g. cancer, infections, respiratory disease, arrhythmias)

Panel 4: Known adverse effects of statin therapy

- The only adverse events that have been reliably shown to be caused by statin therapy are myopathy (defined as muscle pain or weakness combined with large increases in creatine kinase blood levels) and new onset diabetes mellitus, along with a probable increase in strokes due to bleeding (i.e. haemorrhagic strokes)
- Typically, treatment of 10,000 patients for 5 years with a standard statin regimen (such as atorvastatin 40mg daily) would be expected to cause about 5 cases of myopathy, 50-100 new cases of diabetes, and 5 haemorrhagic strokes
- Despite reports based largely on non-randomized observational studies, there is not good evidence that statin therapy causes adverse effects on any other health outcomes – chiefly muscle pain and weakness – that prevent a large proportion of patients from continuing it long-term (so-called “statin intolerance”)
- Large-scale randomized evidence rules out excesses of muscle pain and weakness with statin therapy of more than about 10-20 cases annually per

10,000 treated patients, with only about 1 of those cases being associated with large CK elevations (i.e. myopathy) and requiring statin discontinuation

- Absolute excesses of adverse events that are caused by statin therapy are not more than about 100-200 (i.e. 1-2%) per 10,000 patients treated for 5 years, and it is unlikely that large adverse effects on serious adverse events await discovery.
- The harmful effects of statin therapy can usually be reversed without any residual effects by stopping it, whereas the harmful effects of heart attacks or strokes that occur because statin therapy has not been used can be devastating

Figure legends

Figure 1: Similar proportional reductions in risks of major vascular events per mmol/L LDL-reduction in randomized trials of statin therapy among people with different presenting characteristics

Adapted from CTT collaborative meta-analyses.[33] Rate ratios (RRs) are plotted for the combined comparisons of major vascular event rates (MVE) in randomized trials of routine statin therapy versus no routine statin therapy and of more versus less intensive statin therapy, weighted per 1·0 mmol/L LDL cholesterol (LDL-C) reduction at 1 year. RRs are shown with horizontal lines denoting 99% confidence intervals (CIs) and diamonds denoting 95% CIs. CHD=coronary heart disease.

Figure 2: Different shape of association of blood levels of total cholesterol with rates of coronary heart disease mortality when plotted on (a) arithmetic versus (b) logarithmic scales

Adapted from Prospective Studies Collaborative meta-analysis.[154] The log-linear association in Figure 2(b) indicates that the same absolute difference in cholesterol level is associated with the same proportional difference in coronary heart disease mortality throughout the cholesterol range in the observational studies included (and studies in other populations indicate this association continues at lower levels[302,303]).

Figure 3: Proportional major vascular event reductions versus absolute LDL cholesterol reductions in randomized trials of routine statin therapy versus no routine statin use and of more intensive versus less intensive regimens

Based on CTT meta-analyses.[33] Proportional risk reductions are plotted against the average LDL-reduction at 1 year in meta-analyses of trials of routine statin therapy versus no routine statin therapy with average LDL reduction above and below 1.1 mmol/L and of trials of more versus less intensive statin therapy with a further 0.5 mmol/L LDL-reduction. These risk reductions relate to the average effects observed in these trials including the first year of study treatment (when the risk reduction is

smaller) and to the LDL-reductions achieved at 1 year (rather than the average LDL-difference for the scheduled study treatment period), which may under-estimate the effects of actually taking statin therapy long-term (see Figure 4 and its legend).

Figure 4: Proportional reductions in risks of major vascular events per mmol/L reduction in LDL cholesterol during each year of scheduled statin treatment

Adapted from CTT collaborative meta-analyses.[33] Symbols and conventions as in Figure 1. For each time period, RRs weighted by trial-specific LDL-reductions at 1 year relate to participants at risk of a first post-randomization major vascular event during the time period in the meta-analysis of trials of routine statin therapy versus no routine statin therapy. Consequently, the overall RR of 0.76 for the period after the first year indicates that risk is reduced by about one quarter in each year that treatment continues (i.e. the absolute benefits increase with increasing duration of treatment). As non-compliance to the randomly assigned treatment increased with longer duration in the trials (in part due to study statin therapy being stopped, but more commonly due to statin therapy being started in the control group), the per mmol/L reductions based on LDL-reductions at 1 year are likely to under-estimate the reductions in MVE risk per mmol/L LDL-reduction later in these trials.

Figure 5: Predicted absolute reductions in risks of major vascular events by lowering LDL cholesterol with statin therapy for 5 years (after the first year) in people at different levels of absolute risk

Based on CTT collaborative meta-analyses.[32] Lifetable estimates derived from major vascular event risks in respective categories and risk reductions (after the first year) per mmol/L LDL-reduction. The risk groups are equivalent to annual rates of major coronary events of 0.8%, 1.6%, 3.2% and 5.6% and vascular death of 0.3%, 1.0%, 2.3% and 5.8%. The National Institute for Health and Clinical Excellence (NICE) recommends that statin therapy is considered for those individuals without known cardiovascular disease (CVD) who have estimated 10-year risk of developing CVD (defined as myocardial infarction, CHD death, angina, stroke or transient ischemia) of at least 10%.[159] This CVD event was not available in the CTT meta-analyses, so it

was estimated by multiplying observed vascular death rates within risk categories by 3-4, yielding 10-year CVD risk of 9-12% and 30-40% for the lowest two groups.[32]

Figure 6: Effects of lowering LDL cholesterol with statin therapy on cause-specific mortality in meta-analyses of randomized trials of statin therapy

Adapted from CTT collaborative meta-analyses. [31,33] Combined comparisons in randomized trials of routine statin therapy versus no routine statin therapy and of more versus less intensive statin therapy. Symbols and conventions as in Figure 1.

Figure 7: Effects of lowering LDL cholesterol with statin therapy on site-specific cancer in meta-analyses of randomized trials of statin therapy

Adapted from CTT collaborative meta-analyses. [31,51] Combined comparisons in randomized trials of routine statin therapy versus no routine statin therapy and of more versus less intensive statin therapy. Symbols and conventions as in Figure 1. GI=gastrointestinal; GU=genitourinary.

Table legends

Table 1: Illustrative example of the robustness to mis-classified outcomes ("false positives") and missing outcomes ("false negatives") of within-trial comparisons of the effects of treatment in randomized controlled trials

Table 2: Absolute differences in health outcomes with different control rates that would have a 90% probability of being detected (i.e. "statistical power") at a p-value of 0.01 in randomized controlled trials of different size

Table 3: Average relative reductions in LDL cholesterol levels with different doses of commonly used statins[156,159]

Webtable: Muscle-related events reported in randomised trials of statin therapy involving at least 1000 participants and 2 years of scheduled study treatment that are eligible for the CTT Collaborative meta-analyses (excluding those trials that were not blinded by placebo control)[181]

Absolute error	Active (10,000)	Control (10,000)	Relative reduction	Absolute reduction	z-score*
True events	800 (8.0%)	1000 (10.0%)	20%	2.0%	4.9
Extra false outcomes (evenly distributed*)					
+ 10%	890 (8.9%)	1090 (10.9%)	18%	2.0%	4.7
+ 20%	980 (9.8%)	1180 (11.8%)	17%	2.0%	4.6
Missing real outcomes (unevenly distributed*)					
- 10%	720 (7.2%)	900 (9.0%)	20%	1.8%	4.7
- 20%	640 (6.4%)	800 (8.0%)	20%	1.6%	4.4

* For context, a z-score of 4.0 is equivalent to a p-value <0.0001

Table 1: Illustrative example of the robustness to mis-classified outcomes ("false positives") and missing outcomes ("false negatives") of within-trial comparisons of the effects of treatment in randomized controlled trials

* The numbers of participants in whom true events would not have occurred would be slightly different between the treatment groups, but this produces little imbalance in the numbers of false events that can be recorded among such patients in the two treatment groups when true events are relatively uncommon (as in this example). Consequently, false events have been approximately evenly distributed because they would not be affected by treatment assignment. By contrast, there would be fewer real outcomes to be missed in the active treatment group (since the treatment reduces the rate of the outcome), so the numbers of missed real outcome events are unevenly distributed between the treatment groups.

Number of patients	Control rate of health outcome			
	20%	15%	10%	5%
5,000	4.4%	3.9%	3.3%	2.4%
10,000	3.1%	2.8%	2.3%	1.7%
20,000	2.2%	1.9%	1.6%	1.2%
100,000	1.0%	0.9%	0.7%	0.5%

Table 2: Absolute differences in health outcomes with different control rates that would have a 90% probability of being detected (i.e. "statistical power") at a p-value of 0.01 in randomized controlled trials of different size

Statin	Daily dose of different statins				
	5 mg	10 mg	20 mg	40 mg	80 mg
Pravastatin	15%	20%	24%	29%	33%
Simvastatin	23%	27%	32%	37%	42%
Atorvastatin	31%	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	58%

Table 3: Average relative reductions in LDL cholesterol levels with different doses of commonly used statins[156,159]

Shaded boxes indicate regimens that can produce about a halving or more in LDL cholesterol levels (largely irrespective of patient characteristics, including presenting levels of cholesterol). The 2016 cost for generic atorvastatin 40 mg daily in the UK is about £2 per 28 days of treatment;[283] rosuvastatin 20 mg daily currently costs about £25 per month,[304] but it became available as a generic in the USA during 2016.

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