Statins in the primary prevention of cardiovascular disease

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Abstract | Statins are widely used in the evidence-based lowering of cardiovascular disease (CVD) risk. The use of these drugs for secondary prevention of CVD is well founded, but their expanding use in primary prevention—in individuals without documented CVD—has raised some concerns. Firstly, evidence suggests that, in primary prevention, statins substantially decrease CVD morbidity, but only moderately reduce CVD mortality. Secondly, long-term statin use might cause adverse effects, such as incident diabetes mellitus. Thirdly, the cost-effectiveness of such a strategy is unclear, and has to be balanced against the risk of 'overmedicating' the general population. Data clearly support the use of statins for primary prevention in high-risk individuals, in whom the strategy is cost-effective and the benefits exceed the risks. Whether primary prevention is beneficial in individuals at low or moderate risk is not certain. Therefore, the prescription of statins for primary prevention should be individualized on the basis of clinical judgment, particularly for low-risk individuals. In appropriately selected individuals, statins should also be used for primary prevention of ischaemic stroke and transient ischaemic attack.

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Introduction

Cardiovascular disease (CVD) is the main cause of mortality and one of the most-important causes of morbidity in the world. Major contributors are coronary heart disease (CHD) and myocardial infarction (MI), as well as cerebrovascular diseases, such as ischaemic stroke, all of which place an intolerable burden not only on the quality of life of patients, but also on economies and health-care resources.[1] Dyslipidaemia is one of the most-important causal risk factors for CVD, and targeting this condition is, therefore, an important health-care priority.[2] Evidence supports the reduction of the LDL-cholesterol level as the primary objective of dyslipidaemia management, and statins are the drugs of choice in the vast majority of patients.

The most-important landmark trials, conducted almost 2 decades ago, clearly showed the beneficial effects of statins in secondary prevention in reducing all-cause and CVD mortality as well as cardiovascular events.[3–5] These findings were subsequently confirmed in several meta-analyses.[6,7] Randomized controlled trials conducted in the 1990s showed similar benefits of statins in primary prevention—that is, in individuals without documented CVD. However, the issue of primary prevention with statins remains unresolved, particularly in individuals at low cardiovascular risk, but also in those at intermediate or high risk. In this Review, the evidence for the use of statins in the primary prevention of CVD is discussed.

Competing interests
The author declares associations with the following companies: Abbot, AstraZeneca, Bayer, and Sanofi. See the article online for full details of the relationships.

Current use of statins

In a large European survey of primary prevention, the control of cholesterol levels in patients at high risk of CVD was shown to be inadequate.[8] About half of the patients who were receiving lipid-lowering medication, principally statins, were not achieving the target total-cholesterol level of <5.0 mmol/l (~190 mmol/l) as defined in current guidelines.[8] The majority of cardiologists and primary-care physicians support the concept of preventive cardiology and treatment of hypercholesterolaemia to target levels, but these aspirations are not always reflected in clinical practice, and the perceptions, knowledge, and awareness of the general public about CVD risk factors, including dyslipidaemia, are insufficient.[9–12] Although primary prevention tends to be underexploited and overlooked, various studies have shown that this strategy can produce a substantially larger reduction in CHD mortality than that from secondary prevention, mainly by decreasing the serum cholesterol level in asymptomatic individuals.[13] However, various questions about long-term statin use for primary prevention remain unanswered, such as its efficacy in decreasing CVD morbidity and mortality, its safety and links with incident diabetes mellitus and cancer, and its impact on quality of life. These questions are of utmost importance, given that approximately three-quarters of patients who take statins do so for primary prevention.

The use of statins in primary prevention is recommended in various guidelines, but the exact advice differs. In the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III guidelines, the use of statins for primary prevention is recommended if the LDL-cholesterol level is ≥190 mg/dl

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Key points

- Large clinical trials and meta-analyses suggest that lowering the LDL-cholesterol level with statins in primary prevention modestly reduces all-cause mortality and substantially decreases the rate of cardiovascular events
- Statins are recommended for primary prevention in nearly all high-risk individuals, whereas an individualized approach is recommended in those at moderate or low risk
- Statins should be used for primary prevention of cardiovascular disease in women in the same manner as in men
- Statins reduce cardiovascular risk when used for primary prevention in elderly individuals, but their use, particularly in high doses, requires clinical judgment and an individualized approach
- Statins should be used for primary prevention of ischaemic stroke and transient ischaemic attack, at least in appropriately selected individuals
- Low-cost, generic forms of statins are particularly cost-effective for primary prevention, especially in high-risk individuals

(~5.0 mmol/l), is discretionary if the LDL-cholesterol level is 160–189 mg/dl (~4.1–4.9 mmol/l), but is not advised for ostensibly healthy individuals with an LDL-cholesterol level <160 mg/dl (~4.1 mmol/l), unless they have two or more risk factors for CVD.[14] In the ESC/European Atherosclerosis Society guidelines for the management of dyslipidaemia, and in the 2012 European guidelines on CVD prevention, statins are recommended as the drugs of choice for the treatment of hypercholesterolaemia, but their use is determined by CVD-risk estimation according to Systematic Coronary Risk Estimation (SCORE) charts, rather than by any particular target LDL-cholesterol level.[15,16] This individualized approach has been adopted as a result of an awareness that total CVD risk is part of a continuum, and that the threshold values that are used to define 'high risk' are somewhat arbitrary and grounded on the risk levels at which benefit is evident in clinical trials.[15] In the previous version of the European guidelines, these cut-offs resulted in an arbitrary division of the asymptomatic population into two groups: those at high risk (SCORE >5%), in whom preventive action should be maximized (interpreted by many physicians, who were strongly influenced by the drug industry, to mean that everyone in this group should be taking lipid-lowering drugs), and those with SCORE <5%, to whom no preventive action was recommended and no drugs prescribed. The Writing Group of the 2012 European guidelines considered this categorical approach, although quite popular in clinical medicine, to be wrong.[17,18]

The guideline target LDL-cholesterol levels, having been defined by extrapolating data from trials, do not necessarily produce the expected outcomes.[15] Indeed, the standard method of estimating the LDL-cholesterol level—the widely used Friedewald equation—has been shown to produce underestimates.[19] Patients with a very low LDL-cholesterol level can be misclassified, with nearly one-quarter of individuals with an estimated LDL-cholesterol level <1.8 mmol/l (70 mg/dl) actually having a higher level of LDL cholesterol when it is measured directly. Additionally, no guidelines should be considered a substitute for clinical judgment of individual patients in everyday practice.[20]

Statins seem to reduce CVD risk in nearly all individuals regardless of their baseline LDL-cholesterol level, but the benefit of such a strategy depends on their underlying risk and the degree to which statin use reduces that risk.[21] Accordingly, the highest-risk patients benefit most, whereas individuals at moderate or even low risk might also benefit from statins, but to a lesser extent.[22,23] The phenomenon that individuals taking statins for primary prevention over the long term are more likely than patients who have survived a cardiovascular event to be nonadherent to therapy after only 6 months must also be considered.[24,25]

The lifelong risk of CVD in patients with diabetes is as high as that in patients with previous CVD in the absence of diabetes, particularly if they have other risk factors or target-organ damage, such as microalbuminuria.[15,26] Therefore, the use of statins in patients with diabetes is considered secondary prevention and will not be discussed in this article. Similarly, chronic kidney disease is also recognized to be a CVD-risk equivalent, and statin use in these patients is also considered secondary prevention and is, therefore, beyond the scope of this Review.[15,27]

Other conditions also warrant an aggressive approach to screening and statin therapy for dyslipidaemia, although whether such treatment should be considered primary prevention is questionable. For example, patients who have undergone solid-organ transplantation often have lipid abnormalities, but careful titration of the statin dose is necessary to avoid interactions with immunosuppressive drugs.[13,28,29] Patients with HIV often have dyslipidaemia, and HAART ('highly active antiretroviral treatment') exacerbates lipid abnormalities and necessitates statin treatment. Statin use might reduce all-cause mortality in these patients, but the benefit in individuals without comorbidities is questionable, and the interaction with HAART, possibly leading to adverse effects, is well documented.[30,31] Autoimmune diseases, particularly those with an inflammatory component, including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and antiphospholipid syndrome, are characterized by increased CVD mortality and various lipid abnormalities, but no evidence exists that these patients benefit from statin use.[15]

Outcomes of primary prevention

Clinical trials

Only a small number of large trials of statins in primary prevention have been conducted. The first was the West of Scotland Coronary Prevention Study (WOSCOPS).[32] This double-blind, placebo-controlled trial showed the effectiveness of a statin (pravastatin, 40 mg per day) in reducing the combined incidence of nonfatal MI and death from CHD in 6,595 men (mean total-cholesterol level 272 ± 23 mg/dl or 7.0 ± 0.6 mmol/l, which at the time was considered moderately hypercholesterolaemic), with no history of MI.[32] Long-term follow-up data from WOSCOPS indicate that men to whom statins were prescribed for 5 years during the clinical-trial period had fewer cardiovascular events a decade after

completion of the trial, even though a large majority of those included in the study cohort had stopped taking their cholesterol-lowering medication. About 10 years after the end of the trial, the risk of nonfatal MI or death from CHD was 10.3% and 8.6% in the placebo and statin groups, respectively ($P = 0.02$).[33] Over the entire follow-up period (~15 years), the rate was 15.5% versus 11.8% ($P < 0.001$).[33] The investigators speculate that statin use resulted in stabilization of existing plaques and, therefore, conferred a long-term benefit, even after individuals stopped taking the drugs.

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[34,35] reduction of the LDL-cholesterol level with a statin (lovastatin, 20–40 mg per day) reduced the incidence of fatal or nonfatal MI, unstable angina, or sudden cardiac death in 6,605 individuals (mean LDL-cholesterol level 3.89 ± 0.43 mmol/l or 150 ± 17 mg/dl, which would be considered normal according to contemporary standards), but a below-average HDL-cholesterol level. The number needed to treat over 5 years to prevent one cardiovascular event was 46 among men, but the data also showed that the benefit from a reduction in the LDL-cholesterol level from primary prevention extended to women and older individuals (aged >65 years). The results of AFCAPS/TexCAPS[34,35] emphasize that, in primary prevention, targeting patients at high risk can produce a large effect at fairly low cost.

The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial[36–38] involved 8,214 Japanese men and women without CVD, but with mild-to-moderate hypercholesterolaemia. The results showed that even small-to-moderate changes in LDL-cholesterol level achieved with low doses of a statin (pravastatin, 10–20 mg per day) in this low-risk population significantly reduced the relative risk of CHD.[36–38]

The Anglo–Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA)[39] involved 19,342 patients with hypertension and at least three other risk factors for CVD. A total of 10,305 patients with a nonfasting total-cholesterol concentration ≤250 mg/dl (~6.5 mmol/l)—that is, not meeting the conventional criterion for dyslipidaemia—were randomly assigned to receive a low dose of a statin (atorvastatin, 10 mg per day) or placebo. The trial was stopped earlier than scheduled (median follow-up 3.3 years), because of a clear reduction in the rate of nonfatal MI and fatal CHD in the statin group compared with placebo (100 versus 154 events, respectively; HR 0.64, $P = 0.0005$).[39]

The latest, but also most-controversial, trial of a statin in primary prevention was Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER).[40] This randomized, double-blind, placebo-controlled trial was designed to investigate whether a statin (rosuvastatin, 20 mg per day) would decrease the rate of cardiovascular events in 17,802 apparently healthy men and women with a fairly low LDL-cholesterol level (≤130 mg/dl, ~3.4 mmol/l) and a high level of C-reactive protein detected using the high-sensitivity assay (hs-CRP; ≥2 mg/l, ~19 nmol/l).[40] The trial was stopped earlier than planned (median follow-up 1.9 years), because of a significant reduction in the primary composite end point (MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes) with rosuvastatin compared with placebo (HR 0.53, 95% CI 0.40–0.69, $P < 0.00001$).[40] Therefore, individuals with an elevated hs-CRP level seem to benefit from statin use, regardless of their LDL-cholesterol level. However, the early (but appropriate) cessation of the trial might have resulted in overestimation of the therapeutic benefit and underestimation of the risk.[41] The results have even been attributed to a reduction in the hs-CRP level rather than to LDL-cholesterol lowering by the statin.[42]

Meta-analyses

Several meta-analyses have been published on the effects of statins in primary prevention of CVD.[43–46] Only meta-analyses published since 2006 with access to contemporary trial data are considered in this Review. The results generally indicate a modest 9–17% relative risk reduction in all-cause, short-term (<5-year) mortality.[43–46] Therefore, if only short-term mortality data are considered, the evidence for the use of statins in the primary prevention of CVD is relatively weak.

One of the problems with most of the meta-analyses is that they included data from not only individuals without clinically manifest CVD, but also patients with pre-existing CHD or stroke. For example, one analysis included five trials in which only patients with known clinical peripheral vascular disease or demonstrable carotid artery atherosclerosis were enrolled, as well as two trials with patients who had diabetes.[44] Therefore, these meta-analyses do not provide accurate information specifically about primary prevention, and the distinction between primary and secondary prevention is ambiguous. Another problem is that, owing to the lack of such data, the meta-analyses did not take into consideration the long-term effects of statins. Moreover, in only one meta-analysis were the effects of statins on CVD morbidity assessed.[46] Statins decreased the rate of major coronary events, major cerebrovascular events, nonfatal MI, and revascularizations, but the investigators cautioned against their use in individuals at low risk of CVD (<1% annual all-cause mortality risk), because of the quality, early discontinuation, and inclusion of patients with established CVD in some trials.

In a meta-analysis of 11 randomized controlled trials that included a total of 65,229 participants, with approximately 244,000 person-years of follow-up, and 2,793 deaths, statin use (mean duration 3.7 years) resulted in a borderline-significant 7–9% reduction in all-cause mortality in a high-risk, primary-prevention population.[47] This reduction translated into seven fewer deaths for every 10,000 person-years of statin use.[47] This meta-analysis did not show a significant correlation between on-treatment difference in LDL-cholesterol level and the relative reduction in all-cause mortality. However, two of the trials in the analysis involved only patients with

diabetes (although without clinically manifest CHD), which is highly likely to have influenced the results, given that diabetes is a CHD risk equivalent. Furthermore, the investigators who performed this meta-analysis did not assess data on CVD morbidity.

A meta-analysis of individual patient data from 27 randomized trials involving a total of 175,149 individuals at low risk of CVD showed that, in those with a 5-year risk of major cardiovascular events <10%, each 1 mmol/l reduction in the LDL-cholesterol level produced by statin use resulted in an absolute reduction in major cardiovascular events (nonfatal MI, coronary death, coronary revascularization, or stroke) of about 11 per 1,000 patients treated over 5 years.[48] In individuals with no history of CVD, the reduction in the LDL-cholesterol level with statins decreased CVD mortality (rate ratio [RR] per 1.0 mmol/l reduction 0.85, 95% CI 0.77–0.95, $P = 0.004$) and, as the risk of nonvascular causes of death was not increased (RR 0.97, 95% CI 0.88–1.07), also decreased all-cause mortality (RR 0.91, 95% CI 0.85–0.97, $P = 0.007$; Figure 1). This substantial benefit greatly exceeds any known hazards of statins and, therefore, clearly supports the use of statins in primary prevention, even in individuals at low risk of CVD. As in a previous analysis by this group, no difference was observed in the relative risk reduction between groups at high or low risk of CVD. The size and the use of individual patient data allowed this meta-analysis to provide reliable data on the benefits of statin use in primary versus secondary prevention, as well as on the effects of age, sex, and incidence of adverse effects.

In another study, prediction tools were developed, and lifetime outcomes were estimated with or without statins in primary prevention using 5-year follow-up data from 2,428 participants.[49] Statin use was projected to increase life expectancy by 0–2 years, and CVD-free life expectancy by 0.1–2.8 years. In fact, many patients with a low SCORE risk had similar or greater gains in life expectancy with statin use than their higher-risk counterparts. For example, a woman aged 55 years who did not smoke and who had a 10-year risk of 2% could achieve a similar gain in CVD-free life expectancy with statin use as a man aged 65 years who smoked and had a 10-year risk of 15%.[49] Both of these individuals would gain about 1 year in their CVD-free life expectancy with statin use.

Taken together, these data indicate that the proportional benefits of statin use are similar in primary and secondary prevention. However, the absolute benefits of primary prevention are much smaller than those of secondary prevention.[48]

Adverse effects of statins

The safety profile of statins is very good, as shown in a meta-analysis of 35 randomized controlled trials involving a total of 74,102 participants (follow-up 1.5–64.8 months).[50] Well-documented adverse effects include myopathy, which is rare, and rhabdomyolysis, which is extremely rare. Increased activity of liver enzymes occurs occasionally and is reversible. Most individuals who develop adverse effects from statins do so soon after they start taking the drug, so the frequency of adverse effects when expressed as a percentage of current users decreases over time. Conversely, statin-induced myopathy can develop years after starting to take the drug, so the absolute number of patients with this condition increases with duration of statin use.

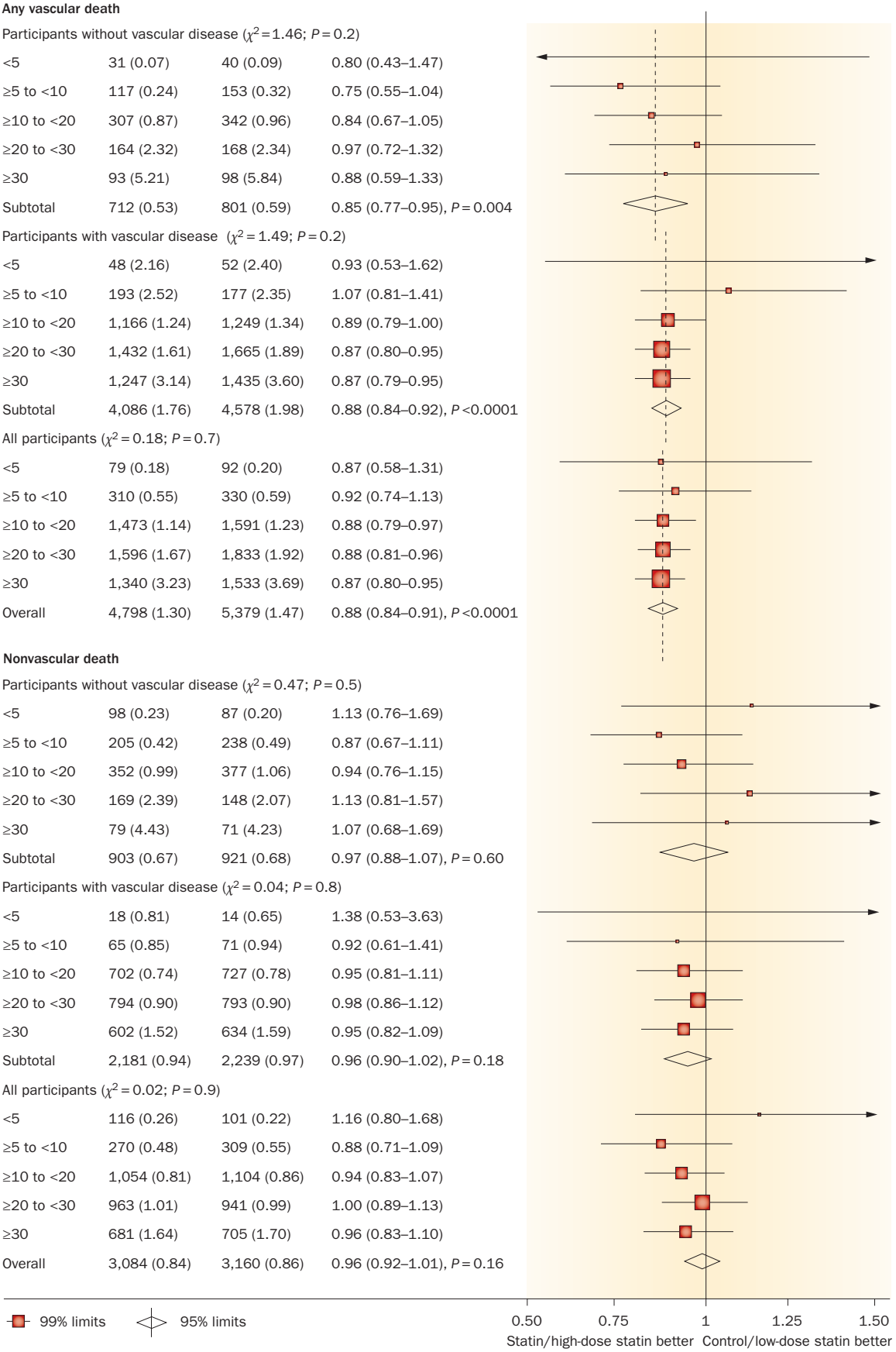
Figure 1 | Effects on vascular and nonvascular deaths per 1.0 mmol/l reduction in the LDL-cholesterol level with statin use, according to level of 5-year MVE risk. Abbreviations: MVE, major vascular event; RR, rate ratio. Reprinted from Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* **380** (9841), 581–590 (2012). © With permission from Elsevier. ►

In a survey of the FDA Reporting System database, muscle-related adverse events were linked to statin use.[51] Statin potency, measured per milligram of LDL-cholesterol level lowering, seemed to be a predictor of the risk of myopathy (rosuvastatin was associated with a greater risk than either atorvastatin or simvastatin, which were associated with a greater risk than either lovastatin or pravastatin). Fluvastatin—the least-potent statin, but associated with a high risk of adverse events—is an exception to this trend.[51] The aetiology of statin-induced myopathy is not fully understood, but several potential contributing mechanisms are suspected (Figure 2).

A meta-analysis of 72 trials involving a total of 159,458 patients (follow-up 0.5–6.1 years) showed no significant difference between the use of various statins and placebo in the incidence of rhabdomyolysis (0.25% versus 0.25%; OR 1.05, 95% CI 0.84–1.31) or elevated creatine kinase level (OR 1.09, 95% CI 0.85–1.41).[52] A significant effect of statin use on elevated aspartate and alanine aminotransferase was reported.[52] Nevertheless, results of a *post-hoc* analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) trial[53] suggest that statins might exert beneficial effects in patients with elevated transaminases. In observational studies, statin use has been associated with pancreatitis, but in patients with a normal or mildly elevated triglyceride level, statin use is, in fact, associated with a reduced risk of pancreatitis.[54]

Concerns that a lipid-lowering treatment might contribute to an increase in noncardiovascular morbidity or mortality (from conditions such as cancer or depression, or from suicide), memory loss, or psychiatric disorders have not been substantiated.[45,48,55–59] Conversely, statin use has been associated in some reports with a reduced risk of recurrence among women diagnosed with stage I–III breast carcinoma, and with a reduced risk of colorectal, gastric, liver, and uterine cancer.[7,60–62] These data are in accordance with some early meta-analyses that suggested that statin use did not increase the overall incidence of cancer, as well as with a meta-analysis from 2012, which involved 175,000 patients and showed that statin use (median duration 5 years) had no effect on the incidence of, or mortality from, any form of cancer.[48,63–65] The finding was consistent across subgroups of patients, including the elderly (even those aged ≥75 years at

5-year MVE risk at baseline (%)	Events (% per annum) Statin/high-dose statin	Control/low-dose statin	RR (CI) per 1.0 mmol/l reduction in LDL-cholesterol level
Any vascular death			
Participants without vascular disease ($\chi^2 = 1.46$; $P = 0.2$)			
<5	31 (0.07)	40 (0.09)	0.80 (0.43–1.47)
≥5 to <10	117 (0.24)	153 (0.32)	0.75 (0.55–1.04)
≥10 to <20	307 (0.87)	342 (0.96)	0.84 (0.67–1.05)
≥20 to <30	164 (2.32)	168 (2.34)	0.97 (0.72–1.32)
≥30	93 (5.21)	98 (5.84)	0.88 (0.59–1.33)
Subtotal	712 (0.53)	801 (0.59)	0.85 (0.77–0.95), $P = 0.004$
Participants with vascular disease ($\chi^2 = 1.49$; $P = 0.2$)			
<5	48 (2.16)	52 (2.40)	0.93 (0.53–1.62)
≥5 to <10	193 (2.52)	177 (2.35)	1.07 (0.81–1.41)
≥10 to <20	1,166 (1.24)	1,249 (1.34)	0.89 (0.79–1.00)
≥20 to <30	1,432 (1.61)	1,665 (1.89)	0.87 (0.80–0.95)
≥30	1,247 (3.14)	1,435 (3.60)	0.87 (0.79–0.95)
Subtotal	4,086 (1.76)	4,578 (1.98)	0.88 (0.84–0.92), $P < 0.0001$
All participants ($\chi^2 = 0.18$; $P = 0.7$)			
<5	79 (0.18)	92 (0.20)	0.87 (0.58–1.31)
≥5 to <10	310 (0.55)	330 (0.59)	0.92 (0.74–1.13)
≥10 to <20	1,473 (1.14)	1,591 (1.23)	0.88 (0.79–0.97)
≥20 to <30	1,596 (1.67)	1,833 (1.92)	0.88 (0.81–0.96)
≥30	1,340 (3.23)	1,533 (3.69)	0.87 (0.80–0.95)
Overall	4,798 (1.30)	5,379 (1.47)	0.88 (0.84–0.91), $P < 0.0001$
Nonvascular death			
Participants without vascular disease ($\chi^2 = 0.47$; $P = 0.5$)			
<5	98 (0.23)	87 (0.20)	1.13 (0.76–1.69)
≥5 to <10	205 (0.42)	238 (0.49)	0.87 (0.67–1.11)
≥10 to <20	352 (0.99)	377 (1.06)	0.94 (0.76–1.15)
≥20 to <30	169 (2.39)	148 (2.07)	1.13 (0.81–1.57)
≥30	79 (4.43)	71 (4.23)	1.07 (0.68–1.69)
Subtotal	903 (0.67)	921 (0.68)	0.97 (0.88–1.07), $P = 0.60$
Participants with vascular disease ($\chi^2 = 0.04$; $P = 0.8$)			
<5	18 (0.81)	14 (0.65)	1.38 (0.53–3.63)
≥5 to <10	65 (0.85)	71 (0.94)	0.92 (0.61–1.41)
≥10 to <20	702 (0.74)	727 (0.78)	0.95 (0.81–1.11)
≥20 to <30	794 (0.90)	793 (0.90)	0.98 (0.86–1.12)
≥30	602 (1.52)	634 (1.59)	0.95 (0.82–1.09)
Subtotal	2,181 (0.94)	2,239 (0.97)	0.96 (0.90–1.02), $P = 0.18$
All participants ($\chi^2 = 0.02$; $P = 0.9$)			
<5	116 (0.26)	101 (0.22)	1.16 (0.80–1.68)
≥5 to <10	270 (0.48)	309 (0.55)	0.88 (0.71–1.09)
≥10 to <20	1,054 (0.81)	1,104 (0.86)	0.94 (0.83–1.07)
≥20 to <30	963 (1.01)	941 (0.99)	1.00 (0.89–1.13)
≥30	681 (1.64)	705 (1.70)	0.96 (0.83–1.10)
Overall	3,084 (0.84)	3,160 (0.86)	0.96 (0.92–1.01), $P = 0.16$



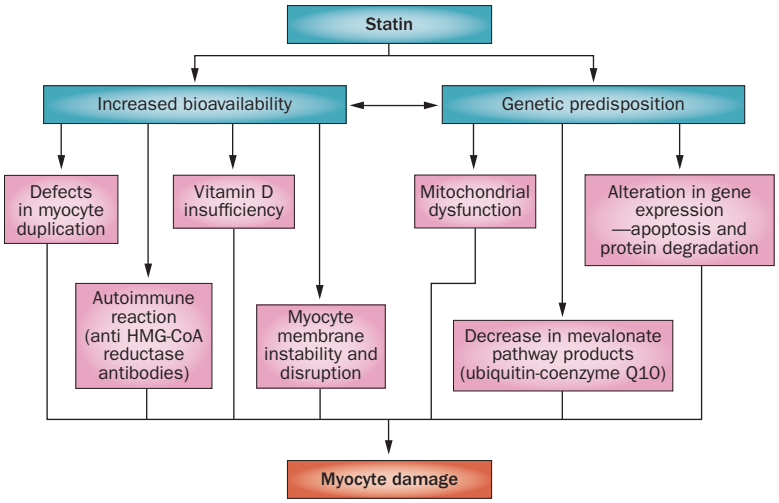


Figure 2 | Possible mechanisms to explain the aetiology of statin-induced myopathy. Abbreviation: HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A.

baseline), women, and those with an initially low level of LDL cholesterol, and irrespective of the type of statin.

Several studies have even indicated a potentially beneficial effect of statins in patients with prostate cancer being treated with radiotherapy, but not among patients who have undergone radical prostatectomy.[66] A lack of association between statin use and the risk of bladder[67] or lung[68] cancer has also been reported. The results of studies on statin use and the risk of oesophageal cancer are not consistent, showing either no association or a reduction in cancer risk, particularly in patients with Barrett oesophagus.[69,70] Interestingly, statin use in patients with cancer seems to be associated with reduced cancer-related mortality, but further research into this effect is required.[71]

In meta-analyses, statins have been associated with a small, but significant, 9–13% increase in incident type 2 diabetes, which translates to one new diagnosis of diabetes per 1,000 person-years of statin use.[72,73] However, investigators in the observational Women's Health Initiative,[74] which involved 153,840 postmenopausal women, reported an even larger increase in the risk developing diabetes after statin use (HR 1.71, 95% CI 1.61–1.83). Age seems to be associated with the risk of incident diabetes in individuals taking statins, given that statin-attributable risk is highest in trials involving elderly patients.[73]

Intensive-dose statin use seems to be associated with a higher risk of incident diabetes than does a moderate-dose strategy. A meta-analysis was performed on five trials with a total of 32,752 participants without diabetes at baseline, in which intensive-dose and moderate-dose statin use were compared.[75] For every 1,000 patient-years, two additional cases of diabetes occurred in the intensive-dose group, which led to an odds ratio of 1.12 for new-onset diabetes, but the intensive strategy also produced a 16% reduction in the risk of cardiovascular events.[75] Therefore, the number needed to harm for intensive statin use compared with moderate-dose statin use was 498 for new-onset diabetes per year, whereas the number needed to treat to prevent one cardiovascular event was 155 per year.[75] The benefits of statins far exceed this risk, at least in secondary prevention, where over a 4-year period, nine cardiovascular events can be prevented for every one incident case of diabetes.[75]

Naturally, the increased use of statins in primary prevention has led to concerns about the possible risk of incident diabetes. However, the data are conflicting and controversial. The results of WOSCOPS[76] suggest that the extended use of statins might be associated with a 30% reduction in the incidence of diabetes, although the risk ratio was only marginally significant ($P = 0.042$). In this *post-hoc* analysis, new-onset diabetes was defined as a >36 mg/dl (~2 mmol/l) rise in the blood glucose level above the baseline value, which is inconsistent with the criterion usually used in clinical practice. Conversely, in JUPITER,[40] an increased risk of developing diabetes with rosuvastatin use existed (270 reports by physicians of incident diabetes in the rosuvastatin group compared with 216 reports in the placebo group; $P = 0.01$). However, a subsequent analysis of participants in this trial showed that the small risk of developing diabetes while taking a statin was limited to those who had impaired fasting glucose or multiple components of the metabolic syndrome—that is, those who were already at high risk of developing diabetes.[77] Nevertheless, even in these patients, the absolute benefit of primary prevention with statins on cardiovascular events outweighed the risk of developing diabetes. In primary prevention with statins, the magnitude of the increased risk of incident diabetes is estimated to be >50-fold smaller than the absolute cardiovascular benefit: approximately 0.2 per 1,000 individuals develop diabetes and 11 major cardiovascular events are prevented over a 5-year period.[48] The adverse effects of statins will, inevitably, have an impact on primary prevention of CVD in general, and should be considered when deciding whether to prescribe a statin to an individual at low or moderate risk (without documented CVD, diabetes, or chronic kidney disease).

Statin use in women

Several studies have suggested that the benefits of statin use overall are similar in women and men, but the evidence for protective effects of statin use in primary prevention is weaker in women than in men. Some, but not all, studies have shown that the management of dyslipidaemia is less likely to be optimal in women than in men.[78–81] One meta-analysis, which included eight randomized controlled trials of individuals without previous CVD (19,052 women and 30,194 men, mean follow-up 3.9 years), showed that statin use reduces the risk of CHD events in men, but not women, and does not reduce the risk of overall mortality in either men or women.[82] However, the under-representation of women might mean that these trials were underpowered to detect reductions in cardiovascular events in women. Another meta-analysis showed a beneficial effect of statins in women with moderate hypercholesterolaemia (mean baseline LDL-cholesterol level 144 mg/dl or ~3.7 mmol/l) in preventing CHD events, but no benefit

in preventing all-cause death.[83] However, in a subsequent meta-analysis that showed a 12% relative risk reduction in total mortality with statin use in high-risk individuals without established CVD, the beneficial effect was similar in women and men.

In a meta-analysis of 18 trials with a total of 141,235 participants, the benefit of statins in reducing CVD events and all-cause mortality was not significantly different between women and men, nor between primary and secondary prevention.[84] Indeed, the reduction in mortality was significant for primary prevention in women, and for secondary prevention in men. Therefore, up-to-date guidelines appropriately recommend statins for primary prevention of CVD in women who are at high risk (according to the level of CVD risk calculated using the available risk-scoring systems), similarly as for men.[15]

A sex-specific outcome analysis of JUPITER revealed similar decreases in the LDL-cholesterol and hs-CRP levels, as well as in the relative risk of the combined primary end point (MI, stroke, hospitalization for unstable angina, arterial revascularization, and cardiovascular death), associated with rosuvastatin use in women as in men.[85] This finding clearly indicates the benefit of statin use in primary prevention, even in women at low CVD risk (approximately 5% Framingham risk score, which includes a population that would not generally qualify for statins according to the NCEP-ATP III guidelines). A meta-analysis of 27 randomized trials showed that statin use reduced the rate of major cardiovascular events by 43% (99% CI 14–62%), even among women at very low risk of CVD (5-year risk <5%).[48] The available evidence suggests that the proportional benefits of statin use on cardiovascular events are similar irrespective of sex, but that the absolute benefits are smaller in women than in men. However, a large trial of statins for primary prevention in women is needed.

Statin use in the elderly

Statins should be used for secondary prevention to reduce the risk of CVD in elderly individuals; however, no clear evidence exists that such treatment prolongs life expectancy.[59] Conversely, statin use reduces CVD morbidity in elderly individuals, even in primary prevention.[45] Whether to give statins to elderly individuals who do not have clinical signs of CVD is becoming increasingly important as life expectancy rises and the elderly population expands. Moreover, statins are substantially underutilized in the elderly, despite their high risk of CVD.[86–91]

Early trials of primary prevention with statins included few elderly individuals. In AFCAPS/TexCAPS,[92] 21% of the participants were aged >65 years, and a subgroup analysis on the basis of sex-stratified median age (>57 years in men, >62 years in women) showed no significant difference in CVD-risk reduction with lovastatin use. In ASCOT,[39] the CVD-risk reduction with atorvastatin was not significantly different in those aged <60 years from those aged ≥60 years. In the MEGA trial,[93] which included postmenopausal women aged ≤80 years and men aged 40–70 years, a subgroup analysis showed no significant difference in CVD-risk reduction with pravastatin between those aged <60 years and those aged ≥60 years, despite differences in the prevalence of CVD risk factors. However, statin use produced larger reductions in CVD risk in older women than in younger women.[93]

The PrOspective Study of Pravastatin in the Elderly at Risk (PROSPER)[94] was the first trial designed specifically to investigate the effects of a statin (pravastatin, 40 mg per day) in the elderly (aged 70–82 years), but involved patients with pre-existing vascular disease or those at high risk of CVD, including stroke. Although this trial was not one of primary prevention, no benefit was seen in individuals without previously diagnosed CVD.[94]

In a substudy of JUPITER, the effects of rosuvastatin use or placebo were analysed in a population of 5,695 asymptomatic individuals aged >70 years.[95] Statin use produced a 48% absolute risk reduction in the incidence of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or CVD death in this cohort. The number needed to treat for 4 years to prevent one cardiovascular event was 24, whereas 36 individuals aged 50–69 years would have to be treated to achieve the same outcome.[95] The results of this trial also showed a fairly short time to achieve this benefit. Individuals taking rosuvastatin had higher rates of some adverse effects than those receiving placebo, including incident diabetes, but given that none of these associations was significant, the safety profile of the drug in the elderly was concluded to be acceptable. Importantly, the benefit of statin use was absent in elderly individuals without hypertension.[96]

Two trials with pravastatin introduced speculation that elderly individuals might be at increased risk of incident cancer from statin use. The PROSPER[94] investigators reported an increased overall incidence of cancer in patients who were receiving pravastatin, but the increase in cancer mortality equalled in magnitude the decrease in CVD mortality, which meant that overall mortality was unchanged.[94] The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial[98] also showed an increase in the incidence of cancer in the elderly subgroup, but was not a trial of primary prevention.[98] Furthermore, the WOSCOPS investigators reported an increase in prostate cancer in pravastatin-treated individuals at 10 years after the completion of the trial.[33] However, meta-analyses have shown no effect of statin use on the incidence of, or mortality from, any type of cancer in the elderly.[65,97]

Age has been identified as a risk factor for developing diabetes during extended statin use; therefore, caution should be exercised when prescribing statins, particularly in high doses, to elderly individuals without clinical signs of CVD.[73] The decision whether to give a statin to elderly individuals for primary prevention should balance the benefits and risks of the drug, the problems of polypharmacy, as well as health economic considerations and a patient's wishes. Furthermore, risk-prediction tools are either less accurate than in younger individuals (Framingham), or not applicable in the elderly (SCORE).

A trial of primary prevention with statins in the very elderly (aged >80 years) is, therefore, urgently needed to address these unanswered questions.

Statin use in children

According to the latest guidelines, children aged <10 years should not be given statins unless they have homozygous or severe heterozygous familial hypercholesterolaemia.[99] Statin treatment should be considered in individuals aged 10–21 years who have an LDL-cholesterol level ≥4.9 mmol/l (190 mg/dl), despite management by lifestyle and diet, or who have an LDL-cholesterol level ≥4.1–4.9 mmol/l (160–189 mg/dl) and a family history of premature CVD in first-degree relatives, or at least two other moderate-level CVD risk factors. Statin treatment should even be considered in children who have an LDL-cholesterol level ≥3.4–4.1 mmol/l (130–159 mg/dl) and at least one high-level CVD risk factor, together with at least two moderate-level CVD risk factors. Statin treatment might also be considered, according to these guidelines, for children aged 8–9 years who have an LDL-cholesterol level ≥3.9 mmol/l (190 mg/dl) despite management by lifestyle and diet, and who have several first-degree family members with premature CVD, or at least one high-level CVD risk factor together with at least two moderate-level CVD risk factors.

Three studies from 2002–2007 showed an improvement in vascular dysfunction and regression of carotid intima–media thickness in children with familial hypercholesterolaemia treated with statins, as well as that early initiation of treatment is associated with reduced intima–media thickness.[100–102] However, no hard evidence shows that statin use in children of any age, other than those with homozygous familial hypercholesterolaemia or an extremely high LDL-cholesterol level, prevents cardiovascular events or reduces mortality. All the trials of the use of statins in children to date have been limited to patients with familial hypercholesterolaemia, and have been focused on efficacy and safety rather than clinical outcomes, but several were underpowered even to detect a difference in safety parameters. Therefore, the long-term safety of statin use in children remains an open question.

Whether statin use can be initiated in children aged <8–10 years is unknown, except on the basis of data in anecdotal reports. The benefits of such a strategy are also unclear, although primordial atherosclerotic changes are evident early in life, and statins might prevent the development of atherosclerotic disease and subsequent cardiovascular events.[103]

Primary prevention of stroke

Early studies showed no clear association between an elevated serum LDL-cholesterol level and the incidence of stroke, probably because of the lack of appropriate aetiopathological patient classification (particularly ischaemic and haemorrhagic stroke). However, the significant association between an elevated LDL-cholesterol level and an increased risk of ischaemic, but not haemorrhagic, stroke is now well established.[104] Authors of current guidelines recommend an assessment of total CVD risk to determine the appropriateness of statin use in primary prevention, with the aim to reach the established target LDL-cholesterol level.[15,16] The universal use of statins is recommended in secondary prevention of noncardioembolic ischaemic stroke and transient ischaemic attack, irrespective of whether dyslipidaemia is present.[15,16] These guidelines are founded largely on meta-analysis data, which indicate a 21.1% reduction in the relative risk of stroke for every 39 mg/dl (~1.0 mmol/l) decrease in the LDL-cholesterol level.[105]

However, few trials of primary prevention with statins have been designed to investigate the effects on stroke. Researchers in WOSCOPS,[32] AFCAPS/TexCAPS,[34,35] and the MEGA trial[36–38] showed no significant reduction in stroke with statin use, but a trend towards net benefit was present. ASCOT-LLA[39] was the first primary prevention trial in which a 27% reduction in fatal and nonfatal stroke with atorvastatin was reported.[39] In JUPITER,[40] rosuvastatin use produced a 48% reduction in the risk of incident stroke among apparently healthy individuals with a low LDL-cholesterol level and a high hs-CRP level, which was consistent across all subgroups evaluated, including women.[40] A meta-analysis confirmed these beneficial effects of statins in the primary prevention of stroke, regardless of sex.[84] A previous meta-analysis also showed a beneficial effect of statins on the incidence of stroke, with no within-class differences between various statins, and no increased incidence of rhabdomyolysis or cancer.[106]

A *post-hoc* analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[107] indicated that, despite a clear overall benefit of secondary prevention on stroke recurrence, a small, but significant, increase in haemorrhagic stroke accompanied statin use. Conversely, another study showed that statin use after ischaemic stroke does not increase the risk of intracerebral haemorrhage.[108] This finding was confirmed in a meta-analysis of 31 randomized controlled trials that included a total of 91,588 individuals in the active group, and 91,215 in the control group.[109] Moreover, even a small increase in the risk of haemorrhagic stroke would be outweighed by the reduction in the risk of ischaemic stroke.[48] These data are consistent with the results of a meta-analysis showing that no increase in the rate of intracerebral haemorrhage occurs among patients prescribed statins for primary prevention.[105] Therefore, the use of statins in the primary prevention of ischaemic stroke and transient ischaemic attack seems justified, at least in appropriately selected individuals (Figure 3).

Cost-effectiveness

A number of studies have shown that statins are generally cost-effective for secondary prevention of CVD.[110–112] Fewer studies have been conducted on the cost-effectiveness of statins for primary than for secondary prevention, but a general principle is that cost-effectiveness increases with the risk level of the

population.[113] The widespread availability of low-cost, generic statins has increased the cost-effectiveness of statin use. In one meta-analysis, the number needed to treat with a generic statin (simvastatin) to prevent one death was calculated to be 170, at a cost of approximately US$18,000 over 4.9 years, whereas the number needed to treat to prevent one major coronary event was 79, at a cost of US$9,000.[114] These data suggest that statins are more cost-effective than aspirin or antihypertensive medication in reducing CVD morbidity and mortality in primary prevention.[115,116] When the cost-effectiveness of the ATP III primary prevention guidelines was assessed using a Markov decision-analytic model, the estimation was that statins could prevent 20,000 MIs and 10,000 CHD-related deaths per year in the USA at a cost of US$42,000 per quality-adjusted life year (QALY).[117] When primary prevention strategies on the basis of the European guidelines for CVD prevention were compared with ATP III guidelines, the European guidelines seemed to yield lower costs per CVD-free year of life gained.[118]

Several cost-effectiveness analyses have been performed using data from JUPITER. A Markov model indicated that prescribing rosuvastatin to individuals with an hs-CRP level >2.0 mg/l and an LDL-cholesterol level ≤130 mg/dl (~3.4 mmol/l) for the primary prevention of CVD was cost-effective (US$35,455 per QALY) for individuals with a Framingham Risk Score >10%, but was not cost-effective (US$90,714 per QALY) for individuals with a score ≤10%.[119] However, this analysis was conducted using the price of branded rosuvastatin, not that of the cheaper, generic form that is now available.

A subsequent study, also using a Markov model of the US population, but incorporating the price of low-cost, generic statins, showed that applying maximum-impact prevention strategies would prevent 27,000 CHD-related deaths per year at a cost of US$21,000 per QALY.[120] According to some researchers, this analysis underestimated the extended benefits of statins for primary prevention, because non-CHD cardiovascular benefits were neglected, and only the clinical and economic benefits of low-intensity or moderate-intensity statin use were considered.[121] A European analysis conducted in the Netherlands, however, showed that even with the low prices of generic statins, their use in primary prevention is not cost-effective for low-risk individuals, particularly when nonadherence was taken into account.[122] According to this study, a 10-year period of statin use costs €35,000 (US$49,000) per QALY gained for men aged 55 years with a 10-year CVD risk of 10%, but increases to >€125,000 (US$164,000) for men of the same age with a CVD risk of only 5%.[122] This study, also using a Markov model, was based on the assumption that nonadherence to statin use was high (60% after 3 years). Nevertheless, a study conducted in the USA showed that low-cost, generic statins are cost-effective for the primary prevention of CVD in patients with mild-to-moderate chronic kidney disease and hypertension.[123] At prices <US$0.10 per pill, statins become not only cost-effective, but also cost-saving, in adults at all levels of CVD risk.[117]

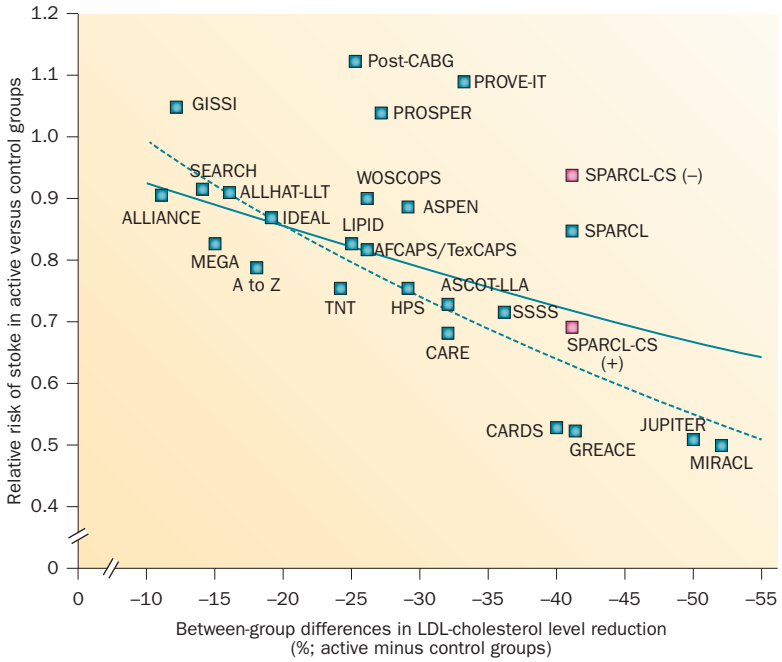


Figure 3 | Association between reduction in LDL-cholesterol concentration and incidence of stroke in major statin trials. Inverse variance-weighted regression lines have been plotted after including all 24 trials (165,792 patients; solid line) and after excluding trials with clearly identified groups of patients in secondary prevention of stroke (SPARCL, and HPS, LIPID, and CARE subgroups with previous cerebrovascular disease; dashed line). Underlying causes of stroke might be important when considering the association between lipid level and stroke risk; therefore, the SPARCL trial results are shown with the inclusion (+) or exclusion (–) of patients with documented carotid stenosis. Abbreviations: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events; GISSI, Gruppo Italino per lo Studio della Sopravvivenza nell'Infarcto Miocardico; GREACE, Greek Atorvastatin and Coronary-Heart-Disease Evaluation; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Though Aggressive Lipid; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; Post-CABG, Post Coronary Artery Bypass Grafting Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; SSS, Scandinavian Simvastatin Survival Study; TNT, Treating to New Targets Study; WOSCOPS, West of Scotland Coronary Prevention Study. Reprinted from Amarenco, P. & Labreuche, J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol.* **8** (5), 453–463 (2009). © With permission from Elsevier.

Conclusions

All the studies on the effects of statins in the primary prevention of CVD indicate that lowering the LDL-cholesterol level produces a modest reduction in overall mortality, at least in the short term, and that substantial decreases in CVD morbidity can be achieved. Moreover, meta-analyses have shown that the reduction in the relative risk of cardiovascular events increases with the

duration of use.[7] However, a clear distinction has to be made between individuals at low or moderate risk and those at high lifetime risk of CVD.[15] Whether those at low or moderate risk benefit from primary prevention with statins is not unequivocally established; however, both men and women in the latter group should be prescribed statins to prevent CVD. This distinction according to the level of risk should be individualized to avoid the prescription of life-long medication to clinically healthy individuals, and also the widespread use of statins causing a dramatic increase in public-health costs without proven cost-effective benefit. Nevertheless, statin use for primary prevention can be cost-effective, especially for individuals at high risk of CVD, particularly when low-cost, generic statins are used. However, further data are needed on the efficacy of statins for primary prevention in individuals at low or moderate risk of CVD.

Review criteria

A search for original articles published in 1990–2012 was performed in the PubMed database using the following key terms, either alone or in combination: "statins", "primary prevention", "adverse effects", "cancer", "incident diabetes", "rhabdomyolysis", "elderly", "women", "children", "stroke", "cost-effectiveness". All articles identified were English-language, full-text papers. The reference lists of identified articles were also searched and the 'related articles' search function in the PubMed database was used to find additional relevant papers.

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