Non-cardiovascular effects associated with statins

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ABSTRACT

Statins form the pharmacologic cornerstone of the primary and secondary prevention of atherosclerotic cardiovascular disease. In addition to beneficial cardiovascular effects, statins seem to have multiple non-cardiovascular effects. Although early concerns about statin induced hepatotoxicity and cancer have subsided owing to reassuring evidence, two of the most common concerns that clinicians have are myopathy and diabetes. Randomized controlled trials suggest that statins are associated with a modest increase in the risk of myositis but not the risk of myalgia. Severe myopathy (rhabdomyolysis) is rare and often linked to a statin regimen that is no longer recommended (simvastatin 80 mg). Randomized controlled trials and meta-analyses suggest an increase in the risk of diabetes with statins, particularly with higher intensity regimens in people with two or more components of the metabolic syndrome. Other non-cardiovascular effects covered in this review are contrast induced nephropathy, cognition, cataracts, erectile dysfunction, and venous thromboembolism. Currently, systematic reviews and clinical practice guidelines indicate that the cardiovascular benefits of statins generally outweigh non-cardiovascular harms in patients above a certain threshold of cardiovascular risk. Literature is also accumulating on the potential non-cardiovascular benefits of statins, which could lead to novel applications of this class of drug in the future.

Introduction

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) form the pharmacologic cornerstone of the primary and secondary prevention of atherosclerotic cardiovascular disease. More than 200 million people worldwide take these drugs, including more than 30 million in the United States.[1]
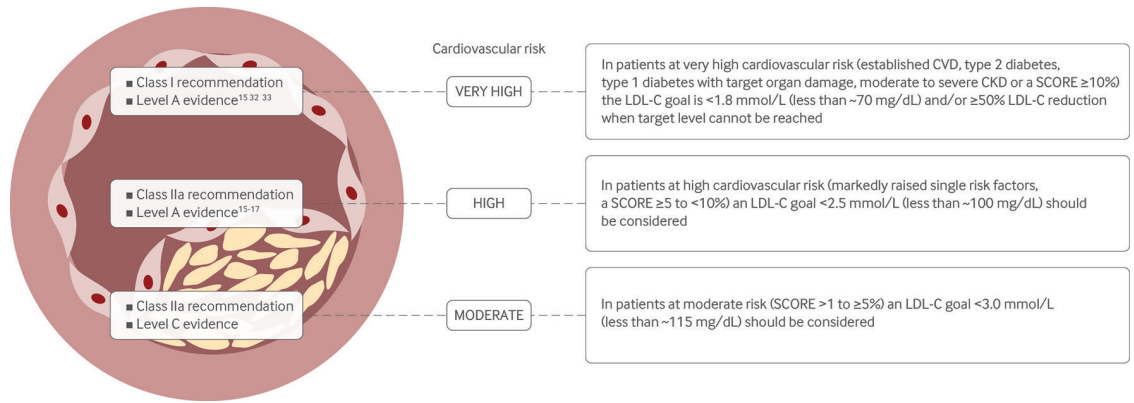
In randomized controlled trials (RCTs) and meta-analyses of primary and secondary prevention, statins have produced a significant reduction in incident myocardial infarction, stroke, and death from cardiovascular disease in all patients, and all-cause mortality in higher risk patients.[2-4] As well as lowering low density lipoprotein cholesterol (LDL-C), statins are also thought to have anti-inflammatory and direct effects on plaque, leading to coronary plaque stabilization and even modest regression of atheroma.[5] Figures 1 and 2 show the most recent guidelines for statin use in Europe and the US.[6 7]

When used for primary prevention, statins are generally prescribed to asymptomatic people for a prolonged period of time. Therefore, the risks must be carefully weighed against the benefits. As well as lipid lowering properties, statins are thought to exert additional effects, known as pleiotropic effects. The pleiotropic benefits of statins may be mediated by a reduction in systemic inflammation, endothelial dysfunction, and platelet hyper-reactivity.[8 9]

SCOPE, SOURCES, AND SELECTION CRITERIA

We searched PubMed for articles published from 4 November 1994 (publication of the Scandinavian Simvastatin Survival Study, the first large randomised controlled trial to describe the effects of statins on clinical outcomes) to 20 March 2014. We used the following search terms and their MeSH terms in strategic combinations to identify relevant articles: "statins", "side effects," "muscle toxicity," "myopathy," "rhabdomyolysis," "diabetes," "liver toxicity," "hepatotoxicity," "dementia," "cognition," "cognitive function," "memory loss," "venous thromboembolism," "acute kidney," "contrast nephropathy," "pancreatitis," "cancer," "chronic obstructive pulmonary disease" and "erectile dysfunction." The authors and editors agreed to focus on these outcomes when the review was commissioned in September 2013, and other outcomes—in particular, neuropathy, amyotrophic lateral sclerosis, lupus, energy, depression, anger, suicidal behavior, and sleep—were considered beyond the scope of the review. We agreed to prioritize the highest grades of evidence—randomized controlled trials, meta-analyses, and systematic reviews. Conclusions were based on the knowledge available in such reports and resources were not available to evaluate the extent of hidden data. Studies were also identified from the references of the trials and meta-analyses. Finally, our reference list was modified on the basis of comments from peer reviewers.

Fig 1 | European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemia.[6] CKD=chronic kidney disease; CVD=cardiovascular disease; LDL-C=low density lipoprotein-cholesterol; SCORE=10 year systematic coronary risk estimation

Cardiovascular risk

- Class I recommendation
- Level A evidence[15 32 33]

VERY HIGH — In patients at very high cardiovascular risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached

- Class IIa recommendation
- Level A evidence[15-17]

HIGH — In patients at high cardiovascular risk (markedly raised single risk factors, a SCORE ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered

- Class IIa recommendation
- Level C evidence

MODERATE — In patients at moderate risk (SCORE >1 to ≥5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered

Conversely, statins could have harmful effects through excessive cholesterol lowering or through other mechanisms. Although statins are well tolerated by most patients, there are widespread concerns about the potential harms associated with their use. Non-cardiovascular harms associated with statins in clinical trials include myopathy and diabetes, and non-cardiovascular benefits include reduced incidence of contrast nephropathy and pancreatitis. Careful accounting for the spectrum of statin effects in future clinical trials and registries could help identify groups of patients who are most likely and least likely to have each type of effect.

This review aims to provide a balanced evaluation and critique of the available evidence on these and other potential non-cardiovascular harms and benefits associated with the use of statins.
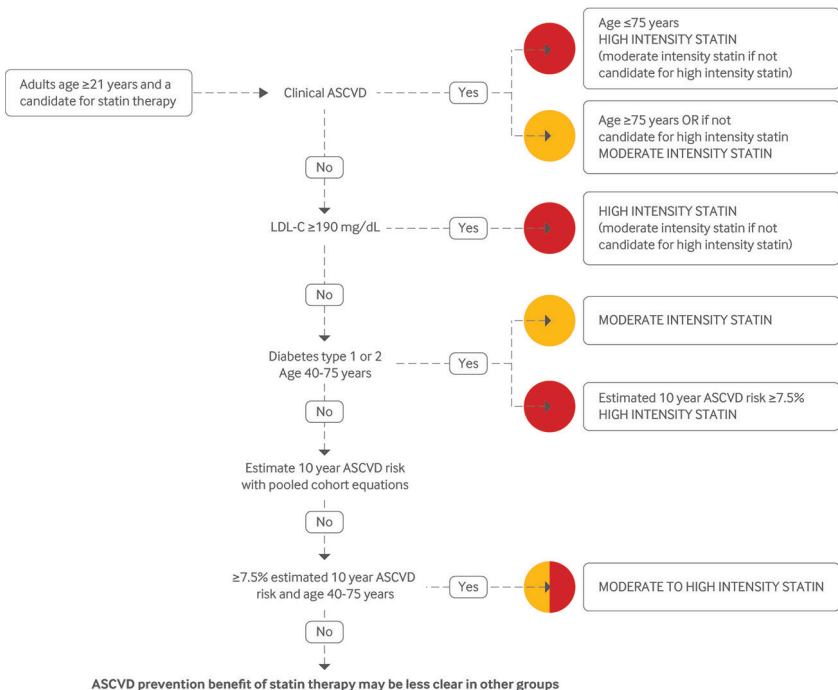
Myopathy

Myopathy occurs in several different forms and the specific definition varies across studies. Rhabdomyolysis is the most severe manifestation of myopathy associated with statins. It is often defined as a creatine kinase concentration at least 40 times greater than the upper limit of normal or increased creatine kinase in association with renal failure.[10 11] Myositis (myopathy) is defined as muscle pain in association with a creatine kinase concentration greater than 10 times the upper limit of normal. Myalgia refers to muscle pain without an increase in creatine kinase.

The Cholesterol Treatment Trialists' (CTT) collaboration conducted a meta-analysis of individual patient level data from 26 RCTs of statin treatment with more than 170 000 patients.[4] The CTT analyzed cases of rhabdomyolysis from the individual trials. The five trials that compared higher versus lower intensity treatment (high intensity treatment is expected to lower LDL-C by ≥50%, moderate intensity by 30-45%) found an excess risk of 4 per 10 000 people treated (14 v 6 cases). In the 21 trials of statin versus placebo, there was an excess risk of rhabdomyolysis of 1 per 10 000 people treated (14 v 9 cases). In the two trials that compared simvastatin 80 mg with 20 mg, all of the excess cases of rhabdomyolysis occurred with the higher versus lower intensity treatment.[12 13] The overall incidence of excess cases of myositis and rhabdomyolysis is estimated at 0.5 per 1000 person years and 0.1 per 1000 person years, respectively.[13]

A systematic review of 35 statin trials (74 102 patients) examined the risks of myopathy associated with statin use.[14] In 16 trials (68 110 patients) that reported rhabdomyolysis, no significant increase was seen in patients allocated to statin versus placebo (relative risk 1.09, 95% confidence interval 0.65 to 1.83). Furthermore, almost 60% of the cases of rhabdomyolysis occurred in patients concurrently taking drugs that are known to interact with statins, such as fibrates. Sixteen trials (41 457 patients) reported increases in creatine kinase according to study specific thresholds, with or without muscle pain, but this increase was also not associated with statin therapy (1.18 compared with placebo, 0.89 to

ASCVD STATIN BENEFIT GROUPS

Heart healthy lifestyle habits are the foundation of ASCVD prevention. In people not receiving cholesterol lowering drugs, recalculate estimated 10 year ASCVD risk every 4-6 years in those aged 40-75 years without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

Adults age ≥21 years and a candidate for statin therapy → Clinical ASCVD → Yes →
- Age ≤75 years HIGH INTENSITY STATIN (moderate intensity statin if not candidate for high intensity statin)
- Age ≥75 years OR if not candidate for high intensity statin MODERATE INTENSITY STATIN

No → LDL-C ≥190 mg/dL → Yes → HIGH INTENSITY STATIN (moderate intensity statin if not candidate for high intensity statin)

No → Diabetes type 1 or 2 Age 40-75 years → Yes →
- MODERATE INTENSITY STATIN
- Estimated 10 year ASCVD risk ≥7.5% HIGH INTENSITY STATIN

No → Estimate 10 year ASCVD risk with pooled cohort equations

No → ≥7.5% estimated 10 year ASCVD risk and age 40-75 years → Yes → MODERATE TO HIGH INTENSITY STATIN

No → **ASCVD prevention benefit of statin therapy may be less clear in other groups**

In selected individuals, consider additional factors that may influence ASCVD risks and potential ASCVD risk, benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment

- HIGH INTENSITY - daily statin treatment lowers LDL-C by ≥50%
- MODERATE INTENSITY - daily statin treatment lowers LDL-C by 30% to <50%

Fig 2 | American Heart Association/American College of Cardiology guidelines for the management of blood cholesterol.[7] ASCVD=atherosclerotic cardiovascular disease; LDL-C=low density lipoprotein-cholesterol

1.56). Myalgias without a documented increase in creatine kinase were reported in 21 studies of 48 138 patients. The relative risk of myalgias with statins compared with placebo was 0.99 (0.96 to 1.03). When examined individually, only atorvastatin was associated with a greater incidence of myalgias when compared with placebo (5.1% v 1.6%; relative difference per 1000 patients 31.9, 2.1 to 61.6; P=0.04).

In the aforementioned study, cerivastatin was analyzed separately (four trials, N=total 2282; 1898 randomized to cerivastatin, 384 randomized to placebo). Treatment with cerivastatin compared with placebo resulted in a 12-fold increased risk of rhabdomyolysis (risk difference 12.4, 5.4 to 19.3; P<0.001).[14] Cerivastatin was withdrawn from the market in 2001 because of the observed increase in rhabdomyolysis.

A third more recent meta-analysis of statin use for primary and secondary prevention also assessed myopathy.[15] Among 14 primary prevention trials (46 262 patients), nine reported myalgias (no increase in creatine kinase) in people taking statins versus placebo. There was no significant difference between the groups (7.9% v 7.6%; absolute risk increase with statins 0.3, −0.2 to 0.8; P=0.41). There was also no significant increase in myositis (0.3% with statins and 0.2% with placebo (0%, −0.1% to 0.1%; P=0.10)) and no increase in rhabdomyolysis (three cases each with statin and placebo; P=0.96).

These meta-analyses of RCT data suggest that statins are associated with a modest increase in the risk of myositis and rhabdomyolysis, but not with myalgia. The risk is largely confined to treatment with high dose statins, particularly simvastatin 80 mg, which is no longer recommended, with the US Food and Drug Administration advising that its use is limited.[16] Statin associated myopathy also occurs at a higher rate in patients who are concurrently prescribed drugs that interact with statins to increase their effective blood level.

Concerns and criticisms

Despite these generally reassuring data from randomized trials there remains widespread concern regarding statin myopathy. Much of the concern arises from uncontrolled observational studies where the incidence of statin associated myalgias is reportedly higher than that reported in randomized trials. In a cross sectional observational study of 3580 adults in the US national health and nutrition examination survey, the prevalence of any musculoskeletal pain in the previous 30 days in statin users and non-users was 22.0% and 16.7%, respectively (odds ratio 1.50, 18.0 to 26.7%; P=0.01).[17] Among 7924 consecutive patients taking a statin in France, the Prediction of Muscular Risk in Observational conditions (PRIMO) study reported that 10.5% of patients reported musculoskeletal pain.[18] Randomized trials have also reported a similarly high incidence of muscle symptoms, but with no difference seen between the statin and placebo treated groups. Over a median five years of follow-up in the Heart Protection Study (HPS),[19 20] 33% of patients allocated to simvastatin and placebo reported muscle pains at some point during the study, and no difference was seen between the groups.

Common criticisms of statin trials are that intolerant patients and patients with chronic kidney disease are excluded.[21] Although some studies such as the HPS and the Treat to New Targets (TNT)[22] study of atorvastatin did have a run-in period, several others did not, including the Scandinavian Simvastatin Survival Study,[23] Air Force/Texas Coronary Atherosclerosis Prevention Study,[24] and the West of Scotland Coronary Prevention Group.[25] Overall, the largest statin trials did not have a run-in phase, whereas most of the moderate to large trials did.

Another common criticism of the external validity of statin trials is that patients with kidney disease have a higher incidence of adverse events and are excluded. In A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), 2776 patients on chronic hemodialysis were randomly assigned to rosuvastatin or placebo.[26] Although the trial did not meet its primary endpoint for efficacy, there was no increase in adverse events with rosuvastatin, including musculoskeletal side effects (22% in statin group, 24% in placebo group; P=0.28) or rhabdomyolysis (three cases in the statin group, two in the placebo group; P=0.66; confidence intervals not reported for either outcome).

More recently, there has been concern about the effect of statins on muscle strength and function. In the Effects of Statins on Skeletal Muscle Function and Performance (STOMP) study, 420 patients were randomly assigned to atorvastatin 80 mg or placebo and followed for six months.[27] The average creatine kinase value rose by 20.8 U/L (1 U/L=0.02 μkat/L) in patients taking atorvastatin (P<0.01 compared with placebo), although none of the values rose to more than 10 times the upper limit of normal, which is indicative of myositis. There was a borderline statistically significant almost two-fold increase in the frequency of myalgias in the atorvastatin versus placebo group (19 v 10; P=0.05; confidence interval not reported). Reassuringly, atorvastatin had no detrimental effect on muscle strength or exercise performance.

Genetic susceptibility to myopathy

Much research has focused on the identification of patients with increased genetic susceptibility to statin myopathy. A genome-wide association study investigated 85 patients with definite simvastatin induced myopathy and 90 controls.[28] A single nucleotide polymorphism in *SLCO1B1*, which encodes an organic anion transporter that regulates the hepatic uptake of statins, was strongly associated with statin induced myopathy. Genetic variants of *SLCO1B1* lead to reduced hepatic uptake and increased levels of statins in the blood, providing the mechanism for increased risk of myopathy. Each copy of the minor allele was associated with a four-fold increased risk of myopathy. When replicated among the 16 664 patients who were genotyped in the HPS, the relative risk for simvastatin induced myopathy associated with each copy of the minor allele was 2.6 (1.3 to 5.0).

Several subsequent reports have confirmed a role for polymorphisms in *SLCO1B1* in statin induced myopathy.[29 30] Interestingly, no association between single nucleotide polymorphisms in *SLCO1B1* and myopathy was seen in a study of patients taking atorvastatin.[31] Therefore, the association between genetic polymorphisms and statin induced myopathy seems to be statin specific, and further research is needed to determine whether genotype guided dosing would help reduce statin myopathy.

Re-challenge

Recent observational data show that most patients who develop symptoms while taking a statin can be safely restarted on a statin. In a cohort of 1605 consecutive patients referred to the Cleveland Clinic for statin intolerance, 1163 (73%) were able to tolerate at least intermittent dosing of a statin for a median of 31 months.[32] Among patients who were able to tolerate statins, 1014 (87%) tolerated daily dosing and the remainder tolerated intermittent dosing. Patients who could tolerate intermittent dosing had a significantly greater reduction in LDL-C compared with intolerant patients (21.3% (standard deviation 4.0%) and 8.3% (2.2%) reduction, respectively; P<0.001). Kaplan-Meier estimates showed that patients who could tolerate any statin dose also had a borderline significant decrease in all-cause mortality (P=0.08). Rosuvastatin was the most commonly tolerated statin in this study.

Similarly, in an observational cohort of 6579 patients whose statin was discontinued because of side effects, 92% of patients could tolerate a statin when "re-challenged."[33] In this cohort, 27% of patients whose statin was discontinued had a documented muscle related side effect, yet nearly all of these patients were able to tolerate a re-challenge. The fact that symptoms often do not recur on re-challenge suggests that they are unrelated to the statin.

Diabetes

Randomized trials have shown a consistent increase in the risk of incident diabetes associated with statin therapy. Although the mechanism underlying this association is unclear, inhibition of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme) reductase and the resulting reduced expression of insulin sensitive glucose transporter type 4 probably play an important role in impaired glucose metabolism.[34 35] Experimental data suggest that statins may also reduce pancreatic β cell function and promote β cell apoptosis, thereby leading to reduced insulin secretion.[36 37]

In the Justification for the Use of Statins in Primary Prevention (JUPITER) study, patients were randomly assigned to rosuvastatin 20 mg daily or placebo.[2] Incident diabetes reported by a physician was a prespecified secondary endpoint in the trial protocol, and all patients with diabetes were excluded from the trial. Over a median of 1.9 years of follow-up, the frequency of incident diabetes was significantly higher with rosuvastatin than with placebo (3.0% v 2.4%, P=0.01; confidence intervals not reported). In people diagnosed with diabetes, the time to diagnosis was only five weeks earlier in those taking rosuvastatin than in those taking placebo.

A subsequent meta-analysis of 13 statin trials included 91 140 patients without diabetes who were randomly assigned to statin or placebo.[38] Over a mean follow-up of four years (weighted average of trials), significantly more patients taking a statin developed incident diabetes (4.9% v 4.5%; odds ratio 1.09, 1.02 to 1.17; number needed to harm (NNH) 250).

A more recent meta-analysis found that the association between statins and incident diabetes is influenced by the dose and potency of statin.[39] The meta-analysis looked at 32 752 patients without baseline diabetes from five statin trials, all of which compared high versus moderate intensity statin therapy. The definitions of diabetes varied across studies, with only TNT[22] and the Incremental Decrease in Clinical Endpoints through Aggressive Lipid Lowering (IDEAL) trial measuring fasting plasma glucose within the trial protocol.[40] Compared with moderate dose statin treatment, intensive dose statins were associated with a 12% increase in the odds of incident diabetes (1.12, 1.04 to 1.22).

The increased risk of incident diabetes associated with statins seems to be confined mainly to people who are already at high risk of diabetes. In JUPITER, 486 diabetes events occurred during follow-up and 77% of events occurred in patients with impaired fasting glucose before randomization.[41] Furthermore, all of the incident diabetes events occurred in patients who had at least one risk factor for diabetes: impaired fasting glucose, body mass index greater than 30, metabolic syndrome, or glycated hemoglobin greater than 6.0% (42 mmol/mol). For trial participants with at least one of the four major risk factors, 134 vascular events or deaths were avoided for every 54 diabetes events. Among trial participants with no major risk factors for diabetes, 86 vascular events or deaths were avoided with no diabetes events. Both groups had significant reductions in relative risk for the primary outcome of major vascular events with rosuvastatin (39% in those with at least one diabetes risk factor, 52% in those with no diabetes risk factors).

Statin trials to date are limited by non-uniform methods of diagnosis and lack of systematic evaluation of diabetes, so additional trial data are needed to clarify the association between statins and the risk of diabetes. However, available data suggest a modest increase in the risk of diabetes with statin therapy, particularly with higher intensity regimens in people with two or more components of the metabolic syndrome. The most recent US guidelines acknowledge the increased risk of diabetes with statins and recommend that individuals on statin therapy be evaluated for new onset diabetes according to current diabetes screening guidelines[7]; there are no specific recommendations based on the intensity of statin therapy.

Liver

Statins are thought to influence liver chemistry by changing lipid metabolism, a phenomenon also seen with other lipid lowering agents.[42]

A meta-analysis of 49 275 patients from 13 placebo controlled clinical trials, 27 276 of whom received a statin, examined the effects of statins on liver toxicity.[43] Five of the trials evaluated pravastatin (n=26 19), four evaluated lovastatin (n=16 085), two evaluated fluvastatin (n=2106), and two trials evaluated simvastatin (n=5065). Over a mean follow-up of 3.6 years, the incidence of liver transaminase levels greater than three times the upper limit of normal in patients treated with any statin and placebo were 1.14% and 1.05%, respectively (odds ratio 1.26, 0.99 to 1.62). When the statins were considered individually, only fluvastatin led to a significant rise in transaminase levels compared with placebo (1.13% v 0.29%; 3.54, 1.1 to 11.6).

A subsequent meta-analysis examined the association between levels of liver transaminases and the size of the reduction in LDL-C with statins.[44] The analysis used the summary data of 75 317 patients in 23 statin treatment arms from 16 RCTs. Among the 23 treatment arms, five

evaluated lovastatin, five evaluated simvastatin, six evaluated pravastatin, one evaluated fluvastatin, and six evaluated atorvastatin. No association was seen between per cent lowering of LDL-C and transaminase increases (R^2 for correlation <0.001; P=0.91). When examined by statin dose, the incidence of increased transaminase for a 10% reduction in LDL-C per 100 000 person years of follow-up for high dose, intermediate dose, and low dose statins was 271, 195, and 114, respectively (P<0.001 for pair-wise comparisons). The association was consistent across each specific statin; for example, high dose atorvastatin was associated with a fourfold greater risk of abnormal liver transaminase levels than low dose atorvastatin (P<0.001).

No cases of liver failure occurred in either meta-analysis of clinical trials. Only 30 cases of statin induced liver failure were reported between 1987 and 2000 in the Western world.[45] The rate of liver failure in statin users is estimated at one case per million person years of use, similar to that in the overall US population.[42]

Among patients who experience increases in alanine aminotransferase while on statins, levels tend to normalise despite continuation of treatment, perhaps because of a reduction in hepatic steatosis.[42 46] Furthermore, this increase in alanine aminotransferase may represent adaptation of the liver to the lower serum cholesterol, rather than direct hepatotoxicity.[47]

Available data suggest that moderate and high dose statins are associated with modestly increased liver transaminases, but that this increase is asymptomatic and generally reversible.

In 2012, the FDA revised the product label for statins, and it no longer recommends routine monitoring of liver function tests in patients taking statins. The US guidelines [7] recommend that baseline transaminase levels should be checked before initiation of statin treatment, and subsequent testing should be done only in the presence of symptoms suggestive of hepatic disease. There is no recommendation for routine periodic monitoring.

Cataracts

Recently, there has been concern that statins may increase the incidence of cataracts. Statins reduce oxidative stress but may also prevent proper epithelial cell development in the lens, thereby providing a potential mechanism for cataracts.[48] Another possible mechanism is that the lens is a mostly avascular structure that relies on endogenous synthesis to meet its cholesterol demands.

RCTs, however, have not shown an association between statins and cataracts. In the Expanded Clinical Evaluation of Lovastatin (EXCEL) trial, 8032 patients were randomly allocated using a parallel group method to lovastatin 40 mg or 20 mg once or twice daily or placebo.[49] Patients underwent slit lamp examination at baseline and at 48 weeks of follow-up. No significant differences were seen between the statin and placebo groups in ocular opacities, visual acuity, cataract extraction, or spontaneously reported ophthalmologic experience.

A subsequent RCT randomized 539 patients to simvastatin 40 mg daily, simvastatin 20 mg daily, or placebo. Detailed ophthalmic assessment at six and 18 months found no significant differences between the groups in any of the measures, including refractive measures, intraocular pressures, and the Oxford grading system of cataracts.[50]

However, although these randomized studies have minimal bias and confounding, they are limited by a relatively brief duration of follow-up.

More recently, observational studies have reported conflicting results for the association between statin use and incident cataracts. A population based study that followed 1299 participants taking statins for five years found that the age adjusted risk for cataracts was 45% lower than in non-users.[51]

Another population based study of more than two million people in the United Kingdom found a 16-40% increased risk of cataracts with statin use.[52] Like all observational studies, however, these studies are inherently limited by "healthy participant" and prescription bias; people who seek medical care are more likely to take statins and less likely to develop medical problems. Thus, for now, there is no robust evidence from randomized trials that statins increase the incidence of cataracts, although the data are limited.

Dementia and cognition

In 2012, the FDA added a warning to the statin product label stating that some patients may experience "ill-defined memory loss" and "confusion." This warning was based mainly on small randomized trials and observational data, including case reports. Since then, the fears of cognitive decline associated with statins have been popularized in the media.[53 54]

Several potential mechanisms have been proposed to explain the association between statins and cognitive function. Excessive inhibition of cholesterol synthesis may impair the integrity of neuronal cell membranes. Lipophilic statins that cross the blood-brain barrier (such as simvastatin and atorvastatin) may also have direct adverse effects on neurons.[55] Conversely, statins may have a beneficial effect on cognition through multiple mechanisms, including improved endothelial function, reduction in free radical formation, and reduction in inflammation.[56] Statins also reduce the incidence of clinical atherosclerotic cardiovascular disease, which is a risk factor for vascular dementia.[3]

RCTs have generally reported null effects on dementia and cognition. The Prospective Study of Pravastatin in the Elderly (PROSPER) trial randomly assigned 5804 adults aged 70-82 years to pravastatin or placebo for a mean follow-up time of 3.5 years.[57] Cognitive function was a prespecified outcome in this trial and was assessed using a battery of neuropsychological tests, including the mini-mental state examination and additional tests of executive function, processing speed, and memory. Cognitive function was assessed before randomization, at baseline, nine months, 18 months, 30 months, and at the end of the study. In this older cohort, cognition declined in all patients, regardless of allocation to statin or placebo, with no difference seen between the groups (P>0.3 for all comparisons).[58]

The HPS also assessed cognitive function, although not at baseline, and only by telephone survey at the time of study completion.[19] Similar to PROSPER, no significant difference in cognition was seen with simvastatin versus placebo.

A recently published systematic review and meta-analysis of randomized trials and rigorous observational studies examined the short term (<1 year) and long term (≥1 year) association between statins and cognition in people without

baseline cognitive dysfunction.[59] For short term cognition, three studies (296 participants) met the inclusion criteria. No significant difference was seen in short term cognition in people taking statins (mean change in digit symbol substitution test 1.65, −0.03 to 3.32).

Eight studies were available for quantitative analysis of long term cognition (23 433 participants in total); three showed no association and five showed benefit in people taking statins. Over a mean follow-up of 6.2 years (range up to 24.9 years), the pooled estimated hazards ratio for the association between statin use and dementia was 0.71 (0.61 to 0.82).

Another recent systematic review of 10 cohort studies of statin users versus non-users reported a 21% decreased risk of Alzheimer's disease (0.79, 0.63 to 0.99) and no increase in the risk of mild cognitive impairment.[60]

Patients with pre-existing chronic kidney disease who take statins are a specific subgroup of interest with regard to dementia and cognitive dysfunction. In the Lipid lowering and Onset of Renal Disease (LORD) study, 57 patients with baseline creatinine greater than 1.4 mg/dL (1 mg/dL=88.4 μmol/L) were randomly assigned to atorvastatin 10 mg daily or placebo and followed for 12 weeks.[61] Neuropsychological testing, which focused on attention and concentration, was performed at baseline and at 12 weeks. No significant difference was seen between the atorvastatin and placebo groups on any of the parameters. Although limited by a small sample size and relatively brief duration of follow-up, this analysis adds to the growing body of evidence that statin use is not associated with short term cognitive dysfunction.

We believe that the next step is a randomized trial specifically designed to test the question of whether statins prevent dementia; however, such a trial presents major ethical and practical challenges, and no such trials are currently being conducted to our knowledge.

Venous thromboembolism

An important pleiotropic effect of statins is a reduction in vascular inflammation and concentrations of thrombotic factors, including C reactive protein and D-dimer.[62] As a result of these observations, venous thromboembolism was studied as a prespecified endpoint in JUPITER.[63] Among the 17 802 JUPITER participants, 94 venous thromboembolism events occurred over 1.9 years of follow-up. The rates of venous thromboembolism were 0.18 and 0.32 per 100 person years in participants assigned to rosuvastatin and placebo, respectively (hazard ratio 0.57, 0.37 to 0.86).

Similar risk reductions with rosuvastatin were seen for provoked and unprovoked venous thromboembolism.

A meta-analysis of 22 statin trials published in 2012 compared the risk of venous thromboembolism with statins versus placebo; published data were available for only two of the studies (JUPITER and PROSPER[64]). Among 105 759 patients randomly allocated to statin or placebo there was no significant difference in the incidence of venous thromboembolism (0.9% v 1.0%; odds ratio 0.89, 0.72 to 1.01). Limitations of this analysis included the variable dose of statins in the different trials and the reliance on unpublished data.

On the basis of these data it is unclear whether there is an association between statins and venous thromboembolism.

Kidney
Contrast induced nephropathy

Acute kidney injury is a common adverse event in patients who are exposed to iodinated contrast media, which are commonly used in diagnostic and interventional cardiovascular procedures. The mechanism of contrast induced nephropathy is thought to involve hemodynamic changes in renal blood flow and direct tubular toxicity.[65] It has been proposed that statins reduce incident contrast induced nephropathy through inhibition of the reabsorption of contrast media from the urinary space, thereby limiting the inflammatory, apoptotic, and oxidative effects resulting from contrast exposure.[66]

A meta-analysis of seven trials (1399 patients) reported a significant reduction in the incidence of contrast induced nephropathy in patients taking high dose statins compared with low dose statins or placebo.[67] All patients in the studies were undergoing coronary angiography and five studies compared high dose statins with placebo; five studies used atorvastatin and two used simvastatin. In six of the studies, contrast induced nephropathy was defined as an increase in serum creatinine of greater than 0.5 mg/dL or by more than 25%; the seventh study defined it as an increase in creatinine by 0.5 mg/dL in the five days after administration of contrast. Overall, the incidence of contrast induced nephropathy was reduced by 49% with high dose statins (relative risk 0.51, 0.34 to 0.76). The incidence of renal failure requiring renal replacement therapy was very low and not different in the high dose statin and control groups. However, the analysis is limited by variable statin regimens across studies, as well as a lack of power to detect differences in length of hospital stay.

More recent RCTs have shown that even a single high dose of a statin reduces the incidence of contrast induced nephropathy. The Novel Approaches for Preventing or Limiting Events (NAPLES) II study randomly assigned patients with chronic kidney disease undergoing elective coronary angiography to a single high dose of atorvastatin 80 mg (202 patients) or placebo (208 patients).[68] Contrast induced nephropathy occurred in 4.5% of patients in the atorvastatin group and 18% of the placebo group (odds ratio 0.22, 0.07 to 0.69; P=0.005). The effect was not modified by diabetes status or severity of chronic kidney disease.

A more recent trial—the Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Acute Kidney Injury in patients with acute coronary syndromes (PRATO-ACS) trial[69]—randomly assigned 504 patients with acute coronary syndrome who were undergoing early invasive coronary angiography to rosuvastatin or placebo. The incidence of contrast induced nephropathy was 6.7% and 15.1% in the rosuvastatin and placebo groups, respectively (odds ratio 0.38, 0.20 to 0.71, P=0.003).

These randomized trials and meta-analyses suggest that pre-treatment with statins before coronary angiography significantly reduces the incidence of contrast induced nephropathy. Future studies should investigate whether pre-treatment with a statin can reduce the incidence of contrast induced nephropathy in other situations—for example, in the setting of computed tomography scans.

Acute kidney injury

The JUPITER RCT, which compared rosuvastatin 20 mg daily with placebo, found no increase in acute kidney injury

(risk ratio 1.19, 0.61 to 2.31), although confidence intervals could not exclude a twofold increase in risk.[70] An observational study of more than two million statin prescriptions in Canada, the UK, and US compared the incidence of acute kidney injury in patients prescribed high dose versus low dose statins.[71] Using propensity score matching, in patients without existing chronic kidney disease, the study reported a 34% increased risk for hospital admission for acute kidney injury at 120 days with high dose versus low dose statins (rate ratio 1.34, 1.21 to 1.43).

The observational nature of this study means that it is limited by confounding by indication, whereby sicker patients are more likely to be prescribed high dose statins. Indeed, among patients taking high dose statins who did not have chronic kidney disease, 6.2% of statin users had heart failure compared with 4.5% of non-users. Among statin users with chronic kidney disease, 31% had a diagnosis of heart failure, compared with only 24% of non-users. Therefore, the effect of high dose statins on incident acute kidney injury remains unclear and requires additional study.

Pancreatitis

A reduction in the cholesterol content of bile, with a resulting decreased risk of gallstones, is proposed as a potential mechanism for the effect of statins on the risk of acute pancreatitis.[72]

A meta-analysis of published and unpublished clinical trials investigated the risk of pancreatitis in patients allocated to statins versus placebo.[73] In 16 placebo controlled trials of 113 800 patients followed over a weighted mean follow-up of 4.1 years, 134 people taking statins and 175 people taking placebo developed pancreatitis (relative risk 0.77, 0.62 to 0.97) and a number needed to treat of 1175 over five years.

Similar to venous thromboembolism, pancreatitis was not a prespecified outcome in statin trials and published data were available for only two of the studies. Despite these limitations, this meta-analysis suggests that statins reduce the incidence of pancreatitis.

Erectile dysfunction

Several studies have investigated the association between statins and erectile dysfunction, with the hypothesis that statins improve erectile function through beneficial effects on the endothelium and increased availability of nitric oxide.[74] In animal models, administration of atorvastatin is associated with improved erection through modulation of penile RhoA-Rho kinase, a pathway that is particularly important in patients with diabetes.[75] There is a concern, however, that statins could theoretically worsen erectile function in some men through decreased synthesis of testosterone.[76]

The Erectile Dysfunction and Statins Trial randomly assigned 173 patients with erectile dysfunction to simvastatin 40 mg or placebo and followed participants for a median of 30 weeks.[77] No significant difference was seen between the groups in questionnaire measured erectile dysfunction (1.28 v 0.07; P=0.27). Patients allocated to simvastatin had a significant improvement in male erectile dysfunction specific quality of life (5% v 2%; P=0.04), although this was a secondary outcome in a trial with a null primary result.

On the basis of these data, no definitive conclusion can be drawn on the effect of statins for erectile dysfunction and further research is needed.

Chronic obstructive pulmonary disease (COPD)

Inflammation is an important component of the pathophysiology of COPD and it is hypothesized that statins may improve outcomes in COPD and resulting secondary pulmonary hypertension through a reduction in neutrophil numbers, T cell activation, and synthesis of endothelin 1.[78] [79]

Two small RCTs have assessed the effect of statins in patients with COPD and secondary pulmonary hypertension. The first randomly assigned 53 patients with COPD and pulmonary hypertension to pravastatin 40 mg daily or placebo and followed them for six months.[80] The primary outcome was exercise time on a six minute walk test. Patients allocated to pravastatin experienced a mean increase in exercise time of 346 seconds, compared with no change in the placebo group (P<0.001). Patients allocated to pravastatin also had significantly lower scores on the subjective Borg dyspnea questionnaire and a mean decrease of 7 mm Hg echocardiographic pulmonary artery systolic pressure. The study was not powered to detect differences in clinical outcomes such as mortality.

The second trial randomly assigned 45 patients with COPD and pulmonary hypertension to atorvastatin or placebo and followed them for six months.[81] No significant differences in six minute walk time or pulmonary artery systolic pressure were seen between the two groups.

A systematic review of mainly observational data showed a reduction in COPD related mortality and exacerbations,[82] although these findings have yet to be confirmed in clinical trials and thus remain exploratory.

Given the high prevalence of COPD and its associated morbidity and mortality, this is an important question that should be investigated in larger randomized trials.

Cancer

Although individual RCTs have reported an excess incidence of gastrointestinal cancer and breast cancer with statin therapy,[57] [83] meta-analyses of randomized trials have found no association between statins and cancer.

The CTT analyzed the risk of cancer in 27 RCTs of statins.[84] Among 67 258 patients allocated to statin and 67 279 patients allocated to placebo for a median of five years, the incidence of any cancer was 1.4% per year in both groups (relative risk 1.00, 0.96 to 1.05). Cancer mortality was 0.5% in both groups and no effect was seen at higher doses of statins. There was also no difference between the groups at 23 individual sites or when cancer was considered in total.

These data from a large, individual patient meta-analysis of randomized trials suggests that statins do not cause an excess risk of cancer.

Fatigue

JUPITER is currently the largest RCT to have assessed the effect of statins on fatigue (n=17 802). The rate of fatigue was nearly identical in patients treated with placebo or rosuvastatin (1.7/100 person years for placebo v 1.8/100 person years and 1.6/100 person years for patients with on-treatment LDL-C levels of <50 mg/dL or ≥50 mg/dL, respectively).[85]

Similarly, the Oxford Cholesterol Study Group found no significant difference in the report of fatigue in a 152 week RCT of 621 participants allocated to simvastatin 20-40 mg daily versus placebo.[86]

In contrast, a research letter from the University of California, San Diego (UCSD) Statin Study of 1016 participants described modest negative effects of statin on a composite outcome of energy and fatigue with exertion scores (EnergyFatigEx).[87] The EnergyFatigEx score was a tertiary, exploratory outcome that was not prespecified and most of the baseline scores were imputed in a study that has never published its primary outcome. Moreover, selective outcome reporting is an important bias to consider given the appearance of this report in the literature eight years after the trial was completed without publication of the primary trial results. In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), a small proportion of older patients with systolic heart failure allocated to rosuvastatin experienced worsening fatigue, although the clinical significance of this finding is also unclear.[88] In summary, although additional RCT data could further clarify the effect of statins on fatigue, the strongest available data at this time are reassuring.

Randomized versus observational evidence

Many patients experience the onset of symptoms in temporal association with starting a statin. This often leads to patients and healthcare providers suggesting that statins are responsible for a variety of side effects, including myalgias and memory loss, even when there are few or no randomized data to support these claims.

Although this assumption is understandable, the evaluation of subjective side effects using observational data is inherently fraught with bias. This concept is illustrated in a recent "N of 1" study of eight patients who experienced myalgias while being treated with statins.[89] Patients who experienced myalgias or myositis while taking a statin were randomly assigned to receive placebo or to be re-challenged with the same statin; each patient served as his or her own control and alternated between statin and placebo. A weekly visual analog scale was used to measure pain and interference with life. For each patient, there was no significant difference between statin and placebo in myalgia score, and five patients resumed statin therapy. This study design may help elucidate the true effect of statins in individual patients for other potential side effects, such as memory loss.

Balance of benefits and harms

Recent US cholesterol treatment guidelines may increase the number of adults eligible for statin treatment by as many as 13 million.[90]

The new guidelines are based on data from multiple large RCTs and meta-analyses that show significant and consistent reductions in cardiovascular events and all cause mortality with statin use in nearly all populations.[91] In the CTT meta-analysis of 22 trials and 134 537 patients, all patients allocated to statins experienced a 21% relative risk reduction per 1.0 mmol/L of LDL-C lowering, regardless of baseline LDL-C and at all levels of cardiovascular risk.[3] On the basis of those data and our review of the non-cardiovascular effects of statins, for most patients, the benefits of statins far outweigh the harms.

Future research

The renewed emphasis on individualized cardiovascular risk assessment promotes an evidence based discussion of the risks and benefits of statin use between patients and clinicians.

Future research should focus on genetic and clinical markers to identify people who may be at higher risk of specific adverse effects associated with statins, an approach that may be particularly promising for myopathy and diabetes. Additional data are needed on the clinical implications of statin related diabetes because it is not yet known whether patients with statin related diabetes are at increased risk of cardiovascular disease, similar to other patients with diabetes, or if that risk is mitigated by the concomitant use of statins.

It is also uncertain whether cessation of statin therapy reverses diabetes and any associated risks in this population. Given the strong patient preferences that are often in play when discussing statin therapy, clinicians could further inform the conversation by modeling the risks of statin therapy. Perhaps this could be done on the basis of clinical characteristics, in a similar way to the estimation of bleeding risk with warfarin therapy.[92]

Earlier statin trials are limited in that effects such as those on diabetes, cognitive function, and erectile dysfunction have only recently come to our attention. Future clinical trials should consider these effects as prespecified outcomes with systematic measurement and adjudication.

Additional data are emerging for effects of statins on sepsis[93] and ventilator associated pneumonia.[94] Undoubtedly, other concerns associated with statins will emerge, particularly as an ever growing proportion of adults becomes eligible for statin treatment. Guidelines from professional societies and advice on drug information labels should adopt a scientific accounting of both benefits and harms, using data from clinical trials and registries to elucidate the frequency of these events and their association with statin use.

Emerging treatments

For those patients who are intolerant to statin therapy or who have persistently raised LDL-C despite statin therapy, there is intense research interest in the development of new agents that block other points of the cholesterol pathway. Nonsense mutations in the proprotein convertase subtilisin/kexin type 9 serine protease gene (*PCSK9*) result in increased clearance of serum LDL, resulting in a 28% lower mean LDL-cholesterol and a 47% reduction in coronary heart disease.[95] On the basis of those data, a synthetic PCSK-9 inhibitor (AMG145) was tested in a phase II RCT in 160 statin intolerant patients.[96] Patients allocated to AMG145 and ezetimibe had a 41-63% reduction in LDL-C compared with 15% with ezetimibe alone (P<0.001). Results of a phase III trial are scheduled for release in 2014. Before incorporation into guidelines, these agents should show not only a reduction in LDL-C, but also a reduction in hard clinical endpoints.

Conclusions

We chose to focus on RCTs and systematic reviews as the highest grade of evidence. On this basis, randomized trials have shown that statins cause a modest increase in the incidence of severe myopathy, but are not associated with a significantly increased risk of myalgias. Muscle toxicity often occurs in the setting of very high dose statins that are no longer recommended (simvastatin 80 mg) or in the presence

FUTURE RESEARCH QUESTIONS

What is the role of genetic markers such as *SLCO1B1* in determining a person's susceptibility to statin induced myopathy?

What is the long term increase in the risk of microvascular and macrovascular complications in statin related diabetes?

Do statins reduce the incidence of long term dementia and improve erectile dysfunction in the setting of a randomized clinical trial?

Can we accurately model the heterogeneity of risks and benefits of statins to support personalized decision making?

Do statins increase the incidence of cataracts when taken over a long period of time?

of drugs that are known to interact with statins—for example, fibrates such as gemfibrozil.

Statins do increase the risk of incident diabetes, although this increased risk is largely confined to patients who have pre-existing risk factors for diabetes, and in the JUPITER trial statins accelerated the time to diagnosis of diabetes by only a mean of five weeks.

Meta-analyses and randomised trials have shown that statins reduce the incidence of contrast induced nephropathy and pancreatitis. Further work is needed to elucidate the association between statins and cognition, erectile dysfunction, COPD, and cataracts.

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