

Statin Safety and Associated Adverse Events A Scientific Statement From the American Heart Association

Connie B. Newman, MD, FAHA, Chair; David Preiss, FRCPath, PhD; Jonathan A. Tobert, MD, PhD, FAHA; Terry A. Jacobson, MD, FAHA, Vice Chair; Robert L. Page II, PharmD, MSPH, FAHA; Larry B. Goldstein, MD, FAHA; Clifford Chin, MD; Lisa R. Tannock, MD, FAHA; Michael Miller, MD, FAHA; Geetha Raghuvver, MD, MPH, FAHA; P. Barton Duell, MD, FAHA; Eliot A. Brinton, MD, FAHA; Amy Pollak, MD; Lynne T. Braun, PhD, FAHA; Francine K. Welty, MD, PhD, FAHA; on behalf of the American Heart Association Clinical Lipidology, Lipoprotein, Metabolism and Thrombosis Committee, a Joint Committee of the Council on Atherosclerosis, Thrombosis and Vascular Biology and Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council

Abstract—One in 4 Americans >40 years of age takes a statin to reduce the risk of myocardial infarction, ischemic stroke, and other complications of atherosclerotic disease. The most effective statins produce a mean reduction in low-density lipoprotein cholesterol of 55% to 60% at the maximum dosage, and 6 of the 7 marketed statins are available in generic form, which makes them affordable for most patients. Primarily using data from randomized controlled trials, supplemented with observational data where necessary, this scientific statement provides a comprehensive review of statin safety and tolerability. The review covers the general patient population, as well as demographic subgroups, including the elderly, children, pregnant women, East Asians, and patients with specific conditions such as chronic disease of the kidney and liver, human immunodeficiency viral infection, and organ transplants. The risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%, and the risk of serious hepatotoxicity is ≈0.001%. The risk of statin-induced newly diagnosed diabetes mellitus is ≈0.2% per year of treatment, depending on the underlying risk of diabetes mellitus in the population studied. In patients with cerebrovascular disease, statins possibly increase the risk of hemorrhagic stroke; however, they clearly produce a greater reduction in the risk of atherothrombotic stroke and thus total stroke, as well as other cardiovascular events. There is no convincing evidence for a causal relationship between statins and cancer, cataracts, cognitive dysfunction, peripheral neuropathy, erectile dysfunction, or tendonitis. In US clinical practices, roughly 10% of patients stop taking a statin because of subjective complaints, most commonly muscle symptoms without raised creatine kinase. In contrast, in randomized clinical trials, the difference in the incidence of muscle symptoms without significantly raised creatine kinase in statin-treated compared with placebo-treated participants is <1%, and it is even smaller (0.1%) for patients who discontinued treatment because of such muscle symptoms. This suggests that muscle symptoms are usually not caused by pharmacological effects of the statin. Restarting statin therapy in these patients can be challenging, but it is important, especially in patients at high risk of cardiovascular events, for whom prevention of these events is a priority. Overall, in patients for whom statin treatment is recommended by current guidelines, the benefits greatly outweigh the risks. (*Arterioscler Thromb Vasc Biol.* 2019;39:e38–e81. DOI: 10.1161/ATV.0000000000000073.)

Key Words: AHA Scientific Statements ■ cognitive function ■ diabetes ■ drug interactions ■ erectile dysfunction ■ hemorrhagic stroke ■ muscle ■ nocebo ■ statin intolerance ■ statin safety

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on July 10, 2018, and the American Heart Association Executive Committee on September 4, 2018. A copy of the document is available at <http://professional.heart.org/statements> by using either “Search for Guidelines & Statements” or the “Browse by Topic” area. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The online Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/ATV.0000000000000073>.

The American Heart Association requests that this document be cited as follows: Newman CB, Preiss D, Tobert JA, Jacobson TA, Page RL 2nd, Goldstein LB, Chin C, Tannock LR, Miller M, Raghuvver G, Duell PB, Brinton EA, Pollak A, Braun LT, Welty FK; on behalf of the American Heart Association Clinical Lipidology, Lipoprotein, Metabolism and Thrombosis Committee, a Joint Committee of the Council on Atherosclerosis, Thrombosis and Vascular Biology and Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol.* 2019;39:e38–e81. doi: 10.1161/ATV.0000000000000073.

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <http://professional.heart.org/statements>. Select the “Guidelines & Statements” drop-down menu, then click “Publication Development.”

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the “Copyright Permissions Request Form” appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).

© 2018 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at <https://www.ahajournals.org/journal/atvb>

DOI: 10.1161/ATV.0000000000000073

The development and use of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) class of drugs, which, according to the prescribing information, reduce low-density lipoprotein cholesterol (LDL-C) on average by 55% to 60% at the maximal doses of the most potent statins, has had a major impact in reducing the incidence of cardiovascular diseases (CVD), including stroke. Nevertheless, these diseases remain the leading cause of death in the United States and globally, accounting for 17.7 million deaths worldwide in 2015, which represents about one-third of all deaths.¹ Starting in 1994, with the publication of the results of 4S (Scandinavian Simvastatin Survival Study),² numerous randomized controlled clinical trials (RCTs) and subsequent meta-analyses proved that statins significantly reduce CVD, including myocardial infarction (MI) and stroke, as well as death from cardiovascular causes.^{3,4}

According to the Centers for Disease Control and Prevention, >25% of US adults >40 years of age take a statin, which translates to >25 million men and women.⁵ Despite the cardiovascular benefits of statins, however, long-term adherence to statin therapy is not optimal.^{6,7} In clinical practice, patients report symptoms that they or their healthcare providers attribute to the statin.^{8,9} This can lead to discontinuation of statin therapy, which is estimated to occur in 10% of patients in the United States,^{6,10} but considerably less often (2%–4%) in many other countries.^{10,11} Other patients might discontinue statin therapy because of fears of side effects, which may or may not be treatment related, based on reports in the lay media¹² or advice from friends or family members. In a nationwide study in Denmark, early statin discontinuation increased from 6% in 1995 to 11% in 2010 and was significantly associated with negative statin news stories.¹² People who discontinued statins early had increased risk of MI and CVD death.¹² Subsequent studies in other countries have also reported an increase in patients stopping statins after negative media coverage¹³ and in major vascular events after stopping statin treatment.¹⁴

The first marketed statin, lovastatin, was approved in the United States in 1987.¹⁵ Other statins approved and available in the United States are simvastatin (1991), pravastatin (1991), fluvastatin (1994), atorvastatin (1997), rosuvastatin (2003), and pitavastatin (2009). These statins are also approved and available in many countries worldwide. All except pitavastatin can be obtained in generic form.

The objective of this scientific statement is to provide a rigorous examination of statin safety and tolerability. We generally discuss statins as a class but highlight differences among them as appropriate. This report covers adverse effects of statins, adverse events associated with but not necessarily caused by statins, and drug interactions. In addition, the safety of statins in a variety of patient groups potentially vulnerable to adverse events is evaluated. The report is organized into the following sections: 1. Assessment of Adverse Events; 2. Adverse Events; 3. Drug-Drug Interactions; 4. Demographic Considerations; 5. Patients With Specific Diseases; and 6. Summary and Conclusions.

1. Assessment of Adverse Events

1.1. Definitions

As defined by the US Food and Drug Administration (FDA), any undesirable experience associated with the use of a

medication is an *adverse event*. Thus, an adverse event is not necessarily caused by the medication. When caused by the medication, these undesirable experiences are called *adverse effects* or *adverse drug reactions*.

Adverse events in a clinical trial are a combination of events that are purely subjective, have subjective and objective components, or are solely objective, such as an increase in blood pressure or an increased risk of newly diagnosed diabetes mellitus. There is no universally accepted method for capturing subjective adverse events.¹⁶ Typically, trialists ask an open-ended question at every clinic visit, such as “Have you had any health problems since your last visit?” In some cases, trialists also ask about a specific symptom or set of symptoms.

Tolerability refers to the degree to which adverse effects of a medication can be endured. Intolerance refers to the inability to tolerate a treatment at any recommended dose, whether or not the symptoms are related to the pharmacological properties of the drug. Most clinical trials report the numbers of patients stopping the study medication because of any adverse event. The difference between the test agent and placebo is a good measure of the overall tolerability of the agent, provided that the blind remains secure throughout the trial.

1.2. Randomized Controlled Trials

In the evaluation of the safety of a drug used long term, the most reliable data are derived from properly designed and conducted large, long-term, double-blind, placebo-controlled randomized trials.^{17–19} The great advantage of this form of investigation is that bias is controlled by random allocation to treatment. There can still be random error, and sometimes other issues within the control of the investigator such as inadequate follow-up or ineffective blinding, but in a well-planned and executed RCT, the results are determined solely by allocation to the test treatment or the control.^{17–19} Most statin RCTs, especially the largest of such trials, were designed primarily to evaluate efficacy in a variety of clinical situations, but they have also generated a large amount of data on safety and tolerability, reported either in the primary publication or secondary articles. RCTs are often referred to by their acronyms. These and the corresponding complete study names are provided in [online Appendix 1](#).

1.3. Meta-analyses

The advantages and disadvantages of meta-analyses have been discussed by Collins et al.¹⁹ Meta-analyses should be regarded as complementary to RCTs and are particularly useful when there is inconsistency between different RCTs testing the same or similar hypotheses. A meta-analysis of several trials, none of which individually produced a robust conclusion, can produce an apparently highly significant result. This, however, is not completely convincing in the absence of a stand-alone individual RCT with a compelling result. Meta-analyses typically are somewhat less rigorous than a well-conducted RCT, because (with a few exceptions) the methods of analysis and the criteria for which trials to include, and how to pool their results, are not published in advance of the analysis.

1.4. Observational Data

The conclusions of this scientific statement are largely driven by the results of RCTs and subsequent meta-analyses. We

needed to rely on observational data for a minority of potential adverse events. For example, when an adverse event was too rare for more than a small number of cases to occur in even the largest available RCT or meta-analysis, observational data were analyzed. Observational studies with a control group, including cohort studies, case-control studies, registry studies, and cross-sectional surveys, are less reliable than RCTs for assessment of causality because of potential biases inherent in these studies^{17,19,20} but can be useful in situations where there is a high excess risk (a hazard ratio [HR] too high to be attributed to unmeasured confounding) in the population exposed to the medication. This usually implies a low risk in the population not exposed to the medication.²⁰

Controlled observational studies can be performed much more quickly and cheaply than RCTs, and in some cases, the HR for a particular adverse effect is so large that it cannot be reasonably attributed to bias.²¹ The relationship between tobacco and lung cancer is a good example in which causality could be established because of the HR >10 comparing lung cancer mortality in lifelong smokers versus never-smokers (after accounting for known confounders).²² In this situation, there is no need for an RCT, which would have been both impractical and unethical. This was also the paradigm that led to the withdrawal of cerivastatin from the market in 2001,¹⁵ after pharmacovigilance data showed that the risk of rhabdomyolysis was much higher than with any other statin.

When adverse events have a very low idiopathic frequency in the general population, case reports can be of value. Case reports have the advantages of minimal cost and effort and can identify a potential serious adverse effect more quickly than other methods. Rhabdomyolysis caused by statins (see 2.1. Muscle) was discovered through case reports, not clinical trials, because statin-induced rhabdomyolysis is rare, but the background rate of idiopathic rhabdomyolysis is rarer still.²³

There are occasional specific situations in which RCTs are not ethical or are impractical. For example, as discussed in 4.4. Pregnancy and Breastfeeding, there has long been a suspicion, but no definite evidence, that statins increase the risk of congenital abnormalities. An RCT of a statin in early pregnancy would be both impractical and ethically indefensible, although possible in late pregnancy. This scientific statement therefore relies mainly on nonrandomized prospective cohort studies to reach its conclusions about statins in pregnancy.

In addition to the peer-reviewed literature, this scientific statement makes use of the prescribing information for statins and drugs that interact with statins. Drug interactions can appear in product labeling before the published literature, particularly if the interaction is revealed by case reports received by regulatory agencies or manufacturers before a pharmacokinetic study is performed.

The prescribing information might be less useful for evaluating adverse effects, with the exception of the “Warnings and Precautions” section. There are often long lists of adverse events, particularly in the “Post-marketing Experience” section, which are reports of an adverse event that occurred during treatment, regardless of causality. There might also be tables of adverse events that occurred in clinical trials, without

Table 1. Muscle Adverse Event Terminology

Adverse Event Term	Definition
SAMS	Muscle symptoms reported during statin therapy but not necessarily caused by the statin
Myalgia	Muscle pain or aches
Myopathy	Unexplained muscle pain or weakness accompanied by CK concentration >10 times ULN
Rhabdomyolysis	Severe form of myopathy, with CK typically >40 times ULN, which can cause myoglobinuria and acute renal failure

CK indicates creatine kinase; SAMS, statin-associated muscle symptoms; and ULN, upper limit of normal.

information on whether the frequency of any of these was significantly different from placebo or other control agent.

In summary, this scientific statement reviews both randomized and observational data. Decisions about causality rely primarily on RCTs, with some exceptions. Our focus on RCTs for the assessment of statin-associated adverse events is consistent with a 2016 review¹⁹ on the interpretation of evidence for statin efficacy and safety.

2. Adverse Events

2.1. Muscle

2.1.1. Myopathy and Rhabdomyolysis

The terminology used to describe muscle adverse effects of statins varies among authors, clinical trials, and consensus groups.²⁴ The terminology used in this statement is provided in Table 1. The original definition of statin-induced myopathy,²⁵ accepted by the FDA and specified in the current prescribing information for all statins that provide a definition, is unexplained muscle pain or weakness accompanied by a creatine kinase (CK) concentration >10 times the upper limit of normal (ULN); that is the terminology used here and in many previous reviews. Statin-induced rhabdomyolysis is a severe form of myopathy without a consistent definition, but with CK typically >40 times the ULN, which usually requires hospitalization, because muscle fiber necrosis results in myoglobinuria that can cause acute renal failure.

Some laboratories do not provide CK normal ranges for men and women separately. However, the ULN is substantially lower for women, presumably because of their smaller muscle mass. In a cohort of 1016 people all 70 years of age in Uppsala, Sweden, Carlsson et al²⁶ found that the ULN for men was 4.98 microkatal per liter (298 U/L), compared with 3.01 microkatal per liter (180 U/L) for women. This should be taken into account when interpreting CK values. In addition, CK values are considerably higher in people of African ancestry than in whites, especially when men ≤55 years of age are compared.²⁷ Median CK in black women appears to be comparable to that of white men, whereas median CK in black men up to the age of 55 years is close to twice as high as in black women.

Rhabdomyolysis during statin treatment was first reported in cardiac transplantation patients taking lovastatin with concomitant cyclosporine.^{28,29} The increased risk of myopathy caused by the interaction between cyclosporine and lovastatin

was quickly recognized (see 3. Drug-Drug Interactions).³⁰ A less severe case that met the definition of myopathy, without concomitant cyclosporine, was detected at about the same time during the course of a phase III study with lovastatin.³¹ These cases were unexpected because animal safety studies had not indicated myotoxicity, although subsequent investigations showed that myopathy could be readily produced in the cyclosporine-treated rat.³² Few drugs have adverse effects on skeletal muscle, but all statins can cause myopathy. These muscle symptoms are typically bilateral and symmetrical and always confined to skeletal muscle.^{33,34} Cardiomyopathy has never been associated with any statin, and in the 2 major trials of statin therapy in participants with heart failure, statins did not lead to symptomatic worsening of the condition or any increase in hospitalization.^{35,36} The excess risk of myopathy relative to placebo is <0.1% in large long-term RCTs with all currently marketed statins at up to maximum recommended doses.³⁷⁻³⁹ The risk is greatest in the first year of therapy⁴⁰ and after a dose increase or the addition of an interacting drug. The risk of rhabdomyolysis is \approx 0.01%⁴ and is potentially preventable by prompt cessation of statin treatment. In a retrospective cohort study, Graham et al²³ searched the hospital records of >250 000 statin users and identified 24 patients who had been admitted to the hospital for rhabdomyolysis. For the statins most commonly used at the time of the study (atorvastatin, simvastatin, and pravastatin), the rate of hospitalization because of rhabdomyolysis was estimated as 0.44 per 10 000 patient-years (95% CI, 0.20–0.84) when used as monotherapy and 5.98 per 10 000 patient-years (95% CI, 0.72–216.0) when used together with a fibrate (predominantly gemfibrozil; see 3. Drug-Drug Interactions). Later studies have established that gemfibrozil has a pharmacokinetic interaction with all statins that is not shared by fenofibrate (see 3. Drug-Drug Interactions). Consequently, gemfibrozil is rarely used today, whereas there is little if any risk of myopathy/rhabdomyolysis using fenofibrate alone⁴¹ or when adding it to a statin.⁴² Nevertheless, the fenofibrate prescribing information recommends caution when using it alone or with a statin.

As is the case for most drug adverse effects, the incidence of myopathy combined with the rarer rhabdomyolysis tends to increase with statin dose. This holds true for lovastatin, simvastatin, pravastatin, rosuvastatin, and pitavastatin, as well as cerivastatin, which was removed from the market in 2001. A clear dose-response relationship for myopathy has not been demonstrated with atorvastatin⁴³ or fluvastatin.⁴⁴ A meta-analysis of pooled individual patient data from early clinical trials of atorvastatin, as well as a cardiovascular outcome trial, comparing the lowest (10 mg) and highest (80 mg) doses of atorvastatin found no significant differences in the incidence of myopathy/rhabdomyolysis, which was well below 0.1% with both doses.^{43,45}

In the EXCEL (Expanded Clinical Evaluation of Lovastatin) RCT,⁴⁶ 8245 patients were randomized to 5 equal groups for 48 weeks: placebo or lovastatin 20 mg once daily, 20 mg twice daily, 40 mg once daily, or 40 mg twice daily. There were 5 cases of myopathy, 1 in the 40-mg once-daily group and 4 in the 40-mg twice-daily group. (One of the 5 patients had preexisting chronic myalgia, and another engaged in regular strenuous exercise; both were able to continue taking lovastatin to the end of the study.) For simvastatin, the

original dose range was 5 to 40 mg once daily, later extended to 80 mg once daily. The incidence of myopathy/rhabdomyolysis in the 5-year HPS (Heart Protection Study) RCT, which compared simvastatin 40 mg/d and placebo in 20 536 participants, was <0.1% in the simvastatin group.⁴⁷ With simvastatin 80 mg, however, a large RCT (SEARCH [Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine]) in 12 064 participants followed up for a mean of 6.7 years showed that the risk of myopathy/rhabdomyolysis was unacceptably high at \approx 0.9% for simvastatin 80 mg compared with 0.02% on simvastatin 20 mg.⁴⁰ The 80-mg dose of simvastatin is still available for very limited prescription but not recommended except for patients who have taken simvastatin 80 mg/d uneventfully for at least 12 months. Thus, the recommended simvastatin dosage range has reverted to the original 5 to 40 mg once daily.

The dosage range of rosuvastatin is 5 to 40 mg once daily. The manufacturer sought approval for an original dosage of 5 to 80 mg, but the FDA and other regulatory agencies determined that the 1% risk of myopathy with rosuvastatin 80 mg was too great to support approval of that dose.⁴⁸ For pitavastatin, the approved dosage range is 1 to 4 mg, although in phase II clinical studies, the drug was studied at doses as high as 64 mg/d.⁴⁹ The incidence of myopathy and asymptomatic increases in CK >10 times the ULN starts to rise at 8 mg/d and increases thereafter with increasing dose.⁴⁹ The manufacturer did not seek approval for doses higher than 4 mg.

Cerivastatin was originally approved with a maximum recommended dose of 0.3 mg/d, which was subsequently extended to 0.4 and 0.8 mg. Postmarketing surveillance found that these higher doses, especially 0.8 mg, were associated with a much greater risk of myopathy and rhabdomyolysis than other statins when given alone, but especially in combination with gemfibrozil,^{23,50} because of drug interactions. Approximately 30 deaths attributed to acute renal failure secondary to rhabdomyolysis were reported to the FDA. Furthermore, even at the maximal 0.8-mg dose, cerivastatin was not especially effective, producing a mean reduction in LDL-C of \approx 40%.⁵¹ Regulatory agencies determined that the risk of rhabdomyolysis associated with cerivastatin across the dosage range was much higher than for other statins, and it was withdrawn worldwide in August 2001.^{23,50} It is still unclear why cerivastatin is so much more myotoxic than other statins. The experience with this drug, however, does demonstrate that the risk of statin myopathy/rhabdomyolysis is not reduced by very high potency per milligram of drug or by smaller reductions in LDL-C.

In addition to varying intrinsic myotoxicity among statins, there is considerable pharmacokinetic variability among the members of the class, with corresponding differences in susceptibility to drug interactions. This is discussed in 3. Drug-Drug Interactions. Most drugs that interact with statins increase the plasma concentration of the statin or its active metabolites, which is equivalent to taking a larger dose, and thereby increases the risk of myopathy/rhabdomyolysis. The most important pharmacokinetic difference among the statins is that only lovastatin, simvastatin, and atorvastatin are cytochrome P450 3A4 (CYP3A4) substrates and consequently are vulnerable to drug interactions with CYP3A4 inhibitors, some of which are commonly used.⁵² Because of

Table 2. Statins in CKD*

Agent	Major Clearance Pathway	Dose Adjustment in Mild-Moderate CKD	Use in ESRD	Use After Transplantation
Atorvastatin	Mainly hepatic	None needed	Can be used	Avoid with cyclosporine
Fluvastatin	Mainly hepatic	None needed	Not studied at doses >40 mg/d	Do not exceed 20 mg/d with cyclosporine†
Lovastatin	Mainly hepatic	Maximum dose 20 mg/d if eGFR <30 mL/min	Not discussed in PI	Avoid with cyclosporine
Pitavastatin	Both hepatic and renal	Maximum dose 2 mg/d	Maximum dose 2 mg/d	Contraindicated with cyclosporine
Pravastatin	Both hepatic and renal	None specified	Maximum dose 20 mg/d	Maximum dose 20 mg/d with cyclosporine
Rosuvastatin	Both hepatic and renal	None specified	Maximum dose 10 mg/d	Maximum dose 5 mg/d with cyclosporine
Simvastatin	Mainly hepatic	None specified	Use caution, start at 5 mg/d	Contraindicated with cyclosporine

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; and PI, prescribing information.

*Table developed from individual statin US prescribing information.

†In ALERT (Assessment of Lescol in Renal Transplantation), a randomized controlled trial in renal transplant patients taking cyclosporine, fluvastatin 80 mg/d was well tolerated, with no difference vs placebo in the incidence of myopathy.⁵⁸

the high first-pass metabolism of lovastatin and simvastatin, the effects of CYP3A4 inhibitors on these statins are greater than on atorvastatin.⁵²

2.1.2. Risk Factors for Myopathy and Rhabdomyolysis

Because of the rarity of myopathy, and especially rhabdomyolysis, for all doses of all statins (except for simvastatin 80 mg), factors predisposing to these adverse effects are not well defined, but as with most drugs, older people appear to be more vulnerable.^{53,54} Hypothyroidism, preexisting muscle disease, and renal impairment are also possible causative factors, and commencement of treatment with an interacting drug is a well-established precipitant. Other suspected risk factors include female sex, diabetes mellitus, and Chinese (and possibly East Asian in general) ancestry.⁵³

In several placebo-controlled cardiovascular outcome trials in patients with chronic kidney disease (CKD),^{55–57} impaired renal function did not appear to be a risk factor for myopathy for statins used at recommended doses for patients with renal insufficiency (Table 2). However, results from the SEARCH RCT did suggest that CKD was a risk factor for simvastatin 80 mg/d.⁵³ To decrease the risk of myopathy, there are maximum dose recommendations for several statins when used in patients with renal impairment (Table 2).

As noted previously, higher statin doses result in higher plasma levels of statins and their active metabolites, which increases the risk of myopathy or rhabdomyolysis. Pasanen et al⁵⁹ reported that blood levels of simvastatin acid (a primary active metabolite of simvastatin) were ≈3 times higher in participants with the c.521CC genotype than in those with the c.521TT reference genotype in *SLCO1B1* on chromosome 12, which encodes OATP1B1 (organic anion transporting polypeptide 1B1), a transporter that facilitates hepatic uptake of statins. A genome-wide association study in participants from the SEARCH RCT⁵³ evaluated 85 subjects who had developed definite myopathy (defined as muscle symptoms with CK >10 times the ULN) or “incipient myopathy” (defined as CK >3 times ULN and >5 times baseline levels, plus alanine aminotransferase [ALT] >1.7 times baseline levels without an

elevated ALT alone at any other visit, with or without muscle symptoms) on simvastatin 80 mg and compared them with 90 participants who were also allocated to simvastatin 80 mg but did not develop definite or incipient myopathy. The only strong genetic association with myopathy involved the *SLCO1B1* c.521C variant allele, which had an odds ratio (OR) for myopathy of 4.5 per copy of the C allele and 16.9 for the CC genotype compared with the TT genotype. However, evidence supporting the association of this or any other polymorphism with myopathy induced by other statins remains limited. Moreover, polymorphisms in the *SLCO1B1* gene account for a small proportion of cases of statin-induced myopathy.

2.1.3. Clinical Approach to Myopathy or Rhabdomyolysis on Statin Therapy

Typically myopathy presents within a few months after starting or increasing the dose of a statin or after introduction of an interacting drug. When a patient reports unexplained muscle aches or weakness, it is important for the clinician to inquire about symptom characteristics. Most commonly, patients present with symptoms that are distributed proximally (eg, hip flexor region, upper chest and shoulders) and bilaterally. Nonspecific lower back pain can also be a presenting feature of statin-induced myopathy.

Before statin-induced myopathy (or rhabdomyolysis) is diagnosed, other causes need to be considered. For example, unusual or strenuous exercise is a common cause of muscle symptoms and can produce substantial elevations in CK.⁶⁰ In addition, hypothyroidism should always be ruled out, because it is associated with muscle weakness and increased CK levels.

CK should be measured in any patient presenting with significant unexplained muscle symptoms or unexplained increases above 3 times the ULN in transaminases, because these enzymes are found in muscle and liver. Failing to measure CK can result in missing a diagnosis of myopathy, which is likely to progress to rhabdomyolysis and possibly acute kidney injury (AKI) if the statin is not stopped. Drug interactions (considered in more detail in 3. Drug-Drug Interactions) are a common cause of elevated CK and

myopathy/rhabdomyolysis and should always be considered. If CK is elevated >10 times the ULN (or >5 times the ULN in a vulnerable patient), the statin should be stopped immediately, as the prescribing information warns, and high fluid intake started; if CK is considerably elevated and the patient is considered to be at risk of acute renal failure based on the CK level and presence of comorbidities, hospitalization might be required. Discontinuation of the statin in a patient with statin-induced myopathy is typically followed by a falling CK and resolution of symptoms, but recovery can be prolonged in patients with more severe muscle injury. If the symptomatology and laboratory abnormalities do not improve soon after discontinuation of statin therapy, the patient should be referred to a muscle specialist to consider other diagnoses such as polymyalgia rheumatica, mitochondrial myopathies, and the very rare statin-associated autoimmune myopathy (or immune-mediated necrotizing myopathy) thought to occur in 2 to 3 patients per 100 000 treated with statins, which is variably reversible with statin discontinuation.⁶¹ If CK is moderately elevated (eg, between 3 and 4 times the ULN), and the symptoms are mild, the statin can be continued, with another measurement in a few days. If the CK concentration is falling or stable, the statin can be continued, with further follow-up and the timing thereof depending on the CK level, symptoms, and medical history.

2.1.4. Athletes/Exercise Enthusiasts

Limited evidence suggests that statins can amplify the CK increases that commonly occur after vigorous exercise.^{62,63} Some practitioners advise the suspension of a statin a day or two before a marathon or other competitive strenuous exercise. Whether this has any meaningful impact on performance or muscle symptoms is unclear given that RCTs investigating fitness or muscle performance have typically not been double-blind⁶⁴ or have yielded no significant differences between statin- and placebo-treated participants.^{65,66}

2.1.5. Muscle Symptoms Without Significant CK Elevations

Drugs that have rare but serious adverse effects typically also have less serious adverse effects of the same type that occur more commonly. For example, anticoagulant drugs occasionally cause major intracranial or gastrointestinal hemorrhage but much more commonly cause bruises, nosebleeds, or bleeding gums. Many patients report adverse events during statin therapy, most commonly muscle symptoms (muscle pain or weakness), and some find the symptoms intolerable and stop the statin. With the knowledge that all statins rarely cause myopathy/rhabdomyolysis, it is natural to expect them to also cause muscle adverse effects that are less serious but more common.

Muscle symptoms are commonly designated as *statin-associated muscle symptoms* (SAMS),²⁴ a term that does not indicate or imply a causal relationship between the statin and the symptoms. Muscle symptoms are common in middle-aged and older people when not treated with statins. SAMS are usually not accompanied by significant elevations in CK or other objective measures.²⁴ The next section reviews data from observational studies and randomized trials that reported SAMS that occurred during statin therapy.

2.1.6. Observational Studies

Observational studies of statins in clinical practice and in surveys can record that an adverse event has occurred and provide a rough estimate of the frequency of the adverse event in that population. However, in general, observational data do not establish causality or quantify the size of an effect^{17,18,21} (exceptions are noted in I. Assessment of Adverse Events).

In USAGE (Understanding Statin Use in America and Gaps in Patient Education Survey),⁶⁷ an internet survey of 10 138 US patients prescribed statins, muscle symptoms that were new or worse after starting a statin were reported by 25% of the 8918 who were current statin users and by 60% of the 1220 who had discontinued statin use. Muscle symptoms were the most common reason cited by patients for statin discontinuation (60%), statin nonadherence (52%), and statin switching (33%). Approximately one-third of those who stopped statin therapy because of muscle adverse events did not talk to their doctor before they discontinued the statin.

In a large, retrospective cohort study in eastern Massachusetts,⁶ 11 124 (10.3%) of 107 835 statin-treated patients were reported as having had a statin-associated adverse event that led to discontinuation of statin therapy. Musculoskeletal complaints accounted for 40% of these discontinuations. Of the 6579 patients rechallenged with statins, 6064 (92%) were found to be on statin therapy 1 year after the reporting of the original statin-related event, which indicates that the vast majority of these patients were subsequently able to tolerate statins.

In a multinational internet survey of 810 statin prescribers (mainly cardiologists) across 13 countries,¹⁰ those surveyed estimated that 6% of their patients were statin intolerant because of intolerable symptoms of any kind. There were large differences between countries: English-speaking countries (United States, United Kingdom, Australia, and Canada) had the highest rates of intolerable symptoms (8%–12%), whereas in several other countries (Japan, Spain, Italy, Sweden), the rate was only 2%. The most common cause of the estimated intolerance was muscle symptoms (64%).

Thus, in the largest observational studies,^{6,10} ≈10% of US patients discontinued statin therapy, and of these discontinuations, roughly half (5%) were because of muscle symptoms.

2.1.7. Placebo-Controlled Randomized Trials

In this section, we consider both RCTs designed to evaluate cardiovascular outcomes and statin safety and RCTs conducted in patients with a history of statin intolerance.

Clinical trials have shown that statins produce a small increase in mean CK (11% on simvastatin 20–40 mg/d⁶⁸; ≈20 U/L on atorvastatin 40 mg/d⁶⁵; 8 U/L on rosuvastatin 20 mg/d⁶⁹). However, this seldom exceeds the ULN for CK and has not been demonstrated to be associated with any discernible clinical effect. Exercise can produce far larger increases.⁶⁰

In double-blind statin RCTs designed to assess effects on CVD outcomes, the incidence of intolerance, represented by numbers of statin and placebo recipients stopping study medication because of any adverse event, has typically been similar between treatment and placebo groups.^{70,71} The majority of

these trials found no significant differences between patients allocated statin or placebo in muscle symptoms.⁹ In a tabular meta-analysis of safety data, Collins et al¹⁹ reported (in a peer-reviewed supplementary appendix) symptomatic musculoskeletal event rates from 15 major statin RCTs included in the CTT (Cholesterol Treatment Trialists) collaboration. This included information on myalgia or muscle aching (or muscle-specific events with a similar description) in 12 trials with >100 000 participants along with a meta-analysis of this outcome in these 12 trials. Muscle symptoms were collected by a general query for adverse events in 10 studies and by a specific query for muscle symptoms in 2 studies. Some data not reported in published articles were obtained by personal communication with the trial investigators, as noted.¹⁹ They were not adjudicated. Nine contributing trials found no significant increase in myalgia or muscle aching in patients allocated to a statin relative to those allocated to placebo. Three trials¹⁹ (the HOPE-3 [Heart Outcomes Prevention Evaluation-3], JUPITER [Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin], and ASPEN [Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints] RCTs) reported small but statistically significant increases in muscle symptoms (up to 1.4% absolute difference) between statin- and placebo-treated groups. The pooled results of the 12 trials found a nonsignificant difference in these muscle symptoms (5162 [11.7%] in participants allocated to statins versus 5015 [11.4%] in participants allocated to placebo; $P=0.10$). This outcome is consistent with results from previous meta-analyses,⁷²⁻⁷⁴ all of which found no significant difference between statin and control. These 3 meta-analyses used tabular rather than individual participant data, and muscle symptoms were not consistently defined and captured in different trials. These factors produce trial-to-trial variability in the absolute numbers of patients with muscle symptoms but do not introduce bias in the evaluation of statin-placebo differences.

None of the 12 trials in the meta-analysis by Collins et al¹⁹ reported a significant difference between the statin and placebo groups in patients discontinuing study treatments specifically because of muscle symptoms (without significant CK increases). Pooling the 8 trials (with ≈ 63 000 participants) that reported these data, 201 participants (0.63%) allocated statin versus 183 (0.58%) allocated placebo discontinued study treatments because of these muscle symptoms ($P=0.37$).

For evaluation of the tolerability and safety of a medication, the quality of evidence provided by placebo-controlled trials is recognized as superior to evidence from pharmacoepidemiologic studies.^{17,19} Nevertheless, various criticisms have been raised, and addressed,^{19,70} regarding statin RCTs. These include the use of active run-in phases intended to exclude those having a potentially drug-related adverse event, which theoretically could lead to an underestimate based on those proceeding to the randomized phase of the study and, related to that, the self- or protocol-directed exclusion of individuals who have previously experienced SAMS; the claim that trial participants are not representative of patients treated in clinical practice (and therefore underestimate statin adverse effects); and the fact that most statin RCTs have not specifically sought information on muscle symptoms.

Of the 15 major placebo-controlled statin trials in the analysis by Collins et al,¹⁹ only 2, the HPS³⁸ and HOPE-3⁷⁵ RCTs, used an active run-in phase (of 4–6 weeks), whereas 11 trials included a placebo run-in. Patients who have reported intolerable muscle symptoms usually tolerate a statin under double-blind conditions, as shown in trials of statin-intolerant patients, discussed in 2.1.8. Randomized Trials in Patients With Intolerable SAMS. Therefore, any exclusion of patients with SAMS from RCTs would have had little impact. In addition, the first statin cardiovascular outcome trial, 4S, recruited patients in Scandinavia at a time when very few patients were taking a statin.² The rate of myalgia in this study was similar in the simvastatin and placebo groups.⁷⁶ The use of a placebo run-in, as has been done in 11 major trials, is a strategy that is also likely to increase (not decrease) the chance of observing a true effect of an intervention, by excluding patients unable to tolerate placebo. Additional reasons why the lack of any statin effect on muscle symptoms is very unlikely to be the result of exclusion of patients who had previously experienced SAMS are presented elsewhere.⁷⁰

All clinical trials have inclusion and exclusion criteria. Nevertheless, the variety of patients studied in ≈ 30 major statin cardiovascular outcome trials⁴ is substantial: >170 000 participants including men and women, various ethnicities, participants >75 years of age, and those with and without coronary heart disease, previous stroke, diabetes mellitus, heart failure, previous organ transplantation, and dialysis. This indicates that statin therapy has been evaluated in a broad array of the types of patients treated in routine care. Collectively, these trials used all 7 of the marketed statins except pitavastatin, and many used the maximum dose recommended for the population studied.

Questioning trial participants about a specific symptom does not necessarily provide higher-quality data than studies that have not specifically sought this information. When the symptom has a high background rate, such as muscle symptoms in older people, direct questioning tends to capture a large number of adverse events of doubtful clinical importance, which leads to a high placebo rate and therefore reduced statistical power. Of the 4 placebo-controlled statin RCTs^{39,47,65,68} that questioned participants about muscle symptoms, none found a significant difference between the statin and placebo groups, as shown in Table 3. On the other hand, none of the 3 (of a total of 12) RCTs that did find a significant difference (the HOPE-3, JUPITER, and ASPEN RCTs, as noted previously) reported the use of specific questioning for muscle symptoms.

The previously discussed meta-analysis by Collins et al¹⁹ using published data from major double-blind RCTs, supplemented with unpublished data from trial investigators, indicates that if muscle symptoms without significant CK elevations occur at a greater rate with statins than placebo, the difference (in people of European origin) can be no more than ≈ 10 to 20 cases per 10 000 patients treated per year (ie, 0.5%–1.0% over 5 years) and therefore too small to be detected reliably even in very large cardiovascular outcome studies. The CTT Collaboration has published a protocol⁷⁷ for analyses of pooled patient-level adverse event data from the statin cardiovascular outcome RCTs that will include >100 000 patients.

Table 3. Muscle Symptoms Elicited Via Specific Queries in Randomized Controlled Trials

Study	Population	Statin	Duration, y	Muscle Symptoms in Statin Group, n/N	Muscle Symptoms in Placebo Group, n/N	P Value
OCS, ⁶⁸ 1994	CVD, mainly CHD	Simvastatin 20 and 40 mg	3.4	117/208 (S20) 108/206 (S40)	106/207	>0.2
HPS, ⁴⁷ 2002	Atherosclerotic disease or diabetes mellitus	Simvastatin 40 mg	4.9	3379/10269	3409/10267	>0.2
CORONA, ³⁵ 2007	Systolic heart failure	Rosuvastatin 10 mg	2.7	225/2514	207/2497	>0.2
STOMP*, ⁶⁵ 2013	Healthy subjects	Atorvastatin 80 mg	0.5	23/232	14/236	0.1

CHD indicates coronary heart disease; CORONA, Rosuvastatin in Older Patients With Systolic Heart Failure; CVD, cardiovascular disease; HPS, Heart Protection Study; OCS, Oxford Cholesterol Study; S20, simvastatin 20 mg; S40, simvastatin 40 mg; and STOMP, Effect of Statins on Skeletal Muscle Function.

*In the STOMP randomized controlled trial, 19 subjects allocated atorvastatin and 10 subjects allocated placebo met the study definition for myalgia, which included a dechallenge/rechallenge ($P=0.08$ by the primary intention-to-treat analysis, $P=0.054$ by per protocol analysis, without multiplicity adjustment for the 6 coprimary end points).

If the pooled adverse muscle event rate on placebo is 5% and the pooled rate on statins is 1% higher at 6% (1.2 relative risk [RR]), the power of this meta-analysis to detect it will exceed 99% with 2-sided $\alpha=0.01$.

2.1.8. Randomized Trials in Patients With Intolerable SAMS

Four double-blind RCTs^{78–83} conducted in patients who reported statin intolerance caused by SAMS have included a statin treatment arm. In these trials, control therapy was either placebo or ≥ 1 active comparators. If caused by statin therapy, SAMS should be reproducible under double-blind conditions, especially in patients in whom these symptoms are intolerable on multiple statins, and few patients should be able to tolerate the test statin. On the other hand, if SAMS are the product of expectations of harm (the nocebo effect, discussed later in this section), SAMS should then occur at similar rates on the test statin and the control agents, as long as the blind is maintained.

One of these studies included a data-driven mid-study design change and is difficult to interpret.⁸³ Joy et al⁷⁸ performed a proof-of-concept “N-of-1” crossover study in 8 patients who had experienced intolerable myalgia on a statin, rechallenging them with the same statin and placebo 3 times in 7 of the 8 patients and twice in the remaining patient. Myalgia was rated using visual analogue scales and other pain measurement techniques. There were no significant differences between statin and placebo, and 5 of the patients resumed statin therapy.

The ODYSSEY ALTERNATIVE RCT (A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients With Primary Hypercholesterolemia Who Are Intolerant to Statins)^{79,80} enrolled 361 patients who could not tolerate at least 2 statins, 1 at its lowest dose, because of muscle symptoms. During the placebo run-in phase, 47 patients withdrew, 25 of whom had muscle symptoms. This left 314 patients to be randomized to alirocumab, ezetimibe, or atorvastatin 20 mg in a 2:2:1 ratio, so the analysis included 126 patients given alirocumab, 125 patients treated with ezetimibe, and 63 taking atorvastatin. The discontinuation rates because of muscle symptoms over the 24-week follow-up period were 15.9%, 20.2%, and 22.2%, respectively, in the 3 treatment groups. Therefore, the rates of muscle symptoms

causing discontinuation were quite similar in the atorvastatin and control groups ($P>0.2$ for alirocumab versus atorvastatin), albeit based on small numbers of discontinuations, and three-quarters of the randomized patients with a well-documented history of SAMS in the ODYSSEY ALTERNATIVE RCT were able to tolerate the test statin.^{80,84}

The GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects-3) RCT^{81,82} recruited patients with intolerable SAMS on at least 2 statins, 1 of which had to be at the lowest recommended dose, as in ODYSSEY ALTERNATIVE. Approximately 80% of the participants reported intolerable SAMS with 3 statins at baseline. To confirm statin intolerance and determine whether such intolerance is causally related to statin therapy, patients were randomized to atorvastatin 20 mg or placebo for up to 10 weeks, and after a 2-week washout period, they were crossed over to the other treatment for up to 10 weeks. Of 491 patients randomized, 133 (27.1%) experienced intolerable muscle symptoms on both atorvastatin and placebo or did not experience such symptoms on either treatment, which indicates that their reported intolerance could not have a pharmacological basis. One hundred thirty patients (26.5%) experienced intolerable symptoms on placebo but not atorvastatin, and 209 patients (42.6%) experienced intolerable symptoms on atorvastatin but not placebo. Interpretation of these data involves comparison of the numbers of subjects who developed intolerable muscle symptoms on atorvastatin only compared with those who developed muscle symptoms on placebo only. The absolute difference between 209 and 130 (ie, 79) represents 16.1% of the 491 patients in the trial, which shows that 1 in 6 of these statin-intolerant patients could be considered to represent the proportion of statin-intolerant patients whose muscle symptoms were actually caused by the statin. A smaller study in statin-intolerant patients with a similar design found a 7% difference between simvastatin 20 mg and placebo.⁸³ Another proposed explanation for the 16% difference in the GAUSS-3 RCT is that some patients unblinded themselves.⁷¹ In any event, it is clear that in a substantial majority of participants in this highly selected group with reported preexisting statin intolerance because of muscle symptoms, the intolerance was not caused by the statin.

These 3 RCTs in patients with apparently well-documented SAMS show that intolerance is not reproducible under

double-blind conditions in a large majority of highly selected patients who would be expected to be at highest risk of SAMS. This finding is consistent with meta-analyses of numerous previous RCTs in a broad array of patient types that have shown that muscle adverse effects actually caused by the statin occur in no more than 1% of treated patients. It is currently not possible to distinguish the small minority of patients with muscle symptoms caused by a statin from the majority in whom the cause is the nocebo effect.⁸⁵ Although questionnaires have been proposed, they have not been validated.⁸⁵

Additional support for the finding that statin intolerance depends on patient expectations is provided by an analysis of muscle symptoms in ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm) comparing the blinded randomized phase of the trial (median duration, 3.3 years) to the subsequent nonblinded, nonrandomized phase (median duration, 2.2 years). There was no difference in muscle symptoms among atorvastatin- and placebo-allocated patients in the blinded phase, but in the unblinded phase, the rate of muscle adverse events was higher in the group taking a statin (Cox proportional HR=1.4; $P=0.0059$).^{86–90} The unblinded phase was similar to routine clinical practice in that patients knew what they were taking, in contrast to a double-blind clinical trial. There were no significant differences in the unblinded phase between statin users and nonusers in the rates of other adverse events, except for musculoskeletal and connective tissue disorders (HR, 1.17 [95% CI, 1.06–1.29]). The study showed a lower rate of statin-associated muscle symptoms in the unblinded phase than in the randomized phase. The rates of the other adverse events of interest (erectile dysfunction, cognitive impairment, and sleep disturbance) were also lower in the unblinded phase than in the blinded phase, but for these, there were no significant differences between patients who had opted to take atorvastatin and those who had not. There could be many reasons for lower rates in the unblinded phase, but the relevant comparisons in both phases are between participants taking atorvastatin versus those not taking it.

A plausible explanation for the disparate results from observational studies and blinded randomized trials is patient expectations of harm, that is, the nocebo effect (Latin for “I will harm”),^{91–95} the inverse of the placebo effect (Latin for “I will please”). The nocebo effect is a normal neuropsychological phenomenon⁹¹ that is the cause of adverse events, usually subjective, that result from expressed or internal expectations of harm from a therapy, but it has received little attention in cardiovascular medicine⁷¹ until recently.^{86,96} Although some authors describe these as not being real or true adverse events,⁹⁷ to the patient they are just as real as adverse events that are caused by the treatment, and they can be severe. As noted previously, reports of muscle symptoms are common in the middle-aged and older population prescribed statins, and patient expectations often lead to attribution of these symptoms (and other common background symptoms) to statin therapy. These expectations are not necessarily conveyed to healthcare providers, and they might be no more than a vague uneasiness with taking a statin. These symptoms occur in people of all types with all levels of education⁹⁸; there is no implication that the patient is in any way abnormal. Dismissing the symptoms, or implying they are invented, can lead to a perception that the clinician is uncaring, and possibly

a desire on the part of the patient to prove the symptoms are real,⁹⁹ which reduces the chances of a successful rechallenge.

There are many sources of expectations of harm from statins.⁷ The risk of myopathy and rhabdomyolysis is prominent in statin patient information leaflets, and clinicians appropriately warn patients to report muscle symptoms if they develop during treatment. Furthermore, internet searches often bring up incorrect information about statin adverse effects, usually exaggerating the hazards, and statin-related news stories often emphasize the negative.^{7,100} Statins are widely prescribed, and the misperception that they commonly cause muscle and other symptoms has existed for many years. The combined effect of these factors could lead many patients to associate background muscle symptoms with statin use or develop new symptoms.

2.1.9. Clinical Approach to Muscle Symptoms

Most clinicians who regularly prescribe statins are aware that statins are well tolerated in clinical trials and by most patients in clinical practice. Nevertheless, when symptoms, most commonly muscle symptoms (which might include pain, aches, stiffness, cramps, weakness, or muscular fatigue), appear soon after starting treatment with a statin, and no other causes are clearly discernible, it is reasonable to recommend a “statin holiday” for 1 to 2 weeks and determine whether symptoms resolve. If so, it can be difficult for both clinicians and patients to believe the symptoms are not caused by the statin. A successful rechallenge without symptoms would provide evidence that the initial SAMS were unrelated to statin therapy, but sometimes the symptoms recur with each rechallenge. Although SAMS can usually be explained by patient expectations of harm, as discussed previously, the symptoms are real and can be severe. SAMS are a common cause of stopping statins and a barrier that impedes long-term adherence.¹⁰ As expected, discontinuation is strongly associated in observational studies with higher cardiovascular event rates.¹⁰¹

When a patient reports muscle symptoms, the possibility of an adverse statin drug interaction should be borne in mind and dealt with, as addressed elsewhere in this statement (see 3. Drug-Drug Interactions). If the symptoms are concerning, it is important to check CK, primarily to assess the possibility of myopathy/rhabdomyolysis, but also because a normal value (if obtained) might help reassure the patient that muscle injury has not occurred and enable continuation of treatment or acceptance of rechallenge with the same statin. The rechallenge is usually done at a lower dose, or with an alternative statin, given daily or several times a week. Measurement of vitamin D might be useful, because vitamin D deficiency can cause muscle pain independent of statin use.¹⁰² Observational studies evaluating the association of low levels of 25-hydroxy vitamin D with muscle symptoms in statin-treated patients have produced conflicting results.^{103–108} No controlled clinical trials have yet addressed whether vitamin D supplementation improves SAMS. Coenzyme Q10 is derived from mevalonate, the product of the enzyme HMG-CoA reductase that is inhibited by statins. It has been proposed as a treatment for muscle symptoms during statin therapy, but the RCT evidence is not supportive,^{83,109} consistent with the conclusion that the muscle symptoms are rarely caused by the statin.

If SAMS do not resolve within a few weeks after statin cessation (and especially with elevated CK levels), other causes for the muscle symptoms, such as an underlying neuromuscular disorder, including polymyalgia rheumatica, severe vitamin D deficiency, or, very rarely, immune-mediated necrotizing myositis, should be considered. If persistent muscle symptoms are clinically significant, the patient should be referred to a neuromuscular specialist for evaluation and treatment. The substantial advantage of remaining on statin therapy should be discussed with the patient. Rechallenge is a practical way forward, because it is usually possible to find a statin regimen the patient will accept. In a large US cohort study, 11 124 of 107 835 subjects (10%) discontinued statin treatment because of adverse events considered statin related. Of these, 6579 (59%) were rechallenged, and in them, some form of statin treatment could be restored in >90%.⁶ Of these, 2721 were rechallenged with the same statin, and 2568 were taking a statin 12 months after the original statin-related event. At 12 months, 1295 patients were taking the same statin, and of these, 996 were taking the original statin at the same or a higher dose. Only 153 patients were not taking a statin. Of the 6579 patients who were rechallenged, 3858 patients were rechallenged with a different statin, and 3496 were taking any statin at 12 months. A total of 362 patients were not taking any statin at 12 months. Therefore, only 515 (7.8%) of the 6579 rechallenged patients were not taking a statin at 12 months.

During rechallenge, patients are likely to believe, quite reasonably, that their symptoms are caused by the statin, especially when they resolve after stopping the statin and then recur on rechallenge. In a typical scenario, a clinician prescribes a statin and appropriately warns a patient of the possibility of myopathy. The patient returns with reports of muscle symptoms with no obvious new cause, and the symptoms resolve on stopping the statin. The clinician typically rechallenges the patient with a lower dose of the same statin or with a different statin, an approach that is often but not always successful.⁶ SAMS that reoccur during rechallenge might convince the patient and sometimes the clinician that the symptoms are indeed caused by the statin. However, because the rechallenge is not usually double-blind in the clinic, a positive rechallenge does not demonstrate unequivocally that the symptoms are pharmacologically related to the statin. While it increases this possibility, it does not prove causality, because some patients may anticipate side effects (the nocebo effect).^{71,86,96} These nonpharmacological symptoms occur in patients of all kinds and are completely normal; there is no implication that the patient is inventing the symptoms.

The frequency of subjective adverse events such as SAMS can be strongly influenced by clinician-patient communication, and strategies have been proposed to minimize patient expectations of harm in other contexts^{94,95} that can be used to preempt or manage SAMS and other symptoms that arise during statin therapy.⁷¹ Supported by a large body of RCTs that showed that statins might cause muscle symptoms in at most 1% of trial participants with a broad range of comorbidities,¹⁹ and by reassuring data from blinded RCTs in participants who have previously reported SAMS on multiple statins that showed subsequent statin tolerance and adherence in a substantial majority,^{80,82,84} clinicians can be confident reassuring patients that although

their symptoms might have started with their statin, it is usually possible to find an acceptable long-term statin regimen.

2.1.10. Conclusions

Statins occasionally cause dose-related myopathy, defined as unexplained muscle pain or weakness accompanied by CK elevations >10 times the ULN, including rhabdomyolysis, in <0.1% of patients at maximal recommended doses. Myopathy and rhabdomyolysis risk is related to circulating active drug concentrations and is therefore higher in the presence of drugs that interfere with statin metabolism.

Many statin-treated patients in routine clinical practice report muscle symptoms, which could cause them to stop the statin; this is a major barrier to effective long-term therapy. Under the double-blind conditions of RCTs in a broad array of patient types, there is little if any difference (at most 1%) in the incidence of muscle symptoms between the statin and placebo. Very few patients in these RCTs discontinued the study medication because of these muscle symptoms, and the difference in muscle-related discontinuation rates between patients allocated to statin and those allocated to placebo was negligible (0.1%) and not significant. When patients with a history of intolerance to multiple statins because of muscle symptoms are rechallenged under double-blind conditions, the intolerance is generally not reproducible.

There is increasing appreciation of the role of patient expectations of harm as the cause of muscle and other symptoms in statin-treated patients. The symptoms can be severe despite the absence of a pharmacological basis in the vast majority of cases, and they should never be dismissed by the clinician. Expectations of harm are generated by appropriate clinician warnings about the small risk of rhabdomyolysis and from negative information in the media. Although muscle symptoms are very unlikely to be caused by the statin, rechallenge with the same statin at a lower dose or a different statin is useful as the first step to restore statin therapy, which might be possible at or near the previous level of intensity. Resuming and maintaining treatment with a statin (when myopathy has been excluded) reduces the risk of atherosclerotic vascular events, which is especially important in high-risk patients, such as those with preexisting CVD.

2.2. Diabetes Mellitus

2.2.1. Newly Diagnosed Diabetes Mellitus

The development of type 2 diabetes mellitus is a long-term process that involves chronic insulin resistance and progressive loss of β -cell function disease that (with very few exceptions) takes place over many years. The higher incidence of diabetes mellitus during statin treatment, relative to placebo, in RCTs typically reflects patients already at high risk of diabetes mellitus progressing to the diabetic state sooner than would otherwise have been the case. Furthermore, because the observed outcome is inevitably the diagnosis of diabetes mellitus, rather than the actual onset of diabetes mellitus, the term *newly diagnosed diabetes mellitus* is used in this document to reflect incident cases of diabetes mellitus, instead of *new-onset diabetes mellitus*, despite the regular use of the latter in the literature.

The possibility that statin therapy might influence the risk of developing diabetes mellitus was first tested in a post hoc

analysis of WOSCOPS (West of Scotland Prevention Study).¹¹⁰ Of 5974 patients without diabetes mellitus at baseline, 57 of 2999 (1.9%) on pravastatin versus 82 of 2975 (2.8%) on placebo developed diabetes mellitus over 5 years, a borderline significant reduction of 30% (HR, 0.70; 95% CI, 0.50–0.98). This analysis applied an unconventional but stringent criterion for the diagnosis of diabetes mellitus, namely, the requirement that fasting glucose must increase from baseline by at least 2 mmol/L. Thereafter, some of the major statin trials looked retrospectively for newly diagnosed diabetes mellitus. A meta-analysis of published study-level data from 5 trials with 39 791 participants in 2008 found no increase in newly diagnosed diabetes mellitus with statin use but could not exclude an increase of up to 19% (RR, 1.03; 95% CI, 0.89–1.19).¹¹¹

The first prospective analysis of effects of statins on the incidence of diabetes mellitus was provided by the JUPITER trial, which included newly diagnosed diabetes mellitus as a prespecified outcome. In this study of 17 802 patients without diabetes mellitus at baseline, physician-reported diabetes mellitus occurred in 0.6% more participants randomized to receive rosuvastatin (270/8901 [3.0%]) than placebo (216/8901 [2.4%]) over a median of 1.9 years (a relative increase of 24%; $P=0.01$).³⁹ There was also a small but statistically significant increase in hemoglobin A_{1c} (HbA_{1c}) on rosuvastatin (median, 5.9%; interquartile range, 5.7%–6.1%) versus placebo (median, 5.8%; interquartile range, 5.6%–6.1%). However, fasting glucose levels at 24 months did not differ among the rosuvastatin and placebo groups.¹¹²

In 2010, a meta-analysis of study-level data from 91 140 participants in 13 randomized trials (limited to CVD outcome trials with >1000 participants and follow-up of >1 year) indicated that statin use was associated with a 9% proportional increase (OR, 1.09; 95% CI, 1.02–1.17) in the risk of being diagnosed with diabetes mellitus compared with placebo or standard care.¹¹³ Weaknesses of this analysis include its use of study-level rather than individual participant data, the fact that newly diagnosed diabetes mellitus was not a prespecified outcome in the vast majority of trials, and the unavoidable need to use differing definitions of diabetes mellitus according to the available data (eg, only some trials measured fasting glucose on a regular basis during follow-up, and those that did so measured it at different frequencies). This analysis estimated that treating 255 individuals with statins for 4 years would result in 1 additional case of diabetes mellitus. Cardiovascular outcomes were not collected for the purposes of this analysis, but it was estimated that for each additional case of diabetes mellitus, ≈5 major coronary events would have been prevented.¹¹³

A subsequent meta-analysis added data from 2 placebo-controlled trials and found that statin therapy increased the risk of newly diagnosed diabetes mellitus by 11%.¹¹⁴ These studies were not able to assess the effect of statin therapy in the context of established diabetes mellitus risk factors, such as adiposity and impaired fasting glycemia, but a separate analysis of 3 major statin trials suggested that the modest diabetogenic effect of statins was present predominantly in those already at high risk of developing diabetes mellitus.¹¹⁵

This evidence of an increased risk of diabetes mellitus on statin therapy compared with placebo or standard care

prompted a further meta-analysis in which pooled study-level data for 32 572 participants without diabetes mellitus from 5 trials were used to assess the effects of intensive- versus moderate-dose therapy (again limited to trials with at least 1000 participants and follow-up of at least 1 year).¹¹⁶ Over a median of 4.9 years, 1449 (8.8%) of 16 408 individuals on intensive statin therapy versus 1300 (8.0%) of 16 344 on moderate-dose therapy were recorded as having developed diabetes mellitus (OR, 1.12; 95% CI, 1.04–1.22). This was estimated to represent an extra 2 cases of diabetes mellitus per 1000 patient-years of treatment (a risk of 0.2% per year of treatment),¹¹⁶ during which time 6.5 cardiovascular events (MI, stroke, or coronary revascularization) per 1000 patient-years were prevented.¹¹⁷

Subsequent data from the HOPE-3 trial in individuals without CVD but at intermediate risk, followed up for a median of 5.6 years, showed no effect of lower-dose rosuvastatin (10 mg/d) on adjudicated cases of reported newly diagnosed diabetes mellitus (232/5987 [3.9%] on rosuvastatin; 226/5987 [3.8%] on placebo; HR 1.02; 95% CI, 0.85–1.23).⁷⁵ Results from the various trials and the major meta-analyses are provided in Table 4.

In a meta-analysis¹²⁰ of study-level data from smaller trials comparing pitavastatin to either placebo or several other statins, there were no significant differences in newly diagnosed diabetes mellitus or impaired glucose metabolism compared with other statins, but the analysis included only 29 new cases of diabetes mellitus (none of which occurred in the 2 placebo-controlled trials) and only ≈1600 person-years of observation. The J-PREDICT trial¹²¹ (Japan Prevention Trial of Diabetes by Pitavastatin in Patients With Impaired Glucose Tolerance) was designed to investigate the effect of pitavastatin added to lifestyle modification on the development of diabetes mellitus in participants with impaired glucose tolerance compared with lifestyle modification alone, but the results of this open-label study have not yet been published in a peer-reviewed journal.

One interpretation of the findings of statin-induced diabetes mellitus, based on an analysis of the JUPITER trial, is that statin therapy simply accelerates the onset of diabetes mellitus in those who would otherwise develop diabetes mellitus, such as patients with pre-diabetes mellitus or the metabolic syndrome.¹¹² This has not yet been directly confirmed in other prospective trials, although as noted above, the diabetogenic risk of statin therapy is largely confined to patients with preexisting multiple risk factors for diabetes mellitus.¹¹⁵ Also unclear is the relationship between duration of statin therapy and risk of newly diagnosed diabetes mellitus. An analysis of study-level data from 20 major statin trials found no relationship between the length of those statin trials and the risk of newly diagnosed diabetes mellitus attributable to statin therapy.¹¹⁴

Stopping statin treatment increases cardiovascular risk; therefore, statins should be continued when diabetes mellitus is diagnosed. Partly for this reason, whether the diabetogenic effect of statins is reversible is unclear. The mechanism of this effect remains an active area of research.^{12,113,114,116,122–125} Some of these data are summarized in [online Appendix 3, Table I](#). Recent mendelian randomization studies found that reduced function variants of not only HMG-CoA reductase^{114,126} but also both PCSK9 (proprotein convertase

Table 4. Newly Diagnosed Diabetes Mellitus in Major Statin Trials and in Meta-analyses of Trials

	Active Arm	Control Arm	New Diabetes Mellitus in Active Arm, n/N (%)	New Diabetes Mellitus in Control Arm, n/N (%)	Odds Ratio (95% CI)
Placebo or standard care controlled trials					
4S ²	S20–40	Placebo	198/2116 (9.4)	193/2127 (9.1)	...
WOSCOPS ¹¹⁰	P40	Placebo	75/2999 (2.5)	93/2975 (3.1)	...
AFCAPS/TexCAPS	L20–40	Placebo	72/3094 (2.3)	74/3117 (2.4)	...
LIPID*	P40	Placebo	126/3496 (3.6)	138/3501 (3.9)	...
GISSI Prevenzione	P20	No treatment	96/1743 (5.5)	105/1717 (6.1)	...
LIPS	F80	Placebo	17/724 (2.3)	14/751 (1.9)	...
HPS ⁴⁷	S40	Placebo	335/7291 (4.6)	293/7282 (4.0)	...
PROSPER ¹¹⁸	P40	Placebo	165/2510 (6.6)	127/2513 (5.1)	...
ALLHAT-LLT	P40	No treatment	238/3017 (7.9)	212/3070 (6.9)	...
ASCOT-LLA ⁸⁶	A10	Placebo	154/3910 (3.9)	134/3863 (3.5)	...
SPARCL ³⁷	A80	Placebo	166/1905 (8.7)	115/1898 (6.1)	...
MEGA	P10–20	No treatment	172/3013 (5.7)	164/3073 (5.3)	...
CORONA ⁹⁵	R20	Placebo	100/1771 (5.6)	88/1763 (5.0)	...
JUPITER ³⁹	R20	Placebo	270/8901 (3.0)	216/8901 (2.4)	...
GISSI-HF ³⁶	R10	Placebo	225/1660 (13.6)	215/1718 (12.5)	...
HOPE-3 ⁷⁵	R10	Placebo	232/5987 (3.9)	226/5987 (3.8)	...
Meta-analysis without HOPE-3 ¹¹⁴	2409/48 150 (5.0)	2181/48 268 (4.5)	1.11 (1.03–1.20)
Meta-analysis with HOPE-3	2641/54 137 (4.9)	2407/54 255 (4.4)	1.10 (1.03–1.18)
Intensive vs moderate-dose therapy trials					
PROVE-IT TIMI	A80	P40	101/1707 (5.9)	99/1688 (5.9)	...
A to Z	S40–80	Placebo/S20	65/1768 (3.7)	47/1736 (2.7)	...
TNT ⁴³	A80	A10	418/3798 (11.0)	358/3797 (9.4)	...
IDEAL ¹¹⁹	A80	S20–40	240/3737 (6.4)	209/3724 (5.6)	...
SEARCH ⁴⁰	S80	S20	625/5398 (11.6)	587/5399 (10.9)	...
Meta-analysis ¹¹⁶	1449/16 408 (8.8)	1300/16 344 (8.0)	1.12 (1.04–1.22)

Full references for all listed trials may be found in [online Appendix 2](#). Ellipses indicate not applicable; 4S, Scandinavian Simvastatin Survival Study; A10, atorvastatin 10 mg; A80, atorvastatin 80 mg; A to Z, Aggrastat to Zocor Trial; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack-Lipid Lowering Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; F80, fluvastatin 80 mg; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico-Heart Failure; GISSI Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico-Prevenzione; HOPE-3, Heart Outcomes Prevention Evaluation-3; HPS, Heart Protection Study; IDEAL, Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; L20–40, lovastatin 20–40 mg; LIPID, Long-term Intervention With Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study; MEGA, Primary Prevention of Cardiovascular Disease with Pravastatin in Japan; P10–20, pravastatin 10–20 mg; P20, pravastatin 20 mg; P40, pravastatin 40 mg; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT TIMI, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22; R10, rosuvastatin 10 mg; R20, rosuvastatin 20 mg; S20, simvastatin 20 mg; S20–40, simvastatin 20–40 mg; S40, simvastatin 40 mg; S40–80, simvastatin 40–80 mg; S80, simvastatin 80 mg; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL, Stroke Prevention with Aggressive Reduction in Cholesterol Levels; TNT, Treat to New Targets; and WOSCOPS, West of Scotland Prevention Study.

*Newly diagnosed diabetes mellitus only available for participants with normal fasting glucose at baseline.

subtilisin/kexin type 9)¹²⁶ and NPC1L1 (Niemann-Pick C1-Like 1)¹²⁷ were all associated with a reduction in LDL-C, a reduction in the prevalence of cardiovascular events, and an increased prevalence of newly diagnosed diabetes mellitus. This suggests that the increase in newly diagnosed diabetes mellitus on statin therapy could be somehow mediated by its LDL-C-lowering effect and thus might be shared by inhibitors of PCSK9 (monoclonal antibodies), NPC1L1 (ezetimibe), and HMG-CoA reductase (statins). This putative link

is strengthened by the finding of a much lower prevalence of diabetes mellitus (adjusted OR=0.49 compared with control subjects) in patients with heterozygous familial hypercholesterolemia (FH), which is usually caused by decreased numbers or function of LDL receptors.¹²⁵

2.2.2. Changes in Measures of Glycemia and Weight

With regard to the potential effect of statins on glycemic control in patients who already have diabetes mellitus, data from

2 RCTs in patients with type 2 diabetes mellitus, AFORRD (Atorvastatin in Factorial With Omega-3 EE90 Risk Reduction in Diabetes; atorvastatin 20 mg/d or placebo in 800 patients) and CARDS (Collaborative Atorvastatin Diabetes Study; atorvastatin 10 mg/d or placebo in 2838 patients), showed that these statin regimens produced absolute increases in HbA_{1c} of 0.3% and 0.1% at 4 months and 4 years of treatment, respectively.^{128–130} In contrast, HPS,¹³¹ in which HbA_{1c} was measured in a random sample of 1087 of the 5963 participants with diabetes mellitus at baseline and after 4.6 years, found no difference between the simvastatin and placebo arms, with an increase of 0.15% versus 0.12%, respectively ($P=0.8$). In a meta-analysis of pooled data for all statin trials with published information on change in HbA_{1c} in those with diabetes mellitus, statin therapy raised HbA_{1c}, but only by 0.12% (95% CI, 0.04%–0.20%) on average.¹³² The relationship between HbA_{1c} and CVD risk in trials of intensive glucose lowering versus standard therapy is weak.¹³³ Therefore, the very small increase in HbA_{1c} seems highly unlikely to introduce any material change in cardiovascular risk.

A meta-analysis of major trials¹¹⁴ has demonstrated that statin therapy increases body weight compared with control by a clinically unimportant amount (0.24 kg) over 4 years.

2.2.3. Conclusions

Statin therapy modestly increases the risk of developing diabetes mellitus via mechanisms not yet understood. The HR is ≈ 1.1 for moderate-dose and 1.2 for intensive statin therapy for 5 years. The risk is largely confined to patients with multiple preexisting risk factors for diabetes mellitus. The absolute risk of statin-induced diabetes mellitus in major trials has been $\approx 0.2\%$ per year. The size of any effect in routine clinical practice will depend on the baseline risk for developing diabetes mellitus in the patient population. In addition, in patients with diabetes mellitus, the average increase in HbA_{1c} with initiation of statin therapy is small and thus is usually of limited clinical significance. Most importantly, however, it is well established that statin therapy substantially reduces cardiovascular events in those with and without diabetes mellitus and that in the latter case, several cardiovascular events are prevented for every new diagnosis of diabetes mellitus. Furthermore, when considering the increase in newly diagnosed diabetes mellitus, it is important to note that this represents a far less dramatic and threatening event than the occurrence of MI, stroke, or cardiovascular death. The increased risk of diabetes mellitus should not deter statin use in patients considered to be at sufficiently high CVD risk to warrant statin treatment, although it is prudent both to increase efforts at diabetes mellitus prevention and to screen for the development of diabetes mellitus in patients at elevated risk for diabetes mellitus, especially in those on intensive statin therapy.

2.3. Liver

2.3.1. Transaminase Elevations

Concern about statin effects on the liver originally stemmed from animal safety studies. Lovastatin causes hepatocellular injury in rats and liver necrosis in rabbits.¹³⁴ Statins may be associated with mild transaminase elevations <3 times the ULN,

sometimes in the context of nonalcoholic fatty liver disease or alcohol use.^{135,136} The best available data find statins also cause dose-related asymptomatic increases >3 times the ULN in liver transaminases, confirmed by a repeat measurement in $\approx 1\%$ of patients.⁴⁶ In TNT (Treat to New Targets),⁴³ which compared atorvastatin 80 mg versus 10 mg daily in 10001 patients followed up for a median of 4.9 years, there were 60 cases of confirmed elevations in transaminases >3 times the ULN on 80 mg compared with 9 cases on 10 mg (1.2% versus 0.2%; $P<0.001$). Elevations in transaminases reflect enzyme release from hepatocytes but do not specifically relate to impaired liver function or hepatocellular injury,¹³⁷ which would require demonstration of alterations in albumin, prothrombin time, or direct bilirubin.^{135,138} For many years, periodic measurement of transaminases was recommended in the prescribing information for all statins, but in 2012, the FDA issued a safety statement recommending transaminase measurement only before starting statin therapy and thereafter when clinically indicated.¹³⁹ The underlying reasoning was that clinically apparent statin hepatotoxicity is very rare, as discussed under 2.3.2. Hepatotoxicity, and monitoring transaminases has never been shown to be useful in preventing it.¹³⁹

When statins increase transaminases, the elevation in ALT is nearly always greater than the increase in aspartate aminotransferase (AST), consistent with a hepatic effect.^{25,46} If AST rises more than ALT, another pathogenesis might be the cause. For example, muscle injury will release AST and ALT (typically with higher AST levels than ALT levels), and this can be readily distinguished from a liver source by measuring CK, which will be elevated if the source is muscle. Alcohol exposure can also increase AST more than ALT.

2.3.2. Hepatotoxicity

There were generally very low rates of severe liver injury in the large statin RCTs, which suggests either that statins do not cause severe liver injury or that the incidence of statin-related severe liver injury is too low to be detected in these clinical trials. In EXCEL, the 48-week RCT of lovastatin versus placebo in >8000 patients, described in the Muscle section, there were no cases of clinically symptomatic hepatitis.⁴⁶ In HPS, in which >20000 patients were randomized to simvastatin 40 mg or placebo for 5 years, there were 6 and 9 cases, respectively, of clinical hepatitis.³⁸ In a meta-analysis of pooled individual patient data from early atorvastatin trials,⁴⁵ noninfectious hepatitis was reported in 5 (0.1%) of 4798 patients taking atorvastatin 80 mg/d. Three of these were in 1 placebo-controlled study in 3086 patients with acute coronary syndrome.¹⁴⁰ Importantly, all cases resolved within 4 weeks of drug discontinuation. In JUPITER, in which nearly 18000 patients were randomized to rosuvastatin 20 mg or placebo for 1.9 years, hepatic disorder was a monitored adverse event, and the rates were similar in the rosuvastatin and placebo groups, 2.4% versus 2.1% ($P=0.13$).³⁹

Severe liver injury related to statin therapy in clinical practice has been described in case reports and registry studies. After >20 years of clinical use, a 2009 literature review identified only 40 case reports of statin-related drug-induced liver injury,¹⁴¹ 2 of which were fatal. Björnsson et al¹⁴² analyzed drug-induced liver injury suspected to be caused by

statins using data from the Swedish Adverse Drug Reactions Advisory Committee collected over 22 years (1988–2010). In Sweden, reporting of serious adverse events that could be caused by a drug has been compulsory since 1975, so the underreporting problem typical of registry studies is substantially mitigated. The authors assessed causality in 73 reports of possible statin-induced liver injury, the largest series thus far reported, and found a high probability of a causal relationship in 7 cases, probable causality in 14 cases, and possible causality in 52 cases. The median elevation in ALT was >10 times the ULN, and 35% had jaundice at presentation. Most of these patients were taking atorvastatin (30 patients) or simvastatin (28 patients), the statins most commonly used in Sweden between 1998 and 2010. When the larger number of prescriptions for simvastatin is taken into account, atorvastatin was significantly more commonly associated with liver injury than simvastatin. The atorvastatin cases were more likely to be of a cholestatic/mixed pattern (57%) than the simvastatin cases (25%), with the remainder showing a hepatocellular pattern. The average time between statin initiation and increase in liver enzymes to >5 times the ULN was 3 months. Three patients were rechallenged with the same statin, with a similar result during the second exposure. The authors concluded that liver injury could be caused by statin therapy but is extremely rare, reported in ≈ 1 in 100 000 individuals treated with statins.¹⁴²

A recent comparison of hepatotoxicity during therapy with simvastatin versus atorvastatin using the UK General Practice Research Database yielded higher incidences, but unlike the Swedish study, in which full medical records were available in most cases, only biochemical end points were used, and statin causality was not evaluated.¹⁴³ However, consistent with the Swedish study, the United Kingdom study suggested a higher risk with high-dose atorvastatin than with high-dose simvastatin.

The postmarketing reviews of statins and hepatotoxicity conducted by the FDA between 2000 and 2009 through the agency's adverse event reporting system also found an extremely low reporting rate of serious liver injury, death, or liver transplantation attributable to statin use (≤ 2 per 1 million patient-years).¹³⁹ There were 75 cases (27 severe liver injury, 37 deaths, and 11 liver transplantations), of which 30 were found to be either possibly or probably associated with statin therapy. No cases were assessed as highly likely or definitively caused by statin therapy. The FDA concluded that there was no increase in the incidence of fatal or severe liver injury despite the growing use of statin therapy since the 1990s. Rechallenge with a statin could result in the same liver injury and is not recommended.

2.3.3. Conclusions

Statins cause asymptomatic, dose-related confirmed elevations >3 times the ULN in transaminases in $\approx 1\%$ of patients, but this alone does not indicate liver injury. Monitoring transaminases is not useful for preventing clinically apparent statin hepatotoxicity, which is extremely rare, occurring in $\approx 0.001\%$ of patients. It is not currently possible to predict in advance which patients will develop serious hepatotoxicity, so providers need to be alert to symptoms and signs of this

rare complication, particularly in patients with preexisting liver disease.

2.4. Neurological Adverse Events

2.4.1. Hemorrhagic Stroke

In Western countries, $\approx 87\%$ of strokes are ischemic and 13% are hemorrhagic (10% parenchymal and 3% subarachnoid hemorrhages).¹⁴⁴ Some epidemiological studies find an inverse relationship between cholesterol levels and the risk of hemorrhagic stroke. For example, data from MRFIT (Multiple Risk Factor Intervention Trial), which included 361 662 men from 22 clinical centers in the United States, showed that the RR for intracranial hemorrhage–associated death was highest in those with the lowest total cholesterol level (<160 mg/dL [<4.14 mmol/L]), whereas the risk of death from ischemic stroke increased with increasing cholesterol.¹⁴⁵ In the Asian Cohort Study, there was a 20% decrease in hemorrhagic stroke per 4.5 mg/dL increase in total cholesterol.¹⁴⁶ The relationship can be more complex if lipid subclasses are considered. One study¹⁴⁷ found that higher high-density lipoprotein cholesterol is associated with a lower risk of ischemic stroke, with no effect of total cholesterol or LDL-C; in contrast, higher high-density lipoprotein cholesterol is associated with a higher risk of hemorrhagic stroke, with higher total cholesterol and LDL-C associated with a lower risk.¹⁴⁷ These and other observational studies that suggested an increased risk of hemorrhagic stroke in populations with lower cholesterol levels raised concern that the risk would also be higher in those treated with statins.

In contrast to epidemiological studies, there is a paucity of data from randomized trials showing an increased risk of hemorrhagic stroke among those treated with statins who have established coronary heart disease or other high-risk conditions but no history of stroke. A tabular data meta-analysis of 23 randomized trials and 19 observational studies (248 391 subjects, 14 784 intracerebral hemorrhages) found no association between statin treatment and increased risk of intracerebral hemorrhage in RCTs (RR, 1.10; 95% CI, 0.86–1.41), cohort studies (RR, 0.94; 95% CI, 0.81–1.10), or case-control studies (RR, 0.60; 95% CI, 0.41–0.88).¹⁴⁸ The analysis, however, combined studies of the effects of statins in primary and secondary stroke prevention populations.

Meta-analysis of published study-level data from statin trials assessing the risk of hemorrhagic stroke among those with no history of stroke (ie, a stroke primary prevention population) found a nonsignificant reduction in the risk of hemorrhagic stroke with statin therapy (RR, 0.81; 95% CI, 0.60–1.08).¹⁴⁹ There is also no evidence of increased risk of brain hemorrhage with high- versus low-intensity statin therapy in a primary stroke prevention population. For example, the risk of brain hemorrhage was similar with high-intensity (mean LDL-C, 77 mg/dL) and low-intensity (mean LDL-C, 101 mg/dL) statin treatment in subjects with stable coronary heart disease, with no relationship between bleeding risk and the quintile of achieved LDL-C.¹⁵⁰ Meta-analysis using individual patient data of 5 trials of more versus less intensive statin therapy in subjects with stable coronary artery disease or acute coronary syndromes found a 16% (99% CI,

1%–29%) reduction in the risk of a first ischemic stroke (RR, 0.84; 99% CI, 0.71–0.99; $P=0.005$), with a nonsignificant increase in hemorrhagic stroke (RR, 1.21; 99% CI, 0.76–1.91; $P=0.3$).⁴ Analysis of individual patient data from 26 statin trials found a 16% (95% CI, 11%–21%; $P<0.0001$) reduction in all strokes per 1.0 mmol/L LDL-C reduction, with a reduction in ischemic stroke (RR, 0.79; 95% CI, 0.74–0.85; $P<0.0001$) and a nonsignificant increase in hemorrhagic stroke (RR, 1.12; 95% CI, 0.93–1.35; $P=0.2$).⁴

Although there is no demonstrable increased risk of hemorrhagic stroke attributable to statin treatment, with an overall reduction in all strokes associated with statin treatment in primary stroke prevention populations, interpretation of data from secondary stroke prevention studies has been more controversial. The study-level meta-analysis by Amarenco et al¹⁴⁹ focused on the effect of statins on hemorrhagic stroke risk in randomized stroke secondary prevention trials and found an increased risk with treatment (RR, 1.73; 95% CI, 1.19–2.50). This estimate is based on post hoc subgroup analyses of 2 trials. In HPS, there was no overall statin-associated increased risk of hemorrhagic stroke, but there was statistical heterogeneity based on the presence or absence of a history of prior cerebrovascular disease ($P=0.03$), with higher risk among those with a history of stroke (1.3% versus 0.7%).¹⁵¹ In SPARCL (Stroke Prevention with Aggressive Reduction in Cholesterol Levels),³⁷ which evaluated the effects of atorvastatin 80 mg/d compared with placebo in 4731 patients with a history of stroke (69%) or transient ischemic attack (31%) followed up for a median of 4.9 years, the overall benefit of atorvastatin 80 mg in reducing recurrent stroke was partially offset by an increased risk of brain hemorrhage (HR, 1.66; 95% CI, 1.08–2.55). There was no relationship between achieved LDL-C and hemorrhagic stroke risk among statin-treated subjects. A study-level meta-analysis by Hackam et al¹⁴⁸ that included cohort, case-control, and randomized trials, however, found no increased risk of recurrent brain hemorrhage associated with statins in patients with a history of cerebrovascular disease (adjusted RR, 0.7; 95% CI, 0.2–3.4).

2.4.1.1. Conclusions

The available data in aggregate show no increased risk of brain hemorrhage with statin use in primary stroke prevention populations. An increased risk in secondary stroke prevention populations is possible, but the absolute risk is very small, and the benefit in reducing overall stroke and other vascular events generally outweighs that risk.

2.4.2. Central Nervous System Function

The prescribing information for all statins notes rare reports of cognitive impairment during postmarketing use. These reports generally describe nonserious reversible forgetfulness, confusion, and other forms of cognitive impairment, but the prescribing information states that a causal link between these effects and any statin has not been established. Complaints such as these are common in middle-aged and older people, regardless of whether or not they are treated with a statin. RCTs are therefore required to evaluate causality.

Cognitive function was specifically assessed in 2 cardiovascular outcome statin trials, HPS⁴⁷ and PROSPER (Prospective Study of Pravastatin in the Elderly at Risk),¹¹⁸

both of which included several thousand patients >70 years of age randomized to simvastatin 40 mg or placebo (for 5 years) and pravastatin 40 mg or placebo (for 3 years), respectively. In both trials, the frequency of cognitive impairment in the statin and placebo groups was similar and not statistically different. A third study randomized 640 patients with mild to moderate Alzheimer disease to atorvastatin 80 mg or placebo for 72 weeks to test the hypothesis that statin therapy could benefit patients with the disease.¹⁵² There was no significant difference in change in cognitive function between the statin and placebo groups. The issue has also been examined in several overviews^{153–155} of both RCTs and observational data, with no conclusive evidence for either cognitive benefit or harm from statin therapy.

Sleep disturbances and insomnia have also been reported in patients taking statins. Although there are anecdotal reports related to nightmares and adverse sleep quality, most notably with lovastatin, simvastatin, and rosuvastatin, evidence from observational studies, some of the large statin RCTs, and the few small RCTs that used polysomnography have not supported this conclusion.^{156–160} For example, in the CARDS trial of patients with type 2 diabetes mellitus, reports of insomnia did not differ among patients randomized to atorvastatin 10 mg/d (3.2%) or placebo (3.8%) during the follow-up period of 3.9 years.¹²⁹ Moreover, in JUPITER, insomnia was reported in 222 patients (2.7%) allocated to rosuvastatin 20 mg/d compared with 205 (2.5%) allocated to placebo over a median of 2 years.¹⁶¹ A recent careful study-level meta-analysis of RCTs providing data on sleep, mood, and physical function found no evidence of adverse effects of statins on these outcomes.¹⁶²

Association of other central nervous system disorders with statin use has been suggested but never proven. Among these is amyotrophic lateral sclerosis (ALS), triggered by a report of a higher than expected number of ALS-like case reports associated with statin use.¹⁶³ There was no dose-response relationship, and the authors were careful to point out that their results should only be considered hypothesis generating. A subsequent pooled meta-analysis of 3 observational studies (2 case-control and 1 retrospective cohort) produced no evidence for an association between statin use and ALS.¹⁶⁴ Overall, there is no conclusive evidence that statins cause ALS or increase ALS disease progression.¹⁶⁴

Other neurodegenerative disorders have also been evaluated with respect to statin use. Observational studies have hypothesized both protective¹⁶⁵ and adverse effects¹⁶⁶ of statins on the risk of developing Parkinson disease, but there has been no reported signal in RCTs.

2.4.2.1. Conclusions

Overall, there is no evidence that statins increase the risk of disorders of the central nervous system, with the possible exception of hemorrhagic stroke.

2.4.3. Peripheral Neuropathy

Peripheral neuropathy is a common clinical problem, affecting ≈8% of the population >55 years of age.¹⁶⁷ In developed countries, the most common cause is diabetes mellitus, but the disorder is associated with a wide variety of diseases and drugs.¹⁶⁷ Data on the frequency of peripheral neuropathy in

patients taking statins are available from both epidemiological studies and RCTs.

A population-based cohort study from the UK General Practitioner Database compared the frequency of peripheral neuropathy among patients aged 40 to 70 years who received at least 1 prescription for a lipid-lowering drug between 1991 and 1997 (n=17 219) with that of patients with hyperlipidemia not prescribed a lipid-lowering medication (n=28 974) and with the general population (n=50 000).¹⁶⁸ There was no significant difference among these comparisons. A nested case-control study in a Danish population between 1994 and 1998 identified 166 new cases of definite, probable, and possible idiopathic peripheral neuropathy, each of whom was matched with 25 control subjects without neuropathy on the basis of age, sex, and index date.¹⁶⁹ Subjects were classified as a current statin user (prescription within 3 months of the index date), as a past user, or as never having been prescribed a statin. Relative to control subjects, the risk of definite or suspected newly diagnosed neuropathy was higher among statin users (OR, 3.7; 95% CI, 1.8–7.6) and even higher among those with definite neuropathy (OR, 14.2; 95% CI, 5.3–38.0). Another case-control study used hospital discharge and mortality databases to identify the date of diagnosis among 2040 patients for whom peripheral neuropathy was the principal reason for admission or death.¹⁷⁰ These were then compared with up to 20 control subjects per case from 36 041 individuals from the general population, matched for age, sex, index date, and primary care provider. A prescription database was used to identify those who had been prescribed a lipid-lowering drug during the year before the index date. The adjusted (thyroid disease, diabetes mellitus, anemia, chronic renal failure, connective tissue disease) OR for newly diagnosed neuropathy was higher among those prescribed statins (OR, 1.22; 95% CI, 1.03–1.45) or fibrates (OR, 1.54; 95% CI, 1.07–2.23). In addition, a small prospective study in 43 individuals found that statin use correlated with peripheral nerve damage over a 3-year period.¹⁷¹

In contrast to these analyses is the result of a subgroup analysis of data from the longitudinal Fremantle Diabetes Study, an observational cohort study.¹⁷² The subgroup included 395 people with type 2 diabetes mellitus who did not have neuropathy at baseline. Both statin use (HR, 0.70; 95% CI, 0.49–0.997; $P=0.048$) and fibrate use (HR, 0.51; 95% CI, 0.27–0.97; $P=0.04$) were independently inversely associated with the development of peripheral sensory neuropathy. This finding was consistent with an analysis of data from the Danish Patient Registry in which 15 679 individuals who had used statins regularly until a diagnosis of diabetes mellitus (statin users) were matched with 47 037 individuals who had never used statins before diagnosis (non-statin users).¹⁷³ Statin users had a lower incidence of diabetic neuropathy (HR, 0.66; 95% CI, 0.57–0.75; $P<0.0001$) than nonusers. These studies were conducted in European or Australian populations.

In the United States, data from the lower-extremity supplement of the 1999 to 2005 National Health and Nutritional Examination Survey were used to evaluate the prevalence of idiopathic peripheral neuropathy among statin users (23.5%) compared with nonusers (13.5%; $P<0.01$).¹⁷⁴ Statin use was

associated with an increased risk of neuropathy (OR, 1.3; 95% CI, 1.1–1.6; $P=0.04$).

The epidemiological studies summarized here are thus inconsistent. The limitations of observational studies and their vulnerability to various sources of confounding have been discussed in 1. Assessment of Adverse Events. In contrast, in large, long-term RCTs, peripheral neuropathy has not been reported more frequently in patients allocated to a statin than in those allocated to placebo.^{47,76,129}

2.4.3.1. Conclusions

Although some observational studies suggest a possible association between statin use (prior or current) and newly diagnosed peripheral neuropathy, the results of such studies are inconsistent, and there is no support of a causal relationship in RCTs. Additional data should be forthcoming from a planned meta-analysis of individual patient safety data from randomized trials of statin therapy. At the present time, however, there is no conclusive evidence for a causal relationship between statin treatment and peripheral neuropathy.

2.5. Steroidogenesis

Because cholesterol is the precursor of all steroid hormones, possible effects on steroidogenesis have been evaluated since the earliest clinical studies with lovastatin and the 2 subsequently approved statins, simvastatin and pravastatin. There are few published data on the other 4 statins, perhaps because concerns were allayed by the absence of clinically significant effects with lovastatin, simvastatin, or pravastatin.

2.5.1. Glucocorticoids

Possible effects of statins on basal and adrenocorticotropic hormone-stimulated cortisol have been examined in several studies, which found no consistent or clinically significant differences between statin and placebo.^{175–179}

2.5.2. Sex Hormones

This section is confined to studies in adults; studies in adolescents are summarized in 4.2. Children and Adolescents.

2.5.2.1. Male Gonadal Function

Studies that examined the effect of statins on male gonadal function are mostly uncontrolled or have small numbers of subjects and therefore limited statistical power. The most comprehensive study randomized 159 men, healthy except for hypercholesterolemia, to simvastatin 20 mg, simvastatin 40 mg, pravastatin 40 mg, and placebo using a double-blind, parallel design and 24-week treatment duration.¹⁸⁰ In addition to measuring basal testosterone, a human chorionic gonadotropin stimulation test to evaluate testosterone reserve and an assay for semen quality were performed at baseline and 24 weeks. No significant between-treatment effects were observed in basal or stimulated testosterone or in free testosterone index, sex hormone-binding globulin, luteinizing hormone, or follicle-stimulating hormone. There were also no significant differences in semen quality. A subsequent RCT by the same group randomized 81 men to simvastatin 80 mg (a dose above the current recommended dosage range; see 2.1. Muscle) or placebo for 12 weeks.¹⁷⁹ Median total, free, and bioavailable testosterone declined by $\approx 10\%$ at 12 weeks

in the simvastatin 80 mg group relative to placebo, but only the change in bioavailable testosterone was statistically significant. There were no significant changes in serum gonadotropin levels or sex hormone-binding globulin, and there were no differences between treatments in testosterone reserve, measured by human chorionic gonadotrophin stimulation test at baseline and 12 weeks.

Plasma testosterone is variable, within and between individuals, and has a wide normal range. The relationship between changes in testosterone levels that remain in the normal range and libido, muscle mass, and bone mass have not been adequately studied. The clinical significance of a 10% decline in bioavailable testosterone with simvastatin 80 mg, a dose no longer used, is not clear. There is no evidence that statins cause erectile dysfunction. The results of 2 recent meta-analyses of double-blind RCTs, one confined to studies that evaluated statins for the treatment of erectile dysfunction¹⁸¹ and the other¹⁸² potentially including any study with erectile dysfunction as an outcome measure, found no evidence that statins impair erectile function. Indeed, both found a significant improvement compared with placebo in erectile function, although the mechanism is unclear.

2.5.2.2. Female Gonadal Function

All statins are contraindicated in pregnancy and should be used in women of reproductive age only in those who are very unlikely to conceive (see 4.4. Pregnancy and Breastfeeding). Consequently, few studies have evaluated female gonadal function in an RCT. Plotkin et al¹⁸³ compared simvastatin 40 mg and placebo in a randomized, double-blind, parallel, placebo-controlled, multicenter study in 81 women. The study spanned 6 consecutive menstrual cycles, of which the second and sixth were monitored hormonally and considered baseline and treatment cycles, respectively. The primary end point was change from baseline in luteal phase length, taken to be the time between the urinary luteinizing hormone peak and the day before the onset of menstruation. As the final common pathway for normal folliculogenesis and ovulation, the luteal phase of the menstrual cycle is a clinically relevant measure of female gonadal function. The mean luteal phase lengths for the simvastatin group were 14.5 and 14.9 days at baseline and in cycle 6, respectively, a nonsignificant difference. The corresponding values in the placebo group were 14.9 and 13.9 days ($P<0.05$). This between-group difference in change from baseline of 1.4 days ($P<0.05$) is difficult to interpret because of the significant reduction in the placebo group luteal phase length. There was no effect of simvastatin on progesterone synthesis as measured by the urinary excretion of pregnandiol, its principal metabolite. The authors concluded that their study provided no evidence for adverse effects on the menstrual cycle but cautioned that statins should only be used in premenopausal women when conception is very unlikely.

2.5.3. Conclusions

Statins have minimal if any effects on steroidogenesis, and none are clinically relevant. They might slightly reduce plasma testosterone, but they do not cause hypogonadism, and their effect on erectile function is not adverse and could be beneficial.

2.6. Cataracts

Early attempts to reduce blood cholesterol by inhibiting cholesterol biosynthesis were disastrous. Triparanol, which inhibits a late step in the pathway, was introduced into clinical use in the mid 1960s but was soon withdrawn because of the development of cataracts in patients of all ages, as well as a variety of cutaneous adverse effects.¹⁸⁴ These side effects were attributable to tissue accumulation of desmosterol, the substrate for the inhibited enzyme 24-dehydrocholesterol reductase. Statins inhibit HMG-CoA reductase, a much earlier step in the pathway of cholesterol synthesis. In dogs, lovastatin and simvastatin produce subcapsular lens opacities when given in doses well above the maximal human dose.¹⁸⁵ These animal data, the triparanol experience, and some uncontrolled clinical trial extension data with lovastatin showing an increase in lens opacities together raised significant concern. Consequently, the initial prescribing information for lovastatin, simvastatin, and pravastatin required monitoring by slit-lamp examination for detection of lens opacities before starting treatment and periodically thereafter.^{15,25}

2.6.1. Randomized Controlled Trials

Substantial effort was devoted to evaluating possible adverse effects of lovastatin, simvastatin, and pravastatin on the human lens. In the 48-week EXCEL study previously described in the Muscle section, there were no differences between the lovastatin and placebo groups in rates of lens opacities in any location by slit-lamp examination or in loss of visual acuity.^{186,187} These data allowed the burdensome requirement for slit-lamp examination before and during therapy to be removed from the prescribing information in 1991. Longer-term data were later provided by 4S, which randomized 4444 patients to simvastatin 20 to 40 mg or placebo for a median of 5.4 years.^{2,76} Slit-lamp examinations were performed at baseline, 1 year, and the end of the study. Ophthalmological data were available at baseline and at least 1 point during follow-up in 3943 patients (89%). The rates of lens opacities were similar in the simvastatin and placebo groups at baseline and during follow-up, as were the rates of lens opacities subdivided by type: posterior subcapsular, anterior subcapsular, wedges and spokes, nuclear opacity, and nuclear sclerosis.

More recently, HOPE-3⁷⁵ and JUPITER³⁹ reported rates of cataracts without any specific requirement for ophthalmological examinations. Among 12 705 participants randomized to rosuvastatin 10 mg compared with placebo in HOPE-3 and followed up for 5.6 years, there was a small but nominally (ie, without adjustment for the multiple comparisons of adverse event rates) significant increase in surgery for cataracts (3.8% versus 3.1%; $P=0.02$). In contrast, in JUPITER, in which 17 802 subjects were followed up for 1.9 years, the incidence of cataracts was slightly but not significantly lower in the group allocated to rosuvastatin 20 mg compared with placebo: 180 (2.0%) versus 196 (2.2%).⁶⁹ Although the duration of treatment in JUPITER was only one-third of that in HOPE-3, JUPITER was considerably larger, and the dose of rosuvastatin was twice that in HOPE-3. Subdividing patients in JUPITER according to whether or not they attained LDL-C below 50 mg/dL provided no suggestion of a risk attributable to very low LDL-C.¹⁶¹ In a substudy of another RCT

that compared the combination of simvastatin and ezetimibe versus placebo in patients with aortic stenosis, the incidence of cataracts was significantly lower in the simvastatin/ezetimibe group.¹⁸⁸

2.6.2. Case-Control and Observational Cohort Studies

Numerous epidemiological studies explored associations between statin treatment and the development of lens opacities or frank cataracts. The hypotheses raised by these studies cover all possibilities: statins can increase the risk of opacities,^{189,190} have a mixed effect,¹⁹¹ or reduce the risk.¹⁹² Importantly, the magnitude of the associations in the cited studies and others is modest, with increases or decreases in the risk of cataracts or lens opacities typically around 30%. In no case has there been a several-fold increase. As discussed in 1. Assessment of Adverse Events, observational studies are subject to several well-known biases, any of which can account for modest associations, regardless of the size of the study and attempts to reduce bias by statistical techniques.^{17,19–21}

2.6.3. Conclusion

The preponderance of the evidence indicates that statins in clinical use do not increase the risk of cataracts.

2.7. Kidney

This section deals with potential adverse renal effects of statins in patients with normal renal function. The use of statins in patients with CKD is considered in 5.3. Chronic Kidney Disease.

2.7.1. Proteinuria and Renal Function

Rosuvastatin can cause dipstick-positive proteinuria and microscopic hematuria at the maximal dose of 40 mg.⁴⁸ These effects are generally transient, not associated with worsening renal function, and of unclear clinical significance. Other statins do not appear to share this effect. A potential mechanism for the proteinuria could be statin-induced reduction of receptor mediated endocytosis,¹⁹³ a process by which proximal tubular cells take up albumin, but this explanation does not account for the hematuria.⁴⁸

A meta-analysis evaluated proteinuria or albuminuria in 29 RCTs in 4968 adult participants who were treated with statins for at least 6 months.¹⁹⁴ Statin treatment compared with placebo or usual care was associated with a small but statistically significant reduction in proteinuria (−0.65 g per 24 hours; 95% CI, −0.94 to −0.37). Comparison of specific agents in individual trials found that atorvastatin was associated with a greater reduction in proteinuria than rosuvastatin. In a meta-analysis combining published data from 47 trials in 128 601 participants, statin therapy very slightly slowed the rate of decline of estimated glomerular filtration rate per year (by 0.41 mL·min^{−1}·1.73 m^{−2}) compared with placebo or usual care groups. Importantly, there was no adverse effect of statins on kidney failure rates (as defined in the component RCTs) collectively or for any individual statin, including rosuvastatin.¹⁹⁴ Additional data from a post hoc analysis of TNT found that in ≈6500 participants with normal estimated glomerular filtration rate and in ≈3100 participants with CKD, the incidence of albuminuria was similar among participants allocated to atorvastatin 10 mg

and those allocated to atorvastatin 80 mg, which suggests that intensive lipid-lowering therapy with atorvastatin does not affect proteinuria.¹⁹⁵ In the JUPITER trial, conducted in >17 000 patients, there were no significant differences between the rosuvastatin 20 mg and placebo groups in renal safety measures, including doubling of creatinine.³⁹ There were no differences between groups in the incidence of acute renal failure (19 and 16 cases, respectively, for rosuvastatin and placebo).⁶⁹

2.7.2. Acute Kidney Injury

Statins can cause AKI via rhabdomyolysis, with acute renal failure if there is sufficient myoglobinuria, although fortunately, fatalities have been rare. It is imperative to stop the statin before renal injury occurs. Overall, AKI caused by rhabdomyolysis is a rare adverse event at the recommended doses of all marketed statins, with an incidence of <1 in 10 000 patients treated (see 2.1. Muscle).¹⁹

A retrospective observational study found that higher-potency statins were associated with increased hospitalization rates for acute renal injury compared with lower-potency statins.¹⁹⁶ This study could well be confounded by indication, because sicker patients are potentially more likely to receive higher-potency statins or have baseline comorbidities that further drive hospitalization rates. A pooled analysis of 24 short- and long-term placebo-controlled trials of atorvastatin, as well as separate analyses of 2 long-term cardiovascular outcome trials of high-dose statin versus low-dose statin, including TNT (atorvastatin 80 mg versus atorvastatin 10 mg) and IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; atorvastatin 80 mg versus simvastatin 20 mg), found no difference between atorvastatin and placebo or between high- and low-dose statin in renal-related serious adverse events or withdrawal of treatment because of renal-related serious adverse events.¹⁹⁷

2.7.2.1. Perioperative Statins and AKI

AKI is a known complication of cardiac surgery, and practice guidelines have recommended perioperative statins because observational studies evaluating patients undergoing cardiac surgery have found an association with reduced incidence of atrial fibrillation and prevention of cardiac surgical complications including AKI.^{198,199} Two recent RCTs, however, did not find a benefit of perioperative statin therapy on the risk of developing AKI.^{200,201} One of these trials, which randomized 1922 patients undergoing cardiac surgery to rosuvastatin 20 mg/d or placebo, reported a statistically significant 5.4% absolute increase in AKI within 48 hours of surgery (237/960 patients randomized to rosuvastatin versus 186/962 patients randomized to placebo; *P*=0.005).²⁰⁰ Another study in 615 perioperative patients undergoing cardiac surgery compared atorvastatin 80 mg/d, and then 40 mg/d, to placebo and found no difference in the risk of developing AKI (the primary end point) among the groups when all participants were considered.²⁰¹ In a subgroup of patients (*n*=36) who were both statin naïve and had prior CKD, there was an increase in AKI (*P*=0.03), but as with any subgroup analysis that is inconsistent with the main result, the significance of this finding is doubtful.

2.7.3. Conclusions

Rosuvastatin at its maximal 40 mg dose can cause transient proteinuria and microscopic hematuria, but statins, including rosuvastatin, do not cause or worsen proteinuria long-term, do not cause acute renal injury in individuals without rhabdomyolysis, and do not worsen renal function. In the setting of cardiac surgery, however, perioperative statin treatment in statin-naïve patients could increase the risk of renal injury.

2.8. Tendonitis and Tendon Rupture

Achilles tenosynovitis can occur in people with FH, who might present with this condition before the diagnosis of FH has been made.²⁰² In addition, initial statin treatment has been associated with Achilles tenosynovitis in patients with FH, but this reaction might be caused in part by the rapid reduction in cholesterol rather than the statin itself.

Case reports of spontaneous tendonitis or tendon rupture in users of statins (who do not have FH) have been reported since 1990.^{203–205} These reports are rare but have raised the question as to whether statin use increases the risk of tendon complications. All data on tendonitis and tendon rupture are from case reports and observational studies. No large RCT has reported a significant excess of tendon disease in patients taking statin compared with placebo.

In a retrospective analysis of cases reported to 31 French pharmacovigilance centers to determine the rates of tendon rupture or tendonitis among statin users, there were 8 reports of tendinous complications from 1990 to 1995, 32 from 1996 to 2000, and 56 from 2001 to 2005.²⁰⁵ Because there was no comparator group in people not using statins, it is unknown whether these rates of tendinopathy while being treated with statins are different from rates in people not taking statins. The increase in reports of tendon disorders between 1990 and 2005 could reflect wider statin use. Tendonitis was more common than tendon rupture, and the incidence of tendon disorders was higher in men than in women.

To gain a better understanding of whether statin therapy is related to tendinopathy, a systematic review was conducted that included 3 cohort studies and 1 case-control study.²⁰⁶ The results were summarized using a best evidence synthesis, and causation was assessed with Bradford Hill criteria.²¹ Tendon rupture was the primary outcome in 3 studies^{207–209} and rotator cuff injury in the other.²¹⁰ None of the studies found a positive association between statin therapy and tendon rupture for the total study population. In the largest study, in $\approx 35\,000$ people taking statins and 70 000 people not taking statins, there was no difference in rates of tendon rupture after adjustment for comorbidities, age, and sex (incidence rate ratio, 1.13; 95% CI, 0.98–1.29).²⁰⁹ Although 1 small study reported no difference in tendon rupture in the entire cohort (93 case subjects and 279 control subjects), an increase was reported in women.²⁰⁷ This result should be viewed cautiously because of the small number of female case subjects, as well as the observational nature of the study, thereby precluding a causality inference. In the cohort study that evaluated rotator cuff injury, in 2475 patients with hyperlipidemia followed up for 11 years, with or without statin therapy, there were fewer cases of rotator cuff damage in patients taking statins than in those not taking

statins (rosuvastatin: HR, 0.41; 95% CI, 0.34–0.49; $P < 0.0001$; simvastatin: HR, 0.62; 95% CI, 0.54–0.71; $P < 0.0001$; other statins: HR, 0.66; 95% CI, 0.60–0.72, $P < 0.0001$).²¹⁰ As an observational study, the data are hypothesis generating, although it is doubtful that a clinical trial will be conducted to evaluate statin treatment for rotator cuff injury.

2.8.1. Conclusions

The only studies of statins and tendonitis or tendon rupture are observational and show no consistent difference between statin users and nonusers. There is no good evidence to suggest that statins increase the risk of tendonitis or tendon rupture.

2.9. Cancer

As noted in the nonclinical toxicology section of the prescribing information and elsewhere,^{134,211} statins are not mutagenic. Rodent carcinogenicity studies are required by regulatory agencies to include the maximum tolerated dose over most of the species' adult lifetime. These studies are generally conducted using 3 doses, and the highest statin dose was typically at least 100 mg/kg (ie, >100 times greater than approved human doses per kilogram). Under these conditions, statins produced tumors of the liver and other sites.¹³⁴ Details for individual statins are provided in the prescribing information.

There is no evidence for carcinogenicity in humans treated at therapeutic doses. An excess of breast cancer with pravastatin 40 mg/d relative to placebo was noted in one²¹² of some 30 cardiovascular outcome trials, and an excess of total cancers in another such study was seen with pravastatin 40 mg/d.¹¹⁸ A few imbalances are expected when multiple comparisons are made in multiple studies, and these results have not been replicated in other studies with pravastatin 40 mg.²¹³ A meta-analysis using individual patient records from 27 statin cardiovascular outcome trials provided no evidence for any carcinogenic effect over a median follow-up of 5 years in $\approx 175\,000$ participants, with almost identical numbers developing cancer with statin or control therapy.²¹⁴ There was no effect of statin treatment on cancer incidence or mortality, collectively or at individual sites, nor was there any evidence that reducing LDL-C to particularly low levels increased the risk of cancer. A few RCTs have followed up study participants for ≥ 10 years after the original study termination date, and these too have found no suggestion of a carcinogenic effect.^{215–219}

A large study using the Danish national registry found reduced cancer mortality and increased cardiovascular mortality in patients who had started taking a statin before the diagnosis of cancer.²²⁰ The latter finding is attributable to bias by indication: statins are prescribed to patients who have or are at high risk of developing atherosclerotic CVD. Given that RCTs consistently show no difference between statin and placebo in cancer incidence or mortality, lower cancer mortality in patients taking statins is also very likely the result of ≥ 1 of the biases that can distort the results of most epidemiological studies. The authors were careful to conclude that their results were no more than hypothesis generating.

The wealth of data on the incidence of cancer in statin cardiovascular trials and their extensions has been well summarized by Collins et al.¹⁹

Table 5. Main Pharmacokinetic Parameters of Statins

Statin	Lova	Simva	Atorva	Prava	Fluva	Rosuva	Pitava
Dose range, mg	10–80	5–40	10–80	20–80	20–80	5–40	1–4
Half-life, h	2	2	14	2	3	19	12
Bioavailability, %	5	5	15	15	25	20	50
Lactone prodrug	Yes	Yes	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	No	No	No	No
CYP2C9 substrate	No	No	No	No	Yes	Yes	Yes
OAT1B1 substrate	Yes	Yes	Yes	Yes	No	Yes	Yes
OAT1B3 substrate	No	No	No	Yes	Yes	Yes	No
P-gp substrate	Yes	Yes	Yes	No	No	No	Yes

Atorva indicates atorvastatin; CYP2C9, cytochrome P450 2C9; CYP3A4, cytochrome P450 3A4; Fluva, fluvastatin; Lova, lovastatin; OAT1B1, organic anion transporting polypeptide B1; OAT1B3, organic anion transporting polypeptide B3; Pitava, pitavastatin; Prava, pravastatin; Rosuva, rosuvastatin; and Simva, simvastatin.

2.9.1. Conclusions

To the extent that the question can be answered given the constraint that RCTs longer than 5 to 7 years are not feasible, statins do not cause cancer. The quantity and quality of cancer incidence data available for statins from RCTs is probably unmatched by any other drug class.

3. Drug-Drug Interactions

Statin metabolism and drug interactions have been covered in depth by the 2016 American Heart Association scientific statement, “Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease,”²²¹ and therefore only a brief description is provided here. In addition, the sections of the statin prescribing information that present information on drug interactions are a particularly useful and concise source of information. Pharmaceutical manufacturers and regulatory agencies are responsible for ensuring that the prescribing information for statins and interacting drugs is updated as new interactions are discovered. However, the drug-drug interactions listed in the package insert are not exhaustive, so having an understanding of the pharmacokinetics of both the substrate and interacting drug is important.

3.1. Pharmacokinetics of Statins Relevant to Drug Interactions

The pharmacokinetics of statins, summarized in Table 5, are complex.⁵² Statins are administered orally as active hydroxy acids, except for lovastatin and simvastatin, which are administered as lactone prodrugs hydrolyzed *in vivo* to the active hydroxy acid forms.^{52,222} Bioavailability, defined as the percentage of administered drug that reaches the systemic circulation, is low for all statins, particularly so for simvastatin and lovastatin ($\approx 5\%$), whereas pitavastatin has the highest ($\approx 50\%$) bioavailability of the statin class.²²¹ All statins undergo hepatic first-pass metabolism, particularly lovastatin and simvastatin, which accounts for their low bioavailability.^{52,223,224} The site of action of statins is the liver, where inhibition of HMG-CoA reductase temporarily depletes intracellular cholesterol and in turn induces production of LDL receptors. Therefore, low

bioavailability is in principle useful to reduce plasma HMG-CoA reductase inhibitory activity in the systemic circulation, where it is not needed. Drugs with very low bioavailability because of extensive hepatic first-pass metabolism, such as simvastatin and lovastatin, tend to be more vulnerable to drug interactions, as discussed in 3.5. Drug Interactions With Statins (see discussion of Table 6).

3.2. Statin Disposition and Metabolism

Statin metabolism begins with hepatic uptake, then metabolism, and finally elimination largely into either the circulation or biliary tract. Statin metabolism requires an interplay of both influx and efflux drug membrane transporters, together with metabolism usually mediated by cytochrome P450 (CYP450) isoenzymes and by glucuronidation.²²⁴

The organic anion transporting polypeptides OATP1B1 and OATP1B3 (organic anion transporting polypeptide 1B3) are primarily responsible for transporting drug substrates from the portal circulation into hepatocytes for metabolism and elimination. All statins are substrates of OATP1B1 or OATP1B3 (online Appendix 3, Table II). The statins that are lactone prodrugs, simvastatin and lovastatin, are hydrolyzed to their hydroxy acid forms either chemically or enzymatically by esterases or paraoxonases.²²⁵ Statins rapidly undergo oxidation through microsomal CYP450. The CYP450 isoenzyme family consists of series of oxidative enzymes involved in the biosynthesis of several physiologically important compounds (eg, steroids and fatty acids), as well as drug metabolism. Most of the CYP450 enzymes are expressed in the liver, but they can be found in significant concentrations in the gastrointestinal tract.

More than 50 different CYP450 enzymes have been isolated in humans; however, only a select few (ie, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) are responsible for drug metabolism.²²¹ The CYP3A4 isoenzyme is the microsomal enzyme that metabolizes lovastatin, simvastatin, and atorvastatin, whereas CYP2C9 is responsible for metabolism of fluvastatin, pitavastatin, and rosuvastatin (Table 5).²²⁶ Pravastatin is the only statin that is not metabolized by the CYP isoenzyme family.

3.3. Excretion

Both the liver and kidney are involved in the elimination of statins from the systemic circulation via bile into the feces and urine, respectively. Hepatic elimination of statins is mediated by hepatic drug membrane transporters, including OATP1B1 and P-glycoprotein.^{221,224,227} The urinary excretion of statins is quite low, with pravastatin being the highest (20%) and atorvastatin the lowest (<2%).

The plasma half-life is relatively short for fluvastatin, lovastatin, and simvastatin, which are dosed in the evening, or in the case of lovastatin and fluvastatin, formulated as extended-release preparations. Dosing of short-acting statins in the evening is more effective than in the morning²²⁸ because hepatic cholesterol biosynthesis reaches a peak at night.²²⁹ Because the mechanism of action of statins is through induction of the LDL receptor,²³⁰ which has a half-life of ≈ 24 hours,²³¹ short-acting statins can be effective. Because atorvastatin, pitavastatin, and rosuvastatin have longer half-lives, these statins can be administered at any time of day.

3.4. Genomic Variation and Effect on Statin Pharmacokinetics

As the focus on precision medicine has increased over the past decade, so has the growth of the field of pharmacogenomics. Single-nucleotide polymorphisms that code for specific drug membrane transporters or phase I metabolic enzymes in individuals and specific ethnic populations have been associated with increased statin exposure and potentially greater risk of adverse effects.²³² The OATP1B1 (*SLCO1B1*) and breast cancer resistance protein (*ABCG2*) genes have been the most studied.^{227,233} However, among all the loci identified, only the *5 allele of the *SLCO1B1* gene has been clearly associated with reduced clearance⁵⁹ and a higher risk of statin-induced myopathy,⁵³ thus far demonstrated only in the case of simvastatin.

3.5. Drug Interactions With Statins

With one important exception, statins are “victims” of drug interactions, not “perpetrators.” If drug A changes the pharmacokinetics, effectiveness, or adverse effect profile of drug B, we refer to drug A as the *perpetrator* and drug B as the *victim*. The only established case in which statins affect the action of another drug is warfarin (and potentially other vitamin K antagonists), via an unknown mechanism. As described in the prescribing information, simvastatin, lovastatin, and rosuvastatin modestly potentiate the action of warfarin, which leads to an increased international normalized ratio, which could require reduction in anticoagulant drug dosage. In most other statin drug interactions, other drugs increase the systemic plasma concentration of the statin or its active metabolites and thus increase plasma HMG-CoA reductase inhibitory activity, which is known to increase the risk of myopathy, including rhabdomyolysis. Most commonly, this is because of inhibition of ≥ 1 of CYP3A4, OAT1B1, and P-glycoprotein. Because the mechanism is competitive inhibition, most drugs perpetrating pharmacokinetic interactions with statins are given in usual doses of at least 100 mg/d in adults, and often several hundred milligrams. This is true for all the interacting drugs shown in

Table 6 except amlodipine and colchicine. According to the simvastatin prescribing information, amlodipine increases the plasma concentration of simvastatin acid (the principal active metabolite) by $\approx 60\%$, a relatively weak interaction. According to its prescribing information, colchicine has been associated with rhabdomyolysis in the absence of a statin, and it has not been shown to affect the pharmacokinetics of any statin. In general, if the usual adult daily dose of a drug is ≤ 50 mg, it is unlikely to have an important effect on the pharmacokinetics of any statin.

Grapefruit juice contains furanocoumarins that inhibit CYP3A4.²³⁴ The prescribing information notes this effect in patients treated with statins that are processed through this pathway (lovastatin, simvastatin, atorvastatin) and recommends avoiding grapefruit juice in the case of lovastatin and simvastatin, which have very similar pharmacokinetic characteristics. Concomitant grapefruit juice substantially increases the plasma concentrations of these statins and their active metabolites,²³⁵ which increases the risk of myopathy. However, the effect is modest if they are taken as recommended in the evening and grapefruit juice (200 mL) is consumed in the morning.²³⁶ Consumption of half a grapefruit a few times weekly is unlikely to be clinically consequential in patients taking simvastatin or lovastatin. An unusually large quantity, 600 mL daily of double-strength juice (ie, typically dilution of frozen concentrate with an equal volume of water) produces a 4.5-fold increase in the plasma concentration area under the curve (AUC) of simvastatin acid, the principal active metabolite,²³⁷ and should be avoided. Daily consumption of 300 mL of grapefruit juice has minimal effects on the pharmacokinetics of atorvastatin.²³⁴

In the case of pharmacokinetic interactions, the FDA takes into account the following 2 measures: the maximal or peak serum concentration (C_{max}) and AUC, the plasma drug concentration-time curve that reflects total body exposure to a medication after administration.²²⁴ For the purpose of making clinical recommendations for the management of statin-drug interactions, an increase in the statin AUC is primarily used, because this measure is consistent with many drug-drug interaction studies. A proposed ranking of the clinical significance of statin-drug interaction is dependent on change in statin AUC when administered with another drug: 1.25- to <2 -fold increase (minor), >2 - to 4.9-fold increase (moderate), and >5 -fold increase (severe).²³⁸

Table 6 is not intended to be comprehensive but shows the principal statin drug interactions that increase the risk of myopathy, as of January 2018. In most cases, this is because of inhibition of pathways involved in statin elimination, especially CYP3A4. Simvastatin and lovastatin are the most vulnerable. As shown in Table 5, they are CYP3A4 substrates, with a low bioavailability because of extensive first-pass hepatic metabolism.⁵² Because only $\approx 5\%$ passes into the systemic circulation, which indicates that 95% is eliminated by the liver, relatively minor inhibition of hepatic elimination of simvastatin and lovastatin can greatly increase their plasma concentrations. For example, if first-pass metabolism is reduced from 95% to 75%, in principle, bioavailability will be increased to 25%, and plasma concentrations of their active

Table 6. Principal Drug Interactions Increasing Myopathy Risk, Usually Through Higher Plasma Concentrations of Statin or Active Metabolites, From US Prescribing Information as of January 2018

Interacting Drug	Lova	Simva	Atorva	Prava	Fluva	Rosuva	Pitava
Gemfibrozil	Avoid	Avoid	Avoid	Avoid	Avoid	Avoid	Avoid
Calcium channel blockers	NDA	NDA	NDA	NDA	NDA
Verapamil	20*	10
Diltiazem	20	10
Amlodipine	...	20
Antiarrhythmics	NDA	NDA	NDA	NDA	NDA
Amiodarone	40	20
Dronedarone	20	10
Macrolides†	NDA	1 mg
Clarithromycin	Avoid	Avoid	C	40	20
Erythromycin	Avoid	Avoid	...	C
Telithromycin	Avoid	Avoid	...	C
Antifungal azoles	NDA	...	NDA	NDA
Itraconazole	Avoid	Avoid	C
Ketoconazole	Avoid	Avoid
Posaconazole	Avoid	Avoid
Voriconazole	Avoid	Avoid
Fluconazole	20 bid
Immunosuppressants
Cyclosporine	Avoid	Avoid	Avoid	20	20	5	Avoid
Miscellaneous	NDA	NDA	NDA	NDA	NDA
Nefazodone	Avoid	Avoid
Danazol	20	Avoid
Ranolazine	C	20
Colchicine	C	C	C	C	C
HIV protease inhibitors and other antiretroviral drugs, hepatitis C protease inhibitors	Numerous interactions; see prescribing information and online Appendix 3, Tables III–V						

Atorva indicates atorvastatin; C, caution advised; Fluva, fluvastatin; Lova, lovastatin; NDA, no interaction requiring dose adjustment; Pitava, pitavastatin; Prava, pravastatin; Rosuva, rosuvastatin; and Simva, simvastatin.

*Doses (mg) are the maximum statin dose recommended if the interacting drug must be given concomitantly.

†Azithromycin is an azalide, not a macrolide, and has minimal effects on statin pharmacokinetics.

metabolites increased 5-fold. Therefore, attention to concomitant therapy is particularly important during treatment with these 2 statins. The importance of drug interactions was apparent in HPS: of the 7 patients allocated to simvastatin 40 mg who developed myopathy/rhabdomyolysis, 4 were taking an interacting CYP3A4 inhibitor (verapamil and erythromycin were each taken by 2 patients).³⁸

The fibrate gemfibrozil can cause myopathy/rhabdomyolysis when given alone.^{23,239} In addition, gemfibrozil is an inhibitor of OATP1B1 and increases the plasma concentration of several statins or their active metabolites.⁵² It has also been reported to inhibit the glucuronidation of statins.²⁴⁰ For these reasons, the gemfibrozil prescribing information advises against concomitant use with all statins. In contrast, fenofibrate has little if any potential to cause myopathy/

rhabdomyolysis when given alone or with a statin²³⁹ and has no clinically important pharmacokinetic interaction with any statin. Nevertheless, the FDA advises caution when statins and fenofibrate are used concomitantly.

3.6. Conclusions

There is considerable variation in the metabolic pathways for the elimination of different statins, and there are numerous important drug interactions, especially with simvastatin and lovastatin. Some statins modestly potentiate the anticoagulant activity of warfarin through an unknown mechanism, but with this exception, statins are always victims of drug interactions, not perpetrators. Interacting drugs can produce large increases in the plasma concentrations of the statin or active metabolites, which in turn increases the risk of myopathy, including rhabdomyolysis.

4. Demographic Considerations

4.1. Older Adults

As a general rule, drugs are eliminated more slowly in the elderly, both via the kidney, because of a lower glomerular filtration rate, and by the liver, because of less effective metabolizing and conjugating enzymes. Consequently, the plasma concentration AUC and the plasma half-life tend to be greater in older people. Clinicians frequently compensate for this by avoiding maximal recommended doses in older patients, especially when using drugs with a narrow therapeutic index. In addition, older people often have >1 disease and consequently are often taking multiple drugs, which increases the risk of drug interactions, although the risk can be reduced substantially by careful attention to all relevant prescribing information.

Statins are no exception to this general rule. With the possible exception of rosuvastatin, the mean AUC with all statins is moderately increased in older patients. Details can be found in the prescribing information, which does not recommend dosage reduction based on age-related pharmacokinetic factors alone.

Approximately 30 statin cardiovascular outcome trials have been performed, typically with several thousand patients followed up for 4 to 5 years. Some of these excluded patients >70 years of age, but many did not, and 1 study, PROSPER,¹¹⁸ specifically enrolled patients 70 to 82 years of age. In the HPS⁴⁷ and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico-Heart Failure) trials,³⁶ 5806 and 2014 participants, respectively, were at least 70 years of age, and in CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure),³⁵ 2054 participants, all with heart failure, were ≥75 years of age. Safety data were published for the patients 65 to 75 years of age who participated in CARDS²⁴¹ and for patients ≥70 years of age in JUPITER.²⁴² No differences were observed in the rate of adverse events between older and younger patients and between older patients allocated to treatment versus those allocated to placebo.

In PROSPER, which compared pravastatin 40 mg to placebo in men and women 70 to 82 years of age with or at high risk for vascular disease, serious adverse event rates were similar between groups, and there were no cases of rhabdomyolysis. As noted in 2.4.2. Central Nervous System Function, cognitive function, assessed prospectively, did not differ between the 2 groups, declining at the same rate in each.

In a nested case-control study of new users of lipid-lowering medications, risk factors for rhabdomyolysis were evaluated.⁵⁴ Age was the single most important risk factor. Compared with statin users <65 years of age, those ≥65 years of age had >4 times the risk of rhabdomyolysis (OR, 4.36; 95% CI, 1.45–14.13). A limitation of this study was that there were very few cases of rhabdomyolysis among the large number of statin users.⁵⁴

SEARCH,⁴⁰ which involved 12 000 high-risk participants, previously described in the Muscle section, found 53 cases of myopathy in the simvastatin 80 mg group compared with 2 in the simvastatin 20 mg group. There were also a similar number of cases of incipient myopathy, which were combined

with the myopathy cases to increase statistical power.⁵³ The 98 cases thus obtained are far more than in any other study, which permits an analysis of risk factors. Age ≥65 years was associated with an approximately doubled rate of statin-induced myopathy/incipient myopathy, and it is likely that a similar result would be obtained with myopathy alone, if there were a sufficient number of cases.

4.1.1. Conclusions

Large, randomized cardiovascular outcome trials of statins have evaluated people ≥65 years of age, including those in their 70s and 80s, for treatment periods of ≈3 to 5 years. On the basis of these data, there is no evidence that statins are unsafe in older people, although the risk of myopathy/rhabdomyolysis could be approximately twice that in younger people. This, however, remains a rare adverse effect. Because older people often have multiple comorbidities and concomitant medications and are more vulnerable to adverse events, clinicians must carefully evaluate benefit versus risk of statin therapy, including the potential for drug interactions, priorities of care, and patient preferences.

4.2. Children and Adolescents

Most children treated with statins have heterozygous FH. Other chronic disease states known to increase risk of atherosclerosis could prompt consideration of statin therapy.²⁴³ These include CKD, Kawasaki disease with coronary artery aneurysms, various cancers, HIV infection, chronic inflammatory conditions such as juvenile rheumatoid arthritis and systemic lupus erythematosus, and solid organ transplantation.²⁴³

The FDA approved lovastatin for use in children with FH ≥10 years of age in 2002, followed by simvastatin, atorvastatin, and fluvastatin; pravastatin and rosuvastatin are approved for use beginning at 8 years of age. There is no recommendation for statin dose adjustments based on body weight; generally, the lowest recommended daily dose is initiated and titrated up based on LDL-C levels. The safety of dose escalation has been explored in several clinical trials in children, with no additional safety issues identified.²⁴⁴ Most children in studies evaluating statins have had diagnoses of heterozygous FH and were generally otherwise healthy, although of course, LDL-C levels were very high and their lifetime risk for CVD was markedly increased. Few studies have explored the safety of statin use in a pediatric cardiac transplant population or in the other disease conditions mentioned above.

The American Heart Association and the American Academy of Pediatrics have both recommended statin therapy for children with high-risk lipid abnormalities as early as 8 years of age.^{243,245,246} Monitoring of muscle enzymes (CK) should be performed as needed based on clinical concern; liver enzymes (AST and ALT) should be monitored periodically. All female adolescents and preadolescents should receive counseling about statin contraindications during pregnancy.²⁴³

The potential for long-term adverse effects of a lifelong medication initiated in childhood should be considered. However, to date, there is no evidence that statin therapy is unsafe in children and adolescents 8 to 10 years of age and older. Overall, children report fewer side effects during treatment with statins than adults.²⁴⁷

It is anticipated that the same drug-drug interactions in adults taking statins, described in 3. Drug-Drug Interactions, apply to children. Statins are well tolerated, with no interactions, when taken with commonly prescribed medications in children and adolescents, such as acne medications, oral contraceptives, and psychotropic medications.

A variety of RCTs, meta-analyses, and observational studies have examined adverse effects of statin therapy in children with heterozygous FH. A 2014 meta-analysis of study-level data by Vuorio et al²⁴⁸ included 8 randomized, double-blind, placebo-controlled studies (total of 1074 participants, mostly with FH), and 6 of these provided safety data for lovastatin, simvastatin, pravastatin, atorvastatin, and rosuvastatin. No safety problems were noted, although the mean treatment period was only 6 months. A 2014 systematic review by the US Preventive Services Task Force concluded that statins were usually well tolerated in children with FH and that adverse events reported did not differ significantly in statin and placebo groups.²⁴⁹ A trial²⁵⁰ of pitavastatin in children and adolescents 6 to 17 years of age was published after the above-mentioned meta-analysis and found no evidence for safety concerns during a 12-week double-blind, placebo-controlled period and a 52-week open-label extension.

4.2.1. Hepatic Side Effects

Fewer than 5% of children treated with statins have been reported to have transient elevations >3 times the ULN in AST and ALT.^{251–256} Meta-analysis found no significant difference between statin and placebo.²⁴⁸

4.2.2. Musculoskeletal Side Effects

No cases of myopathy or rhabdomyolysis have been reported in RCTs in children taking statins.^{248,250} Asymptomatic elevations in CK levels >10 times the ULN have occasionally been reported in children in placebo-controlled trials,^{251,252,254} but in a meta-analysis of study-level data from all trials that reported >10-fold elevations in CK, there was no significant difference between statin and placebo.²⁴⁸

4.2.3. Effects on Growth Velocity

Statins do not affect height and weight increases during maturation.^{250–253,256–258}

4.2.4. Sexual Maturation

There have been no differences between statin and placebo groups in relation to sexual maturation as measured by Tanner staging.^{248,259} Statins did not affect the levels of estradiol in girls or testosterone in boys, nor of follicle-stimulating hormone and luteinizing hormone.^{252,256,260} Long-term safety data in FH are discussed in 5.1. Familial Hypercholesterolemia.

4.2.5. Safety and Tolerability of Statins in Other Chronic Childhood Diseases

Although the data are limited, RCTs and observational studies of statins in children with type 1 diabetes mellitus, systemic lupus erythematosus, Kawasaki disease, or polycystic kidney disease have been conducted. Only RCTs will be discussed here.

In 1 placebo-controlled trial evaluating atorvastatin 10 to 20 mg over 6 months in 42 children with type 1 diabetes mellitus (15±0.3 years of age), insulin sensitivity scores remained

constant in both groups, and atorvastatin was well tolerated. One subject had asymptomatic elevation of CK >10 times the ULN that normalized after atorvastatin discontinuation.²⁶¹

In a 3-year double-blind RCT comparing atorvastatin 10 to 20 mg/d and placebo in 221 children and adolescents with systemic lupus erythematosus (10–20 years of age), safety end points, including Tanner staging, and liver and muscle adverse events did not differ between groups.²⁶²

A randomized, double-blind, placebo-controlled trial of pravastatin 20 to 40 mg/d administered for 3 years in 110 children and young adults (8–22 years of age) with autosomal dominant polycystic kidney disease and normal kidney function found that pravastatin slowed progression of structural kidney disease with no untoward effects.²⁶³

4.2.6. Conclusions

Statins do not appear to affect growth or pubertal development, and there is no evidence of any other undesirable effects in children. Because statin treatment started in children is to be continued for life, collection of long-term safety data should continue whenever feasible.

4.3. East Asians

Since statins were first introduced ≈30 years ago, East Asians (in their home countries) have generally been prescribed lower doses of statins because of the belief that they are more sensitive to medications and have increased responses compared with Western populations. In the case of rosuvastatin, the US prescribing information suggests lower doses for patients of East Asian ancestry because of increased systemic exposure.^{77,264} This was at first based on lower East Asian body mass, but the difference is now believed to be related to pharmacogenetic factors, with differences in metabolism of statins by enzymes and disposition by membrane transporters.^{233,265–269}

4.3.1. Variation in Statin Systemic Exposure

Pharmacokinetic studies have found somewhat higher plasma concentrations (up to ≈2-fold) of some statins or their active metabolites in subjects of East Asian ethnicity compared with whites. This has been demonstrated most clearly for rosuvastatin^{267,270,271} but also for atorvastatin.²⁶⁸ For rosuvastatin, a 5 mg starting dose is recommended in East Asian patients. The evidence for simvastatin is conflicting,^{268,272} but the US prescribing information advises caution if the dose exceeds 20 mg in patients of Chinese origin taking lipid-lowering doses of niacin-containing products. This is based on the results of the THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) RCT.²⁷³ Pharmacokinetic studies of pitavastatin showed no differences in plasma levels in East Asians and whites.^{272,274}

4.3.2. Statin-Associated Adverse Events in Clinical Trials

HPS2-THRIVE²⁷⁵ included 25 673 patients with preexisting CVD all treated with simvastatin 40 mg/d, plus ezetimibe 10 mg/d in patients in whom simvastatin alone did not reduce total cholesterol below 3.5 mmol/L. The study population was 60% northern European (in the United Kingdom and Scandinavia) and 40% Chinese. Participants were randomized to extended-release niacin/laropiprant or placebo and followed up for a median of 4 years.²⁷⁵ In China, 13 cases (0.17%) of myopathy

occurred in the placebo group compared with 4 (0.05%) in Europe, which suggests that East Asian patients have a greater risk of statin-induced myopathy than Europeans.²⁷⁵ One of the 3 RCTs (of 12 total) to show a difference in myalgia rates between statin and placebo was HOPE-3, with 5.8% on rosuvastatin 10 mg versus 4.7% on placebo ($P=0.005$). The patient population in HOPE-3⁷⁵ was much more ethnically diverse than in most previous statin cardiovascular outcome trials; in particular, 29% of the participants were Chinese. The distribution of myalgia among the ethnic groups in HOPE-3 has not yet been reported.

4.3.3. Conclusions

Pharmacokinetic studies suggest greater plasma concentrations of some statins or their active metabolites in subjects of East Asian ethnicity compared with whites. This appears to reflect differences in the prevalence of variant alleles coding for statin-metabolizing enzymes and membrane transporters. Chinese patients appear to be more susceptible to myopathy induced by simvastatin. This is not necessarily a consequence of pharmacokinetic differences; it could be a class effect that reflects greater sensitivity of East Asians to statins in general. Lower doses of statins in East Asians have been recommended by some organizations, as well as in the prescribing information of rosuvastatin and simvastatin.

4.4. Pregnancy and Breastfeeding

The original developmental toxicity studies in rats and rabbits with the first statin available for prescription, lovastatin, produced evidence of fetal abnormalities, predominantly skeletal defects, in rats at a dose of 800 mg·kg⁻¹·d⁻¹.¹³⁴ These effects could be reversed or attenuated by coadministration of mevalonate,²⁷⁶ the product of the enzyme HMG-CoA reductase. On the basis of these results, coupled with concern about the need of the developing fetus for cholesterol for cell membranes and steroidogenesis, lovastatin was contraindicated for use in pregnancy and labeled category X. In 2014, the FDA announced²⁷⁷ that categorization of risk to the fetus as A, B, C, D, or X would be phased out and replaced by more descriptive language.

Although fetal abnormalities were not observed in developmental toxicity studies of subsequent statins,²⁷⁸ all received the category X designation. In addition, the original findings with lovastatin were later shown to be a result of maternal toxicity. This toxicity is largely reversible in the rat despite continued dosing; preventing maternal toxicity during gestation by starting dosing earlier prevented fetal abnormalities.²⁷⁹

Several studies have examined the outcome of pregnancy after statin exposure. Prospective studies, in which pregnant women are followed up through delivery after exposure to a statin in early pregnancy, are more reliable than retrospective studies. In the latter, women who have delivered an infant with a congenital abnormality and matched women who have delivered a normal infant are asked about drug exposure during pregnancy, but this is subject to recall bias.²⁷⁸ In recent years, there have been 3 overviews^{280–282} of the prospective and retrospective studies investigating possible relationships between gestational exposure to a statin and the outcome of pregnancy. None have found a relationship between statin

exposure and any particular congenital abnormality or congenital abnormalities collectively. However, the number of cases with gestational statin exposure and known outcome of pregnancy is limited to a few thousand, so that statistical power is quite limited.

Many women are postponing pregnancy until well into their 30s or later, and an increasing number of women are taking a statin at this age, particularly those with FH or diabetes mellitus.²⁸³ A statin should never be prescribed for a woman who is pregnant or trying to conceive, but half of all pregnancies are unplanned, and so a pregnancy can occur in a woman taking a statin. Inadvertent exposure to a statin during early pregnancy is no longer a rare event, and patients might seek advice on the risk to the fetus in such a situation. Statin exposure during pregnancy can be associated with increased rates of therapeutic abortion, which could reflect either the generally unplanned nature of such pregnancies, fear of statin-induced fetal abnormalities, or both.²⁸⁰

Given the absence of teratogenic effects, providing maternal toxicity is prevented, in high-dose animal studies and the lack of known adverse outcomes from inadvertent statin exposure during human pregnancies, it is unlikely that any statin is a major teratogen. Despite this, however, moderate increases in the risk of any fetal developmental abnormality cannot be excluded.

Statins are contraindicated during lactation because of the potential for transfer into breast milk.

4.4.1. Conclusions

The available evidence does not suggest any major hazard but also does not prove that statins are safe in pregnancy. All statins therefore remain contraindicated in pregnancy, but a woman exposed to a statin during pregnancy can be reassured that the risk of a fetal abnormality is unlikely to be much greater than the background risk, if it is increased at all. Because a definitive answer is not possible, careful screening for congenital abnormalities in utero using ultrasound and other techniques is appropriate in the event of statin exposure in early pregnancy and might provide some assurance to a woman deciding whether to carry the pregnancy to term.

5. Patients With Specific Diseases

5.1. Familial Hypercholesterolemia

FH is a cause of premature atherosclerotic disease²⁴⁶ and is associated with a dramatic 10- to 20-fold increased risk of cardiovascular events.²⁸⁴ Patients with FH could theoretically have more risk of statin adverse effects as a consequence of initiation of statin therapy at a young age, lifelong exposure to statins, and increased use of high doses of high-potency statins in combination with other LDL-lowering medications. This section is confined to adults; statin safety in children with FH is addressed in 4.2. Children and Adolescents.

Although the majority of the data demonstrating risks and benefits of treatment with statins were generated from large-scale, double-blind, placebo-controlled RCTs in patients without FH, there are smaller studies that have specifically targeted patients with FH, including some very early studies^{230,285} that were instrumental in restarting the development

of the first marketed statin, lovastatin, after it had been halted because of reports of serious animal toxicity in a related compound.^{15,286} The good tolerability and efficacy in these studies were confirmed in a phase II placebo-controlled study with lovastatin in 101 patients.²⁸⁷ Hence, the very first documentation of the safety and efficacy of lovastatin in humans was largely in patients with FH.

5.1.1. Adrenal Safety

Early in the development of statins, there was a concern that inhibition of HMG-CoA reductase might lead to adrenal insufficiency as a consequence of decreased cholesterol substrate for cortisol synthesis in patients with FH resulting from decreased LDL receptor activity in the context of decreased cholesterol synthesis, but this was shown not to be the case.¹⁷⁵ Possible effects of statins on steroidogenesis in patients without FH have been previously addressed in Steroidogenesis.

5.1.2. Long-term Treatment and Safety

There are no large, long-term RCTs comparing statin and placebo in adults with FH. Several longitudinal studies have assessed the long-term safety of statins in patients with FH treated for up to 10 years, and none have indicated a concern.^{288–290} These did not identify any new findings compared with studies in patients without FH.

5.1.3. Conclusion

Statin safety appears to be similar in patients with FH and those who do not have FH.

5.2. Prior Intracranial Hemorrhage

There are only very limited data addressing the potential benefits and risks of statins in patients with a history of intracerebral hemorrhage. In SPARCL (see 2.4.1. Hemorrhagic Stroke), ≈2% (n=93) of 4731 subjects with stroke or transient ischemic attack at entry had an intracerebral hemorrhage as an entry event.²⁹¹ Overall, 88 subjects (55 statin treated and 33 given placebo) had a within-trial outcome of brain hemorrhage. Although underpowered for exploratory subgroup analyses, in addition to statin treatment (HR, 1.68; 95% CI, 1.09–2.59), Cox multivariable regression including baseline variables significant in univariable analyses showed that recurrent hemorrhagic stroke risk was higher in those having a hemorrhagic stroke as the entry event (HR, 5.65; 95% CI, 2.82–11.30), in men (HR, 1.79; 95% CI, 1.13–2.84), and with age (10-year increments; HR 1.42; 95% CI, 1.16–1.74). There were no statistical interactions between any of these factors and statin treatment. HR point estimates were consistent with a reduction in recurrent stroke in those with a baseline ischemic stroke (HR, 0.60; 95% CI, 0.48–0.99), but there was no similar reduction among those with a baseline hemorrhagic stroke (HR, 0.80; 95% CI, 0.62–1.27).

Given the overall lack of relevant data, a decision analytic model that simulated clinical trials was used to provide guidance on the use of statins after intracerebral hemorrhage.²⁹² Data regarding the risk of intracerebral hemorrhage in patients with recent intracerebral hemorrhage associated with statin use came from the SPARCL trial. Some statins (simvastatin, lovastatin, and rosuvastatin) moderately potentiate the anticoagulant activity of warfarin (see 3. Drug-Drug

Interactions), but atorvastatin, which does not, was the statin used in SPARCL. A strategy of avoiding statins was favored, particularly among those with a prior lobar hemorrhage regardless of a history of prior CVD. In the setting of primary prevention of ischemic stroke, statin therapy was found to lead to 0.8 quality-adjusted life-years lost (13.0 versus 12.2). The loss was estimated to be smaller in the setting of patients with a history of previous MI (0.2 quality-adjusted life-years). One limitation of this analysis is that because of the lack of clinical trial data for different statins at different doses, the data in this model for risk of intracerebral hemorrhage came from 1 trial, which used 1 statin at its highest dose.

This analysis antedated a retrospective cohort study that included 3481 patients with an intracerebral hemorrhage admitted to any of 20 hospitals over a 10-year period (in SPARCL, subjects were randomized 1–6 months after brain hemorrhage).²⁹³ Compared with nonusers, those who received a statin during the hospitalization had a higher 30-day survival (OR, 4.25; 95% CI, 3.46–5.23) and were more likely to be discharged home or to short-term rehabilitation (OR, 2.57; 95% CI, 2.16–3.06). Those who were receiving a statin before the intracerebral hemorrhage in whom the statin was stopped during the hospitalization had a lower 30-day survival (OR, 0.16; 95% CI, 0.12–0.21) and were less likely to be discharged home or to short-term rehabilitation (OR, 0.26; 95% CI, 0.20–0.35). The study, however, was not randomized and was therefore subject to the biases associated with observational trials, and the data are restricted to short-term statin use.

5.2.1. Conclusions

On the basis of the limited available data, it might be prudent to avoid initiating statin therapy in patients with a prior intracerebral hemorrhage but to continue statin therapy during hospitalization for intracerebral hemorrhage if the risk of ischemic stroke and other cardiovascular events is judged to be high enough to justify the uncertain risk of statin-associated recurrent intracerebral hemorrhage.

5.3. Chronic Kidney Disease

Patients with CKD have significantly increased risk for CVD. Statins, with the exception of atorvastatin and fluvastatin, are subject to some excretion in urine (10%–20% of total excretion), and impaired renal function could lead to increased systemic exposure and increased potential for harm. CKD is a continuum, and the use of statins, as well as the potential for impaired clearance, depends on the CKD stage ([online Appendix 3, Table VI](#)). In patients with end-stage renal disease and patients who have undergone renal transplantation (see 5.6. Transplantation), there are other potential safety concerns because of limited clearance of the drug by dialysis and potential for drug interactions with commonly used immunosuppressive agents in transplantation patients (see 3. Drug-Drug Interactions and 5.6. Transplantation). Table 2 summarizes dose recommendations for statins in patients with CKD.

Initial RCTs of statins tended to exclude patients with CKD because of theoretical safety concerns. LDL-C reduction with a statin, or a statin combined with a cholesterol absorption inhibitor, reduces major cardiovascular events in subjects with non-dialysis-dependent CKD^{57,294,295} (CKD stages 2–4)

but not in patients on dialysis.^{55–57,296} The following sections summarize data for statin safety by CKD stages.

5.3.1. CKD Stages 2 Through 4

UK-HARP-I (United Kingdom Heart and Renal Protection Study I) was a double-blind, placebo-controlled RCT that evaluated the efficacy and safety of simvastatin 20 mg in 448 patients with CKD, who were treated for 1 year.²⁹⁷ There were no significant differences between groups in muscle pain (16% versus 11%, simvastatin and placebo, respectively), muscle weakness, elevations in CK, or liver function tests (LFTs).²⁹⁷

SHARP evaluated major atherosclerotic events in 9720 patients with CKD randomized to ezetimibe 10 mg/d plus simvastatin 20 mg or to placebo.²⁹⁵ The study included 2527 patients on hemodialysis and 496 on peritoneal dialysis. The mean estimated glomerular filtration rate at baseline was 26.6 mL·min⁻¹·1.73 m⁻² excluding the one-third of patients on maintenance dialysis. Overall, during a mean treatment period of 5 years, ezetimibe/simvastatin reduced the risk of major adverse atherosclerotic events by 17% ($P=0.0021$) in the total population. This result showed no heterogeneity between dialysis and nondialysis patients. In the first year of the trial, the safety of simvastatin 20 mg was assessed in 1054 patients randomized to simvastatin 20 mg compared with 4191 patients randomized to placebo and 4193 patients randomized to ezetimibe plus simvastatin.⁵⁷ During this period, there were no differences between subjects allocated to simvastatin 20 mg or placebo in muscle pain, elevations in CK (in the total population and in patients on dialysis or not on dialysis), persistently elevated liver transaminases, hepatitis, complications of gallstones, hospitalizations for gallstones, or pancreatitis. Subsequently, those patients allocated to simvastatin 20 mg were re-randomized to placebo or ezetimibe/simvastatin and followed up for 4 years. Long-term safety data were similar in the 2 treatment groups.²⁹⁵

5.3.2. Hemodialysis

The safety of atorvastatin 20 mg and rosuvastatin 10 mg in patients on dialysis has been evaluated in 2 double-blind, placebo-controlled, long-term cardiovascular outcome trials. The 4D study (German Diabetes and Dialysis Study) in 1255 patients with type 2 diabetes mellitus on maintenance hemodialysis found no significant effect of atorvastatin 20 mg on the primary end point (cardiac death, nonfatal MI, or stroke) during a median follow-up of 4 years.⁵⁵ Of note, fatal stroke was significantly increased in the atorvastatin group (RR, 2.03; 95% CI, 1.05–3.93; $P=0.04$), but nonfatal stroke, total mortality, and noncardiovascular mortality did not differ among the groups. No subject developed rhabdomyolysis or severe liver disease.⁵⁵

AURORA compared rosuvastatin 10 mg/d and placebo in 2776 patients on maintenance hemodialysis who had not taken statins in the preceding 6 months.⁵⁶ Rosuvastatin did not significantly reduce the primary composite end point (cardiovascular death, nonfatal MI, or nonfatal stroke) or individual components of the end point after a median follow-up of 3.8 years. Unlike 4D, rates of fatal stroke were not increased in patients allocated to rosuvastatin. There were 3 cases of rhabdomyolysis in the rosuvastatin group and 2 in the placebo group. Elevations in ALT or CK were rare (<0.5%) and similar

between groups.⁵⁶ Infections, gastrointestinal disorders, musculoskeletal disorders, and newly diagnosed diabetes mellitus did not differ between the groups.

Thus, in patients on hemodialysis, use of statins is not routinely recommended, because there is no clear evidence of cardiovascular benefit. Statins appear safe in this population with advanced disease and multiple concomitant medications.

5.3.3. Peritoneal Dialysis

There are fewer data available on the safety of statins in patients on peritoneal dialysis. Several small clinical studies, as well as the UK-HARP²⁹⁷ and SHARP²⁹⁵ trials, which included some patients on peritoneal dialysis, have found no evidence of harm.^{298–302}

5.3.4. Renal Transplantation

The safety of statin therapy after kidney transplantation is covered in the Transplantation section.

5.3.5. Progression of Renal Disease

SHARP included a prespecified renal end point (progression to end-stage renal disease and doubling of serum creatinine); there was no evidence for benefit or harm.³⁰³ A meta-analysis of published data from 20 trials of statins, with 6452 subjects with CKD, demonstrated a small but significant increase in estimated glomerular filtration rate (0.5 mL·min⁻¹·1.73 m⁻² relative to placebo) between 1 and 3 years of statin therapy but no increase after 3 years of therapy.³⁰⁴ Thus, there is no evidence that statins cause renal deterioration in patients with CKD.

5.3.6. Conclusions

Statin therapy is safe in patients with CKD stages 2 through 4 and in patients on dialysis. There is, however, no clear evidence for cardiovascular benefit in dialysis patients.

5.4. Liver Disease

Statin therapy acts in the liver and is contraindicated in patients with active liver disease. As discussed in 2.3.1, transaminase elevations, statins raise hepatic transaminases in a dose-related manner. Therefore, there is a concern that statins might worsen hepatic function in patients with chronic liver disease. Early clinical trials generally excluded patients with known liver disease or with even mild elevations in LFTs, specifically transaminases (elevations above the ULN or >1.5 or 2 times the ULN), but some later trials included participants with transaminase elevations up to 4 times the ULN. Physicians remain concerned about the risks of statin therapy in patients with preexisting liver disease or elevated transaminases, and as a result, they could be reluctant to start statins in these patients, including those who are at significantly increased cardiovascular risk.³⁰⁵

5.4.1. Elevations in Transaminases

The safety of statins in patients with elevated transaminases was first evaluated in a retrospective cohort study,³⁰⁶ which found a similar incidence of transaminase elevations at 6 months in statin-treated patients with and without elevated transaminases at baseline. Another retrospective cohort study compared LFT changes at 12 months in patients taking lovastatin who had LFTs above the ULN at baseline with those

who did not, as well as with patients with elevated LFTs who were not taking statins.³⁰⁷ Mild to moderate elevations in liver enzymes (up to 10 times baseline in those with elevated ALT or AST at baseline, and up to 10 times the ULN in patients with normal baseline transaminases) in patients taking lovastatin were significantly greater at 12 months in patients with elevated ALT or AST at baseline than in those with normal ALT and AST (6.6% versus 3%; $P=0.03$). However, there was no difference in severe elevations of transaminases, defined as ALT or AST >10 times baseline or >10 times the ULN. No patients met the criteria for Hy's rule,¹³⁷ defined as AST or ALT >3 times the ULN and bilirubin >2 times the ULN.

A post hoc analysis of the open-label IDEAL cardiovascular outcome trial assessed the change in ALT in subjects with elevated levels (above the ULN but <3 times the ULN) at baseline. In 558 and 523 subjects in the simvastatin 20 to 40 mg and atorvastatin 80 mg groups, respectively, with elevated baseline ALT, mean ALT did not increase during treatment but rather decreased from the baseline to the final visit.¹¹⁹

The available data suggest that statin treatment of patients with elevated LFTs up to 3 times the ULN appears safe and does not lead to severe liver disease. There is limited information about the safety of statin therapy in people with persistent elevations in transaminases above 3 or 4 times the ULN, because long-term RCTs typically discontinued statin treatment in these participants.

5.4.2. Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) extends from simple hepatic steatosis to nonalcoholic steatohepatitis when inflammation occurs, potentially leading to fibrosis and advanced liver disease in the form of cirrhosis and hepatocellular carcinoma. The prevalence of NAFLD is increasing because of its association with obesity, diabetes mellitus, and the metabolic syndrome.³⁰⁸ The global prevalence of NAFLD is estimated to range from 6.3% to 33%, with a median of 20% in the general population.³⁰⁹ Evaluation of 12,454 US adults with ultrasound data in the National Health and Nutritional Examination Survey III (1988–1994) found a 19% prevalence of NAFLD.³¹⁰ Individuals with mild NAFLD in the form of hepatic steatosis typically have normal or modestly elevated transaminase levels. It is reasonable to assume that statin RCTs that recruited large numbers of patients with diabetes mellitus^{130,131,311} must have included many participants with NAFLD.

In a double-blind RCT of 36 weeks' duration, which compared pravastatin 80 mg versus placebo in 326 patients with compensated chronic liver disease (64% with NAFLD and 23% with chronic hepatitis C), mean baseline ALT levels were 65.7 IU/L and 77.3 IU/L in the pravastatin 80 mg and placebo groups, respectively.³¹² In most patients, ALT declined with pravastatin treatment. Also, there were no differences between the groups in the incidence of ALT elevations above 2 times the ULN. Postbaseline doubling of ALT did not differ between the pravastatin and placebo groups, including those with baseline ALT >3 times the ULN.

The effect of statins on liver histology in patients with NAFLD or nonalcoholic steatohepatitis has been evaluated

in several small studies. A prospective uncontrolled study of rosuvastatin 10 mg/d for 12 months in 20 patients with biopsy-proven nonalcoholic steatohepatitis found improvement in liver histology and reduction in LFTs in 19 subjects.³¹³ A similar prospective, uncontrolled, open-label study reported improved liver histology after 12 months of atorvastatin therapy.³¹⁴ However, a small double-blind, placebo-controlled RCT evaluating simvastatin therapy in 16 patients (with 10 having repeat liver biopsy at 1 year) did not find improved liver histology or liver enzymes.³¹⁵ Overall, there is no clear evidence that statin therapy reduces progression of liver disease, and statins should not be used for this indication. Statins appear safe in people with NAFLD, however.

5.4.3. Hepatitis B and Hepatitis C

Similar to data in patients with NAFLD, there are a number of small, nonrandomized studies that suggest possible beneficial effects of statins on liver disease in patients with chronic viral hepatitis. For example, in a trial investigating peginterferon therapy in patients with chronic hepatitis C and advanced hepatic fibrosis, the small number of patients taking statins (29 users versus 514 nonusers) had a reduced risk of fibrosis progression (using the Ishak fibrosis score) compared with nonusers.³¹⁶ Statins are associated with a reduction in development of cirrhosis and hepatocellular carcinoma³¹⁷ and a reduction in decompensation and death³¹⁸ in patients with chronic hepatitis C. Furthermore, the addition of fluvastatin (versus no fluvastatin) to pegylated interferon- α and ribavirin in a clinical trial was associated with improved virological responses in certain hepatitis C virus genotypes.^{58,319–321} Given that hepatitis C infection is associated with increased risk of CVD,³²² use of statins in this population to reduce this risk is recommended.

There are limited data regarding the safety of statins in individuals with hepatitis B. In a registry database of patients with chronic hepatitis B in Taiwan, 6543 statin users were found to have a lower incidence of cirrhosis and decompensated cirrhosis compared with nonusers.³²³

5.4.4. Conclusions

Although concerns have been raised regarding the use of statins in patients with chronic liver disease, the data provided to date suggest that statins are safe to use and do not cause progression of liver disease in patients with NAFLD or chronic viral hepatitis C. On that basis, there is no need to avoid statin therapy in patients with stable chronic liver disease and normal or modestly elevated transaminases (up to 3 times the ULN). There are no reliable data showing that statins are safe in advanced or decompensated liver disease.

5.5. Human Immunodeficiency Virus

Since the late 1990s, patients with HIV infection have been successfully treated with active antiretroviral therapy (ART) consisting of various combinations of protease inhibitors (PIs), nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, integrase strand transfer inhibitors, chemokine receptor-5 antagonists, and fusion inhibitors. Consequently, patients with HIV are living longer; however, they experience a higher risk of cardiovascular

events,^{324,325} at least in part because of the high prevalence of dyslipidemia, which is generally treated with statins.

Statins are not perpetrators of interactions with any antiretroviral drug, but they can be victims. Several antiretroviral agents, particularly but not only PIs, interact with statins through pharmacokinetic mechanisms that increase plasma concentrations of statins or active metabolites, which increases the risk of myopathy, including rhabdomyolysis. As noted in 3. Drug-Drug Interactions, lovastatin and simvastatin are particularly vulnerable to drug interactions because of their extensive first-pass metabolism, mainly via CYP3A4. Many of the antiretroviral agents, especially the PIs, are inhibitors (or less commonly inducers) of the cytochrome P450 (CYP) enzyme system, particularly CYP3A4. All statins are substrates for the organic anion transporter proteins OATP1B1 or OATP1B3, and some are substrates for other transporters, including P-glycoprotein.^{224,326} As seen in [online Appendix 3, Table III and Table IV](#), the PIs and pharmacokinetic boosters are inhibitors of CYP3A4, with the exception of tipranavir. All PIs with the exception of fosamprenavir are also inhibitors of OATP. As a general rule, if a patient is receiving a PI-based or a pharmacokinetic booster ART regimen, simvastatin and lovastatin should be avoided; atorvastatin, rosuvastatin, or pravastatin can be considered, but dosing adjustments might be needed depending on the ART regimen.³²⁶ The nonnucleoside reverse-transcriptase inhibitors efavirenz, etravirine, and nevirapine are all inducers of CYP3A4, while efavirenz and etravirine inhibit CYP2C9, respectively; thus, the statin dose might need to be adjusted. No dose adjustments are needed for the nucleoside reverse-transcriptase inhibitors or chemokine receptor-5 antagonists.³²⁶ Pitavastatin remains the only statin that does not exhibit significant interactions with ART and does not require dose adjustments, but it is also the only statin that is not yet available as a generic product and is therefore considerably more costly. In the INTREPID (HIV-Infected Patients and Treatment With Pitavastatin vs Pravastatin for Dyslipidemia) double-blind RCT,³²⁷ pitavastatin 4 mg reduced LDL-C more than pravastatin 40 mg (at 12 weeks, 31.1% versus 20.9%; $P < 0.0001$). A long-term cardiovascular outcome trial, REPRIEVE (Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults), which compares pitavastatin 4 mg versus placebo in adults with HIV on ART, is ongoing and should provide additional safety data for pitavastatin in this population.³²⁸ On the basis of the current Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents and the International Antiviral Society-USA, [online Appendix 3, Table III and Table IV](#) summarize the specific pharmacokinetic drug-drug interactions with ART and statins, as well as statin dosing recommendations.³²⁶

5.5.1. Conclusions

The safety of statins in adults with HIV depends on the potential for drug-drug interactions that increase exposure to the statin. Pitavastatin appears to have the lowest potential for interactions with ART. To ensure statin safety in patients with HIV, the specific statin and its dose should be selected with the aim of avoiding pharmacokinetic interactions with the antiretroviral medications that the patient is taking. Rather than

changing the patient's ART regimen, the choice and dose of statin should be altered if necessary.

5.6. Transplantation

CVD is a major cause of death in cardiac,^{329–331} renal,^{332–335} and liver³³⁶ transplant recipients. Transplantation risk factors that contribute to CVD include the metabolic effects of medications, especially immunosuppressive agents that can lead to a more atherogenic lipoprotein pattern.^{337–341} Consequently, statins are often given to reduce cardiovascular risk. They might also have immunosuppressive effects,^{342–347} reducing the incidence of allograft rejection,^{348,349} but there are few data, and this is not an approved indication for any statin. Pharmacokinetic interactions between statins and transplantation-related therapies can, however, lead to elevated plasma concentrations of statins or their active metabolites. This increases the risk of myopathy, including rhabdomyolysis, as discussed in previous sections (2.1. Muscle and 3. Drug-Drug Interactions). The first reports of rhabdomyolysis caused by a statin were in cardiac transplantation patients,^{28,29} and the interaction of statins with cyclosporine was quickly appreciated,³⁰ although the underlying mechanisms were not understood for many years.

Transplant immunosuppressant regimens can include a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (azathioprine or mycophenolate mofetil), and steroids. As an alternative to azathioprine or mycophenolate, a mammalian target of rapamycin inhibitor (mTOR inhibitor), such as sirolimus or everolimus, can be substituted. According to the FDA-approved prescribing information for these agents and for statins, only cyclosporine has clinically meaningful interactions with any statin. This was confirmed by a 2014 review.²²⁴ Although tacrolimus, sirolimus, and everolimus are all substrates for CYP3A4 and OATP1B1, unlike cyclosporine they are not inhibitors at therapeutic doses, which for adults are a few milligrams daily compared with hundreds of milligrams for cyclosporine. They might, therefore, be victims of drug interactions, but not perpetrators. Cyclosporine can interact with statins via several mechanisms. This immunosuppressant is an inhibitor of CYP3A4 at therapeutic doses, and as previously noted, the statins that are CYP3A4 substrates include lovastatin, simvastatin, and atorvastatin. The prescribing information advises that atorvastatin, simvastatin, lovastatin, and pitavastatin should be avoided when patients are managed with cyclosporine. In addition to CYP3A4, cyclosporine inhibits statin efflux transport mechanisms, including P-glycoprotein and OATP1B1. The 3 remaining statins can be used with cyclosporine, but dose reductions are recommended: fluvastatin up to 20 mg/d; pravastatin up to 20 mg/d; and rosuvastatin up to 5 mg/d (Table 6).

5.6.1. Clinical Studies in Transplant Recipients

There is only 1 large statin RCT in patients with transplanted organs, ALERT (Assessment of Lescol in Renal Transplantation Trial).^{58,350} This trial investigated the cardiac and renal effects and the safety and tolerability of the immediate-release formulation of fluvastatin 40 to 80 mg/d compared with placebo in adult renal transplant recipients managed on cyclosporine, with a follow-up period of at least 5 years.³⁵⁰

The safety population comprised 1045 patients randomized to the fluvastatin group and 1049 to the placebo group. There were no significant differences in rates of adverse events, including CK and ALT elevations, musculoskeletal symptoms, and infection, in those who received fluvastatin 40 and 80 mg compared with placebo. Similar numbers of patients in both groups were discontinued from study medication because of clinical or laboratory adverse events.

The open-label 2-year extension study of ALERT also investigated the safety of the extended-release (80 mg) form of fluvastatin compared with the immediate-release formulation or placebo.³⁵⁰ All patients continued to receive cyclosporine immunosuppression. Of 2102 patients in the ALERT core study, 1787 were eligible for the extension study. Data on 1647 patients were analyzed. No significant differences were found with respect to the number of patients who discontinued the study medication, the number of adverse events, rates of infection or malignancy, or significant laboratory increases (either ALT or CK). Furthermore, no cases of rhabdomyolysis were reported.³⁵⁰

Numerous smaller, mostly observational studies have evaluated the safety and tolerability of statins in adult transplant recipients.^{348,351–366} Overall, the studies are consistent with the results of ALERT, indicating that statins have a good safety profile in solid organ transplant recipients, when used carefully in accordance with the prescribing information. Notably, many of these studies included patients treated with cyclosporine and lovastatin, simvastatin, or atorvastatin. There are also a small number of studies in pediatric transplant recipients, again indicating a good safety profile for statins in these patients.^{367–369}

5.6.2. Conclusions

There are pharmacokinetic interactions between cyclosporine and all statins. Pravastatin, fluvastatin, and rosuvastatin are recommended by the FDA for use in cyclosporine-treated patients, at reduced doses. Other transplant immunosuppressant agents have no important interactions with statins. One large, randomized, placebo-controlled trial of fluvastatin 40 and 80 mg/d in renal transplant recipients strongly suggests that reducing the dose of fluvastatin is not necessary in adults taking cyclosporine. Also, numerous smaller observational studies suggest that other statins have a good safety profile with cyclosporine in this population when used at reduced doses by experienced transplant practitioners.

6. Summary and Conclusions

6.1. Adverse Effects of Statins

Myopathy, defined as unexplained muscle pain or weakness accompanied by increases in CK above 10 times the ULN, is the hallmark adverse effect of statins, but it is rare, occurring in <1 in 1000 patients treated with maximum recommended doses, and with an even lower risk at lower doses. Rhabdomyolysis is a severe form of myopathy that occurs in \approx 1 in 10000 patients and can cause acute renal failure because of myoglobinuria. Prompt cessation of therapy usually reverses myopathy/rhabdomyolysis. Myopathy is specific to skeletal muscle, but after 30 years of investigation, the

mechanism is still unknown. Raised plasma concentrations of statins or their active metabolites, which can result from a variety of interacting drugs, as well as variant alleles that reduce organic anion transporter activity, increase the risk of myopathy/rhabdomyolysis. Even rarer than rhabdomyolysis is an autoimmune myopathy that is variably reversible on stopping statin treatment and could require immunotherapy.

SAMS are commonly reported in observational studies, but data from meta-analyses of double-blind statin RCTs shows that if myalgia and other nonserious statin muscle symptoms are causally related to statin therapy, the incidence is very low, no greater than 1%. The best explanation for this large discrepancy is patient misattribution to statin treatment of the background muscle symptoms common in middle-aged and older people. This probably occurs because many patients expect harm from the statin (ie, the nocebo effect).

In meta-analyses of RCTs of up to 5 years' duration, moderate-intensity statin therapy increases the risk of newly diagnosed type 2 diabetes mellitus by \approx 10%, and the increased risk is \approx 20% with high-intensity statin therapy. This corresponds to an estimated annual rate of \approx 0.2% in the general population, although this estimate is dependent on the risk of diabetes mellitus in the population. The risk appears to be restricted to patients who are otherwise at increased risk of developing diabetes mellitus. Statins also produce very small increases in HbA_{1c} (\approx 0.1%) in patients with diabetes mellitus. The mechanism is presently unknown. Severe liver toxicity is a very rare adverse effect of statins, estimated to occur in \approx 1 in 100000 people. Dose-dependent asymptomatic elevations in transaminases above 3 times the ULN are more common and occur in \approx 1 in 100 people in clinical trials. These are usually transient and are typically not associated with signs or symptoms of liver disease.

The data underlying this analysis of adverse effects of statins are largely derived from RCTs. The exceptions are myopathy/rhabdomyolysis and severe liver toxicity, where in general the incidence is too low to be evaluated in clinical trials, but the population incidence of these adverse events without an identifiable cause is very low, such that observational data are useful. The cardiovascular benefits of statin therapy in patients for whom it is recommended by current guidelines greatly outweigh the risks (Table 7). The absolute benefit of statin treatment for an individual patient is dependent on the patient's cardiovascular risk and the amount of LDL-C reduction during statin treatment. Our conclusions are in close agreement with a 2016 assessment of statin safety by a large multinational group of authors.¹⁹

6.2. Adverse Events Associated With Statins but Without Good Evidence for a Causal Relationship

SAMS are common but usually not causally related to a statin. A variety of other adverse events have also been associated with statin use, but evidence for causality is again very weak, if not lacking altogether. These include peripheral neuropathy, cognitive dysfunction, sleep disturbances, Alzheimer disease, and Parkinson disease. Similarly, there is no evidence that statins cause cancer, tendonitis or tendon rupture, proteinuria, or AKI (except possibly in the perioperative setting, but data

Table 7. Perspective on Benefit/Risk of Statin Therapy in 10 000 Patients on Statins for 5 Years, Achieving 2 mmol/L (77 mg/dL) Reduction in LDL-C

Benefit*	Estimated Number of Patients With Benefit or Adverse Effect†
MVEs prevented (secondary prevention)	1000
MVEs prevented (primary prevention)	500
Risk	
Newly diagnosed diabetes mellitus	100
Muscle symptoms without significant CK increase	<100
Myopathy‡	5
Rhabdomyolysis	1
Autoimmune myopathy	<1
Hemorrhagic stroke§	10
Severe liver disease	<1

CK indicates creatine kinase; LDL-C, low-density lipoprotein cholesterol; and MVEs, major vascular events (myocardial infarction, stroke, coronary revascularization procedure).

*Benefit refers only to first events.

†Based on estimates of the Cholesterol Treatment Trialists' Collaboration⁴ and Collins et al,¹⁹ with additional risk data covered in this review.

‡Myopathy attributable to statin therapy is defined as unexplained muscle pain or weakness accompanied by elevation in CK >10 times the upper limit of normal.

§In people with prior cerebrovascular disease taking statins, hemorrhagic stroke is possibly causally related.

are limited). Although cataract development was a concern when the first statin was approved in 1987, most trials have found that statins do not increase the risk of lens opacities or cataracts. Statins inhibit the rate-limiting step in the cholesterol biosynthesis pathway and could potentially reduce steroid hormone production, but clinically evident effects have not been identified. Small reductions, $\approx 10\%$, in plasma testosterone have been reported in some studies, but plasma testosterone is highly variable within and between individuals. The observed changes are small and, even if real, not clinically significant. Statins are not associated with hypogonadism and have no harmful effects on erectile function.

6.3. Demographic Considerations

RCTs reveal no particular hazard of statins in older adults, including those ≥ 75 years of age; however, because of the comorbidities and use of multiple medications in older people, statins should be prescribed cautiously. Statins are well tolerated in children with FH and do not alter growth or puberty. In East Asian populations, plasma concentrations of statins or their active metabolites tend to be greater, which leads to increased risk of adverse effects, especially myopathy/rhabdomyolysis, with higher doses. Therefore, lower doses should be considered in patients of East Asian descent.

Statins are contraindicated in pregnancy, largely because of early reproductive toxicology studies with lovastatin in rodents combined with a theoretical concern about the need of the developing fetus for cholesterol; however, prospective observational studies on fetal abnormalities after exposure of mothers to statins during pregnancy do not suggest any major

hazards. A small risk of congenital abnormalities cannot be ruled out, but there is no evidence to support the termination of pregnancy in a patient who has been exposed to a statin during early gestation.

6.4. Specific Diseases

There is some RCT evidence that statins increase the risk of hemorrhagic stroke in patients with prior cerebrovascular disease, with an HR of ≈ 1.7 , but the absolute risk is low. In patients with prior cerebrovascular disease, statins reduce the risk of total stroke (by reducing ischemic stroke) and MIs, which outweighs the potential increased risk of hemorrhagic stroke. In patients without a history of cerebrovascular disease, however, there is no detectable increase in the risk of hemorrhagic stroke.

There is no evidence that statins are harmful in patients with CKD, including those on dialysis, when appropriate doses are given; however, the lack of proof of cardiovascular benefit in patients with end-stage renal disease suggests that initiating statin treatment in these patients is generally not warranted. Limited data suggest that statins are safe to use in patients with NAFLD and nonalcoholic steatohepatitis and in patients with elevations in transaminases up to 3 times the ULN. Data on safety in people with more serious liver disease are insufficient, and statin treatment is generally discouraged.

In patients with HIV infection or hepatitis C, some antiviral therapies interact with some statins, raising plasma concentrations of statins or their active metabolites, which increases the risk of myopathy/rhabdomyolysis. Pitavastatin has the fewest interactions. The statin and its dose should be selected carefully to avoid pharmacokinetic drug interactions with the antiviral therapy chosen for the individual patient. Cyclosporine, commonly used in patients with organ transplants, also interacts with statins, although clinical trials show that some statins can be used safely in these patients at appropriate doses.

6.5. Overall Conclusions

Over 30 years of clinical investigation have shown that statins exhibit few serious adverse effects. Myopathy including rhabdomyolysis attributable to statin therapy occurs in <0.1% of treated patients. Nonserious muscle symptoms are commonly reported during statin treatment and interfere with treatment compliance, but overall, <1% of statin-treated patients have muscle symptoms of pharmacological origin. Severe liver toxicity is very rare, reported in $\approx 0.001\%$ of patients. Statins modestly increase the risk of newly diagnosed diabetes mellitus in clinical trials of up to 5 years' duration. The HR in meta-analyses of clinical trials is ≈ 1.1 for moderate-dose statin therapy and 1.2 for intensive statin therapy. The risk is largely confined to patients with multiple preexisting risk factors for diabetes mellitus. In a general patient population, the absolute risk of statin-induced newly diagnosed diabetes mellitus is $\approx 0.2\%$ per year, although this estimate is dependent on population risk and will be greater in patients with pre-diabetes mellitus or clinical characteristics that are associated with higher risk of diabetes mellitus (eg, metabolic syndrome). Although the evidence is not conclusive, statins

possibly increase the risk of hemorrhagic stroke in patients with a history of cerebrovascular disease.

With the exception of hemorrhagic stroke and the possible exception of newly diagnosed diabetes mellitus and some cases of autoimmune necrotizing myositis, statin adverse effects can almost always be reversed by stopping

treatment. In contrast, an MI or ischemic stroke permanently damages an individual’s heart or brain and can be fatal. Thus, in the patient population in whom statins are recommended by current guidelines, the benefit of reducing cardiovascular risk with statin therapy far outweighs any safety concerns.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers’ Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Connie B. Newman	New York University School of Medicine‡	None	None	None	None	None	None	None
Terry A. Jacobson	Emory University	Amgen (investigator)*; Amarin (steering committee, clinical trial)*; Regeneron/Sanofi (investigator)*	None	None	None	None	None	None
Lynne T. Braun	Rush University Medical Center, Rush College of Nursing	None	None	None	None	None	UpToDate*	None
Eliot A. Brinton	Utah Lipid Center	None	None	Amgen‡; Kowa‡; Regeneron*; Sanofi‡	None	None	Amgen*; Kowa*; Regeneron*; Sanofi*	None
Clifford Chin	Cincinnati Children’s Hospital Medical Center Heart Institute	None	None	None	None	None	None	None
P. Barton Duell	Oregon Health and Science University, Knight Cardiovascular Institute	Esperion‡; Regeneron‡; Retrophin‡; University of Pennsylvania‡; Regenxbio‡	None	None	None	None	Akcea*; Daiichi-Sankyo*; Esperion*; Kastle*; Regeneron*; Regenxbio*; Retrophin*; Sanofi*	None
Larry B. Goldstein	University of Kentucky	None	None	None	None	None	None	None
Michael Miller	University of Maryland	None	None	None	None	None	None	None
Robert L. Page II	University of Colorado Denver	None	None	None	None	None	None	None
Amy Pollak	Mayo Clinic	None	None	None	None	None	None	None
David Preiss	University of Oxford (United Kingdom)	None	The Medicines Company (grant to the University of Oxford [his employer] for a clinical trial on which he is an investigator of the PCSK9 synthesis inhibitor inclisiran and receives no personal fees from the grant)*	None	None	None	None	None
Geetha Raghuv eer	Children’s Mercy Hospitals and Clinics	None	None	None	None	None	None	None

(Continued)

Writing Group Disclosures Continued

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Lisa R. Tannock	University of Kentucky & Veterans Affairs Medical Center	None	Endocrine Society (on lipid guideline writing committee, unpaid)*	None	None	None	None	None
Jonathan A. Tobert	University of Oxford (United Kingdom)§	None	None	None	None	None	None	None
Francine K. Welty	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

‡Dr. Newman is now affiliated with but not employed by New York University School of Medicine.

§Dr. Tobert is now affiliated with but not employed by the University of Oxford.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Jane Armitage	University of Oxford (United Kingdom)	None	None	None	None	None	None	None
John JV McMurray	University of Glasgow (United Kingdom)	None	None	None	None	None	None	None
Paul D. Thompson	Hartford Hospital	Sanofi (industry grant to hospital)†; Regeneron (industry grant to hospital)†; Esperion (industry grant to hospital)†; Amarin (industry research grant to hospital)	None	Amgen†; Regeneron-Sanofi†; Amarin*	Various law firms†	AbbVie†; Abbott†; General Electric†; Johnson & Johnson†; CVS†; Medtronic†; Sarepta*	Sanofi*; Regeneron*; Esperion†; Amgen*	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

References

- World Health Organization. Cardiovascular Diseases Fact Sheet 2017. <http://www.who.int/mediacentre/factsheets/fs317/en/>. Accessed January 9, 2018.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
- Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins [published corrections appear in *Lancet*. 2005;366:1358 and *Lancet*. 2008;371:2084]. *Lancet*. 2005;366:1267–1278. doi: 10.1016/S0140-6736(05)67394-1
- Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, Collins R; for the Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681. doi: 10.1016/S0140-6736(10)61350-5
- Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003–2012. *NCHS Data Brief*. 2014;(177):1–8.
- Zhang H, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, Turchin A. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med*. 2013;158:526–534. doi: 10.7326/0003-4819-158-7-201304020-00004
- Yusuf S. Why do people not take life-saving medications? The case of statins. *Lancet*. 2016;388:943–945. doi: 10.1016/S0140-6736(16)31532-X
- Grundy SM. Statin discontinuation and intolerance: the challenge of lifelong therapy. *Ann Intern Med*. 2013;158:562–563. doi: 10.7326/0003-4819-158-7-201304020-00010
- Newman CB, Tobert JA. Statin intolerance: reconciling clinical trials and clinical experience. *JAMA*. 2015;313:1011–1012. doi: 10.1001/jama.2015.1335

10. Hovingh GK, Gandra SR, McKendrick J, Dent R, Wieffer H, Catapano AL, Oh P, Rosenson RS, Stroes ES. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. *Atherosclerosis*. 2016;245:111–117. doi: 10.1016/j.atherosclerosis.2015.12.015
11. Rosenson RS, Gandra SR, McKendrick J, Dent R, Wieffer H, Cheng LI, Catapano AL, Oh P, Kees Hovingh G, Stroes ES. Identification and management of statin-associated symptoms in clinical practice: extension of a clinician survey to 12 further countries. *Cardiovasc Drugs Ther*. 2017;31:187–195. doi: 10.1007/s10557-017-6727-0
12. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J*. 2016;37:908–916. doi: 10.1093/eurheartj/ehv641
13. Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, Bhaskaran K. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. *BMJ*. 2016;353:i3283. doi: 10.1136/bmj.i3283
14. Serban MC, Colantonio LD, Manthripragada AD, Monda KL, Bittner VA, Banach M, Chen L, Huang L, Dent R, Kent ST, Muntner P, Rosenson RS. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. *J Am Coll Cardiol*. 2017;69:1386–1395. doi: 10.1016/j.jacc.2016.12.036
15. Tobert JA. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. *Nat Rev Drug Discov*. 2003;2:517–526. doi: 10.1038/nrd1112
16. Bent S, Padula A, Avins AL. Brief communication: better ways to question patients about adverse medical events: a randomized, controlled trial [published correction appears in *Ann Intern Med*. 2006;145:156]. *Ann Intern Med*. 2006;144:257–261.
17. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med*. 2000;342:1907–1909. doi: 10.1056/NEJM200006223422511
18. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet*. 2001;357:373–380. doi: 10.1016/S0140-6736(00)03651-5
19. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy [published correction appears in *Lancet*. 2017;389:602]. *Lancet*. 2016;388:2532–2561. doi: 10.1016/S0140-6736(16)31357-5
20. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet*. 2001;357:455–462. doi: 10.1016/S0140-6736(00)04017-4
21. Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295–300.
22. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004;328:1519. doi: 10.1136/bmj.38142.554479.AE
23. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA*. 2004;292:2585–2590. doi: 10.1001/jama.292.21.2585
24. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgözoğlu L, Nordestgaard BG, Bruckert E, De Backer G, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, März W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN; for the European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy: European Atherosclerosis Society Consensus Panel statement on assessment, aetiology and management. *Eur Heart J*. 2015;36:1012–1022. doi: 10.1093/eurheartj/ehv043
25. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol*. 1988;62:28J–34J.
26. Carlsson L, Lind L, Larsson A. Reference values for 27 clinical chemistry tests in 70-year-old males and females. *Gerontology*. 2010;56:259–265. doi: 10.1159/000251722
27. Neal RC, Ferdinand KC, Ycas J, Miller E. Relationship of ethnic origin, gender, and age to blood creatine kinase levels. *Am J Med*. 2009;122:73–78. doi: 10.1016/j.amjmed.2008.08.033
28. Norman DJ, Illingworth DR, Munson J, Hosenpud J. Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. *N Engl J Med*. 1988;318:46–47. doi: 10.1056/NEJM198801073180110
29. East C, Alivizatos PA, Grundy SM, Jones PH, Farmer JA. Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. *N Engl J Med*. 1988;318:47–48. doi: 10.1056/NEJM198801073180111
30. Tobert JA. Reply to Norman et al. and East et al. *N Engl J Med*. 1988;318:48.
31. Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. *JAMA*. 1988;260:359–366. doi: 10.1001/jama.1988.03410030075032
32. Smith PF, Eydeloth RS, Grossman SJ, Stubbs RJ, Schwartz MS, Gernershausen JI, Vyas KP, Kari PH, MacDonald JS. HMG-CoA reductase inhibitor-induced myopathy in the rat: cyclosporine A interaction and mechanism studies. *J Pharmacol Exp Ther*. 1991;257:1225–1235.
33. Ballantyne CM, Corsini A, Davidson SM, Holdaas H, Jacobson TA, Leitersdorf E, März W, Reckless JP, Stein EA. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med*. 2003;163:553–564.
34. Armitage J. The safety of statins in clinical practice. *Lancet*. 2007;370:1781–1790. doi: 10.1016/S0140-6736(07)60716-8
35. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarsen A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J; for the CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357:2248–2261. doi: 10.1056/NEJMoa0706201
36. Tavazzi L, Maggioni AP, Marchioni R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G; for the GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231–1239. doi: 10.1016/S0140-6736(08)61240-4
37. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillensen H, Simunovic L, Szarek M, Welch KM, Zivin JA; for the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack [published correction appears in *N Engl J Med*. 2018;378:2450]. *N Engl J Med*. 2006;355:549–559. doi: 10.1056/NEJMoa061894
38. Armitage J, Bowman L, Collins R, Parish S, Tobert J. Effects of simvastatin 40 mg daily on muscle and liver adverse effects in a 5-year randomized placebo-controlled trial in 20,536 high-risk people. *BMC Clin Pharmacol*. 2009;9:1–10.
39. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207. doi: 10.1056/NEJMoa0807646
40. Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R; for the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial [published correction appears in *Lancet*. 2011;377:126]. *Lancet*. 2010;376:1658–1669. doi: 10.1016/S0140-6736(10)60310-8
41. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; for the FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial [published correction appears in *Lancet*. 2006;368:1415]. *Lancet*. 2005;366:1849–1861. doi: 10.1016/S0140-6736(05)67667-2
42. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus [published correction appears in *N Engl J Med*. 2010;362:1748]. *N Engl J Med*. 2010;362:1563–1574. doi: 10.1056/NEJMoa1001282
43. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK; for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435. doi: 10.1056/NEJMoa050461
44. Benghozi R, Bortolini M, Jia Y, Isaacsohn JL, Troendle AJ, Gonasus L. Frequency of creatine kinase elevation during treatment with fluvastatin. *Am J Cardiol*. 2002;89:231–233.

45. Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. *Am J Cardiol*. 2006;97:61–67. doi: 10.1016/j.amjcard.2005.07.108.
46. Dujovne CA, Chremos AN, Pool JL, Schnaper H, Bradford RH, Shear CL, Higgins J, Downton M, Franklin FA, Nash DT, Gould AL, Lagendorfer A. Expanded clinical evaluation of lovastatin (EXCEL) study results, IV: additional perspectives on the tolerability of lovastatin. *Am J Med*. 1991;91(1B):25S–30S.
47. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22. doi: 10.1016/S0140-6736(02)09327-3
48. Lubas W, Parks M. FDA medical review(s): CRESTOR tablets, NDA 21-366-N000 [resubmission amendment]. February 12, 2003. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-366_Crestor_Medr_P1.pdf. Accessed October 15, 2018.
49. Chowdhury IN, Gortler D. Pitavastatin clinical review, NDA 22-363. 2009. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022363s000_MedR_P1.pdf. Accessed December 3, 2016.
50. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med*. 2002;346:539–540. doi: 10.1056/NEJM200202143460721
51. Isaacsohn J, Insull W Jr, Stein E, Kwiterovich P, Patrick MA, Brazg R, Dujovne CA, Shan M, Shugrue-Crowley E, Ripa S, Tota R; for the Cerivastatin Study Group. Long-term efficacy and safety of cerivastatin 0.8 mg in patients with primary hypercholesterolemia. *Clin Cardiol*. 2001;24(suppl):IV1–IV9.
52. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther*. 2006;80:565–581. doi: 10.1016/j.cpt.2006.09.003
53. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R; for the SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy: a genomewide study. *N Engl J Med*. 2008;359:789–799.
54. Schech S, Graham D, Staffa J, Andrade SE, La Grenade L, Burgess M, Blough D, Stergachis A, Chan KA, Platt R, Shatin D. Risk factors for statin-associated rhabdomyolysis. *Pharmacoepidemiol Drug Saf*. 2007;16:352–358. doi: 10.1002/pds.1287
55. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E; for the German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis [published correction appears in *N Engl J Med*. 2005;353:1640]. *N Engl J Med*. 2005;353:238–248. doi: 10.1056/NEJMoa043545
56. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; for the AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis [published correction appears in *N Engl J Med*. 2010;362:1450]. *N Engl J Med*. 2009;360:1395–1407. doi: 10.1056/NEJMoa0810177
57. SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J*. 2010;160:785–794 e10. doi: 10.1016/j.ahj.2010.08.012
58. Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, Grönhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambühl P, Olsson AG, Hartmann A, Solbu DO, Pedersen TR; Assessment of LEScol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet*. 2003;361:2024–2031. doi: 10.1016/S0140-6736(03)13638-0
59. Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet Genomics*. 2006;16:873–879. doi: 10.1097/01.fpc.0000230416.82349.90
60. Clarkson PM, Kearns AK, Rouzier P, Rubin R, Thompson PD. Serum creatine kinase levels and renal function measures in exertional muscle damage. *Med Sci Sports Exerc*. 2006;38:623–627. doi: 10.1249/01.mss.0000210192.49210.fc
61. Mammen AL. Statin-associated autoimmune myopathy. *N Engl J Med*. 2016;374:664–669. doi: 10.1056/NEJMra1515161
62. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Stagers J, Guyton JR. Lovastatin increases exercise-induced skeletal muscle injury. *Metabolism*. 1997;46:1206–1210.
63. Parker BA, Augeri AL, Capizzi JA, Ballard KD, Troyanos C, Baggish AL, D'Hemecourt PA, Thompson PD. Effect of statins on creatine kinase levels before and after a marathon run. *Am J Cardiol*. 2012;109:282–287. doi: 10.1016/j.amjcard.2011.08.045
64. Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, Fletcher J, Meers GM, Ruebel M, Laughlin MH, Dellsperger KC, Fadel PJ, Thyfault JP. Simvastatin impairs exercise training adaptations. *J Am Coll Cardiol*. 2013;62:709–714. doi: 10.1016/j.jacc.2013.02.074
65. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, Chipkin S, Pescatello LS, Simpson K, White CM, Thompson PD. Effect of statins on skeletal muscle function. *Circulation*. 2013;127:96–103. doi: 10.1161/CIRCULATIONAHA.112.136101
66. Panza GA, Taylor BA, Dada MR, Thompson PD. Changes in muscle strength in individuals with statin-induced myopathy: a summary of 3 investigations. *J Clin Lipidol*. 2015;9:351–356. doi: 10.1016/j.jacl.2015.01.004
67. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol*. 2012;6:208–215. doi: 10.1016/j.jacl.2012.03.003
68. Keech A, Collins R, MacMahon S, Armitage J, Lawson A, Wallendszus K, Fatemian M, Kearney E, Lyon V, Mindell J, Mount J, Painter R, Parish S, Slavin B, Sleight P, Youngman L, Peto R. Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J*. 1994;15:255–269.
69. Roberts M. CRESTOR (Rosuvastatin calcium) NDA 21-366/S-016; JUPITER; Briefing Document for United States Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee Meeting of December 15, 2009. <https://wayback.archive-it.org/7993/20170405221029/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM193831.pdf>. Accessed October 2, 2016.
70. Tobert JA, Newman CB. Statin tolerability: in defence of placebo-controlled trials. *Eur J Prev Cardiol*. 2016;23:891–896. doi: 10.1177/2047487315602861
71. Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. *J Clin Lipidol*. 2016;10:739–747. doi: 10.1016/j.jacl.2016.05.002
72. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, Krumholz HM. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation*. 2006;114:2788–2797. doi: 10.1161/CIRCULATIONAHA.106.624890
73. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J*. 2014;168:6–15. doi: 10.1016/j.ahj.2014.03.019
74. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur J Prev Cardiol*. 2014;21:464–474. doi: 10.1177/2047487314525531
75. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, López-Jaramillo P, Leiter LA, Dans A, Avezum A, Piegas LS, Parkhomenko A, Keltai M, Keltai M, Sliwa K, Peters RJ, Held C, Chazova I, Yusuf K, Lewis BS, Jansky P, Khunti K, Toff WD, Reid CM, Varigos J, Sanchez-Vallejo G, McKelvie R, Pogue J, Jung H, Gao P, Diaz R, Lonn E; for the HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2021–2031. doi: 10.1056/NEJMoa1600176
76. Pedersen TR, Berg K, Cook TJ, Faergeman O, Haghfelt T, Kjekshus J, Miettinen T, Musliner TA, Olsson AG, Pyörälä K, Thorgeirsson G, Tobert JA, Wedel H, Wilhelmsen L. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1996;156:2085–2092.
77. Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for analyses of adverse event data from randomized controlled trials of statin therapy. *Am Heart J*. 2016;176:63–69. doi: 10.1016/j.ahj.2016.01.016
78. Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. *Ann Intern Med*. 2014;160:301–310. doi: 10.7326/M13-1921
79. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, Gipe D. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and

- rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. *J Clin Lipidol*. 2014;8:554–561. doi: 10.1016/j.jacl.2014.09.007
80. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, Kopecky SL, Baccara-Dinet MT, Du Y, Pordy R, Gipe DA; for the ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–769. doi: 10.1016/j.jacl.2015.08.006
 81. Nissen SE, Dent-Acosta RE, Rosenson RS, Stroes E, Sattar N, Preiss D, Mancini GB, Ballantyne CM, Catapano A, Gouni-Berthold I, Stein EA, Xue A, Wasserman SM, Scott R, Thompson PD; for the GAUSS-3 Investigators. Comparison of PCSK9 inhibitor evolocumab vs ezetimibe in statin-intolerant patients: design of the goal achievement after utilizing an anti-PCSK9 antibody in statin-intolerant subjects 3 (GAUSS-3) Trial. *Clin Cardiol*. 2016;39:137–144. doi: 10.1002/clc.22518
 82. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Ceška R, Lepor N, Ballantyne CM, Gouni-Berthold I, Elliott M, Brennan DM, Wasserman SM, Somaratne R, Scott R, Stein EA; for the GAUSS-3 Investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016;315:1580–1590. doi: 10.1001/jama.2016.3608
 83. Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. *Atherosclerosis*. 2015;238:329–335. doi: 10.1016/j.atherosclerosis.2014.12.016
 84. Newman CB, Tobert JA. Comment on the article by Moriarty et al. *J Clin Lipidol*. 2016;10:209–210. doi: 10.1016/j.jacl.2015.11.005
 85. Rosenson RS, Miller K, Bayliss M, Sanchez RJ, Baccara-Dinet MT, Chibedi-De-Roche D, Taylor B, Khan I, Manvelian G, White M, Jacobson TA. The statin-associated muscle symptom clinical index (SAMS-CI): revision for clinical use, content validation, and inter-rater reliability. *Cardiovasc Drugs Ther*. 2017;31:179–186. doi: 10.1007/s10557-017-6723-4
 86. Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, Collins R, Sever P; for the ASCOT Investigators. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet*. 2017;389:2473–2481. doi: 10.1016/S0140-6736(17)31075-9
 87. Pedro-Botet J, Rubiés-Prat J. Statin-associated muscle symptoms: beware of the nocebo effect. *Lancet*. 2017;389:2445–2446. doi: 10.1016/S0140-6736(17)31163-7
 88. Zhou Z, Curtis A, Breslin M, Nelson M. Concerns related to the nocebo effect. *Lancet*. 2017;390:1831–1832. doi: 10.1016/S0140-6736(17)32427-3
 89. Gupta A, Godec T, Sever P. Concerns related to the nocebo effect: authors' reply. *Lancet*. 2017;390:1832. doi: 10.1016/S0140-6736(17)32423-6
 90. Adhyaru BB, Jacobson TA. Unblinded ASCOT study results do not rule out that muscle symptoms are an adverse effect of statins. *Evid Based Med*. 2017;22:210. doi: 10.1136/ebmed-2017-110783
 91. Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med*. 2010;16:1277–1283. doi: 10.1038/nm.2229
 92. Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch Arztebl Int*. 2012;109:459–465. doi: 10.3238/arztebl.2012.0459
 93. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA*. 2012;307:567–568. doi: 10.1001/jama.2012.115
 94. Faasse K, Petrie KJ. The nocebo effect: patient expectations and medication side effects. *Postgrad Med J*. 2013;89:540–546. doi: 10.1136/postgradmedj-2012-131730
 95. Bingel U; for the Placebo Competence Team. Avoiding nocebo effects to optimize treatment outcome. *JAMA*. 2014;312:693–694. doi: 10.1001/jama.2014.8342
 96. Backes JM, Ruisinger JF, Gibson CA, Moriarty PM. Statin-associated muscle symptoms: managing the highly intolerant. *J Clin Lipidol*. 2017;11:24–33. doi: 10.1016/j.jacl.2017.01.006
 97. Mancini GB, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, Gupta M, Hegele RA, Ng D, Pearson GJ, Pope J, Tashakkor AY. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Consensus Working Group Update (2016). *Can J Cardiol*. 2016;32(suppl):S35–S65. doi: 10.1016/j.cjca.2016.01.003
 98. Chavarria V, Vian J, Pereira C, Data-Franco J, Fernandes BS, Berk M, Dodd S. The placebo and nocebo phenomena: their clinical management and impact on treatment outcomes. *Clin Ther*. 2017;39:477–486. doi: 10.1016/j.clinthera.2017.01.031
 99. Wessely S. Responding to mass psychogenic illness. *N Engl J Med*. 2000;342:129–130. doi: 10.1056/NEJM200001133420212
 100. Nissen SE. Statin denial: an internet-driven cult with deadly consequences. *Ann Intern Med*. 2017;167:281–282. doi: 10.7326/M17-1566
 101. Zhang H, Plutzky J, Shubina M, Turchin A. Continued statin prescriptions after adverse reactions and patient outcomes: a cohort study. *Ann Intern Med*. 2017;167:221–227. doi: 10.7326/M16-0838
 102. Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. *Osteoporos Int*. 2002;13:187–194. doi: 10.1007/s001980200012
 103. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, Rysz J, Muntner P, Toth PP, Jones SR, Rizzo M, Kees Hovingh G, Farnier M, Moriarty PM, Bittner VA, Lip GY, Banach M; for the Lipid and Blood Pressure Meta-analysis Collaboration (LBPAC) Group. Analysis of vitamin D levels in patients with and without statin-associated myalgia: a systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol*. 2015;178:111–116. doi: 10.1016/j.ijcard.2014.10.118
 104. Kurnik D, Hochman I, Vesterman-Landes J, Kenig T, Katzir I, Lomnický Y, Halkin H, Loebstein R. Muscle pain and serum creatine kinase are not associated with low serum 25(OH) vitamin D levels in patients receiving statins. *Clin Endocrinol (Oxf)*. 2012;77:36–41. doi: 10.1111/j.1365-2265.2011.04321.x
 105. Riphagen IJ, van der Veer E, Muskiet FA, DeJongste MJ. Myopathy during statin therapy in the daily practice of an outpatient cardiology clinic: prevalence, predictors and relation with vitamin D. *Curr Med Res Opin*. 2012;28:1247–1252. doi: 10.1185/03007995.2012.702102
 106. Riche KD, Arnall J, Rieser K, East HE, Riche DM. Impact of vitamin D status on statin-induced myopathy. *J Clin Transl Endocrinol*. 2016;6:56–59. doi: 10.1016/j.jcte.2016.11.002
 107. Calza L, Magistrelli E, Colangeli V, Borderi M, Contadini I, Bon I, Re MC, Viale P. Significant association between statin-associated myalgia and vitamin D deficiency among treated HIV-infected patients. *AIDS*. 2017;31:681–688. doi: 10.1097/QAD.0000000000001397
 108. Taylor BA, Lorson L, White CM, Thompson PD. Low vitamin D does not predict statin associated muscle symptoms but is associated with transient increases in muscle damage and pain. *Atherosclerosis*. 2017;256:100–104. doi: 10.1016/j.atherosclerosis.2016.11.011
 109. Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, Toth PP, Jones SR, Rizzo M, Glasser SP, Lip GY, Dragan S, Mikhailidis DP; for the Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2015;90:24–34. doi: 10.1016/j.mayocp.2014.08.021
 110. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation*. 2001;103:357–362.
 111. Coleman CI, Reinhart K, Kluger J, White CM. The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials. *Curr Med Res Opin*. 2008;24:1359–1362. doi: 10.1185/030079908X292029
 112. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet*. 2012;380:565–571. doi: 10.1016/S0140-6736(12)61190-8
 113. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–742. doi: 10.1016/S0140-6736(09)61965-6
 114. Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, Sofat R, Stender S, Johnson PC, Scott RA, Leusink M, Verweij N, Sharp SJ, Guo Y, Giambartolomei C, Chung C, Peasey A, Amuzu A, Li K, Palmén J, Howard P, Cooper JA, Drenos F, Li YR, Lowe G, Gallacher J, Stewart MC, Tzoulaki I, Buxbaum SG, van der A DL, Forouhi NG, Onland-Moret NC, van der Schouw YT, Schnabel RB, Hubacek JA, Kubinova R, Baceviciene M, Tamosiunas A, Pajak A, Topor-Madry R, Stepniak U, Maljutina S, Baldassarre D, Sennblad B,

- Tremoli E, de Faire U, Veglia F, Ford I, Jukema JW, Westendorp RG, de Borst GJ, de Jong PA, Algra A, Spiering W, Maitland-van der Zee AH, Klungel OH, de Boer A, Doevendans PA, Eaton CB, Robinson JG, Duggan D, Kjekshus J, Downs JR, Gotto AM, Keech AC, Marchioli R, Tognoni G, Sever PS, Poulter NR, Waters DD, Pedersen TR, Amarenco P, Nakamura H, McMurray JJ, Lewsey JD, Chasman DI, Ridker PM, Maggioni AP, Tavazzi L, Ray KK, Seshasai SR, Manson JE, Price JF, Whincup PH, Morris RW, Lawlor DA, Smith GD, Ben-Shlomo Y, Schreiner PJ, Fornage M, Siscovick DS, Cushman M, Kumari M, Wareham NJ, Verschuren WM, Redline S, Patel SR, Whittaker JC, Hamsten A, Delaney JA, Dale C, Gaunt TR, Wong A, Kuh D, Hardy R, Kathiresan S, Castillo BA, van der Harst P, Brunner EJ, Tybjaerg-Hansen A, Marmot MG, Krauss RM, Tsai M, Coresh J, Hoogeveen RC, Psaty BM, Lange LA, Hakonarson H, Dudbridge F, Humphries SE, Talmud PJ, Kivimäki M, Timpson NJ, Langenberg C, Asselbergs FW, Voevoda M, Bobak M, Pikhart H, Wilson JG, Reiner AP, Keating BJ, Hingorani AD, Sattar N; DIAGRAM Consortium; MAGIC Consortium; InterAct Consortium. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet*. 2015;385:351–361. doi: 10.1016/S0140-6736(14)61183-1
115. Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Wun CC, Kastelein JJ, Colhoun H, Barter P. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol*. 2011;57:1535–1545. doi: 10.1016/j.jacc.2010.10.047
116. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556–2564. doi: 10.1001/jama.2011.860
117. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117–125. doi: 10.1016/S0140-6736(08)60104-X
118. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobble SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; for the PROSPER Study Group: PROSpective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623–1630.
119. Tikkanen MJ, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, Kastelein JJ, Holme I, Pedersen TR; for the IDEAL Investigators. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. *Int J Cardiol*. 2013;168:3846–3852. doi: 10.1016/j.ijcard.2013.06.024
120. Vallejo-Vaz AJ, Kondapally Seshasai SR, Kurogi K, Michishita I, Nozue T, Sugiyama S, Tsimikas S, Yoshida H, Ray KK. Effect of pitavastatin on glucose, HbA1c and incident diabetes: a meta-analysis of randomized controlled clinical trials in individuals without diabetes. *Atherosclerosis*. 2015;241:409–418. doi: 10.1016/j.atherosclerosis.2015.06.001
121. Yamazaki T, Kishimoto J, Ito C, Noda M, Odawara M, Terauchi Y, Shiba T, Kitazato H, Iwamoto Y, Akanuma Y, Kadowaki T. Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (the J-PREDICT study): rationale, study design, and clinical characteristics of 1269 patients. *Diabetol Int*. 2011;2:134–140.
122. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. 1994;17:961–969.
123. Tragante V, Asselbergs FW, Swerdlow DI, Palmer TM, Moore JH, de Bakker PI, Keating BJ, Holmes MV. Harnessing publicly available genetic data to prioritize lipid modifying therapeutic targets for prevention of coronary heart disease based on dysglycemic risk. *Hum Genet*. 2016;135:453–467. doi: 10.1007/s00439-016-1647-9
124. White J, Swerdlow DI, Preiss D, Fairhurst-Hunter Z, Keating BJ, Asselbergs FW, Sattar N, Humphries SE, Hingorani AD, Holmes MV. Association of lipid fractions with risks for coronary artery disease and diabetes. *JAMA Cardiol*. 2016;1:692–699. doi: 10.1001/jamacardio.2016.1884
125. Besseling J, Kastelein JJ, Defesche JC, Hutten BA, Hovingh GK. Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. *JAMA*. 2015;313:1029–1036. doi: 10.1001/jama.2015.1206
126. Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, Voros S, Giugliano RP, Davey Smith G, Fazio S, Sabatine MS. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med*. 2016;375:2144–2153. doi: 10.1056/NEJMoa1604304
127. Lotta LA, Sharp SJ, Burgess S, Perry JRB, Stewart ID, Willems SM, Luan J, Ardanaz E, Arriola L, Balkau B, Boeing H, Deloukas P, Forouhi NG, Franks PW, Grioni S, Kaaks R, Key TJ, Navarro C, Nilsson PM, Overvad K, Palli D, Panico S, Quirós JR, Riboli E, Rolandsson O, Sacerdote C, Salamanca EC, Slimani N, Spijkerman AM, Tjonneland A, Tumino R, van der A DL, van der Schouw YT, McCarthy MI, Barroso I, O'Rahilly S, Savage DB, Sattar N, Langenberg C, Scott RA, Wareham NJ. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 diabetes: a meta-analysis. *JAMA*. 2016;316:1383–1391. doi: 10.1001/jama.2016.14568
128. Holman RR, Paul S, Farmer A, Tucker L, Stratton IM, Neil HA; for the Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes Study Group. Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD): a randomised controlled trial. *Diabetologia*. 2009;52:50–59. doi: 10.1007/s00125-008-1179-5
129. Newman CB, Szarek M, Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Demicco DA, Auster S, Fuller JH; for the CARDS Investigators. The safety and tolerability of atorvastatin 10 mg in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diab Vasc Dis Res*. 2008;5:177–183. doi: 10.3132/dvdr.2008.029
130. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH; for the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696. doi: 10.1016/S0140-6736(04)16895-5
131. Collins R, Armitage J, Parish S, Sleight P, Peto R; for the Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016.
132. Erqou S, Lee CC, Adler AI. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. *Diabetologia*. 2014;57:2444–2452. doi: 10.1007/s00125-014-3374-x
133. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet*. 2009;373:1765–1772. doi: 10.1016/S0140-6736(09)60697-8
134. MacDonald JS, Gerson RJ, Kornbrust DJ, Kloss MW, Prahallada S, Berry PH, Alberts AW, Bokelman DL. Preclinical evaluation of lovastatin. *Am J Cardiol*. 1988;62:16J–27J.
135. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ*. 2005;172:367–379. doi: 10.1503/cmaj.1040752
136. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol*. 2003;98:960–967. doi: 10.1111/j.1572-0241.2003.07486.x
137. Senior JR. Evolution of the Food and Drug Administration approach to liver safety assessment for new drugs: current status and challenges. *Drug Saf*. 2014;37(suppl 1):S9–S17. doi: 10.1007/s40264-014-0182-7
138. Bays H, Cohen DE, Chalasani N, Harrison SA; The National Lipid Association's Statin Safety Task Force. An assessment by the Statin Liver Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(suppl):S47–S57. doi: 10.1016/j.jacl.2014.02.011
139. U.S. Food and Drug Administration. 2012: FDA Drug Safety Communication: important safety label changes to cholesterol-lowering statin drugs. <http://www.fda.gov/drugs/drugsafety/ucm293101.htm>. Accessed September 20, 2016.
140. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T; for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711–1718.
141. Russo MW, Scobey M, Bonkovsky HL. Drug-induced liver injury associated with statins. *Semin Liver Dis*. 2009;29:412–422. doi: 10.1055/s-0029-1240010

142. Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing. *J Hepatol*. 2012;56:374–380. doi: 10.1016/j.jhep.2011.07.023
143. Clarke AT, Johnson PC, Hall GC, Ford I, Mills PR. High dose atorvastatin associated with increased risk of significant hepatotoxicity in comparison to simvastatin in UK GPRD cohort. *PLoS One*. 2016;11:e0151587. doi: 10.1371/journal.pone.0151587
144. Mozaffarian D, Benjamin E, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; on behalf of the American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2016 update: a report from the American Heart Association [published correction appears in *Circulation*. 2016;133:e599]. *Circulation*. 2016;133:e38–e360. doi: 10.1161/CIR.0000000000000350
145. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904–910. doi: 10.1056/NEJM198904063201405
146. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, MacMahon S, Woodward M; for the Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol*. 2003;32:563–572.
147. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusuf K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S; for the INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3
148. Hackam DG, Woodward M, Newby LK, Bhatt DL, Shao M, Smith EE, Donner A, Mamdani M, Douketis JD, Arima H, Chalmers J, MacMahon S, Tirschwell DL, Psaty BM, Bushnell CD, Aguilar MI, Capapangan DJ, Werring DJ, De Rango P, Viswanathan A, Danchin N, Cheng CL, Yang YH, Verdell BM, Lai MS, Kennedy J, Uchiyama S, Yamaguchi T, Ikeda Y, Mrkobrada M. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. *Circulation*. 2011;124:2233–2242. doi: 10.1161/CIRCULATIONAHA.111.055269
149. Amarencu P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol*. 2009;8:453–463. doi: 10.1016/S1474-4422(09)70058-4
150. Waters DD, LaRosa JC, Barter P, Fruchart JC, Gotto AM Jr, Carter R, Breazna A, Kastelein JJ, Grundy SM. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2006;48:1793–1799. doi: 10.1016/j.jacc.2006.07.041
151. Collins R, Armitage J, Parish S, Sleight P, Peto R; for the Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757–767. doi: 10.1016/S0140-6736(04)15690-0
152. Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, Schwam E, Schindler R, Hey-Hadavi J, DeMicco DA, Breazna A; for the LEADe Investigators. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology*. 2010;74:956–964. doi: 10.1212/WNL.0b013e3181d6476a
153. Rojas-Fernandez CH, Goldstein LB, Levey AI, Taylor BA, Bittner V; for the National Lipid Association's Safety Task Force. An assessment by the Statin Cognitive Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(suppl):S5–S16. doi: 10.1016/j.jacl.2014.02.013
154. Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia: systematic review and methodological commentary. *Nat Rev Neurol*. 2015;11:220–229. doi: 10.1038/nrneurol.2015.35
155. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database Syst Rev*. 2016;(1):CD003160. doi: 10.1002/14651858.CD003160.pub3
156. Eckernäs SA, Roos BE, Kvidal P, Eriksson LO, Block GA, Neafus RP, Haigh JR. The effects of simvastatin and pravastatin on objective and subjective measures of nocturnal sleep: a comparison of two structurally different HMG CoA reductase inhibitors in patients with primary moderate hypercholesterolaemia. *Br J Clin Pharmacol*. 1993;35:284–289.
157. Kamei Y, Shirakawa S, Ishizuka Y, Usui A, Uchiyama M, Watanabe T, Fukuzawa H, Kariya T. Effect of pravastatin on human sleep. *Jpn J Psychiatry Neurol*. 1993;47:643–646.
158. Kostis JB, Rosen RC, Wilson AC. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *J Clin Pharmacol*. 1994;34:989–996.
159. Partinen M, Pihl S, Strandberg T, Vanhanen H, Murtoimäki E, Block G, Neafus R, Haigh J, Miettinen T, Reines S. Comparison of effects on sleep of lovastatin and pravastatin in hypercholesterolemia. *Am J Cardiol*. 1994;73:876–880.
160. Roth T, Richardson GR, Sullivan JP, Lee RM, Merlotti L, Roehrs T. Comparative effects of pravastatin and lovastatin on nighttime sleep and daytime performance. *Clin Cardiol*. 1992;15:426–432.
161. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin: the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol*. 2011;57:1666–1675. doi: 10.1016/j.jacc.2010.09.082
162. Swiger KJ, Manalac RJ, Blaha MJ, Blumenthal RS, Martin SS. Statins, mood, sleep, and physical function: a systematic review. *Eur J Clin Pharmacol*. 2014;70:1413–1422. doi: 10.1007/s00228-014-1758-y
163. Edwards IR, Star K, Kiuru A. Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from VigiBase. *Drug Saf*. 2007;30:515–525.
164. Zheng Z, Sheng L, Shang H. Statins and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013;14:241–245. doi: 10.3109/21678421.2012.732078
165. Sheng Z, Jia X, Kang M. Statin use and risk of Parkinson's disease: a meta-analysis. *Behav Brain Res*. 2016;309:29–34. doi: 10.1016/j.bbr.2016.04.046
166. Paul R, Choudhury A, Borah A. Cholesterol: a putative endogenous contributor towards Parkinson's disease. *Neurochem Int*. 2015;90:125–133. doi: 10.1016/j.neuint.2015.07.025
167. England JD, Asbury AK. Peripheral neuropathy. *Lancet*. 2004;363:2151–2161. doi: 10.1016/S0140-6736(04)16508-2
168. Gaist D, García Rodríguez LA, Huerta C, Hallas J, Sindrup SH. Are users of lipid-lowering drugs at increased risk of peripheral neuropathy? *Eur J Clin Pharmacol*. 2001;56:931–933.
169. Gaist D, Jeppesen U, Andersen M, García Rodríguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case-control study. *Neurology*. 2002;58:1333–1337.
170. Corrao G, Zambon A, Bertù L, Botteri E, Leoni O, Contiero P. Lipid lowering drugs prescription and the risk of peripheral neuropathy: an exploratory case-control study using automated databases. *J Epidemiol Community Health*. 2004;58:1047–1051. doi: 10.1136/jech.2003.013409
171. Otruba P, Kanovsky P, Hlustik P. Treatment with statins and peripheral neuropathy: results of 36-months a prospective clinical and neurophysiological follow-up. *Neuro Endocrinol Lett*. 2011;32:688–690.
172. Davis TM, Yeap BB, Davis WA, Bruce DG. Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia*. 2008;51:562–566. doi: 10.1007/s00125-007-0919-2
173. Nielsen SF, Nordestgaard BG. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study. *Lancet Diabetes Endocrinol*. 2014;2:894–900. doi: 10.1016/S2213-8587(14)70173-1
174. Tierney EF, Thurman DJ, Beckles GL, Cadwell BL. Association of statin use with peripheral neuropathy in the U.S. population 40 years of age or older. *J Diabetes*. 2013;5:207–215. doi: 10.1111/1753-0407.12013
175. Illingworth DR, Corbin D. The influence of mevinolin on the adrenal cortical response to corticotropin in heterozygous familial hypercholesterolemia. *Proc Natl Acad Sci U S A*. 1985;82:6291–6294.
176. Fojo SS, Hoeg JM, Lackner KJ, Anchors JM, Bailey KR, Brewer HB Jr. Adrenocortical function in type II hyperlipoproteinemic patients treated with lovastatin (mevinolin). *Horm Metab Res*. 1987;19:648–652. doi: 10.1055/s-2007-1011900
177. Mol MJ, Stalenhoef AF, Stuyt PM, Hermus AR, Demacker PN, Van 't Laar A. Effects of inhibition of cholesterol synthesis by simvastatin on the production of adrenocortical steroid hormones and ACTH. *Clin Endocrinol (Oxf)*. 1989;31:679–689.

178. Candrina R, Balestrieri G, Salvi A, Di Stefano O, Spandrio S, Giustina G. Cortisol secretion in patients on simvastatin. *Lancet*. 1990;335:53.
179. Dobs AS, Schrott H, Davidson MH, Bays H, Stein EA, Kush D, Wu M, Mitchel Y, Illingworth RD. Effects of high-dose simvastatin on adrenal and gonadal steroidogenesis in men with hypercholesterolemia. *Metabolism*. 2000;49:1234–1238. doi: 10.1053/meta.2000.7716a
180. Dobs AS, Miller S, Neri G, Weiss S, Tate AC, Shapiro DR, Musliner TA. Effects of simvastatin and pravastatin on gonadal function in male hypercholesterolemic patients. *Metabolism*. 2000;49:115–121.
181. Cui Y, Zong H, Yan H, Zhang Y. The effect of statins on erectile dysfunction: a systematic review and meta-analysis. *J Sex Med*. 2014;11:1367–1375. doi: 10.1111/jsm.12497
182. Kostis JB, Dobrzynski JM. The effect of statins on erectile dysfunction: a meta-analysis of randomized trials. *J Sex Med*. 2014;11:1626–1635. doi: 10.1111/jsm.12521
183. Plotkin D, Miller S, Nakajima S, Peskin E, Burkman R, Richardson D, Mitchel Y, Waldstreicher J, Liu M, Shapiro D, Santoro N. Lowering low density lipoprotein cholesterol with simvastatin, a hydroxy-3-methylglutaryl-coenzyme a reductase inhibitor, does not affect luteal function in premenopausal women. *J Clin Endocrinol Metab*. 2002;87:3155–3161. doi: 10.1210/jcem.87.7.8635
184. Kirby TJ. Cataracts produced by triparanol (MER-29). *Trans Am Ophthalmol Soc*. 1967;65:494–543.
185. Gerson RJ, MacDonald JS, Alberts AW, Kornbrust DJ, Majka JA, Stubbs RJ, Bokelman DL. Animal safety and toxicology of simvastatin and related hydroxy-methylglutaryl-coenzyme A reductase inhibitors. *Am J Med*. 1989;87:28S–38S.
186. Lattes AM, Keates EU, Taylor HR, Chremos AN, Shear CL, Lippa EA, Gould AL, Hurley DP. The human lens after 48 weeks of treatment with lovastatin. *N Engl J Med*. 1990;323:683–684. doi: 10.1056/NEJM199009063231015
187. Lattes AM, Shear CL, Lippa EA, Gould AL, Taylor HR, Hurley DP, Stephenson WP, Keates EU, Tupy-Visich MA, Chremos AN. Expanded clinical evaluation of lovastatin (EXCEL) study results. II: assessment of the human lens after 48 weeks of treatment with lovastatin. *Am J Cardiol*. 1991;67:447–453.
188. Bang CN, Greve AM, La Cour M, Boman K, Gohlke-Bärwolf C, Ray S, Pedersen T, Rossebø A, Okin PM, Devereux RB, Wachtell K. Effect of randomized lipid lowering with simvastatin and ezetimibe on cataract development (from the Simvastatin and Ezetimibe in Aortic Stenosis Study). *Am J Cardiol*. 2015;116:1840–1844. doi: 10.1016/j.amjcard.2015.09.026
189. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ*. 2010;340:c2197.
190. Leuschen J, Mortensen EM, Frei CR, Mansi EA, Panday V, Mansi I. Association of statin use with cataracts: a propensity score-matched analysis. *JAMA Ophthalmol*. 2013;131:1427–1434. doi: 10.1001/jamaophthalmol.2013.4575
191. Fong DS, Poon KY. Recent statin use and cataract surgery. *Am J Ophthalmol*. 2012;153:222–228.e1. doi: 10.1016/j.ajo.2011.08.001
192. Tan JS, Mitchell P, Roachchina E, Wang JJ. Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol*. 2007;143:687–689. doi: 10.1016/j.ajo.2006.11.027
193. Sidaway JE, Davidson RG, McTaggart F, Orton TC, Scott RC, Smith GJ, Brunskill NJ. Inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase reduce receptor-mediated endocytosis in opossum kidney cells. *J Am Soc Nephrol*. 2004;15:2258–2265. doi: 10.1097/01.ASN.0000138236.82706.EE
194. Su X, Zhang L, Lv J, Wang J, Hou W, Xie X, Zhang H. Effect of statins on kidney disease outcomes: a systematic review and meta-analysis. *Am J Kidney Dis*. 2016;67:881–892. doi: 10.1053/j.ajkd.2016.01.016
195. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, Wilson DJ, Zuckerman A, Wenger NK; for the TNT (Treating to New Targets) Investigators. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008;51:1448–1454. doi: 10.1016/j.jacc.2007.11.072
196. Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, Raymond CB, Lafrance JP, Levy A, Garg AX, Ernst P; Canadian Network for Observational Drug Effect Studies. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ*. 2013;346:f880.
197. Bangalore S, Fayyad R, Hovingh GK, Laskey R, Vogt L, DeMicco DA, Waters DD; for the Treating to New Targets Steering Committee and Investigators. Statin and the risk of renal-related serious adverse events: analysis from the IDEAL, TNT, CARDS, ASPEN, SPARCL, and other placebo-controlled trials. *Am J Cardiol*. 2014;113:2018–2020. doi: 10.1016/j.amjcard.2014.03.046
198. Bellomo R. Perioperative statins in cardiac surgery and acute kidney injury. *JAMA*. 2016;315:873–874. doi: 10.1001/jama.2016.0245
199. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e652–e735. doi: 10.1161/CIR.0b013e31823c074e
200. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z, Collins R, Casadei B. Perioperative rosuvastatin in cardiac surgery. *N Engl J Med*. 2016;374:1744–1753. doi: 10.1056/NEJMoa1507750
201. Billings FT 4th, Hendricks PA, Schilderout JS, Shi Y, Petracek MR, Byrne JG, Brown NJ. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. *JAMA*. 2016;315:877–888. doi: 10.1001/jama.2016.0548
202. Beechey D, Coupe B, Benbow EW, Morgan J, Kwok S, Charlton-Menys V, France M, Durrington PN. Familial hypercholesterolaemia commonly presents with Achilles tenosynovitis. *Ann Rheum Dis*. 2006;65:312–315. doi: 10.1136/ard.2005.040766
203. Chazerain P, Hayem G, Hamza S, Best C, Ziza JM. Four cases of tendinopathy in patients on statin therapy. *Joint Bone Spine*. 2001;68:430–433.
204. Pullatt RC, Gadarla MR, Karas RH, Alsheikh-Ali AA, Thompson PD. Tendon rupture associated with simvastatin/ezetimibe therapy. *Am J Cardiol*. 2007;100:152–153. doi: 10.1016/j.amjcard.2007.02.068
205. Marie I, Delafenêtre H, Massy N, Thuillez C, Noblet C; for the Network of the French Pharmacovigilance Centers. Tendinosis disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990–2005 and review of the literature. *Arthritis Rheum*. 2008;59:367–372. doi: 10.1002/art.23309
206. Teichtahl AJ, Brady SR, Urquhart DM, Wluka AE, Wang Y, Shaw JE, Cicuttini FM. Statins and tendinopathy: a systematic review. *Med J Aust*. 2016;204:115–121.e1.
207. Beri A, Dwamena FC, Dwamena BA. Association between statin therapy and tendon rupture: a case-control study. *J Cardiovasc Pharmacol*. 2009;53:401–404. doi: 10.1097/FJC.0b013e3181a0ce8b
208. Savvidou C, Moreno R. Spontaneous distal biceps tendon ruptures: are they related to statin administration? *Hand Surg*. 2012;17:167–171. doi: 10.1142/S0218810412500153
209. Contractor T, Beri A, Gardiner JC, Tang X, Dwamena FC. Is statin use associated with tendon rupture? A population-based retrospective cohort analysis. *Am J Ther*. 2015;22:377–381. doi: 10.1097/MJT.0000000000000039
210. Lin TT, Lin CH, Chang LC, Chi CH, Chang ST, Sheu WH. The effect of diabetes, hyperlipidemia, and statins on the development of rotator cuff disease: a nationwide, 11-year, longitudinal, population-based follow-up study. *Am J Sports Med*. 2015;43:2126–2132. doi: 10.1177/0363546515588173
211. Ciaravino V, Kropko ML, Rothwell CE, Hovey CA, Theiss JC. The genotoxicity profile of atorvastatin, a new drug in the treatment of hypercholesterolemia. *Mutat Res*. 1995;343:95–107.
212. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wu CC, Davis BR, Braunwald E; for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009. doi: 10.1056/NEJM199610033351401
213. Pfeffer MA, Keech A, Sacks FM, Cobbe SM, Tonkin A, Byington RP, Davis BR, Friedman CP, Braunwald E. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. *Circulation*. 2002;105:2341–2346.
214. Cholesterol Treatment Trialists' (CTT) Collaboration. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. *PLoS ONE*. 2012;7:e29849. doi: 10.1371/journal.pone.0029849
215. Strandberg TE, Pyörälä K, Cook TJ, Wilhelmsen L, Faergeman O, Thorgeirsson G, Pedersen TR, Kjekshus J; for the 4S Group. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian

- Simvastatin Survival Study (4S). *Lancet*. 2004;364:771–777. doi: 10.1016/S0140-6736(04)16936-5
216. Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet*. 2011;378:2013–2020. doi: 10.1016/S0140-6736(11)61125-2
 217. Lloyd SM, Stott DJ, de Craen AJ, Kearney PM, Sattar N, Perry I, Packard CJ, Briggs A, Marchbank L, Comber H, Jukema JW, Westendorp RG, Trompet S, Buckley BM, Ford I. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *PLoS One*. 2013;8:e72642. doi: 10.1371/journal.pone.0072642
 218. Hague WE, Simes J, Kirby A, Keech AC, White HD, Hunt D, Nestel PJ, Colquhoun DM, Pater H, Stewart RA, Sullivan DR, Thompson PL, West M, Glasziou PP, Tonkin AM; for the LIPID Study Investigators. Long-term effectiveness and safety of pravastatin in patients with coronary heart disease: sixteen years of follow-up of the LIPID study. *Circulation*. 2016;133:1851–1860. doi: 10.1161/CIRCULATIONAHA.115.018580
 219. Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of West of Scotland Coronary Prevention Study. *Circulation*. 2016;133:1073–1080. doi: 10.1161/CIRCULATIONAHA.115.019014
 220. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med*. 2012;367:1792–1802. doi: 10.1056/NEJMoa1201735
 221. Wiggins BS, Saseen JJ, Page RL 2nd, Reed BN, Sneed K, Kostis JB, Lanfear D, Virani S, Morris PB; on behalf of the American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology, Council on Hypertension, Council on Quality of Care and Outcomes Research, Council on Functional Genomics and Translational Biology. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e468–e495. doi: 10.1161/CIR.0000000000000456
 222. Corsini A, Maggi FM, Catapano AL. Pharmacology of competitive inhibitors of HMG-CoA reductase. *Pharmacol Res*. 1995;31:9–27.
 223. García MJ, Reinoso RF, Sánchez Navarro A, Prous JR. Clinical pharmacokinetics of statins. *Methods Find Exp Clin Pharmacol*. 2003;25:457–481.
 224. Kellick KA, Bottorff M, Toth PP; for the National Lipid Association's Safety Task Force. A clinician's guide to statin drug-drug interactions. *J Clin Lipidol*. 2014;8(suppl):S30–S46. doi: 10.1016/j.jacl.2014.02.010
 225. Duggan DE, Vickers S. Physiological disposition of HMG-CoA reductase inhibitors. *Drug Metab Rev*. 1990;22:333–362. doi: 10.3109/03602539009041088
 226. Fischer V, Johanson L, Heitz F, Tullman R, Graham E, Baldeck JP, Robinson WT. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor fluvastatin: effect on human cytochrome P-450 and implications for metabolic drug interactions. *Drug Metab Dispos*. 1999;27:410–416.
 227. Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev*. 2011;63:157–181. doi: 10.1124/pr.110.002857
 228. Lovastatin Study Group II. Therapeutic response to lovastatin (mevinolin) in nonfamilial hypercholesterolemia: a multicenter study. *JAMA*. 1986;256:2829–2834. doi: 10.1001/jama.1986.03380200067023
 229. Parker TS, McNamara DJ, Brown CD, Kolb R, Ahrens EH Jr, Alberts AW, Tobert J, Chen J, De Schepper PJ. Plasma mevalonate as a measure of cholesterol synthesis in man. *J Clin Invest*. 1984;74:795–804. doi: 10.1172/JCI111495
 230. Bilheimer DW, Grundy SM, Brown MS, Goldstein JL. Mevinolin and colestipol stimulate receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. *Proc Natl Acad Sci U S A*. 1983;80:4124–4128.
 231. Brown MS, Goldstein JL. Regulation of the activity of the low density lipoprotein receptor in human fibroblasts. *Cell*. 1975;6:307–316.
 232. Canestaro WJ, Austin MA, Thummel KE. Genetic factors affecting statin concentrations and subsequent myopathy: a HuGENet systematic review. *Genet Med*. 2014;16:810–819. doi: 10.1038/gim.2014.41
 233. Elsby R, Hilgendorf C, Fenner K. Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. *Clin Pharmacol Ther*. 2012;92:584–598. doi: 10.1038/clpt.2012.163
 234. Reddy P, Ellington D, Zhu Y, Zdrojewski I, Parent SJ, Harmatz JS, Derendorf H, Greenblatt DJ, Browne K Jr. Serum concentrations and clinical effects of atorvastatin in patients taking grapefruit juice daily. *Br J Clin Pharmacol*. 2011;72:434–441. doi: 10.1111/j.1365-2125.2011.03996.x
 235. Lilja JJ, Neuvonen M, Neuvonen PJ. Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. *Br J Clin Pharmacol*. 2004;58:56–60. doi: 10.1111/j.1365-2125.2004.02095.x
 236. Rogers JD, Zhao J, Liu L, Amin RD, Gagliano KD, Porras AG, Blum RA, Wilson MF, Stepanavage M, Vega JM. Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Clin Pharmacol Ther*. 1999;66:358–366. doi: 10.1053/cp.1999.v66.a101208
 237. Lilja JJ, Kivistö KT, Neuvonen PJ. Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. *Clin Pharmacol Ther*. 2000;68:384–390. doi: 10.1067/mcp.2000.110216
 238. Rodrigues AD. Prioritization of clinical drug interaction studies using *in vitro* cytochrome P450 data: proposed refinement and expansion of the "rank order" approach. *Drug Metab Lett*. 2007;1:31–35.
 239. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol*. 2005;95:120–122. doi: 10.1016/j.amjcard.2004.08.076
 240. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos*. 2002;30:1280–1287.
 241. Neil HA, DeMicco DA, Luo D, Betteridge DJ, Colhoun HM, Durrington PN, Livingstone SJ, Fuller JH, Hitman GA; for the CARDS Study Investigators. Analysis of efficacy and safety in patients aged 65–75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care*. 2006;29:2378–2384. doi: 10.2337/dc06-0872
 242. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med*. 2010;152:488–496, W174. doi: 10.7326/0003-4819-152-8-201004200-00005
 243. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, Hayman LL, Daniels SR. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation*. 2007;115:1948–1967. doi: 10.1161/CIRCULATIONAHA.107.181946
 244. National Heart, Lung, and Blood Institute. Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Full Report. 2011. <https://www.nhlbi.nih.gov/node/80139>. Accessed June 17, 2018.
 245. Daniels SR, Greer FR; for the Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008;122:198–208. doi: 10.1542/peds.2008-1349
 246. Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, McCrindle B, Raal F, Rader D, Santos RD, Lopes-Virella M, Watts GF, Wierzbicki AS; on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2015;132:e397]. *Circulation*. 2015;132:2167–2192. doi: 10.1161/CIR.0000000000000297
 247. Luirink IK, Hutten BA, Wiegman A. Optimizing treatment of familial hypercholesterolemia in children and adolescents. *Curr Cardiol Rep*. 2015;17:629. doi: 10.1007/s11886-015-0629-1
 248. Vuorio P, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, Drogari E. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2014;(7):CD006401. doi: 10.1002/14651858.CD006401.pub3
 249. Lozano P, Henrikson NB, Dunn J, Morrison CC, Nguyen M, Blasi PR, Anderson ML, Whitlock EP. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US preventive services task force. *JAMA*. 2016;316:645–655. doi: 10.1001/jama.2016.6176
 250. Braamskamp MJ, Stefanutti C, Langslet G, Drogari E, Wiegman A, Hounslow N, Kastelein JJ; for the PASCAL Study Group. Efficacy and safety of pitavastatin in children and adolescents at high

- future cardiovascular risk. *J Pediatr*. 2015;167:338–343.e5. doi: 10.1016/j.jpeds.2015.05.006
251. Stein EA, Illingworth DR, Kwiterovich PO Jr, Liacouras CA, Siimes MA, Jacobson MS, Brewster TG, Hopkins P, Davidson M, Graham K, Arensman F, Knopp RH, DuJovne C, Williams CL, Isaacsohn JL, Jacobsen CA, Laskarzewski PM, Ames S, Gormley GJ. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 1999;281:137–144.
 252. de Jongh S, Ose L, Szamosi T, Gagné C, Lambert M, Scott R, Perron P, Dobbelaere D, Saborio M, Tuohy MB, Stepanavage M, Sapre A, Gumbiner B, Mercuri M, van Trotsenburg AS, Bakker HD, Kastelein JJ; for the Simvastatin in Children Study Group. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation*. 2002;106:2231–2237.
 253. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr*. 2003;143:74–80. doi: 10.1016/S0022-3476(03)00186-0
 254. Avis HJ, Hutten BA, Gagné C, Langslet G, McCrindle BW, Wiegman A, Hsia J, Kastelein JJ, Stein EA. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. *J Am Coll Cardiol*. 2010;55:1121–1126. doi: 10.1016/j.jacc.2009.10.042
 255. Braamskamp MJ, Kusters DM, Wiegman A, Avis HJ, Wijburg FA, Kastelein JJ, van Trotsenburg AS, Hutten BA. Gonadal steroids, gonadotropins and DHEAS in young adults with familial hypercholesterolemia who had initiated statin therapy in childhood. *Atherosclerosis*. 2015;241:427–432. doi: 10.1016/j.atherosclerosis.2015.05.034
 256. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Bülller HR, Sijbrands EJ, Kastelein JJ. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 2004;292:331–337. doi: 10.1001/jama.292.3.331
 257. Hedman M, Matikainen T, Föhr A, Lappi M, Piippo S, Nuutinen M, Antikainen M. Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia: a prospective clinical follow-up study. *J Clin Endocrinol Metab*. 2005;90:1942–1952. doi: 10.1210/jc.2004-1541
 258. Clauss SB, Holmes KW, Hopkins P, Stein E, Cho M, Tate A, Johnson-Levonas AO, Kwiterovich PO. Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics*. 2005;116:682–688. doi: 10.1542/peds.2004-2090
 259. O’Gorman CS, Higgins NT, O’Neill MB. Systematic review and meta-analysis of statins for heterozygous familial hypercholesterolemia in children: evaluation of cholesterol changes and side effects. *Pediatr Cardiol*. 2009;30:482–489. doi: 10.1007/s00246-008-9364-3
 260. Rodenburg J, Vissers MN, Trip MD, Wiegman A, Bakker HD, Kastelein JJ. The spectrum of statin therapy in hyperlipidemic children. *Semin Vasc Med*. 2004;4:313–320. doi: 10.1055/s-2004-869588
 261. Canas JA, Ross JL, Taboada MV, Sikes KM, Damaso LC, Hossain J, Caulfield MP, Gidding SS, Mauras N. A randomized, double blind, placebo-controlled pilot trial of the safety and efficacy of atorvastatin in children with elevated low-density lipoprotein cholesterol (LDL-C) and type 1 diabetes. *Pediatr Diabetes*. 2015;16:79–89. doi: 10.1111/pedi.12245
 262. Schanberg LE, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, Mieszkalski KL, Ilowite NT, Eberhard A, Imundo LF, Kimura Y, von Scheven E, Silverman E, Bowyer SL, Punaro M, Singer NG, Sherry DD, McCurdy D, Klein-Gitelman M, Wallace C, Silver R, Wagner-Weiner L, Higgins GC, Brunner HI, Jung L, Soep JB, Reed AM, Provenzale J, Thompson SD; for the Atherosclerosis Prevention in Pediatric Lupus Erythematosus Investigators. Use of atorvastatin in systemic lupus erythematosus in children and adolescents. *Arthritis Rheum*. 2012;64:285–296. doi: 10.1002/art.30645
 263. Cadnapaphornchai MA, George DM, McFann K, Wang W, Gitomer B, Strain JD, Schrier RW. Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2014;9:889–896. doi: 10.2215/CJN.08350813
 264. Huang SM, Temple R. Is this the drug or dose for you? Impact and consideration of ethnic factors in global drug development, regulatory review, and clinical practice. *Clin Pharmacol Ther*. 2008;84:287–294. doi: 10.1038/clpt.2008.144
 265. Choi MK, Shin HJ, Choi YL, Deng JW, Shin JG, Song IS. Differential effect of genetic variants of Na(+)-taurocholate co-transporting polypeptide (NTCP) and organic anion-transporting polypeptide 1B1 (OATP1B1) on the uptake of HMG-CoA reductase inhibitors. *Xenobiotica*. 2011;41:24–34. doi: 10.3109/00498254.2010.523736
 266. Keskitalo JE, Zolk O, Fromm MF, Kurkinen KJ, Neuvonen PJ, Niemi M. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. *Clin Pharmacol Ther*. 2009;86:197–203. doi: 10.1038/clpt.2009.79
 267. Birmingham BK, Bujac SR, Elsby R, Azumaya CT, Zalikowski J, Chen Y, Kim K, Ambrose HJ. Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. *Eur J Clin Pharmacol*. 2015;71:329–340. doi: 10.1007/s00228-014-1800-0
 268. Birmingham BK, Bujac SR, Elsby R, Azumaya CT, Wei C, Chen Y, Mosqueda-Garcia R, Ambrose HJ. Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect? *Eur J Clin Pharmacol*. 2015;71:341–355. doi: 10.1007/s00228-014-1801-z
 269. Lee HK, Hu M, Lui SSH, Ho CS, Wong CK, Tomlinson B. Effects of polymorphisms in ABCG2, SLCO1B1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid response in Chinese patients. *Pharmacogenomics*. 2013;14:1283–1294. doi: 10.2217/pgs.13.115
 270. Senkino H, Onishi T. Phase I study of ZD4522 (rosuvastatin), a new HMG-CoA reductase inhibitor: evaluation of tolerance and pharmacokinetics in healthy adult male volunteers after single and repeated oral administration. *J Clin Ther Med*. 2005;21:187–203.
 271. Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H, Moore R, Lee C, Chen Y, Schneck D. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther*. 2005;78:330–341. doi: 10.1016/j.clpt.2005.06.013
 272. Hasunuma T, Tohkin M, Kaniwa N, Jang IJ, Yimin C, Kaneko M, Saito Y, Takeuchi M, Watanabe H, Yamazoe Y, Uyama Y, Kawai S. Absence of ethnic differences in the pharmacokinetics of moxifloxacin, simvastatin, and meloxicam among three East Asian populations and Caucasians. *Br J Clin Pharmacol*. 2016;81:1078–1090. doi: 10.1111/bcp.12884
 273. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J; for the HPS Thrive Collaborative Group. Effects of extended-release niacin with laropirant in high-risk patients. *N Engl J Med*. 2014;371:203–212.
 274. Warrington S, Nagakawa S, Hounslow N. Comparison of the pharmacokinetics of pitavastatin by formulation and ethnic group: an open-label, single-dose, two-way crossover pharmacokinetic study in healthy Caucasian and Japanese men. *Clin Drug Investig*. 2011;31:735–743. doi: 10.2165/11592480-000000000-00000
 275. Haynes R, Jiang L, Hopewell JC, Li J, Chen F, Parish S, Landray MJ, Collins R, Armitage J, Collins R, Armitage J, Baigent C, Chen Z, Landray M, Chen Y, Jiang L, Pedersen T, Landray M, Bowman L, Chen F, Hill M, Haynes R, Knott C, Rahimi K, Tobert J, Sleight P, Simpson D, Parish S, Baxter A, Lay M, Bray C, Wincott E, Leijenhurst G, Skattebol A, Moen G, Mitchell Y, Kuznetsova O, MacMahon S, Kjekshus J, Hill C, Lam TH, Sandercock P, Peto R, Hopewell JC; for the HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25,673 high-risk patients of ER niacin/laropirant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34:1279–1291. doi: 10.1093/eurheartj/eh055
 276. Minsker DH, MacDonald JS, Robertson RT, Bokelman DL. Mevalonate supplementation in pregnant rats suppresses the teratogenicity of mevinolinic acid, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme a reductase. *Teratology*. 1983;28:449–456. doi: 10.1002/tera.1420280316
 277. Food and Drug Administration, HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling: Final rule. *Fed Regist*. 2014;79:72064–72103.
 278. Pollack PS, Shields KE, Burnett DM, Osborne MJ, Cunningham ML, Stepanavage ME. Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. *Birth Defects Res A Clin Mol Teratol*. 2005;73:888–896. doi: 10.1002/bdra.20181
 279. Lankas GR, Cukierski MA, Wise LD. The role of maternal toxicity in lovastatin-induced developmental toxicity. *Birth Defects Res B Dev Reprod Toxicol*. 2004;71:111–123. doi: 10.1002/bdrb.20005
 280. Kusters DM, Hassani Lahsinoui H, van de Post JA, Wiegman A, Wijburg FA, Kastelein JJ, Hutten BA. Statin use during pregnancy: a systematic review and meta-analysis. *Expert Rev Cardiovasc Ther*. 2012;10:363–378. doi: 10.1586/erc.11.196
 281. Zarek J, Delano KE, Nickel C, Laskin CA, Koren G. Are statins teratogenic in humans? Addressing the safety of statins in light of potential

- benefits during pregnancy. *Expert Rev Obstet Gynecol*. 2013;8:513–524. doi: 10.1586/17474108.2013.842684
282. Karalis DG, Hill AN, Clifton S, Wild RA. The risks of statin use in pregnancy: a systematic review. *J Clin Lipidol*. 2016;10:1081–1090. doi: 10.1016/j.jacl.2016.07.002
 283. Brown WV, Morris PB, Wild RA. JCL roundtable: managing lipid disorders in young women. *J Clin Lipidol*. 2016;10:1058–1066. doi: 10.1016/j.jacl.2016.08.007
 284. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ; for the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(suppl):S9–S17. doi: 10.1016/j.jacl.2011.03.452
 285. Illingworth DR, Sexton GJ. Hypocholesterolemic effects of mevinolin in patients with heterozygous familial hypercholesterolemia. *J Clin Invest*. 1984;74:1972–1978. doi: 10.1172/JCI111618
 286. Endo A. A historical perspective on the discovery of statins. *Proc Jpn Acad Ser B Phys Biol Sci*. 2010;86:484–493.
 287. Havel RJ, Hunninghake DB, Illingworth DR, Lees RS, Stein EA, Tobert JA, Bacon SR, Bolognese JA, Frost PH, Lamkin GE, Lees AM, Leon AS, Gardner K, Johnson G, Mellies MJ, Rhymen PA, Tun P. Lovastatin (mevinolin) in the treatment of heterozygous familial hypercholesterolemia: a multicenter study. *Ann Intern Med*. 1987;107:609–615. doi: 10.7326/0003-4819-107-5-609
 288. Langslet G, Bogsrud MP, Halvorsen I, Fjeldstad H, Retterstøl K, Veierød MB, Ose L. Long-term follow-up of young adults with familial hypercholesterolemia after participation in clinical trials during childhood. *J Clin Lipidol*. 2015;9:778–785. doi: 10.1016/j.jacl.2015.08.008
 289. Mata N, Alonso R, Badimón L, Padró T, Fuentes F, Muñiz O, Perez-Jiménez F, López-Miranda J, Díaz JL, Vidal JI, Barba A, Piedecausa M, Sanchez JF, Irigoyen L, Guallar E, Ordoñas JM, Mata P. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). *Lipids Health Dis*. 2011;10:94. doi: 10.1186/1476-511X-10-94
 290. Stein EA, Amerena J, Ballantyne CM, Brice E, Farnier M, Guthrie RM, Harats D, Ma PT, Le Maulf F, Melezínková H, Gold A, Sager P. Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. *Am J Cardiol*. 2007;100:1387–1396. doi: 10.1016/j.amjcard.2007.06.029
 291. Goldstein LB, Amarencu P, Szarek M, Callahan A, Hennerici M, Sillesen H, Zivin J, Welch KMA; for the SPARCL Investigators. Secondary analysis of hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. *Neurology*. 2008;70:2364–2370.
 292. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: a decision analysis. *Arch Neurol*. 2011;68:573–579. doi: 10.1001/archneurol.2010.356
 293. Flint AC, Conell C, Rao VA, Klingman JG, Sidney S, Johnston SC, Hemphill JC, Kamel H, Davis SM, Donnan GA. Effect of statin use during hospitalization for intracerebral hemorrhage on mortality and discharge disposition. *JAMA Neurol*. 2014;71:1364–1371. doi: 10.1001/jamaneurol.2014.2124
 294. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, Craven T, West M. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation*. 2004;110:1557–1563. doi: 10.1161/01.CIR.0000143892.84582.60
 295. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Crane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairititchai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Maffham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; for the SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192. doi: 10.1016/S0140-6736(11)60739-3
 296. Cholesterol Treatment Trialists' (CTT) Collaboration. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol*. 2016;4:829–839. doi: 10.1016/S2213-8587(16)30156-5
 297. Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, Cairns HS, Collins R, Foley RN, Frighi V, Kourelis K, Ratcliffe PJ, Rogerson M, Scoble JE, Tomson CR, Warwick G, Wheeler DC. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis*. 2005;45:473–484. doi: 10.1053/j.ajkd.2004.11.015
 298. Akçiçek F, Ok E, Duman S, Kürsüd S, Unsal A, Alev M, Atabay G, Başçı A. Lipid-lowering effects of simvastatin and gemfibrozil in CAPD patients: a prospective cross-over study. *Adv Perit Dial*. 1996;12:261–265.
 299. Harris KP, Wheeler DC, Chong CC; Atorvastatin in CAPD Study Investigators. A placebo-controlled trial examining atorvastatin in dyslipidemic patients undergoing CAPD. *Kidney Int*. 2002;61:1469–1474. doi: 10.1046/j.1523-1755.2002.00262.x
 300. Hufnagel G, Michel C, Vrtovsnik F, Queffeuou G, Kossari N, Mignon F. Effects of atorvastatin on dyslipidaemia in uraemic patients on peritoneal dialysis. *Nephrol Dial Transplant*. 2000;15:684–688.
 301. Li PK, Mak TW, Chiu K, Mak GY, Leung CB, Lui SF, Lam CW, Lai KN. Effect of lovastatin on serum lipid profile in the treatment of dyslipoproteinaemia in uraemic patients on continuous ambulatory peritoneal dialysis. *Aust N Z J Med*. 1993;23:252–257.
 302. Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing chronic renal dialysis. *Am J Kidney Dis*. 2002;39:283–290. doi: 10.1053/ajkd.2002.30547
 303. Haynes R, Lewis D, Emberson J, Reith C, Agodoa L, Cass A, Craig JC, de Zeeuw D, Feldt-Rasmussen B, Fellström B, Levin A, Wheeler DC, Walker R, Herrington WG, Baigent C, Landray MJ; for the SHARP Collaborative Group. Effects of lowering LDL cholesterol on progression of kidney disease. *J Am Soc Nephrol*. 2014;25:1825–1833. doi: 10.1681/ASN.2013090965
 304. Nikolic D, Banach M, Nikfar S, Salari P, Mikhailidis DP, Toth PP, Abdollahi M, Ray KK, Pencina MJ, Malyszko J, Rysz J, Rizzo M; for the Lipid and Blood Pressure Meta-Analysis Collaboration Group. A meta-analysis of the role of statins on renal outcomes in patients with chronic kidney disease: is the duration of therapy important? *Int J Cardiol*. 2013;168:5437–5447. doi: 10.1016/j.ijcard.2013.08.060
 305. Bader T. Liver tests are irrelevant when prescribing statins. *Lancet*. 2010;376:1882–1883. doi: 10.1016/S0140-6736(10)62142-3
 306. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology*. 2004;126:1287–1292.
 307. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. *Am J Med Sci*. 2005;329:62–65.
 308. Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol*. 2013;10:686–690. doi: 10.1038/nrgastro.2013.171
 309. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ; for the American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association [published correction appears in *Am J Gastroenterol*. 2012;107:1598]. *Am J Gastroenterol*. 2012;107:811–826. doi: 10.1038/ajg.2012.128
 310. Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, Brancati FL, Clark JM. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol*. 2013;178:38–45. doi: 10.1093/aje/kws448
 311. Knopp RH, d'Emden M, Smilde JG, Pocock SJ; on behalf of the ASPEN Study Group. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). *Diabetes Care*. 2006;29:1478–1485. doi: 10.2337/dc05-2415
 312. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R; for the Pravastatin in Chronic Liver Disease Study Investigators. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology*. 2007;46:1453–1463. doi: 10.1002/hep.21848

313. Kargiotis K, Athyros VG, Gioulema O, Katsiki N, Katsiki E, Anagnostis P, Boutari C, Doumas M, Karagiannis A, Mikhailidis DP. Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome. *World J Gastroenterol*. 2015;21:7860–7868. doi: 10.3748/wjg.v21.i25.7860
314. Kimura Y, Hyogo H, Yamagishi S, Takeuchi M, Ishitobi T, Nabeshima Y, Arihiro K, Chayama K. Atorvastatin decreases serum levels of advanced glycation endproducts (AGEs) in nonalcoholic steatohepatitis (NASH) patients with dyslipidemia: clinical usefulness of AGEs as a biomarker for the attenuation of NASH. *J Gastroenterol*. 2010;45:750–757. doi: 10.1007/s00535-010-0203-y
315. Nelson A, Torres DM, Morgan AE, Fincke C, Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: a randomized placebo-controlled trial. *J Clin Gastroenterol*. 2009;43:990–994. doi: 10.1097/MCG.0b013e31819c392e
316. Simon TG, King LY, Zheng H, Chung RT. Statin use is associated with a reduced risk of fibrosis progression in chronic hepatitis C. *J Hepatol*. 2015;62:18–23. doi: 10.1016/j.jhep.2014.08.013
317. Simon TG, Bonilla H, Yan P, Chung RT, Butt AA. Atorvastatin and fluvastatin are associated with dose-dependent reductions in cirrhosis and hepatocellular carcinoma, among patients with hepatitis C virus: results from ERCHIVES. *Hepatology*. 2016;64:47–57. doi: 10.1002/hep.28506
318. Mohanty A, Tate JP, Garcia-Tsao G. Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis. *Gastroenterology*. 2016;150:430–440. e1. doi: 10.1053/j.gastro.2015.10.007
319. Atsukawa M, Tsubota A, Kondo C, Itokawa N, Narahara Y, Nakatsuka K, Hashimoto S, Fukuda T, Matsushita Y, Kidokoro H, Kobayashi T, Kanazawa H, Sakamoto C. Combination of fluvastatin with pegylated interferon/ribavirin therapy reduces viral relapse in chronic hepatitis C infected with HCV genotype 1b. *J Gastroenterol Hepatol*. 2013;28:51–56. doi: 10.1111/j.1440-1746.2012.07267.x
320. Selic Kurincic T, Lesnicar G, Poljak M, Meglic Volkar J, Rajter M, Prah J, Baklan Z, Kotar T, Matic M. Impact of added fluvastatin to standard-of-care treatment on sustained virological response in naïve chronic hepatitis C patients infected with genotypes 1 and 3. *Intervirology*. 2014;57:23–30. doi: 10.1159/000354541
321. Ali N, Allam H, Bader T, May R, Basalingappa KM, Berry WL, Chandrakesan P, Qu D, Weygant N, Bronze MS, Umar S, Janknecht R, Sureban SM, Huycke M, Houchen CW. Fluvastatin interferes with hepatitis C virus replication via microtubule bundling and a doublecortin-like kinase-mediated mechanism [published correction appears in *PLoS One*. 2013;8]. *PLoS One*. 2013;8:e80304. doi: 10.1371/journal.pone.0080304
322. Ambrosino P, Lupoli R, Di Minno A, Tarantino L, Spadarella G, Tarantino P, Nasto A, Celentano A, Di Minno MN. The risk of coronary artery disease and cerebrovascular disease in patients with hepatitis C: a systematic review and meta-analysis. *Int J Cardiol*. 2016;221:746–754. doi: 10.1016/j.ijcard.2016.06.337
323. Huang YW, Lee CL, Yang SS, Fu SC, Chen YY, Wang TC, Hu JT, Chen DS. Statins reduce the risk of cirrhosis and its decompensation in chronic hepatitis B patients: a nationwide cohort study [published correction appears in *Am J Gastroenterol*. 2018;113:447]. *Am J Gastroenterol*. 2016;111:976–985. doi: 10.1038/ajg.2016.179
324. Dubé MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT, Henry WK, Currier JS, Sprecher D, Glesby MJ; for the Adult AIDS Clinical Trials Group Cardiovascular Subcommittee; HIV Medical Association of the Infectious Disease Society of America. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2003;37:613–627. doi: 10.1086/378131
325. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D, Rodríguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff M, Watson C, Armah KA, Doebler D, Bryant K, Justice AC. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173:614–622. doi: 10.1001/jamainternmed.2013.3728
326. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents Living With HIV. Department of Health and Human Services. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed October 26, 2016.
327. Aberg JA, Sponseller CA, Ward DJ, Kryzhanovski VA, Campbell SE, Thompson MA. Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial [published correction appears in *Lancet HIV*. 2017;4:e283]. *Lancet HIV*. 2017;4:e284–e294. doi: 10.1016/S2352-3018(17)30075-9
328. Gilbert JM, Fitch KV, Grinspoon SK. HIV-related cardiovascular disease, statins, and the REPRIEVE trial. *Top Antivir Med*. 2015;23:146–149.
329. Valantine HA. Role of lipids in allograft vascular disease: a multicenter study of intimal thickening detected by intravascular ultrasound. *J Heart Lung Transplant*. 1995;14:S234–S237.
330. Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb S, Levvey BJ, Meiser B, Rossano JW, Yusen RD, Stehlik J. The registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Heart Transplantation Report—2015; focus theme: early graft failure. *J Heart Lung Transplant*. 2015;34:1244–1254. doi: 10.1016/j.healun.2015.08.003
331. Dipchand AI, Rossano JW, Edwards LB, Kucheryavaya AY, Benden C, Goldfarb S, Levvey BJ, Lund LH, Meiser B, Yusen RD, Stehlik J; for the International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Eighteenth Official Pediatric Heart Transplantation Report—2015; focus theme: early graft failure. *J Heart Lung Transplant*. 2015;34:1233–1243. doi: 10.1016/j.healun.2015.08.002
332. Traynor C, Jenkinson A, Williams Y, O’Kelly P, Hickey D, Denton M, Magee C, Conlon PJ. Twenty-year survivors of kidney transplantation. *Am J Transplant*. 2012;12:3289–3295. doi: 10.1111/j.1600-6143.2012.04236.x
333. Matas AJ, Gillingham KJ, Humar A, Kandaswamy R, Sutherland DE, Payne WD, Dunn TB, Najarian JS. 2202 Kidney transplant recipients with 10 years of graft function: what happens next? *Am J Transplant*. 2008;8:2410–2419. doi: 10.1111/j.1600-6143.2008.02414.x
334. Vanrenterghem YF, Claes K, Montagnino G, Fieuws S, Maes B, Villa M, Ponticelli C. Risk factors for cardiovascular events after successful renal transplantation. *Transplantation*. 2008;85:209–216. doi: 10.1097/TP.0b013e318160254f
335. Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Change in mortality risk over time in young kidney transplant recipients. *Am J Transplant*. 2011;11:2432–2442. doi: 10.1111/j.1600-6143.2011.03691.x
336. Pruthi J, Medkiff KA, Esrason KT, Donovan JA, Yoshida EM, Erb SR, Steinbrecher UP, Fong TL. Analysis of causes of death in liver transplant recipients who survived more than 3 years. *Liver Transpl*. 2001;7:811–815. doi: 10.1053/jlts.2001.27084
337. Beckebaum S, Klein C, Varghese J, Sotiropoulos GC, Saner F, Schmitz K, Gerken G, Paul A, Cicinnati VR. Renal function and cardiovascular risk profile after conversion from ciclosporin to tacrolimus: prospective study in 80 liver transplant recipients. *Aliment Pharmacol Ther*. 2009;30:834–842. doi: 10.1111/j.1365-2036.2009.04099.x
338. Courivaud C, Kazory A, Simula-Faivre D, Chalopin JM, Ducloux D. Metabolic syndrome and atherosclerotic events in renal transplant recipients. *Transplantation*. 2007;83:1577–1581. doi: 10.1097/01.tp.0000266898.93894.3d
339. Chin C, Rosenthal D, Bernstein D. Lipoprotein abnormalities are highly prevalent in pediatric heart transplant recipients. *Pediatr Transplant*. 2000;4:193–199.
340. Rickenbacher PR, Kemna MS, Pinto FJ, Hunt SA, Alderman EL, Schroeder JS, Stinson EB, Popp RL, Chen I, Reaven G, Valantine HA. Coronary artery intimal thickening in the transplanted heart: an *in vivo* intracoronary ultrasound study of immunologic and metabolic risk factors. *Transplantation*. 1996;61:46–53.
341. Bianchi G, Marchesini G, Marzocchi R, Pinna AD, Zoli M. Metabolic syndrome in liver transplantation: relation to etiology and immunosuppression. *Liver Transpl*. 2008;14:1648–1654. doi: 10.1002/lt.21588
342. Cutts JL, Bankhurst AD. Suppression of lymphoid cell function *in vitro* by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by lovastatin. *Int J Immunopharmacol*. 1989;11:863–869.
343. Chakrabarti R, Engleman EG. Interrelationships between mevalonate metabolism and the mitogenic signaling pathway in T lymphocyte proliferation. *J Biol Chem*. 1991;266:12216–12222.
344. Kurakata S, Kada M, Shimada Y, Komai T, Nomoto K. Effects of different inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, pravastatin sodium and simvastatin, on sterol synthesis and immunological functions in human lymphocytes *in vitro*. *Immunopharmacology*. 1996;34:51–61.

345. Katznelson S, Wang XM, Chia D, Ozawa M, Zhong HP, Hirata M, Terasaki PI, Kobashigawa JA. The inhibitory effects of pravastatin on natural killer cell activity *in vivo* and on cytotoxic T lymphocyte activity *in vitro*. *J Heart Lung Transplant*. 1998;17:335–340.
346. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med*. 2000;6:1399–1402. doi: 10.1038/82219
347. Rudich SM, Mongini PK, Perez RV, Katznelson S. HMG-CoA reductase inhibitors pravastatin and simvastatin inhibit human B-lymphocyte activation. *Transplant Proc*. 1998;30:992–995.
348. Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, Chia D, Terasaki PI, Sabad A, Cogert GA, Trosian K, Hamilton MA, Moriguchi JD, Kawata N, Hage A, Drinkwater DC, Stevenson LW. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med*. 1995;333:621–627. doi: 10.1056/NEJM199509073331003
349. Chin C, Lukito SS, Shek J, Bernstein D, Perry SB. Prevention of pediatric graft coronary artery disease: atorvastatin. *Pediatr Transplant*. 2008;12:442–446. doi: 10.1111/j.1399-3046.2007.00827.x
350. Holdaas H, Fellström B, Cole E, Nyberg G, Olsson AG, Pedersen TR, Madsen S, Grönhagen-Riska C, Neumayer HH, Maes B, Ambühl P, Hartmann A, Staffler B, Jardine AG; for the Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study [published correction appears in *Am J Transplant*. 2006;6:1986]. *Am J Transplant*. 2005;5:2929–2936. doi: 10.1111/j.1600-6143.2005.01105.x
351. Ballantyne CM, Radovanecvic B, Farmer JA, Frazier OH, Chandler L, Payton-Ross C, Cocanougher B, Jones PH, Young JB, Gotto AM Jr. Hyperlipidemia after heart transplantation: report of a 6-year experience, with treatment recommendations. *J Am Coll Cardiol*. 1992;19:1315–1321.
352. Keogh A, Macdonald P, Kaan A, Aboyoum C, Spratt P, Mundy J. Efficacy and safety of pravastatin vs simvastatin after cardiac transplantation. *J Heart Lung Transplant*. 2000;19:529–537.
353. Patel DN, Pagani FD, Koelling TM, Dyke DB, Baliga RR, Cody RJ, Lake KD, Aaronson KD. Safety and efficacy of atorvastatin in heart transplant recipients. *J Heart Lung Transplant*. 2002;21:204–210.
354. Wenke K, Meiser B, Thiery J, Nagel D, von Scheidt W, Krobot K, Steinbeck G, Seidel D, Reichart B. Simvastatin initiated early after heart transplantation: 8-year prospective experience. *Circulation*. 2003;107:93–97.
355. Magnani G, Carinci V, Magelli C, Potena L, Reggiani LB, Branzi A. Role of statins in the management of dyslipidemia after cardiac transplant: randomized controlled trial comparing the efficacy and the safety of atorvastatin with pravastatin. *J Heart Lung Transplant*. 2000;19:710–715.
356. Mehra MR, Uber PA, Vivekananthan K, Solis S, Scott RL, Park MH, Milani RV, Lavie CJ. Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. *J Am Coll Cardiol*. 2002;40:1609–1614.
357. Türk S, Yildiz A, Tükek T, Akkaya V, Aras U, Türkmen A, Uras AR, Sever MS. The effect of fluvastatin of hyperlipidemia in renal transplant recipients: a prospective, placebo-controlled study. *Int Urol Nephrol*. 2001;32:713–716.
358. Serón D, Oppenheimer F, Pallardó LM, Lauzurica R, Errasti P, Gomez-Huertas E, Bosmans JL, Sanchez-Plumed J, Romero R, Marques M, Fulladosa X, Moreso F. Fluvastatin in the prevention of renal transplant vasculopathy: results of a prospective, randomized, double-blind, placebo-controlled trial. *Transplantation*. 2008;86:82–87. doi: 10.1097/TP.0b013e318174428d
359. Renders L, Mayer-Kadner I, Koch C, Schärffe S, Burkhardt K, Veelken R, Schmieder RE, Hauser IA. Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. *Nephrol Dial Transplant*. 2001;16:141–146.
360. Marzoa-Rivas R, Crespo-Leiro MG, Paniagua-Marin MJ, Llinares-García D, Muñoz-García J, Aldama-López G, Piñón-Esteban P, Campo-Pérez R, Castro-Beiras A. Safety of statins when response is carefully monitored: a study of 336 heart recipients. *Transplant Proc*. 2005;37:4071–4073. doi: 10.1016/j.transproceed.2005.09.163
361. Grigioni F, Carigi S, Potena L, Fabbri F, Russo A, Musuraca AC, Coccolo F, Magnani G, Ortolani P, Leone O, Arpesella G, Magelli C, Branzi A. Long-term safety and effectiveness of statins for heart transplant recipients in routine clinical practice. *Transplant Proc*. 2006;38:1507–1510. doi: 10.1016/j.transproceed.2006.02.071
362. Imagawa DK, Dawson S 3rd, Holt CD, Kirk PS, Kaldas FM, Shackleton CR, Seu P, Rudich SM, Kinkhabwala MM, Martin P, Goldstein LI, Murray NG, Terasaki PI, Busuttill RW. Hyperlipidemia after liver transplantation: natural history and treatment with the hydroxy-methylglutaryl-coenzyme A reductase inhibitor pravastatin. *Transplantation*. 1996;62:934–942.
363. Taylor PJ, Kubler PA, Lynch SV, Allen J, Butler M, Pillans PI. Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. *Ann Pharmacother*. 2004;38:205–208. doi: 10.1345/aph.1D388
364. Zachoval R, Gerbes AL, Schwandt P, Parhofer KG. Short-term effects of statin therapy in patients with hyperlipoproteinemia after liver transplantation: results of a randomized cross-over trial. *J Hepatol*. 2001;35:86–91.
365. Martin JE, Cavanaugh TM, Trumbull L, Bass M, Weber F Jr, Aranda-Michel J, Hanaway M, Rudich S. Incidence of adverse events with HMG-CoA reductase inhibitors in liver transplant patients. *Clin Transplant*. 2008;22:113–119. doi: 10.1111/j.1399-0012.2007.00780.x
366. Aliabadi AZ, Mahr S, Dunkler D, Grömmner M, Zimpfer D, Wolner E, Grimm M, Zuckermann AO. Safety and efficacy of statin therapy in patients switched from cyclosporine A to sirolimus after cardiac transplantation. *Transplantation*. 2008;86:1771–1776. doi: 10.1097/TP.0b013e3181910eb2
367. Penson MG, Fricker FJ, Thompson JR, Harker K, Williams BJ, Kahler DA, Schowengerdt KO. Safety and efficacy of pravastatin therapy for the prevention of hyperlipidemia in pediatric and adolescent cardiac transplant recipients. *J Heart Lung Transplant*. 2001;20:611–618.
368. Seipelt IM, Crawford SE, Rodgers S, Backer C, Mavroudis C, Seipelt RG, Pahl E. Hypercholesterolemia is common after pediatric heart transplantation: initial experience with pravastatin. *J Heart Lung Transplant*. 2004;23:317–322. doi: 10.1016/S1053-2498(03)00193-1
369. Chin C, Gamberg P, Miller J, Luikart H, Bernstein D. Efficacy and safety of atorvastatin after pediatric heart transplantation. *J Heart Lung Transplant*. 2002;21:1213–1217.