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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Statin-Associated Side Effects

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ABSTRACT

Hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins are well tolerated, but associated with various statin-associated symptoms (SAS), including statin-associated muscle symptoms (SAMS), diabetes mellitus (DM), and central nervous system complaints. These are "statin-associated symptoms" because they are rare in clinical trials, making their causative relationship to statins unclear. SAS are, nevertheless, important because they prompt dose reduction or discontinuation of these life-saving mediations. SAMS is the most frequent SAS, and mild myalgia may affect 5% to 10% of statin users. Clinically important muscle symptoms, including rhabdomyolysis and statin-induced necrotizing autoimmune myopathy (SINAM), are rare. Antibodies against HMG-CoA reductase apparently provoke SINAM. Good evidence links statins to DM, but evidence linking statins to other SAS is largely anecdotal. Management of SAS requires making the possible diagnosis, altering or discontinuing the statin treatment, and using alternative lipid-lowering therapy. (J Am Coll Cardiol 2016;67:2395–410) © 2016 by the American College of Cardiology Foundation.

Hydroxy-methyl-glutaryl-coenzyme-A (HMG-CoA) reductase inhibitors or statins have revolutionized the treatment of hypercholesterolemia and the management of patients with increased cardiovascular disease (CVD) risk. Statins are well tolerated, but are associated with skeletal muscle, metabolic, neurological, and other possible side effects. Such reports are labeled as statin-associated symptoms (SAS) because there is no consensus that statins are actually causative. SAS is favored over the term *statin intolerance* because many patients with SAS can tolerate reduced doses of these drugs.

SAS are clinically important. Statin-associated muscle symptoms (SAMS), the most common statin side effect, are reported by 10% (1) to 25% (2) of patients receiving statin therapy. In an internet survey of former statin users, 60% reported SAMS (2) and 62% reported stopping statin therapy because of side effects (2). Cessation of statin treatment is associated with worse cardiovascular outcomes. A meta-analysis of 15 statin studies observed a 45% increase in all-cause mortality and a 15% increase in CVD events in patients taking <80% of their prescribed statin therapy versus patients who were more adherent (3). The present review will review current knowledge on SAS and suggest strategies for their management.

STATIN-ASSOCIATED MUSCLE SYMPTOMS

The American College of Cardiology (ACC) and the American Heart Association (AHA) (4), a Canadian Working Group (CWG) (5), and the National Lipid Association (NLA) (6) have proposed definitions for SAMS (**Table 1**).

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ABBREVIATIONS AND ACRONYMS

CK = creatine kinase

CNS = central nervous system

CVD = cardiovascular disease

DM = diabetes mellitus

HMG-CoA = hydroxy-methyl-glutaryl-coenzyme A

RCCT = randomized controlled clinical trial

SAMS = statin-associated muscle symptoms

SAS = statin-associated symptoms

SINAM = statin-induced necrotizing autoimmune myopathy

ULN = upper limit of normal

The European Phenotype Standardization Project has also defined SAMS, with the ultimate purpose of determining associated genetic factors (7) (**Table 2**).

All definitions recognize that SAMS can occur without creatine kinase (CK) elevations, and that this is the most frequent SAMS presentation. The defined syndromes range from myalgia to marked CK elevations and/or clinical rhabdomyolysis. This implies that these syndromes are gradations of the same pathological pathway. This is likely, as patients developing rhabdomyolysis often had milder prodromal symptoms (8), but not proven. A European Atherosclerosis Society Consensus Panel avoided many of the labels used by the other groups and divided SAMS on the basis of whether or not the patient had symptoms and the magnitude of the CK elevation (9).

These definitions are useful for labeling patients in clinical trials, but are less useful in clinical practice. The ACC/AHA (4) and CWG (5) defined rhabdomyolysis as a CK >10× the upper limit of normal (ULN), which is approximately 2,000 U/l. This definition is used by most clinical trials, but this magnitude of CK elevation alone may not be clinically dangerous because the effect of muscle injury and myoglobinuria on kidney function depends not only on the degree of CK elevation, but also on the hydration status and general health of the patient. The NLA's use of CK values to stage myonecrosis (6) is useful for case definition, but CK elevations do not necessarily indicate myonecrosis and may only represent sarcolemmal injury and CK leak. The NLA requires muscle weakness to diagnose myositis (6), and weakness is frequently reported by patients, but rarely objectively documented, even in those reporting statin myalgia (10). Finally, muscle creatine released during muscle injury is metabolized to creatinine; thus, serum creatinine levels may increase in rhabdomyolysis without necessarily indicating renal injury (11). Consequently, these definitions are useful for quantifying SAMS in clinical trials, but less useful in clinical practice where the clinical diagnosis of SAMS depends primarily on subjective clinical assessment.

TABLE 1 Definitions of SAMS by Expert Panels

ACC/AHA (4)	CWG (5)	NLA (6)
Myopathy: any muscle symptom (SAMS)	Myopathy: any muscle symptom	Myalgia: aching, stiffness, cramps
Myalgia: SAMS CK = NL	Symptomatic myalgia	Myopathy: weakness
	Myalgia CK ≤ULN	Myositis: inflammation
	Myositis CK >ULN	Myonecrosis CK 3× ULN
	Rhabdomyolysis CK >10× ULN	Mild CK >3, <10× ULN
		Moderate CK >10, <50× ULN
		Severe CK >50× ULN
		Clinical rhabdomyolysis CK >ULN and creatinine >0.5 mg/dl baseline
Myositis: SAMS CK >ULN	HyperCKemia	
	Mild G1 >ULN ≤5× ULN	
	Mild G2 >5, ≤10× ULN	
	Modest >10, ≤50× ULN	
	Severe >50× ULN	
Rhabdomyolysis: CK >10× ULN		

ACC/AHA = American College of Cardiology/American Heart Association; CK = creatine kinase; CWG = Canadian Work Group; NL = normal limits; NLA = National Lipid Association; SAMS = statin-associated muscle symptoms; ULN = upper limit of normal.

THE CLINICAL DIAGNOSIS OF SAMS

STATIN-ASSOCIATED MYALGIA. The diagnosis of SAMS, such as myalgia and cramps, is subjective for both patient and physician because there are no validated clinical tests or diagnostic criteria. CK levels are frequently normal in patients with possible SAMS, whereas many asymptomatic patients on statin therapy have elevated CK levels. The NLA has proposed a point/scoring system (6) on the basis of observational studies, such as the PRIMO (PRedIction of Muscular Risk in Observational Conditions) study (1) and our STOMP (Effect of STatins On Skeletal Muscle Performance) study (12) (**Table 3**).

STOMP randomized 420 statin-naïve subjects to either placebo or atorvastatin 80 mg daily for 6 months. STOMP predefined myalgia, requiring subjects to report unexplained new or increased myalgia, cramps, or muscle aching that lasted at least 2 weeks, resolved within 2 weeks of treatment cessation, and returned within 4 weeks of drug reinitiation. Subjects were called every 2 weeks and queried about muscle symptoms. Twenty-three atorvastatin and 14 placebo subjects reported new, unexplained muscle pain (chi-square = 3.16; p = 0.08). Of these, 19 atorvastatin and 10 placebo subjects met the study myalgia definition (chi-square = 3.74; p = 0.054). The NLA expert panel used the STOMP results and other data to create a clinical profile of true statin myalgia. For example, atorvastatin-treated subjects in the STOMP study with myalgia predominantly reported aching, cramps, or fatigue in the thigh and calf muscles, whereas placebo-treated subjects reported generalized fatigue, pain in areas of prior injury, or groin pain. Time from drug initiation to pain onset was short in the STOMP atorvastatin-treated subjects (35 ± 31 days vs. 61 ± 33 days, p = 0.045) and in other studies; thus, onset in <4 weeks receives more points than later

onset. This scoring system reflects both research and clinical experience, but has not been validated. Also, as STOMP was a 6-month study, the NLA criteria do not apply to patients on more prolonged statin therapy.

The absence of definitive diagnostic tests requires that the diagnosis of statin myalgia and other mild SAMS be on the basis of clinical criteria (6). Consensus maintains that muscle pain and aching (myalgia), cramps, and weakness can be manifestations of SAMS. Symptoms are usually bilateral and involve large muscle groups, including the thigh, buttock, back, and shoulder girdle musculature. In contrast, cramping is usually unilateral and may involve small muscles of the hands and feet. Symptoms may be more frequent in physically active patients (1). Symptoms often appear early after starting stain therapy or after an increase in dose and usually resolve or start to dissipate within weeks after cessation of therapy, although it may take several months for symptoms to totally resolve. Persistence of symptoms for more than 2 months after drug cessation should prompt a search for other causes or for underlying muscle disease possibly provoked by statin therapy. Different statins usually produces similar symptoms, but some patients tolerate one statin better than another. The reappearance of symptoms with statin rechallenge and their disappearance with drug cessation offers the best evidence that the symptoms are truly SAMS. Unfortunately, such clinical drug challenges are unblinded and subjective.

Our Coenzyme Q10 in Statin Myopathy study (13) illustrates the difficulty in diagnosing SAMS. This study used a double-blind, placebo-controlled, crossover design to confirm statin myalgia in 120 patients with a well-documented history of SAMS. Subjects stopped all cholesterol-lowering drugs for 4 weeks, and were randomized to simvastatin 20 mg daily or placebo for 8 weeks, washed out for 4 weeks, and crossed over to alternative therapy. Only 35.8% of patients (n = 43) experienced myalgia on simvastatin only (labeled “true myalgics”), whereas 17.5% (n = 21) had no symptoms on simvastatin or placebo, 29.2% (n = 35) experienced pain on placebo, but not on simvastatin, and 17.5% (n = 21) experienced pain on both simvastatin and placebo. The dose of simvastatin used was only 20 mg, perhaps too low to confirm SAMS in a brief trial, but almost as many patients experienced muscle pain on placebo as on simvastatin. Consequently, a large portion of purported SAMS is likely nonspecific and confounds both the diagnosis and treatment of statin myalgia.

TABLE 2 The European Phenotype Standardization Project Statin-Associated Myotoxicity Phenotype

SRM Classification	Phenotype	Definition
SRM 0	CK elevation <4× ULN	No muscle symptoms
SRM 1	Myalgia, tolerable	Muscle symptoms without CK elevation
SRM 2	Myalgia, intolerable	Muscle symptoms, CK <4× ULN, complete resolution on dechallenge
SRM 3	Myopathy	CK elevation >4× ULN <10× ULN ± muscle symptoms, complete resolution on dechallenge
SRM 4	Severe myopathy	CK elevation >10× ULN <50× ULN, muscle symptoms, complete resolution on dechallenge
SRM 5	Rhabdomyolysis	CK elevation >10× ULN with evidence of renal Impairment + muscle symptoms or CK <50× ULN
SRM 6	Autoimmune-mediated necrotizing myositis	HMGCR antibodies, HMGCR expression in muscle biopsy, incomplete resolution on dechallenge

Adapted with permission from Alfirevic et al. (7).

HMGCR = 3-hydroxy-3-methyglutaryl-coenzymeA reductase; SRM = statin-related myotoxicity; other abbreviations as in Table 1.

This problem also confounds estimating the incidence and prevalence of SAMS. The PRIMO study obtained questionnaires on 7,924 French patients treated for at least 3 months with fluvastatin 80 mg, atorvastatin 40 to 80 mg, pravastatin 40 mg, or simvastatin 40 to 80 mg daily (1). Muscular symptoms were reported by 10.5% of participants, but this was

TABLE 3 Proposed Statin Myalgia Index Score

Clinical symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Nonspecific asymmetric, intermittent	1
Temporal pattern	
Symptoms onset <4 weeks	3
Symptoms onset 4–12 weeks	2
Symptoms onset >12 weeks	1
Dechallenge	
Improves upon withdrawal (<2 weeks)	2
Improves upon withdrawal (2–4 weeks)	1
Does not improve upon withdrawal (>4 weeks)	0
Challenge	
Same symptoms reoccur upon rechallenge <4 weeks	3
Same symptoms reoccur upon rechallenge 4–12 weeks	1
Statin myalgia clinical index score	
Probable	9–11
Possible	7–8
Unlikely	<7

Adapted with permission from Rosenson et al. (6).

an observational, unblinded, uncontrolled, retrospective study. Other studies have reported rates of musculoskeletal pain as high as 23% in statin users, but also noted high rates in comparison subjects (14).

Randomized controlled, double-blinded clinical trials of statin therapy have failed to identify SAMS in participants, possibly because of study design. A systematic review identified 1,012 reports of statin randomized controlled clinical trials (15). Among 42 trials that qualified for detailed analysis, only 4 reported average CKs, and only 1 queried participants specifically for muscle symptoms using predefined criteria. A total of 26 studies reported muscle symptoms, which occurred in 12.7% and 12.4% of statin- and placebo-treated subjects, respectively. This tiny difference approached statistical significance ($p = 0.06$), but only because of the large sample size.

Only STOMP (12), to our knowledge, was designed specifically to examine skeletal muscle side effects. Only 9.4% of the atorvastatin-treated and 4.6% of the placebo-treated study population met the study definition of SAMS, suggesting that the background noise of skeletal muscle symptoms is ≈5% and that the true incidence of SAMS is only ≈5% of the treated population. Subjects in the STOMP study were treated for only 6 months, however, and the average age was only 44 years, so higher rates of SAMS might be detected with longer treatment in older subjects. We interpreted the results to indicate more myalgia in statin users, whereas some statin trialists maintain that myalgia does not exist and that STOMP failed to prove its existence because the p value was 0.054 and not <0.05.

RHABDOMYOLYSIS. Most clinical statin trials diagnose rhabdomyolysis as CK >10× ULN, without other causes of muscle injury (15). Most authorities propose diagnosis of rhabdomyolysis by similar increases in CK plus evidence of renal compromise. Not all instances of marked CK increases during statin therapy indicate clinically important rhabdomyolysis. Some patients have chronically elevated CK levels or idiopathic hyperCKemia without statin therapy, an argument for determining baseline CK levels before statin therapy (4). Exercise alone can produce remarkable CK increases in the absence of statin therapy, especially after "eccentric" exercise, where the muscle contracts while being stretched, such as during downhill ambulation or lowering a weight. The average CK level in 15 participants in the 1979 Boston Marathon, a notoriously uphill and downhill course, was 3,424 international units (IU) the day after the race (16). We observed CK values >2,000 U/l, the criterion used for rhabdomyolysis in many studies, in 111 of 203 subjects 4 days after they performed 50 maximal eccentric contractions of the elbow flexor muscles. CK values were >10,000 U/l in 51 of these subjects. No subjects developed visible myoglobinuria or developed compromised renal function (17). This exercise-related increase in CK is magnified by statin treatment (18,19). CK levels after downhill walking in men randomly assigned to either lovastatin 40 mg daily ($n = 22$) or placebo ($n = 27$) increased in both the lovastatin and placebo groups, but were 62% and 77% higher the first and second days after exercise in the lovastatin group (18). Exercise-induced increases in CK, magnified by statin use, should always be considered in statin-treated patients presenting with increases in CK.

Rhabdomyolysis, a CK >10× ULN, occurred in 0.10% of statin-treated and 0.04% of placebo-treated patients in randomized controlled clinical trials (15). Subjects were observed from 0.5 to 6.1 years, giving an extremely low yearly incidence of rhabdomyolysis (15). The incidence of rhabdomyolysis in clinical practice has been examined using national health records (20) and health insurance databases (21,22). An examination of health claims from 473,343 patients treated with lipid-lowering agents, of whom 86% received statin monotherapy, found 144 claims coded for rhabdomyolysis, of which 44 were confirmed by physician review (22). The incidence of statin-associated rhabdomyolysis was 2.0 cases/10,000 person-years of treatment, and ranged from 0.3 cases for lovastatin to 8.4 cases for cerivastatin. The rates were 0.6 for atoravastatin and 1.2 for rosuvastatin/10,000 person-years. Cerivastatin has been removed from the market because of its rhabdomyolysis risk, so the current incidence of rhabdomyolysis is approximately 1 case/10,000 person-years.

RISK FACTORS FOR SAMS. Increased serum statin concentrations or reduced body muscle mass increase the risk of SAMS, by increasing the chance that the statin will reach sufficient muscle concentration to produce symptoms. Advanced age, female sex, physical disability, and lower body mass index are associated with both lower plasma volumes and reduced muscle mass, and are probable SAMS risk factors (23,24). Hypothyroidism increases drug levels by inhibiting statin catabolism. Similarly, higher statin doses increase the risk of SAMS, explaining the clinical observation that symptoms appeared after an increase in statin dose. Colchicine and other compounds, such as alcohol, that have toxic muscle effects can also increase the risk of SAMS, as do factors altering statin catabolism.

Statins are catabolized by the cytochrome P450 system (CYP) of isoenzymes, which are primarily

hepatic. These enzymes transform lipophilic compounds into hydrophilic compounds for excretion. The exception is pravastatin, which undergoes sulfonation in the liver and is not metabolized by CYP 450 (25). Lovastatin, simvastatin, and atorvastatin are metabolized predominantly by the CYP3A4 isoenzyme (25).

Approximately 75% of medications are metabolized by CYP and approximately one-half of these are metabolized by the 3A4 isoenzyme (26). Medications that are also metabolized by CYP3A4 can increase serum statin concentrations by competing for catabolism. These drugs include the azole antifungals, macrolide or "mycin" antibiotics, tricyclic antidepressants, protease inhibitors, and calcium-channel blockers, as well as other agents, such as cyclosporine, tacrolimus, sirolimus, amiodarone, danazol, midazolam, nefazodone, tamoxifen, sildenafil, and warfarin (25).

CYP3A4 is also present in the intestinal mucosa, probably to catabolize possible toxins before their absorption (27). Intestinal CYP inactivates vulnerable statins before their absorption. Inhibition of intestinal CYP3A4 reduces intestinal statin catabolism and increases their absorption and serum concentrations. Grapefruit and other tropical juices, such as starfruit and pomegranate, contain CYP3A4 inhibitors and increase statin systemic concentrations (27). The inhibitory effect on CYP3A4 persists for >24 h; therefore, large amounts of these juices or moderate amounts taken repetitively can have clinically significant effects on statin serum concentrations (27).

Fluvastatin (25), pitavastatin (25,28), and rosuvastatin (25) are metabolized primarily by the CYP2C9 enzyme, with minor contributions from CYP3A4 (fluvastatin), CYP2C8 (fluvastatin, pitavastatin), and CYP2C19 (rosuvastatin) (25). These statins have less risk of drug interaction because there are fewer medications dependent on non-3A4 pathways.

The overall effect of concomitant medications on SAMS is confusing because of the complex interaction of statin absorption, hepatic uptake from portal blood, hepatic metabolism, and entry and exit from skeletal muscle. Tropical fruit juices decrease intestinal CYP3A4 statin metabolism, but do not affect hepatic metabolism once the statin is absorbed (29), probably minimizing their clinical effect. Organic anion transporter proteins (OATPs), specifically OATP1B1, encoded by the *SLCO1B1* gene, mediate hepatic uptake from portal blood (30). A genome-wide scan of the SEARCH (Study of Effectiveness of Additional Reductions in Cholesterol & Homocysteine) database, demonstrated that definite (CK >10× baseline) or incipient myopathy (CK >3× ULN and 5× baseline with an alanine aminotransferase level >1.7× baseline with or without symptoms), was 4.5× more likely with 1 allele of the rs4149056 single-nucleotide polymorphism in SLCO1B1 and 16.9× with 2 alleles than in those without this single-nucleotide polymorphism (30). This is the most consistent genetic factor affecting statin metabolism (31). OATPs were thought to be absent from the skeletal muscle sarcolemma, leading to the theory that water-soluble statins, such as pravastatin and rosuvastatin, were less myotoxic because of their reduced ability to pass through the lipid-rich sarcolemma. OATP2B1 was identified on cultured human skeletal muscle cells and documented to transport atorvastatin and rosuvastatin (32), suggesting that statin solubility is less important than other factors (32). Cyclosporine inhibits CYP3A4 and CYP2C9, but because pravastatin is not metabolized by CYP, it should not be affected by concomitant cyclosporine use. Nevertheless, pravastatin serum levels do increase with cyclosporine use (33), probably because cyclosporine inhibits the multidrug resistance protein that transports drugs from cells (34). Gemfibrozil was the concomitant drug most frequently associated with statin-associated rhabdomyolysis, but gemfibrozil is not a potent inhibitor of CYP3A4 (35) and would not be expected to affect statin levels on this basis alone. Gemfibrozil does, however, interfere with statin glucuronidation (35), a pathway now recognized as an important avenue for statin clearance (36).

Serious SAMS are more common with simvastatin than with the other available statins, which prompted the Food and Drug Administration (FDA) to recommend avoiding the 80 mg dose (37). This recommendation was on the basis of results from the A to Z (38) and SEARCH (39) trials. In A to Z, 1 of 251 and 1 of 755 subjects treated with simvastatin 80 mg had CK values >10× and 50× ULN, respectively. In the SEARCH database, CK values >10× ULN and 40× ULN were observed in 1 of 106 and 1 of 246 subjects on simvastatin 80 mg, respectively (39).

Because of these vagaries, it is probably best to evaluate the risk of concomitant medications on SAMS on the basis of reports of clinical outcomes and studies evaluating serum levels of the statin-drug combination, rather than on the drug's effect on metabolic and transporter pathways alone. Our analysis of the FDA database from 1990 to 2002 identified 3,339 cases of rhabdomyolysis, 58% associated with (but not necessarily due to) concomitant drug therapy (40). Fibrates, primarily gemfibrozil, were associated with 38% of these cases, digoxin with 5%, cyclosporine with 4%, warfarin with 4%, macrolide

antibiotics with 3%, mibefidil (a discontinued antihypertensive) with 2%, and azole antifungals with 1% of cases (40). Clinicians should probably be most cautious of the combination of a statin with gemfibrozil, cyclosporine, macrolide antibiotics, and azole antifungals.

STATIN-INDUCED NECROTIZING AUTOIMMUNE MYOPATHY. SAMS and any associated CK elevation should resolve promptly with the cessation of statin therapy. The exception is statin-induced necrotizing autoimmune myopathy (SINAM). SINAM presents with proximal muscle weakness, markedly elevated CK levels, and persistence of symptoms and CK elevations despite drug discontinuation. Muscle biopsies show myonecrosis, often with few inflammatory cells (41). Antibodies against HMG-CoA reductase are detected in 94% of patients with SINAM (42), and an enzyme-linked immunosorbent assay (ELISA) test is commercially available. SINAM is associated with variants in the human leukocyte antigen (HLA) gene *HLA-DR11* and the DRB1*11:01 allele (43). Recognition of SINAM is important because immunosuppressive therapy is required to prevent progression to severe, often irreversible muscle weakness.

The mechanism by which statins produce SINAM is not clear. Statins block the activity, but also increase the production, of HMG-CoA reductase. This increased production could lead to abnormal protein processing in genetically susceptible patients, with resultant antigen and antibody production (43). The disease may persist despite drug cessation because satellite cells mobilized to replace damaged muscle cells contain large amounts of HMG-CoA reductase and thereby may maintain the immunogenic process (42). SINAM is estimated to occur in 1 of 100,000 statin users (42). CK levels average >6,000 IU and symptoms are severe (41), but the incidence will likely increase as milder cases are detected with increased appreciation of the disease and use of the ELISA test.

MANAGEMENT OF PATIENTS WITH SAMS. Managing the patient with possible SAMS and other SAS discussed subsequently requires reassessing the benefit of statin therapy, making the tentative diagnosis, eliminating contributing factors, reassuring the patient, trying alternative statins and doses, and prescribing alternative treatment strategies. True SAMS is more likely when more of the typical clinical features are present, as suggested by the NLA scoring system (6). We stop the statin entirely until symptoms have resolved to assess the time course of symptom resolution and to establish the symptom baseline for rechallenge. CK measurements are useful to exclude clinically threatening muscle injury and to assist with the diagnosis, as increases in CK levels from baseline may help identify patients with "true myalgia" (13). It is important to exclude potentially contributing factors, such as hypothyroidism, vitamin D deficiency and other medications, and to evaluate the patient for other muscle diseases. Severe vitamin D deficiency alone can produce myopathy. Vitamin D therapy has been suggested to be related to statin myalgia (24,44) and as treatment for SAMS (45), but these reports (44) failed to use standardized assessments of symptoms and were unblinded. We do replenish vitamin D, when appropriate, but do not generally recommend coenzyme Q10 (CoQ10) supplementation because a meta-analysis (46) and our randomized, double-blind clinical trial (13), demonstrated that CoQ10 is not effective (13).

We consider it critical to reassure patients that statins are extremely safe and effective, and that SAMS is reversible with drug cessation. Many patients are concerned about statin side effects, and negative media reports about statins are associated with their early discontinuation (47). Media reports and other information may cause some patients to expect symptoms. This *nacebo* (Latin for "I shall harm") effect, the opposite of the placebo effect (48), almost certainly contributes to some patients' reports of symptoms during statin therapy (48). Many patients can tolerate the drugs once the fear that the symptoms will progress and become permanent is addressed. Indeed, over 90% of patients who reported SAS and managed in academic medical centers are subsequently able to tolerate a statin (49).

After symptoms have resolved, we rechallenge the patient with at least 2 different statins and alternative statin regimens. Many patients can be treated using low-dose statin and combination therapy. Statins with longer half-lives, such as rosuvastatin (50), atorvastatin (50), and probably pitavastatin, can be given every other day, or even less frequently (51). Rosuvastatin ≤10 mg twice weekly produces a 26% reduction in low-density lipoprotein cholesterol (LDL-C) (52). This regimen, in combination with ezetimibe, can reduce low-density lipoprotein (LDL) almost as much as high-dose statin treatment.

Other out-of-favor medications should also be considered. Niacin failed to reduce CVD events in 2 recent trials (53,54), but all subjects were on statin treatment. The baseline LDL-C values in these trials averaged only 72.5 (53) and 63 (54) mg/dl, levels, where the benefit of any regimen may be difficult to prove in a limited-duration clinical trial. Niacin in the Coronary Drug Project, before statins were available,

reduced recurrent myocardial infarction (a secondary endpoint) by 29% (14.7% to 10.4%; $p < 0.05$) at 6.2 years and total deaths by 11% (58.2% to 50.2%; $p = 0.0004$) at 15 years (55). Subjects presumably stopped niacin therapy at the end of the trial (55), suggesting a "legacy effect" from the prior niacin treatment. Niacin has its risks. Subjects treated with the combination of statin, niacin, and laropiprant experienced a 2.9% absolute increase in the frequency of serious adverse events in the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) trial compared with the statin-only group, and a 0.7% increase in musculoskeletal events (54). Interestingly, the incidence of myopathy in Chinese participants in the niacin and laropiprant arm was 10× higher than in European participants (54), consistent with other evidence of increased sensitivity to statins in Asians (56). SAMS would be of less concern with niacin use in statin-intolerant patients. Cholestyramine reduced CVD events by 19% in the Lipid Research Centers study, although these results would not be deemed significant today because they were tested with a 1-tailed Student *t* test (57). Gemfibrozil is presently little used because of the risk of rhabdomyolysis when combined with statin therapy, but gemfibrozil did decrease cardiac events by 34% in the Helsinki Heart Study (58) and by 22% in the VA-HIT (Veterans High Intensity Treatment) study (58) when used without statins. Similarly, fenofibrate added to a statin produced a 4.9% absolute reduction in CVD events in diabetic patients with baseline high-density lipoprotein cholesterol <34 mg/dl and triglycerides >204 mg/dl in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial. This did not reach statistical significance ($p = 0.06$) (59), but still indicates a 94% probability that fenofibrate was effective. Consequently, alternative lipid-lowering regimens should be considered when statins are not tolerated.

The human monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9), alirucoumab and evolocumab, have been approved for use as adjunctive therapy to diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C. This implies that these agents can be used for patients with SAS and SAMS.

POSSIBLE MECHANISMS PRODUCING SAMS. Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway that produces cholesterol, farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP) (60). FPP and GGPP activate a variety of small guanosine triphosphate (GTP)-binding regulatory proteins by prenylation or the addition of specific carbon atoms to the protein.

Multiple mechanisms have been suggested as contributing to SAMS. Reduced sarcolemmal or T-tubule cholesterol is a possible mechanism, in part because electron microscopic analyses of skeletal muscle in statin users show disruptions in T-tubule architecture (61). The T-tubular system is responsible for calcium release during muscle contraction. Increased myocyte concentrations of the plant sterol campesterol in simvastatin-treated subjects raised the possibility that increased plant sterols provoke the myopathic process (62). Reductions in CoQ10, a mitochondrial transport protein also produced by the mevalonate pathway, were also proposed as a possible mechanism (63).

The best evidence suggests that statins affect muscle by activating the phosphoinositide 3-kinase (PI3K)/Akt pathway. This pathway can lead to either muscle hypertrophy via activation of the mechanistic target of rapamycin (mTOR) or muscle atrophy via activation of the forkhead box class O protein group (FOXO). FOXO activates muscle-specific ubiquitin ligases, including atrogin-1 and muscle-specific ring finger (MuRF)-1. Atrogin-1 and MuRF-1 cause protein degradation and muscle atrophy (64). Akt phosphorylation leads to FOXO phosphorylation, which prevents FOXO from entering the nucleus (60). It is proposed that decreased FFP from statin therapy reduces production of the small prenylated proteins that phosphorylate Akt. This allows unphosphorylated FOXO to enter the nucleus and increase expression of atrogenic proteins (60). Interestingly, FOXO also activates the transcription of pyruvate dehydrogenase kinase (PDK) (65). Up-regulation of PDK inactivates the muscle pyruvate dehydrogenase complex, limiting carbohydrate oxidation (65). Consequently, the same mechanisms that increase SAMS may also produce glucose intolerance with statin therapy.

Supporting the theory of PI3K/Akt pathway involvement in SAMS is the observation that GGPP prevents muscle injury with in vitro models of SAMS (60). Also, atrogin-1 is increased in muscle biopsies from subjects with SAMS (66) and atrogin-1 gene expression and protein content is reduced after exercise in statin-treated subjects (67). Opposing this concept is the fact that statins do not produce muscle atrophy and do not increase skeletal muscle protein synthesis (68), indicating that absence of atrophy is not due to compensatory protein production.

Statins also appear to impair mitochondrial function (69). Type II mitochondrial-poor, glycolytic, skeletal muscle fibers are most vulnerable to statin

injury (70), suggesting that mitochondria protect against the injury. Overexpression of PGC1α, which stimulates mitochondrial proliferation, also protects against statin muscle injury in experimental models (66). Exercise training usually increases skeletal muscle mitochondrial content, but simvastatin-treated subjects failed to increase their maximal oxygen uptake and markers of mitochondrial content after exercise training (71). Mitochondrial oxidative phosphorylation (OXPHOS), measured by high-resolution respirometry of human muscle biopsy samples, is lower in simvastatin-treated patients than in healthy controls (72). Statins could affect mitochondrial function by reducing CoQ10, and reduced CoQ10 levels have been observed in some (62,72), but not all biopsy studies (63). Alternatively, any statin mitochondrial effects could be related to decreased GGPP because decreases in GTPases stimulate the mitochondrial cell death apoptotic pathway (60,73). Also, increased atrogin-1 activity is associated with mitochondrial dysfunction (70), further linking reduced GGPP production, the Akt pathway, and FOXO regulation with mitochondrial dysregulation. Decreased mitochondrial function could also affect glucose disposal, as skeletal muscle is a major consumer of glucose.

DIABETES MELLITUS WITH STATIN THERAPY. WOSCOPS (West of Scotland Coronary Prevention Study) randomized men 45 to 64 years of age to pravastatin 40 mg/day (n = 2,999) or placebo (n = 2,975) for 3.5 to 6.1 years and demonstrated a 30% reduction in new diabetes mellitus (DM) in the statin-treated subjects (74). In contrast, the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study (75) randomized healthy men and women with LDL-C levels ≤130 mg/dl and high-sensitivity C-reactive protein levels (hs-CRP) ≥2.0 mg/dl to rosuvastatin 20 mg/day (n = 8,901) or placebo (n = 8,901) for ≈2 years. The number of new DM cases was 0.6% higher with rosuvastatin (n = 270 vs. 216; p = 0.01). The JUPITER study was the first trial to observe an increase in DM, possibly because inclusion required elevated hs-CRP, a marker for insulin resistance (76), and 41% of statin-treated and 41.8% of placebo-treated JUPITER participants had the metabolic syndrome (75).

Several meta-analyses have examined the statin-diabetes relationship. The most recent (77) examined 20 statin trials including 129,170 participants followed for a mean of 4.2 years. Only 3,858 statin-treated and 3,481 placebo-treated subjects developed new DM (odds ratio [OR]: 1.12; 95% confidence interval [CI]: 1.06 to 1.18). Pre- and post-treatment body weight was available in 15 trials at a mean follow-up of 3.9 years. Body weight increased 0.24 kg more in statin-treated subjects (95% CI: 0.10 to 0.38 kg). There was no relationship between LDL-C change at 1 year and DM onset or between LDL-C and change in body weight.

Another meta-analysis (78) included 5 studies that compared intense (atorvastatin or simvastatin 80 mg daily [QD]) and moderate (pravastatin 40 mg, simvastatin 10 to 40 mg, and atorvastatin 10 mg QD) statin therapy in 32,752 patients. New DM occurred in 4.4% and 4% of subjects receiving high- or moderate-dose statin treatment, respectively; a small, but statistically significant difference (OR: 1.12; 95% CI: 1.04 to 1.22). This equated to 2 additional diabetic patients, but 6.5 fewer cardiovascular events in the intense statin group over 1,000 patient-years of therapy. Only 1 additional case of DM per year would occur for every 498 patients treated with intense versus moderate statin therapy. Therefore, intense statin therapy would prevent 3.2 CVD events for each new case of DM.

RISK FACTORS FOR STATIN-ASSOCIATED DM. The risk of DM during statin therapy increases with the usual DM risk factors, statin dose (78), and ethnicity. In JUPITER subjects who at baseline had 1 or more DM risk factors, including fasting glucose >100 mg/dl, body mass index >30 kg/m^2, or hemoglobin A1C >6, had a 28% (OR: 1.28; 95% CI: 1.07 to 1.54) increased risk of DM during the study versus those lacking these factors (79). There were no new cases of DM among those with no DM risk factors at baseline (79). Female sex, increased age, and Asian ethnicity also increase risk. Women in JUPITER treated with statins had more new DM than those on placebo (1.53 vs. 1.03/100 person-years; hazard ratio [HR]: 1.49; 95% CI: 1.11 to 2.01; p = 0.008). The increase in DM was smaller and not statistically significant in men (1.36 vs. 1.20/100 person-years, HR: 1.14; 95% CI: 0.91 to 1.43; p = 0.24) (80), but testing for heterogeneity by sex was not significant (p = 0.16). The association between statins and risk of new DM was greater in trials with older participants (p = 0.019) (81). A substudy of the WHI (Women's Health Initiative) evaluated the overall effect of statins on incident DM risk in 161,808 post-menopausal women 50 to 79 years of age (82). Approximately 7% of women used statins at baseline, and 10,242 developed new DM over 1,004,466 person-years of follow-up. Baseline statin use was associated with a 48% increased risk for new DM (HR: 1.48; 95% CI: 1.38 to 1.59) after adjusting for potential cofounders. Women of Asian and Pacific Islander origin had a higher risk of DM (HR: 1.78;

95% CI: 1.32 to 2.40) compared with Caucasians (HR: 1.49; 95% CI: 1.38 to 1.62), African Americans (HR: 1.18; 95% CI: 0.96 to 1.45), and Hispanics (HR: 1.57; 95% CI: 1.14 to 2.17). Individuals of Asian descent experience greater cholesterol reductions (56) and more side effects (83) at the same statin dose than Caucasians, possibly because of genetic variants in statin metabolism (56), so it is possible that the increase in DM in this ethnic group represents the same phenomenon. Importantly, the association of statin use and new DM in WHI occurred with all statins, making this a class effect.

MECHANISMS FOR STATIN-ASSOCIATED DM. How statins increase the risk of DM is not clear, but the lower cholesterol levels produced by statins may contribute to the effect. High serum cholesterol levels are associated with a reduced risk of DM. The Netherlands Familial Hypercholesterolemia Screening Study examined genes affecting LDL receptor-mediated transmembrane cholesterol transport in 63,320 relatives of patients with familial hypercholesterolemia (FH), of whom 25,137 were found to have genetic defects causing FH (84). DM was present in 2.93% of subjects without FH and in only 1.75% of subjects with FH. The prevalence was 1.49% higher in the non-FH group, even after adjusting for relevant variables ($p < 0.001$). The magnitude of LDL-C increase in FH varies with the genetic defect. Patients with genetic defects blocking LDL receptor synthesis have LDL levels greater than in patients with a defective, but synthesized, LDL receptor, whose LDL levels are greater than those in patients with variants affecting only apolipoprotein (apo) B. Consistent with the concept that increased LDL-C "protects" against DM, the prevalence of DM was 1.12% in LDL receptor-negative patients, 1.44% in those with defective LDL receptors, and 1.91% in those with defects in apo B. Such results suggest that lower cholesterol levels are responsible for the increase in DM with statin therapy.

Similarly, a meta-analysis of genetic data from 43 studies demonstrated that 2 single-nucleotide polymorphisms (rs17238484-G and rs12916-T) in the HMG-CoA reductase gene reduced LDL-C levels 2.3 mg/dl and increased the risk of DM by 2% (95% CI: 0% to 5%) and 6% (95% CI: 3% to 9%), respectively. Both genes were also associated with increased body weight and waist circumference, and rs17238484-G was associated with increased glucose and insulin levels (77). Such genetic observations cannot determine whether LDL levels or some associated effect on the mevalonate pathway is responsible for the increased DM risk.

Changes in cellular cholesterol content could impair insulin secretion by disrupting voltage-gated calcium-channel function in pancreatic beta cells (85), thereby reducing fusion of insulin granules with the cell membrane for subsequent export. Alternatively, statins could reduce peripheral insulin sensitivity or glucose metabolism by reducing myocyte mitochondrial function or affecting other aspects of muscle metabolism. Statins alter activity of the FOXO gene group, whose downstream targets include genes involved in carbohydrate oxidation (65). Other possibilities include deleterious effects on adipocyte (86) and pancreatic beta cell (87) mitochondrial function, and reduced expression of the adipocyte insulin-responsive glucose transporter (GLUT4) (88,89).

Thus, all statins appear to produce a small increase in the relative and absolute risk of new onset DM, but this risk is greatly exceeded by their benefit. The mediating mechanism for this effect is unknown, but could be related to LDL-C reduction, and therefore might also occur with other powerful lipid-lowering agents, such as the PCSK-9 inhibitors.

EFFECTS OF STATINS ON THE CENTRAL NERVOUS SYSTEM

POSSIBLE ADVERSE EFFECTS OF STATINS ON COGNITION. Hyperlipidemia is an established risk factor for the incidence and progression of Alzheimer's disease (AD) and dementia (90). There are, however, ≈60 case reports of statin-associated memory loss or dementia that often resolve with cessation of statin therapy (91). This number of reports is low, given the widespread use of these medications, but some have suggested that statin effects on memory are easily overlooked or mistakenly attributed to aging or concurrent disease (92). Two randomized clinical trials involving 308 adults treated with 10 or 40 mg of simvastatin for 6 months and 209 adults treated with 20 mg lovastatin for 6 months found that hypercholesterolemic adults experienced small decrements in cognition with statin therapy (93,94). The University of California San Diego Statin Effects Study, a self-reported, web-based dataset, reported that 422 (59%) of 722 patients with SAS, experienced cognitive problems (92). The authors concluded that statins were definitely or probably responsible in 121 (75%) of the 171 patients with cognitive symptoms. This report is appropriately discounted because of issues with nonblinding and lack of objective memory measurements. In contrast to these primarily case reports, larger cross-sectional studies have failed to find a relationship between statin use and cognitive

decrements. These results from larger studies suggest that if statin central nervous system (CNS) effects do exist, as suggested by the anecdotal reports, they are extremely rare.

Both the Cardiovascular Health Study and the Heart and Estrogen/Progestin Replacement Study observed that statins are associated with reduced cognitive decline in older adults (95,96). A meta-analysis of 7 observational studies concluded that statins reduce the risk of cognitive impairment (97) and the incidence of AD (98,99). Others have suggested that statins also slow the progression of cognitive impairment in subjects with AD and dementia (100,101). In contrast, other studies suggest that statins do not lower the incidence of AD (102–104), slow cognitive decline, or improve cognition in adults with dementia or AD (103) or in healthy adults (105–107). These include the LEADe (Lipitor's Effect in Alzheimer's Dementia) study, which found no effect of 80 mg atorvastatin in mild to moderate AD patients (108), and a meta-analysis reporting no effect when statins were given in controlled trials for at least 6 months to patients with dementia (109). Similarly, the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study found no difference in neuropsychological test performance or cognitive decline in patients given pravastatin or placebo for 3.5 years (110).

Meta-analyses of cognitive side effects, including 16 (111) and 25 (112) studies have found almost no evidence of adverse cognitive side effects with statin therapy. Consequently, the 2014 Assessment by the Statin Cognitive Safety Taskforce of the NLA concluded that statins are not associated with adverse effects on memory and cognition (113). Nevertheless, the FDA in 2012, on the basis of reports in the FDA Adverse Event Reporting System, changed the label for statins to state that, "Memory loss and confusion have been reported with statin use. These reported events were generally not serious and went away once the drug was no longer being taken" (114). This change in safety labeling remains controversial, given the paucity of strong evidence linking statins to adverse cognitive side effects (112) compared with the larger body of evidence supporting their safety.

DIRECT EFFECTS OF STATINS ON THE BRAIN. Clinical trials involving the effects of statins on cognition have typically assessed cognitive function using traditional cognitive tests, which have yielded small effect sizes and demonstrated high intra-subject variability (115). Measures that directly assess brain structure, cerebral blood flow, cholesterol turnover, and neuronal activation could provide insight as to whether and how statins affect the CNS, but there are few such studies and those available have yielded mixed results. A decrease in hippocampal volume is associated with AD and age-related memory impairments, but there are few studies on the effect of statins on the hippocampus and they have been inconsistent (116,117).

MECHANISMS FOR POSSIBLE STATIN CNS EFFECTS. Statins could affect the CNS directly by inhibiting CNS cholesterol synthesis or indirectly by altering other substances involved in cognitive function. Cholesterol is relatively inert in the brain, with a half-life of 6 months to 5 years, and with only 0.02% of total cholesterol volume turning over daily (118). Thus, direct inhibition of cholesterol synthesis seems to be an unlikely mechanism for the possible CNS effects of statins, especially short term. 24S-hydroxycholesterol (24S-C-OH) originates in the brain. Studies investigating the effect of statins on cholesterol turnover, assessed by the serum 24S-C-OH to total cholesterol ratio, have been equivocal (119–122). Moreover, statins differ in their ability to cross the blood-brain barrier, with lipophilic compounds crossing more freely than hydrophilic compounds; thus, the possible effect of any statin probably depends on the statin itself, as well as its dose and duration of treatment.

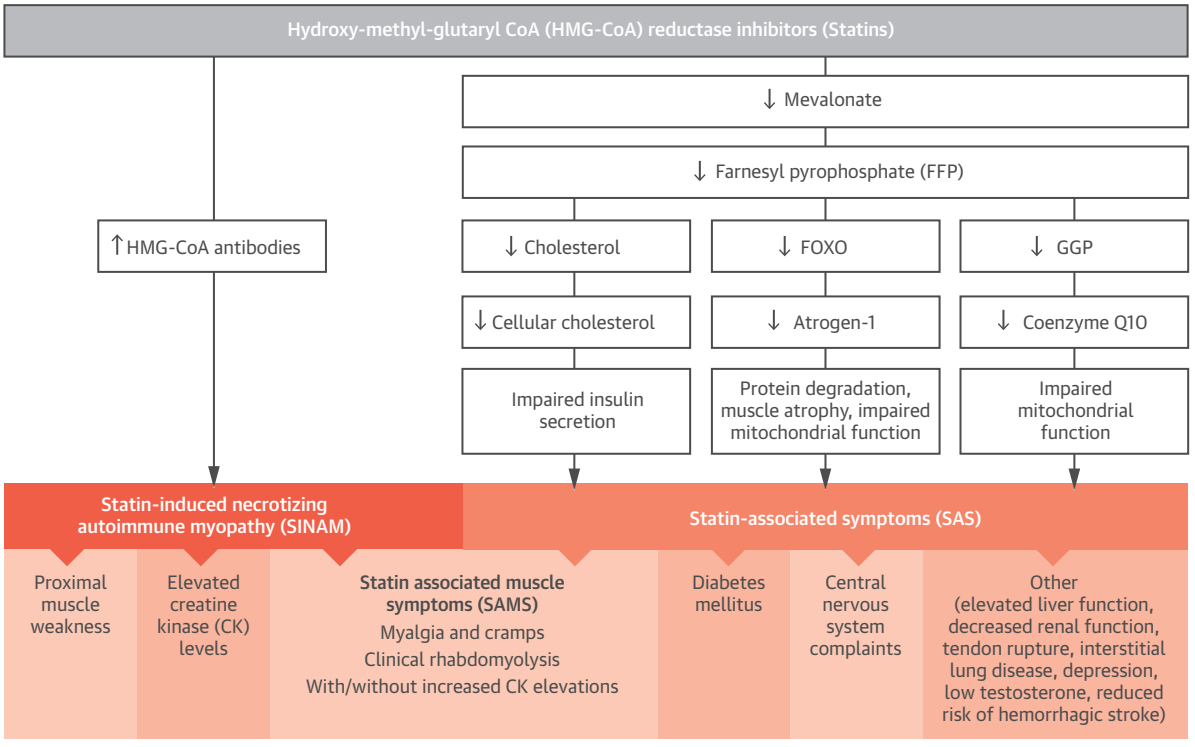
Statins also affect other compounds and processes affecting brain function. Statins inhibit isoprenoid production, and reducing the isoprenoid farnesyl pyrophosphate facilitates neuron potentiation and learning in animal models. Statins also reduce neuroinflammation and amyloid-β concentrations in animal models of AD (123). Such results support the concept that statin should enhance, rather than disrupt, cognitive function.

OTHER POSSIBLE STATIN SIDE EFFECTS

We searched PubMed for relevant meta-analyses and reviews of possible statin side effects using a Boolean search strategy ("statin" AND "side effect" AND "meta-analysis" OR "review"). Publications were reviewed in detail if the abstract suggested relevance to this review and were published in English, written after 2004, and reported on human subjects. The following sections address the other possible statin side effects identified in this search (**Central Illustration**).

ELEVATED LIVER FUNCTION TESTS. Statins are frequently associated with increases in liver function tests (LFTs), especially during early statin treatment

CENTRAL ILLUSTRATION **Statin-Associated Side Effects**



Thompson, P.D. et al. J Am Coll Cardiol. 2016;67(20):2395–410.

↓ = decreased function; ↑ = increased function; CK = creatine kinase; CNS = central nervous system symptoms; DM = diabetes mellitus; FFP = farnesyl pyrophosphate; FOXO = forkhead box protein group; GGP = geranylgeranyl pyrophosphate; HMG-CoA = hydroxyl-methyl-glutaryl-coenzyme A reductase; r = rhabdomyolysis; SAMS = statin-associated muscle symptoms; SAS = statin-associated symptoms; SINAM = statin-induced necrotizing autoimmune myopathy.

(approximately first 12 weeks) (124), but there are very few reports of liver failure directly attributed to statins (125). This may be because clinicians are aware of possible liver abnormalities, monitor LFTs, and stop treatment, but recent recommendations do not require routine LFT monitoring because of the rarity of important liver disease with statins (126).

DECREASED RENAL FUNCTION. High potency statins (rosuvastatin ≥10 mg, atorvastatin 20 mg, or simvastatin 40 mg) have been associated with a 34% higher rate of hospitalization for acute kidney injury within 120 days of drug initiation than less potent statin doses (127). Acute kidney injury was defined using a validated algorithm and ICD-9 diagnostic codes. In contrast, randomized controlled clinical trials (RCCTs) have not observed statin-induced kidney injury (128). In the PLANET I (Renal Effects of Atorvastatin and Rosuvastatin in Diabetic Patients with Progressive Renal Disease) study (129), atorvastatin 80 mg reduced the urinary protein to creatinine ratio after 52 weeks of treatment more than rosuvastain 10 and 40 mg, but neither drug worsened this ratio. A meta-analysis found that both atorvastatin and rosuvastatin reduced the decline in glomerular filtration rate compared with placebo, but that new onset dipstick proteinuria was more frequent with rosuvastatin than with atorvastatin (130). This difference disappeared when studies using rosuvastatin 40 mg were eliminated. Overall, available studies do not suggest that statins deleteriously affect renal function.

TENDON RUPTURE. We found 247 cases of tendon rupture listed in the FDA Adverse Event Reporting System (AERS) database as of 2006 (131). The explanation for any possible statin-tendon relationship is that tendons require matrix metalloproteinase

(MMP)-9 to repair damaged collagen and that statins reduce MMP-9 activity, possibly retarding tendon repair and increasing the risk of tendon pathology (131). A population-based retrospective, cohort analysis did not observe any relationship between statin use and tendon rupture among 800,000 men and women ≤64 years of age (132), so any possible relationship between tendon pathology and statin use is largely anecdotal and speculative.

HEMORRHAGIC STROKE. Statins reduce the incidence of stroke, which was unexpected because cholesterol had not been considered a stroke risk factor (133). In contrast, low cholesterol levels were known to be associated with an increased risk of hemorrhagic stroke (134,135). A systematic review and meta-analysis of 23 prospective studies, including more than 1.4 million subjects with 7,960 hemorrhagic strokes, demonstrated that the risk of stroke decreased 10% for every 38.66 mg/dl or 1 mmol/l increase in total and LDL cholesterol with 95% CIs of -9% to -20% and -23% to +5%, respectively (136). The HPS (Heart Protection Study) study observed an increase in hemorrhagic stroke in subjects with prior cerebrovascular disease treated with simvastatin 40 mg daily (137). Similarly, the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial observed an increase in hemorrhagic strokes, but a reduction in recurrent ischemic strokes, among stroke survivors treated with atorvastatin 80 mg daily (138). Neither the HPS nor the SPARCL study had sufficient subjects with prior hemorrhagic stroke to evaluate statin use in these patients. Studies in subjects without prior cerebrovascular disease have not observed an increase in hemorrhagic stroke (138). Overall, statins reduce the incidence of ischemic stroke and other vascular events in subjects with and without prior cerebrovascular disease, but appear to increase the risk of hemorrhagic stroke in patients with prior ischemic strokes.

INTERSTITIAL LUNG DISEASE. Interstitial lung disease (ILD) attributed to statin use was first described in 1995 (139). Our literature review and search of the FDA AERS database yielded 14 published case reports and 162 cases of statin-induced ILD (140). An update of this search identified 2 additional case reports (141,142). In contrast, a cohort (143) and case-control study (144) both found no association between statin use and ILD. To our knowledge, the only large study linking statin use and ILD is COPDGene (145). COPDGene examined 2,115 smokers and found that 38% of subjects with ILD were taking statins compared with 27% of subjects without ILD ($p = 0.04$). How statins could exacerbate ILD is unknown, but effects on lipid metabolism via phospholipidosis (146) and the immune system via cytokine enhancement (147) have been proposed as possible mechanisms. Nevertheless, the relationship between statins and ILD is largely anecdotal and speculative.

LOWER TESTOSTERONE. Statins appear to lower testosterone production, however, the magnitude of reduction is negligible. In a recent meta-analysis of placebo-controlled randomized trials, statins lowered testosterone by −0.44 nmol/l (148). Such average changes are unlikely to be of any clinical significance.

DEPRESSION. Depressive symptoms have been associated with low total cholesterol and LDL-C in men (149) and women (150), but such findings could result from reverse causation, whereby depression leads to poor nutritional intake with resultant reductions in cholesterol. Membrane cholesterol is essential for serotonin receptor function. Theoretically, a reduction in cholesterol could alter serotonergic binding and signaling (151). A review of the relationship between statins and depression found depressive symptoms to correlate positively with statin use and this relationship was associated with cholesterol depletion and decreased serotonin receptor activity (152). In contrast, another review found no effect of statins on symptoms of depression (153); thus, the evidence that statins affect mood and depression is inconclusive. Studies in this area are limited because few have assessed long-term statin use, various statins with possible variable blood-brain barrier penetration have been used, and many excluded participants with depression or comorbidities likely to coexist with depression.

SLEEP. An analysis of the FDA's AERS reports from 2004 to 2014 strongly suggests that statin use is associated with an increased risk for sleep disturbances, with insomnia as the most frequently reported side effect (154). In contrast, a review and meta-analysis identified 5 placebo-controlled trials examining statins and sleep (155). Statins had no effect on sleep duration, sleep efficiency, or entry into stage 1 sleep. Statins did reduce wake time and the number of awakenings. Such results suggest that any possible effects of statins on sleep are beneficial.

CONCLUSIONS

SAS, and especially SAMS, the predominant statin-associated symptom, appear to be frequent in clinical practice, but not different between statin-treated and control subjects in RCCTs. SAMS is important

because it reduces patient adherence to life-saving statin treatment. The diagnosis of SAMS is difficult because there are no validated tests or clinical criteria, except for increases in CK, but CK increases are absent in most myalgic patients. The mechanisms causing SAMS are not defined, but probably result from decreased production of noncholesterol endpoints of the mevalonate pathway. Patient management requires patient reassurance, diagnosis by clinical criteria and statin discontinuation/rechallenge, and treatment using different statins or alternative dosing strategies, often in combination with other lipid-lowering agents such as bile sequestrant resins, fibric acid derivatives, niacin, and PCSK9 inhibitors.

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