Statin Intolerance

Alan S. Brown, MD,[1] Karol E. Watson, MD, PhD[2]
[1]Division of Cardiology, Advocate Heart Institute at Advocate Lutheran General Hospital, Park Ridge, IL;
[2]Departments of Medicine & Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Statins are critical medications to prevent and treat cardiovascular disease[2] and they are generally very well tolerated. In some instances, however, statin intolerance may limit use of these lifesaving medications. Statin intolerance has many definitions but is commonly diagnosed when a patient is unable to continue statin therapy due to perceived, or objectively documented, adverse effects. A very high rate of discontinuation of statin therapy warrants a closer look at the implications from the standpoint of cardiovascular risk in statin-intolerant patients, as well as an evaluation of the available options to help patients maintain their statin therapy and understand the potential benefits of such therapy.

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KEY WORDS

Statin • Statin intolerance • Statin-associated muscular side effects • Cognitive effects • Diabetes mellitus • Statin discontinuation

Statin intolerance is a common problem even in patients with established atherosclerosis or diabetes. In a review of more than 540,000 patients from a large database who are at high risk due to known atherosclerosis or diabetes, and who had been started on statin therapy, 53% of patients discontinued their statin therapy with the median time to discontinuation of 15 months.[1] Interestingly, patients with a recent acute coronary syndrome or stroke had a slightly lower discontinuation rate of 47.9% versus those with other high-risk features such as diabetes or peripheral artery disease. Higher rates of discontinuation were also noted in younger patients and in women.[1] This very high rate of discontinuation of statin therapy warrants a closer look at the implications from the standpoint of cardiovascular risk in these statin-intolerant patients as well as an evaluation of the available options to help patients maintain their statin therapy and understand the potential benefits of such therapy.

Defining the Problem

Statins are critical medications to prevent and treat cardiovascular diseases[2] and they are generally very well tolerated. In some instances, however, statin intolerance may limit use of these lifesaving medications. Statin intolerance has many definitions but is commonly diagnosed when a patient is unable to continue statin therapy due to perceived, or objectively documented, adverse effects. Statin intolerance may be defined from either a patient or provider perspective. From a patient's perspective, statin intolerance may be defined as

any unacceptable or intolerable symptom that the patient attributes to his or her statin, leading to discontinuation. From a provider perspective, statin intolerance may be defined by objective evidence of statin-induced dysfunction such as abnormal liver function tests or elevated muscle enzymes such as creatinine kinase (CK) and is often not solely defined by patient symptoms. This difference may partially explain why the true incidence of statin intolerance is difficult to ascertain.

Statin intolerance has many definitions but is commonly diagnosed when a patient is unable to continue statin therapy due to perceived, or objectively documented, adverse effects.

Statins and Muscle Side Effects

The most common presentation of statin intolerance is muscular complaints,[3] and they are commonly categorized together as statin-associated muscular side effects (SAMS). Muscular complaints may take the form of pain (myalgia), weakness indicating muscle disease (myopathy), muscle inflammation (myositis), or asymptomatic elevation of creatinine kinase. Estimates vary, but the incidence of myalgia with statin therapy has been reported to be approximately 10% to 15%.[4] Most of the reported muscular effects are minor and are not life threatening, and estimates of more serious muscular adverse effects are much lower. As mentioned above, it is difficult to ascertain the true incidence of statin intolerance. Low rates of adverse events are reported in statin clinical trials; however, clinical trial experience sometimes differs from clinical reality. A randomized trial of high-intensity statin versus placebo was performed to identify the true incidence of statin intolerance. The Statins on Skeletal Muscle Function and Performance (STOMP) trial[5] randomized 420 statin-naive individuals to either atorvastatin, 80 mg daily, or placebo, then assessed incidence of myalgia at 6 months. Twenty-three of 203 (11.3%) of the atorvastatin-assigned participants and 19 of 217 (8.8%) of the placebo-assigned participants reported new, unexplained myalgia, and, of these, 19 atorvastatin and 10 placebo participants met the study myalgia definition yielding a placebo-subtracted incidence of statin associated myalgia of 2.5%. The most comprehensive study of statin-related adverse events in clinical practice is the Prediction of Muscular Risk in Observational conditions (PRIMO) study.[6] PRIMO was an observational study of muscular symptoms in an unselected population of 7924 patients receiving high-dose statin therapy in an outpatient setting in France. PRIMO attempted to define the relative incidence of muscular symptoms in patients on different statins. At the time PRIMO was initiated, rosuvastatin and pitavastatin were not available, thus PRIMO evaluated 7924 adults with hyperlipidemia receiving high-dose statin therapy at least 3 months prior to the study or had discontinued high-dose statin therapy due to muscular side effects during the 3 months immediately prior to the study. The first important finding from the trial was that most patients develop their symptoms within the first or second month after initiating treatment. A few patients, however, developed muscle symptoms as far out as 13 months after initiation of therapy. In the PRIMO study, simvastatin, 40 to 80 mg/day, had the highest percentage of patients with muscular symptoms at 18.2% followed by atorvastatin, 40 to 80 mg/day with an incidence of 14.9%. Pravastatin had fewer symptoms with an incidence of 10.9% and fluvastatin, 80 mg/day, had the lowest incidence of symptoms at 5.1%. No such head-to-head comparisons have been done more recently after the release of rosuvastatin and pitavastatin.

The most serious SAMS is rhabdomyolysis. The US Food and Drug Administration (FDA) defines rhabdomyolysis as creatinine kinase of greater than 50 times the upper limit of normal or >10,000 IU/L with renal compromise. Rhabdomyolysis associated with statin therapy is extremely rare and estimated to occur with an incidence of only 1 per 1 million person-years. A systematic review[7] identified several clinical conditions that are concomitant with statin-associated rhabdomyolysis (Table 1), thus careful patient selection and consideration can greatly reduce this very rare risk. Mild-to-moderate increases in creatinine kinase are sometimes seen in statin-treated patients who have no muscle-related complaints. An asymptomatic increase in creatinine kinase almost certainly does not indicate muscle damage and does not necessitate discontinuation of the statin.

Several factors can increase the risk of statin-induced myopathy. These factors include advanced age, renal insufficiency, hepatic dysfunction, hypothyroidism, certain dietary factors such as grapefruit juice in patients taking statins that are metabolized by the cytochrome P450 3A4 system, polypharmacy, and multiple chronic diseases. Statins that have a high systemic exposure, such as those with higher doses or high bioavailability as well

TABLE 1

Causal Factors in 25 Patients With Rhabdomyolysis: Results From 25 Million Person-years of Follow-up (1990-1999) in the UK General Practice Research Database

Drug overdose	7
Alcohol excess	2
Infection	6
Trauma, exercise	4
Epilepsy (convulsions)	2
Genetic predisposition	1
Hypothermia	1
Lipid-lowering drugs	1
No recognized cause	1

Data from Black C and Jick H.[8]

as those whose metabolic pathway have high potential for drug-drug interactions, are more likely to increase the risk of myopathy.[8] Harper and Jacobsen published a proposed algorithm for identifying statin-induced myalgia (Figure 1.)[9]

In 2014, the National Lipid Association Task Force on statin safety published a comprehensive review of the literature regarding the safety and side effects of statins.[10] They reviewed the incidence and attributable risk from statins for cognitive dysfunction, liver toxicity, muscle toxicity, and potential for increasing the risk of diabetes mellitus.

Statins and Hepatic Side Effects

In early statin clinical trials, liver function test (LFT) abnormalities were seen, so healthcare professionals were advised to regularly follow LFTs. However, over the course of many millions of patient-years of use, the FDA found that statin liver damage is rare, and LFTs are not effective at predicting or preventing this rare side effect. Therefore, in 2012 the FDA changed its guidance concerning regular LFT monitoring. The FDA advisory stated that "FDA is now recommending that LFTs be performed before statin treatment begins and then as needed if there are symptoms of liver damage."[11] It is not uncommon for patients to have baseline abnormalities in LFTs. Some of these abnormalities may be related to non-alcoholic fatty liver disease (NAFLD). Patients with NAFLD are not at increased risk of statin-induced hepatotoxicity.[12]

Statins and Cognitive Side Effects

After an extensive review of the literature regarding cognitive side effects and statins, the task force concluded that there was no clear association between the statins as a class and adverse effects on cognition.[10] It was recognized that rare individuals report cognitive dysfunction but there was no evidence from randomized, prospective clinical trials of a significant effect on cognition. It was pointed out that the FDA indicated that the symptoms were not serious in those rare individuals and were reversible within a few weeks after discontinuation of the statin. Consideration for decreasing the dose or stopping the statin was recommended while weighing the risk versus benefit of statin therapy in individual patients. The importance of careful evaluation of patients reporting cognitive difficulties to rule out other underlying neuropsychiatric disorders or early dementia was emphasized.

Statins and New-onset Diabetes Mellitus

The National Lipid Association (NLA) Task Force on Statin Safety evaluated the risk of statin treatment as a cause of access cases of diabetes mellitus.[10] The committee noted that a meta-analysis of statin trials indicated that statin use is associated with a relatively modest but significant increase in the risk for development of type 2 diabetes. The increase in risk is approximately 10% to 12% in those patients who have other risk factors for development of diabetes such as obesity or impaired fasting glucose. It also appears that the increased risk is higher when more intensive statin regimens are used. Meta-analyses also conclude, however, that statins reduce the risk of myocardial infarction, coronary revascularization, stroke, and cardiovascular death by 25% to 30% with larger reductions

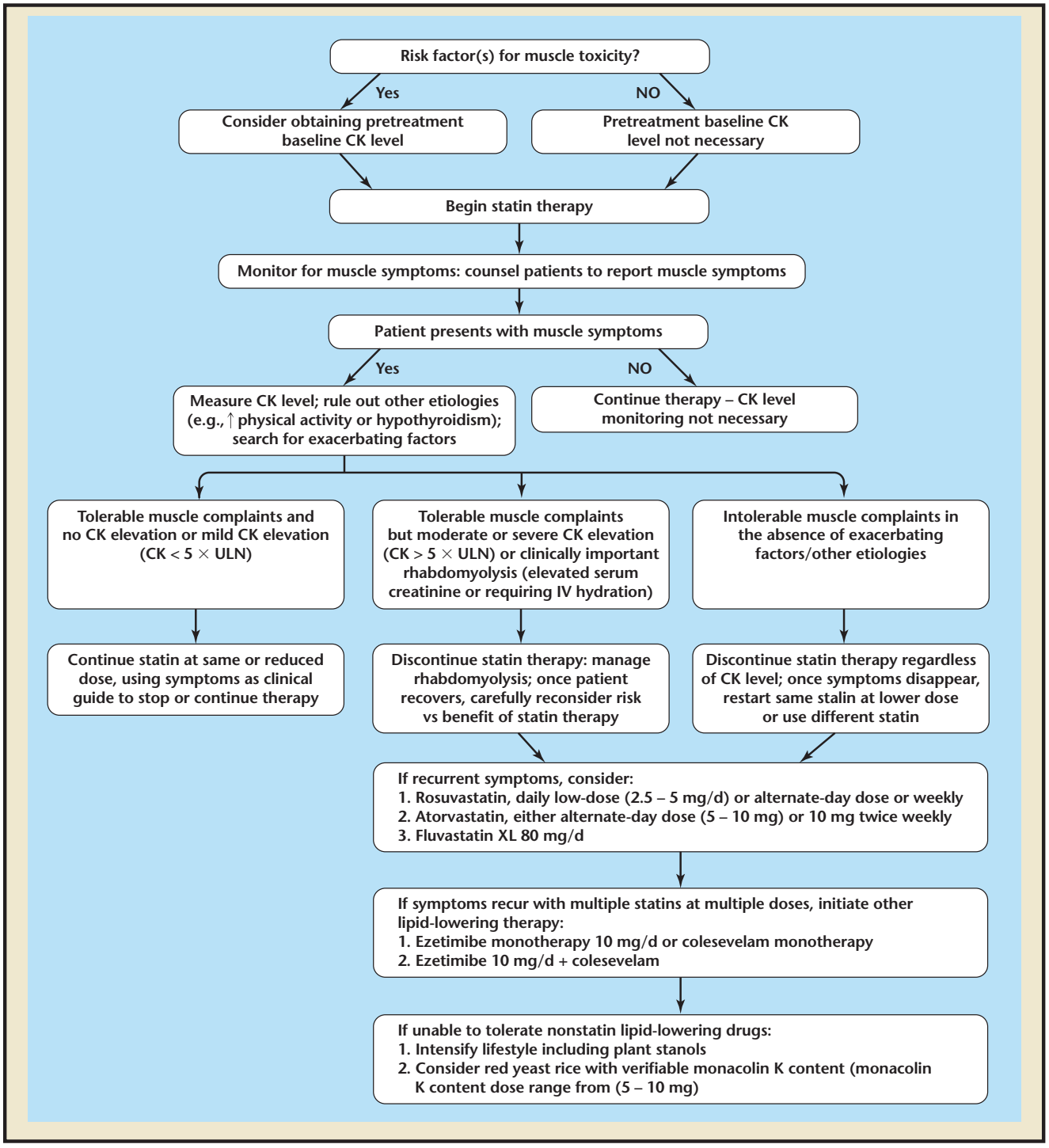

Figure 1. Proposed algorithm for identifying statin-induced myalgia. CK, creatine kinase; ULN, upper limit of normal. Reproduced with permission from Harper C and Jacobson T.[9]

noted for more intensive statin therapy. One can conclude, therefore, that the available data suggest that there are many fewer cardiovascular events occurring due to statin therapy than cases of diabetes caused by such therapy. The task force recommended following the current clinical guidelines for aggressive management of patients who have pre-diabetes or who currently have a diagnosis of diabetes mellitus. In patients who have pre-diabetes, aggressive lifestyle management was recommended, including weight loss and exercise, to reduce the risk of developing type 2 diabetes mellitus.

Statins and Drug Interactions

The 2014 NLA Task Force on Statin Safety also reviewed drug interactions.[10] Drug interactions with statins and other medications are numerous. The interactions are highly dependent on the metabolic pathway for the statin as well as for the concomitant therapy. The task force provided the details for drug interactions with multiple therapies (Table 2). It should be obvious that statin metabolism is quite complex and is related to

TABLE 2

Comparison of Drug-drug Interactions Across All Statins

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3 (moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
Simvastatin/ lovastatin	Protease inhibitors	Amiodarone	Afatinib	Barbiturates
	Boceprevir	Amlodipine	Aprepitant	Carbamazepine
	Clarithromycin	Conivaptan	Fosaprepitant	Clopidogrel
	Cobicistat	Diltiazem	Bosentan	Nevirapine
	Elvitegravir	Dronedarone	Colchicine	
	Emtricitabine	Efavirenz	Dalfopristin/quinupristin	
	Tenofovir	Other fibrates	Daptomycin	
	Cyclosporine	Fluconazole	Digoxin	Oxcarbazepine
	Danazol	Grapefruit juice	Esomeprazole	Rifabutin
	Delavirdine	Imatinib	Fluvoxamine	Rifapentine
	Erythromycin	Lomitapide	Fosphenytoin	
	Gemfibrozil	Ranolazine	Lansoprazole	
	Itraconazole	Simeprivir	Niacin/niacinamide	
	Ketoconazole	Ticagrelor	Omeprazole	
	Nefazodone	Troleandomycin	Pantoprazole	
	Posaconazole	Verapamil	Phenytoin	
	Red yeast rice		Quinine	
	Telaprevir		Repaglinide	
	Telithromycin		Rifampin	
	Voriconazole		St. John's wort	
			Warfarin	
Atorvastatin	Posaconazole	Boceprevir	Amiodarone	Barbiturates
	Red yeast rice	Clarithromycin	Antacids	Carbamazepine
	Telithromycin	Conivaptan	Aprepitant	Cimetidine
	Voriconazole	Cyclosporine	Fosaprepitant	Clopidogrel
		Darunavir	Atazanavir	Miconazole
		Delavirdine	Bosentan	Nevirapine
		Digoxin	Colchicine	Oral contraceptives
		Diltiazem	Colestipol	Oxcarbazepine

(*continued*)

Table 2 (*continued*)

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3 (moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
		Erythromycin	Dalfopristin/quinupristin	Pioglitazone
		Fluconazole	Danazol	Rifabutin
		Fosamprenavir	Daptomycin	Rifapentine
		Gemfibrozil	Efavirenz	Spironolactone
		Grapefruit juice		
		Imatinib	Esomeprazole	
		Itraconazole	Fosphenytoin	
		Ketoconazole	Indinavir	
		Lopinavir/ritonavir	Lansoprazole	
		Nefazodone	Mifepristone	
		Nelfinavir	Niacin/niacinamide	
		Other fibrates	Nilotinib	
		Saquinavir	Omeprazole	
		Simeprivir		
		Telaprevir	Pantoprazole	
		Tipranavir	Phenytoin	
		Troleandomycin	Quinine	
		Verapamil	Ranolazine	
			Rifampin	
			St. John's wort	
			Warfarin	
Rosuvastatin	Red yeast rice	Antacids	Colchicine	Erythromycin
		Atazanavir	Daptomycin	Oral contraceptives
		Clarithromycin	Darunavir	
		Cyclosporine	Indinavir	
		Fosamprenavir	Itraconazole	
		Gemfibrozil and other fibrates	Niacin/niacinamide	
		Lopinavir/ritonavir	Warfarin	
		Nelfinavir		
		Ritonavir		
		Saquinavir		
		Simeprivir		
		Telithromycin		
Pravastatin	Red yeast rice	Bile acid resins	Boceprevir	
		Clarithromycin	Colchicine	
		Cyclosporine	Daptomycin	
		Darunavir	Itraconazole	

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3 (moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
		Erythromycin	Niacin/niacinamide	
		Gemfibrozil and other fibrates	Orlistat	
		Simeprivir		
		Telithromycin	Warfarin	
Fluvastatin	Red yeast rice	Cyclosporine	Amiodarone	Clopidogrel
		Erythromycin	Antiretroviral protease inhibitors	Irbesartan
		Gemfibrozil and other fibrates	Cholestyramine	Rifabutin
		Telithromycin	Cimetidine	Rifapentine
			Colchicine	Zafirlukast
			Daptomycin	
			Delavirdine	
			Diclofenac	
			Digoxin	
			Efavirenz	
			Ethanol	
			Fluconazole	
			Fluoxetine	
			Fluvoxamine	
			Glyburide	
			Imatinib	
			Niacin/niacinamide	
			Nilotinib	
			Omeprazole	
			Phenytoin	
			Ranitidine	
			Rifampin	
			Sulfinpyrazone	
			Sulfonamides	
			Voriconazole	
			Warfarin	
Pitavastatin	Cyclosporine	Atazanavir	Colchicine	Warfarin
	Red yeast rice	Darunavir	Niacin/niacinamide	
		Erythromycin	Raltegravir	
		Fosamprenavir		

(*continued*)

Table 2 (*continued*)

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3 (moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
		Gemfibrozil and other fibrates		
		Lopinavir/ritonavir		
		Rifampin		
		Ritonavir		
		Saquinavir		
		Simeprivir		
		Telithromycin		
		Tipranavir		

Adapted from Kellick KA et al.[10]

the metabolism, excretion, distribution, and absorption of the drugs. Because of the variety of characteristics of different statins, the drug interactions vary from statin to statin. It is important for the clinician to be as familiar as possible with the potential drug interactions for their preferred statin and for them to refer to the pharmacy should there be any concern about statin interactions with other concomitant therapy. One should avoid the use of a statin that has the potential for a severe interaction with the medication currently being used by the patient. Statin dosing should be adjusted to the maximum dose for the milder or more moderate interactions with careful follow-up for potential toxicity.[10]

The Risks of Statin Discontinuation

It is extremely rare for SAMS to result in death, disability, or permanent damage,[8] and statins are phenomenally beneficial medications in patients at cardiovascular risk. Thus, it is important to keep patients on their statin therapy. One of the biggest risks of statin intolerance is that a patient will self-discontinue statin therapy, and recent evidence demonstrates that statin intolerance is associated with poorer cardiovascular outcomes. In a recent study, investigators studied 105,329 Medicare beneficiaries who began moderate- or high-intensity statin therapy after a hospitalization for myocardial infarction.[13] They evaluated statin-intolerant patients by identifying patients who down-titrated their statin dosage, switched from a statin to ezetimibe, or who were diagnosed as having rhabdomyolysis or a statin adverse event. Of these patients, 1.65% met the definition of statin intolerance and 52.8% of the cohort had high statin adherence. The results showed that compared with those with high statin adherence, the statin-intolerant patients had a 36% higher rate of recurrent myocardial infarction, and a 43% higher rate of coronary heart disease events. There was no difference in all-cause mortality (Figure 2).

Another recent study of patients with a prior history of ischemic stroke or transient ischemic attack (TIA) evaluated the effect of discontinuing statin therapy after the index event and the effect on outcomes.[14] A total of 45,151 ischemic stroke patients were evaluated and divided into three groups. A statin-discontinuation group did not receive statins between day 91 and day 180 after the index event. A second group of patients was categorized as a statin-reduced group and were placed on low-intensity statin therapy, or changed from high- to moderate-intensity statin therapy between days 91 and 180 after the index event. The third group was categorized as a statin-maintained group and included patients on high- or moderate-intensity statin therapy during the same period. The breakdown of these patients revealed that 74.5% were in the statin-maintained group, 7% were in the statin-reduced group, and 18.5% were not on any statin therapy. There were a total of 2120 recurrent strokes during the 1-year follow-up of the study. Multivariable analysis was performed and, compared with the statin-maintained group, the discontinuation of statins

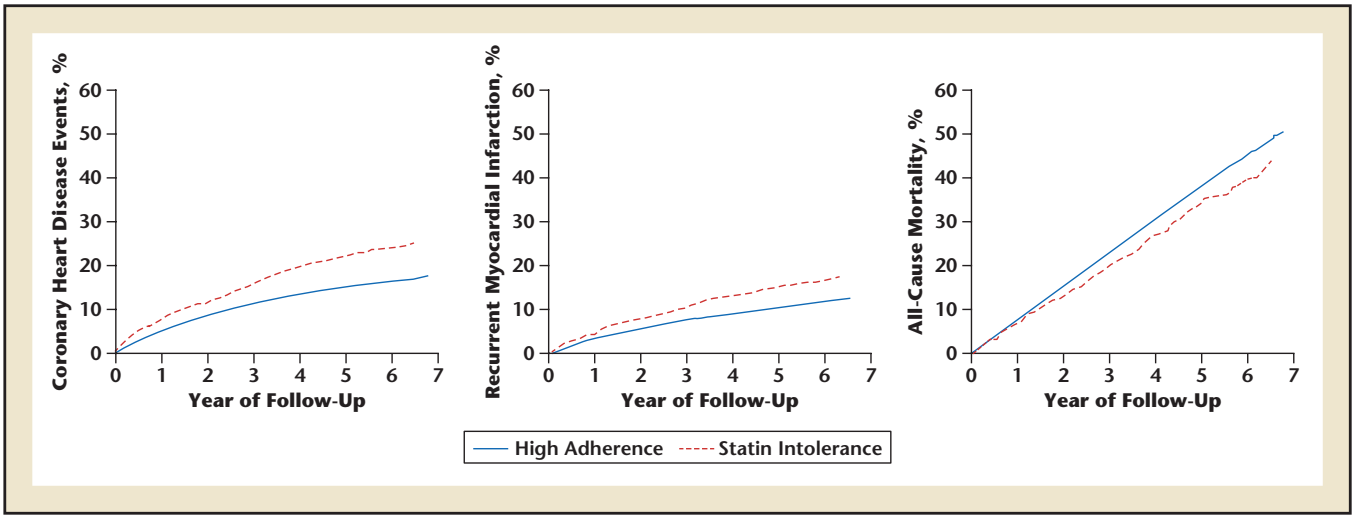

Figure 2. Cumulative incidence for recurrent MI, CHD events, and all-cause mortality for beneficiaries with statin intolerance and high adherence to high-intensity statins. Cumulative incidence for recurrent myocardial infarction and coronary heart disease events were adjusted for the competing risk of all-cause mortality. CHD, coronary heart disease; MI, myocardial infarction. Reproduced with permission from Serban MC et al.[13]

was associated with an increased hazard ratio of recurrent ischemic or hemorrhagic stroke of 42%. The statin-reduced group, however, did not show any additional risk.

Compared with the statin-maintained group, the discontinuation of statins was associated with higher risks of ischemic stroke (5.6% vs 3.9%; adjusted HR, 1.45; 95% CI, 1.30-1.61; $P < 0.0001$), all-cause mortality (1.4% vs 1.0%; adjusted HR, 1.37; 95% CI, 1.11-1.70; $P = 0.003$), all major events (7.8% vs 5.6%; adjusted HR, 1.38; 95% CI, 1.26-1.51; $P < 0.0001$), and any hospitalization (31.7% vs 27.1%; adjusted HR, 1.19; 95% CI, 1.14-1.24; $P < 0.0001$). Statin discontinuation had a neutral effect on intracerebral hemorrhage and on myocardial infarction.

Statin-reduced therapy was not associated with increased risk of ischemic stroke, intracerebral hemorrhage, all-cause mortality, myocardial infarction, or all major events.

One can conclude from these and other studies that there is a penalty to be paid for statin intolerance. Patients who discontinue their therapy, or who have their statin discontinued by their physicians, suffer an increased risk of cardiovascular events including myocardial infarction and stroke. These facts illustrate the importance of having a strategy to understand the causes and potential treatment options for patients who have intolerance to statins. When discussing statin tolerance, one must consider potential safety issues such as drug interactions or serious adverse reactions such as myositis. In addition, a strategy needs to be developed for those patients who have less serious side effects such as myopathy. Although serious toxicity from statins is extremely rare, the incidence of less serious side effects related to the statin, such as myopathy, likely approaches 10%. Patients, however, report a higher incidence of real or perceived side effects on statins. The USAGE survey[15] published by the National Lipid Association suggested that patients report side effects in as high as 29% of statin users. Whether the patient's symptoms are real or perceived, they must be taken seriously and evaluation for other underlying diseases should be considered.

Clinical Advice on Treating Patients With Statin Intolerance

When a patient presents with muscle-related symptoms on statin therapy, it is important to check a creatine phosphokinase (CPK) level. If the patient's CPK is greater than 10 times the upper limit of normal, rhabdomyolysis should be considered, the statin should be stopped immediately, and IV hydration initiated. This occurs extremely rarely and, more commonly, no CPK elevation or minimal elevation will be present. A careful history should be obtained to rule out contributing factors such as consumption of grapefruit juice or use of other medications that may increase statin levels, such as macrolide antibiotics, fibrates, and calcium channel blockers. Strenuous exercise can also increase the incidence of statin-induced muscle-related symptoms. One should also rule out hypothyroidism and consider obtaining a vitamin D level, which, if low, may contribute to muscle symptoms. The data regarding replacement of vitamin D or the use of supplements such as coenzyme

Q10 specifically to reduce muscle symptoms do not show consistent benefit.[16]

Switching patients to an alternate statin and forewarning the patient that they may have to try multiple statins to find one that they can tolerate it is often helpful.[17] Using longer-acting statins, such as rosuvastatin, at low doses or at a reduced frequency such as once or twice a week, often provides relief of symptoms as well as reasonable reductions in LDL cholesterol.[18]

The use of lower dose statins and adding additional agents such as ezetimibe, PCSK9 inhibitors, or bile acid resins as necessary to improve efficacy is also often helpful.

Conclusions

In clinical practice, the incidence of statin-induced side effects seems to be significantly higher than what has been seen in clinical trials. It is very important for the clinician to understand the factors that may increase the risk of statin toxicity,

In clinical practice, the incidence of statin-induced side effects seems to be significantly higher than what has been seen in clinical trials.

MAIN POINTS

- In a review of more than 540,000 patients from a large database who are at high risk due to known atherosclerosis or diabetes, and who had been started on statin therapy, 53% of patients discontinued their statin therapy with the median time to discontinuation of 15 months. This very high rate of discontinuation of statin therapy warrants a closer look at the implications from the standpoint of cardiovascular risk in these statin-intolerant patients, as well as an evaluation of the available options to help patients maintain their statin therapy and understand the potential benefits of such therapy.
- The most common presentation of statin intolerance is muscular complaints, and they are commonly categorized together as statin-associated muscular side effects (SAMS). Muscular complaints may take the form of pain (myalgia), weakness indicating muscle disease (myopathy), muscle inflammation (myositis), or asymptomatic elevation of creatinine kinase. Estimates vary, but the incidence of myalgia with statin therapy has been reported to be approximately 10% to 15%.
- Rare individuals report cognitive dysfunction but there is no evidence from randomized, prospective clinical trials of a significant effect on cognition. The US Food and Drug Administration has indicated that the symptoms were not serious in those rare individuals and were reversible within a few weeks after discontinuation of the statin.
- The National Lipid Association Task Force on Statin Safety evaluated the risk of statin treatment as a cause of access cases of diabetes mellitus. The committee noted that a meta-analysis of statin trials indicated that statin use is associated with a relatively modest but significant increase in the risk for development of type 2 diabetes. The increase in risk is approximately 10% to 12% in those patients who have other risk factors for development of diabetes such as obesity or impaired fasting glucose.
- It is important for the clinician to be as familiar as possible with the potential drug interactions for their preferred statin and for them to refer to the pharmacy should there be any concern about statin interactions with other concomitant therapy.
- Patients who discontinue their therapy, or who have their statin discontinued by their physicians, suffer an increased risk of cardiovascular events including myocardial infarction and stroke. These facts illustrate the importance of having a strategy to understand the causes and potential treatment options for patients who have intolerance to statins.
- Switching patients to an alternate statin and forewarning the patient that they may have to try multiple statins to find one that they can tolerate it is often helpful. Using longer-acting statins, such as rosuvastatin, at low doses or at a reduced frequency such as once or twice a week, often provides relief of symptoms as well as reasonable reductions in low-density lipoprotein cholesterol. The use of lower-dose statins and adding additional agents such as ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, or bile acid resins as necessary to improve efficacy is also often helpful.

such as advanced age, polypharmacy, renal insufficiency, drug interactions, and genetic factors. Muscle-related symptoms are the most common side effects reported by patients while on statins, and a careful investigation is required to rule out secondary causes of muscle symptoms such as hypothyroidism or primary neuromuscular disease. Strategies such as reducing the dose of statin, switching to alternative statins, or alternate-day or twice-weekly dosing can all be considered to improve tolerability. Because there is a small but finite risk for increasing the incidence of diabetes, especially in patients with prediabetes, as well as a small but finite risk of serious adverse events on statins, each patient should be carefully assessed for the benefit of therapy versus potential risks. In most cases, patients at significant risk for cardiovascular disease warrant an aggressive attempt at finding a successful path for tolerating statin therapy. ■

Dr. Brown has served as a consultant for Akcea, Amgen, Kastle, Kowa, Merck, Regeneron, and Sanofi; and is on the Speakers' Bureau for Amgen, Regeneron, and Sanofi. Dr. Watson has served as a consultant to Amgen and Beohringer Ingelheim; and is on the Speakers' Bureau for Boehringer Ingelheim.

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