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Statin-Associated Muscle Symptoms

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Preface

Lovastatin was approved by the FDA in July 1987, over 30 years ago. Since then, multiple clinical outcome trials have so consistently demonstrated their ability to reduce cardiovascular disease (CVD) events that the question with statins is often not who should be treated but who should not receive these life-saving drugs. Some authorities have recommended that statins be added to the water supply.

Statins benefit most patients, but they cause side effects that limit effectiveness in some individuals. The most frequently reported side effect is statin-associated muscle symptoms (SAMS), a loosely defined set of symptoms that includes muscle pain, cramping, aching, and stiffness that are attributed to the statin. These are labeled "statin-associated" because there is ongoing debate as to whether or not statins actually cause these symptoms. Part of the debate is due to the fact that the mechanism or mechanisms for SAMS are unknown but could involve altered calcium flux, oxidative stress, mitochondrial function, cell membrane integrity, and apoptotic signaling, since all are implicated in the etiology of SAMS.

We have had a long and interesting journey in studying how statins affect skeletal muscle. Paul distinctly remembers hearing a lecture on lovastatin in the late 1980s which mentioned that lovastatin could increase blood creatine kinase (CK) levels. Paul noted that comment because he had an interest in exercise-related rhabdomyolysis since medical school. At about the same time, Paul was involved in an industry-sponsored trial comparing the effects of lovastatin and fluvastatin on lipid levels. Several of the subjects had demonstrated an increase CK levels soon after exercise. One subject had a CK of 21,400 U/L, 5 days after a weight-lifting session. Paul subsequently embarked on a double-blind, placebo-controlled study which demonstrated that lovastatin-treated subjects experience a 40% higher increase in CK the day after 45 minutes of downhill walking.

Beth, an exercise physiologist, joined Paul in Hartford 10 years ago, and we have continued studies on how statins affect skeletal muscle. These studies have combined our personal interests in exercise and human performance with our interest in lipid metabolism. The mix is even more complex, however, because Paul's interest in lipid metabolism came from his attempts to explain how exercise increases HDL since muscle neither secretes nor directly catabolizes lipoproteins. Many others have been involved in these statin studies. Evan Stein, MD, is a well-known statin researcher who delivered the lecture that mentioned CK levels. Peter Herbert, MD, was an internationally

known lipid expert and Paul's mentor at Brown. Eileen Cullinane, DVM; Linda Bausserman, PhD; and Stan Sady, MD, PhD, were Paul's collaborators at Brown. John Guyton, MD, at Duke obtained the funding for the lovastatin downhill walking study. John was approached by a pharmaceutical company to perform studies and included Paul. Joe Zmuda, PhD, and Richard Zimet, PhD, helped perform that study. Neil Moyna, PhD; Amanda Zaleski, PhD; Gregory Panza, MS; and C. Michael White, PharmD, have been invaluable collaborators at Hartford Hospital.

But, why this book? It has been our experience that patients report SAMS, clinicians treat SAMS, and researchers study SAMS, but often in very disparate settings. We know of no comprehensive textbook that combines the three worlds of patient experience, clinician insight, and investigator knowledge. Indeed, one of our conclusions after reading and editing each chapter was that the study of SAMS requires a collaborative, multidisciplinary approach that has been lacking. The lack of such cohesive clinical and scientific collaborations may contribute to the continuing uncertainty surrounding SAMS, despite it being the most frequently reported side effect of one of the most commonly prescribed classes of drugs.

To create this book, we compiled a list of all the "unsolved problems" surrounding SAMS. We identified the experts in the field who could best present these topics in a way that might elicit new ideas and solutions. To our surprise, almost every author we asked agreed to contribute. We are ever grateful to them for showcasing their collective expertise within these pages.

Several facts are undeniable: CVD is still the leading cause of death in the United States and the world, and statins are an incredibly powerful drug for reducing CV risk. To improve statin use and effectiveness, SAMS need to be better studied, defined, and treated, and this textbook represents what we believe to be a step in that direction.

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Introduction

Beth A. Taylor and Paul D. Thompson

The first commercially available statin, lovastatin, was approved by the Federal Drug Administration in 1987. Over thirty years later, statins are unequivocally considered to be a (if not THE) cornerstone of cardiovascular disease (CVD) prevention and treatment. Why? Statins lower low-density lipoprotein cholesterol by 25–50% depending on the intensity of therapy. Consequently they reduce rates of total and CVD mortality, cardiac and cerebrovascular events, and revascularization by 25–40%, with individual impact varying by baseline LDL-C and magnitude of LDL-C reduction [1]. At a cost of <$300 year/prescription, it is no wonder that these cost-effective and well-tolerated drugs are among the first tools a clinician employs when treating a patient with established CVD or increased CVD risk.

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However, no good deed goes unpunished, and statin drugs are not without side effects. The first cases of lovastatin-associated rhabdomyolysis were reported in cardiac transplant patients in 1988 [2, 3]. Reports of increased CK levels associated with exercise in statin users were reported in 1990 [4]. Despite almost 30 years of such reports and investigations, today we still know remarkably little about statin-associated muscle symptoms (SAMS). The physiological mechanisms of SAMS are not conclusively established and are likely multifaceted. For example, alterations in cellular calcium handling, apoptosis, membrane integrity, and mitochondrial function are among the possible contributors to SAMS [5]. Systemic mechanisms such as low vitamin D levels [6] and exercise-associated exacerbation of muscle damage [7] also appear to have causality to SAMS in some, but not all, individuals.

There are also gaps in our knowledge of how to diagnose and treat SAMS. There are no direct assessments or biomarkers of SAMS besides an increase in CK levels that accompany symptoms in some SAMS patients. Clinicians must rely on patient self-report and drug cessation or drug dechallenge-rechallenge paradigms to confirm the diagnosis, but such approaches cannot avoid the expectation of harm or nocebo effect in some of these patients. Muscle symptoms in SAMS are also nonspecific and variable. Patients report a spectrum of complaints from cramps to pain to weakness that can occur bilaterally or unilaterally,

in upper/lower/torso muscles or tendons. These symptoms can appear days, months, or even years after initiation of statin therapy. Many patients complain of symptoms bilaterally in large muscle groups that start relatively soon after treatment initiation [8], but many do not. This variability in CK values, symptoms, and symptom onset plus the clinician's dependence on patient self-report of symptoms makes the certain diagnosis of SAMS nearly impossible.

Similarly, treatment strategies such as coenzyme Q10 [9] and vitamin D supplementation may or may not mitigate SAMS. Clinicians are often forced to decrease the statin dose or abandon these drugs altogether. Poor statin adherence is documented to increase the risk of CVD events [10, 11]. Indeed, there is not even consensus that statins cause SAMS in the absence of overt muscle damage as evidenced by increased CK levels [12, 13]. Up to 30–50% of SAMS appear either nonspecific and attributed to non-statin-associated reasons such as aging, disease, or other medications or caused by the nocebo effect, prompted by media reports critical of statins [14], social media, and patient bias [15, 16].

Nevertheless, several facts are undeniable. Approximately 10% of patients report SAMS [17, 18], and SAMS are the primary reason for statin discontinuation. Indeed, 60% of former statin users report having experienced muscle side effects [19]. Patients stopping statins due to intolerance have a markedly increased risk of cardiovascular events with resultant greater healthcare costs [20, 21]. The Centers for Disease Control and Prevention reported that 26% of US adults >40 years of age and 48% of adults >75 years of age report use of a cholesterol-lowering drug and 93% of these use a statin [22]. The 2013 American College of Cardiology and the American Heart Association (ACC-AHA) guidelines for the treatment of cholesterol expanded the number of US adults eligible for statin therapy from 43.2 million (37.5% of US adults) to 56.0 million (48.6%) [23]. Moreover, it has also been estimated that 49.7% of US adults with a high 10-year CVD risk of ≥20% are not receiving statins [24]. Expanding statin use in the United States to the 5.27 million untreated high-risk and 20.29 million untreated moderate-risk adults would prevent 384,000 and 616,000 CVD events, respectively, over 10 years [24]. But effectively expanding statin use to more individuals will require an improved understanding and management strategy of SAMS. Alternative cholesterol-lowering therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and ezetimibe do exist, but their use is limited by expense and effectiveness, respectively, which is also true for agents in development such as bempedoic acid. Thus, an improved understanding of SAMS is critical for directing patients to these alternatives when appropriate.

This textbook seeks to examine the many uncertainties surrounding SAMS, starting with the debate about their very existence and the difficulties in describing and defining their presentation and prevalence. The patient experience, risk factors, and strategies for diagnosis and management are explored. Further chapters present the role of genetics, interventions, and mechanisms in SAMS, as well as interactions between SAMS and physical activity, inherited muscle disease, and inflammation. Each chapter, written by the experts in the field, presents the latest research as well as the controversies surrounding the research and its translation into practice. The aim is to provide in a single source the most updated evidence to inform clinicians and researchers about best patient practice while highlighting essential unanswered questions. Indisputably, the extent to which statins can reduce CVD mortality and morbidity will not be fully realized until we address the nagging issues surrounding SAMS, which remain the most frequently reported yet surprisingly unresolved side effect of these life-saving drugs.

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Statin-Associated Muscle Symptoms Are Real

Peter P. Toth

Introduction

The statins are high affinity inhibitors of the rate-limiting step of cholesterol biosynthesis, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) and have been used in clinical settings since the late 1980s with the introduction of lovastatin [1]. These drugs induce substantial reductions in low-density lipoprotein cholesterol (LDL-C) by decreasing the hepatic production of cholesterol and increasing the systemic clearance of LDL particles via upregulation of the LDL receptor along the surface of hepatocytes. The statins have been unequivocally shown to reduce risk for nonfatal myocardial infarction and ischemic stroke, need for revascularization, hospitalization for unstable angina, atherosclerotic disease progression, as well as cardiovascular (CV) and all-cause mortality [2–4]. These substantial reductions in cardiovascular disease (CVD)-related endpoints have made statin therapy the first-line intervention for patients with dyslipidemia in guidelines promulgated throughout the world, with many millions of patients eligible for therapy based on LDL-C elevation and stratified risk for CV events [5–7].

In general, currently available statins have been shown to be quite safe. There is, however, potential for the development of some important statin-related adverse events. There is a small but detectable signal for the new onset of diabetes mellitus [8, 9], though this issue largely impacts patients who are already pre-diabetic or have metabolic syndrome [10]. Risk for elevations in hepatic transaminases was identified early [1], but risk for liver failure approximates that observed in the general population not being treated with a statin [11]. In the majority of patients experiencing transaminitis, transaminase elevations are most likely attributable to oscillations in the inflammatory tone of the hepatic parenchyma secondary to hepatic steatosis. The United States Food and Drug Administration no longer recommends that hepatic function panels be routinely measured in patients being treated with statins because the diagnostic yield is so low. Neurocognitive impairment has been described in case reports and small non-randomized studies, but no evidence for it was found in a recent randomized, carefully performed study with even very aggressive LDL-C lowering [12]. Statins are not associated with increased cancer risk [13]. A controversial potential side effect is hemorrhagic stroke, which even

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in meta-analyses does not reach statistical significance and whose real-world importance has been repeatedly called into question [3].

After three decades of research on statins, it is clear that statin-associated muscle symptoms (SAMS) are the most commonly occurring adverse event associated with these molecules and constitute the most frequent reason cited by patients for their premature discontinuation. This is a major global health issue as statin discontinuation rates are high, and they are associated with increased CV morbidity and mortality [14] (Fig. 2.1). Among Medicare patients who sustained an acute MI, patients who stopped their statin prematurely had a 1.5-fold higher risk of recurrent MI or of CVD events compared to those who remained adherent over a median follow-up of 1.9 years [15]. Defining the relationship between statins and SAMS is the primary objective of this chapter. The SAMS induced by statins have a highly heterogeneous etiology and can be

quite challenging to manage. Are the SAMS real? Yes, and they occur commonly. Premature statin discontinuation due to SAMS adversely impacts CV risk management.

Defining Statin-Associated Muscle Symptoms

Statin intolerance has been defined recently by a number of specialty societies. These are summarized in Table 2.1. Because this chapter focuses on SAMS, herein statin intolerance is defined as not being able to tolerate a dose of a statin that would provide a degree of LDL-C reduction commensurate with a patient's CV risk due to SAMS. The SAMS are varied and can include myalgia, cramping, motor weakness, myopathy, rhabdomyolysis, and autoimmune mediated necrotizing myositis. The most useful set of definitions for SAMS is the European Phenotype

Fig. 2.1 Comparison of acute cardiovascular events among participants in the Copenhagen Heart Study who remained adherent with statin therapy versus those who discontinued prematurely. (Reproduced from Nielsen and Nordestgaard [55] by permission of Oxford University Press)
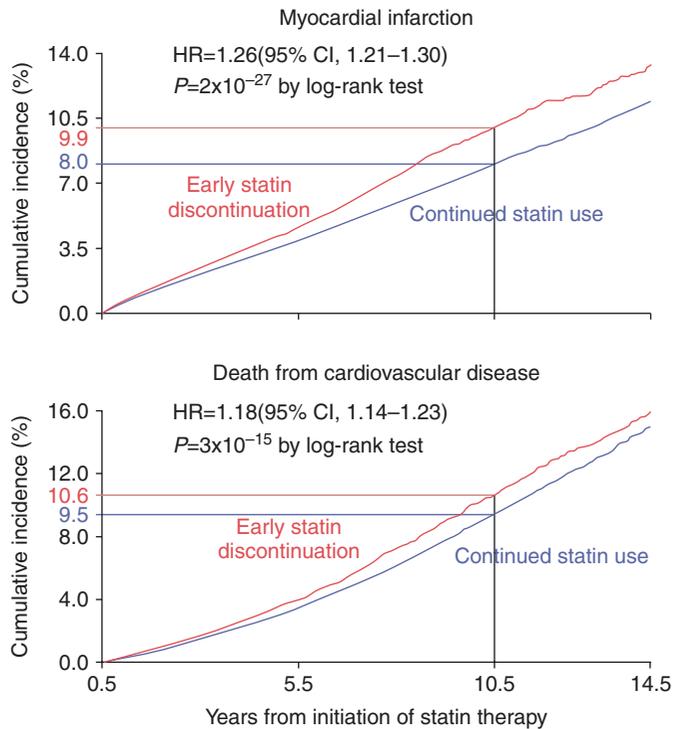
Individuals	No. of statin users at risk			
Early statin discontinuation	84 800	26 865	4534	828
Continued statin use	424 000	147 083	31 735	6465

Table 2.1 Definition of statin intolerance

Group	Year	Definition
National Lipid Association [20]	2014	Adverse effects relating to quality of life, leading to decisions to decrease or stop the use of an otherwise beneficial drug
International Lipid Panel [21]	2015	An inability to tolerate a dose of statin required to reduce a person's cardiovascular risk sufficiently from their baseline risk and could result from different statin-related side effects, including muscle symptoms, headache, sleep disorders, dyspepsia, nausea, rash, alopecia, erectile dysfunction, gynecomastia, and arthritis
European Atherosclerosis Society [22]	2015	The assessment of the probability of SAMS being due to a statin take into account the nature of the muscle symptoms, the elevation in CK levels, and their temporal association with statin initiation, discontinuation, and rechallenge
Canadian Consensus Working Group [23]	2016	A clinical syndrome characterized by significant symptoms and biomarker abnormalities that is documented by challenge/dechallenge/rechallenge using at least 2 statins (including atorvastatin and rosuvastatin) that is not due to drug-drug interactions or untreated risk factors for intolerance

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Standardization Project Statin-Associated Myotoxicity Phenotypes (Table 2.2).

Myalgia is highly prevalent throughout the population and is a subjective symptom with no objective biomarkers to either diagnose or exclude the diagnosis. Statin-induced myalgia resolves with statin discontinuation. Myalgia should be carefully distinguished from arthralgia, two complaints patients frequently intermingle. Myalgia is patient reported and typically not associated with weakness or skeletal muscle tenderness on physical examination. Cramping, both daytime and nocturnal, can occur. If the patient began an exercise regimen simultaneously with the initiation of statin therapy, this may simply reflect muscle deconditioning or mild dehydration. Myopathy is accompanied by such muscle symptoms as myalgia, weakness, and muscle tenderness, as well as elevations in serum creatine kinase (CK) in the range of 4–10 times the upper limit of normal (ULN). The increase in serum CK, if induced by statin therapy, reflects some degree of muscle injury/myocyte necrosis and normalizes with cessation of statin therapy. Rhabdomyolysis correlates with more extensive muscle injury and is associated with greater elevations in CK, myoglobinuria, and renal impairment. Rhabdomyolysis is a medical emergency and should be treated with immediate cessation of statin therapy, aggressive intravenous hydration, electrolyte management, and other means of

Table 2.2 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	HMGCR antibodies, HMGCR expression in muscle biopsy,
	necrotizing myositis	incomplete resolution on dechallenge

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physiologic support as necessitated by patient status. More rarely a patient may experience an autoimmune-driven myositis (necrotizing autoimmune myopathy) attributable to the development of antibodies to HMG CoA reductase and macrophage driven destruction of myocytes [16]. This may require the use of corticosteroids to ameliorate [17]. In other rare cases, statin therapy may unmask hereditary mitochondriopathies and metabolic derangements (McArdle disease, carnitine palmitoyl-transferase-2 deficiency, etc.) that may require muscle biopsy and more specialized care [18].

Incidence of SAMS with Statin Therapy

In randomized, prospective, double-blinded trials of statin therapy, the incidence of myalgias and other SAMS is relatively low and estimated to range from 1.5% to 5% [19]. This is likely an underestimate because patients with a history of myalgia or myopathy were routinely excluded from such trials. Moreover, if during the run-in phase a patient developed SAMS, they were also likely excluded from participation. Another potential reason for underestimating the true incidence of SAMS in these trials is because most of them did not systematically ask participants if they were experiencing SAMS. In clinical practice, of necessity patients with SAMS or a history of SAMS are not excluded from eligibility for statin therapy unless they experienced rhabdomyolysis.

In the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, the incidence of myalgia in the statin- and placebo-treated groups were 16% and 15.4%, respectively, for a net excess of 0.6% [20]. Among participants enrolled in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), 62% and 60% of statin- and placebo-treated patients experienced SAMS, respectively, with a net excess of 2% among statin users [21]. This study clearly revealed that even among patients treated with placebo, the incidence of SAMS was

remarkably high. Participants in the Heart Protection Study were asked at time of every follow-up visit whether or not they were experiencing SAMS (mylagia or muscle weakness). After 5 years the incidence of SAMS was 32.9% and 33.1% in the statin- and placebo-treated groups, respectively, a surpirising finding [22]. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial was an active comparator trial using simvastatin at 20 and 80 mg dose daily [23]. The higher simvastatin dose resulted in higher rates of both myalgia (43.5% vs. 41.6%) and myopathy (2.3% vs 0.2%) compared to the low dose, indicating a dose-response relationship. Consistent with results from the SEARCH trial, the A to Z trial also demonstrated a substantially higher hazard of simvastatin 80 mg vs. 20 mg: there were 9 cases of rhabdoymolysis and 0 cases in the 80 mg and 20 mg treated groups, respectively [24]. This prompted the Food and Drug Administration to withdraw approval for use of the 80 mg dose of simvastatin among patients not previously treated with this drug.

In response to some of the reservations cited above, Peto and Collins performed an important new analysis of SAMS in the prospective, randomized trials of statins [25]. Among participants in statin trials in which participants were asked about SAMS, there is no discernible difference between statin- and placebo-treated groups (Table 2.3). In statin trials that did not actively inquire about SAMS, there were modest between-group differences (5.0% vs. 4.5% in statin and placebo groups, respectively). Importantly, among 9 trials with no run-in phase and, hence, no elimination because of a history of SAMS, the incidence of SAMS for statin and placebo were 5.2% vs. 4.8%, repsectively. These authors argue: (1) unblinded observational studies can be affected by misatrribution bias (patients inaccurately attribute symptoms to statin usage); (2) randomized, blinded studies are the best means by which to study both efficacy and safety; and (3) "*patients should be told that taking an effective statin regimen will halve their risk of a heart attack or stroke (with absolute benefit depending on their absolute risk) and only slightly increase their likelihood of*

Table 2.3 Muscle-related symptoms ever reported in the 11 blinded randomized trials of statin therapy versus matching placebo involving ≥1000 participants (88,000 total) and scheduled treatment of ≥2 years (mean 5 years)

Systematically asked about muscle symptoms?	Run-in period on a statin before randomization?		
	Yes	No	Total
Yes	HPS 3380/10,269 vs. 3410/10,267	CORONA 225/2514 vs. 207/2497	HPS and CORONA 3605/12,783 vs. 3617/12,764
	32.9% vs. 33.2%	8.9% vs. 8.3%	28.2% vs. 28.3% Excess −0.1% SE 0.6%
No	HOPE-3367/6361 vs. 296/6344	8 other trials 1190/24,933 vs. 1102/24,929	9 trials 1557/31,294 vs. 1398/31,273
	5.8% vs. 4.7%	4.8% vs. 4.4%	5.0% vs. 4.5% Excess 0.5% SE 0.2%
Total	HPS and HOPE- 33747/16,630 vs. 3706/16,611	9 trials 1415/27447 vs. 1309/27,426	All 11 trials 5162/44,077 vs. 5015/44,037
	22.5% vs. 22.3% Excess 0.2% SE 0.5%	5.2% vs. 4.8% Excess 0.4% SE 0.2%	11.7% vs. 11.4% Excess 0.3% SE 0.2%, NS

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CORONA Controlled Rosuvastatin Multinational Trial in Heart Failure, *HOPE-3* Heart Outcomes Prevention Evaluation-3, *HPS* Heart Protection Study, *SE* standard error

developing muscle pain or weakness (if symptoms occur but CK levels remain normal, patients should be advised that the symptoms are unlikely to have been caused by the statin)." Because statin-induced SAMS are highly publicized in virtually every form of media, this is also likely to heighten the effect of attribution bias. In a comprehensive analysis of available clinical trial evidence, it was shown that if one were to treat 10,000 patients for 5 years with a high potency statin (e.g., atorvastatin 40 mg daily), this would result in approximately 5 cases of myopathy and possibly one case of rhabdomyolysis [26]. Estimates for the incidence of statin-induced myopathy and rhabdomyolysis are approximately 1/1000–1/10,000 and 1/100,000 patients per year, respectively [27]. Hence, risk of serious muscle injury with accompanying myocyte necrosis attributable to statin therapy is relatively low and, consequently, seldom enountered in clinical practice. Risk for myopathy and rhabdomyolysis is influenced by physiological status, renal and hepatic dysfunction, potential for drug interactions, as well as comorbidities as summarized in Table 2.4. Avoiding drug interactions is among the most important and practical means by which to avoid SAMS.

Table 2.4. Factors increasing risk of statin-associated myopathy

Drug Interactions (concomitant use with gemfibrozil, cyclosporine, azole antifungal agents, etc.)
Age (>80 years; especially women)
Small muscle mass
Hypothyroidism
Infections
Carbon monoxide poisoning
Polymyositis
Dermatomyositis
Illicit drug abuse (cocaine, amphetamines, heroin, phencyclidine hydrochloride)
Vitamin D deficiency
Genetic myopathies
Hypothyroidism
Mitochondriopathies
Hepatic Insufficiency
Multisystem diseases (especially diabetic chronic kidney disease)
Acute illness/surgery/trauma
Alcohol abuse
Exercise
Seizures

Adapted from Pasternak [57]

Myopathy must of course be differentiated from myalgia, the latter being much more commonly encountered and likely the most frequent reason for referral to a specialty lipidology clinic.