Canadian Journal of Cardiology 27 (2011) 635–662

Review

Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Proceedings of a Canadian Working Group Consensus Conference

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ABSTRACT

While the proportion of patients with significant statin-associated adverse effects or intolerance is very low, the increasing use and broadening indications have led to a significant absolute number of such patients commonly referred to tertiary care facilities and specialists. This report provides a comprehensive overview of the evidence pertaining to a broad variety of statin-associated adverse effects followed by a consensus approach for the prevention, assessment, diagnosis, and management. The overview is intended both to provide clarification of the untoward effects of statins and to impart confidence in managing the most common issues in a fashion that avoids excessive

RÉSUMÉ

Bien que la proportion de patients ayant des effets indésirables importants ou une intolérance associés aux statines soit très faible, leur utilisation croissante et leurs indications diversifiées ont mené à un nombre important de patients couramment dirigés vers des établissements et des spécialistes en soins tertiaires. Ce rapport fournit un survol complet de la preuve concernant une grande variété d'effets indésirables associés aux statines suivi par une approche consensuelle de la prévention, de l'évaluation, du diagnostic et de la gestion. Ce survol est destiné à fournir à la fois une clarification des effets déplorables des statines et à donner confiance en la gestion des enjeux les plus fréquents de manière à éviter

Statins (HMG-CoA reductase inhibitors) are among the most widely prescribed classes of medicines in the world. Since their restricted entry into clinical practice in 1984 and the public release of lovastatin in 1987, statins have ranked among the best studied medications. Clinical trials over more than 2 decades have shown that statins are safe and prevent cardiovascular (CV) deaths, major CV events (stroke, myocardial infarction), and total mortality.[1-3] Cholesterol lowering to prevent coronary artery disease (CAD) and total cardiovascular disease (CVD) has been credited with some of the gains made in the reduction of CVD incidence worldwide.[4]

While statins are proven to be well tolerated agents, the large and growing number of patients who are receiving these drugs creates a significant absolute number of people who are intolerant of statin therapy or who suffer side effects. Indeed, the genesis of this project was the recognition among a group of Canadian specialists that a large proportion of their caseload was dedicated to handling patients with suspected statin-related problems. Additionally, true or perceived drug intolerances undermine compliance, which is critical for fully achiev-

Received for publication March 16, 2011. Accepted May 19, 2011.

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See page 656 for disclosure information.

ancillary testing and/or subspecialty referral except when truly necessary. The ultimate goal is to ensure that patients who warrant cardiovascular risk reduction can be treated optimally, safely, and confidently with statin medications or alternatives when warranted.

les tests auxiliaires excessifs ou les références en sous-spécialités, ou les deux, excepté lorsque cela est vraiment nécessaire. Le but ultime est de s'assurer que les patients qui bénéficieraient d'une réduction du risque cardiovasculaire peuvent être traités de manière optimale, en sûreté et en toute confiance par des statines ou d'autres solutions lorsqu'elles sont justifiées.

ing the benefits of chronic, generally life-long, lipid-lowering therapy. Thus, the primary goal of this report is to inform Canadian healthcare providers of the current understanding of statin-associated side effects in order to help them better deal with patients with suspected statin adverse effects, and hopefully to limit both ancillary testing and referral of statin-intolerant patients to specialists.

Methods

The preliminary stage was an informal review of recent (up to December, 2010) literature on statin side effects and therapy for statin intolerance (G.B.J.M.). From that review, a list of subtopics was identified for specific side effects and their management and a subsequent literature search was undertaken using online databases, including PubMed and Embase, to compile studies of relevance. Through the literature search, Canadian physicians who had either published in the area of statin intolerance in particular or the area of lipid treatment and risk reduction, or individuals with experience in guideline-writing were asked to participate. Invitations were sent to these individuals outlining the expectations and the dates for submission of manuscripts and slides as well as the date for the consensus meeting. Several were unable to accept and so a second set of invitations was circulated. It was not possible to identify a Canadian hepatologist or nephrologist to participate in the meeting but both subspecialties were represented in the external review group (see below). It must be emphasized that all coauthors contributed to the final content of all sections through the review of multiple drafts and approval of the final manuscript. For the initial meeting, however, assignments were as follows: Baker (muscle effects), Bergeron (neurological effects, insomnia, hepatic effects), Gupta (renal effects, alopecia, erectile dysfunction), Genest (diabetes, pharmacology of statin drugs, emerging therapies), Pope (rheumatologic effects), Mancini (overall editor-in-chief, interstitial lung disease, prevention of statin intolerance, diagnosis of statin intolerance, management approaches for muscle and hepatic-related problems), Frohlich (prevention of statin intolerance, diagnosis of statin intolerance), Hegele (nongenetic and genetic predisposition), Fitchett (dietary and health behaviour measures, statin-based therapies, treatments targeting symptom relief), and Ng (nonstatin alternatives and adjuncts).

Each expert reviewed the evidence provided through the search and also independently augmented the search using the references from the compiled studies and other articles already available to them. In December 2010, the multidisciplinary panel of Canadian specialists convened to present, discuss, and debate their findings. Literature was updated to May 2011. Three external reviewers were asked to provide comments on the second to last and final draft (see *Acknowledgements* section). Consensus was reached through discussion at the consensus conference and through review of the multiple drafts.

General Background

In addition to common, nonspecific, mild symptoms or transient side effects encountered with almost any medication, such as gastrointestinal discomfort, fatigue, and skin involvement, statins have more specific effects.[5] The main concerns with statins usually pertain to elevated liver enzymes and adverse muscle effects. While these effects will dominate this review, there are many other purported effects that can lead to medical assessment, diagnostic testing, and inappropriate discontinuation of therapy, even though such complaints may be unrelated to statin therapy. Accordingly, many of these effects will also be discussed.

Adverse Effects

Adverse muscle effects

Muscle complaints constitute the major symptom limiting the use of statins. The clinical features of statin myopathy include symptoms such as muscle aches or myalgia, weakness, stiffness, and cramps. These muscle-related side effects (MRSEs) may or may not be associated with elevations in serum creatine kinase (CK) levels.

Definitions. There is great variability in the criteria used to diagnose statin myopathy in pharmacologic studies and by regulatory and professional bodies and agencies. Current definitions of statin-associated muscle complaints are shown in Table 1.[6] The term "statin-associated" reflects the fact that association does not automatically imply causality.

Skeletal muscle-related adverse effects of statin therapy range from myalgias to rhabdomyolysis. Because categorical definitions are not uniform, interpretation of the literature on this topic can be confusing. In 2006, an expert panel developed guidelines to facilitate comparisons between the statins and to promote greater consistency amongst future studies but limitations still exist.[7]

Myopathy is a collective term that encompasses all forms of muscle disease including toxic, acquired, and hereditary disorders. The term does not necessarily connote symptoms or any degree of CK elevation. For example, several myopathies may present with normal CK levels, including steroid myopathy, critical-illness myopathy, pediatric dermatomyositis, myotonic dystrophy type 2, and the periodic paralyses. Indeed, biopsy evidence suggests that even some statin-induced myopathic changes may be present in the context of normal CK levels.[8]

Table 1. Definitions for statin-associated myopathy

Clinical entity	ACC/AHA/NHLBI	NLA	FDA
Myopathy	General term referring to any disease of muscles	Symptoms of myalgia (muscle pain or soreness), weakness or cramps, plus CK > 10 times ULN	CK ≥ 10 times ULN
Myalgia	Muscle ache or weakness without CK elevation	NA	NA
Myositis	Muscle symptoms with CK elevation	NA	NA
Rhabdomyolysis	Muscle symptoms with significant CK elevation (typically > 10 times ULN), and creatinine elevation (usually with brown urine and urinary myoglobin)	CK > 10,000 U/L or CK > 10 times ULN plus an elevation in serum creatinine or medical intervention with intravenous hydration	CK > 50 times ULN and evidence of organ damage, such as renal compromise

ACC, American College of Cardiology; AHA, American Heart Association; CK, creatine kinase; FDA, US Food and Drug Administration; NA, not available; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; ULN, upper limit of normal.

Reproduced with permission from Joy and Hegele.[6]

Myalgia refers to muscle discomfort that may mimic flu-like symptoms and usually involves the proximal musculature, ie, shoulder and pelvic girdle and upper arm and/or thighs. These most commonly develop within the first 6 months of starting statin therapy[9,10] but their onset can also be delayed for several years.[10] The myalgias typically resolve within 2 months of discontinuing the statin. Statin-related muscular complaints may aggravate pre-existing myofascial pain in patients with fibromyalgia[10-12] and may trigger polymyalgia rheumatica-like symptoms.[13,14] These classic features should be borne in mind when evaluating the many types of atypical symptoms sometimes suspected of being statin-associated.

Historically, myositis refers to conditions in which the serum CK is elevated above the upper limit of normal (ULN) but ≤10 times the ULN whereas rhabdomyolysis is associated with a CK > 10 times the ULN. However, the determination that a specific CK elevation of > 10 times ULN should define rhabdomyolysis is arbitrary and fails to differentiate gradations of muscle breakdown. Therefore, to address this, hyperCKemia is a term often used to reflect the degree and severity of muscle breakdown, irrespective of symptoms, and is categorized into mild (< 10 times ULN), moderate (10-50 times ULN), and marked (> 50 times ULN). Finally, rhabdomyolysis may have secondary consequences such as hyperkalemia, hypocalcemia, cardiac arrhythmia or arrest, disseminated intravascular coagulation, or renal failure.[15] Myoglobin in sufficient quantity or concentration is toxic to the renal tubules and this toxicity may be modulated by patient factors such as degree of hydration, concomitant drug use, and other factors affecting renal function. Accordingly, although many definitions of rhabdomyolysis (Table 1) currently invoke concomitant renal dysfunction, the latter is not an inevitable consequence of rhabdomyolysis even when muscle breakdown is clinically significant nor is it a necessary component for the diagnosis. When myoglobinuria-induced renal dysfunction or other complications are present, however, it represents a much more serious outcome with greater morbidity. An integrated system for use of these terms is proposed in Table 2. Further complicating this terminology are patients with benign, chronic, and asymptomatic elevations of CK that are commonly encountered. Under these circumstances, changes in CK are more logically evaluated with respect to the patient-specific baseline value and this will be discussed further in sections on management.

Mechanisms of myopathic reactions. Statins produce myopathic reactions in two distinct forms—toxic and immune-mediated. Pathophysiologic explanations of statin-induced myopathy have focused primarily on toxic mechanisms. However, recently an immune-mediated form of necrotizing myopathy (NM) has emerged as a rare but fulminant form of statin myopathy (see *Immune-Mediated NM* section and Fig. 2). It is unknown whether the two forms of myopathy can co-exist or if a toxic insult can trigger a secondary immunologic event.

The cellular mechanisms accounting for the toxic effect of statins on muscle are unknown but numerous hypotheses have been suggested.[6] Cellular hypoprenylation due to the physiochemical inhibition of HMG-CoA reductase and the resultant

Table 2. Integrated Canadian Working Group consensus terminology for myopathic syndromes and hyperCKemia*

Terms	Laboratory characteristics	Clinical characteristics
Myopathy	NA	General term referring to any disease of muscle
Symptomatic myopathy		
Myalgia	CK ≤ ULN	Muscle ache/weakness
Myositis	CK > ULN	Muscle ache/weakness
Rhabdomyolysis	CK > 10 times ULN (CK > 10,000 U/L)	Muscle ache/weakness; Renal dysfunction may result from myoglobinuria; Need for hydration therapy
HyperCKemia		
Mild, grade 1	CK > ULN, ≤ 5 times ULN	May/may not have myositis
Mild, grade 2	CK > 5 times ULN, ≤ 10 times ULN	May/may not have myositis
Moderate	CK > 10 times ULN, ≤ 50 times ULN	May/may not have rhabdomyolysis with/without renal dysfunction
Severe	CK > 50 times ULN	May/may not have rhabdomyolysis with/without renal dysfunction

CK, creatine kinase; NA, not applicable; ULN, upper limit of normal.

* In patients with benign or idiopathic and chronic elevations of CK, symptom and severity descriptors should be referenced to the patient-specific baseline level of CK.

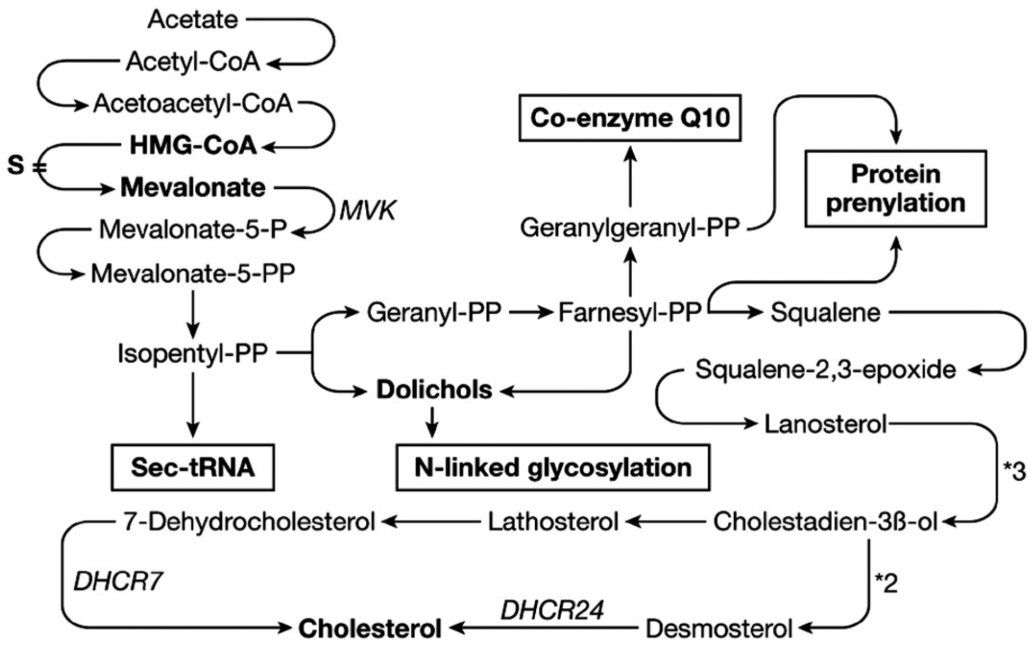

Figure 1. Downstream effects of statins (HMG-CoA reductase inhibitors) on the biosynthetic pathways of the isoprenoids and cholesterol. Statins (S) selectively impair the rate-limiting enzyme, 3-hydroxy-3-methylglutaryl coenzyme A, which suppresses cholesterol synthesis. However, the isoprenoids are secondarily reduced. This leads to an impairment of multiple pathways, including: (1) selenocysteine (Sec) transfer RNA (tRNA) isopentenylation, (2) dolichol-mediated *N*-linked glycosylation, (3) protein prenylation by farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate, which may affect up to 2% of mammalian cellular proteins, and (4) coenzyme Q_{10} tail synthesis, which may influence antioxidant and respiratory chain capacities within the cell. The association of myopathy with mevalonate kinase *(MVK)* deficiency but not the distal enzymopathies, eg, sterol-C5 desaturase *(SC5DL),* 3-hydoxysterol-delta-24-reductase *(DHCR24),* and sterol-delta-7-reductase *(DHCR7),* suggests that the intervening isoprenoids may be involved in statin myopathy. **(*2)** and **(*3)** indicate the number of nonenzymatic rearrangements occurring between 2 intermediaries. Adapted and reproduced by permission from Baker.[16]

disruption of small G-protein function, due to reduced isoprenoid intermediaries (ie, geranygeranyl pyrophosphate and farnesyl pyrophosphate), exerts pleiotropic effects on numerous signalling pathways leading to alterations in protein handling and gene expression (Fig. 1).[16]

Pharmacokinetic risk factors for statin myopathy. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) collaborative study[17] reinforced the importance of the *SLCO1B1* gene, originally identified as an important determinant of statin plasma levels by Tirona et al.,[18] demonstrating odds ratios for the development of simvastatin-induced myopathy of 4.5 and 16.9 for heterozygous and homozygous C allele transitions at the single nucleotide polymorphism (SNP) rs4149056. This common SNP in the *SLCO1B1* gene encodes a common nonsynonymous Val174Ala amino acid alteration (ie, *SLCO1B1*∗5). It was estimated that the C variant could account for 60% of the myopathic symptoms in affected individuals. Such data provide compelling evidence that pharmacokinetic factors influence myopathy risk. Interestingly, the rs4149056 C allele was associated with higher statin levels whereas the rs2306283 G allele was associated with both lower statin levels and myopathy risk. However, CC homozygotes (at SNP rs4149056) do not uniformly develop myopathy presumably because the ultimate metabolic pathway(s) which permit expression of the myopathy at the level of skeletal muscle must also be involved in 1 way (eg, genetic [carnitine palmitoyl transferase II (CPTII) deficiency][19]) or another (eg, pharmacologic [fibrate][20]). Unfortunately, many of these pathways remain poorly understood. But to fully assess the risk for developing statin myopathy both pharmacokinetic and pharmacodynamic factors must be conjointly scrutinized. Given that all statins require hepatic transporters for their transmembrane flux, it is assumed that polymorphisms in these proteins affect serum levels of particular statins and thus the risk for myopathy. However, a genome-wide association study has only been completed for simvastatin.

Plasma statin levels do not adequately predict risk for statin myopathy, and, therefore, transsarcolemmal flux represents an additional target to further assess whether interindividual variation may influence statin myotoxicity. Organic anion transport polypeptide 2B1 (OATP2B1) is expressed on the sarcolemma and mediates the uptake of statins into skeletal muscle. The multidrug resistance-associated proteins MRP1, MRP4, and MRP5 are also present in skeletal muscle and function as statin efflux transporters such that adenoviral cotransduction into primary human skeletal muscle myoblasts with OATP2B1 afforded cytoprotection against statin exposure.[21] Statin transporters in both liver and skeletal muscle appear to be important determinants of myopathy risk as their expression and kinetics dictate statin levels in both the plasma and sarcoplasm. Finally, there might be differences in how these metabolic factors and pathways affect different members of the statin class.

Myocellular metabolic dysfunction induced by statins. Numerous studies suggest that blood levels of coenzyme Q_{10}

are reduced by statin treatment.[22-39] This effect is most likely a function of lipoprotein reduction as these proteins serve as carriers for coenzyme Q_{10}.[22,29] Studies examining myocellular coenzyme Q_{10} levels are conflicting. Two reports have documented increases of 9.0% to 46.6% after 1 to 6 months of simvastatin therapy (20 mg per day).[30,31] Päivä et al.[40] noted a 34% reduction after 8 weeks of simvastatin (80 mg per day) but not atorvastatin (40 mg per day) treatment. Citrate synthase was reduced to 55% of baseline activity suggesting that statins may impair mitochondrial biogenesis. Vladutiu et al.[19] found reduced skeletal muscle coenzyme Q_{10} levels in 47% of 41 biopsy specimens from statin-intolerant patients with varying CK levels. Lamperti et al.[31] found no difference in muscle coenzyme Q_{10} levels between statin-tolerant and statin-myositis patients. Despite these discrepant findings, the triggering of MELAS-like (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndromes in 2 patients treated with statins supports the contention that mitochondrial fidelity may be sensitive to HMG-CoA reductase inhibitors.[33,41] Finally, as 2 independent pharmacogenomic studies have found significant associations between statin-intolerant patients and the *COQ2* gene, more work is needed to clarify the role of coenzyme Q_{10} in statin myopathy.[42,43]

In addition to impairing oxidative phosphorylation[44] statins may unmask or worsen muscular symptoms in patients with preexisting metabolic myopathies (eg, McArdle disease and CPTII deficiency), whether latent or manifest.[45] Several lipophilic statins exhibited mitochondrial toxicity through various mechanisms involving electron transport and beta oxidation, leading to dissipation of the mitochondrial membrane potential, cytochrome c release, and a progressive increase in apoptosis.[46]

Statins may also impair calcium handling in skeletal muscle. For example, simvastatin has been shown to trigger: (1) mitochondrial depolarization and Ca^{2+} efflux (through the permeability transition pore and sodium-calcium exchanger); (2) sarcoplasmic reticulum Ca^{2+}-uptake and/or overload; and (3) large-amplitude Ca^{2+}-transients.[47] In addition, simvastatin-induced long-lasting fura-2 Ca^{2+}-transients in human skeletal muscle led to activation of calpain and caspaces 3 and 9. Calcium chelation and ryanodine, via inhibition of Ca^{2+}-induced Ca^{2+} release, has been shown to abrogate these effects.[48]

In these and other scenarios, 2 pathways need to become disrupted in order to manifest muscle effects. Statins may therefore unmask muscle pain, weakness, or serum CK elevations in an asymptomatic carrier (recessive condition) or preoligosymptomatic patient (dominant or acquired condition). Further support of this can be found in the report of combined partial deficiencies of CPTII and mitochondrial complex I presenting as hyperCKemia.[49] This pharmacogenomic multiple pathway synergism model is an attractive explanation for the numerous potential neuromuscular manifestations of statin therapy (Table 3).[50,51]

Table 3. Neuromuscular diseases associated with statin therapy

- Acid maltase deficiency
- Amyotrophic lateral sclerosis
- Carnitine palmitoyl transferase II deficiency
- Cytoplasmic body myopathy
- Dermatomyositis
- Hyaline inclusion myopathy
- Inclusion body myositis
- McArdle disease
- Malignant hyperthermia
- Mitochondrial myopathy, ie, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Muscle phosphorylase B kinase deficiency
- Myasthenia gravis
- Myoadenylate deaminase deficiency
- Myotonic dystrophy types I and II
- Necrotizing myopathy
- Peripheral neuropathy (length-dependent, mononeuritis multiplex)
- Polymyositis (paraneoplastic, idiopathic)
- Recurrent acute myoglobinuria due to Lipin-1 mutation
- Rippling muscle disease (sporadic/autoimmune)
- Spinobulbar muscular atrophy

Adapted from Baker and Samjoo.[51]

Immune-Mediated NM. Immune factors may play a role in the development of statin myopathy/myositis in a certain subset of patients. Indeed several reports have emerged documenting the induction of inflammatory myopathies (ie, polymyositis and dermatomyositis) by statins in a timeframe consistent with a toxic effect.[9,52-57] In contrast to these reports, which exhibited robust inflammatory infiltrates on muscle biopsy, an immune myopathy may develop manifesting major histocompatibility (MHC)-1 upregulation without inflammation.[58] An in vitro study employing 2 skeletal muscle-derived cell lines found that statins downregulated or had no effect on MHC-1 expression.[59] A more recent histologically distinct statin myopathy has been described that lacks inflammatory cells, except for the macrophages engulfing necrotic muscle fibres, responds to immune therapy, and is presumably autoimmune. It is referred to as an NM.[60] NMs can be idiopathic, paraneoplastic, or secondary to a connective tissue disorder. The observation that a NM can develop after statin discontinuation suggests that previously restricted epitopes may be exposed by statin therapy through a toxic mechanism and this may trigger a subsequent autoimmune myopathy manifesting necrotizing and/or inflammatory changes (Fig. 2). An initial report of autoantibodies recognizing both 100- and 200-kD proteins in statin-treated NM patients supports an autoimmune hypothesis.[61] More recent work has determined that the 100-kD autoantibody targets HMG-CoA reductase.[62] Interestingly, statins increase plasma lipidic proinflammatory markers[63] potentially magnifying or perpetuating an autoimmune response against HMG-CoA reductase which is expressed at high levels in regenerating muscle fibres.[62]

Clinical impact of muscle side effects. As indicated above, estimates of the incidence of statin myopathy depend on the clinical definition used, but also on the type of data used to derive the estimate, such as randomized clinical trials (RCTs), cohort studies, or voluntary notifications to regulatory authorities. In RCTs, statin myopathy incidence is approximately 1.5% to 5.0%.[5,64] This low rate may, however, be related to systematic exclusion of individuals who have a history of statin-related intolerance or who develop biochemical abnormalities during the unblinded, run-in phase before randomization. Also, some RCTs defined muscle-related effects by elevated plasma CK levels only. In addition, individuals who have experienced prior statin intolerance would likely not enrol in clinical trials, while enrolled patients might be motivated to minimize reporting of mild statin-related myalgias. Further-

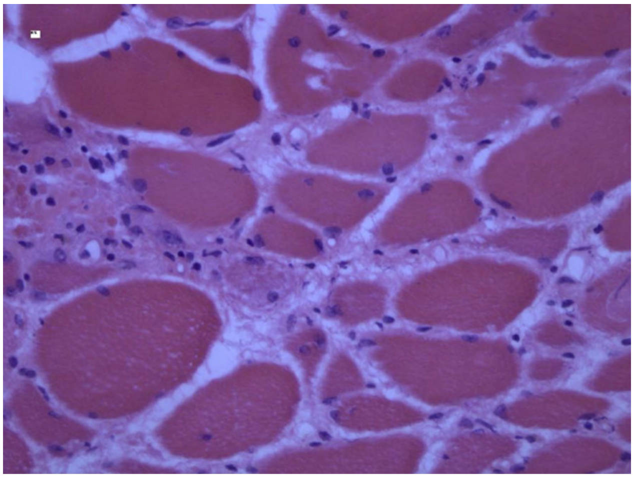

Figure 2. Severe statin-associated necrotizing myopathy with secondary inflammatory infiltrate. This biopsy image is from an 81-year-old man with a creatine kinase (CK) level of 2500 U/L while receiving 60 mg of prednisone daily for 1 month. He received intravenous immune globulin (0.5 g/kg per day for 5 days) 1 month prior to the biopsy. Image provided by Dr Steven K. Baker.

more, once corrected for placebo, the incidence of muscle-related side effects occurring in clinical trial participants falls even further to 190/100,000 or 0.19%.[65] Meta-analysis of 21 double-blind RCTs (total 48,138 patients) revealed a nonsignificant difference in myalgia incidence among those treated with statins vs placebo (relative risk [RR] 0.99, 95% confidence interval [CI], 0.96-1.03).[66] However, subjects on atorvastatin experienced more myalgias than those on placebo (5.1% vs 1.6%, $P = 0.04$; relative difference per 1000 patients 31.9; 95% CI, 2.1-61.6). A larger analysis of 30 RCTs (total 83,858 patients) revealed 49 vs 44 cases of myositis and 7 vs 5 cases of rhabdomyolysis among patients treated with statins vs placebo, respectively.[67] In a review of 20 clinical trials, the prevalence of a myopathy with minor muscle pain was 195 cases per 100,000 patients,[5] while the incidence of rhabdomyolysis was 1.6 cases per 100,000 patient-years. In a review by Wilke et al.,[68] severe statin-induced myopathy, defined by CK > 10 times ULN was determined to affect approximately 0.1% of patients using statin monotherapy. Most recently, the 2010 Cholesterol Treatment Trialists (CTT) meta-analysis observed that the excess of rhabdomyolysis was 4 per 10,000 in the 5 trials of more vs less intensive statin therapy (14 vs 6 cases) compared with 1 per 10,000 in the 21 trials of standard statin regimens vs control (14 vs 9 cases).[69] All excess cases of rhabdomyolysis with more intensive therapy were attributable to 2 trials of 80 mg vs 20 mg simvastatin daily;[69] these 2 trials have also reported definite excesses in the incidence of myopathy with 80 mg simvastatin daily, which has contributed to reduced use of simvastatin 80 mg in clinical practice.

In a cohort study of historical pharmacy and medical data for 215,191 patients exposed to statins,[70] myopathy with mildly elevated serum CK was seen in 640 cases per 100,000 patients, but was reduced to 160 cases per 100,000 patients using a stricter cut point of CK > 1500 U/L or > 10 times ULN. In hospitalized patients with rhabdomyolysis, the incidence of statin-related rhabdomyolysis was about 0.044 per 100,000 patient-years and increased to 0.6 per 100,000 patient-years for combination therapy with a fibrate.[71] The large observational **P**rédiction du **Ri**sque **M**usculaire en **O**bservationnel (PRIMO) study of 7924 French patients exposed to high-dose statins found that 10.5% experienced some type of muscle-related symptom over a 12-month period.[72]

Among voluntary notification databases, the Food and Drug Administration (FDA) Adverse Events Reporting System (AERS) has reported that rhabdomyolysis occurs in statin-treated patients at a rate of 0.70 per 100,000 patient-years.[65] Also, the 2001 FDA AERS rates of fatal rhabdomyolysis were 1 reported case per: 5.2, 8.3 , 23.4, and 27.1 million prescriptions for lovastatin, simvastatin, atorvastatin, and pravastatin, respectively. These low rates starkly contrasted with the rate of 1 reported case of fatal rhabdomyolysis per approximately 316,000 prescriptions of cerivastatin, which was subsequently withdrawn from the market.[73] No case of fatal rhabdomyolysis has yet been reported with fluvastatin.[65] Thus, while rates of myalgia are higher in clinical practice than in clinical trials and the FDA AERS database, the rates of rhabdomyolysis are still reassuringly low (approximately 0.1 to 0.2 per 1000 person-years) and comparable to those reported in clinical trials.[74] Considering all patients using statin therapy, including those using combined therapy,[75] a realistic estimate of severely affected individuals in the United States with CK > 10 times ULN is between 0.2% and 0.5%.[6,73-75] Finally, it is important to bear in mind that there is a host of other problems that may mimic statin-associated myopathy or cause elevation of CK (Table 4).[6]

Neurological effects

Potential neurological concerns of statin use include hemorrhagic stroke, cognitive decline and peripheral neuropathy.

Table 4. Differential diagnosis of myopathy or creatine kinase elevations not due to lipid-lowering therapy

Muscle Symptoms
● Physical exertion
● Viral illness
● Vitamin D deficiency
● Hypo- or hyperthyroidism
● Cushing syndrome or adrenal insufficiency
● Hypoparathyroidism
● Fibromyalgia
● Polymyalgia rheumatica
● Polymyositis
● Systemic lupus erythematosus
● Tendon or joint disorder
● Trauma
● Seizure or severe chills
● Peripheral arterial disease (exertional buttock, thigh, calf symptoms)
● Medications (glucocorticoids, antipsychotics, antiretroviral drugs, illicit drugs [cocaine or amphetamines])
CK Elevations
● Physical exertion
● Hypothyroidism
● Metabolic or inflammatory myopathies
● Alcoholism
● Neuropathy or radiculopathy
● Seizure or severe chills
● Trauma
● Medications (illicit drugs [cocaine or amphetamines], antipsychotics)
● Ethnicity (black patients may have elevated baseline CK levels)
● Idiopathic hyperCKemia (high CK with no demonstrable cause)

CK, creatine kinase.

Reproduced with permission from Joy and Hegele.[6]

The 2010 CTT meta-analysis shows that the RR for hemorrhagic stroke was 1.21 (95% CI, 1.05-1.41) per 1.0 mmol/L low-density lipoprotein (LDL) cholesterol reduction (P = 0.01).[69] However, the absolute size of the potential hazard was approximately 50 times smaller than the definite CV benefits for patients who are at high risk of occlusive vascular events.[69]

By a patient survey-based analysis, 171 patients (34-86 years of age) who self-reported memory or other cognitive problems in a previous statin study were investigated.[76] The findings suggest that cognitive problems associated with statin therapy have variable onset and recovery courses, a clear relation to statin potency and significant negative effect on quality of life. However, the systematic review by Law and Rudnicka concluded that there was no detectable increased risk of cognitive decline.[5] When given in late life to people at risk of vascular disease, statins had no effect in preventing Alzheimer's disease or dementia.[77] In community-dwelling elderly participants (median age, 72 years), 137 who were receiving statins and 411 matched controls, tests of global cognitive performance, frontal-executive function, verbal fluency, and memory were similar in both groups after a median duration of 2 years and after adjusting for confounding variables.[78]

Although raised as a potential adverse effect, the systematic review of Law and Rudnicka showed no detectable increased risk for peripheral neuropathy associated with statin use.[5]

Neuropsychiatric effects and insomnia

Early research suggested that lowering cholesterol concentrations could be associated with an increase in violent or suicidal deaths.[79] Other studies found that both chronically low and medically lowered serum cholesterol were associated with an increased incidence of depression.[80,81] More recently, 8 reports on the effect of statins on 1 or more of 6 mood states, namely depression, anxiety, hostility, fatigue, confusion, and vigour in adults older than 18 years, were reviewed and showed conflicting evidence of any relationship between statins and mood.[82] Another review using an Italian database of spontaneous adverse drug reaction found 5 frequently reported psychiatric events associated with statin use, namely insomnia, somnolence, agitation, confusion, and hallucination, but showed that only insomnia was more frequent for statins compared with all other drugs, while confusion was reported with a lower frequency.[83] A higher prevalence of decreased sleep in hypercholesterolemic patients taking lovastatin as compared with those receiving pravastatin was observed in some clinical trials.[84-86] It has been suggested that these differences may be related to the higher lipophilicity of lovastatin and its ability to cross the blood-brain barrier. However, more recent data do not indicate a significant effect of lovastatin or pravastatin on objective measures of sleep.[87] The findings of a possible risk of sleep disturbance associated with statins that might depend on the ease with which they cross the blood-brain barrier must be confirmed by additional data and, for now, should be interpreted with caution.[83]

Hepatic effects

Hepatotoxicity fears contribute to underutilization of statins and can result in premature discontinuation of a potentially life-saving drug therapy.[88] While many drugs may cause liver disease, the evidence indicates that significant liver pathology attributable to statins is rare.[5] The most commonly reported hepatic adverse effect is the phenomenon known as "transaminitis" in which liver enzyme levels are elevated in the absence of histopathological changes. Although the underlying mechanism remains unclear, it may result from altered lipid components within the hepatocyte membrane, leading to increased permeability and subsequent "leakage" of liver enzymes.[89] In fact, the phenomenon is observed with all classes of lipid-lowering drugs including resins which are not absorbed. Therefore, this effect may be secondary to the lipid-lowering process itself and is not specific to statins. When it occurs, it is usually hepatocellular and only very rarely cholestatic. The incidence of elevated aminotransferase levels (more than 3 times ULN) with different types of statins generally does not exceed 3% of treated patients (Table 5).[90] Indeed, in RCTs reversible dose-related elevations of serum transaminases occur in only 1.2% of patients taking high statin doses.[91] This class effect is usually asymptomatic, reversible, dose-related, similar among all statins, and not correlated to the level of LDL cholesterol (LDL-C) reduction. Most cases of "transaminitis" resolve spontaneously without the need for drug discontinuation. In many large clinical trials, no significant differences were observed when statins were compared with placebo.[89] Thus, when serious hepatotoxicity is encountered in a statin-treated patient, undiagnosed, nonstatin-related liver diseases should be strongly considered in the differential diagnosis.

Table 5. Rates of aminotransferase elevation and drug discontinuation for available statins

Statin	Number of prescriptions written in 2004 (millions)	Incidence of AST or ALT level > 3 times ULN (%)	Rate of discontinuation (%)
Atorvastatin	62.5	0-0.7	NA
Fluvastatin	1.9	1.2	0.6
Lovastatin	7.4	0.6	0.2
Pravastatin	12.0	1.3	0.1
Rosuvastatin	6.3	0	0
Simvastatin	23.8	1.8	0.5

ALT, alanine aminotransferase; AST, aspartate aminotransferase, NA, not available; ULN, upper limit of normal.

Reproduced with permission from Bhardwaj.[90]

In pooled data from 3 randomized trials of pravastatin, with a total of 45,000 person-years follow-up, both gall bladder disorders (186 vs 208 [1.9% vs 2.1%]) and other hepatobiliary disorders (69 vs 89 [0.7% vs 0.9%]) were less common in statin-treated patients than in participants who received placebo.[92] Also, from the United States FDA AERS, Law and Rudnicka estimated the rate of liver failure among patients on statins to be about 0.5 per 100,000 person-years of use, an extremely low incidence that is probably no greater than the risk of liver failure in the general population among persons not taking statins (Table 6).[5,90]

In very rare cases in which true statin-related hepatotoxicity (suggested as an increase in alanine aminotransferase [ALT] level of more than 10 times ULN) has been demonstrated, no characteristic histological pattern of liver injury has been established.[89] Isolated cases of autoimmune hepatitis during statin treatment have been described with variable degrees of severity.[93] Statin-related acute liver failure is extremely unusual and the incidence almost similar to that of idiopathic acute liver failure in the general population.[89,90]

Table 6. Types of liver injury associated with statin use

Type of liver injury	Frequency	Comment
Asymptomatic elevations in aminotransferases	0.1%-3.0%	Dose-dependent; class effect; clinically not significant
Clinically significant acute liver injury	Very rare	May be seen in combination with other medications
Fulminant hepatic failure	Extremely rare (isolated case reports)	It was estimated that risk of fulminant liver failure is 2 per million
Autoimmune hepatitis	Case reports	Statins may induce AIH in genetically susceptible individuals

AIH, autoimmune hepatitis.
Reproduced with permission from Bhardwaj.[90]

Baseline elevation of serum liver enzymes is very frequently associated with dyslipidemia, obesity, and diabetes mellitus, which share features of nonalcoholic fatty liver disease (NAFLD). NAFLD is the hepatic manifestation of the metabolic syndrome and insulin resistance but its natural history is not yet well understood.[94] Some estimates suggest that 1-third of American adults could be affected.[95] Although control of hyperlipidemia with lipid-lowering drugs has been controversial in NAFLD, evidence has begun to accumulate that statins are safe in these patients. Studies in individuals with suspected NAFLD and elevated liver enzyme levels revealed that the incidence and magnitude of liver enzyme elevations in statin-treated patients were not significantly different from those not taking statins.[88,96] The Dallas Heart Study revealed a lack of relationship between statin use and more severe worsening of hepatic steatosis or elevated ALT values.[97] Recent studies suggest that statin treatment may in fact improve liver enzyme levels as well as hepatic steatosis.[98-100] Overall, these results suggest that statins can generally be used safely in patients with NAFLD with appropriate monitoring.

Other chronic liver diseases, such as viral hepatitis (B or C) and/or cirrhosis may also be present in patients requiring statin therapy. Although baseline liver enzymes could be higher in patients with hepatitis C, there was no significant difference in the incidence of mild-moderate to severe increases in liver enzyme levels between statin-treated groups with or without infection.[101] Thus, statins appear to be safe in patients with chronic hepatitis B and C as is the case with stable noncirrhotic or compensated cirrhosis from other causes. However, more extensive hepatic impairment may alter statin pharmacokinetics and metabolism, and may lead to abnormally high serum levels. There has been concern about impaired biliary excretion of statin metabolites in subjects with severe cholestatic liver disease. But recent data suggest that statins are well tolerated in patients with primary biliary cirrhosis (PBC).[101] A retrospective review of 58 statin-treated out of 609 patients with PBC showed no adverse effects over a mean follow-up of 41 months.[102] Thus, although the atherogenicity of the dyslipidemia seen in cholestatic liver disease is debated, patients with CVD or intermediate to high risk of CVD events need not be denied statins with careful monitoring.

Unfortunately, the interactions between alcohol intake and statin treatment have been poorly studied because most randomized trials have excluded patients with excessive alcohol intake (defined as $>$ 21 units per week). This issue commonly presents diagnostic challenges in the follow-up of statin-treated patients.

Current evidence does not support the continued monitoring of liver transaminase values in statin-treated patients and patients with chronic but compensated liver disease can be treated safely with statins.[103] While labelling in Canada still promotes serial testing of liver enzymes for at least up to a year and regularly thereafter, it is notable that current US statin labelling now recommends monitoring of liver transaminase values only at baseline and at the time of dose increases or when symptoms warrant.[104]

Renal effects

Reports of rosuvastatin-associated renal effects, largely proteinuria and hematuria, initially caused widespread concern.[64] As a result, submission data for all statins were reviewed by the FDA, which eventually concluded that statins, including rosuvastatin, did not cause renal toxicity.[64] The review, however, did demonstrate that all statins have been reported to be associated with proteinuria and/or hematuria, and that the incidence of these renal findings was low.[64]

It remains unclear if statins are causally associated with hematuria; if so, the mechanism remains unexplained. On the other hand, considerable evidence suggests that statin-associated proteinuria is a benign condition.[105] Albumin uptake in the proximal renal tubule requires receptor-mediated endocytosis, which is partly dependent upon mevalonate.[106] HMG-CoA reductase inhibition with statins leads to reduced mevalonate availability, resulting in reduced albumin uptake in the proximal renal tubule, and resultant proteinuria.[107] This concept is further supported by the observation that coadministration of mevalonate can reverse receptor-mediated endocytosis impairment induced by statin therapy.[108] Thus, proteinuria associated with statins may be a physiologic and benign response, related to altered protein reabsorption rather than an indication of diminished glomerular membrane integrity or frank toxicity.

Further reassurance can be found in the results of large clinical trials with statins. In the Assessment of Lescol in Renal Transplantation (ALERT) trial, the incidence of either graft loss or doubling of serum creatinine did not differ significantly between participants given fluvastatin or placebo.[109] In the recently presented Study of Heart and Renal Protection (SHARP), the combination of simvastatin plus ezetimibe therapy in patients with chronic kidney disease actually reduced CV events, without an associated increase in adverse effects on renal outcomes.[110] In the Deutsche Diabetes Dialyse Studie (4D) study, there was no signal of increased mortality or heightened adverse effects of atorvastatin 20 mg in patients with diabetes and end-stage renal disease.[111] Similar conclusions were made in **A** Study to Evaluate the **U**se of **R**osuvastatin in Subjects **O**n **R**egular Haemodialysis: An **A**ssessment of Survival and Cardiovascular Events (AURORA) using rosuvastatin 10 mg.[112]

In the **J**ustification for the **U**se of Statins in **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study, there was a small, statistically significant increase in glomerular filtration rate (GFR) with rosuvastatin therapy compared with placebo.[3] In a meta-analysis of 13 clinical trials examining the effects of lipid-altering drugs in general on renal function, the conclusion was that lipid-altering therapies may actually pre-

Table 7. Meta-analysis of statin trials and incident diabetes

Study	Proportion of patients with new-onset diabetes (%)		Relative risk, statin vs placebo	95% CI
	Statins	Placebo		
WOSCOPS (*N* = 5974)	1.9%	2.8%	0.69	0.49-0.96
HPS (*N* = 14,543)	4.6%	4.0%	1.14	0.98-1.33
ASCOT (*N* = 7773)	3.9%	3.5%	1.14	0.90-1.43
LIPID (*N* = 7937)	4.3%	4.6%	0.95	0.77-1.16
CORONA (*N* = 3534)	5.6%	5.0%	1.13	0.86-1.49
JUPITER (*N* = 17,802)	3.0%	2.4%	1.25	1.05-1.49
Combined all above (*N* = 57,593)	3.8%	3.5%	1.06	0.93-1.22 (*P* = 0.38)
Combined all above, except WOSCOPS (*N* = 51,619)	4.0%	3.5%	1.13	1.03-1.23 (*P* = 0.008)

ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CI, confidence interval; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; HPS, Heart Protection Study; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; WOSCOPS, West of Scotland Coronary Prevention Study.

Adapted from Rajpathak et al.[118]

serve GFR and decrease proteinuria in patients with renal disease.[113] The **P**rospective Eva**l**uation of Proteinuri**a** and Re**n**al Function in Non-diab**et**ic Patients With Progressive Renal Disease (PLANET) 1 and 2 trials compared atorvastatin 80 mg to rosuvastatin 10 mg and 40 mg in diabetic and nondiabetic patients with pre-existing proteinuria who were receiving concomitant angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[114] Over a period of 1 year, atorvastatin was shown to reduce proteinuria while leaving estimated GFR unchanged whereas rosuvastatin showed no change in proteinuria and a dose-related decrease in estimated GFR. How such changes might impact on progression to dialysis or event outcomes is unknown. The Renal Expert Panel of the National Lipid Association concluded that statins do not cause acute kidney injury (except in a very rare subset of patients who develop rhabdomyolysis), renal tubular or glomerular damage, hematuria or chronic kidney disease and that statins may be safely used in patients with chronic kidney disease, whether or not they are receiving dialysis. Routine monitoring of proteinuria or renal function in statin-treated patients was considered unwarranted.[115]

Diabetes

In an exploratory, prespecified analysis of the **W**est **o**f **S**cotland **Co**ronary **P**revention **S**tudy (WOSCOPS), pravastatin was found to decrease the incidence of new-onset diabetes.[116] In contrast, the JUPITER trial reported 216 subjects using placebo (2.4%) and 270 (3.0%) using rosuvastatin with incident diabetes ($P = 0.01$).[3] An analysis of the characteristics in patients who went on to be diagnosed with diabetes showed an important incidence at baseline of the metabolic syndrome and especially elevated body mass index (BMI). A systematic literature search for randomized statin trials that reported data on incident diabetes was conducted that included 57,593 patients with mean follow-up of 3.9 years during which 2082 incident diabetes cases accrued.[117,118] A small, 13% increase in diabetes (RR 1.13 [95% CI, 1.03-1.23]) with no evidence of heterogeneity across trials, was observed. This estimate was attenuated and no longer significant when the hypothesis-generating WOSCOPS trial was included (RR 1.06 [95% CI, 0.93-1.25]) and also resulted in significant heterogeneity ($P = 0.03$) (Table 7).[118]

This novel finding spurred further investigations on whether statins may alter insulin sensitivity in patients without pre-existing diabetes mellitus. A systematic literature search of trials that reported data on insulin sensitivity/resistance using pravastatin, atorvastatin, rosuvastatin, or simvastatin compared with placebo and/or control, excluding patients with diabetes, was carried out. A total 1146 patients were included, with patients receiving pravastatin in 3 trials, atorvastatin in 5 trials, rosuvastatin in 5 trials, and simvastatin in 5 trials. Pravastatin was found to significantly improve insulin sensitivity whereas simvastatin significantly worsened insulin sensitivity. But when pooled as a class, statins had no significant impact on insulin sensitivity as compared with placebo or control (Fig. 3).[119] Accordingly, these findings have not altered current recommendations for the prevention of CVD in nondiabetic subjects as the vascular benefits markedly outweigh the small increased risk for developing diabetes.[120]

Rheumatologic

Tendinitis, arthralgia, arthritis, and polymyalgia rheumatica (PMR) have been reported in statin users as have tendon ruptures. However such data are often uncontrolled and, thus, the association with statins remains unresolved.[13,121-126] Tendinitis from statins may be due to inhibition of matrix metalloproteinase (MMP)-9 secretion by inhibiting the RhoA/ROCK pathway, thereby providing at least 1 plausible mechanism to explain a potential association.[127] There were 96 cases reported in a 15-year study at 31 sites in France.[126] Sixty percent of the cases occurred within the first year of treatment and some patients who were rechallenged redeveloped tendinitis. However a case control study of 154,000 patients did not show an association between tendon ruptures and statins.[128]

A weak association between statins and hip osteoarthritis has been reported.[129] However, an association with improved bone mineral density and fewer fractures has also been observed.[130] These observations may be the result of confounding, as often patients with elevated cholesterol have a higher BMI resulting in less osteoporosis than individuals with lower BMI. Moreover, a mechanism for statin-mediated bone density change is not known.

Statin use in rheumatoid arthritis (RA) has the potential to interact with drugs such as methotrexate commonly used to modify the progression of RA. Liver enzyme elevation secondary to methotrexate can have cumulative toxicity whereas those due to statins are generally benign and reversible. Thus, in practice it may be difficult to discern which drug is causing the

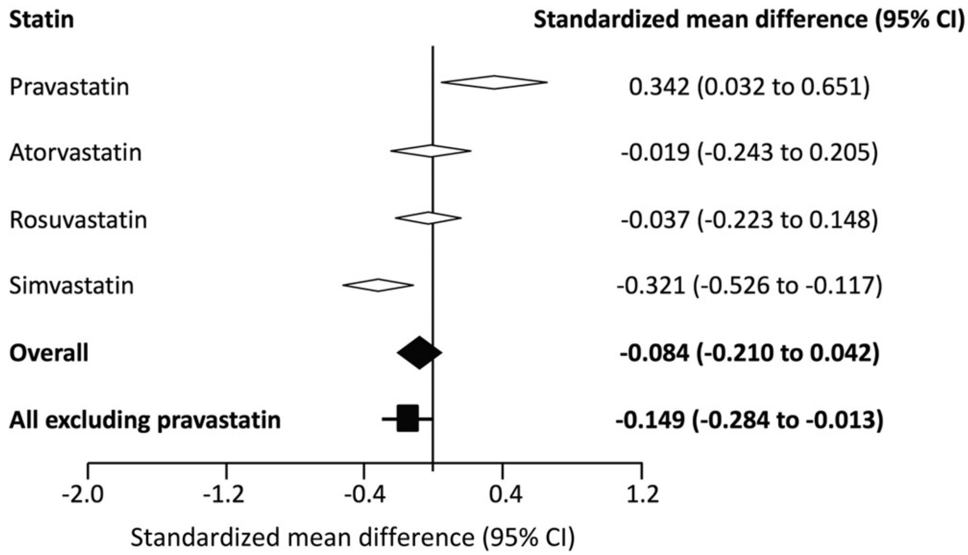

Figure 3. Insulin resistance in large-scale statin trials. Improved insulin sensitivity is implied by values to the right of the line of unity. CI, confidence interval. Adapted from Baker et al.[119]

transaminitis. Also myalgias from statins may mimic a flare of some rheumatic diseases such as PMR, fibromyalgia, or myositis.[12-14,72]

It is important to recognize that there is some evidence suggesting that statins may have added benefits in inflammatory diseases such as RA and systemic lupus erythematosus. These diseases have increased CVD risk beyond what can be explained by traditional CV risk factors.[131-133] In such patients, statins may decrease CVD risk not only by reduction of cholesterol but also by potential anti-inflammatory effects.[134,135] Moreover, statins might prevent or slow the development of RA by reducing inflammatory cell adhesion and monocyte recruitment to endothelial cells, altering smooth muscle migration, improving MMPs, and decreasing interleukin (IL)-6-induced C-reactive protein production.[135] Apoptosis in RA synoviocytes occurs through a mitochondrial and caspase 3-dependent pathway and by inhibition of the geranylgeranyl pathway. There is reduction of class II MHC protein and gene expression by interferon with statins resulting in less T-cell activation. Statins also reduce the production of proinflammatory cytokines (interferon gamma and tumour necrosis factor alpha).[134] One clinical trial adding atorvastatin to standard disease-modifying drugs in RA showed a significant but small improvement in RA.[136] However, a study from a large administrative database did not suggest that statins altered RA activity because they did not affect either the need to initiate or the ability to stop oral steroids.[137] Further research will be required to establish whether statins have a beneficial effect on mechanisms that aggravate RA. But statin use in active RA is relatively low and this is not commensurate with the known, excess CVD risk in RA.[138-140] Accordingly, the potential CVD risk reduction afforded by statins in addition to their possible role in improving, not aggravating, the inflammatory process makes it particularly important to continue statins in such patients unless firm evidence of statin-associated intolerance is documented.

Cancer

The CTT undertook meta-analyses of individual participant level data from RCTs of more vs less intensive statin regimens (5 trials; 39,612 individuals; median follow-up 5.1 years) and of statin vs control (21 trials; 129,526 individuals; median follow-up 4.8 years).[69] The authors found no significant effects on deaths due to cancer or other nonvascular causes (RR 0.97; 95% CI, 0.92-1.03; $P = 0.3$) or on cancer incidence (RR 1.00; 95% CI, 0.96-1.04; $P = 0.9$), even at low plasma LDL-C concentrations.[69] This very large analysis can be considered to provide a definitive final word on the absence of association between statin use and cancer incidence.

Alopecia

Steroid hormones, in particular androgens, influence hair growth in men and women.[141] Statins, by interfering with cholesterol biosynthesis, may theoretically modulate androgen production. Reports of alopecia in statin-treated patients are rare, with an incidence of less than 0.5%-1.0%.[142-147] There are limited data to suggest that statins actually cause alopecia, although there have been several case reports of recurrent hair loss with statins.[148-150] If indeed statins do cause hair loss, statin-induced alopecia should likely be reversible upon drug discontinuation. Reports of alopecia in statin-treated patients may also simply reflect the natural background alopecia incidence rather than representing a true drug effect.

Erectile dysfunction

Erectile dysfunction (ED) commonly occurs in men with multiple CV risk factors or with overt CVD.[151] In fact, ED and coronary heart disease are considered to be manifestations of a common vascular pathology.[151] Approximately 20%-40% of men with metabolic syndrome, diabetes, and CVD have low testosterone levels and hypogonadism.[152] Statins are commonly utilized in such populations, based on overwhelming evidence for CV event reduction. Even though ED is not typically related to low testosterone levels and hypogonadism, especially in the CV patient, it has been theorized that statins, by blocking cholesterol production, may impact adrenocortical function or steroidogenesis, and thus contribute to ED (Fig. 1). Alternately, there is reason to consider that statins may actually improve ED by virtue of their pleiotropic effects, including enhanced nitric oxide-mediated endothelial function.[153] Lipid-lowering therapy per se has also been associated with an improvement in ED,[154] and an enhanced response to phosphodiesterase-5 inhibitors.[155]

Numerous studies have been performed to determine if statins reduce steroidogenesis in a clinically meaningful manner. Available data suggest that pravastatin, fluvastatin, simvastatin, and atorvastatin do not significantly affect adrenocortical or testicular steroidogenesis.[156-162] Studies evaluating the effect of statins on testosterone levels in larger sample sizes have yielded mixed results.[163,164] Population studies, while demonstrating that ED commonly occurs in men eligible for or treated with statins, have not confirmed a causal association.[163,164] In the Scandinavian Simvastatin Survival Study (4S), there was no difference over a period of 6 years between men treated with simvastatin 20 to 40 mg vs placebo in the incidence of sexual adverse experiences.[165]

In summary, there are no objective data to confirm that statins either induce or reverse ED or alter steroidogenesis.

Interstitial lung disease

Fernandez et al. provide a systematic review of rare case publications and of FDA AERS reports of interstitial lung disease felt to be related to statin use.[166] The mechanism underlying this association is unknown but given that so few patients have been identified, it is postulated that the association with statins may be by chance alone or that this lung reaction may require some genetic or other predisposing factors. The authors noted that multiple statins have been associated with this rare reaction and they concluded that, if it is a real association, it would have to be considered a class effect.

Clinical Assessment of Predisposition and Risk Factors for Adverse Effects From Statins

In practice, it is important to have an appreciation of predisposing factors, including drug interactions, which may underlie adverse effects of statins.

Nongenetic risk factors

A survey of nongenetic factors associated with development of statin intolerance was reported in the PRIMO study.[72] Patients in PRIMO developed muscle symptoms after a median of 1 month and ranging up to 12 months after initiation of statin therapy.[72] A commonly reported symptom trigger was unusually heavy physical exertion.[73] Predictors for developing myopathy included a history of: muscle pain with prior lipid-lowering treatment (odds ratio [OR] 10.12; 95% CI, 8.23-12.45; $P < 0.0001$); unexplained muscle cramps (OR 4.14; 95% CI, 3.46-4.95; $P < 0.00001$); prior CK elevation (OR 2.4; 95% CI, 1.55-2.68; $P < 0.0001$); family history of muscle symptoms (OR 1.93; 95% CI, 1.10-3.34; $P = 0.022$), family history of muscle symptoms while using lipid-lowering therapy (OR 1.89; 95% CI, 1.12-3.17; $P = 0.017$); or hypothyroidism (OR 1.71; 95% CI, 1.10-2.65; $P = 0.017$). Interestingly, statin treatment for more than 3 months (OR 0.28; 95% CI, 0.21-0.37; $P < 0.0001$), and antidepressant use (OR 0.51; 95% CI, 0.35-0.74; $P = 0.0004$) were associated with reduced myopathy risk.[65] There is also evidence to suggest that persons with diabetes may be more prone to statin-associated side effects.[167] In contrast to general myopathy, recent evidence suggests that rhabdomyolysis is dose-dependent.[168] Predisposing factors for statin-related myopathy are summarized in Table 8.[6]

Genetic predisposition to statin intolerance

As suggested above, genetic predisposition to statin intolerance can be subdivided into predisposition that stems from carrying rare mutations that are associated with intrinsic muscle diseases or predispositions imparted by common genetic polymorphisms affecting statin drug metabolism or other pathways.[169] Relatively rare genetic disorders that contribute to risk for statin myopathy include inflammatory myopathies, mitochondrial myopathies, inherited autosomal recessive disorders of exercise intolerance, disorders of calcium homeostasis, and amyotrophic lateral sclerosis, to name a few.[169] Among 110 patients with statin myopathy, approximately 10% had rare heterozygous mutations in 1 of several genes that normally cause rare myopathy syndromes,[19] suggesting that genetic susceptibility to statin myopathy may be comprised of a complex mixture of rare DNA variants and common DNA polymor-

Table 8. Predisposing factors for statin-associated myopathy

Endogenous factors
- Advanced age (> 80 years)
- Female sex
- Asian ethnicity
- Low body mass index, small body frame, frailty
- History of pre-existing/unexplained muscle/joint/tendon pain
- History of CK elevation
- Family history of myopathy
- Family history of myopathy with statin therapy
- Metabolic muscle disease (eg, McArdle disease, carnitine palmityl transferase II deficiency, myadenylate deaminase deficiency)
- Severe renal disease
- Acute/decompensated hepatic disease
- Hypothyroidism (untreated)
- Diabetes mellitus
- Genetic polymorphisms of CYP isozymes

Exogenous factors
- High statin dose
- Alcohol abuse
- Illicit drug use (cocaine, amphetamines)
- Antipsychotics
- Drug-statin interactions*
- Fibrates (particularly gemfibrozil)
- Nicotinic acid
- Amiodarone
- Verapamil
- Warfarin
- Cyclosporine
- Macrolide antibiotics
- Azole antifungals
- Protease inhibitors
- Nefazodone
- Large quantities of grapefruit (> 1 quart per day), pomegranate juice (?)
- Surgery with severe metabolic demands
- Heavy and/or unaccustomed exercise

CK, creatine kinase; CYP, cytochrome.
*See Table 11 for mechanisms underlying interactions.
Adapted from Joy and Hegele.[6]

Table 9. Genetic factors associated with myopathy with statin therapy

Gene	Statin	Variant	Outcome
Drug metabolism			
CYP2C8	Cerivastatin	475delA	Rhabdomyolysis
CYP2D6	Fluvastatin	CYP2D6 *3 *5	SI
CYP2D6	Simvastatin	CYP2D6 *4	Myopathy
CYP3A5	Simvastatin	CYP3A5 *1, *3, *5	"Muscle damage"
SLCO1B1	Simvastatin	SNP in intron 11	Mild myopathy, increased CK
SLCO1B1	Multiple	T521C, V174A	Myopathy (except fluvastatin)
ABCB1	Multiple	Various	Elevated statin levels
Muscle metabolism			
COQ2	Multiple	Haplotype	2-fold increase SI
CPT2	Multiple	S113L	Rhabdomyolysis
PYGM	Multiple	R50X	Rhabdomyolysis
AMPD1	Multiple	Q12XþP48L	Rhabdomyolysis
Other pathways			
AGTR1	Multiple	SNP in intron 3	Elevated CK
NOS3	Multiple	D298E	Elevated CK
APOE	Multiple	E4	Reduced compliance

CK, creatine kinase; SI, statin intolerance; SNP, single nucleotide polymorphism.

Adapted from Link et al.,[17] Baker and Samjoo,[51] Fiegenbaum et al.,[170] Frudakis et al.,[171] and Hermann et al.[172]

phisms. The association of these disorders with statin myopathy has been reviewed by Baker and Samjoo.[51]

Common DNA polymorphisms in several genes (Table 9), including those encoding cytochrome (CYP) P450 enzymes, intestinal P-glycoproteins and OATP are inconsistently associated with statin myopathy.[17,170-173] DNA polymorphisms of genes involved in metabolism of coenzyme Q_{10} and serotonin pain receptors were also inconsistently associated with statin myopathy.[42,174,175] The above-mentioned DNA polymorphism in the *SLCO1B1* gene encoding OATP1B1 was strongly associated with simvastatin-associated myopathy defined as CK $>$ 10 times ULN,[17] but this association was not seen in patients with atorvastatin-associated myopathy.[173] The role of common genetic polymorphisms in predisposing to serious statin myopathy is a subject of intense interest, but at present there is insufficient data to warrant pharmacogenetic testing of patients to determine such risk. Simple measures, such as avoiding the 80-mg dose of simvastatin may be as cost-effective at present as performing the genetic test to identify the approximately 1% of homozygotes who have a high relative, but not necessarily absolute, increased risk of developing severe myopathy. Accordingly, genetic testing at this time for either preventing or managing statin intolerance or for selecting statin drug choices is not endorsed.

Clinical pharmacology of HMG-CoA reductase inhibitors and drug interactions

Understanding, preventing, and managing statin side effects in some patients is markedly enhanced by an appreciation of the basic pharmacology of this class of drugs. By blocking HMG-CoA reductase, statins prevent the downstream production of ubiquinone and prenylated isoprenoids, of which the latter are required for normal skeletal muscle function (Fig. 1).[16] Reduced ubiquinone levels are associated with mitochondrial dysfunction, noted in statin myopathy.[25] Dysprenylation of signal transduction molecules and altered glycosylation of membrane proteins may deprive muscle fibres from growth signals rendering them susceptible to mechanical stress.[176]

Many drugs, including some statins, are metabolized by the CYP P450 enzymes. The CYP P450 superfamily is a large and diverse group of enzymes, the function of which is to catalyze the oxidation of organic substances. The CYP 450 enzymes are primarily membrane-associated proteins, located either in the inner membrane of mitochondria or in the endoplasmic reticulum. CYPs metabolize thousands of endogenous and exogenous chemicals. Statins are differentially metabolized by the P450 enzyme system—a factor that may provide some guidance to clinicians in cases of statin intolerance.[177]

Simvastatin, lovastatin, and atorvastatin are metabolized by CYP3A4 (simvastatin is also metabolized by CYP2C8); their plasma concentrations, and therefore risk of myotoxicity, are greatly increased by strong inhibitors of CYP3A4 (eg, itraconazole and ritonavir). Weak or moderately potent CYP3A4 inhibitors (eg, verapamil and diltiazem) can be used cautiously with lower doses of CYP3A4-dependent statins. Fluvastatin is metabolized by CYP2C9. The exposure to fluvastatin is increased by less than 2-fold by inhibitors of CYP2C9. Pravastatin, rosuvastatin, and pitavastatin (the latter not available in Canada at this time) are excreted mainly unchanged, and their plasma concentrations are not significantly increased by pure CYP3A4 inhibitors (Table 10).[177] Cyclosporine inhibits CYP3A4, P-glycoprotein (multidrug resistance protein 1), OATP1B1, and some other hepatic uptake transporters. Gemfibrozil and its glucuronide inhibit CYP2C8 and OATP1B1. These effects of cyclosporine and gemfibrozil explain the increased plasma statin concentrations and, together with pharmacodynamic factors, the increased risk of myotoxicity when coadministered with statins. Inhibitors of OATP1B1 may also decrease the efficacy of statins by interfering with their entry into their primary site of action, namely the hepatocytes. Interactions may also occur between enzyme inducers and CYP3A4 substrate statins, as well as between gemfibrozil and CYP2C8 substrate antidiabetic agents (Fig. 4 and Table 11). Knowledge of the pharmacokinetic and pharmacodynamic properties of lipid-lowering drugs and their interaction mechanisms helps to avoid adverse interactions, without compromising therapeutic benefits.[178,179]

Prevention of Statin Intolerance

There are several measures that healthcare providers and their patients can take to reduce the risk of statin intolerance. These include comprehensive pretreatment assessment, patient counselling, and ongoing monitoring.

Pretreatment assessment

Before prescribing a statin, the clinician should first conduct a thorough pretreatment assessment, including a comprehensive personal and family history, a physical examination, and appropriate laboratory investigations. The indication for statin use to address the specific dyslipidemia and/or to lower CVD risk should be concordant with current guidelines and should be well documented in the patient record.[120] Items from lists of endogenous and exogenous risk factors for adverse effects that are relevant to the patient must be considered (Tables 4 and 8). Signs of muscle disease, wasting, or frailty may indicate an enhanced potential for statin-associated muscle side effects.

Table 10. Pharmacokinetics of statins

Parameter	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Cerivastatin	Atorvastatin	Rosuvastatin
CYP450 metabolic pathway	CYP3A4	None	CYP3A4 > CYP3A5	CYP2C9 > CYP3A4 > CYP2C8	CYP3A4 > CYP2C8	CYP3A4	< 10% via CYP2C9, CYP2C19
Other metabolic pathways	–	Sulfation	–	–	–	–	–
Bioavailability (%)	<5	18	<5	19-29	60	12	20
Absorption (%)	30	34	60-80	98	98	30	Rapid
Lipophilicity	Yes	No	Yes	Yes	Yes	Yes	No
Elimination half-life (h)	2.9	1.3-2.8	2-3	0.5-2.3	2.1-3.1	15-30	20.8
Urine excretion (%)	10	20	13	5	30	2	10
Fecal elimination (%)	83	70	58	95	70	98	90

Cerivastatin is no longer marketed.
CYP, cytochrome.
Adapted from Neuvonen et al.[177]

One should also obtain baseline levels of CK and liver enzymes so that subsequent abnormalities can be evaluated and explained rationally for the patient. Abnormalities in either of these tests before therapy should raise the suspicion of underlying illnesses, not just the potential for statin-related adverse effects. Thyroid-stimulating hormone should also be measured as hypothyroidism is both a risk factor for statin myopathy as well as a secondary cause of elevated LDL-C. Baseline urinary protein is worth measuring in order to exclude nephrotic syndrome as a cause of secondary dyslipidemia. A baseline creatinine (and/or estimated GFR) should be documented because some renal-excreted statins may require dose adjustments (Table 10) and significant renal dysfunction is considered to increase the risk of adverse effects. Atorvastatin and pravastatin do not require dose adjustment in renal insufficiency.

Counselling

Once a decision is made to begin statin therapy, clinicians should inform their patients about the possibility of statin-associated side effects, emphasizing the fact that these drugs are usually well tolerated by the great majority of people using them. One should mention the likely time course of such effects (eg, early vs late side effects) and explain which are transient effects that can be expected with most medications. There is generally no harm in stopping statins transiently in the nonacute situation. Thus, patients should be advised to stop medications if significant systemic symptoms or significant muscle-related symptoms arise and to call the prescribing physician who may wish to obtain blood tests while the patient is symptomatic.

Monitoring

Monitoring the effect of statin therapy on parameters indicative of lipid-lowering efficacy is generally performed at 6-12 weeks. The degree of lipid-lowering achieved is not generally correlated with the likelihood of emergence of symptoms. Because of the rarity of serious adverse events, some advocate no routine monitoring of CK and ALT/aspartate aminotransferase. However, in practice, the public consciousness about adverse effects and the commonness of symptoms such as myalgia suggests that it is prudent to measure CK and ALT/aspartate aminotransferase at 6-12 weeks, usually at the time of a repeat lipid assessment. Patients should be asked to avoid unaccustomed or severe physical exertion, particularly resistance exercises, for a few days prior to testing. This testing provides reassurance to many patients and also establishes a "new baseline" for these biomarkers during statin therapy (see Figures 5 and 6). Over the longer term, these laboratory tests may not be necessary on a routine basis in asymptomatic patients (see Figures 5 and 6).

Diagnosis of Statin Intolerance

A diagnosis of statin intolerance should be entertained only when a patient reports symptoms associated with use of a statin (with or without abnormal laboratory findings), symptoms resolve when the statin is stopped, and the symptoms recur with the same or a different statin. These obvious and axiomatic criteria, however, are seldom met in clinical practice. Consequently, many who need treatment go without it. A further consequence is that of a skewed perception of statin-

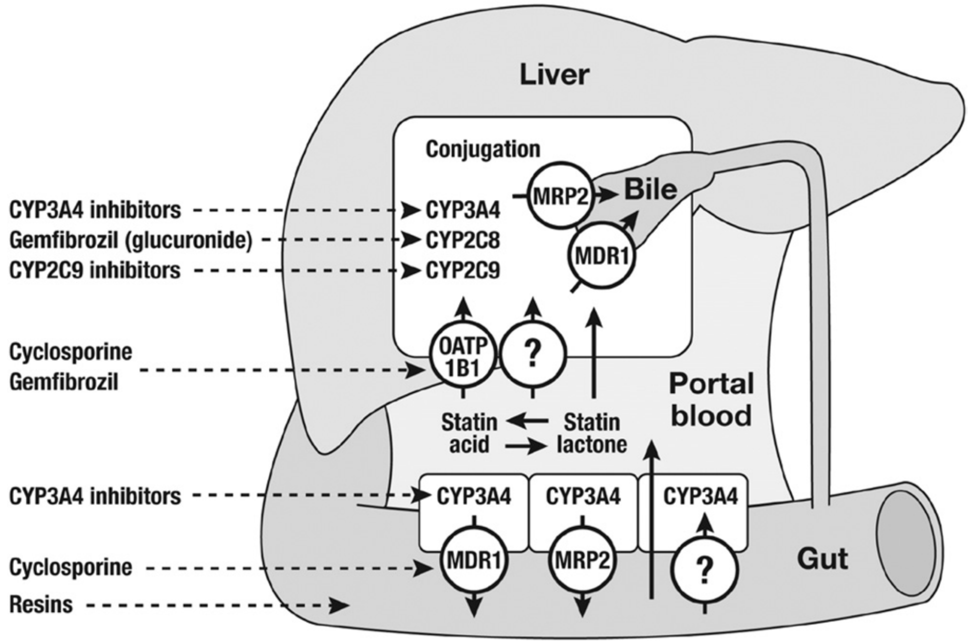

Figure 4. Sites of interactions affecting pharmacokinetics of statins. In addition to inhibitors, inducers can also change the activity of cytochrome (CYP) enzymes and transporters. The question marks indicate other uptake transporters, (eg, OATP2B1 in the gut wall and OATP1B3, OATP2B1, and sodium-dependent taurocholate cotransporting polypeptide in the hepatocyte). MDR1, multidrug resistance protein 1 (P-glycoprotein); MRP2, multidrug resistance associated protein 2; OATP, organic anion transporting polypeptide. Reprinted by permission from MacMillan Publishers Ltd: *Clinical Pharmacology and Therapeutics,* Neuvonen et al.,[177] © 2006.

associated side effects by both healthcare providers and patients. The application of these criteria is particularly important to consider when evaluating the less common and poorly founded adverse effects discussed above, such as insomnia or ED. Special considerations for the more common effects pertaining to muscle and liver, however, are emphasized below.

Among the major difficulties in making a diagnosis of statin-induced myalgia are the lack of specific biomarkers and the high background prevalence of muscle symptoms, irrespective of medication. Careful history taking, rechallenge with medications and the elimination of other causes are essential in making a diagnosis. Ruling out common causes of elevated CK is essential (see Table 4).[6] Clinical circumstances will often allow the identification of concomitant conditions predisposing to myopathy. In more severe or less obvious cases, an electromyogram and/or muscle biopsy may be required. Table 8 outlines some of the risk factors identified in statin-associated myopathy, which should be addressed before making a diagnosis of statin-induced myopathy. Heavy physical exertion and hypothyroidism are relatively easy to identify, but more advanced examination and imaging techniques are required if, for example, radiculopathies or spinal cord compression syndromes are suspected. Myopathies secondary to metabolic causes or inflammation may be exacerbated by statin treatment and these occurrences warrant referral to a specialist.

Table 11. Select drug-statin metabolic interactions

Type of interaction	Examples of drugs
Inhibition of CYP3A4	● "Azole" antifungals: itraconazole, ketoconazole, miconazole ● Macrolide antibiotics: erythromycin, telithromycin, clarithromycin ● Protease inhibitors: amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir ● Fibrates: gemfibrozil, bezafibrate, fenofibrate, ciprofibrate ● Verapamil, diltiazem ● Warfarin
Inhibition of CYP2C9	● Amiodarone ● Omeprazole
OATP1B1	● Gemfibrozil ● Cyclosporine
Various mechanisms	● Digoxin ● Colchicine ● Niacin

CYP, cytochrome; OATP, organic anion transporting polypeptide.
Adapted from Neuvonen et al.[177]

Therapy for Statin Intolerance

For patients who demonstrate actual intolerance to statin therapy, there are several therapeutic options that may be considered, including the use of different or lower dose statins. Additionally, nonstatin alternatives or adjuncts for lowering LDL-C may be warranted. Interventions to alleviate the symptoms of myalgia while continuing to take statins have also been considered.

Dietary and health behaviour measures

Dietary and health behaviour measures constitute the cornerstones of cholesterol management and must be emphasized repeatedly for all patients with or at risk of CVD and especially for those who are having difficulties with pharmacotherapy. A reduction of dietary fat, especially saturated fat, is generally far more effective than a reduction in dietary cholesterol. Indeed, reducing dietary cholesterol leads to variable change in plasma cholesterol. Subjects who comply with the National Cholesterol Education Program (NCEP) Step 2 diet, namely limiting the daily cholesterol intake to 200 mg, showed no overall significant reduction of plasma LDL-C.[180] However, a range of studies have demonstrated wide variations of LDL-C from no change to a 40%-50% reduction with the same diet.[181] It is well recognized that some individuals are hyperresponders to increased dietary cholesterol and may therefore derive the greatest benefit from a low-cholesterol diet.

Replacing saturated fat and transfats with mono- and polyunsaturated fat reduces plasma cholesterol levels. A diet enriched with both olive oil and sunflower oil that had 12.9% saturated fat, 15.1% mono unsaturated fat, and 7.9% polyunsaturated fat lowered LDL-C by 17.9% compared with a mixed natural diet (19.3% saturated fat, 11.5% mono unsaturated fat, 4.6% polyunsaturated fat).[182] Olive oil or peanut oil supplemented diets with reduced saturated fat intake have similar reductions of LDL-C to the NCEP Step 1 diet without the increase in triglycerides that is sometimes observed.[183]

Increased intake of plant sterols (also known as phytosterols or stanols) reduces plasma LDL-C levels. A meta-analysis of 59 studies showed that LDL-C was reduced by approximately 0.3 mmol/L with a diet enriched with plant sterols.[184] Supplementing the diet with margarine, butter spreads, nuts, leafy vegetables, and breakfast cereals enriched with plant sterols to a dose of 0.4 g taken twice daily, in association with a low saturated fat diet, is likely to provide the greatest benefit in most people.

Viscous fibre such as beta glucans in oats, barley, and psyllium, increases bile acid loss, as well as reduces postprandial hyperglycemia and insulin levels.[185] It may also stimulate reverse cholesterol transport by altering nutrient absorption.[186]

The Portfolio Diet[187] has a very low saturated fat content (based on milled whole wheat cereals and low-fat dairy foods), a high plant sterol level (1.0 g/1000 kcal), soy protein (21.4 g/1000 kcal), viscous fibres (9.8 g/1000 kcal), and almonds (14 g/1000 kcal). The Portfolio Diet compared with a very low saturated fat diet alone, reduced LDL-C 30% over a 4-week period. The LDL-C reduction achieved with the Portfolio Diet is comparable to that achieved with first generation statins, such as lovastatin 20 mg daily.[188]

Health behaviour interventions such as increased physical activity and weight loss are important measures to reduce CV risk. Increased physical activity in conjunction with a low fat and/or cholesterol diet can reduce LDL-C. The NCEP Step 2 diet alone did not reduce LDL-C. However when combined with an exercise program LDL-C was reduced 13% in men and 9% in women.[180]

Weight loss is associated with a modest reduction of LDL-C. A meta-analysis[189] indicates that for every kg of weight loss, total cholesterol, LDL-C, and triglycerides are reduced by 0.05, 0.02, and 0.015 mmol/L respectively. High-density lipoprotein (HDL) cholesterol may also fall in the short-term but if weight loss is maintained HDL increased 0.007 mmol/L per kg loss.

Red yeast rice has become very popular as a "natural" alternative to conventional statin therapy even though the lipid-lowering effect is attributable to lovastatin-like compounds. In a study of 43 patients[190] with a history of statin discontinuation due to myalgias, randomized to red yeast rice at 2400 mg twice daily or pravastatin at 20 mg daily, 5% of the red yeast rice and 9% (difference not significant) of the pravastatin-treated patients discontinued treatment because of recurrent muscle symptoms. Similar reductions of LDL-C were observed with red yeast rice (30%) and pravastatin (27%). In a subsequent randomized placebo-controlled trial with 62 patients intolerant of statins, red yeast rice was shown to lower LDL-C by 1.1 mmol/L compared with 0.28 mmol/L in the patients receiving placebo.[191] No differences were observed in pain severity scores, CK, or liver enzymes in the treatment or placebo groups. Available formulations have widely varying active ingredients that are similar to lovastatin and there is also the potential for toxic by-products. Consequently until red yeast rice products are regulated and standardized, they cannot be recommended as alternatives to statin therapy.[192]

Statin-Based strategies

For the patient who has to discontinue statin therapy because of adverse effects, rechallenge (after resolution of the symptoms) with either the same or lower dose of the same statin, or an alternative statin, is generally recommended. This step is critical for both diagnosis of statin intolerance and for aiding in the formulation of alternate treatment plans and yet it is seldom pursued in clinical practice. Moreover, this strategy is the most likely to result in the greatest, sustained reduction of LDL-C than alternatives.

Fluvastatin XL 80 mg daily (as a slow release preparation) was tolerated in 97% of patients with prior statin intolerance due to muscle related symptoms and LDL-C was reduced 32.8%.[193] Tolerable MRSEs developed in 17% of these patients. It is possible that fluvastatin is well tolerated as it is not a CYP P450 3A4 or glucuronidation substrate and it has low lipophilicity which slows entry into muscle cells. However, patients were not rechallenged initially with the statin purported to have caused the adverse effect and so some of the initial, reported intolerance may not have been true intolerance.

In another study, 57% of patients intolerant of usual dose statins were able to tolerate simvastatin 0.825-8.75 mg daily.[194] Of these patients 30% had some degree of muscle pain. Low-dose simvastatin reduced LDL-C by 26% and of the patients able to tolerate the statin, 20% achieved LDL-C $<$ 2.5 mmol/L.

Several groups have evaluated altered rosuvastatin regimens for statin-intolerant patients.[195-198] In 1 study of 61 patients with statin intolerance (50 with myalgia), all but 1 patient were able to tolerate rosuvastatin 5-10 mg daily. Both doses reduced LDL-C by 42%.[195] Reduced frequency dosing with rosuvastatin was also reviewed in a retrospective analysis that included 51 patients with statin intolerance (76% due to myalgia). Alternate-day rosuvastatin at a mean dose of 5.6 mg was tolerated in 72.5% of patients. LDL-C was reduced 34.5% by this regimen.[196] A retrospective analysis of 7 patients treated with 5 mg or 10 mg alternate-day dosing of rosuvastatin revealed an LDL-C reduction of 25.9% and 37.9%, respectively.[197] Finally, once-weekly dosing of rosuvastatin 5-20 mg has also been reported among 10 patients with statin intolerance.[198]

LDL-C was reduced 29% (range 6%-62%) in the 8 patients who were able to tolerate the weekly dosing.

Nonstatin alternatives and adjuncts

Ezetimibe. Ezetimibe acts by directly inhibiting the cholesterol transporter Niemann Pick C 1-like 1 (NPC1L1) located primarily in brush border of the proximal small bowel.[199] It significantly reduces absorption of both dietary and biliary cholesterol resulting in lower LDL-C. It is associated with relatively low circulating levels and overall low incidence of adverse reactions. As monotherapy, ezetimibe 10 mg daily reduces LDL-C on average by about 15%-20% but a large variability in efficacy has been reported.[200]

Athyros et al. examined the safety and efficacy of combining daily 10 mg ezetimibe with twice-weekly atorvastatin for high risk individuals who could not tolerate daily atorvastatin as monotherapy.[201] Of the 56 subjects enrolled in the study, treatment with ezetimibe 10 mg daily was well tolerated, with only 2 withdrawals. A mean 20% reduction of LDL-C was achieved at 12 weeks. Addition of atorvastatin 10 mg twice weekly was also well tolerated; only 3 additional subjects withdrew the treatment by the end of the 12-week study period. The combination of ezetimibe and nondaily atorvastatin resulted in a mean LDL-C reduction of 37% from baseline. There was no increase in CK levels or transaminases when compared with the baseline.

In subjects with a history of MRSEs with a variety of statins, Stein et al. randomized 199 medium- to high-risk dyslipidemic subjects to: (1) fluvastatin XL 80 mg daily alone, (2) ezetimibe 10 mg daily alone, or (3) fluvastatin XL 80 mg per day plus ezetimibe 10 mg per day for 12 weeks in a double-blind, double-dummy trial.[202] Mean baseline LDL-C levels were 4.58, 4.63, and 4.55 mmol/L respectively. Fluvastatin XL lowered LDL-C by 32.8% compared with 15.6% with ezetimibe ($P < 0.0001$); the fluvastatin XL/ezetimibe combination lowered LDL-C by 46.1% (between-group difference vs ezetimibe −30.4%, $P < 0.0001$). Proportions of patients achieving their target LDL-C were 84% with the fluvastatin XL/ezetimibe combination, 59% with fluvastatin XL, and 29% with ezetimibe. MRSEs were the most frequent type of adverse event, overall reported in 37 patients (19%) and of mild to moderate intensity in most cases. MRSEs led to study discontinuation in 5 patients (8%) given ezetimibe, 3 patients (4%) given fluvastatin XL, and 2 patients (3%) given fluvastatin XL and ezetimibe. In a Kaplan-Meier analysis of time to first MRSE there was no indication for an increased risk of MRSE recurrence with fluvastatin XL. Differences in recurrence of MRSEs were not statistically different between treatment groups but tended to be lower in patients on fluvastatin XL and ezetimibe combination therapy (hazard ratio, 0.52; 95% CI, 0.23-1.19) compared with patients receiving ezetimibe monotherapy.

Ezetimibe and colesevelam (a bile acid sequestrant similar to cholestyramine but not yet available in Canada), representing 2 nonstatin drugs with different mechanisms of action, were also tested for their efficacy and safety either alone or in combination in a small cohort of patients either intolerant to statin or refusing to use statin drugs.[203] Patients were initially randomized to either ezetimibe 10 mg daily or colesevelam 1.875 g twice daily for 6 weeks before the alternate agent was added for an additional 6 weeks. The second agent was then withdrawn and the patient maintained on the original dose for another 6 weeks. Colesevelam and ezetimibe monotherapy resulted in a 23% and 26% reduction in LDL-C from their respective baselines. Combination therapy with colesevelam or ezetimibe resulted in an additional reduction in LDL-C and non-HDL-C levels of approximately 20% ($P < 0.005$) and 16% ($P < 0.01$), respectively, compared with monotherapy with either agent. This suggests that combining drugs that work primarily in the intestine can be considered in statin-intolerant patients.

Niacin. Niacin at daily doses from 500 to 2000 mg lowers not only LDL-C but also effectively lowers triglycerides and raises HDL-C.[204] Niacin decreases the hepatic secretion of very LDL (VLDL) from the liver and decreases free fatty acid (FFA) mobilization from the periphery. However, the high incidence of flushing remains the major cause for withdrawal of this drug. Skin flushing can be attenuated by taking aspirin 325 mg (uncoated) 30 minutes prior to the niacin. Some practitioners advocate ingestion with meals, or yogurt or applesauce and avoidance of spicy meals and excess alcohol during the early weeks of use after which most flushing abates. An escalating dose schedule of available niacin preparations to reach the full dose in several weeks rather than starting with the full dose can improve tolerability. Some patients try to use over the counter "no flush" preparations but these are generally ineffective and also impart a risk of hepatotoxicity. Similarly, older, slow-release niacin had less flushing and the advantage of a once- or twice-daily dosing schedule but these were more hepatotoxic. More modern, extended-release forms of niacin, including Niaspan (1-2 g per day) (Abbott Laboratories, Abbot Park, IL, USA) increase tolerability and decrease the side effect profile of the drug. A specific inhibitor of flushing (laropiprant) has been formulated together with niacin in a single pill and is undergoing clinical trials.[205] Other side effects of niacin include hepatotoxicity, hyperuricemia, hyperglycemia, gastritis, and acanthosis nigricans all of which require monitoring during chronic therapy.

Several trials have shown clinical event reduction with niacin as monotherapy. The Coronary Drug Project demonstrated niacin's ability to reduce mortality in patients with previous history of myocardial infarction.[206] Niacin therefore represents a strong candidate as an alternate for statins. This status may be further bolstered by the results of the **A**therothrombosis **I**ntervention in **M**etabolic Syndrome with Low **H**DL/High Triglycerides and **I**mpact on **G**lobal **H**ealth Outcomes (AIM-HIGH) and the **T**reatment of **H**DL to **R**educe the **I**ncidence of **V**ascular **E**vents HPS2 (THRIVE) studies that examine the effects of niacin on CVD prevention in addition to statin therapy. Results are expected in 2012-2013.

Fibrates. Fibrates act as a ligand to the peroxisome proliferator-activated receptor (PPAR)α receptor and lower plasma triglyceride and raise HDL-C primarily through coordinated upregulation of lipoprotein lipase, inhibition of apolipoprotein C3 and upregulation of apolipoprotein AI. Fibrates also have a modest LDL-C lowering effect either as monotherapy or in combination with other agents.

Three derivatives of fibric acid are currently available. Gemfibrozil is used at a dosage of 600 mg twice daily and is indicated in cases of hypertriglyceridemia and in the secondary prevention of CVD in patients with low HDL-C levels. Fenofibrate is used to treat hypertriglyceridemia and combined hyperlipoproteinemia. The dosage is 200 mg per day; a new formulation is available to allow dosage from 48 mg (especially in cases of renal failure) to 160 mg per day. Bezafibrate is available as a slow release preparation at 200-400 mg daily. It is the first pan-PPAR (alpha, delta, and gamma) agonist.[207] In addition to its effectiveness in triglyceride lowering and raising of HDL-C, it has also been shown to improve insulin resistance and beta cell function in diabetic subjects,[208] while reducing the incidence of new-onset diabetes in obese subjects.[209]

There is evidence for CVD risk reduction with fibrate therapy. Gemfibrozil as monotherapy was used in the **V**eterans **A**ffairs **H**igh-Density Lipoprotein Cholesterol **I**ntervention **T**rial (VA-HIT) in men with a history of myocardial infarction and with HDL-C $\leq$ 1.0 mmol/L, LDL-C $\leq$ 3.6 mmol/L and triglyceride $\leq$ 3.4 mmol/L. Significant reduction of CVD was seen, including in persons with diabetes and also in the subgroup with metabolic dyslipidemia (high triglycerides and low HDL-C).[210] The ability of fenofibrate as monotherapy to reduce CVD was tested in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial. Although fenofibrate treatment did not result in a significant reduction in the primary outcome when compared with placebo, post hoc analysis revealed that participants who met the criteria for metabolic syndrome showed a nearly significant 5-year CVD risk reduction. Those with metabolic dyslipidemia (triglycerides > 2.3 mmol/L and low HDL-C) were at highest risk of CVD (17.5% over 5 years) and also received the most benefit in risk reduction (27% RR reduction).[211] In the original Bezafibrate Infarction Prevention (BIP) trial (a cohort with history of previous myocardial infarction), bezafibrate therapy failed to significantly reduce the primary end points for the entire cohort.[212] However, subgroup analysis showed that subjects with metabolic syndrome did benefit.[213] A recent 16-year mortality follow-up study showed that the patients allocated to the bezafibrate group experienced an 11% reduction ($P = 0.06$) in total mortality. Furthermore, bezafibrate-allocated patients with an upper-tertile HDL-C response to therapy achieved a significant 22% reduction in risk of death whereas those with a low HDL-C response showed no benefit.[214] A meta-analysis of fibrate studies has shown a decrease in myocardial infarction, but no effect on mortality.[215] In the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the male subgroup with higher triglycerides and lower HDL-C appeared to benefit the most from treatment with fenofibrate.[216]

The side effects of fibrates include rash, gastrointestinal effects (abdominal discomfort, increased bile lithogenicity), ED, elevated transaminase levels, interaction with oral anticoagulants, and elevated plasma homocysteine levels, especially with fenofibrate and, to a lesser extent, with bezafibrate. Because fibrates increase lipoprotein lipase activity, LDL-C levels may increase in patients with hypertriglyceridemia treated with this class of medications. Fibrates, especially gemfibrozil, can inhibit the glucuronidation of statins and thus retard their elimination. For this reason, combination of gemfibrozil with statins is contraindicated.

Bile acid sequestrants. Bile acid sequestrants such as cholestyramine and colestipol noncovalently bind bile acids in the intestine and prevent their enterohepatic recirculation, indirectly resulting in lowering of LDL-C.[217] Bile acid sequestrants generally share the same structure as polymeric compounds belonging to the class of ion exchange resins. They are not well-absorbed from the gut and, along with the bound bile acids, are excreted via the feces.

Use of these agents as monotherapy is expected to reduce LDL-C by approximately 15%. Higher doses of cholestyramine have been shown to reduce LDL-C by up to 30%. But often the use is limited by significant adverse gastrointestinal effects and poor palatability but these can be minimized by a gradual titration.[218] Bile acid binding resins also bind fat-soluble vitamins, such as vitamins A, D, E, and K but frank deficiencies are rare. Because these drugs also interfere with the absorption of other medications, very careful dosing schedules must be implemented. Colesevalam is generally better tolerated because of its greater specificity for bile acids but it is not yet available in Canada.

LDL apheresis. LDL apheresis is a method to selectively remove LDL from either plasma or whole blood using several different techniques, each with remarkably similar LDL-C lowering of 50% to 75%.[219,220] Side effects are uncommon: approximately 4% in a series of over 5000 procedures.[221] Most side effects are minor except for anaphylactoid reactions seen specifically with the dextran sulfate cellulose adsorption procedure in patients taking angiotensin converting enzyme inhibitors. Long-term treatment once to twice weekly has been reported to induce regression of xanthoma and atherosclerotic plaques.[222-224] LDL apheresis is mainly indicated for very high-risk subjects with very high cholesterol levels refractory to all pharmacological treatments.

Emerging therapies. There are a number of cholesterol-reducing therapies that are in development and may become useful for statin-intolerant patients.

Mipomersen (ISIS 301012). Mipomersen is a parenteral phosphorothioate antisense inhibitor of apolipoprotein B. It is thus considered a "biological" medication. By blocking the protein synthesis of apo B in the liver, it prevents the formation of VLDL and LDL particles. In a small, phase II clinical trial, patients were randomized into 4 cohorts, with doses ranging from 50 to 300 mg (4:1 active treatment/placebo ratio). After 6 weeks of treatment, the LDL-C level was reduced by 21% from baseline in the 200-mg per week dose group ($P < 0.05$) and 34% from baseline in the 300-mg per week dose group ($P < 0.01$), with a concomitant reduction in apo B of 23% ($P < 0.05$) and 33% ($P < 0.01$), respectively. Injection site reactions were the most common adverse event. Elevations in liver transaminase levels ($\geq$ 3 times ULN) occurred in 4 (11%) of 36 patients assigned to active treatment; 3 of these patients were in the highest dose group. The authors concluded that mipomersen has an incremental LDL-C–lowering effect when added to conventional lipid-lowering therapy.[225] Thus, mipomersen may prove useful in severe hypercholesterolemia, especially familial hypercholesterolemia, where the response to statins may be absent or insufficient because of a lack of the LDL receptor.[226,227]

CETP inhibitors. The inhibition of cholesteryl ester transfer protein (CETP) by pharmacologic agents mimics the genetic heterozygous CETP deficiency state. Torcetrapib proved toxic and increased mortality, an effect primarily attributed to off-target effects on systemic blood pressure. But 2 other CETP inhibitors, anacetrapib and dalcetrapib, are still undergoing clinical trials. The more buoyant HDL particles induced in patients on these agents appear to promote cellular cholesterol efflux efficiently. Reported side effects include elevation in hepatic transaminase levels but neither dalcetrapib nor anacetrapib increase blood pressure nor alter aldosterone levels, as was noted with torcetrapib. Anacetrapib raises HDL-C by 138% and lowers LDL-C by 40%.[228] Dalcetrapib has little effect on LDL-C. Phase 3 outcome trials with both agents are underway.

PCSK9 inhibitors. Proprotein convertase kexin/Subtilisin type 9 (PCSK9) is a protein secreted by the liver and is involved in recycling the LDL receptor to an endocytic degradation pathway. Thus, excess PCSK9 decreases the number of LDL receptors and, conversely, a decrease in PCSK9, or a lack of function, is associated with increased LDL receptors. Thus, human diseases caused by loss of function of PCSK9 are associated with marked decrease in LDL-C whereas gain of function of PCSK9 is associated with marked increases in LDL-C to levels seen in familial hypercholesterolemia due to defects in the *LDL-R* gene. Several companies have made humanized monoclonal antibodies or antisense oligonucleotides directed against PCSK9. In proof-of-concept experiments, injection of PCSK9 in mice was shown to reduce serum cholesterol.[229] Trials are underway to determine the pharmacokinetics and safety of these agents as a potential adjunct to currently available therapies, especially refractory familial hypercholesterolemia.

Lomitapide. Lomitapide is the first member of a new class of oral medications that inhibit the activity of microsomal triglyceride transfer protein (MTP) and thus reduce the assembly and secretion of apo B containing lipoproteins by up to 80%.[230] Trials are underway to determine the pharmacokinetics and safety of lomitapide as a potential adjunct to currently available therapies. This class of medication may be especially beneficial for homozygous and refractory familial hypercholesterolemia patients, particularly those who are intolerant of statins.

Treatments targeting muscle symptom relief

All the strategies discussed so far have the dual goal of reducing adverse symptoms while still lowering cholesterol. There are several modalities that have been investigated as purely symptomatic therapies for patients experiencing muscle symptoms while taking statins.

Coenzyme Q_{10}. Coenzyme Q_{10} is an important cofactor for mitochondrial electron transport and oxidative phosphorylation. Ubiquinone and cholesterol are synthesized from mevalonate which is formed from HMG-CoA by the action of HMG-CoA reductase (see Fig. 1), the enzyme inhibited by statin drugs. Consequently, coenzyme Q_{10} depletion has been considered as a possible cause of MRSEs of statin therapy and a target for symptomatic relief. But clinical trials with coenzyme Q_{10} in patients with MRSEs have shown mixed results. A study with 32 patients[231] intolerant of statin treatment due to myopathic symptoms randomized to either coenzyme Q_{10} 100 mg daily or vitamin E, showed that coenzyme Q_{10} reduced pain severity 40% ($P < 0.001$) whereas no benefit was observed with vitamin E. In another study[232] of 44 statin-intolerant patients coenzyme Q_{10} 200 mg did not permit patients to tolerate reinitiation of simvastatin more often than placebo. A systematic review[233] concluded that there was insufficient evidence to prove there was an etiologic role of coenzyme Q_{10} deficiency in statin-associated myopathy or a role of supplementation for pain relief. The group did not support use of this intervention at this time but many patients remain resistant to this advice.

Vitamin D. Vitamin D has been suggested as a treatment to relieve statin-induced myalgia. Of 128 patients with myalgia and 493 subjects using statin treatment without myalgia, vitamin D levels were the same.[234] But in 38 vitamin D-deficient patients given vitamin D 50,000 U per week for 12 weeks there was resolution of myalgia in 92%. A placebo-controlled trial is needed to decide the true value of vitamin D for relief of statin myalgia.[235] It should be noted that severe Vitamin D deficiency is associated with intrinsic, nonstatin related muscle disease (Table 4).

Vitamin E. Vitamin E was shown to have no value for pain relief in 1 controlled trial.[231] Tonic water and minerals (eg, magnesium) have been used to relieve various muscular symptoms and night cramps however no adequate clinical trials in the setting of statin-induced myalgia have been conducted.[236,237]

Thus, there is currently no strategy solely targeting the relief of muscle symptoms while taking statins that can be recommended definitively. Management of this side effect generally requires consideration of intensification of dietary and health behaviour interventions in conjunction with changes in the lipid-lowering medications themselves.

Management Approach for Muscle Symptoms or HyperCKemia

This management scenario can be broadly divided into those patients who have muscle symptoms and those who have asymptomatic elevation of CK (Fig. 5). The ultimate goal is to achieve lipid-lowering with minimal or no symptoms of myalgia and with either normal or mild hyperCKemia (CK $\leq$ 10 times ULN). The following recommendations use terminology pertaining to subjects with a normal, baseline CK. High CK prior to initiation of therapy may be seen in patients with idiopathic hyperCKemia, patients of African descent, or habitual, heavy exercisers (see Table 4). The general principles are the same for patients with these benign, asymptomatic, and chronic forms of elevated CK but any changes in CK after initiation of statin should be considered with respect to the patient-specific baseline CK.

Any symptom of muscle pain and/or weakness justifies the diagnosis of "myopathy." But if the CK is $\leq$ ULN, then this is generally termed "myalgia." As there is no definitive evidence that statin-induced myalgias predispose to subsequent or more severe muscle side effects, the decision to discontinue the statin should be patient-driven according to tolerance. In general, if symptoms are more than minor or not easily tolerated, the

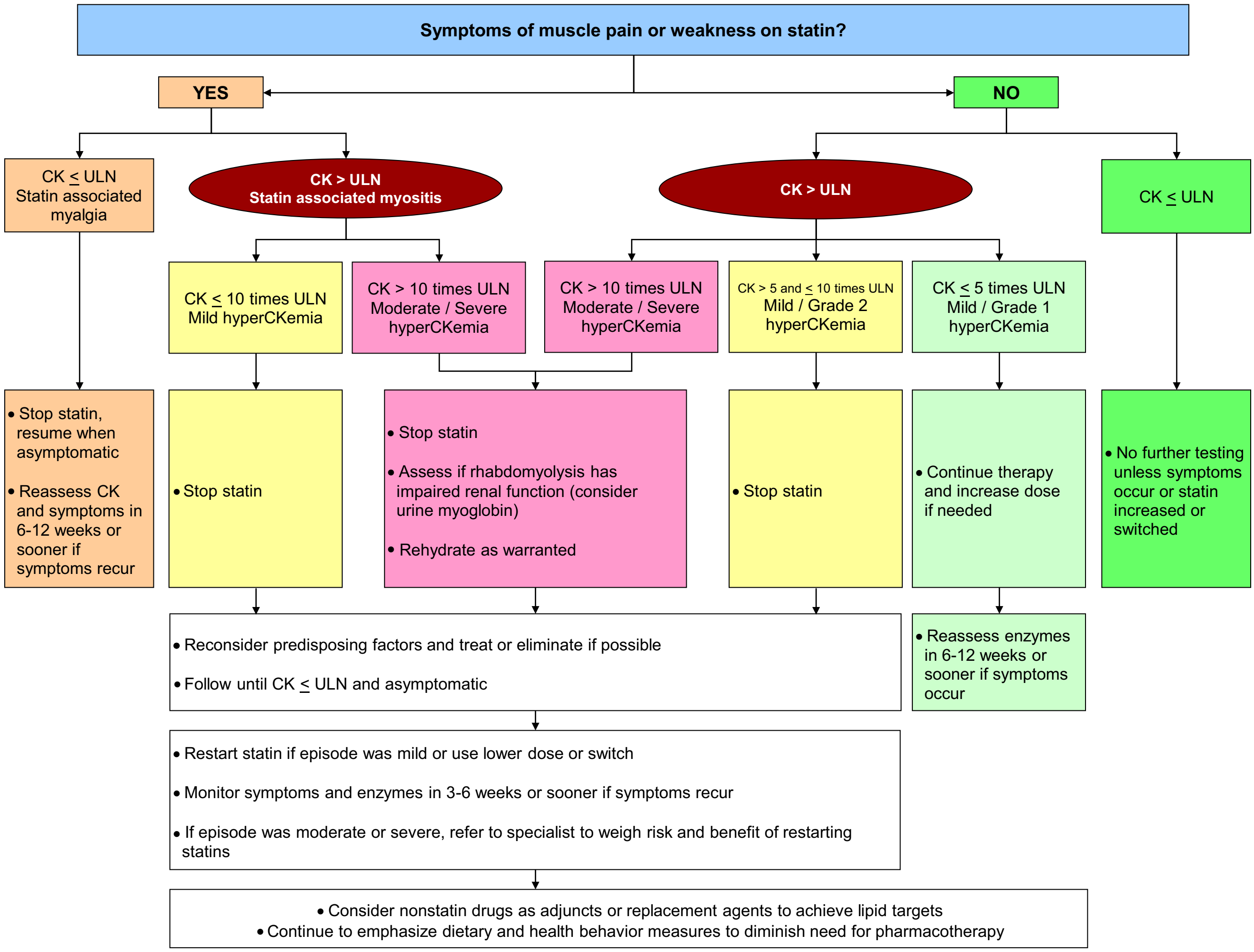

Figure 5. Management approach for muscle symptoms or hyperCKemia. CK, creatine kinase; ULN, upper limit of normal.

statin should be stopped until the patient is asymptomatic and then the same drug at the same dose should be restarted. Symptoms and serum CK should be reassessed at 6 to 12 weeks or sooner if the symptoms recur. Recurrence is suggestive of a statin intolerance and lower dose statin strategies using the same drug should be considered. Failure with this option would solidify intolerance for that specific statin. Alternatively, the statin can be switched and the patient followed as outlined above. Failure to identify a tolerated statin at a tolerated dose is unusual. If a statin cannot be used or if the amount of statin that is tolerated does not achieve adequate lipid-lowering, then the statin should either be replaced or supplemented with a nonstatin class of lipid-lowering agent.

If a symptomatic patient has a CK that is > ULN then this patient is considered to have "myositis." If the CK is ≤10 times ULN, the statin should be stopped, risk factors for statin adverse effects should be reevaluated (eg, addition of new drugs) and eliminated or treated if possible (see Tables 4 and 8). When the patient is asymptomatic with a normal CK, lower dose statin strategies and/or a statin switch should be considered. Follow-up should occur within 3 to 6 weeks or sooner to evaluate both symptoms and CK levels.

If a symptomatic patient has a CK that is > 10 times ULN then rhabdomyolysis must be considered and the statin must be stopped. Reassessment of possible reasons should be considered as above but, in addition, careful assessment of hydration status and renal function is required and any abnormalities should be treated accordingly. A urine myoglobin may be considered under these circumstances. Once recovered fully, lipid therapy with lower dose strategies as outlined for the patient with "myositis" should be considered after weighing the severity of the episode and the benefits and risks of statin resumption. However, this should be undertaken by a specialist familiar with these complications and their treatment. Close follow-up of CK and symptoms will be required on at least a monthly basis for 3 to 6 months or with any dose change or statin switch.

Patients who are asymptomatic at their first follow-up and with a CK ≤ ULN require no further CK testing unless the dose or the statin is changed. If the CK is > ULN but < 5 times ULN, the patient can be considered to have mild/grade 1 hyperCKemia. Statin therapy should be continued and even intensified if necessary and both symptoms and CK should be re-evaluated at 6 to 12 weeks. Normalization or stability of CK may be noted at the next visit in which case therapy can be continued and further CK testing is not warranted unless symptoms arise. If symptoms arise, CK should be measured and managed accordingly as outlined above.

Asymptomatic patients with a CK ≥ 5 times ULN and ≤ 10 times ULN can be considered to have mild/grade 2 hyperCKemia. The statin should be stopped and the patient re-assessed in 6 to 12 weeks or until the hyperCKemia resolves. At that point, the same statin at a lower dose should be restarted. Symptoms and CK should be re-assessed in 6 to 12 weeks or sooner if symptoms occur.

An asymptomatic patient with a CK > 10 times ULN can be considered to have at least moderate hyperCKemia warranting cessation of the statin and evaluation of hydration and renal function as described for rhabdomyolysis.

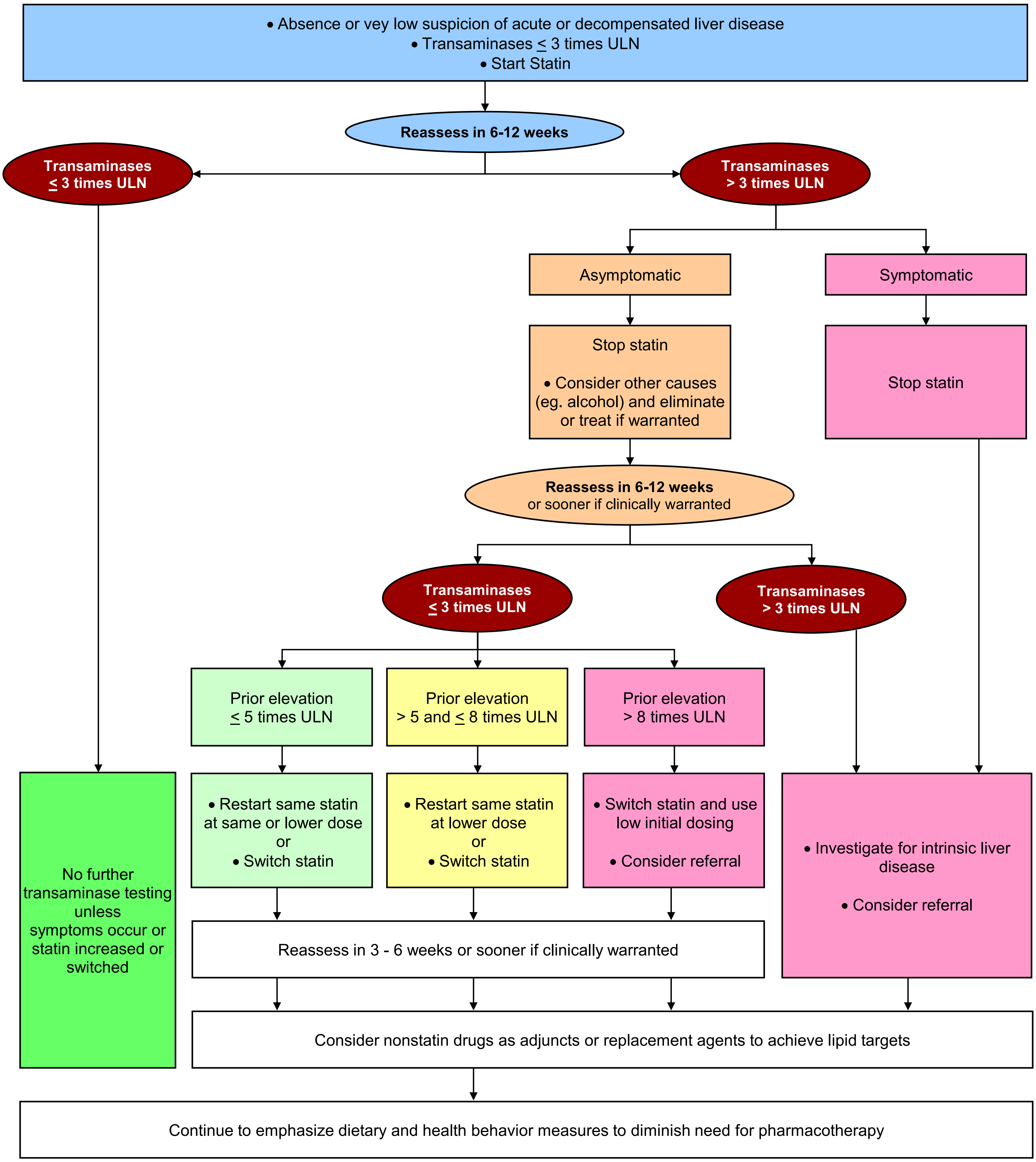

Figure 6. Management approach for patients with liver disease and/or transaminitis. ULN, upper limit of normal.

The patient should be advised that these iterative processes will be required to ultimately achieve an asymptomatic or minimally symptomatic state with drug therapy that is efficacious with either normal CK or mild hyperCKemia.

Management Approach for Liver Disease and Transaminitis

Patients being considered for statin therapy should be evaluated for possible chronic liver disease. By definition, jaundice is a sign of decompensated liver disease and such individuals should be treated with caution, ideally in conjunction with their hepatologist or gastroenterologist, if statins are deemed important. But in the absence of liver decompensation, even patients with cirrhosis or chronic hepatitis B or C may safely receive statin therapy. Patients with NAFLD or nonalcoholic steatohepatitis can also be treated with statins and they may actually improve as a result of the statin therapy.[98-100] Chronic transaminitis in association with normal bilirubin, albumin, and prothrombin time indicates absence of any serious degree of liver decompensation but clinical judgement is required as to whether to proceed with statin therapy. Alternatively one could first seek a consultation from a hepatologist. Certainly, if the baseline transaminase levels are > 3 times ULN, statin therapy should not be initiated without further investigation.

It is important to exclude hepatotoxicity caused by other medications (eg, methotrexate in a patient with RA) or from the use of drugs that might interact with a statin. Excessive alcohol use, even in the absence of liver disease, must be addressed as a part of the therapeutic behaviour intervention recommended to all patients. Elimination or reduction to prudent levels of use will improve nutrition and help achieve weight goals. Furthermore, persistent excess use of alcohol will confuse the interpretation of liver enzyme abnormalities in the context of statin therapy and also impart an added risk for myopathic side effects. Evidence of jaundice, nausea, vomiting, fatigue, lethargy, right upper quadrant pain, fever, rash, or hepatomegaly before or during statin therapy warrants thorough investigation. Finally, patients with acute hepatitis should not be considered for statin therapy until the episode has fully resolved.

The usual scenario facing practitioners is an asymptomatic patient with either normal or mildly elevated (≤ 3 times ULN) transaminases who warrants statin therapy (Fig. 6). Such patients should be treated and transaminases remeasured in 6 to 12 weeks. If the levels remain normal or ≤ 3 times ULN, further measurements are unnecessary except if the patient develops symptoms or if the dose is increased or the statin changed. If the levels are > 3 times ULN and the patient asymptomatic, the vast majority of abnormalities will resolve with continued therapy. However, patients often do not accept this reassurance.[238,239] In such cases, discontinuation and reassessment in 6 to 12 weeks is a reasonable strategy. Persistent elevation after a 6-12 week period of discontinuation warrants consideration of other causes of liver disease including viral, autoimmune, or alcoholic hepatitis along with the effects of other hepatotoxins. Resolution warrants reinitiation of statin at either the same or lower dose. Referral should be considered if transaminitis was > 8 times ULN. Repeated elevation of transaminases with the same statin would identify a specific statin intolerance justifying consideration of other statins. It is most common to be able to find a statin at a dose that does not cause chronic, sustained transaminitis ≥ 3 times ULN. If a statin cannot be found or if the amount of statin does not achieve adequate lipid-lowering, then the statin should either be replaced or supplemented with a nonstatin class of lipid-lowering agent.

Summary and Conclusions

Statins remain 1 of the most important advances in the therapy of dyslipidemia and for the reduction of CVD event risk. The extensive experience with this class of drugs has substantiated its efficacy and safety. Moreover, this experience has helped to clarify the nature of specific side effects, of which those related to muscle represent the most tangible clinical issue. In contrast, possible long-term risks of diabetes or hemorrhagic stroke are far outweighed by the CVD event risk reduction benefits. Also, almost all lipid-lowering medications share some nonspecific effects, including benign liver transaminitis. The array of other statin-related concerns—such as cancer, alopecia, tendon rupture, renal dysfunction, and ED—have reassuring evidence regarding a lack of association with long-term toxicity or causality. The increased numbers of patients receiving these drugs in order to reduce death and disability from CVD has created a substantial, absolute number of patients who will require assessment for side effects, both specific and nonspecific, and both real and imagined. This review provides a foundation for minimizing the risk of clinically relevant adverse events in the first place and for reassuring healthcare providers and patients regarding many perceived side effects that have not been substantiated. A framework for identifying true statin intolerance is provided for the practitioner who may, thereby, confidently rule out or possibly pinpoint unique interactions between specific patients, specific statins, and specific doses of statins. Additionally, a comprehensive set of strategies for dealing with the most common scenarios involving muscle and liver issues is provided. It is hoped that this overview helps provide greater confidence for dealing with this increasing clinical scenario so that ancillary, wasteful testing and excessive subspecialty referral can be avoided, while at the same time, improving compliance for patients likely to benefit from statin therapy.

Acknowledgements

The authors acknowledge the expert critiques and advice provided during the final stages of writing this paper by Dr Lawrence A. Leiter (Director, Lipid Clinic, Division of Endocrinology and Metabolism, Department of Medicine, University of Toronto, Toronto, Ontario), Dr Adeera Levin (Head, Division of Nephrology, Department of Medicine, University of British Columbia, Vancouver, British Columbia), and Dr Urs P. Steinbrecher (Division of Gastroenterology/Hepatology, Department of Medicine, University of British Columbia, Vancouver, British Columbia).

Funding Sources

The consensus conference and subsequent writing of this paper were supported by a grant to Dr G.B. John Mancini through the University of British Columbia from Merck Canada. A portion of this grant was used to provide to all authors an honourarium to support creation of talks, to draft components of the proceedings, and to aid in editing of the entire manu-

script. All authors were provided travel and hotel costs to attend the consensus conference.

Disclosures

See Appendix I for disclosure information.

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Appendix I. Author disclosures

Author	Consulting fees/honouraria	Research/research grants
Baker, Steven	Amgen, AstraZeneca	None
Bergeron, Jean	AstraZeneca, Pfizer, Roche, Sepracor, Solvay	Abbott, AstraZeneca, Genzyme, Merck, Pfizer, Regeneron Roche, Sanofi-Aventis, Servier, Schering
Fitchett, David	AstraZeneca, Bayer, Boerhinger-Ingelheim, Bristol-Myers, Merck-Schering, Novartis, Roche, Sanofi-Aventis, Servier	None
Frohlich, Jiri	Merck, Roche	Pfizer
Genest, Jacques	Amgen, AstraZeneca, Merck, Novartis, Roche	AstraZeneca, Merck
Gupta, Milan	Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Lilly, Merck, Novartis, Sanofi-Aventis, Pfizer, Servier	AstraZeneca, Pfizer
Hegele, Robert	Abbott, AstraZeneca, Boehringer-Ingelheim, Genzyme, Merck, Pfizer, Roche, Sepracor	Merck, Pfizer
Mancini, G.B. John	AstraZeneca, GlaxoSmithKline, Roche, Merck, Sepracor, Servier	Merck
Ng, Dominic	AstraZeneca, Merck, Novo Nordisk, Sepracor, Tribute Pharmaceutical	None
Pope, Janet	None	None