Statin intolerance is a clinical syndrome that is: (1) characterized by inability to use statins for long-term reduction of lipids and/or cardiovascular risk because of significant symptoms and/or biomarker abnormalities that can be temporally attributed to the initiation or dose escalation of statins; if appropriate, drug withdrawal and rechallenge can strengthen the association; (2) either “complete” (intolerant to any statin at any dose) or “partial” (intolerant to some statins at some doses); and (3) not attributable to established predispositions such as drug-drug interactions, untreated hypothyroidism, febrile illness, etc.

Because many statins are available, a pragmatic additional consideration to the 3 characterizations of statin intolerance already mentioned has been proposed whereby intolerance to at least more than the starting dose of 1 statin and any dose of another statin is considered to represent clinical statin intolerance. The latter is encompassed by the definition of a partial statin intolerance. Further complicating this clinical arena are multiple reports of diverse, nonspecific, rare, and probably idiosyncratic adverse effects that are inevitable with commonly
effect of statins. In contrast, the linkage between statin therapy and incident diabetes is more firm. However, this risk is more strongly associated with traditional risk factors for new-onset diabetes than with statin itself and any possible negative effect of new-onset diabetes during statin treatment is far outweighed by the cardiovascular risk reduction benefits. Additional studies are also discussed, which support the principle that systematic statin rechallenge, and lower or intermittent statin dosing strategies are the main methods for dealing with suspected statin intolerance at this time.

Methods
A literature search was undertaken extending from January 1, 2011 to May 16, 2013. Embase, MedLine, and PubMed were comprehensively searched using search terms (Supplemental Table S1) pertaining to statin therapy, adverse effects, and clinical management. Identified abstracts were reviewed manually to assure relevance to this review article, and then full articles were categorized in more detail. Two authors (G.B.J.M.) and (A.Y.T.) drafted the report which was then iteratively reviewed, edited, and approved by remaining members of the Canadian Consensus Working Group, who also added new citations. Case reports pertaining to purported statin-induced complications are not reviewed herein but are instead summarized (Supplemental Table S2). Reports with more extensive patient numbers and analyses are summarized in the main text (see the Adverse Effects section). In general, when both types of studies were available, conclusions were most strongly influenced by results of randomized clinical trials (RCTs) or meta-analyses of RCTs than by analyses from large databases because the latter might often be affected by residual confounding. Reports focused on pleiotropic benefits of statins are not a focus of this review.

Adverse Effects
Myopathy
Adverse muscle effects resulting from statin use have been extensively reported in the literature.2 Table 1 shows the Canadian Consensus Working group definitions.1 Statin-induced rhabdomyolysis is dose-dependent, with a reported risk of approximately 0.04%-0.2%, a mortality rate of 7.8%, and a rate of 0.15 deaths per million prescriptions.3 Less severe myopathies are also dose-dependent and occur at a rate of approximately 0.1%-1%.1

Although transient and asymptomatic creatine kinase (CK) elevations are common, persistently elevated CK levels can also occur. Although most do not necessitate a muscle biopsy,4 CK levels must be checked repeatedly to detect persistence and possible onset of myopathy (symptomatic or not). Pre-existing diagnoses (eg, spinal stenosis, polyradiculopathy, etc) associated with muscle pain should not diminish the possibility of a statin-associated worsening even when CK levels are normal.6

Toxic effects of statins. The molecular mechanisms explaining statin myopathy remain unknown but pre-existing deficiencies in energy production might contribute to symptom development.5 Recent in vivo and in vitro studies have suggested that statin therapy might provoke cellular oxidative stress, and impairments of mitochondrial function and muscular calcium homeostasis leading to myotoxicity.6,7 Decreased skeletal muscle coenzyme Q10 content was accompanied by a reduction in maximal mitochondrial oxidative phosphorylation in simvastatin-treated patients, compared with control subjects who had not been exposed to statins. This observation might partially account for the underlying mechanism for statin-induced myalgia and exercise intolerance.10

Muscle cramping is generally considered to be a neurogenic phenomenon rather than myogenic, however, statins have been implicated in a study using population databases which reported an augmented risk of 1.16 (95% confidence interval [CI], 1.04-1.29; P = 0.004) for nocturnal leg cramps in adults using statins who were 50 years old or older.11 Using 31-phosphorus magnetic resonance (MR) spectroscopy, the effects of statins on mitochondrial oxidative function during and after exercise on a calf flexion pedal ergometer have been assessed. Metabolic recovery time was adversely affected during statin therapy in the absence of any symptoms or overt CK changes.12 Whether this potential derangement is more pronounced in symptomatic statin-intolerant patients is unknown. But because it is known that patients with pre-existing mitochondrial disease might be prone to statin intolerance, this method might have a future role in assessing statin-associated muscle problems.13 However, the observation that many symptomatic patients can be successfully treated with an alternative statin implies the existence of multiple pathogenic mechanisms that might act singly or in
### Table 1. Integrated Canadian Working Group consensus terminology for myopathic syndromes and hyperCKemia

<table>
<thead>
<tr>
<th>Term</th>
<th>Laboratory</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy</td>
<td>NA</td>
<td>General term referring to any disease of muscle</td>
</tr>
<tr>
<td>Symptomatic myopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>CK ≤ ULN</td>
<td>Muscle ache/weakness</td>
</tr>
<tr>
<td>Myositis</td>
<td>CK &gt; ULN</td>
<td>Muscle ache/weakness</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>CK &gt; 10 times ULN (CK &gt; 10,000 U/L)</td>
<td>Muscle ache/weakness; renal dysfunction might result from myoglobinuria; need for hydration therapy</td>
</tr>
<tr>
<td>HyperCKemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, grade 1</td>
<td>CK &gt; ULN, ≤ 5 times ULN</td>
<td>Might/might not have myositis</td>
</tr>
<tr>
<td>Mild, grade 2</td>
<td>CK &gt; 5 times ULN, ≤ 10 times ULN</td>
<td>Might/might not have myositis</td>
</tr>
<tr>
<td>Moderate</td>
<td>CK &gt; 10 times ULN, ≤ 50 times ULN</td>
<td>Might/might not have rhabdomyolysis with/ without renal dysfunction</td>
</tr>
<tr>
<td>Severe</td>
<td>CK &gt; 50 times ULN</td>
<td>Might/might not have rhabdomyolysis with/ without renal dysfunction</td>
</tr>
</tbody>
</table>

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.

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

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concert among patients, highlighting the need for further research. Furthermore, there is evidence to suggest that patients with proven mitochondrial disease can tolerate statins.14,15

**Immune-mediated effects of statins.** Statin myopathy might persist after drug discontinuation1 and might require immunosuppressive therapy.16 A number of studies have associated statin use with a variety of inflammatory myopathies including polymyositis, dermatomyositis, and necrotizing myopathy as outlined in a recent systematic review.16 The concept of statin-induced or unmasked autoimmune myopathy is strengthened by identification of a serum anti-3-hydroxy-methylglutaryl coenzyme A reductase (HMGCR) antibody in some symptomatic patients.17 In statin-exposed patients, the HMGCR antibodies correlated with elevated CK levels and arm and leg strength in a small cohort.17 The subsequent inflammatory myositis might be very persistent and not improve despite statin withdrawal. With immunosuppressive treatment, antibody levels declined, CK levels declined, and arm and hip strength improved,17 suggesting a phenotypic difference between statin-exposed and statin-naive anti-HMGCR-positive patients. This antibody is especially found in patients with necrotizing autoimmune myopathy and might be the reason that the disease continues after the statin is discontinued.8 Relationships between anti-HMGCR myopathy and HLA classes in statin intolerant patients might be a focus for future studies.8 However, the prevalence of these antibodies in statin users, with and without symptoms was unknown until a recent study in subjects taking part in the Atherosclerosis Risk in Communities (ARIC) study. Nearly 2000 patients were studied and no individual was found to have such antibodies, including patients with documented statin intolerance or statin-tolerant patients taking maximal doses. Thus, this type of myopathy is quite rare because the antibody reaction might be idiosyncratic, and establishing direct pathogenicity requires further research.19

**Role of exercise.** Investigating the effect of statin therapy on exercise tolerance is a relatively new and controversial arena, but emerging evidence suggests that exercise might exacerbate statin-associated side effects, possibly through an inflammatory mechanism.20 Simvastatin attenuated cardiorespiratory adaptations and skeletal muscle mitochondrial biogenesis in 37 exercise-trained, sedentary, overweight, or obese adults with at least 2 metabolic syndrome risk factors.21 An exercise-related increase in serum total CK 24 hours after running a marathon was observed to be greater in statin users compared with control subjects, particularly in older patients.22 The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) was a blinded, controlled study that assessed symptoms and measured CK, exercise capacity, and muscle strength before and after either atorvastatin 80 mg or placebo (6-month trial) in 420 healthy, statin-naïve subjects.23 High-dose atorvastatin did not decrease average muscle strength or exercise performance, but more atorvastatin-treated subjects than placebo-treated subjects developed myalgia and higher average CK level, suggesting that high-dose statins might produce mild muscle injury in the context of exercise.24

**Central nervous system**

**Cognitive impairment.** The US Food and Drug Administration (FDA) recently mandated label changes on statins, warning of memory loss and confusion. These adverse effects have not emerged as consistent signals in large clinical trials and, when encountered, have generally not been serious and have reversed with statin cessation. Time to onset has been highly variable, ranging from 1 day to many years after initiation of statin treatment. Statin-associated cognitive changes are rare, and insufficient evidence is currently available to establish causality or association with fixed or progressive dementia or Alzheimer’s disease.25 There is no clear association with type or dose of statins, even though 1 literaturreview suggested a need to consider the effect of hydrophilic and lipophilic statins on cognition, aggression, and other quality of life domains.26 A randomized trial of the effects of simvastatin provides partial support for minor decrements in cognitive functioning.27 In another study, lovastatin neither caused psychological distress nor substantially altered cognitive function, and the small attenuation on neuropsychological tests of attention and psychomotor speed were of uncertain clinical significance.28 A narrative literature review concluded that statin-associated cognitive impairment is rare, potentially resolvable by switching from lipophilic to hydrophilic statins, and far outweighed by the cardiovascular benefits.29 A recent, comprehensive meta-analysis of randomized clinical trials found no significant relationship between statin therapy and cognitive decline or adverse cognitive events in cognitively healthy people and those with dementia.30 Two meta-analyses of randomized trials of patients with Alzheimer’s disease have shown a neutral effect of statins on cognitive function.31,32
Fatigue, headache, dizziness. A questionnaire-based, cross-sectional study reported relatively higher incidences of headache, dizziness, and paresthesia during statin therapy compared with control subjects not receiving statins. Risk factors identified for these adverse reactions were male sex, alcohol consumption, duration of therapy more than 5 years, and high-dose lovastatin. Golomb et al. reported on patients in a single centre studied for tertiary or exploratory, noncardiac end points in a randomized clinical trial comparing placebo, simvastatin 20 mg, and pravastatin 40 mg. Patients (n = 1016) reported on “energy” and a subset (397 patients) also reported on “fatigue with exertion.” An “EnergyFatigueEx” index was analyzed using imputational methods for missing data. The exploratory report showed statistical deterioration in this composite index that was more evident for simvastatin than for pravastatin and of somewhat greater magnitude in women. However, the clinical relevance of the findings of this relatively small and so far nonreplicated study is unclear.

Psychiatric. Definite psychiatric complications from statin therapy have not been well established. A study of 409 patients after cardioverter-defibrillator implantation found that statin therapy was associated with impaired health status pertaining to physical, social, and emotional domains. Moreover, there was a borderline significant association between statin therapy and depression but no association with anxiety. In contrast, a retrospective, observational study consisting of more than 46,000 patients concluded that there was no increased risk of developing psychological disorders including schizophrenia, psychosis, major depression, and bipolar disorder in a military cohort of propensity score-matched statin users and nonusers. Other groups have suggested a potential beneficial effect of statin use on depression in patients with coronary heart disease. Accordingly, it is difficult to accept a direct link between statin usage and psychiatric adverse effects based on these studies.

Intracranial hemorrhage. The association of subarachnoid hemorrhage and lipid-lowering therapy has been re-evaluated in a meta-analysis of 31 randomized controlled trials incorporating more than 180,000 patients. Active statin therapy was not associated with a significant increase in intracranial hemorrhage. Moreover, a significant reduction in all strokes and even all-cause mortality was observed in the aggregated results of the trials. A small post hoc analysis from a prospective, randomized, placebo-controlled trial of 80 mg of atorvastatin daily demonstrated a significant increase in hemorrhagic strokes in the statin arm compared with the placebo arm (hazard ratio, 1.66; 95% CI, 1.08-2.55), but this increase was offset by a considerably larger decrease in ischemic events. Similar findings are reported in a recent meta-analysis. In a single study of 163 patients with spontaneous intracranial hemorrhage, statin users were older, had significantly lower cholesterol levels, and higher prevalence of hypertension, dyslipidemia, diabetes, and antiplatelet use. However, age and statin use were independently associated with the presence and increased number of micro hemorrhages; statin-treated patients had almost twice as many cortico-subcortical microbleeds compared with untreated patients, detected using MR imaging. It is not clear if the confounding risk factors for bleeding could be adequately taken into account statistically in this small study.

Ophthalmological

An early concern over a possible association between statins and cataracts has been alleviated by findings from clinical trials and through clinical experience. However, this issue has been raised again in several recent reports. Cataracts are a known complication of diabetes mellitus (DM) and most patients with DM, based on their high cardiovascular (CV) risk, receive statins. In a cross-sectional study of 780 patients with type 2 diabetes at a very high risk of diabetic retinopathy and cataracts, there was no evidence of an association between statin use or other lipid-lowering agents and cataract formation. These findings are in contrast to a cross-sectional analysis of 6397 patients, suggesting statin use is associated with age-related cataracts, including nuclear sclerosis (odds ratio [OR], 1.48; 95% CI, 1.09-2.00) and posterior subcapsular cataract (OR, 1.48; 95% CI, 1.07-2.04). These abnormalities occurred on average 2.4-3.4 years earlier in diabetic statin users compared with control subjects not using statins.

A case-control study consisting of approximately 48,000 participants reported that the proportion of statin users appeared to be greater among those with cataract surgery (64.3%) compared with those without a diagnosis of cataract or cataract surgery (55.5%). Interestingly, after adjustment for age, sex, race, smoking status, DM, and coronary artery disease, longer-term statin use was found to be protective against cataract extraction (OR, 0.93; P = 0.02), and shorter-term use was associated with cataract surgery (OR, 1.11; P < 0.0001). Age-stratified logistic regression analysis showed that statin use of 5 years or more was protective against cataract surgery in the younger age group (50-64 years), and statin use of less than 5 years was associated with an increased risk of surgery in younger and older age groups. Finally, a recently published propensity score-matched analysis also showed an increased risk for cataract in statin users vs non-users, which was noted also in patients with no known comorbidities for cataract formation.

Rheumatologic and dermatologic

Assessment of musculoskeletal side effects in patients with arthritis is complex. In a cross-sectional study based on the National Health and Nutrition Examination Survey (NHANES), investigators noted no association between musculoskeletal side effects and statin use in patients with arthritis, whereas in patients without arthritis, musculoskeletal symptoms were significantly associated with statin use. In a cohort of 508 patients 40 years old or older with a first-time diagnosis of rheumatoid arthritis (RA), there was no consistent trend of increasing risk of RA with increased cumulative duration, cumulative daily doses, or number of prescriptions of statins. However, a small positive trend between the potency of statin treatment and the risk of RA was found. This study is different from others in which previous use of statins was considered protective against the development of RA. Also, other older reports have demonstrated that statins could improve RA disease activity, but...
Hepatic effects

The mechanisms of statin-induced adverse liver effects are not entirely understood and in practice, alcohol- and nonalcohol-related underlying fatty liver disease might complicate statin association. Although elevation of liver enzymes is observed in a small proportion of patients taking statins, an even smaller fraction of these patients might progress to clinically significant statin-associated hepatitis. Pharmacovigilance data consisting of 9360 cases of adverse drug events as defined by the WHO Reaction Terminology resulted in statins being associated with an increased odds ratio of 3.0 (95% CI, 1.3-6.9; P < 0.05) for causing any hepatic adverse drug reaction, with elevated liver enzymes as the most common. A recent analysis of the Swedish Adverse Drug Reactions Advisory Committee estimated the incidence of statin-related transaminitis at 1.2 per 100,000 patients taking statins. Most patients experienced liver abnormalities approximately 3 to 4 months after therapy initiation and with a reproducible pattern of liver injury on re-exposure after recovery. Atorvastatin and simvastatin were the most responsible agents, particularly for cholestatic/mixed patterns and hepatocellular injury patterns, respectively. In this cohort, there was a "high probability" of statin causality for the death of 1 patient who died of acute liver failure and also another who required liver transplantation. There was a "possible" statin-related case in a patient who died from acute liver failure. In contrast to other reported cases, these patients each had a thorough diagnostic work-up that excluded common comorbidities that might have affected outcomes. Statin-induced jaundice is calculated at a risk of 1 in 17,434 users per year, based on a population in Iceland. Periodic monitoring of liver enzyme levels does not appear to be effective in detecting or preventing serious liver injury from statin use, thus justifying the discontinuation of the previous recommendation for routine, serial liver enzyme monitoring during chronic statin therapy.

Use of statins in patients with compensated liver disease is generally considered to be safe. Malaguarnera et al. performed a randomized assessment of the addition of rosuvastatin 5 mg/d in patients with nonalcoholic fatty liver disease and hepatitis C being treated with α-interferon and ribavirin. In addition to improved lipid levels, the statin-treated group showed reductions in viremia associated with reduced hepatic fibrosis and hepatosteatosis along with an improvement in sustained virological response. Another prospective, randomized trial observed that after 12 weeks, atorvastatin (10 mg/d) and pitavastatin (2 mg/d) reduced transaminitis in 189 patients with mild to moderate elevation of alanine aminotransferase; all subjects were not alcoholics and serologically negative for viral hepatitis markers, and none had been treated with statins for more than 3 months before screening.

Gastrointestinal

A cross-sectional questionnaire-based study reported flatulence as the most prevalent statin-induced gastrointestinal side effect with 4.8% of patients discontinuing statin therapy because of any gastrointestinal side effects. Other observed side effects included swallowing difficulty, dyspepsia, constipation, diarrhea, nausea and vomiting, and abdominal cramps, with risk factors identified as female sex, East Indian race, consumption of alcohol, higher lovastatin dose, secondary dyslipidemia, DM, and concurrent β-blocker administration. However, the aggregate of data and meta-analyses of clinical trials indicate that the incidence of such adverse effects is not greater in statin-treated patients compared with control subjects who had not been exposed to statins.

Renal

Controversy exists regarding the effects of high-potency statins on renal function. In 72,488 patient-years of follow-up in 36 studies of rosuvastatin involving more than 40,000 patients, renal impairment or renal failure were reported in only 536 participants. Rates of renal end points were higher in patients with risk factors for renal problems (eg, hypertension, heart failure, diabetes, or patients with baseline estimated glomerular filtration rate less than 60 mL/min/1.73 m²) but there was no difference even in these groups between placebo- and statin-treated patients or between the maximal 40 mg and 10 mg daily doses. In addition, 2 meta-analyses that assessed benefits and harms of statin use in patients with renal disease showed no deterioration and a trend toward improvement or maintenance of renal function. These current meta-analyses also showed decreased mortality and
cardiovascular events in patients with chronic kidney disease, but showed little or no benefit in persons receiving dialysis and uncertain effects in kidney transplant recipients. One small study concluded that pitavastatin might be safe and well tolerated in subjects with severe renal impairment and not using hemodialysis.

A large retrospective study quantified the association between acute kidney injury (AKI) and use of high-potency statins vs low-potency statins by analyzing data from more than 2 million patients 40 years old or older and newly treated with statins; high-potency statin treatment was defined as ≥10 mg rosuvastatin, ≥20 mg atorvastatin, and ≥40 mg simvastatin, with all other statins and doses defined as low potency. In patients with nonchonic kidney disease, current users of high-potency statins were 34% more likely to be hospitalized with AKI within 120 days after starting treatment and users of high potency statins with chronic kidney disease did not have as large an increase in admission rate. These observations from administrative databases appear quite discordant with randomized trial data.

An association between statin therapy and hematuria and proteinuria has been well established. Statin-induced microalbuminuria is thought to be secondary to statin interference with the tubular reabsorption of albumin. In 2 observational, cross-sectional descriptive studies, the prevalence of microalbuminuria was greater among patients taking statins. This mechanism of microalbuminuria is not believed to be indicative of renal dysfunction.

DM

An increased incidence of new-onset type 2 DM has been associated with several drugs including thiazide diuretics, β-blockers, glucocorticoids, niacin, protease inhibitors, and statins. These findings contrast with protective effects of statins on β-cell function, through immunomodulatory mechanisms which have been postulated, but not substantiated. An FDA drug safety communication reports that statins appear to moderately increase the risk of developing DM, and regular screening for diabetes should be considered, especially for patients taking high-dose statins and patients with multiple risk factors for DM.

In a retrospective analysis of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, participants were stratified on the basis of having none or at least 1 of 4 major risk factors for developing DM: metabolic syndrome, impaired fasting glucose, elevated body mass index (BMI), or elevated hemoglobin A1c. In participants with 1 or more DM risk factors, statin therapy was associated with a 28% increased risk of developing DM, and for participants with no major risk factors, statin allocation was not associated with an increase in DM. The absolute numbers of new cases of DM was approximately 31 and 34 events per 1000 person-years for atorvastatin and rosuvastatin, respectively. Similarly, in a large cohort with hypertension and dyslipidemia, a retrospective study reported that the risk of new-onset DM was higher among users of pravastatin than among nonusers, and patients who took fluvastatin, lovastatin, and rosuvastatin were at lower risk of developing new-onset DM than nonusers; simvastatin and atorvastatin demonstrated a neutral effect. An in-hospital cohort was followed for a median of 7.2 years, and annual rates of diabetes were reported modestly greater in statin users (2.4% vs 2.1%; P < 0.001), which were more than offset by attenuation of major adverse cardiovascular events and in-hospital mortality rates.

Last, a large study included 153,840 nondiabetic women participating in the Women’s Health Initiative (WHI) at baseline, of which 7.04% reported taking statin medications. There were 10,242 incident cases of self-reported DM over 1,004,466 person-years of follow-up; all types of statin therapy at baseline were associated with an increased risk of DM after adjusting for potential confounders. A specific effect on glucose levels with concomitant use of pravastatin and paroxetine was noted in the FDA’s Adverse Event Reporting System that was not observed when either was given separately, and not observed with other selective serotonin reuptake inhibitors.

The brain-derived neurotrophic factor Val66Met variant might influence statin-associated insulin resistance and increased risk of DM. Results suggest that in a metabolically high-risk population with schizophrenia, but not bipolar disorder, the brain-derived neurotrophic factor Val66Met allele alone and in combination with statin medications is associated with greater insulin resistance.

In contrast to these results, Ko et al. studied more than 17,000 older patients with myocardial infarction and at 5 years, observed similar rates of new-onset DM in patients receiving intensive-dose and moderate-dose statins (13.6% vs 13.0%, respectively; P = 0.19) although the former was found effective in reducing repeat hospitalization for acute coronary syndrome. A recent analysis of 3 large trials emphasized that fasting glucose levels and features of the metabolic syndrome are more consistent determinants of DM than statin use. Thus, the development of new-onset DM with statin treatments appears to be relatively uncommon in comparison with the expected CV benefits, related mainly to use of highest doses and most apparent in patients already at risk for development of DM. Moreover, cardiovascular benefits of statins have previously been demonstrated specifically in patients with metabolic syndrome who are at risk for developing diabetes and in those with established diabetes.

Erectile dysfunction and gynecomastia

Conflicting data are available regarding an association of statin use with erectile dysfunction (ED). This might be partially attributable to overlapping risk factors for ED and cardiovascular pathology necessitating statin therapy. Statins might be protective against ED, secondary to their contribution to an overall enhanced endothelial function. A prospective randomized trial observed that 10 mg of atorvastatin daily was inferior to regular tadalaflie use, but superior to no medications, in improving ED, particularly in patients with dyslipidemia.
Data from the Italian spontaneous adverse drug reaction-reporting database suggested a possible association between gynecomastia and statins as a drug class, particularly with higher potencies. However, this isolated observation has never been replicated in other studies or databases.

**Interstitial lung disease**

Interstitial lung disease is considered to be an idiosyncratic and rare reaction to statin therapy. However, using regression analyses and after adjustments for covariates such as high cholesterol or coronary artery disease, statin use in smokers in the Chronic Obstructive Pulmonary Disease Gene (COPDGene) study was associated with an increased risk of interstitial lung abnormalities, not necessarily clinical interstitial lung disease. Furthermore, in an animal model, pretreatment with statins augmented bleomycin-induced lung inflammation and fibrosis, possibly through increased mitochondrial reactive oxygen species generation that enhanced nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome activation. Currently, however, all dyslipidemia guidelines support use of statins to prevent an increased risk of cardiovascular disease in smokers. In addition, other analyses suggest a benefit of statins for other pulmonary conditions including pneumonia, influenza, and chronic obstructive pulmonary disease. In fact, the combination of statins and either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with a reduction in chronic obstructive pulmonary disease hospitalization and total mortality in low and high cardiovascular risk cohorts.

**Cancer**

The concern of statins promoting cancer has been dispelled by a large collaborative meta-analysis published in 2010, which reinforced the safety of statin therapy and lack of association with incidence of cancer. Moreover, an analysis of nearly 46,000 propensity-matched pairs of older adults showed no differences in rates of any type of cancer over 10 years, between patients taking a statin and those not taking a statin. Furthermore, investigators using sophisticated methods to investigate an association between statin and specific subtypes of colorectal cancer based on anatomical location and molecular markers did not show any association.

A population-based case-control study found no evidence to support either beneficial or harmful associations between statin use and bladder cancer risk. Similar findings were noted regarding the risk of long-term statin use and overall cancer risk, but intriguingly, potential protective effects of statins for lowering the risk of melanoma, endometrial cancer, and non-Hodgkin lymphoma were observed. Moreover, statin use was possibly associated with improved cancer-free and overall survival in 255 patients after heart transplantation. In a large population-based study, the risk of glioma was reduced among long-term statin users (OR, 0.76; 95% CI, 0.59-0.98) compared with subjects who had never used statins, and was inversely related to the intensity of statin treatment among users, particularly in patients 60 years old or younger. In a population-based cohort study of 260,864 hepatitis C virus-infected patients, an inverse dose-response relationship between statin use and hepatocellular carcinoma risk was observed. Last, a prospective study in 50 women with a history of breast cancer concluded that simvastatin appears to modulate estrone sulfate concentrations and their potential chemopreventive activity in breast cancer warrants further investigation.

In contrast, in a study that assessed pathological characteristics of 588 radical prostatectomy specimens, an increased rate of high Gleason score, pathologic stage, and recurrences were noted in patients receiving statins for more than 2 years.

**Endogenous and Exogenous Risk Factors for Statin Intolerance and Adverse Effects**

A summary of endogenous and exogenous risk factors for statin intolerance and adverse effects is provided in Table 2.

**Genetic considerations**

Much of the genetic work is driven by the fact that statin-associated muscle symptoms dominate our clinical focus. There is growing evidence that some carriers of genetic polymorphisms in the enzymes and transporters implicated in statin disposition, particularly the rs4149056 variant in the solute carrier organic anion transporter gene (SLCO1B1), are at increased risk of statin-induced adverse effects and specifically myotoxicity with very high doses of simvastatin in particular. A common nonsynonymous coding variant in SLCO1B1 has been demonstrated to be strongly associated with the risk of development of simvastatin (80 mg daily)-induced myopathy in a whole-genome association analysis of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) study. A recent review reported statin-induced myopathy in a family with 2 patients who were carriers of the rare allele of the SLCO1B1 rs4363657 polymorphism, re-enforcing the potential effect of such genetic factors on the risk of myopathy with statin use. In 25 cases of severe statin-associated myopathy, Brunham et al. reported that SLCO1B1 rs4149056 genotype was significantly associated with myopathy in patients who received simvastatin, but not in patients who received atorvastatin. Other common SLCO1B1 variants were examined in a large population of patients with DM who were receiving diverse statins; the rs4149056 (Val174Ala) genotype was associated with higher intolerance and less cholesterol-lowering in response to statins, whereas the rs2306283 (Asp130Asn) genotype was associated with lower intolerance rates. Another genomic study suggested that presence of individual intronic single nucleotide polymorphisms in SLCO1B1 might predict the ability of simvastatin and rosuvastatin to lower LDL cholesterol (LDL-C).

A genome-wide association study was undertaken in a group with severe statin myopathy vs a statin-tolerant group of patients and resulted in identification of 3 single-nucleotide polymorphisms in the “eyes shut” homolog (EYS) on chromosome 6, suggestive of an association with risk. The EYS gene products have similarities to members of the Notch signalling pathway and to agrin, leading these investigators to postulate that the polymorphisms might affect the maintenance and regeneration of skeletal muscle.

The C3453T polymorphism in ABCB1 also appears to explain some heterogeneity of adverse response to statins. The T allele appears to be more frequent than the C allele in
### Table 2. Predisposing factors for statin-associated adverse effects

<table>
<thead>
<tr>
<th>Endogenous factors</th>
<th>Exogenous factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age (older than 80 years)</td>
<td>High statin dose*</td>
</tr>
<tr>
<td>Female sex</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Asian ethnicity</td>
<td>Illicit drug use (cocaine, amphetamines)</td>
</tr>
<tr>
<td>Low body mass index, small body frame, frailty</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>History of pre-existing/unexplained muscle/joint/tendon pain</td>
<td>Drug–statin interactions</td>
</tr>
<tr>
<td>History of creatine kinase elevation</td>
<td>Fibrates (particularly gemfibrozil)</td>
</tr>
<tr>
<td>Family history of myopathy</td>
<td>Nicotinic acid</td>
</tr>
<tr>
<td>Family history of myopathy with statin therapy</td>
<td>Heavy and/or unaccustomed exercise</td>
</tr>
<tr>
<td>Neuromuscular diseases (eg, 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 [MEAS: mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes], muscle phosphorylase B kinase deficiency, myasthenia gravis, myoadenylate deaminase deficiency, myotonic dystrophy types I and II, necrotizing myopathy, peripheral neuropathy [length-dependent, mononeuropathies] polymyositis [idiopathic, paraneoplastic], recurrent acute myoglobinuria [Lipin-1 mutation], rippling muscle disease (sporadic, autoimmune), spinobulbar muscular atrophy)</td>
<td>Severe renal disease</td>
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<tr>
<td>Patients with atorvastatin-induced myalgia.</td>
<td>Acute/compensated hepatic disease</td>
</tr>
<tr>
<td>Hypertension/heart failure (renal side effects mainly)</td>
<td>Hypothyroidism (untreated)</td>
</tr>
<tr>
<td>Hypothyroidism (untreated)</td>
<td>Diabetic mellitus</td>
</tr>
<tr>
<td>Genetic polymorphisms (eg, cytochrome P isoenzymes, SLC01B1 gene variants, “eyes shut” homolog [EYS] on chromosome 6, C34356T polymorphism)</td>
<td>Genetic polymorphisms (eg, cytochrome P isoenzymes, SLC01B1 gene variants, “eyes shut” homolog [EYS] on chromosome 6, C34356T polymorphism)</td>
</tr>
<tr>
<td>in ABCB1, ABCG2 polymorphisms, ryanodine receptor (RYRI) gene, brain-derived neurotrophic factor [BDNF] Val66Met variant, Lipin-1 [LIPIN1] mutation, rs9806699 variant in glycine amidinotransferase (GATM)</td>
<td>in ABCB1, ABCG2 polymorphisms, ryanodine receptor (RYRI) gene, brain-derived neurotrophic factor [BDNF] Val66Met variant, Lipin-1 [LIPIN1] mutation, rs9806699 variant in glycine amidinotransferase (GATM)</td>
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<td>Exoenogenous factors</td>
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<td>High statin dose*</td>
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<tr>
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<td>Illicit drug use (cocaine, amphetamines)</td>
<td>Illicit drug use (cocaine, amphetamines)</td>
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<td>Antipsychotics</td>
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<td>Drug–statin interactions</td>
<td>Drug–statin interactions</td>
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<td>Fibrates (particularly gemfibrozil)</td>
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<td>Warfarin</td>
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<td>Cyclosporine</td>
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<td>Macrolide antibiotics</td>
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<td>Azole antifungals</td>
<td>Azole antifungals</td>
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<tr>
<td>Protease inhibitors</td>
<td>Protease inhibitors</td>
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<tr>
<td>Nefazodone</td>
<td>Nefazodone</td>
</tr>
<tr>
<td>Large quantities of grapefruit (&gt; 1 quart per day), pomegranate juice (?)</td>
<td>Large quantities of grapefruit (&gt; 1 quart per day), pomegranate juice (?)</td>
</tr>
<tr>
<td>Surgery with severe metabolic demands</td>
<td>Surgery with severe metabolic demands</td>
</tr>
<tr>
<td>Heavy and/or unaccustomed exercise</td>
<td>Heavy and/or unaccustomed exercise</td>
</tr>
</tbody>
</table>

* See text for specific precautions regarding simvastatin and lovastatin use. Modified from Mancini et al.1 with permission from Elsevier.

**Clinical pharmacology and drug-drug interactions**

Although clinicians have long accepted the relationship between dose of statins and symptoms and rhabdomyolysis, this relationship has not always been clear from information pertaining to individual statins. Holbrook et al.112 evaluated all cases of statin-associated rhabdomyolysis reported to Health Canada’s Canadian Vigilance Program and to the FDA’s Adverse Event Reporting System; considering all statins and using atorvastatin 10 mg daily as the reference dose potency, risk of rhabdomyolysis increased by a factor of 4 for a 4-fold increase in dose and by 11 for an 8-fold increase in dose.112 Patients were an average age of 64 years old, 2/3 were male, and cases often showed secondary consequences such as renal dysfunction (17% of cases), acute renal failure (20% of cases), dialysis (5% of cases), or death (8% of cases). A slightly updated review of cases reported to the FDA found a male:female preponderance (5:3), an association with very young age groups (younger than 10 years old), and body weight less than 50 kg, onset within a month of drug exposure in more than 50% of cases, and a higher risk of fatal outcome when complicated by renal dysfunction.113

In a prospective study of patients receiving statins compared with an age- and sex-matched control group, only 3.2% of the entire cohort complained of muscle symptoms and, among these, objective weakness was noted in only 15%. Adverse reactions, noted in up to 21% of patients and only 5.9% of control subjects, were predicted by older age, longer duration of statin use, DM, stroke, and lower BMI.114

The risks of many statin-induced adverse effects are related to drug serum levels. Coprescription with certain other drugs can increase serum statin concentrations. Practitioners should remain aware of drug–drug interactions generally related to shared metabolic pathways, particularly CYP3A4.115,128,129

In contrast, a large retrospective cohort study spanning 18 years independently evaluated muscle toxicity, renal dysfunction, and hepatic dysfunction secondary to drug interactions, finding no difference in the relative hazards for patients prescribed a CYP3A4-dependent statin substrate vs a non-CYP3A4-dependent statin substrate with a concomitant CYP3A4 inhibitor.130 Although statins are not generally considered to have a marked effect on coagulation, the effect of simultaneous statin therapy and warfarin use on the
international normalized ratio suggests relatively larger effects of rosuvastatin on international normalized ratio compared with pitavastatin.\textsuperscript{131}

From a practical perspective, it is important to emphasize that practitioners should no longer use the 80-mg dose of simvastatin because of the increased risk of myopathy, and such doses are to be continued only in patients already known to be doing well with long-term therapy. Most of this risk has been observed with concomitant use of amiodarone, diltiazem, and amiodipine. With amiodipine, simvastatin should not exceed 20 mg, and it should not exceed 10 mg if amiodarone, verapamil, or diltiazem are being used. Simvastatin should not be used at all with antifungal agents, gemfibrozil, cyclosporine, or the macrolide antibiotics. Lovastatin has properties similar to simvastatin and is also contraindicated for use with antifungal agents, macrolide antibiotics, protease inhibitors, and nefazodone. Lovastatin should be avoided when cyclosporine or gemfibrozil are required. Doses should not exceed 20 mg when using danazol, diltiazem, or verapamil, and should not exceed 40 mg when using amiodarone.

**Diagnosis of Statin Intolerance**

The challenge of making a diagnosis of statin intolerance, as defined in the introductory section, is amplified by a recent detailed study of a cohort of patients referred to a lipid clinic for statin intolerance attributable to muscle pain without CK elevation (myalgia) and compared with statin-tolerant patients.\textsuperscript{132} Although more statin-intolerant patients were white and hypertensive, there was no increased prevalence of renal disease, DM, thyroid disease, electrolyte abnormalities, or potentially interacting medications, all of which are considered to predispose to intolerance.\textsuperscript{132} Although most were intolerant to 2 or more statins, more than half of the cases were successfully rechallenged with an alternative statin.\textsuperscript{132}

The role of routine laboratory monitoring of liver enzymes or CK after initiation of statin therapy remains controversial. Recommendations for only symptom-based investigations are supported by a recent study.\textsuperscript{133,134} There are, however, 2 main reasons for persisting with a baseline and 1-time, follow-up analysis after initiation, dose change, or change in statin type. First, some patients are highly cognizant or concerned about statin adverse effects and derive reassurance from lack of any adverse liver/muscle enzyme changes when these are presented. Second, in the rare case of symptoms arising after statins are initiated or changed, the inability of the practitioner to explain whether any abnormalities are new or preceding the statin change is viewed as poor practice. These factors heavily influenced the Canadian Consensus Group guideline recommendations.\textsuperscript{1} Routine monitoring outside of these circumstances of initiation or change are not warranted and should instead be performed selectively for assessment of symptoms that emerge during chronic therapy.

A pilot study assessed the use of statin metabolites to aid diagnosis of statin intolerance.\textsuperscript{134} A ratio of atorvastatin lactone to acid ratio greater than 1.1 in self-reported atorvastatin-intolerant patients had a positive and negative predictive value of 79% and 61%, respectively, for recurrence of muscle symptoms during rechallenge with atorvastatin.\textsuperscript{134} These performance parameters are not sufficient to avoid the need for standard rechallenge attempts at this time.

Imaging is not a primary diagnostic procedure in the evaluation of most statin-intolerant patients except when needed to exclude underlying causes that might complicate the clinical picture (eg, detection of radiculopathy with MR or computed tomography studies). In acute phases, ultrasonography might demonstrate normal or increased size, low echogenicity, and elevated perfusion of affected muscles. However, in chronic cases, this modality might show reductions in size and perfusion with increased echogenicity of affected muscles.\textsuperscript{135} Edematous changes are better depicted using MR imaging where a close correlation has been found between MR signal intensity on T2-weighted images and contrast-enhanced T1-weighted images and inflammatory activity caused by myositis.\textsuperscript{135}

The prediction of statin adverse effects has been proposed. A large prospective cohort study consisting of more than 2 million patients evaluated the performance of the QStatin score for predicting the 5-year risk of developing AKI, cataract, liver dysfunction, and myopathy with good discriminative and calibration properties except for predicting risk of developing liver dysfunction.\textsuperscript{136} The score is based on an assessment of age, BMI, ethnicity, and smoking status, among other risk factors, but the rarity and complexity of the genesis of AKI, cataract, and myopathy based on randomized clinical trials suggests that this method retains major confounding factors not yet well understood and the score should not be used to preclude statin use if indications for their use are present.

**Therapy for Statin Intolerance**

Table 3 outlines the principles of therapy previously described.\textsuperscript{1} The following update provides further support.

**Statin-based therapies**

Effective patient-practitioner dialogue might increase persistence of statin use, particularly when the patient has concerns about side effects and drug costs.\textsuperscript{137} A retrospective study showed that after documentation of simvastatin-induced myopathy, no statistical difference in tolerability rates between atorvastatin, rosuvastatin, pravastatin, and...
fluvastatin were observed; 62%-81% of these patients subsequently developed statin myopathy to 1 or more statins. Fibrates, cholestyramine, and ezetimibe were statistically better tolerated in this cohort, with only 17%-32% of patients developing myopathy.

Despite this, use of a statin rechallenge in most patients experiencing adverse effects was corroborated in a large retrospective cohort study, which reported that of the 11,124 patients in whom statins were discontinued at least temporarily because of clinical events or symptoms believed to have been caused by statin use, 92% of those who were rechallenged were still taking a statin 12 months after the statin-related event; among the 2721 patients who were rechallenged with the same statin they were using when they had an event, 1295 were receiving the same statin 12 months later, and 996 of them were receiving the same or a higher dose. A retrospective analysis of medical records of 1605 patients from the Cleveland Clinic further suggests that most patients with previous statin intolerance can tolerate a subsequent trial of statin. Subsequently, statin-induced adverse events might have other causes or might be specific to individual statins rather than the entire drug class.

Evidence for lipid-lowering efficacy of intermittent doses of high-potency statins continues to emerge. Intermittent statin dosing can be an effective therapeutic strategy in some patients and might result in reduction of LDL-C and achievement of LDL-C goals. In 58 statin-intolerant patients, intermittent rosvastatin resulted in clinically relevant reductions in LDL-C levels and improved compliance. Whole-body cholesterol synthesis was greater in intermittent rosvastatin dosing, but no differences in plasma drug concentrations were observed, suggesting that the improved tolerability was independent of plasma rosvastatin levels. LDL-C lowering of more than 10% was achieved with weekly 5-10 mg of rosvastatin in a small, randomized, double-blind trial in patients with a history of statin-associated myalgia.

In a multicentre retrospective observational study, rosvastatin 5 mg was found to be safe and biochemically effective, either as daily or intermittent therapy in 325 patients intolerant to other conventional statin regimens. Daily rosvastatin (n = 134) reduced mean total cholesterol (TC) by 31%, triglycerides (TG) by 15%, and LDL-C by 43% (P < 0.001). Rosuvastatin 5 mg 2-3 times weekly (n = 79) reduced TC by 26%, TG by 16%, and LDL-C by 32% (P < 0.001). Weekly rosvastatin (n = 11) reduced TC by 17%, LDL-C by 23% (P < 0.001), but had no effect on TG. Targets were attained in 17% of coronary heart disease risk-equivalent patients and 41% of primary prevention patients according to National Cholesterol Education Program criteria and 27% and 68% using UK targets.

Treatments targeting muscle symptom relief

Vitamin D. Vitamin D deficiency is a rare cause of myopathy and unrecognized, mild deficiencies might represent a reversible cause of statin-associated myalgia or myositis. One hundred fifty patients were selected on the basis of intolerance to 1 or more statins because of myalgia or myositis and with low serum 25-hydroxy (OH) vitamin D (< 32 ng/mL). Vitamin D at a dose of 50,000 units twice per week for 3 weeks was provided to patients while they were not taking statins and then continued once per week with introduction of statin therapy after the initial 3 weeks of supplementation. Eighty-seven percent of patients were symptom-free and tolerant of statin use over a median follow-up of 8.1 months although only 78% achieved normal serum vitamin D levels.

In contrast, Kurnik et al. retrospectively observed no differences in serum vitamin D levels among patients requiring a switch from atorvastatin to another statin because of muscle pain or other reasons, compared with those who required no switch; surprisingly, CK levels were marginally lower in patients in the lowest quartile of serum 25-OH vitamin D levels. This observed lack of association between statin-induced myopathy and 25-OH vitamin D was corroborated by another study. Thus, placebo-controlled trials of this intervention either in patients with low serum vitamin D or in the more general population of statin-intolerant patients are needed.

Coenzyme Q10. Coenzyme Q10 enzyme deficiency has been suggested as a potential mechanism for statin-induced myopathy, although the role of supplementation remains controversial. In a recent study of 28 patients, decreased muscle pain and sensitivity was observed after a 6-month administration of coenzyme Q10 at a dose of 30 mg twice daily. Fedacko et al. evaluated the possible benefits of coenzyme Q10 and selenium supplementation administered to 60 patients with statin-associated myopathy in a small double-blind study. Selenium (200 μg/d) and coenzyme Q10 (200 mg/d) supplementation of statin-treated patients resulted in symptomatic attenuation of statin-associated myopathy in absolute numbers and intensity. In contrast, a similarly designed double-blind study reported that coenzyme Q10 supplementation (60 mg twice daily) for 3 months did not produce a greater response than placebo in the treatment of presumed statin-induced myalgias.

Nonstatin lipid-lowering therapies. A double-blind, randomized clinical trial showed safety and efficacy of using nutraceutical drinks containing niacin, phytosterol esters, L-carnitine, vitamin C, Co-Q10, and red yeast rice in 79 subjects with statin intolerance.

Future nonstatin pharmacologic treatments that might play a role in helping patients with high cardiovascular disease risk who have true statin intolerance include microsomal triglyceride transfer protein inhibitors, and novel parenteral RNA interference therapies and even monoclonal antibodies that improve uptake of LDL particles (plasma proprotein convertase subtilisin/kexin type 9 or “PCSK9” inhibitors). For instance, a study of mipomersen, an apolipoprotein B synthesis inhibitor, studied in 33 high-risk subjects with severe genetic dyslipidemia showed that after 26 weeks, LDL-C was reduced by 47 ± 18% (P < 0.001 vs placebo). Apolipoprotein B and lipoprotein(a) were also significantly reduced by 46% and 27%, respectively (P < 0.001 vs placebo).

PCSK9 binds to LDL receptors, promoting their degradation and increasing LDL-C levels. A randomized, double-blind, phase II study assessed the efficacy and tolerability of AMGEN145, a human monoclonal antibody to PCSK9, in patients with statin intolerance because of muscle-related side
The overall analysis suggests that statin intolerance and adverse effects remain of major clinical importance. Statin intolerance is a clinical syndrome requiring careful consideration of many factors (Table 2), including drug-drug interactions, elimination of reversible factors, and systematic dechallenge and rechallenge, when feasible, before a specific statin intolerance can be considered.1,2,3 There are currently no routine tests or assays that are warranted in the evaluation of statin intolerance or adverse effects except for muscle and liver enzyme assays when symptoms warrant. The role of exercise testing combined with imaging might eventually have a clinical role.20-24,255 Despite the focus on statin-related adverse effects in both the lay and academic literature, a very recent meta-analysis provides extremely reassuring evidence that the class as a whole cannot be shown in randomized clinical trials to be associated with myalgia, CK elevation, cancer, or even discontinuations when compared with placebo control.154,155 However, the same analysis also confirms higher risk of DM (OR, 1.09) and transaminase elevations (OR, 1.51), particularly with very high statin doses, and also shows numerous statistically significant differences in the propensity for specific adverse events among different statins and statin dosages (Table 4).154 The overall results of this critical meta-analysis are reassuring for patients who use and physicians who prescribe this class of agents. However, the observations in aggregate also indicate that when lower doses and/or less potent statins are adequate to achieve guideline-supported lipid targets, such approaches should be used, especially in patients reporting difficulties with long-term statin use. This principle is concordant with good medical practice, and also adheres to recommended statin intolerance management approaches (Table 3).1,155

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### Disclosures

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### References


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**Table 4. Odds ratios for selected adverse effects of statins**

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<thead>
<tr>
<th>Effect</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term adverse effects</td>
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<tr>
<td>Cancer</td>
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<td>All statins</td>
<td>0.96</td>
<td>0.91-1.02</td>
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<td>Diabetes mellitus</td>
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<td>All statins</td>
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<td>Short-term adverse effects</td>
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<td>Discontinuations</td>
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Data derived from Naci et al.154 as reported in the Results section for all statins and extracted from Figures 4 and 5 of that article for specific drug-level and dose-level analyses that resulted in odds ratios > 1.00 and a confidence interval not spanning 1.00.


**Supplementary Material**

To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2013.09.023.