"Latest Update on Statins for Diabetes".

Module 5

Safety and Tolerability of Statins in Diabetes Management

CONTENT

Introduction

Hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) inhibitors (commonly known as statins) have been one of the most widely prescribed groups of drugs in the world since their introduction to the market more than twenty years ago. Currently, there are six statin drugs available on the market – pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin and fluvastatin. Because pitavastatin is more commonly prescribed in Asian patients, trial results are more generalizable to the wider Asian population.1 Statins inhibit HMG-CoA, which is a rate limiting step in cholesterol biosynthesis.2 Statin therapy has been shown to be effective in lowering low density lipoprotein cholesterol (LDL-C) levels 20-50%, as well as lowering triglyceride levels 10-20% and causing a possible rise in serum high density lipoprotein cholesterol (HDLC) levels (5-10%).2-4 Despite growing interest in the non-cardiovascular benefits of statins, there has so far been little evidence to support their use in this setting. There is a strong body of evidence supporting the cardiovascular benefits of stating therapy. A January 2013 Cochrane Review article based on 18 randomised control trials with a total of 56,934 participants found that statin therapy reduced all-cause mortality [odds ratio (OR) 0.86, 95% confidencre Interval (CI) 0.79-0.94], reduced fatal and non-fatal cardiovascular events [relative risk (RR) 0.75 95% CI 0.67-0.80], and reduced the incidence of fatal and non-fatal stroke (RR 0.78, 95% CI 0.68-0.89).2 The Cholesterol Treatment Trialists' (CTT) Collaboration in 2010 performed a meta-analysis of 26 trials (21 comparing statins to placebo and five comparing low and high intensity statin therapy), with a total of more than 170,000 participants and a median follow-up of nearly five years. This meta-analysis found an overall reduction in all-cause mortality of 10% for every 1.0 mmol/L reduction in LDL-C levels (RR 0.90, 95% CI 0.87-0.93) ($p < 0.001$).5 Additionally, there were significant reductions in major vascular events including both myocardial infarction and ischaemic stroke. Due to the overwhelming body of evidence supporting its use, statin therapy is recommended according to the guidelines of the American Heart Association6 and the European Society of Cardiology.7 Recently, concern has been expressed regarding the over-prescription of statin drugs as well as the potential for severe adverse effects from statin therapy. This has resulted in several patients ceasing statin therapy amid questions about the potential risk of long-term statin use.8 The aim of this article is to the review the current literature regarding the overall safety of statin therapy.

COMPARISON OF PITAVASTATIN TO OTHER STATINS

Pitavastatin is a fully synthetic HMG-CoA reductase inhibitor, and one of the most widely prescribed statins in Asia.9 Compared to other statin drugs, pitavastatin use showed a greater increase in patient HDL-C levels compared to atorvastatin in a head-to-head randomized controlled trial at 52 weeks in female patients with glucose intolerance and high LDL-C levels.9 The CHIBA trial assessed the efficacy of pitavastatin 2 mg vs. atorvastatin 10 mg in 201 Japanese patients with hypercholesterolemia, finding an equivalent reduction in LDL-C levels in both statins.10 A head-to-head trail comparing pitavastatin (2 mg/day) to atorvastatin (10 mg/day) and rosuvastatin (2.5 mg/day) in patients with high LDL-C levels showed that pitavastatin was comparable to the other two statins with regards to both LDL-C reduction and safety.1 The LIVES study is the largest post-market surveillance investigation assessing real world outcomes and safety in over 20,000 Japanese patients subsequent to treatment with pitavastatin, with follow-up at 104 weeks.11 The authors found that pitavastatin demonstrated a consistent reduction in LDL-C (31.3%) and triglycerides (21%), and an increase in HDL-C levels (5.9%) with no significant adverse events.11

Muscle: Myopathy and Rhabdomyolysis

The terminology used to describe muscle adverse effects of statins varies among authors, clinical trials, and consensus groups.24 The terminology used in this statement is provided in Table 1. The original definition of statin-induced myopathy,25 accepted by the FDA and specified in the current prescribing information for all statins that provide a definition, is unexplained muscle pain or weakness accompanied by a creatine kinase (CK) concentration >10 times the upper limit of normal (ULN); that is the terminology used here and in many previous reviews. Statin-induced rhabdomyolysis is a severe form of myopathy without a consistent definition, but with CK typically >40 times the ULN, which usually requires hospitalization, because muscle fiber necrosis results in myoglobinuria that can cause acute renal failure.

ome laboratories do not provide CK normal ranges for men and women separately. However, the ULN is substantially lower for women, presumably because of their smaller muscle mass. In a cohort of 1016 people all 70 years of age in Uppsala, Sweden, Carlsson et al26 found that the ULN for men was 4.98 microkatals per liter (298 U/L), compared with 3.01 microkatals per liter (180 U/L) for women. This should be taken into account when interpreting CK values. In addition, CK values are considerably higher in people of African ancestry than in whites, especially when men ≤55 years of age are compared.27 Median CK in black women appears to be comparable to that of white men, whereas median CK in black men up to the age of 55 years is close to twice as high as in black women.

Rhabdomyolysis during statin treatment was first reported in cardiac transplantation patients taking lovastatin with concomitant cyclosporine.28,29 The increased risk of myopathy caused by the interaction between cyclosporine and lovastatin was quickly recognized (see 3. Drug-Drug Interactions).30

A less severe case that met the definition of myopathy, without concomitant cyclosporine, was detected at about the same time during the course of a phase III study with lovastatin.31 These cases were unexpected because animal safety studies had not indicated myotoxicity, although subsequent investigations showed that myopathy could be readily produced in the cyclosporine-treated rat.32 Few drugs have adverse effects on skeletal muscle, but all statins can cause myopathy. These muscle symptoms are typically bilateral and symmetrical and always confined to skeletal muscle.33,34 Cardiomyopathy has never been associated with any statin, and in the 2 major trials of statin therapy in participants with heart failure, statins did not lead to symptomatic worsening of the condition or any increase in hospitalization.35,36 The excess risk of myopathy relative to placebo is <0.1% in large long-term RCTs with all currently marketed statins at up to maximum recommended doses.37–39 The risk is greatest in the first year of therapy40 and after a dose increase or the addition of an interacting drug. The risk of rhabdomyolysis is ≈ 0.01%4 and is potentially preventable by prompt cessation of statin treatment. In a retrospective cohort study, Graham et al23 searched the hospital records of >250 000 statin users and identified 24 patients who had been admitted to the hospital for rhabdomyolysis. For the statins most commonly used at the time of the study (atorvastatin, simvastatin, and pravastatin), the rate of hospitalization because of rhabdomyolysis was estimated as 0.44 per 10 000 patient-years (95% CI, 0.20–0.84) when used as monotherapy and 5.98 per 10 000 patient-years (95% CI, 0.72–216.0) when used together with a fibrate (predominantly gemfibrozil; see 3. Drug-Drug Interactions). Later studies have established that gemfibrozil has a pharmacokinetic interaction with all statins that is not shared by fenofibrate (see 3. Drug-Drug Interactions). Consequently, gemfibrozil is rarely used today, whereas there is little if any risk of myopathy/rhabdomyolysis using fenofibrate alone41 or when adding it to a statin.42 Nevertheless, the fenofibrate prescribing information recommends caution when using it alone or with a statin. As is the case for most drug adverse effects, the incidence of myopathy combined with the rarer rhabdomyolysis tends to increase with statin dose. This holds true for lovastatin, simvastatin, pravastatin, rosuvastatin, and pitavastatin, as well as cerivastatin, which was removed from the market in 2001. A clear dose-response relationship for myopathy has not been demonstrated with atorvastatin43 or fluvastatin.44 A meta-analysis of pooled individual patient data from early clinical trials of atorvastatin, as well as a cardiovascular outcome trial, comparing the lowest (10 mg) and highest (80 mg) doses of atorvastatin found no significant differences in the incidence of myopathy/rhabdomyolysis, which was well below 0.1% with both doses.43,45 In the EXCEL (Expanded Clinical Evaluation of Lovastatin) RCT,46 8245 patients were randomized to 5 equal groups for 48 weeks: placebo or lovastatin 20 mg once daily, 20 mg twice daily, 40 mg once daily, or 40 mg twice daily. There were 5 cases of myopathy, 1 in the 40-mg once-daily group and 4 in the 40-mg twice-daily group. (One of the 5 patients had preexisting chronic myalgia, and another engaged in regular strenuous exercise; both were able to continue taking lovastatin to the end of the study.) For simvastatin, the original dose range was 5 to 40 mg once daily, later extended to 80 mg once daily. The incidence of myopathy/rhabdomyolysis in the 5-year HPS (Heart Protection Study) RCT, which compared simvastatin 40 mg/d and placebo in 20 536 participants, was <0.1% in the simvastatin group.47 With simvastatin 80 mg, however, a large RCT (SEARCH [Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine]) in 12 064 participants followed up for a mean of 6.7 years showed that the risk of myopathy/rhabdomyolysis was unacceptably high at ≈0.9% for simvastatin 80 mg compared with 0.02% on simvastatin 20 mg.40 The 80-mg dose of simvastatin is still available for very limited prescription but not recommended except for patients who have taken simvastatin 80 mg/d uneventfully for at least 12 months. Thus, the recommended simvastatin dosage range has reverted to the original 5 to 40 mg once daily.

The dosage range of rosuvastatin is 5 to 40 mg once daily. The manufacturer sought approval for an original dosage of 5 to 80 mg, but the FDA and other regulatory agencies determined that the 1% risk of myopathy with rosuvastatin 80 mg was too great to support approval of that dose.48 For pitavastatin, the approved dosage range is 1 to 4 mg, although in phase II clinical studies, the drug was studied at doses as high as 64 mg/d.49 The incidence of myopathy and asymptomatic increases in CK >10 times the ULN starts to rise at 8 mg/d and increases thereafter with increasing dose.49 The manufacturer did not seek approval for doses higher than 4 mg.

Table 1. Risk factors associated with statin toxicity

Female gender
Age > 80
Hypothyroidism
Alcohol abuse
Polypharmacy
Multisystem diseases e.g. chronic kidney disease, diabetes mellitus, chronic liver disease
Frailty
Specific drug interactions (see section of pharmacokinetics)

Cerivastatin was originally approved with a maximum recommended dose of 0.3 mg/d, which was subsequently extended to 0.4 and 0.8 mg. Postmarketing surveillance found that these higher doses, especially 0.8 mg, were associated with a much greater risk of myopathy and rhabdomyolysis than other statins when given alone, but especially in combination with gemfibrozil,23,50 because of drug interactions. Approximately 30 deaths attributed to acute renal failure secondary to rhabdomyolysis were reported to the FDA. Furthermore, even at the maximal 0.8-mg dose, cerivastatin was not especially effective, producing a mean reduction in LDL-C of ≈40%.51 Regulatory agencies determined that the risk of rhabdomyolysis associated with cerivastatin across the dosage range was much higher than for other statins, and it was withdrawn worldwide in August 2001.23,50 It is still unclear why cerivastatin is so much more myotoxic than other statins. The experience with this drug, however, does demonstrate that the risk of statin myopathy/rhabdomyolysis is not reduced by very high potency per milligram of drug or by smaller reductions in LDL-C.

In addition to varying intrinsic myotoxicity among statins, there is considerable pharmacokinetic variability among the members of the class, with corresponding differences in susceptibility to drug interactions. This is discussed in 3. Drug-Drug Interactions. Most drugs that interact with statins increase the plasma concentration of the statin or its active metabolites, which is equivalent to taking a larger dose, and thereby increases the risk of myopathy/rhabdomyolysis. The most important pharmacokinetic difference among the statins is that only lovastatin, simvastatin, and atorvastatin are cytochrome P450 3A4 (CYP3A4) substrates and consequently are vulnerable to drug interactions with CYP3A4 inhibitors, some of which are commonly used.52 Because of the high first-pass metabolism of lovastatin and simvastatin, the effects of CYP3A4 inhibitors on these statins are greater than on atorvastatin.52

Risk Factors for Myopathy and Rhabdomyolysis

Because of the rarity of myopathy, and especially rhabdomyolysis, for all doses of all statins (except for simvastatin 80 mg), factors predisposing to these adverse effects are not well defined, but as with most drugs, older people appear to be more vulnerable.53,54 Hypothyroidism, preexisting muscle disease, and renal impairment are also possible causative factors, and commencement of treatment with an interacting drug is a well-established precipitant. Other suspected risk factors include female sex, diabetes mellitus, and Chinese (and possibly East Asian in general) ancestry.53

In several placebo-controlled cardiovascular outcome trials in patients with chronic kidney disease (CKD),55–57 impaired renal function did not appear to be a risk factor for myopathy for statins used at recommended doses for patients with renal insufficiency (Table 2). However, results from the SEARCH RCT did suggest that CKD was a risk factor for simvastatin 80 mg/d.53 To decrease the risk of myopathy, there are maximum dose recommendations for several statins when used in patients with renal impairment.

As noted previously, higher statin doses result in higher plasma levels of statins and their active metabolites, which increases the risk of myopathy or rhabdomyolysis. Pasanen et al59 reported that blood levels of simvastatin acid (a primary active metabolite of simvastatin) were ≈3 times higher in participants with the c.521CC genotype than in those with the c.521TT reference genotype in SLCO1B1 on chromosome 12, which encodes OATP1B1 (organic anion transporting polypeptide 1B1), a transporter that facilitates hepatic uptake of statins. A genome-wide association study in participants from the SEARCH RCT53 evaluated 85 subjects who had developed definite myopathy (defined as muscle symptoms with CK >10 times the ULN) or "incipient myopathy" (defined as CK >3 times ULN and >5 times baseline levels, plus alanine aminotransferase [ALT] >1.7 times baseline levels without an elevated ALT alone at any other visit, with or without muscle symptoms) on simvastatin 80 mg and compared them with 90 participants who were also allocated to simvastatin 80 mg but did not develop definite or incipient myopathy. The only strong genetic association with myopathy involved the SLCO1B1 c.521C variant allele, which had an odds ratio (OR) for myopathy of 4.5 per copy of the C allele and 16.9 for the CC genotype compared with the TT genotype. However, evidence supporting the association of this or any other polymorphism with myopathy induced by other statins remains limited. Moreover, polymorphisms in the SLCO1B1 gene account for a small proportion of cases of statin-induced myopathy.

Clinical Approach to Myopathy or Rhabdomyolysis on Statin Therapy

Typically myopathy presents within a few months after starting or increasing the dose of a statin or after introduction of an interacting drug. When a patient reports unexplained muscle aches or weakness, it is important for the clinician to inquire about symptom characteristics. Most commonly, patients present with symptoms that are distributed proximally (eg, hip flexor region, upper chest and shoulders) and bilaterally. Nonspecific lower back pain can also be a presenting feature of statin-induced myopathy.

Before statin-induced myopathy (or rhabdomyolysis) is diagnosed, other causes need to be considered. For example, unusual or strenuous exercise is a common cause of muscle symptoms and can produce substantial elevations in CK.60 In addition, hypothyroidism should always be ruled out, because it is associated with muscle weakness and increased CK levels.

CK should be measured in any patient presenting with significant unexplained muscle symptoms or unexplained increases above 3 times the ULN in transaminases, because these enzymes are found in muscle and liver. Failing to measure CK can result in missing a diagnosis of myopathy, which is likely to progress to rhabdomyolysis and possibly acute kidney injury (AKI) if the statin is not stopped. Drug interactions (considered in more detail in 3. Drug-Drug Interactions) are a common cause of elevated CK and myopathy/rhabdomyolysis and should always be considered. If CK is elevated >10 times the ULN (or >5 times the ULN in a vulnerable patient), the statin should be stopped immediately, as the prescribing information warns, and high fluid intake started; if CK is considerably elevated and the patient is considered to be at risk of acute renal failure based on the CK level and presence of comorbidities, hospitalization might be required. Discontinuation of the statin in a patient with statin-induced myopathy is typically followed by a falling CK and resolution of symptoms, but recovery can be prolonged in patients with more severe muscle injury. If the symptomatology and laboratory abnormalities do not improve soon after discontinuation of statin therapy, the patient should be referred to a muscle specialist to consider other diagnoses such as polymyalgia rheumatica, mitochondrial myopathies, and the very rare statin-associated autoimmune myopathy (or immune-mediated necrotizing myopathy) thought to occur in 2 to 3 patients per 100 000 treated with statins, which is variably reversible with statin discontinuation.61

If CK is moderately elevated (eg, between 3 and 4 times the ULN), and the symptoms are mild, the statin can be continued, with another measurement in a few days. If the CK concentration is falling or stable, the statin can be continued, with further follow-up and the timing thereof depending on the CK level, symptoms, and medical history.

Athletes/Exercise Enthusiasts

Limited evidence suggests that statins can amplify the CK increases that commonly occur after vigorous exercise.62,63 Some practitioners advise the suspension of a statin a day or two before a marathon or other competitive strenuous exercise. Whether this has any meaningful impact on performance or muscle symptoms is unclear given that RCTs investigating fitness or muscle performance have typically not been double-blind64 or have yielded no significant differences between statin- and placebo-treated participants.65,66

Muscle Symptoms Without Significant CK Elevations

Drugs that have rare but serious adverse effects typically also have less serious adverse effects of the same type that occur more commonly. For example, anticoagulant drugs occasionally cause major intracranial or gastrointestinal hemorrhage but much more commonly cause bruises, nosebleeds, or bleeding gums. Many patients report adverse events during statin therapy, most commonly muscle symptoms (muscle pain or weakness), and some find the symptoms intolerable and stop the statin. With the knowledge that all statins rarely cause myopathy/rhabdomyolysis, it is natural to expect them to also cause muscle adverse effects that are less serious but more common.

Muscle symptoms are commonly designated as statin-associated muscle symptoms (SAMS),24 a term that does not indicate or imply a causal relationship between the statin and the symptoms. Muscle symptoms are common in middle-aged and older people when not treated with statins. SAMS are usually not accompanied by significant elevations in CK or other objective measures.24 The next section reviews data from observational studies and randomized trials that reported SAMS that occurred during statin therapy.

Clinical Approach to Muscle Symptoms

Most clinicians who regularly prescribe statins are aware that statins are well tolerated in clinical trials and by most patients in clinical practice. Nevertheless, when symptoms, most commonly muscle symptoms (which might include pain, aches, stiffness, cramps, weakness, or muscular fatigue), appear soon after starting treatment with a statin, and no other causes are clearly discernible, it is reasonable to recommend a "statin holiday" for 1 to 2 weeks and determine whether symptoms resolve. If so, it can be difficult for both clinicians and patients to believe the symptoms are not caused by the statin. A successful rechallenge without symptoms would provide evidence that the initial SAMS were unrelated to statin therapy, but sometimes the symptoms recur with each rechallenge. Although SAMS can usually be explained by patient expectations of harm, as discussed previously, the symptoms are real and can be severe. SAMS are a common cause of stopping statins and a barrier that impedes long-term adherence.10 As expected, discontinuation is strongly associated in observational studies with higher cardiovascular event rates.101

When a patient reports muscle symptoms, the possibility of an adverse statin drug interaction should be borne in mind and dealt with, as addressed elsewhere in this statement (see 3. Drug-Drug Interactions). If the symptoms are concerning, it is important to check CK, primarily to assess the possibility of myopathy/rhabdomyolysis, but also because a normal value (if obtained) might help reassure the patient that muscle injury has not occurred and enable continuation of treatment or acceptance of rechallenge with the same statin. The rechallenge is usually done at a lower dose, or with an alternative statin, given daily or several times a week. Measurement of vitamin D might be useful, because vitamin D deficiency can cause muscle pain independent of statin use.102 Observational studies evaluating the association of low levels of 25-hydroxy vitamin D with muscle symptoms in statin-treated patients have produced conflicting results.103–108 No controlled clinical trials have yet addressed whether vitamin D supplementation improves SAMS. Coenzyme Q10 is derived from mevalonate, the product of the enzyme HMG-CoA reductase that is inhibited by statins. It has been proposed as a treatment for muscle symptoms during statin therapy, but the RCT evidence is not supportive,83,109 consistent with the conclusion that the muscle symptoms are rarely caused by the statin.

If SAMS do not resolve within a few weeks after statin cessation (and especially with elevated CK levels), other causes for the muscle symptoms, such as an underlying neuromuscular disorder, including polymyalgia rheumatica, severe vitamin D deficiency, or, very rarely, immune-mediated necrotizing myositis, should be considered. If persistent muscle symptoms are clinically significant, the patient should be referred to a neuromuscular specialist for evaluation and treatment. The substantial advantage of remaining on statin therapy should be discussed with the patient.

Table 1. Muscle Adverse Event Terminology

Adverse Event Term	Definition
SAMS	Muscle symptoms reported during statin therapy but not necessarily caused by the statin
Myalgia	Muscle pain or aches
Myopathy	Unexplained muscle pain or weakness accompanied by CK concentration >10 times ULN
Rhabdomyolysis	Severe form of myopathy, with CK typically >40 times ULN, which can cause myoglobinuria and acute renal failure

CK indicates creatine kinase; SAMS, statin-associated muscle symptoms; and ULN, upper limit of normal.

Agent	Major Clearance Pathway	Dose Adjustment in Mild-Moderate CKD	Use in ESRD	Use After Transplantation
Atorvastatin	Mainly hepatic	None needed	Can be used	Avoid with cyclosporine
Fluvastatin	Mainly hepatic	None needed	Not studied at doses >40 mg/d	Do not exceed 20 mg/d with cyclosporine‡
Lovastatin	Mainly hepatic	Maximum dose 20 mg/d if eGFR <30 mL/min	Not discussed in PI	Avoid with cyclosporine
Pitavastatin	Both hepatic and renal	Maximum dose 2 mg/d	Maximum dose 2 mg/d	Contraindicated with cyclosporine
Pravastatin	Both hepatic and renal	None specified	Maximum dose 20 mg/d	Maximum dose 20 mg/d with cyclosporine
Rosuvastatin	Both hepatic and renal	None specified	Maximum dose 10 mg/d	Maximum dose 5 mg/d with cyclosporin
Simvastatin	Mainly hepatic	None specified	Use caution, start at 5 mg/d	Contraindicated with cyclosporine

CKD indicates chronic kidney disease; EGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; and PI, prescribing information.

Nearly all of the statin drugs are associated with musculoskeletal side effects. Myalgia is the most common symptom, and myositis is less common and associated with a rise in creatine kinase (CK). Rhabdomyolysis is the most severe musculoskeletal form observed, with a rise in CK greater than 10x the upper limit of normal with associated features including myoglobinuria, renal impairment and serum electrolyte abnormalities.12 Overall, the rates of severe musculoskeletal side effects from the current statin drugs are low.12,13 There are variable rates of myopathy reported in the literature ranging from 0.1-10%, but it must be noted that many of these studies use different definitions, have variable methods of data collection and have high rates of reporting bias. Khan et al. (2015) assessed the patient characteristics of more than 10,000 statin users in the United States. Myalgia was a common cause of discontinuation, with over 60% of patients who had ceased statin therapy reporting musculoskeletal side effects compared with only 25% in current statin users.13 Of the nine trials included in the Cochrane Review which reported musculoskeletal side effects, 3551 participants out of a total of 37,939 patients developed symptoms of myalgia (9.4%). There was no evidence of excess risk with a pooled estimate of 1.03 (95% CI, 0.97-1.09). Rhabdomyolysis occurred very rarely, affecting just 3 out of 19,410 participants in a total of six trials (0.02%).2 The Heart Protection Study which investigated the use of simvastatin compared with placebo in a group of more than 20,000 patients reported an annual myopathy risk of 0.01%, with a total of five cases of rhabdomyolysis in the treatment arm compared with three in the placebo arm. Forty-nine patients (0.5%) in the statin arm and 50 (0.5%) in the placebo arm had ceased therapy due to side effects.14 The large Cholesterol Treatment Trialists' meta-analyses found overall rates of rhabdomyolysis were 1 per 10,000 patients in both the statin and placebo groups. The more intensive statin group had a slightly higher risk of rhabdomyolysis (4 per 10,000) compared with 2 per 10,000 in the less intensive group. The LIVES observational study reported only one case of rhabdomyolysis and one case of muscle weakness amongst 20,000 patients treated with pitavastatin.11 Although the overall incidence of adverse effects was 10.4%, the proportion of patients who had myalgia and other musculoskeletal side effects was not reported.11 All of the major statin trials including large metaanalyses have concluded that severe musculoskeletal side effects from statin use are rare, and that the overall benefits of statin therapy outweigh this small risk (with current recommendations for close clinical monitoring of patients. The exact mechanism of statin-related myopathy is unknown, though it involves a complex interplay of drug, patient-related factors and concomitant therapy.15 Statins have been associated with mitochondrial dysfunction associated with a reduction in co-enzyme Q10 levels.15,16 Another mechanism is the lowering of farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are end products of the mevalonate pathway and thus involved in maintenance of cell growth.15 Statins have also been shown to alter cholesterol content in skeletal muscle cells which alters the flow of ion channels including calcium, making them vulnerable to cell injury and death.15 Drug-related factors increase the risk of statin toxicity; more intensive statin therapies and higher doses have been associated with higher rates of toxicity.5 Although more potent statins were assumed to have higher rates of myopathy, this phenomenon has not been clearly demonstrated.17 The interactions between statins and other drugs is a very strong risk factor in the development of toxicity. Statin rechallenge remains a clinical dilemma in patients who develop musculoskeletal side effects. Importantly, such statin use has to be individualised to every patient, and there are several factors which warrant consideration. A recent study found that increased age, body mass index and female gender were all associated with poor tolerance to statin rechallenge.18 Statin-related myalgia should only be diagnosed following clinical assessment to exclude other causes of myalgia and weakness. It is not uncommon for elderly patients to have underlying arthritis, tendonitis or neuropathy which may be misdiagnosed as myalgia related to statins, and rare inflammatory myopathy should also be excluded.19

The overall cardiovascular risk for each patient should be assessed so clinicians have a better understanding of the larger risk vs. benefit analysis, which is crucial for informed consent.16 A recent randomised trial did not find any improvement in statin-related myalgia with the addition of co-enzyme Q10.20 Fung et al. (2012)19 reported outcomes in patients attending a large lipid clinic, describing overall rates of statin-related myopathy in 108/ 1056 patients. However, further clinical assessment showed that 55 other patients had musculoskeletal symptoms that were unrelated to statin therapy. Interestingly, the patients with statin-related myopathy were more likely to be female (62%), with a higher median erythrocyte sedimentation rate (14 vs. 8 mm/hr, p = 0.035) and were more likely to be prescribed simvastatin (98.1%).19 There were similar rates of myopathy with rechallenge using atorvatstain, rosuvastatin, pravastatin and fluvastatin (between 60-80%), although the study was not sufficiently large to conclusively answer this clinical question. Monotherapy with ezetimibe or fibrates was associated with lower rates of myopathy (between 17-31%).19 The authors commented that "…atorvatstain and rosuvastatin were both reasonable choices. They have an added advantage of long half-lives enabling alternate day or twice weekly dosing strategy further minimizing the occurrence of statin myopathy." 19 Based on currently available evidence, it is reasonable for patients with mild musculoskeletal complaints or established mild rises in CK to continue with statin therapy at lower dosing regimens, with close clinical monitoring. Patients with serious adverse effects such as rhabdomyolysis should not continue with statin therapy, and monotherapy with ezetimibe could be considered. For the spectrum of patients whose circumstances fall in between these two categories, we would suggest careful clinical assessment to exclude other causes of myalgia. Treatment decisions need to be based on the cardiovascular risk of each patient. If cardiovascular risk is high then we would suggest rechallenging with another statin such as atorvatstatin or rosuvastatin with a modified dosing regimen (such as twice weekly) with close clinical observation (Table 1).

Table 2. Pharmacokinetic properties of statins

	Pitavastatin	Atorvastatin	Rosuvastatin	Simvastatin	Pravastatin	Fluvastatin
Half life (hours)	12	15-30	19	2-3	1.3-2.8	0.5-2.3
Bioavilability (%)	60	12	20	5	18	19-29
Protein binding (%)	> 99	80-90	88	94-98	43-55	> 99
Solubility	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic
Metabolism (cytochrome P450)	CYP2C9	CYP3A4	CYP2C9	CYP3A4, 3A5	-	CYP2C9
Urinary excretion (%)	< 2	2	10	13	20	6
Faecal excretion (%)	80	70	90	58	71	90
Common drug interactions (increase toxicity risk)	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metroniadazole Gemfibrozil	Amiodarone Grapefruit Juice Protease inhibitors Azole antifungals Macrolide antibiotics Verapamil Cyclosporin Sildenafil Tacrolimus Colchicine	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metroniadazole Gemfibrozil	Amiodarone Grapefruit Juice Protease inhibitors Azole antifungals Macrolide antibiotics Verapamil Cyclosporin Sildenafil Tacrolimus Colchicine	Colchicine Gemfibrozil	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metroniadazole Gemfibrozil

HEPATIC DYSFUNCTION

Statin therapy has been associated with elevated hepatic transaminases in up to 1-3% of patients.21 This usually is dose dependent and occurs within the first three months of commencing therapy, and is not usually associated with any long-term hepatic dysfunction.21 There also appears to be no significant differences amongst the different statin drugs with regards to rates of hepatotoxicity. Russo et al.21 reported a total of 22 cases involving statin use in a prospective registry of 1188 patients with drug-induced liver injury between 2004 and 2012. Of these patients, the majority were female (68%), with a varied latency of onset from 34 days to 10 years (median 155 days) associated with a variety of cellular injury mechanisms. Interestingly, they reported that the condition of four of these patients progressed to chronic liver disease, mainly of the autoimmune phenotype.21 A Cochrane Review more than 18 trials examining the role of statin therapy in primary prevention reported weak evidence of an increased risk of elevated hepatic enzymes with statin use (RR 1.16 95% CI 0.87-1.54).2 Another large meta-analyses focusing on the side effect profile of 35 statin trials found a slightly increased rate of elevation in liver enzymes with statin use compared with placebo (1.4% vs. 1%, 4.2 patients per 1000 cases).22 The LIVES study reported liver function test derangement in two patients while another seven patients had liver disorders or hepatic dysfunction of a different nature related to pitavastatin use (of the 20,000 patients included).11 The clinical significance of this "transaminitis" is uncertain, with the vast majority of patients being asymptomatic. Cases of hepatic failure due to statin use have otherwise been exceedingly rare, with case reports providing the primary bulk of evidence. Although it is useful to assess baseline liver function, routine monitoring of liver function tests is not recommended. Patients with mild derangement of LFT's use can safely continue statin therapy with close monitoring.

DIABETES MELLITUS

Statins have been shown to increase the risk of diabetes mellitus in that they can disrupt insulin signalling pathways, affect pancreatic beta cell function and may contribute to increased insulin resistance.23,24 A metaanalysis by Satter et al. of 13 trials found an increased risk of new onset diabetes after a median four-year follow up of 9% (HR 1.09, 95% CI 1.02-1.17). This correlated to a new case of diabetes mellitus for every 255 patients treated for at least four years with statin therapy.23,25 A meta-analyses in 2011 by Preiss et al. of five large randomised control trials with 32,752 patients found increased rates of diabetes with intensive dose statin regimen compared with moderate dose regimen (1449 vs. 1300 patients). Overall statin therapy was associated with an increased risk of new onset diabetes (OR 1.12 95% CI 1.04-1.22).26 A recent meta-analysis found that the risk of diabetes mellitus was increased with the use of more potent statins at higher doses.27 Hyun et al. (2015) reported an increased insulin resistance in nondyslipidemic Asian patients following statin use.28

Interestingly, not all statin drugs have been shown to be diabetogenic. Of the 1197 patients in the LIVES study who had diabetes mellitus as well as hypercholesterolemia, treatment with pitavastatin was not found to affect glucose metabolism. However, 1 patient had new onset diabetes mellitus during follow-up.11 A reduction in HbA1c at 104 weeks was noted in patients who were on treatment for diabetes at baseline (reduction of 0.28%, $p < 0.001$). Multivariate analysis showed that the percentage change in LDL and triglyceride levels were all clinical factors which influenced the decrease in HbA1c.11 There is evidence to suggest that some statins are potentially diabetogenic, and the risk appears to be dose-related.27 However, diabetic patients are one of the groups that benefits most from statin therapy with regards to cardiovascular risk. There is no convincing evidence indicating that statin therapy in diabetics may contribute to worsening glycaemic control. Overall, the cardiovascular protective benefits of statins outweigh the concerns associated with risk of diabetes mellitus.29 It is important that patients are informed of this risk prior to commencing therapy and routine monitoring of blood glucose levels is recommended.

RENAL

Statins can influence the kidney in two main pathways. Rhabdomyolysis can induce tubular obstruction causing tubular injury and ischaemia. Statin therapy can be associated with a benign proteinuria due to inhibition of the tubular reabsorption of small molecular weight proteins.30 The clinical significance of this mild proteinuria is unknown, as the protein differs from that of other glomerular diseases.30 There has been no evidence of long-term renal dysfunction from statin therapy. There is some evidence regarding the protective effects of statin therapy. A large meta-analysis examining 27 studies with over 39,000 patients conducted by Sandhu et al. (2006)31 found a statistically significant reduction in the decline of glomerular filtration rate (GFR) (0.93 ml/min per year, 95% CI 0.10-1.76) in patients on statin therapy compared to controls in patients with cardiovascular disease.31 There was no significant difference in patients with diabetic or hypertensive kidney disease.31 Bianchi et al. (2004)32 also noted a reduction in proteinuria with the addition of atorvastatin to the combination with angiotensin converting enzyme inhibitors and angiotensin-converting enzymes.32 The LIVES study noted a rise in eGFR of 5.4 ml/min) at the end of the follow-up period with the use of pitavastatin.11 Multivariate analysis showed that the absence of proteinuria at baseline and an increase in HDL levels were associated with improvement in GFR.11 More recently there have been negative trials, primarily the PREVENDIT,33 ESPLANADE34 and PLANET35 trials, that all found no reduction in proteinuria with statin use. There remains concern regarding possible acute kidney injury following the introduction of statin therapy.36 Dormuth et al.37 conducted a large real-world retrospective observational analysis of more than 2 million patients on statin therapy with no prior history of chronic kidney disease, and another 59,636 patients with chronic kidney disease. Within 4 months of statin therapy there were 4691 hospitalisations for acute kidney injury (AKI) in patients with no prior kidney disease (0.2%), and 1896 hospitalisations in those patients with known chronic kidney disease (3%). Patients with high potency statins were 34% more likely to be hospitalised with AKI for patients with no prior kidney disease compared to low intensity regimens.37 A similar finding was not significant in patients with chronic kidney disease. The authors found that this increase in AKI risk was strongest in the first 4 months following initiation of statin therapy.37 There is a large proportion of patients on statin therapy with underlying chronic kidney disease (CKD).

Chronic kidney disease is a strong predictor and risk factor for cardiovascular disease. Based on the large 4-D38 and AURORA39 trials, there is currently no significant evidence to suggest a protective role of statin therapy for patients on dialysis. Both of these trials found no significant benefit in overall mortality or cardiovascular outcomes.38,39 However, in patients who are not dialysis-dependent, statins have been shown to improve cardiovascular outcomes.40 Overall, statins are well-tolerated in patients with CKD with no significant increase in adverse events. The UK-HARP-1 study41 which investigated the safety of statin use in the CKD population found no significant increase in CK levels or LFT derangement. Other large trials investigating statin use in this population have also reported similar findings.38,40 It is worth noting that combination therapy with ezetimibe was associated with higher rates of myalgia in the SHARP study.40 We would suggest continued statin therapy in patients with CKD with clinical monitoring for adverse effects similar to non-CKD patients. We would avoid the use of high dose statin therapy or combination therapy with fibrates or ezetimibe unless patients have increased cardiovascular risk, or have not achieved adequate LDL level reduction. In the dialysis population we would not suggest commencing statin therapy in patients with mildly elevated LDL levels. Statin therapy should be considered in patients following acute coronary syndrome or in patients with high cardiovascular risk, although vigilance is required to monitor for adverse effects. We would avoid the use of high dose statins or combination therapy with fibrates/ezetimibe, despite the lack of conclusive evidence suggesting an increase in complication rates.

MALIGNANCY

The role of statins in malignancy is somewhat clouded by an array of mixed evidence suggesting both a protective role as well as being a potential risk factor. Animal studies have shown the link between high dose statin therapy and liver tumours in rodent models.42 However a recent clinical trial showed a reduction in liver cancers with statin use.42 Both the Cochrane Review of statin therapy in primary prevention and the Cholesterol Treatment Trialists' meta analyses have not shown any increase in cancer risk with statin therapy.2,5 The Heart Protection study and the West Scotland Coronary Prevention Study (WOSCOPS), which have extended follow-up periods of more than 10 years, have also not shown any difference in the rates of malignancy with long-term statin therapy.14,43 A recent meta-analysis suggested that long-term statin use reduced the risk of some haematological malignancies.44 Statin use was associated with a reduction in malignancy risk in postmenopausal women in the Women's Health Initiative.45 The sources of evidence will continue to improve once long-term follow-up data of the early statin trials are published. However, it is reassuring that long-term statin therapy appears to be safe for the majority of patients.

NEUROLOGICAL

There have been case reports of statin use associated with peripheral neuropathy, mood symptoms and irritability.46 To date, there is no proven association between statin use and increase in suicide.47 Despite some early reports of an increase in haemorrhagic stroke with statin use, this has not been substantiated in larger clinical trials and the protective aspects from recurrent ischaemic stroke outweigh these potential risks.30,48 There has been some concern regarding cognitive dysfunction in patients on long-term statin therapy.30 Interestingly, statins have also been shown in some retrospective studies to reduce the risk of Alzheimer's disease.49

The mechanisms that may be involved include the interaction with cholesterol and amyloid processing, as well as the indirect effect via stroke prevention. A recent systematic review did not find any overall increased risk of dementia with long-term statin use.49

RESPIRATORY

There have been case reports of interstitial lung disease associated with statin use.50 The mechanism for cellular injury is not well understood, and patients have usually responded to corticosteroid or immunosuppressive therapy. A recent cohort study did not demonstrate any increased risk of interstitial lung disease with statin use.50 Statins can safely be prescribed in patients with chronic respiratory diseases, and routine monitoring of lung function is not recommended in the absence of symptoms.

DRUG INTERACTIONS

Clinically, it is important to note that statin drugs have multiple potential drug interactions which may increase the risk of myopathy and other drug toxicities. All statin drugs other than pravastatin are metabolised by the cytochrome p450 group of enzymes. Inhibitors of these enzymes may increase levels of statins and may be associated with an increased risk of toxicity. Atorvastatin, simvastatin and pravastatin are also substrates for P-glycoprotein, which are active transport drug channels in the gastrointestinal tract. A summary of common drug interactions and pharmacokinetic properties is provided in Table 2.

COMMON DRUG INTERACTIONS

The combined use of statin and fibrate drugs for mixed dyslipidemia is associated with an increased risk of myopathy up to 5%.19 Gemfibrozil interacts with multiple statin drugs via the CYP3A4 enzyme and glucoronic dation pathways, and should be avoided. Grapefruit juice is a potent inhibitor of cytochrome p450 3A4 and can increase the risk of toxicity with atorvastatin, lovastatin and simvastatin. Patients should be advised to avoid grapefruit juice if on these medications. Pravastatin has the least drug interactions amongst the statin drugs and should be considered in patients who are on immunosuppression post-transplantation and in HIV patients on protease inhibitors. Due to the interaction with cyclosporine, other statin drugs if prescribed should be low dosing regimens with frequent clinical monitoring for side effects. Anti-epileptic drugs such as phenytoin, carbamazepine and phenobarbitone are potent inducers of cytochrome p450 enzymes and may be associated with reduced statin drug levels. A dose adjustment or a switch to pravastatin may be required in these patients.

Summary

• Hydroxymethyl glutaryl coenzyme A reductase (HMGCoA) inhibitors, commonly called statins are one of the most commonly prescribed medications in Asia.

• Statins are the most potent drugs that lower LDL cholesterol.

• There is extensive evidence to suggest that statin therapy has significant mortality and morbidity benefit for both primary and secondary prevention from cardiovascular disease.

• Myalgia is the most common side effect from statin use with rates from 1-10% of patients.

• Rhabdomyolysis is the most serious adverse effect from statin use and is very rare (less than 0.1%).

• The most common risk factors for statin-related myopathy include hypothyroidism, polypharmacy, alcohol abuse and patients with multiple medical co-morbidities.

• Derangement in liver function tests is common, affecting up to 1% of patients; however the clinical significance of this is unknown.

• Some statin drugs are potentially diabetogenic and the risk appears to increase in those on higher doses.

• Pitavastatin is not associated with an increased risk of diabetes mellitus.

• Statins have not be proven to increase the risk of malignancy, dementia, mood disorders, interstitial lung disease and acute interstitial nephritis.

• Statins have multiple drug interactions, primarily those which interact with the cytochrome p450 enzymes.

• Statins can safely be used in patients with CKD, although clinicians should be cautious in using high-dose statins and combination therapy with fibrates/ezetimibe.

• Pravastatin has the least drug interactions amongst the statin drugs.

• Overall statin drugs appear to be safe in the vast majority of patients and the protective benefits of statin therapy far outweigh the potential risks.

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