

Statin Therapy: Review of Safety and Potential Side Effects

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Background: Hydroxymethyl glutaryl coenzyme A reductase inhibitors, commonly called statins, are some of the most commonly prescribed medications worldwide. Evidence suggests that statin therapy has significant mortality and morbidity benefit for both primary and secondary prevention from cardiovascular disease. Nonetheless, concern has been expressed regarding the adverse effects of long term statin use. The purpose of this article was to review the current medical literature regarding the safety of statins.

Methods: Major trials and review articles on the safety of statins were identified in a search of the MEDLINE database from 1980 to 2016, which was limited to English articles.

Results: Myalgia is the most common side effect of statin use, with documented rates from 1-10%. Rhabdomyolysis is the most serious adverse effect from statin use, though it occurs quite rarely (less than 0.1%). The most common risk factors for statin-related myopathy include hypothyroidism, polypharmacy and alcohol abuse. 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 patients on higher doses. Pitavastatin has not been associated with increased risk of diabetes. Statins have not been proven to increase the risk of malignancy, dementia, mood disorders or acute interstitial nephritis. However, statins do have multiple drug interactions, primarily those which interact with the cytochrome p450 enzyme group.

Conclusions: Overall, statin drugs appear to be safe for use in the vast majority of patients. However, patients with multiple medical co-morbidities are at increased risk of adverse effects from long-term statin use.

Key Words: Dyslipidemia • Hypercholesterolemia • Statin

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, atorva-

statin, 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

Statin 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 (HDL-C) 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 statin therapy. A January 2013 Cochrane Review article based on 18 randomised

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control trials with a total of 56,934 participants found that statin therapy reduced all-cause mortality [odds ratio (OR) 0.86, 95% confidence 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 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 trial 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

MUSCULOSKELETAL

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 meta-analyses 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 atorvastatin, 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 "...atorvastatin 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 atorvastatin or rosuvastatin with a modified dosing regimen (such as twice weekly) with close clinical observation (Table 1).

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-analysis 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.

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)

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 meta-analysis 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-analysis 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 non-dyslipidemic 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 PREVENT-IT,³³ ESPLANADE³⁴ and PLANET³⁵ trials, that all found no reduction in proteinuria with statin use.

There remains concern regarding possible acute kid-

ney 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 glucuronidation.

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
Bioavailability (%)	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 Metronidazole Gemfibrozil	Amiodarone Grapefruit Juice Protease inhibitors Azole antifungals Macrolide antibiotics Verapamil Cyclosporin Sildenafil Tacrolimus Colchicine	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metronidazole Gemfibrozil	Amiodarone Grapefruit Juice Protease inhibitors Azole antifungals Macrolide antibiotics Verapamil Cyclosporin Sildenafil Tacrolimus Colchicine	Colchicine Gemfibrozil	Diclofenac Amiodarone Azole antifungals Protease inhibitors Metronidazole Gemfibrozil

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.³⁸

SUMMARY

- Hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) 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 been 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.

CONFLICTS OF INTEREST

None to declare.

REFERENCES

1. Saku K, Zhang B, Noda K. Randomized head-to-head comparison of pitavastatin, atorvastatin, and rosuvastatin for safety and efficacy (quantity and quality of LDL)-The PATROL trial. *Circ J* 2011; 75(6):1493-505.
2. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;1(1).
3. Huang WC, Lin TW, Chiou KR, et al. The effect of intensified low density lipoprotein cholesterol reduction on recurrent myocardial infarction and cardiovascular mortality. *Acta Cardiol Sin* 2013;29(5):404-12.
4. Odden MC, Pletcher MJ, Coxson PG, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States; statins for primary prevention in U.S. adults aged 75 years or older. *Ann Intern Med* 2015;162(8):533-41.
5. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376(9753):1670-81.
6. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25 Suppl 2):S1-45.
7. Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation, Authors/ Task Force Members, Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;32(14):1769-818.
8. Logue J, AL-Ghibiwi H, Alamri AA, Preiss D. Systematic review of studies exploring reasons for statin non-adherence and of randomised controlled trials of interventions to improve adherence. *Atherosclerosis* 2015;241(1):e52.
9. Sasaki J, Ikeda Y, Kuribayashi T, et al. A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance. *Clin Ther* 2008;30(6):1089-101.
10. Yokote K, Bujo H, Hanaoka H, et al. Multicenter collaborative randomized parallel group comparative study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients: collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). *Atherosclerosis* 2008;201(2):345-52.
11. Yokote K, Shimano H, Urashima M, Teramoto T. Efficacy and safety of pitavastatin in Japanese patients with hypercholesterolemia: LIVES study and subanalysis. *Expert Rev Cardiovasc Ther* 2011;9(5):555-62.
12. Pedro-Botet J, Núñez-Cortés JM, Flores JA, Rius J. Muscle symptoms related with statin therapy in general practice. *Atherosclerosis* 2011;211(1):e197.
13. Khan A, Maki KC, Ito MK, et al. Statin associated muscle symptoms: characteristics of patients and recommendations by providers. *J Clin Lipidol* 2015;9(3):460.
14. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360(9326):7-22.
15. Bitzur R, Cohen H, Kamari Y, Harats D. Intolerance to statins: mechanisms and management. *Diabetes Care* 2013;36(Supplement 2):S325-30.
16. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society consensus panel statement on assessment, aetiology and management. *Eur Heart J* 2015;36(17):1012-22.
17. García-Rodríguez LA, Massó-González EL, Wallander MA, Johansson S. The safety of rosuvastatin in comparison with other statins in over 100,000 statin users in UK primary care. *Pharmacoepidemiol Drug Saf* 2008;17(10):943-52.
18. Clark D, Brennan D, Rocco M, et al. Clinical characteristics associated with complete statin intolerance: the Cleveland clinic experience. *J Am Coll Cardiol* 2016;67(13_S):1895.
19. Fung EC, Crook MA. Statin myopathy: a lipid clinic experience on the tolerability of statin rechallenge. *Cardiovasc Ther* 2012; 30(5):e212-8.
20. Buettner C, Davis RB, Phillips RS, Mittleman MA. COQ10 does not improve statin myalgia—a randomized controlled trial. *Atherosclerosis* 2015;241(1):e206.
21. Russo MW, Hoofnagle JH, Gu J, et al. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network.

- Hepatol Baltim Md* 2014;60(2):679-86.
22. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006;114(25):2788-97.
 23. Bang CN, Okin PM. Statin treatment, new-onset diabetes, and other adverse effects: a systematic review. *Curr Cardiol Rep* 2014;16(3):461.
 24. Cederberg H, Stančáková A, Yaluri N, et al. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia* 2015;58(5):1109-17.
 25. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375(9716):735-42.
 26. Preiss D, Seshasai SRK, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305(24):2556-64.
 27. Navarese EP, Buffon A, Andreotti F, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. *Am J Cardiol* 111(8):1123-30.
 28. Hyun M, Choi BG, Seo HS, et al. Risk of increased insulin resistance with statin therapy for non-dyslipidemic asians. *Atherosclerosis* 2015;241(1):e196-7.
 29. Castro MR, Simon G, Cha SS, et al. Statin use, diabetes incidence and overall mortality in normoglycemic and impaired fasting glucose patients. *J Gen Intern Med* 2016;31(5):502-8.
 30. Brown WV. Safety of statins. *Curr Opin Lipidol* 2008;19(6):558-62.
 31. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006;17(7).
 32. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kidney Dis* 2003;41(3):565-70.
 33. Atthobari J, Brantsma AH, Gansevoort RT, et al. The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and an observational cohort study. *Eur Ren Assoc* 2006;21(11):3106-14.
 34. Ruggenenti P, Perna A, Tonelli M, et al. Effects of add-on fluvastatin therapy in patients with chronic proteinuric nephropathy on dual renin-angiotensin system blockade: the ESPLANADE trial. *Clin J Am Soc Nephrol* 2010;5(11):1928-38.
 35. de Zeeuw D, Anzalone DA, Cain VA, et al. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. *Lancet Diabetes Endocrinol* 2015;3(3):181-90.
 36. Bangalore S, Fayyad R, Hovingh GK, et al. Statin and the risk of renal-related serious adverse events: analysis from the IDEAL, TNT, CARDS, ASPEN, SPARCL, and other placebo-controlled trials. *Am J Cardiol* 2014;113(12):2018-20.
 37. Dormuth CR, Hemmelgarn BR, Paterson JM, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ* 2013;346:f880.
 38. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;353(3):238-48.
 39. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;360(14):1395-407.
 40. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;377(9784):2181-92.
 41. Baigent C, Landray M, Leaper C, et al. First United Kingdom heart and renal protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis Off J Natl Kidney Found* 2005;45(3):473-84.
 42. McGlynn KA, Hagberg K, Chen J, et al. Statin use and risk for primary liver cancer in the clinical practice research datalink. *J Natl Cancer Inst [Internet]* 2015;107(4).
 43. Ford I, Murray H, Packard CJ, et al. Long-term follow-up of the West of Scotland coronary prevention study. *N Engl J Med* 2007;357(15):1477-86.
 44. Pradelli D, Soranna D, Zamboni A, et al. Statins use and the risk of all and subtype hematological malignancies: a meta-analysis of observational studies. *Cancer Med* 2015;4(5):770-80.
 45. Wang A, Aragaki AK, Tang JY, et al. Statin use and all-cancer mortality: prospective results from the Women's health initiative. *Br J Cancer* 2016;115(1):129-35.
 46. Gaist D, Jeppesen U, Andersen M, et al. Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002;58(9):1333-7.
 47. Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med* 2003;163(16):1926-32.
 48. Jhuo SJ, Tsai WC, Lin TH, et al. Statin dose and the risk of intracerebral hemorrhage: a population-based longitudinal study in Taiwan. *Acta Cardiol Sin* 2016;32(1):23-30.
 49. Ott BR, Daiello LA, Dahabreh IJ, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015;30(3):348-58.
 50. Saad N, Camus P, Suissa S, Ernst P. Statins and the risk of interstitial lung disease: a cohort study. *Thorax* 2013;68(4):361-4.