



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Sivashanmugarajah, A;Fulcher, J;Sullivan, D;Elam, M;Jenkins, A;Keech, A

Title:

Suggested clinical approach for the diagnosis and management of 'statin intolerance' with an emphasis on muscle-related side-effects

Date:

2019-09-01

Citation:

Sivashanmugarajah, A., Fulcher, J., Sullivan, D., Elam, M., Jenkins, A. & Keech, A. (2019). Suggested clinical approach for the diagnosis and management of 'statin intolerance' with an emphasis on muscle-related side-effects. *Internal Medicine Journal*, 49 (9), pp.1081-1091. <https://doi.org/10.1111/imj.14429>.

Persistent Link:

<https://hdl.handle.net/11343/286350>

A Suggested Clinical Approach for the Diagnosis and Management of ‘Statin Intolerance’ with an Emphasis on Muscle-Related Side-Effects

Authors: Anosh Sivashanmugarajah^{1,2}, Jordan Fulcher^{1,2}, David Sullivan³, Marshall Elam⁴, Alicia Jenkins^{1,5} and Anthony Keech^{1,2}

Affiliations:

Dr Anosh Sivashanmugarajah – Medical Registrar, Royal Prince Alfred Hospital

Dr Jordan Fulcher – Honorary Cardiologist, Royal Prince Alfred Hospital

Associate Professor David Sullivan – Associate Professor, Head of the Department of Clinical Biochemistry at Royal Prince Alfred Hospital

Professor Marshall Elam – Professor, University of Tennessee

Professor Alicia Jenkins – Professor, Diabetes and Vascular Medicine

Professor Anthony Keech – Professor, Medicine, Cardiology and Epidemiology

Institutions:

- 1) National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Camperdown, NSW, 2050
- 2) Royal Prince Alfred Hospital, Camperdown, Sydney, NSW, 2050
- 3) NSW Health Pathology, Royal Prince Alfred Hospital, Camperdown, Sydney, NSW, 2050
- 4) University of Tennessee
- 5) Department of Medicine, University of Melbourne, St. Vincent’s Hospital, Fitzroy, Melbourne, VIC, 3065

Corresponding author:

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/imj.14429](https://doi.org/10.1111/imj.14429)

Prof. Anthony Keech

NHMRC Clinical Trials Centre, Medical Foundation Building, Locked Bag 1450,
NSW

Email: tony@ctc.usyd.edu.au

Phone and Fax: tel 02-9562-5003; fax: 02-9562-5387

Word count: Summary: 180; Main paper: 3009; **Tables: 3; Figures: 1**

Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) levels by HMG-CoA reductase inhibitors (statins), ezetimibe, resins or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduces cardiovascular disease (CVD) event rates¹. Owing to their efficacy, favourable side-effect profile, cost-effectiveness and ≈40-years of clinical trial evidence, statins are first-line therapies for hypercholesterolaemia. For each statin-induced 1.0 mmol/L LDL-C reduction major vascular events and all-cause mortality are reduced by 21% and 9%, respectively². Many Australians use statins; in the 2016–17 financial year, atorvastatin and rosuvastatin were the two most dispensed medications by the Pharmaceutical Benefits Scheme (PBS)³. The most reported statin side-effect is muscle pain, with an incidence of ≈10% in general practice but only 1.5–5% in randomised controlled trials (RCTs)⁴. The RCT incidence is thought to be underestimated due to exclusion of patients with a history of statin intolerance⁵ and lack of criteria distinguishing true statin-associated muscle symptoms (SAMS) from non-statin related muscle pain⁶. Other conditions often categorised as statin intolerance include myositis, rhabdomyolysis and abnormal liver function.

While statin side-effects can reduce quality of life, they can also compromise adherence to a potentially life-saving treatment, hence are an impediment to effective CVD prevention and treatment⁷. This thematic review provides approaches to defining and managing statin intolerance. We performed a comprehensive search of databases (PubMed, Embase, CINAHL, Scopus and the Cochrane Database of Systematic Reviews) for English-language original and review articles published between 1980 and 2018, and selected articles based on relevance, recency, quality and calibre. We also sourced recent guidelines and drew on specialist experience.

Statins

Statins selectively and competitively inhibit (predominantly hepatic) HMG-CoA reductase, which catalyses the rate-limiting step from HMG-CoA to mevalonate in the endogenous cholesterol biosynthesis pathway. This reduces hepatic cholesterol and upregulates hepatic LDL-C receptors, extracting more LDL from blood⁸. Statins also modestly lower triglyceride (13%) and increase HDL-C (5%) levels, and have pleiotropic effects (e.g., vasodilation, increase endothelial progenitor cells, anti-inflammatory, anti-oxidant and anti-platelet/anti-thrombotic actions)⁹.

While sharing a common mechanism of action, statins differ in their chemical structure, pharmacokinetics and lipid-modifying efficacy, as summarised in Table 1^{10,11}. Generally newer statins reduce LDL-C more^{12,13}. Hydrophilic statins (e.g., rosuvastatin, pravastatin), have less tissue absorption, except for the liver, and potentially fewer drug interactions due to lower dependence on cytochrome p450 for hepatic clearance. Contrary to popular belief, side-effects are similar for lipophilic and hydrophilic statins in the long-term in patients with an acute myocardial infarction.¹⁴

Statin intolerance

As many features may be associated with statin intolerance, the definition of statin intolerance ideally incorporates all of the following parameters:

- A. **Inability to tolerate a recommended statin dose** to attain the desired CVD risk reduction due to symptoms, signs and/or biochemical tests potentially indicative of statin intolerance, which affects a patient's adherence to their prescribed statin.
- B. Symptoms and/or biochemical abnormalities **resolve with statin cessation** (this may take *days to weeks*).
- C. Symptoms and/or biochemical abnormalities recur with re-challenge to statin (this may take *days to weeks*). Ensure there are no contraindications to statin therapy (e.g., rhabdomyolysis) before re-challenge.
- D. Items A, B and C have been met for two different statins.
- E. Prior to confirming a statin intolerance diagnosis, **alternative explanations** are excluded by a comprehensive history, examination and relevant investigations.

Commonly reported statin side-effects are myalgia and (usually subclinical) elevations of creatine kinase (CK) or hepatic enzymes. Less common side-effects include arthralgia, sleep disturbance and impaired concentration. Frequently reported side-effects are given in Table 2¹⁵⁻²⁴. Abnormal liver function tests (LFTs) often reflect non-alcoholic fatty liver disease (NAFLD) secondary to obesity, diabetes or alcohol rather than statin hepatotoxicity. Generally, side-effects occur within three months after drug commencement or dosage increase, or are triggered by an intercurrent condition or other medications (Table 3)¹⁰. Some drugs (e.g., antibiotics clarithromycin, erythromycin) inhibit the cytochrome P450 isoenzyme CYP3A4, which increases statin concentrations and

thus the risk of rhabdomyolysis, acute renal injury and all-cause mortality²⁵. The Food and Drug Administration Adverse estimates a statin-induced rhabdomyolysis rate of 0.70/100,000 patient-years¹⁰.

There is international consensus for definitions of statin-associated myopathy and hepatic effects. Myalgia refers to muscle symptoms (e.g., aches, weakness) without CK elevation, whereas myositis refers to muscle symptoms with CK elevation²⁶. Statin-induced muscle toxicity may present as fatigue, muscle weakness, pain, tenderness or cramps, which are usually proximal and symmetrical, but may be generalised²⁷. Statin myopathy incidence varies by definition and dataset. A statin RCTs meta-analysis found 0.05% of patients treated with statins over five years experienced myositis²⁸. Placebo-controlled RCTs demonstrate that most symptoms attributed to statins in routine clinical practice are not caused by the statin (misattribution)²⁹. For example, the three-year primary prevention HOPE-3 trial noted muscle pain/weakness in 5.8% of participants prescribed rosuvastatin and in 4.7% of participants on placebo³⁰. In RCTs, statin myopathy incidence is estimated at 1.5–5%⁴. Some RCTs only reported muscle-related side-effects based on marked (e.g., 10-fold upper limit of normal (ULN)) plasma CK elevations¹⁶. Distinct molecular changes have been shown in patients with statin-induced myalgia undergoing statin re-challenge, such as mitochondrial stress, cell senescence and apoptosis³¹, supporting a genetic susceptibility, though there are no routine tests^{31,32}. Furthermore, there is a rare autoimmune response to statins (antibodies develop to HMG-CoA reductase): ‘statin-induced necrotising autoimmune myopathy’³¹ (see below), which we have also observed (including without large CK rises) in non-statin-exposed individuals. CK rises may be asymptomatic and muscle symptoms can occur without CK elevations¹⁶. Elevated CK levels, even over 5-fold ULN, can occur with exercise or hypothyroidism^{15,33-35}. The most serious muscle-related statin side-effect is rhabdomyolysis, which is usually defined clinically (muscle ache/weakness; laboratory parameters (CK >10-fold ULN) or CK >10 000 U/L)

or myoglobinuria (which may cause renal dysfunction and is treated by statin cessation and hydration)^{15,26}.

Liver side-effects, the second most common statin side-effect, typically manifest as asymptomatic transaminase elevations ('transaminitis')¹⁷. Elevated levels (>3-times ULN) occur in $\leq 3\%$ of statin-treated patients, and most resolve spontaneously within weeks without drug discontinuation¹⁸. Baseline elevated liver enzymes are often associated with dyslipidaemia, obesity and diabetes, NAFLD, and alcohol excess¹⁵. It is questionable whether statin-associated liver enzyme elevation *per se* threatens hepatic function. Frank hepatitis is a very rare statin side-effect, generally seen with concomitant drugs use (e.g., intravenous antibiotics (Table 3))¹⁰. An observational study implied a possible protective effect of statins on liver function in chronic hepatitis³⁶. As LFT and CK abnormalities are common clinically, pre-statin levels are useful if symptoms arise, but statin guidelines do not recommend routine monitoring of LFTs or CK^{15,37}.

Statins increase risk of new-onset (Type 2) diabetes (NOD) $\approx 9-27\%$ ^{19,20}, with greater risk with intensive versus lower-dose therapy. Individual study results are contrasting, but NOD does seem to be a class effect. Intensive statin therapy did not increase NOD risk in subjects with normal glucose tolerance at baseline. NOD risk is higher in those with metabolic syndrome or impaired glucose tolerance, and probably reflects a small glucose rise, shifting people over the diagnostic threshold for diabetes. Conversely, NOD risk is minimal in patients without diabetes risk factors²¹⁻²³. NOD mechanisms are not fully elucidated. A Mendelian randomisation study found an increased diabetes risk relating to genetically lower LDL-C, suggesting the risk may not be directly statin-specific³⁸. There are currently insufficient trial data (in terms of both population size and duration) for other lipid-lowering therapies to make any comparisons. Other biological evidence suggests a more statin-specific mechanism. In murine studies,

statins upregulate a phosphatase and tensin homologue on Chromosome 10, which can induce insulin resistance³⁹. Direct inhibition of HMG-CoA reductase and statin-activated hepatic gluconeogenesis may also play a role in NOD⁴⁰. Patients prescribed a statin are usually at higher CVD risk due to obesity, physical inactivity, dyslipidaemia and hypertension, which are common in pre-diabetes. It is unknown whether statin cessation can reverse recently diagnosed NOD. Given that statins mitigate CVD risk, to an extent vastly exceeding the risks of developing diabetes, there is an undisputed net cardiovascular and mortality benefit from statin therapy⁴¹. However, the increased diabetes risk should be discussed with patients.

Diagnosis

A diagnosis of statin intolerance should only be made when symptoms, signs or abnormal biochemistry develop after statin use, resolve after statin cessation, and recur with exposure to the same or another statin. This is seldom met in clinical practice and thus many who may benefit from statin treatment go without. Healthcare providers and patients can have a skewed perception of statin side-effects, often fuelled by the media^{29,42,43}. Social media can be particularly influential for less common or poorly-founded statin adverse effects, such as insomnia or erectile dysfunction. Other barriers to diagnosis include a lack of specific biomarkers and the high background prevalence of muscle symptoms and abnormal LFTs^{10,15,44}. Furthermore, the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm) demonstrated the 'nocebo' effect, whereby there were excess muscle-related adverse event reports only when patients and their doctors were aware of statin use, and not when its use was masked⁴⁵. Thorough history taking, statin re-challenge and elimination of other potential causes are pivotal in diagnosis (Table 3)¹⁰. In severe cases, an electromyogram and/or muscle or liver biopsy may be required. However, normal electromyograms do not exclude statin-induced myotoxicity⁴⁶.

Management

Treatments include changing statins, low-dose statins (including alternate day dosing) and alternative medications, including bile acid-binding resins, ezetimibe, nicotinic acid and PCSK9 inhibitors^{10,15}. Major limitations in changing medications (until recently) have been the significantly smaller LDL-C reduction with non-statin alternatives, and their side-effects. Recently approved PCSK9 inhibitors provide substantial LDL-C lowering (~50–70%, independent of concomitant statin use) with a good safety profile to date. Over-the-counter (OTC) LDL-lowering alternatives include red yeast rice (RYR), a weak natural source of lovastatin^{15,47}. There is no compelling evidence for treating statin muscle symptoms with OTC supplements such as magnesium or coenzyme Q10^{33,48,49}. Unfortunately, media coverage of statin side-effects is often linked with dietary advice likely to increase saturated fat consumption. Furthermore, healthy eating patterns, such as the Mediterranean diet, are often construed to include saturated fat when they are high in mono- and polyunsaturated alternatives. Consequently, dietary alternatives to statin therapy, including plant sterols, are not widely implemented. In select cases, it is also important to identify autoantibodies to HMG-CoA reductase as a cause of severe myositis and statin intolerance. Some patients may have necrotising autoimmune myositis, a recently identified rare (16 in 10 000 000 people)⁵⁰ condition, necessitating specific specialist management, involving immunosuppression³¹. Predisposing risk factors for statin-induced myopathy and myositis, such as autoimmune conditions affecting muscle, carnitine palmitoyl transferase II (CPT-II) deficiency, severe vitamin D deficiency and other causes of myopathy or CK elevations not due to lipid drugs need to be considered (Table 3)¹⁰.

Figure 1 depicts a flowchart to manage statin intolerance, which is consistent with the National Prescribing Service (NPS) MedicineWise SAMS Management Algorithm⁵¹.

Lifestyle factors

It is important to emphasise healthy lifestyle benefits, such as replacing saturated fats and transfats with foods rich in mono- and polyunsaturated fats and plant sterols (e.g., special spreads, milk and yoghurts that can lower LDL-C \approx 10%)⁵². Better diet and exercise can lower LDL-C by 10–15%¹. While smaller than the results achievable with statins, they have undisputed additional benefits.

Statin reintroduction

After assessing effects of statin cessation, the next step involves re-challenging with a lower dose of the same or an alternative statin. This is most likely to result in the greatest, sustained LDL-C reduction than alternatives^{53,54}. For example, slow release fluvastatin XL 80mg daily was tolerated by 97% of patients with prior (muscle-related) 'statin intolerance' symptoms, and LDL-C was reduced by 32.8%⁵⁵. Goldberg *et al.*⁵⁶ conducted a retrospective study of patients unable to tolerate a daily statin who were successfully treated using non-daily statin dosing. Non-daily rosuvastatin lowered LDL-C by $34 \pm 21\%$, $p < 0.001$. The 'non-daily dosing' strategy may be better described as an 'extended dosing interval', which is associated with lower drug levels and larger swings in drug concentrations^{56,57}. Non-daily dosing is better with atorvastatin and rosuvastatin, which have longer elimination half-lives^{10,11}. Anecdotally, we find this strategy useful. Prospective clinical trials are desirable, including evaluation of whether statin-intolerant patients have higher than expected plasma statin concentrations with daily dosing and the effects of non-daily dosing. As yet, there are no studies evaluating clinical event rates with these strategies.

Non-statin prescription LDL-C lowering drugs

Ezetimibe

Ezetimibe reduces LDL-C by 15–25% by reducing absorption of dietary and biliary cholesterol through direct inhibition of Niemann Pick C1-like 1 (NPC1L1) protein in the proximal small bowel brush border. Drug efficacy relates to whether a patient is a high absorber or not of cholesterol from the gut⁵⁸. In 2015, the IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT), demonstrated that adding ezetimibe 10mg to simvastatin 40mg daily in post-acute coronary syndrome patients reduced CVD events versus simvastatin alone⁵⁹. Ezetimibe has very good tolerance, safety and efficacy, with less side-effects compared to upward titration of moderate-dose statin¹⁵.

Resins

Bile acid sequestrants (resins), such as colestipol and cholestyramine, reduce LDL-C by \approx 15–26%, raise HDL-C modestly, but can also raise triglycerides, particularly if fasting triglycerides are elevated⁶⁰. While resins can reduce CVD events⁶¹, tolerability and adherence are poor, predominantly due to gastrointestinal side-effects⁶⁰.

Drugs predominantly lowering triglycerides

Fibrates, peroxisome proliferator-activated receptor alpha (PPAR-alpha) agonists, lower triglycerides by 30%. Among individuals with high triglyceride and low HDL-C levels, large fibrate trials demonstrate statin-like benefits on CVD risk reduction. Meta-analyses of fibrates suggest a 35% reduction in CVD risk in those with dyslipidaemia⁶²⁻⁶⁴.

Nicotinic acid and its analogues lower triglycerides by 40%, raise HDL-C and modify other lipid fractions. Poor tolerability due to gastrointestinal side-effects, flushing and worsening glucose intolerance affects adherence and treatment allocation in clinical trials. Recent larger-scale studies have failed to demonstrate benefits of niacin on CVD risk⁶².

High dose (4–9 g/day) fish oil supplementation lowers triglyceride levels by 20–30%. A meta-analysis (20 trials, n=63,000), with mostly secondary CVD prevention did not demonstrate substantial reduction in the primary composite cardiovascular endpoints. However, CVD death, available in 13 trials, was reduced by 14% versus placebo ($P<0.001$)^{62,65}. The REDUCE-IT trial showed that with hypertriglyceridaemia despite statin use 2g icosapent ethyl b.d. (a highly purified eicosapentaenoic acid ethyl ester) significantly reduced ischaemic events, including cardiovascular death⁶⁶. The five-year VITAL trial demonstrated that 2000 IU/day of Vitamin D3 or n-3 fatty acids (1g/day) did not reduce primary CVD or cancer events in healthy middle-aged men and women⁶⁷.

PCSK9 inhibitors

PCSK9 regulates ligand binding and degradation of the hepatic LDL receptor. PCSK9 inhibitors, administered as subcutaneous injections two to four-weekly, are monoclonal antibodies that inactivate PCSK9, reducing LDL receptor degradation and increasing receptor recirculation to the hepatocyte surface, consequently lowering circulating LDL-C⁶⁸ by 50–70%, with or without background statin¹⁵. Approved PCSK9 inhibitors are alirocumab and evolocumab, which are fully humanised antibodies. In the FOURIER trial, in statin-treated patients evolocumab reduced LDL-C from a median baseline of 2.4mmol/l to 0.78mmol/l ($p<0.001$) and lowered composite CVD events by 11.3%⁶⁹. Current indications for PCSK9 inhibitors are as an adjunct to diet and maximally tolerated statin for adults with heterozygous familial hypercholesterolaemia (FH), homozygous FH (evolocumab) or clinical atherosclerotic CVD who require additional LDL-C lowering⁷⁰. Evolocumab has recently become available on the Pharmaceutical Benefits Scheme (PBS)⁷¹.

LDL apheresis

Lipid apheresis, usually two-weekly, is safe and effective for severe hyperlipidaemia, usually FH, reducing LDL-C by 65–70%. A cell separator separates plasma from blood cells, then apolipoprotein B is adsorbed by anti-apolipoprotein B antibodies or dextran sulfate. While there are some Australian centres, costs exceed those for anti-PCSK9 therapy, and time, invasiveness and local availability are limiting⁷².

Bempedoic acid

A new, once-daily, oral drug being investigated as an option for statin-associated muscle side-effects is bempedoic acid, which inhibits ATP citrate lyase, an enzyme earlier in the cholesterol biosynthesis pathway than HMG-CoA reductase. Unlike statins, bempedoic acid is activated by an enzyme in hepatocytes, but not skeletal muscle. Phase 2 studies demonstrated LDL-C lowering of 20–30%, increasing to 40–50% with ezetimibe co-administration. While statin-intolerant trial patients reported numerically higher rates of muscle-related adverse events compared to statin-tolerant patients, only a very small percentage discontinued therapy for these symptoms⁷³. Phase 3 trials are underway^{74,75}.

Nutraceuticals

Nutraceuticals include RYR, phytosterols, bergamot, soy products and polyunsaturated omega-3 fatty acids. There are no long-term outcome studies of CVD morbidity or mortality⁷⁶. None have sufficiently robust evidence to be incorporated in guidelines. We briefly discuss some of these studies below.

Coenzyme Q10

Coenzyme Q10 (ubiquinone) is a pivotal cofactor in the mitochondrial electron transport chain and oxidative phosphorylation. Ubiquinone and cholesterol are synthesised from mevalonate, involving HMG-CoA reductase. As statins inhibit this enzyme, less coenzyme Q10 is synthesised, a postulated cause of muscle

side-effects. There are favourable anecdotal reports and small trials, but a recent well-designed RCT (including a run-in period to validate statin myalgia) and a meta-analysis of small RCTs failed to demonstrate benefit of coenzyme Q10 supplementation^{77,78}.

Red yeast rice

RYR, *Monascus purpureus*, produces a naturally occurring lovastatin and reduces LDL-C and triglycerides by 27.7% and 15.8%, respectively (at 600mg b.d). In a systematic review (10 RCTs) 1200mg RYR and 10mg simvastatin had similar lipid effects, but these trials were small and lacked excellent methodology. Side-effects include myalgia, dizziness and gastrointestinal upset⁷⁹.

Magnesium supplements

Magnesium is a HMG-CoA reductase controller rather than an inhibitor. Statins and magnesium reduce clotting, inflammation and atheroma and have similar pleiotropic effects⁸⁰. A meta-analysis demonstrated no lipid benefits⁸¹. A 50mg/day increment in self-reported total magnesium intake was associated with 22% lower coronary artery calcification ($p < 0.001$)⁸². Lipid effects may differ with the orotate formulation⁸³ and is sometimes recommended for myalgia. Magnesium orotate improves mitochondrial respiratory chain function⁸⁴. Robust studies and RCTs are necessary before magnesium supplements can be recommended for statin intolerance.

Conclusions

While statins offer major CVD benefit and a generally excellent safety profile, their widespread use and common misconceptions have resulted in frequent 'statin intolerance' diagnoses, of which only a subset may be truly intolerant. Alternate diagnoses (Table 3)¹⁰ should be considered. We, the NPS⁵¹ and international bodies recommend structured diagnostic and management

approaches^{10,15}. Along with new universal definition(s), we provide a practical flowchart for clinicians. Alternate statins, low-dose statins and non-statin drugs may be helpful. Additional trials are merited. Careful management will maximise the number of patients benefiting from statin therapy.

Acknowledgements

AS was partly supported by a University of Sydney and NHMRC Clinical Trials Centre Summer Student Scholarship. JF was supported by scholarships from the NHMRC Clinical Trials Centre and the University of Sydney; AJJ was supported by an NHMRC Practitioner Fellowship and is a Sydney Medical Foundation Fellow; AK was supported by an NHMRC Senior Principal Research Fellowship.

Conflicts of interest

The authors have no conflicts of interest to declare.

References:

- 1) Wadhera KR, Steen LD, Khan I, Guigliano RP, Foody JM. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. *J Clin Lipidol* 2016; **10**: 472–489.
- 2) Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015; **385**: 1397–1405.
- 3) Pharmaceutical Benefits Scheme. Expenditure and prescriptions twelve months to 30 June 2017. Available from: <http://www.pbs.gov.au/info/statistics/expenditure-prescriptions-twelve-months-to-30-june-2017>
- 4) Gluba-Brzozka A, Franczyk B, Toth PP, Rysz J, Banach M. Molecular mechanisms of statin intolerance. *Arch Med Sci* 2016; **12**: 645–658.
- 5) Ward CN, Watts FG, Eckel HR. Statin toxicity– mechanistic insights and clinical implications. *Circ Res* 2019; **124**: 328–350.
- 6) Rosenson SR, Baker S, Banach M, Borow KM, Braun LT, Brukert E, et al. Optimizing cholesterol treatment in patients with muscle complaints. *J Am Coll Cardiol* 2017; **70**: 1290–1301.
- 7) Keen IH, Krishnarajah J, Bates RT, Watts GF. Statin myopathy: the fly in the ointment for the prevention of cardiovascular disease in the 21st century? *Expert Opin Drug Saf* 2014; **13**: 1227–1239.
- 8) Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005; **19**: 117–125.

- 9) Antonopoulos AS, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. *Curr Pharm Des* 2012; **18**: 1519–1530.
- 10) Mancini GB, Tashakkor AY, Baker S. Diagnosis, prevention and management of statin adverse effects and intolerance: Canadian Working Group Consensus Update. *Can J Cardiol* 2013; **29**: 1553–1568.
- 11) Australian Government: Department of Health. Therapeutic Goods Administration. Available from: <https://www.tga.gov.au/>
- 12) Cilia DD Jr, Gibson DM, Whitfield LR. Pharmacodynamic effects and pharmacokinetics of atorvastatin after administration to normocholesterolemic subjects in the morning and evening. *J Clin Pharmacol* 1996; **36**: 604–609.
- 13) Plakogiannis R, Cohen H, Taft D. Effects of morning versus evening administration of atorvastatin in patients with hyperlipidaemia. *Am J Health Syst Pharm* 2005; **62**: 2491–2494.
- 14) Kim CM, Ahn Y, Jang YS, Cho KH, Hwang SH, Lee MG, et al. Comparison of clinical outcomes of hydrophilic and lipophilic statins in patients with acute myocardial infarction. *Korean J Intern Med* 2011; **26**: 294–303.
- 15) Mancini GB, Baker S, Bergeron J, Fitchett D, Frolich J, Genest J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Consensus Working Group Update (2016). *Can J Cardiol* 2016; **32**: S35–S65.
- 16) Parker AB, Thompson DP. Effect of statins on skeletal muscle: exercise, myopathy, and muscle outcomes. *Exerc Sport Sci Rev* 2012; **40**: 188–194.

- 17) Golomb AB, Evans AM. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008; **8**: 373–418.
- 18) Calderon MR, Cubeddu XL, Goldberg BR, Schiff ER. Statins in the treatment of dyslipidaemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. *Mayo Clin Proc* 2010; **85**: 349–356.
- 19) Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; **375**: 735–742.
- 20) Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011; 305: 2556–2564.
- 21) Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012; **380**: 565–571.
- 22) Waters DD, Ho JE, Boekholdt SM, DeMicco DO, Kastelein JJ, Messig M, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy effect of baseline risk factors for diabetes. *J Am Coll Cardiol* 2013; **61**: 148–152.
- 23) Kohli P, Waters DD, Nemr R, Arsenault BJ, Messig M, DeMicco DA, et al. Risk of new-onset diabetes and cardiovascular risk reduction from high-dose statin therapy in prediabetics and non-pre-diabetics: an analysis from TNT and IDEAL. *J Am Coll Cardiol* 2015; **65**: 402–404.
- 24) MIMS Australia. Available from <http://www.mims.com.au/>

- 25) Patel AM, Shariff S, Bailey DG, Juurlink DN, Gandhi S, Mamdani M, et al. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. *Ann Intern Med* 2013; **158**: 869–876.
- 26) Pasternak CR, Smith CS, Bairey-Merz NC, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Stroke* 2002; **33**: 2337–2341.
- 27) Alfirevic A, Neely D, Armitage J, Chinoy H, Cooper RG, Laaksonen R, et al. Phenotype standardization for statin-induced myotoxicity. *Clin Pharmacol Ther* 2014; **96**: 470–476.
- 28) Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for analyses of adverse event data from randomized controlled trials of statin therapy. *Am Heart J* 2016; **176**: 63–69.
- 29) Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016; **388**: 2532–2561.
- 30) Yusuf S, Bosch J, Dagenais G, Xu J, Xavier D, Lui L, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016; **374**: 2021–2031.
- 31) Elam BM, Majmudar G, Mozhui K, Gerling IC, Vera SR, Fish-Trotter H, et al. Patients experiencing statin-induced myalgia exhibits a unique program of skeletal muscle gene expression following statin re-challenge. *PLoS One*. 2017; **12**: e0181308.
- 32) Norata GD, Tibolla G, Catapano AL. Statins and skeletal muscle toxicity: from clinical trials to everyday practice. *Pharmacol Res* 2014; **88**: 107–113.

- 33) Moghadam-Kia S, Oddis V C, Aggarwal R. Approach to asymptomatic creatine kinase elevation. *Cleve Clin J Med* 2016; **83**: 37–42.
- 34) Tokinaga K, Oeda T, Suzuki Y, Matsushima Y. HMG-CoA reductase inhibitors (statins) might cause high elevations of creatine phosphokinase (CK) in patients with unnoticed hypothyroidism. *Endocr J* 2006; **53**: 401–405.
- 35) Chaudhary N, Duggal AK, Makhija P, Puri V, Khwaja JA. Statin induced bilateral foot drop in a case of hypothyroidism. *Ann Indian Acad Neurol* 2015; **18**: 331–334.
- 36) Wong JC, Chan HL, Tse YK, Yip TC, Wong VW, Wong GL. Statins reduce the risk of liver decompensation and death in chronic viral hepatitis: a propensity score weighted landmark analysis. *Aliment Pharmacol Ther* 2017; **46**: 1001–1010.
- 37) Ministry of Health. Cardiovascular disease risk assessment (New Zealand primary care handbook 2012, updated 2013). Available from: <http://pro.healthmentoronline.com/assets/cardio-vascular-disease-risk-assessment-updated-2013-dec13.pdf>
- 38) Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med* 2016; **375**: 2144–2153.
- 39) Birnbaum Y, Nanhwan MK, Ling S, Perez-Polo JR, Ye Y, Bajaj M. PTEN upregulation may explain the development of insulin resistance and type 2 diabetes with high dose statins. *Cardiovasc Drugs Ther* 2014; **28**: 447–457.
- 40) Swerdlow DI, Sattar N. A dysglycaemic effect of statins in diabetes: relevance to clinical practice? *Diabetologia* 2014; **57**: 2433–2435.

- 41) Wang KL, Liu CJ, Chao TF, Chen SJ, Wu CH, Huang CM, et al. Risk of new-onset diabetes mellitus versus reduction in cardiovascular events with statin therapy. *Am J Cardiol* 2014; **113**: 631–636.
- 42) Chee JY, Chan VHH, Tan CN. Understanding patients' perspective of statin therapy: can we design a better approach to the management of dyslipidaemia? A literature review. *Singapore Med J* 2014; **55**: 416–421.
- 43) Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, 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**: 1012–1022.
- 44) Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, et al. Statin intolerance—an attempt at a unified definition. Position paper from an international lipid expert panel. *Arch Med Sci* 2015; **11**: 1–23.
- 45) Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet* 2017; **389**: 2473–2481.
- 46) Camerino MG, Musumeci O, Conte E, Musaraj K, Fonzino A, Barca E, et al. Risk of myopathy in patients in therapy with statins: identification of biological markers in a pilot study. *Front Pharmacol* 2017; **8**: 500.
- 47) Gerards MC, Terlouw RJ, Yu H, Koks CH, Gerdes VE. Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain—a systematic review and meta-analysis. *Atherosclerosis* 2015; **240**: 415–423.

- 48) Fedacko J, Pella D, Fedackova P, Hanninen O, Tuomainen P, Jarcuska P, et al. Coenzyme Q(10) and selenium in statin-associated myopathy treatment. *Can J Physiol Pharmacol* 2013; **91**: 165–170.
- 49) Bookstaver DA, Burkhalter NA, Hatzigeorgiou C. Effect of coenzyme Q10 supplementation on statin-induced myalgias. *Am J Cardiol* 2012; **110**: 526–529.
- 50) Khan NAJ, Khalid S, Ullah S, Malik MU, Makhoul S. Necrotizing autoimmune myopathy: a rare variant of idiopathic inflammatory myopathies. *J Invest Med High Impact Case Rep* 2017; **5**: 2324709617709031.
- 51) NPS MedicineWise. SAMS Management Algorithm 2017. Available from <https://cdn2.scrvt.com/08ab3606b0b7a8ea53fd0b40b1c44f86/939f941da81483d0/9e56a18edebf/SAMS-Management-Algorithm.pdf>
- 52) Heart Foundation. Position Statement. Phytosterol/stanol enriched foods 2017. Available from: https://www.heartfoundation.org.au/images/uploads/publications/Heart_Foundation_Position_Statement_-_Phytosterolstanol_enriched_foods_2017.pdf
- 53) Zhang H, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med* 2013; **158**: 526–534.
- 54) Mampuya WM, Frid D, Rocco M, Huang J, Brennan DM, Hazen SL, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. *Am Heart J* 2013; **166**: 597–603.
- 55) Bitzur R, Cohen H, Kamari Y, Haratz D. Intolerance to statins: mechanisms and management. *Diabetes Care* 2013; **36**: S325–S330.

- 56) Goldberg AS, Degorter MK, Ban MR, Kim RB, Hegele RA. Efficacy and plasma drug concentrations with non-daily dosing of rosuvastatin. *Can J Cardiol* 2013; **29**: 915–919.
- 57) Kennedy SP, Barnas GP, Schmidt MJ, Glisczinski MS, Paniagua AC. Efficacy and tolerability of once-weekly rosuvastatin in patients with previous statin intolerance. *J Clin Lipidol* 2011; **5**: 308–315.
- 58) Rizzo M, Rini BG. Ezetimibe, cardiovascular risk and atherogenic dyslipidaemia. *Arch Med Sci* 2011; **7**: 5–7.
- 59) Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; **372**: 2387–2397.
- 60) Liwa CA, Barton NE, Cole CW, Nwokocha CR. Bioactive plant molecules, sources and mechanism of action in the treatment of cardiovascular disease. In: Badal S, Delgoda R (eds.). *Pharmacognosy*, New York: Academic Press; 2017; 315–336.
- 61) The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984; **251**: 351–364.
- 62) Keech A, Jenkins A. Triglyceride-lowering trials. *Curr Opin Lipidol* 2017; **28**: 477–487.
- 63) Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analyses. *Lancet* 2010; **375**: 1875–1884.
- 64) Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P. Fibrates effect on cardiovascular risk is greater in patients with high triglyceride

levels or atherogenic dyslipidaemia profile: a systematic review and meta-analysis. *J Cardiovasc Pharmacol* 2011; **57**: 267–272.

- 65) Kotwal S, Jun M, Sullivan D, Perkovic D, Neal B. Omega-3 fatty acids and cardiovascular outcomes: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2012; **5**: 808–818.
- 66) Bhatt D, Steg G, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. cardiovascular risk reduction with icosapent ethyl for hypertriglyceridaemia. *N Engl J Med* 2019; **380**: 11–22.
- 67) Keaney J, Rosen C. VITAL signs for dietary supplementation to prevent cancer and heart disease. *N Engl J Med* 2019; **380**: 91–93.
- 68) Everett MB, Smith JR, Hiatt RW. Reducing LDL with PCSK9 inhibitors—the clinical benefit of lipid drugs. *N Engl J Med* 2015; **373**: 1588–1591.
- 69) Sabatine SM, Giugliano PR, Keech AC, Hornapour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; **376**: 1713–1722.
- 70) Toklu B, Amirian J, Giugliano PR. Current indications, cost and clinical use of anti-PCSK9 monoclonal antibodies. American College of Cardiology Expert Analysis 2016. Available from: <https://www.acc.org/latest-in-cardiology/articles/2016/05/18/14/34/current-indications-cost-and-clinical-use-of-anti-pcsk9-monoclonal-antibodies>
- 71) Pharmaceutical Benefits Scheme. Evolocumab. Available from: <http://www.pbs.gov.au/medicine/item/10958R-11193D>
- 72) Liu M, Garberich R, Strauss C, Davin T, Knickelbine T. Usefulness of lipid apheresis in the treatment of familial hypercholesterolaemia. *J Lipids*. 2014; **2014**: 864317.

- 73) Thompson PD, MacDougall DE, Newton RS, Margulies JR, Hanselman JC, Orloff DG, et al. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. *J Clin Lipidol* 2016; **10**: 556–567.
- 74) Esperion Therapeutics. Evaluation of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin-intolerant treated with bempedoic acid (ETC-1002) or placebo. Available from: <https://ClinicalTrials.gov/show/NCT02993406>
- 75) Esperion Therapeutics. Assessment of the long-term safety and efficacy of bempedoic acid (CLEAR Harmony OLE). Available from: <https://ClinicalTrials.gov/show/NCT03067441>
- 76) Banach M, Patti AM, Giglio RV, Cicero AFG, Atanosov AG, Bajraktari G, et al. The role of nutraceuticals in statin-intolerant patients. *J Am Coll Cardiol* 2018; **72**: 96–118.
- 77) Taylor BA, Lorson L, White CM, Thompson PD. A randomised trial of Coenzyme Q10 in patients with confirmed statin myopathy. *Atherosclerosis* 2015; **238**: 329–335.
- 78) Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, et al. Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomised controlled trials. *Mayo Clinic Proc.* 2015; **90**: 24–34.
- 79) Ong YC, Aziz Z. Systematic review of red yeast rice compared with simvastatin in dyslipidaemia. *J Clin Pharm Ther* 2016; **41**: 170–179.
- 80) Rosanoff A, Seelig MS. Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals. *J Am Coll Nutr* 2004; **23**: 501S–505S.

- 81) Simental-Mendia EL, Simental-Mendia M, Sahebkar A, Rodriguez-Moran M, Guerrero-Romero F. Effect of magnesium supplementation on lipid profile: a systematic review and meta-analysis of randomised controlled trials. *Eur J Clin Pharmacol* 2017; **73**: 525–536.
- 82) Hruby A, O'Donnell CJ, Jacques PF, Meigs JB, Hoffmann U, McKeon NM. Magnesium intake is inversely associated with coronary artery calcification: the Framingham Heart Study. *JACC Cardiovasc Imaging* 2014; **7**: 59–69.
- 83) Jellinek H, Takacs E. Course of the progression of experimentally induced arteriosclerotic vessel wall changes after treatment with magnesium orotate. *Arzneimittelforschung* 2000; **50**: 1071–1077.
- 84) Grober U, Schmidt J, Kisters K. Magnesium in prevention and therapy. *Nutrients* 2015; **7**: 8199–8226.

TABLE 1 – PHARMACOKINETIC PROPERTIES & COMPARATIVE EFFICACY OF STATINS (MAXIMUM DOSE) AVAILABLE IN AUSTRALIA

	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin
Introduction in Australia	1991	1994	1996	1997	2006
Dose range - mg	5 – 80*	10 – 80	80	10 – 80	5 – 40
Serum LDL-C reduction (%)	41	34	24	50	63
Serum HDL-C increase (%)	12	12	8	6	10
Serum triglyceride reduction (%)	18	24	10	29	28
Lipoprotein (a) levels	#Long-term use decreased levels	Minimal Δ	Minimal Δ	Minimal Δ	Minimal Δ
Elimination half-life - hr	2	1.8	1.2	14	19
Optimal dosing time	Evening	Bedtime	Bedtime	Any time	Any time
Bioavailability- %	5	18	24	12	20
Food-Drug interaction - Bioavailability	Nil	Decreased	Decreased	Decreased	Nil
Solubility	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Hydrophilic
Protein binding - %	95 – 98	~50	>98	98	90
Liver Metabolism - CYP 450 type	3A4	No	2C9	3A4	Limited
Renal excretion - %	13	20	6	<5	10
Dosage reduction in Renal disease	Yes	Nil	Nil	Nil	Yes
For Creatinine clearance < 30mL/min/1.73m²	Dose: > 10mg/day (caution)	Monitor renal function			Starting: 5mg once daily Dose: < 10mg once daily
* Only recommended to be prescribed in Australia to patients already tolerating this dose prior to 6 Dec, 2011 (TGA) #Long-term: median, 677 days					

Key: mg (milligrams); LDL-C (low-density lipoprotein cholesterol); HDL-C (high density lipoprotein cholesterol); CYP450 (Cytochrome P450);

For more details, please see TABLE 2: MAJOR SIDE

<p>Hepatic effects</p>	<p>‘Transaminitis’ – elevation of hepatic enzymes in the absence of any histopathological changes. Usually asymptomatic, reversible, dose-related. Similar among all statins. Does not correlate with the level of LDL-C reduction. Most cases of ‘transaminitis’ resolve spontaneously without drug discontinuation. If serious hepatotoxicity remains undiagnosed, consider a differential diagnosis.</p>
<p>Muscle complaints & Myopathy</p>	<p>Include: proximal, symmetric muscle myalgia, aches, soreness, stiffness, cramps or weakness (may or may not be associated with elevated circulating CK levels)</p>
<p>Glycaemic control and Diabetes</p>	<p>Increased risk of a new diabetes diagnosis by 9 – 27%; More potent statins have a higher risk than less potent statins but there is a strong net benefit favouring statin continuation. The risk is minimal in patients without risk factors for diabetes.</p>

(low-density lipoprotein cholesterol); hr (hour); Δ = change.

references 10 and 11 EFFECTS OF STATINS

Poorly founded adverse effects

Gastrointestinal effects,
Renal effects, cataracts, dermatological effects and alopecia,
Neurological effects,
Neuropsychiatric effects & insomnia,
Rheumatological effects,
Cancer,
Sexual health,
Interstitial lung disease



For details, please see references 15 – 24

Key: LDL-C (low-density lipoprotein C); CK (creatine kinase); NOD (new-onset diabetes)

TABLE 3: STATIN-INDUCED MYOPATHY & DIFFERENTIAL DIAGNOSIS OF MYOPATHY OR CK ELEVATIONS NOT DUE TO LIPID-LOWERING THERAPY

PREDISPOSING RISK FACTORS FOR STATIN-INDUCED MYOPATHY			
Unmodifiable	Potentially Modifiable		
	Lifestyle	Acquired	Medications
<ul style="list-style-type: none"> - Advanced age (>80 years) - Female sex - Asian ethnicity - Family history of myopathy - Family history of myopathy with statin therapy - Genetic polymorphisms of CYP450 isoenzymes 	<ul style="list-style-type: none"> - Low BMI, small body frame - Alcohol abuse - Illicit drug use (cocaine, amphetamines) - Heavy and/or unaccustomed exercise 	<ul style="list-style-type: none"> - Frailty - History of pre-existing/unexplained muscle/joint/tendon pain - History of CK elevation - Metabolic muscle diseases - Severe renal disease - Acute decompensated hepatic disease - Hypothyroidism (untreated) - Diabetes mellitus - Surgery with severe metabolic demands 	<ul style="list-style-type: none"> - High statin dose <u>Drug-statin interactions</u> - Psychotropics (nefazodone, fluvoxamine) - Fibrates (especially gemfibrozil [note fenofibrate is not associated with this greatly increased risk]) - Nicotinic acid - Amiodarone - Verapamil - Warfarin - Cyclosporin - Macrolide antibiotics (clarithromycin and erythromycin) - Azole antifungals (fluconazole, ketoconazole, itraconazole) - Protease inhibitors (indinavir, ritonavir)

DIFFERENTIAL DIAGNOSIS OF MYOPATHY OR CK ELEVATIONS NOT DUE TO LIPID-LOWERING THERAPY

Endocrine	Rheumatology/ Immunology	Vascular	Neurology	Medications	Infection	Other
<ul style="list-style-type: none"> - Hypo- or hyperthyroidism - Cushing syndrome - Adrenal insufficiency - Hypoparathyroidism 	<ul style="list-style-type: none"> - Vitamin D deficiency - Fibromyalgia - Polymyalgia rheumatica - Polymyositis - Systemic lupus erythematosus - Tendon or joint disorder 	<ul style="list-style-type: none"> - Peripheral arterial disease (exertional buttock, thigh, calf symptoms) 	<ul style="list-style-type: none"> - Seizures - Neuropathy or radiculopathy - Past polio 	<ul style="list-style-type: none"> - Glucocorticoids - Antipsychotics - Antiretroviral drugs - Illicit drugs [cocaine, amphetamines] 	<ul style="list-style-type: none"> - Viral illness 	<ul style="list-style-type: none"> - Physical exertion - Trauma - Severe chills - Alcoholism - Deep massage causing muscle injury - Ethnicity ('black')

- Metabolic or
inflammatory myopathies

patients)
- Idiopathic hyperCKaemia
(high CK with no
demonstrable cause)

For details, please see reference 10

Key: CYP450 (Cytochrome P450); BMI (Body mass index); CK (creatin kinase)

A Suggested Clinical Approach for the Diagnosis and Management of ‘Statin Intolerance’ with an Emphasis on Muscle-Related Side-Effects

Authors: Anosh Sivashanmugarajah^{1,2}, Jordan Fulcher^{1,2}, David Sullivan³, Marshall Elam⁴, Alicia Jenkins^{1,5} and Anthony Keech^{1,2}

Affiliations:

Dr Anosh Sivashanmugarajah – Medical Registrar, Royal Prince Alfred Hospital

Dr Jordan Fulcher – Honorary Cardiologist, Royal Prince Alfred Hospital

Associate Professor David Sullivan – Associate Professor, Head of the Department of Clinical Biochemistry at Royal Prince Alfred Hospital

Professor Marshall Elam – Professor, University of Tennessee

Professor Alicia Jenkins – Professor, Diabetes and Vascular Medicine

Professor Anthony Keech – Professor, Medicine, Cardiology and Epidemiology

Institutions:

- 1) National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Camperdown, NSW, 2050
- 2) Royal Prince Alfred Hospital, Camperdown, Sydney, NSW, 2050
- 3) NSW Health Pathology, Royal Prince Alfred Hospital, Camperdown, Sydney, NSW, 2050
- 4) University of Tennessee
- 5) Department of Medicine, University of Melbourne, St. Vincent’s Hospital, Fitzroy, Melbourne, VIC, 3065

Corresponding author:

Prof. Anthony Keech

NHMRC Clinical Trials Centre, Medical Foundation Building, Locked Bag 1450, NSW

Email: tony@ctc.usyd.edu.au

Phone and Fax: tel 02-9562-5003; fax: 02-9562-5387

Word count: Summary: 180; Main paper: 3009; **Tables: 3; Figures: 1**

Author Manuscript

FIGURE 1: WHAT TO DO WHEN STATIN INTOLERANCE IS SUSPECTED?

WHAT TO DO WHEN STATIN INTOLERANCE IS SUSPECTED?

- History & Examination
- Consider Differential Diagnosis (Table 3)
 - Check for predisposing patient risk factors (Table 3)
 - Blood tests (FBC, LFT's, U&E's, eGFR, TFT's, CK, , urinary myoglobin (if rhabdomyolysis suspected) and autoantibodies to HMG-CoA Reductase if NAM is suspected)
 - Exclude other causes for reported symptoms, signs and biochemical abnormalities
- **If rhabdomyolysis is suspected (based on a combination of symptoms, CK, creatinine and urine analysis for myoglobinuria), immediate referral to hospital is recommended**

Withhold statin and review patient with repeat biochemistry in 2 -- 4 weeks if $CK \leq 5 \times ULN$, LFTs $> 3 \times ULN$ OR in 6 -- 8 weeks if $CK \geq 5 -- 10 \times ULN$

If symptoms or CK / LFT elevations persist, investigate for other causes and manage accordingly (Table 3)

Once asymptomatic and if no contraindications (e.g. rhabdomyolysis), attempt a statin rechallenge (either with a lower dose of the same statin or a different statin according to the clinical scenario, including patient preference)

Consider adding ezetimibe in higher vascular risk patients

If problems recur and/or $CK > 5 \times ULN$

If problems do not recur, titrate 4 – 6 weekly to achieve desired statin dosage LDL-C target

Consider:

Ceasing statin until symptoms resolve and/or CK is within normal range

OR Lower dose statin

OR Alternative statin

OR Intermittent (alternate day) dosing (with low dose start / slow titration)

Able to tolerate statins but with muscle symptoms

- Discuss likely net benefit
- Consider continuing statins +/- simple analgesia

Completely unable to tolerate statins

- Use non-statin medications to achieve lipid targets and/or reduce CVD risk:
 - Ezetimibe
 - Bile Resins
 - PCSK 9 inhibitors (private prescription currently) only for FH patients or severe hypercholesterolaemia with CHD
 - Consider fibrate if low HDL-C, high TG
 - High dose Metamucil
 - Policosanol-containing foods (e.g. margarines, milks)
 - Prescribed fish oils

References:

52) NPS MedicineWise. SAMS Management Algorithm. 2017 June 19. Available [here](#)

Key: FBC (full blood count); LFT (liver function tests); U&Es (urea and electrolytes); eGFR (estimated glomerular filtration rate); TFTs (thyroid function tests); CK (creatinine kinase); HMG-CoA Reductase (3-hydroxy-3-methyl-glutaryl-CoA Reductase); NAM (necrotising autoimmune myopathy); LDL-C (low-density lipoprotein cholesterol); HDL-C (high-density lipoprotein cholesterol); TG (triglycerides); PCSK9 (proprotein convertase subtilisin/kexin type 9); FH (familial hypercholesterolaemia); CHD (coronary heart disease); CVD (Cardiovascular Disease)

Summary

Hyperlipidaemia is a major risk factor for cardiovascular morbidity and mortality. 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors ('statins') are first-line therapies for hyperlipidaemia. For each 1.0 mmol/l reduction in low-density lipoprotein (LDL)-cholesterol, statins reduce the risk of major vascular events by 21% and all-cause mortality by 9%. Owing to their clinical effectiveness and excellent safety profile, many Australians are prescribed statins. There has been widespread reporting of possible side-effects, particularly muscle pains. Conversely, statin cessation relating to possible side-effects exposes patients to increased risk of vascular events and death. Although there is clinical consensus for diagnosing rare side-effects (e.g. myopathy or rhabdomyolysis), confirming that statins cause other less common side-effects (e.g., memory impairment) is difficult as strong randomised trial evidence related to statins and non-muscle-related side-effects is lacking. A stepwise approach to possible statin intolerance, consistent definitions and a simple flowchart may improve diagnosis and management. An increasing array of potential treatments are emerging, including intermittent statin dosing, new LDL-lowering drugs, LDL apheresis and supplements. Optimal statin use and management of statin intolerance should improve cardiovascular care and clinical outcomes.

Keywords: statins, statin intolerance, lipids, cardiovascular disease, alternative therapies