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

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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 rates[1]. 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%, respectively[2]. 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 under-estimated due to exclusion of patients with a history of statin intolerance[5] and lack of criteria distinguishing true statin-associated muscle symptoms (SAMS) from non-statin related muscle pain[6]. 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 treatment[7]. 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 blood[8]. 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 stain 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 2[15-24]. 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 mortality[25]. The Food and Drug Administration Adverse estimates a statin-induced rhabdomyolysis rate of 0.70/100,000 patient-years[10].

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 elevation[26]. Statin-induced muscle toxicity may present as fatigue, muscle weakness, pain, tenderness or cramps, which are usually proximal and symmetrical, but may be generalised[27]. 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 myositis[28]. 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 placebo[30]. 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 elevations[16]. Distinct molecular changes have been shown in patients with statin-induced myalgia undergoing statin re-challenge, such as mitochondrial stress, cell senescence and apoptosis[31], 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 elevations[16]. 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 ≤3% of statin-treated patients, and most resolve spontaneously within weeks without drug discontinuation[18]. Baseline elevated liver enzymes are often associated with dyslipidaemia, obesity and diabetes, NAFLD, and alcohol excess[15]. 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 hepatitis[36]. 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) ≈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 factors[21-23]. 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-specific[38]. 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 resistance[39]. Direct inhibition of HMG-CoA reductase and statin-activated hepatic gluconeogenesis may also play a role in NOD[40]. 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 therapy[41]. 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 masked[45]. 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 myotoxicity[46].

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 immunosuppression[31]. 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 Algorithm[51].

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 ≈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 ± 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 gut[58]. 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 alone[59]. Ezetimibe has very good tolerance, safety and efficacy, with less side-effects compared to upward titration of moderate-dose statin[15].

Resins

Bile acid sequestrants (resins), such as colestipol and cholestyramine, reduce LDL-C by ≈15–26%, raise HDL-C modestly, but can also raise triglycerides, particularly if fasting triglycerides are elevated[60]. While resins can reduce CVD events[61], tolerability and adherence are poor, predominantly due to gastrointestinal side-effects[60].

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 dyslipidaemia[62-64].

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 risk[62].

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 death[66]. 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 women[67].

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-C[68] by 50–70%, with or without background statin[15]. 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 lowering[70]. 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 limiting[72].

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 symptoms[73]. 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 mortality[76]. 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 upset[79].

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 effects[80]. A meta-analysis demonstrated no lipid benefits[81]. 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 formulation[83] and is sometimes recommended for myalgia. Magnesium orotate improves mitochondrial respiratory chain function[84]. 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 NPS[51] 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.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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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 C); HDL-C (high density lipoprotein C); hr (hour); CYP450 (Cytochrome P450); Δ = change.

For more details, please see **TABLE 2: MAJOR SIDE EFFECTS OF STATINS** ***references 10 and 11***

Hepatic effects	'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.
Muscle complaints & Myopathy	Include: proximal, symmetric muscle myalgia, aches, soreness, stiffness, cramps or weakness (may or may not be associated with elevated circulating CK levels)
Glycaemic control and Diabetes	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.

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**
- Advanced age (>80 years) **- Female sex** **- Asian ethnicity** **- Family history of myopathy** **- Family history of myopathy with statin therapy** **- Genetic polymorphisms of CYP450 isoenzymes**	- Low BMI, small body frame - Alcohol abuse - Illicit drug use (cocaine, amphetamines) - Heavy and/or unaccustomed exercise	- 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	- High statin dose Drug-statin interactions - 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**
- Hypo- or hyperthyroidism **- Cushing syndrome** **- Adrenal insufficiency** **- Hypoparathyroidism**	- Vitamin D deficiency - Fibromyalgia - Polymyalgia rheumatica - Polymyositis - Systemic lupus erythematosis - Tendon or joint disorder	- Peripheral arterial disease (exertional buttock, thigh, calf symptoms)	- Seizures -Neuropathy or radiculopathy - Past polio	- Glucocorticoids - Antipsychotics - Antiretroviral drugs - Illicit drugs [cocaine, amphetamines]	- Viral illness	- 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 (creatine kinase)

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

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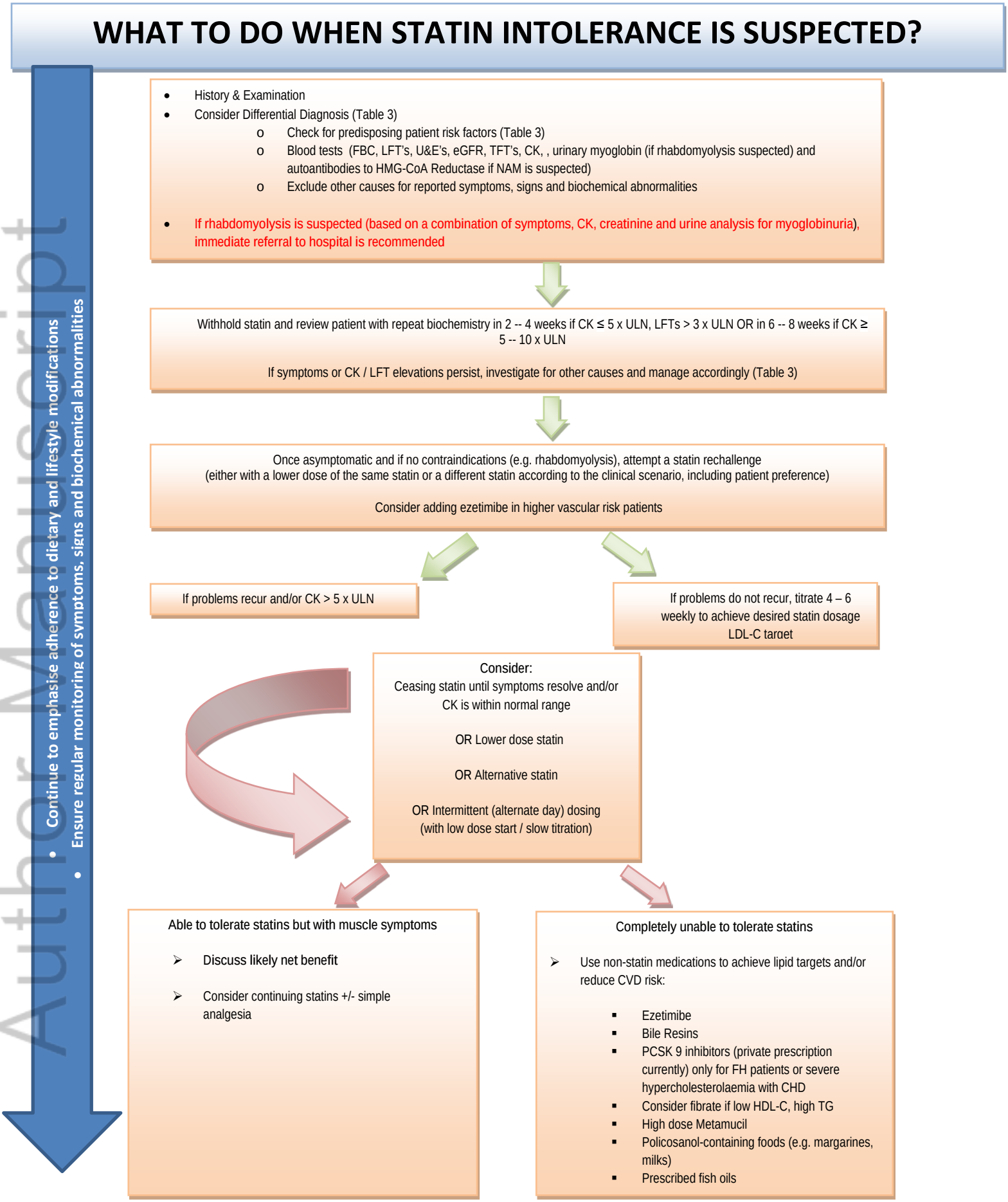
FIGURE 1: WHAT TO DO WHEN STATIN INTOLERANCE IS SUSPECTED?



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Key: FBC (full blood count); LFT (liver function tests); U&Es (urea and electrolytes); eGFR (estimated glomerular filtration rate); TFTs (thyroid function tests); CK (creatine 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