

Clinical update

# Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

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Statin-associated muscle symptoms (SAMS) are one of the principal reasons for statin non-adherence and/or discontinuation, contributing to adverse cardiovascular outcomes. This European Atherosclerosis Society (EAS) Consensus Panel overviews current understanding of the pathophysiology of statin-associated myopathy, and provides guidance for diagnosis and management of SAMS. Statin-associated myopathy, with significant elevation of serum creatine kinase (CK), is a rare but serious side effect of statins, affecting 1 per 1000 to 1 per 10 000 people on standard statin doses. Statin-associated muscle symptoms cover a broader range of clinical presentations, usually with normal or minimally elevated CK levels, with a prevalence of 7–29% in registries and observational studies. Preclinical studies show that statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, thereby providing a potential link between statins and muscle symptoms; controlled mechanistic and genetic studies in humans are necessary to further understanding. The Panel proposes to identify SAMS by symptoms typical of statin myalgia (i.e. muscle pain or aching) and their temporal association with discontinuation and response to repetitive statin re-challenge. In people with SAMS, the Panel recommends the use of a maximally tolerated statin dose combined with non-statin lipid-lowering therapies to attain recommended low-density lipoprotein cholesterol targets. The Panel recommends a structured work-up to identify individuals with clinically relevant SAMS generally to at least three different statins, so that they can be offered therapeutic regimens to satisfactorily address their cardiovascular risk. Further research into the underlying pathophysiological mechanisms may offer future therapeutic potential.

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Statin • Muscle symptoms • Myalgia • Myopathy • Statin intolerance • Mitochondrial • Consensus statement • Lipids • Cholesterol

## Introduction

Statin therapy is the cornerstone for prevention and treatment of cardiovascular disease (CVD), and is generally safe and well tolerated.<sup>1</sup> In randomized, controlled trials (RCTs), adverse event rates (including complaints of muscle pain) are similar in statin and placebo groups,<sup>2–4</sup> and compare favourably with event rates for other agents commonly used in CVD prevention, such as angiotensin-converting enzyme inhibitors<sup>5</sup> and beta-blockers.<sup>6</sup> However, statins do cause a rare side-effect known as myositis, defined as muscle symptoms in association with a substantially elevated serum creatine kinase (CK) concentration. Creatine kinase is the enzyme released from damaged muscle cells, and CK elevations  $>10\times$  the upper limit of normal (ULN) occur in 1 per 1000 to 1 per 10 000 people per year,<sup>7</sup> depending on the statin, its dose, and the presence of other risk factors. Over the last decade, a series of observational studies have attributed a number of other adverse effects to statins, including musculoskeletal complaints, gastro-intestinal discomfort, fatigue, liver enzyme elevation, peripheral neuropathy, insomnia, and neurocognitive symptoms. In addition, randomized trials have shown a small increase in the risk of incident diabetes.<sup>8–10</sup> Muscle symptoms, the most prevalent of these effects, are the focus of this review.

In contrast to RCTs, patient registries, together with clinical experience, indicate that 7–29% of patients complain of statin-associated muscle symptoms (SAMS).<sup>11–15</sup> These are usually associated with normal or slightly elevated CK concentrations. Statin-associated muscle symptoms likely contribute significantly to the very high discontinuation rates of statin therapy (up to 75%) within 2 years of initiation.<sup>16</sup> Indeed, in 65% of former statin users, the main reason for statin non-adherence or discontinuation was the onset of side effects, predominantly muscle-related effects.<sup>13</sup> Such non-adherence/discontinuation from treatment may have a marked impact on CVD benefit, as suggested by the higher mortality in elderly secondary prevention patients with low vs. high adherence to statin therapy (24% vs. 16%, respectively; adjusted hazard ratio, 1.25;  $P = 0.001$ ).<sup>17</sup> Similarly, a meta-analysis showed a 15% lower CVD risk in patients who were adherent to statins compared with those with low adherence.<sup>18</sup>

The clinical presentation of muscle symptoms is highly heterogeneous, as reflected by the variety of definitions in the literature (see Supplementary material online, Table S1). Muscle pain or aching, stiffness, tenderness or cramp (often referred to as 'myalgia'<sup>19</sup>) attributed by patients to their statin use is usually symmetrical but may be localized, and can be accompanied by muscle weakness; any of these effects occur predominantly without an elevation of CK.

As indicated above, reported rates of muscle symptoms are invariably lower in blinded RCTs when compared with those in registries and observational studies, with myalgia rates similar in subjects on statin or placebo.<sup>2–4,20,21</sup> Admittedly, patients with comorbidities that would predispose to an increased risk for musculoskeletal symptoms may have been underrepresented in RCTs. In addition, dedicated questionnaires

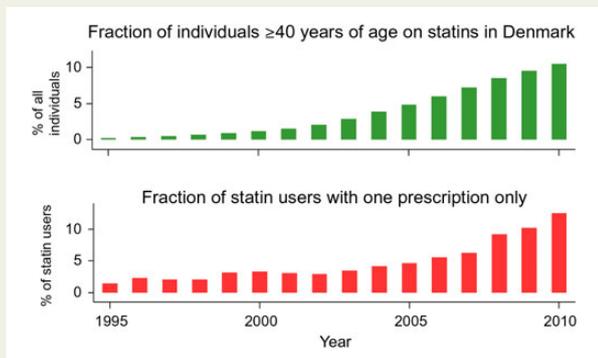
into muscle complaints are not always incorporated within trial methodology. Conversely, the lack of a placebo comparator in observational studies precludes the ability to establish a causal relationship between statin and muscle complaints. The Effects of Statins on Muscle Performance (STOMP) study is, to our knowledge, the only randomized, double-blind, placebo-controlled study specifically designed to examine the effect of statins on skeletal muscle symptoms and performance.<sup>22</sup> Among the 420 statin-naïve subjects randomized to atorvastatin 80 mg daily or placebo for 6 months, 9.4% of the statin-treated and 4.6% of control subjects met the study definition of myalgia ( $P = 0.054$ ), suggesting that the incidence of muscle complaints due to the statin is considerably less than that reported in observational trials. The STOMP study also found no differences in the measures of muscle strength or exercise performance between statin-treated and placebo subjects. Few other RCTs have queried for muscle complaints among participants.<sup>20</sup> Muscle complaints in other clinical trials have been similar in statin-treated and placebo subjects.<sup>4,20,23,24</sup> However, even a small increase in myalgia rates would still represent a substantial number of patients given the widespread use of statins.

From a treatment viewpoint, Zhang *et al.*<sup>14</sup> showed that 90% of patients reporting SAMS to one statin were able to tolerate an alternative statin with continued use after 12 months, suggesting that statin-attributed symptoms may have had other causes or were not generalizable to other statins. Similar results were reported by Mampuya *et al.*<sup>25</sup> Furthermore, increased prescription of statins itself appears to be associated with increased non-adherence or discontinuation, as illustrated for Denmark over the period 1995–2010 (Figure 1).<sup>26,27</sup> Different factors may have contributed to this finding. Increased media coverage of statins and their perceived side-effects, as well as wider prescription in primary prevention where the benefits may be less obvious to patients, may be contributing to greater non-adherence and discontinuation.

Here, this European Atherosclerosis Society (EAS) Consensus Panel provides an overview of the science underlying the pathophysiology of statin-induced myopathy, as well as guidance for clinicians on the diagnosis and management of SAMS. We have avoided the use of the term 'statin intolerance', as this is not specific for muscle symptoms. These recommendations can assist in improving the likelihood that patients experiencing SAMS receive optimal low-density lipoprotein-cholesterol (LDL-C) lowering therapy to minimize their risk for CVD.

## Assessment and diagnosis of statin-associated muscle symptoms

While consensus groups including the American Heart Association/American College of Cardiology<sup>28</sup> and the National Lipid Association<sup>19</sup> have presented definitions of SAMS based on symptoms



**Figure 1** Trends in statin use (upper panel) and statin non-adherence/discontinuation (lower panel) in adults  $\geq 40$  years, in Denmark over the period 1995–2010. Statin use from 1 January 1995 to 31 December 2010 was classified according to the Anatomical Therapeutic Classification of Drugs code C10AA, as registered in the national Danish Registry of Medicinal Products Statistics, recording information on all prescribed drugs dispensed at all Danish pharmacies from 1995 onwards (for details see references<sup>26,27</sup>). The percentage of the Danish population aged  $\geq 40$  years on statins increased from  $<1\%$  in 1995 to  $11\%$  in 2010. Correspondingly, non-adherence or discontinuation (defined as the percentage of patients starting statins who only redeemed one prescription) increased from  $2\%$  in 1995 to  $13\%$  in 2010. Figure designed by Dr Sune F. Nielsen and Prof Børge G. Nordestgaard.

and the magnitude of CK elevation, less attention has been paid to clinical diagnostic criteria. Indeed, a definitive diagnosis of SAMS is difficult because symptoms are subjective and there is no 'gold standard' diagnostic test. Importantly, there is also no validated muscle symptom questionnaire, although the National Lipid Association has proposed a symptom scoring system based on the STOMP trial and the PRIMO survey (see Supplementary material online, Table S2).<sup>19</sup> Consequently, we suggest that assessment of the probability of SAMS being due to a statin take account of the nature of the muscle symptoms, the elevation in CK levels and their temporal association with statin initiation, discontinuation, and re-challenge. Note that this is a clinical definition, which may not be appropriate for regulatory purposes.

In the absence of a standardized classification of SAMS, we propose to integrate all muscle-related complaints (e.g. pain, weakness, or cramps) as 'muscle symptoms', subdivided by the presence or absence of CK elevation (Table 1). Pain and weakness in typical SAMS are usually symmetrical and proximal, and generally affect large muscle groups including the thighs, buttocks, calves, and back muscles. Discomfort and weakness typically occur early (within 4–6 weeks after starting statin therapy<sup>22</sup>), but may still occur after many years of treatment. Onset of new symptoms may occur with an increase in statin dose or initiation of an interacting drug. The symptoms appear to be more frequent in physically active individuals.<sup>11</sup> Statin-associated muscle symptoms often appear more promptly when patients are re-exposed to the same statin.

In the vast majority of cases, SAMS are not accompanied by marked CK elevation.<sup>24,29</sup> For SAMS with CK elevations  $> 10 \times$  ULN, usually referred to as myopathy, the incidence is approximately 1 per 10 000 per year with a standard statin dose (e.g. simvastatin 40 mg daily). The risk varies, however, among different statins, and increases not only with the dose of statin, but also with factors associated with increased statin blood concentrations (e.g. genetic factors, ethnicity, interacting drugs, and patient characteristics) (see Box 1).<sup>30</sup> Rhabdomyolysis is a severe form of muscle damage associated with very high CK levels with myoglobinaemia and/or myoglobinuria with a concomitantly increased risk of renal failure. The incidence of rhabdomyolysis in association with statin therapy is  $\sim 1$  in 100 000 per year.<sup>7</sup> In view of the rarity of CK elevations during statin therapy, it is not recommended to routinely monitor CK. Even if an asymptomatic elevation of CK is detected, the clinical significance is unclear.

Statin-associated muscle symptoms are more likely to be caused by statins when elevated CK levels decrease after cessation of either the statin or the interacting drug, or when symptoms regress markedly within a few weeks of cessation of the statin and/or reappear within a month of drug re-challenge. Time to reappearance of symptoms is also influenced by the dose of statin and the duration of the re-challenge. Individual patient drug–placebo clinical trials have been suggested as an approach to confirming diagnosis of SAMS,<sup>31</sup> but are not feasible in the routine outpatient setting.

## Management of statin-associated muscle symptoms

If a patient complains of muscle symptoms, the clinician needs to evaluate risk factors which can predispose to statin-associated myopathy, exclude secondary causes (especially hypothyroidism and other common myopathies such as polymyalgia rheumatica, or increased physical activity), and review the indication for statin use. The clinician should bear in mind that other commonly prescribed drugs such as anti-inflammatory (glucocorticoids), antipsychotic (risperidone, haloperidol), immunosuppressant or antiviral agents (human immunodeficiency virus protease inhibitors), lipid-modifying drugs (gemfibrozil), as well as substances of abuse (alcohol, opioids, and cocaine) may also cause muscle-related side effects. Several factors including female sex, ethnicity, multisystem disease, and small body frame predispose to SAMS (see Box 1), with the presence of an increasing number of factors associated with greater risk.<sup>9,30,32–34</sup> Additionally, pharmacokinetic drug–drug interactions (DDIs) that increase statin exposure increase the risk of statin-associated myopathy (Box 2). Concomitant treatment with a statin and medication(s) that inhibit cytochrome P450 (CYP450) isoenzymes, organic anion transport protein 1B1 (OATP1B1), or P-glycoprotein 1 (P-gp) has been associated with increased risk of new or worsening muscle pain (see *Overview of the pathophysiology of statin-induced myopathy* section). Polypharmacy, including both prescribed and self-prescribed or over the counter medications (e.g. vitamins, minerals and herbal remedies), is a potential cause of DDIs with statins. In addition, pharmacogenetic considerations may be relevant, potentially influencing plasma concentrations of statins and in turn statin–drug interactions.

**Table 1** Definitions of statin-associated muscle symptoms proposed by the EAS Consensus Panel

Symptoms	Biomarker	Comment
Muscle symptoms	Normal CK	Often called 'myalgia'. May be related to statin therapy. Causality is uncertain in view of the lack of evidence of an excess of muscle symptoms in blinded randomized trials comparing statin with placebo.
Muscle symptoms	CK >ULN <4 × ULN CK >4 <10 × ULN	Minor elevations of CK in the context of muscle symptoms are commonly due to increased exercise or physical activity, but also may be statin-related; this may indicate an increased risk for more severe, underlying muscle problems. <sup>19</sup>
Muscle symptoms	CK >10 × ULN	Often called myositis or 'myopathy' by regulatory agencies and other groups (even in the absence of a muscle biopsy or clinically demonstrated muscle weakness). Blinded trials of statin vs. placebo show an excess with usual statin doses of about 1 per 10 000 per year. <sup>4</sup> Pain is typically generalized and proximal and there may be muscle tenderness and weakness. May be associated with underlying muscle disease.
Muscle symptoms	CK >40 × ULN	Also referred to as rhabdomyolysis when associated with renal impairment and/or myoglobinuria.
None	CK >ULN <4 × ULN	Raised CK found incidentally, may be related to statin therapy. Consider checking thyroid function or may be exercise-related.
None	CK >4 × ULN	Small excess of asymptomatic rises in CK have been observed in randomized blinded trials in which CK has been measured regularly. Needs repeating but if persistent, then clinical significance is unclear.

CK, creatine kinase; ULN, upper limit of the normal range.

Once secondary causes and predisposing factors have been excluded, this EAS Consensus Panel recommends a review of the need for ongoing statin therapy (see Box 3 and Figure 2).

### Patients with muscle symptoms with serum creatine kinase <4 × upper limit of normal

The majority of patients who complain of muscle symptoms have normal or mild/moderately elevated CK levels (<4 × ULN).<sup>35</sup> For patients at low CVD risk, their need for a statin should be reassessed and the benefits of therapeutic lifestyle changes, such as cessation of cigarette smoking, blood pressure control, and adoption of a Mediterranean style diet, should be balanced against the risk of continuing statin therapy. Conversely, for those patients at high CVD risk, including those with CVD or diabetes mellitus, the benefits of ongoing statin therapy need to be weighed against the burden of muscle symptoms. Withdrawal of statin therapy followed by one or more re-challenges (after a washout) can often help in determining causality; additional approaches include the use of an alternative statin, a statin at lowest dose, intermittent (i.e. non-daily) dosing of a highly efficacious statin, or the use of other lipid lowering medications (see below).

### Patients with muscle symptoms and elevated serum creatine kinase levels (>4 × upper limit of normal)

For patients at low CVD risk who have symptoms with CK >4 × ULN, the statin should be stopped and the need for statin reassessed. If considered important, a lower dose of an alternative statin should be tried and CK monitored. For patients at high CVD risk with muscle symptoms and a CK of >4 × ULN (but <10 × ULN), statin therapy can be continued with concomitant monitoring of CK, but stopped

(at least temporarily) if the levels exceed 10 × ULN. In this case, that particular statin regimen should not be restarted. If CK levels decrease after stopping the statin, restarting at a lower statin dose with CK monitoring should be tried. If, however, CK elevation persists, there may be an underlying myopathy (e.g. hypothyroidism or a metabolic muscle disorder), and referral to a neuromuscular specialist should be considered.

In patients with a CK >10 × ULN for which no secondary cause (e.g. exercise) can be found, statin therapy should be stopped because of the potential risk of rhabdomyolysis. If the CK level subsequently returns to normal, re-challenge with a lower dose of an alternative statin and careful monitoring of symptoms and CK may be considered. If rhabdomyolysis is suspected, statin should not be reintroduced. Rhabdomyolysis should be considered if there is severe muscular pain, general weakness and signs of myoglobinaemia or myoglobinuria. These patients, and those with very high CK levels (e.g. >40 × ULN), should be referred for evaluation of renal damage (urinalysis, serum creatinine levels). Intravenous hydration and urine alkalinisation are recommended for the treatment of rhabdomyolysis depending on severity and the presence of kidney injury.<sup>36</sup> If indicated, non-statin LDL-C lowering agents should be used (see below).

## Current therapy for patients with statin-associated muscle symptoms

### Statin-based therapies

If symptoms/CK abnormalities resolve after discontinuation of statin, either treatment with the same statin at a lower dose or switching to an alternative statin should be considered. If tolerated, doses can be up-titrated to achieve LDL-C goal, or as much LDL-C reduction that can be achieved with minimal muscle complaints. If these strategies are not tolerated, alternate day or twice-weekly dosing can be

### Box 1 Risk factors for statin-associated muscle symptoms. Adapted from Mancini et al.<sup>9</sup>

Anthropometric	<ul style="list-style-type: none"> <li>Age &gt;80 years old (general caution advised for age &gt;75)</li> <li>Female</li> <li>Low body mass index</li> <li>Asian descent</li> </ul>
Concurrent conditions	<ul style="list-style-type: none"> <li>Acute infection</li> <li>Hypothyroidism (untreated or undertreated)</li> <li>Impaired renal (chronic kidney disease classification 3, 4, and 5) or hepatic function</li> <li>Biliary tree obstruction</li> <li>Organ transplant recipients</li> <li>Severe trauma</li> <li>Human immunodeficiency virus</li> <li>Diabetes mellitus</li> <li>Vitamin D deficiency</li> </ul>
Surgery	<ul style="list-style-type: none"> <li>Surgery with high metabolic demands. The American Heart Association recommends temporary cessation of statins prior to major surgery<sup>120</sup></li> </ul>
Related history	<ul style="list-style-type: none"> <li>History of creatine kinase elevation, especially &gt;10× the upper limit of the normal range</li> <li>History of pre-existing/unexplained muscle/joint/tendon pain</li> <li>Inflammatory or inherited metabolic, neuromuscular/muscle defects (e.g. McArdle disease, carnitine palmitoyl transferase II deficiency, myoadenylate deaminase deficiency, and malignant hyperthermia)</li> <li>Previous statin-induced myotoxicity</li> <li>History of myopathy while receiving another lipid-lowering therapy</li> </ul>
Genetics	<ul style="list-style-type: none"> <li>Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporters</li> </ul>
Other risk factors	<ul style="list-style-type: none"> <li>High level of physical activity</li> <li>Dietary effects (excessive grapefruit or cranberry juice)</li> <li>Excess alcohol</li> <li>Drug abuse (cocaine, amphetamines, heroin)</li> </ul>

considered to achieve the LDL-C goal. Despite methodological limitations (small size, retrospective, open label, or non-randomized design), studies have shown that either alternate day or twice-weekly dosing strategies can reduce LDL-C by 12–38%, and, importantly, are tolerated by ~70% of previously intolerant patients.<sup>37</sup> Generally, lower doses of a high intensity statin with a long half-life (atorvastatin, rosuvastatin, and pitavastatin) are more appropriate.

### Non-statin based lipid-lowering therapy

If LDL-C remains above target despite maximally tolerated statin dosage, addition of an alternative LDL-C lowering agent should be

### Box 2 Factors that influence the pharmacokinetics of statins and risk for statin-associated muscle symptoms (SAMS)

- Pre-existing risk factors and co-morbidities: see Box 1
- High-dose statin therapy
- Polypharmacy
- Drug–drug interactions: concomitant use of certain drugs including gemfibrozil, macrolides, azole antifungal agents, protease inhibitors, and immunosuppressive drugs such as cyclosporine, and inhibitors of CYP450 isoenzymes, OATP 1B1, or P-gp, can affect the metabolism of statins, increase their circulating levels and, consequently, the risk for SAMS.
- Pharmacogenetic considerations may be relevant (see Overview of the pathophysiology of statin-induced myopathy)

CYP450, cytochrome P450; OATP 1B1, organic anion-transporting polypeptide 1B1; P-gp, P-glycoprotein 1.

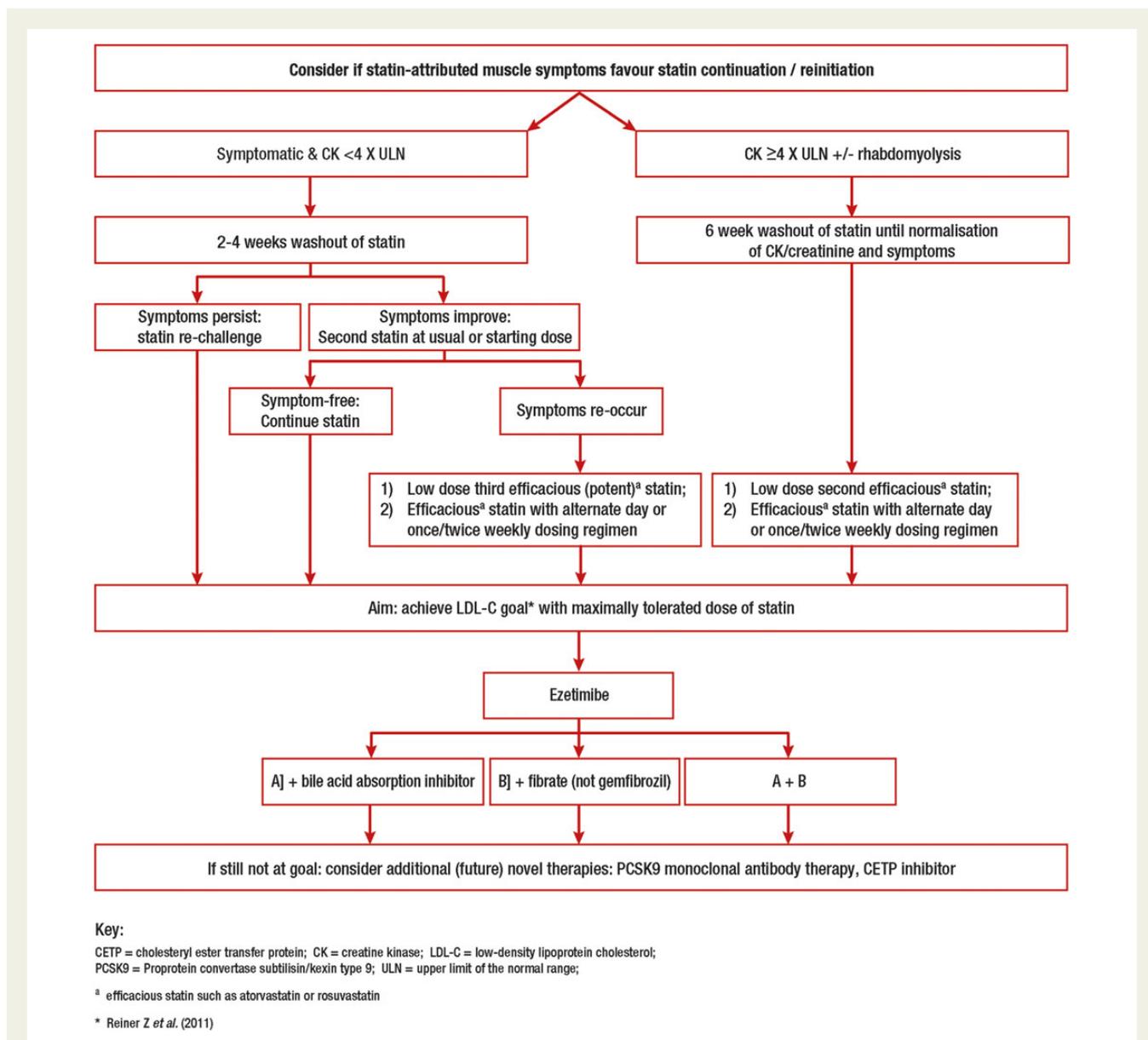
### Box 3 Management of statin-associated muscle symptoms

- Ensure that there is an indication for statin use and that the patient is fully aware of the expected benefit in cardiovascular disease risk reduction that can be achieved with this treatment
- Ensure that there are no contraindications to statin use
- Counsel patients regarding the risk of 'side effects' and the high probability that these can be dealt with successfully
- Emphasize dietary and other lifestyle measures
- Use statin-based strategies preferentially notwithstanding the presence of statin-attributed muscle-related symptoms
- If re-challenge does not work; use a low or intermittent dosing preferably of a different (potent or efficacious) statin
- Use non-statin therapies as adjuncts as needed to achieve low-density lipoprotein cholesterol goal
- Do not recommend supplements to alleviate muscle symptoms as there is no good evidence to support their use

Reproduced with permission from Mancini et al.<sup>9</sup>

considered in patients at high CVD risk to improve LDL-C reduction.<sup>38,39</sup> Ezetimibe reduces LDL-C by 15–20%, is easy to take with few side effects,<sup>40</sup> and has been shown to reduce CVD events.<sup>41</sup> In patients with SAMS, the combination of ezetimibe plus fluvastatin XL reduced LDL-C by 46% and was as well tolerated as ezetimibe alone.<sup>42</sup> Bile acid sequestrants can reduce LDL-C levels by 15–25% depending on the type and dose used, and may also improve glycaemia in patients with diabetes.<sup>43,44</sup> Colesevelam is easier to take and better tolerated than earlier formulations. The combination of a bile acid sequestrant and ezetimibe can reduce LDL-C by ~30–35%.

Fenofibrate can lower LDL-C by 15–20% in patients with high baseline levels who do not have concomitant hypertriglyceridaemia.<sup>45</sup> This fibrate is easy to take, and has shown an excellent safety record in the Action to Control Cardiovascular Risk in Diabetes and Fenofibrate Intervention and Event Lowering in Diabetes trials, although additional CVD benefit has not been demonstrated, and serum creatinine was reversibly increased during treatment.<sup>46,47</sup> Unlike gemfibrozil, there is no increased risk of rhabdomyolysis



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**Figure 2** Therapeutic flow-chart for management of patients with statin-associated muscle symptoms.

when fenofibrate is added to a statin.<sup>48</sup> Niacin also lowers LDL-C levels by 15–20%,<sup>49</sup> but recent large randomized trials showed a significant excess of adverse effects and no significant CVD benefit when added to background statin treatment; therefore, niacin derivatives are no longer available for prescription in Europe.<sup>50,51</sup>

Physicians and health care professionals should therefore consider the use of ezetimibe as first choice, potentially followed by bile acid sequestrants or fibrates in combination with ezetimibe, as needed to achieve LDL-C lowering consistent with guidelines.

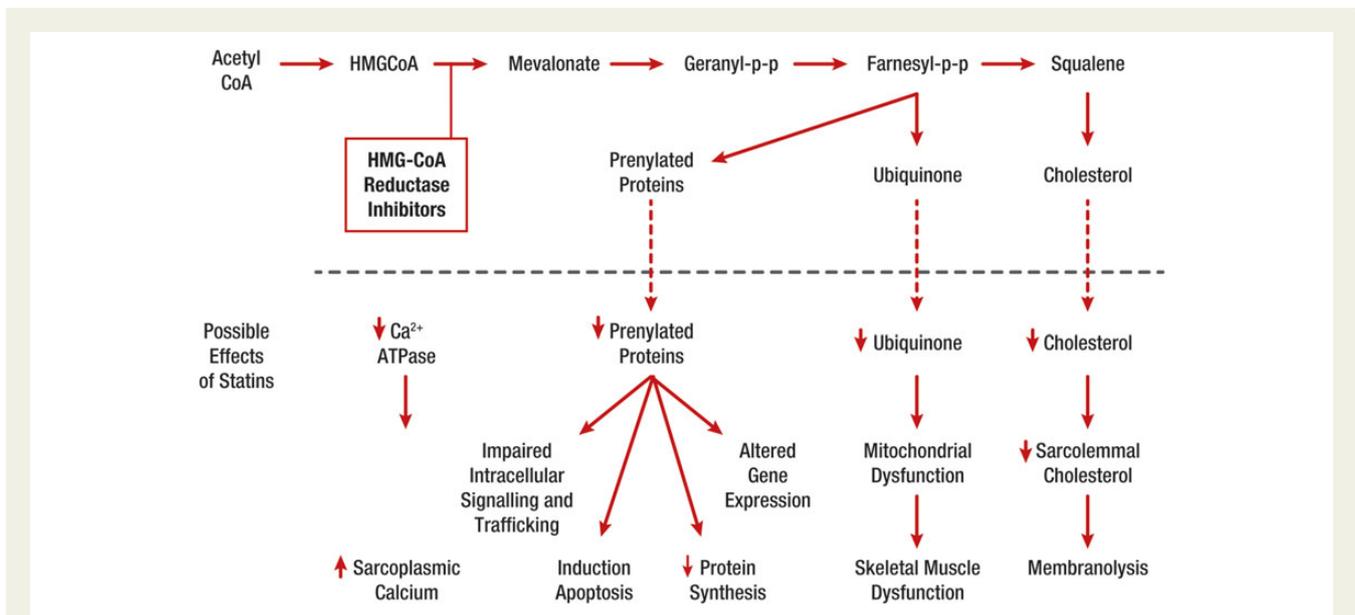
### Nutraceuticals

In addition to adoption of a low saturated fat diet and avoidance of trans fats, consumption of viscous fibre (mainly psyllium, 10 g daily) and foods with added plant sterols or stanols (2 g daily) has also been shown to reduce LDL-C by 7% and 10%, respectively.<sup>52,53</sup>

The Portfolio diet, incorporating plant sterols, soya protein, viscous fibres, and nuts, has the potential to reduce LDL-C levels by 20–25%.<sup>54</sup> This Panel believes that these approaches are appropriate either alone or in association with statin or non-statin drug regimens in patients with SAMS.

### Complementary therapies

A number of complementary therapies, including ubiquinone (coenzyme Q10 [CoQ10]) and vitamin D supplementation, have been suggested to improve statin tolerability. A double-blind RCT and a meta-analysis,<sup>55,56</sup> however, failed to substantiate that CoQ10, even at high doses, reduced symptoms in patients with SAMS. Evidence for the effectiveness of vitamin D is also controversial,<sup>57–60</sup> although many patients with SAMS are found to have low blood



**Figure 3** Effects potentially involved in statin-related muscle injury/symptoms (Reproduced with permission from Needham and Mastaglia 2014).<sup>79</sup> A number of statin-mediated effects have been proposed including reduced levels of non-cholesterol end-products of the mevalonate pathway; reduced sarcolemmal and/or sarcoplasmic reticular cholesterol; increased myocellular fat and/or sterols; inhibition of production of prenylated proteins or guanosine triphosphate (GTP)ases; alterations in muscle protein catabolism; decreased myocellular creatine; changes in calcium homeostasis; immune-mediated effects of statins and effects on mitochondrial function—see Figure 4 and Box 4. Ca<sup>2+</sup>ATPase, calcium ATPase; HMG CoA, 3-hydroxy-3-methyl-glutaryl-CoA; PP, pyrophosphate.

levels of vitamin D. Hence, this Panel does not recommend supplementation with either CoQ10 or vitamin D to treat or prevent SAMS.

Red yeast rice (*Monascus purpureus*) is a fermented product that has been shown to reduce LDL-C levels by 20–30% in short-term RCTs.<sup>61</sup> This effect is partly due to the presence of monacolin K, a product similar to lovastatin that inhibits hepatic cholesterol synthesis, as well as plant sterols that reduce cholesterol absorption. While recent data suggest that red yeast rice is an effective, well-tolerated approach,<sup>62</sup> there remain a number of outstanding issues, including the lack of robust evidence that red yeast rice is efficacious and tolerated in the long term, lack of standardization with variable drug bioavailability in different preparations, and possible toxic effects due to contaminants. Furthermore, red yeast rice may also elicit SAMS because of the statin-like content. Long-term, rigorously designed RCTs are needed before red yeast rice could be recommended to patients with increased CVD risk.

## Future low-density lipoprotein-lowering therapies for patients with statin-associated muscle symptoms

Two classes of novel therapies, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and cholesteryl ester transfer protein (CETP) inhibitors, offer potential as alternatives for the management of patients with persistent SAMS.

### PCSK9 inhibitors

PCSK9 is a circulating protein that binds to the LDL receptor and targets it for degradation.<sup>63</sup> First identified in 2003 and shown to be related to autosomal-dominant hypercholesterolaemia, PCSK9 has become a therapeutic target for potentially reducing LDL-C in humans.<sup>64,65</sup> Clinical development of human monoclonal antibodies has progressed very rapidly, with the most advanced being evolocumab, alirocumab, and bococizumab. Studies have consistently shown large LDL-C reductions of 50–60% in a variety of patient groups,<sup>64,65</sup> including those identified as statin intolerant,<sup>66–68</sup> with a very low rate of muscle symptoms, thus reinforcing the concept that statin rather than LDL-C lowering is implicated in the causation of myopathy. In clinical trials including over 6000 patients treated for 3 to 12 months, the tolerability of these subcutaneously administered drugs has been very good, with few injection site reactions and no significant liver function abnormalities or CK elevations.<sup>69,70</sup> Four large CVD outcomes trials are ongoing and initial results are anticipated in 2017.<sup>71–74</sup>

### Cholesteryl ester transfer protein inhibitors

Cholesteryl ester transfer protein mediates the heteroexchange of triglycerides and cholesteryl esters between lipoproteins. Inhibitors of CETP can markedly increase high-density lipoprotein cholesterol, and two members of this class in advanced development, anacetrapib and evacetrapib, equally lower LDL-C by 25–40%.<sup>75,76</sup> The mechanism for LDL-C lowering involves increased fractional removal rates for LDL apolipoprotein B from plasma although the molecular basis for this is unclear. Importantly, no side effects involving the

#### Box 4 Statin-induced myopathy mediated by abnormal mitochondrial function: what is the evidence?

- Histochemical findings: muscle biopsies from four patients with statin-associated myopathy and normal creatine kinase (CK) levels showed findings consistent with abnormal mitochondrial function, including increased intramuscular lipid content, diminished cytochrome oxidase staining, and ragged red fibres.<sup>80</sup> One study showed muscle injury in 25 of 44 patients with myopathy and in one patient taking statin without myopathy,<sup>81</sup> whereas another study reported unchanged muscle structure in 14 of 18 patients with statin-induced increased CK levels.<sup>82</sup>
- Decreased mitochondrial DNA (mtDNA): reduced levels were found in skeletal muscle biopsies taken from patients treated with simvastatin 80 mg/day for 8 weeks but not in those treated with atorvastatin 40 mg/day.<sup>83</sup> There was a positive overall correlation between changes in muscle ubiquinone and the change in mtDNA/nuclear DNA ratios ( $R = 0.63, P < 0.01$ ), which was strongest in the simvastatin group ( $R = 0.76, P < 0.002$ ). A cross-sectional study in 23 patients with simvastatin- or atorvastatin-induced myopathy also revealed low mtDNA/nuclear DNA ratios.<sup>84</sup>
- Activity of complex III of the mitochondrial respiratory chain: activity of this complex and concentrations of high-energy phosphates were found to be unchanged in statin-treated patients, suggesting that mitochondrial function was not compromised.<sup>82,85</sup> Another study reported lower expression of complex I, II, III, and IV after 8 weeks of simvastatin, but not after atorvastatin treatment despite similar reduction in coenzyme Q10 (CoQ10, also known as ubiquinone).<sup>86</sup> Of note, these studies were performed at rest, and may not reflect mitochondrial function during exercise.
- Lower mitochondrial oxidative phosphorylation (OXPHOS): this was observed in chronic simvastatin users (mean  $\pm$  SD,  $5 \pm 5$  years) compared with untreated persons. Mitochondrial density assessed by citrate synthase activity (CSA) did not differ between the two groups, but there was an increase in the ratio of mitochondrial voltage-dependent anion channels (VDAC) to CSA suggesting more channels per mitochondrion. Voltage-dependent anion channel helps regulate mitochondrial calcium content, and an increase in mitochondrial calcium content facilitates apoptosis. Mitochondrial OXPHOS can also be assessed *in vivo* from post-exercise phosphocreatine recovery using <sup>31</sup>P-phosphorus magnetic resonance spectroscopy. These measurements showed a prolonged recovery half-life during statin treatment even in the absence of any symptoms or overt CK changes.<sup>87</sup>
- Effects of exercise. Using respiratory exchange ratios during exercise as an indirect measure of mitochondrial function, several small studies have suggested the possibility of statin-induced abnormalities in mitochondrial function during exercise.<sup>88</sup>

musculoskeletal system have been identified with CETP inhibitors. Two large clinical trials to determine whether anacetrapib or evacetrapib reduce CVD events in high-risk patients are underway.<sup>77,78</sup>

## Overview of the pathophysiology of statin-induced myopathy

Our understanding of the pathophysiology of SAMS and statin-induced myopathy remains elusive, although several mechanisms have been proposed (see Figure 3, Supplementary material online, Table S3).<sup>79</sup> Interest has focused primarily on altered cellular energy utilization and mitochondrial function (Figure 4, Box 4).<sup>80–95</sup> Abnormal mitochondrial function with depletion of CoQ10

have been reported during statin therapy, even in asymptomatic statin users. Some argue that this may be unmasking previously undiagnosed mitochondrial pathology (see Supplementary material online, Table S4).<sup>96</sup> Notably, insulin-resistant obese individuals, or those with a family history of, or with overt type 2 diabetes, frequently exhibit reduction in both muscle ATP turnover and oxidative capacity.<sup>97,98</sup> The effects of statins on muscle mitochondria have been detected by various methods ranging from morphometry to *in vivo* magnetic resonance spectroscopy, all of which test different features of mitochondrial function.<sup>96</sup>

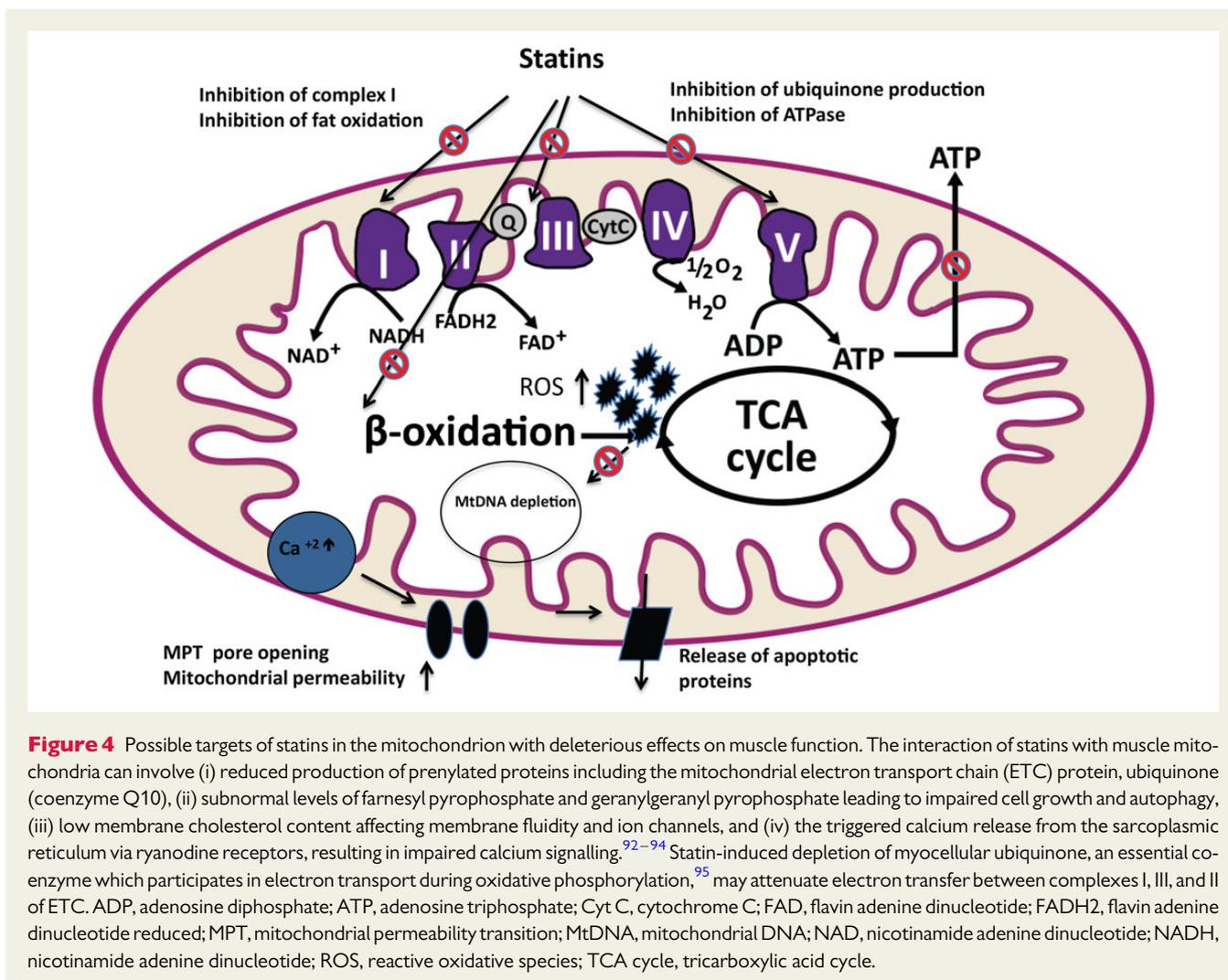
Based on these observations, it is likely that statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, each of which may contribute to the onset of muscle symptoms.<sup>99</sup> However, progress has been hampered by the fact that myopathy has been difficult to induce with statin treatment in preclinical models.<sup>100–103</sup> Only recently, mice with genetically induced deficiency of lipin-1, a phosphatidic acid phosphatase, were shown to develop myopathy/myositis that was associated with impaired autophagy and the presence of abnormal mitochondria.<sup>104</sup> In this model, myopathy/myositis could be aggravated by co-administration of statins, whereas both lipin-1 deficiency and statins were found to attenuate autolysosome maturation.

In patients, persistent myopathy has been suggested to reflect structural muscle damage.<sup>81</sup> Muscle biopsy studies in a limited number of patients with SAMS and normal CK levels suggested a role for abnormal mitochondrial function.<sup>80,81</sup> Conversely, other studies in patients with statin-induced SAMS with CK elevations were unable to demonstrate structural abnormalities in muscle cells.<sup>82</sup> Although rare, it has also been suggested that statins may trigger idiopathic inflammatory myositis or immune-mediated necrotizing myopathy. Thus, statins increase the risk for development of anti-HMG-CoA-reductase antibodies, dependent upon statin exposure, male gender, diabetes, and genetic background.<sup>35,105</sup> Overall, notwithstanding promising preclinical data, it is still not clear what the underlying pathophysiological mechanism(s) is in patients with SAMS.

## Genetic susceptibility to statin-associated muscle symptoms

While genetic testing in patients with statin myopathy has not yet become commonplace, there are some clear genetic signals, with variants of genes encoding drug transporters in both the liver and skeletal muscle that increase serum statin concentration linked to muscle side effects (see Supplementary material online, Table S5).<sup>106–109</sup> The most significant associations have been single-nucleotide polymorphisms (SNPs) in *SLCO1B1*, encoding OATP1B1.<sup>110</sup> The SEARCH genome-wide association study of *SLCO1B1* variants identified a defective rs4149056 SNP in strong linkage disequilibrium with the c.521T\_C SNP, which, in homozygotes, was associated with an 18% risk of muscle symptoms with high-dose simvastatin compared with heterozygotes (3%); in those without risk alleles, the risk of muscle symptoms was 0.6%.<sup>111</sup>

An increased frequency of pathogenic variants in muscle-disease-associated genes has been reported,<sup>96,112–114</sup> with a 13- to 20-fold higher incidence in subjects with severe myopathy compared



**Figure 4** Possible targets of statins in the mitochondrion with deleterious effects on muscle function. The interaction of statins with muscle mitochondria can involve (i) reduced production of prenylated proteins including the mitochondrial electron transport chain (ETC) protein, ubiquinone (coenzyme Q10), (ii) subnormal levels of farnesyl pyrophosphate and geranylgeranyl pyrophosphate leading to impaired cell growth and autophagy, (iii) low membrane cholesterol content affecting membrane fluidity and ion channels, and (iv) the triggered calcium release from the sarcoplasmic reticulum via ryanodine receptors, resulting in impaired calcium signalling.<sup>92–94</sup> Statin-induced depletion of myocellular ubiquinone, an essential coenzyme which participates in electron transport during oxidative phosphorylation,<sup>95</sup> may attenuate electron transfer between complexes I, III, and II of ETC. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Cyt C, cytochrome C; FAD, flavin adenine dinucleotide; FADH<sub>2</sub>, flavin adenine dinucleotide reduced; MPT, mitochondrial permeability transition; MtDNA, mitochondrial DNA; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide; ROS, reactive oxidative species; TCA cycle, tricarboxylic acid cycle.

with the general population.<sup>96,112,113</sup> In one study, 17.1% of patients with severe statin myopathy and 16.1% of patients with non-statin-induced exertional rhabdomyolysis had pathogenic variants in 12 muscle disease genes studied vs. 4.5% of statin-tolerant controls.<sup>113</sup> Other candidate genes for statin-induced myalgia have been identified,<sup>115</sup> each with a plausible pathophysiological relationship to muscle metabolism, but without adequate evidence to support their clinical relevance. Glycine amidinotransferase (GATM) catalyses a critical step in hepatic and renal synthesis of creatine, used in muscle to form creatine phosphate, which is a major source of energy storage in muscle. Two independent studies showed that genotypes associated with statin-induced down-regulation of expression of the gene encoding GATM were associated with protection from statin-induced myopathy.<sup>116</sup> Other investigators, however, were unable to replicate the association between the rs9806699 GATM SNP and statin myopathy.<sup>117</sup> Clearly, further studies will be required to determine a mechanistic basis for a contribution of genetic variation in GATM to the risk of SAMS. Potential non-disease candidate genes whose products might be determinants of statin-attributed muscle symptoms include those encoding enzymes involved in drug metabolism and disposition, mitochondrial function, or ubiquitination.<sup>79,118</sup>

Genotyping of patients with personal or family histories of muscle disease who develop SAMS has been suggested as a means of diagnosing underlying muscle disease.<sup>19</sup> Candidates for genetic testing may also include patients with documented prolonged statin-associated muscle symptoms >6 months post-therapy,<sup>112</sup> and symptomatic patients with plasma CK >4 × ULN.<sup>114</sup> Targeted next-generation sequencing of muscle disease genes in these high-risk individuals will certainly become more prominent in diagnosing individuals at risk. Identification of underlying genetic risk factors may contribute to improved therapeutic compliance through careful monitoring of conservative therapy. At present, however, there is insufficient evidence to recommend genetic testing as a part of the diagnostic work-up of patients with SAMS.

## Conclusions

Lowering LDL-C with statin therapy reduces CVD risk by up to 40% in a wide range of patients. Given that the main reason for statin non-adherence/discontinuation relates to the onset of (perceived) side effects, it follows that the high prevalence of SAMS reported from observational studies is likely to adversely affect the CVD benefits of

statins.<sup>119</sup> Strategies to prevent the loss of effective statin therapy because of SAMS are still lacking. In the absence of a gold standard definition, this EAS Consensus Panel proposes to base the probability of SAMS being caused by statins on the nature of symptoms and their temporal relationship with statin initiation, statin discontinuation (or dechallenge), and repetitive re-challenge (Figure 2). Optimal therapy should combine a maximally tolerated, or even non-daily statin dose, together with non-statin-based lipid-lowering therapies in order to achieve LDL-C targets.

This Consensus Panel also highlights the need for further research into the pathophysiology of SAMS. Accumulating preclinical data show that statins decrease mitochondrial function, and alter muscle protein degradation, providing a possible pathophysiological link between statins and muscle symptoms. Studies in the clinical setting are a priority to further understanding of these mechanisms, and may offer therapeutic potential. In the absence of therapies to prevent these symptoms, this Consensus Panel recommends that the response of patients with SAMS to three or more statins should be considered for referral to specialized settings. By recognizing SAMS and adhering to a structured work-up, the Panel anticipates that individuals with clinically relevant SAMS will be offered alternative and/or novel therapeutic regimens that can satisfactorily address their CVD risk.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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The Panel met three times in London, Barcelona and Madrid at meetings chaired by MJC and HNG. The first meeting critically reviewed the literature, and the second and third meetings scrutinized drafts of this review. Each drafted section and the complete draft was revised by ES, MJC, and HNG. All Panel members agreed to the conception and design of the review, contributed to interpretation of available data, and suggested revisions. All Panel members approved the final document before submission.

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