

# Risk Factors and Drug Interactions Predisposing to Statin-Induced Myopathy

## Implications for Risk Assessment, Prevention and Treatment

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### Abstract

HMG-CoA reductase inhibitors (‘statins’) represent the most effective and widely prescribed drugs currently available for the reduction of low-density lipoprotein cholesterol, a critical therapeutic target for primary and secondary prevention of cardiovascular atherosclerotic disease. In the face of the established lipid lowering and the emerging pleiotropic properties of statins, the patient population suitable for long-term statin treatment is expected to further expand. An overall positive safety and tolerability profile of statins

has been established, although adverse events have been reported. Skeletal muscle-related events are the most common adverse events of statin treatment. Statin-induced myopathy can (rarely) manifest with severe and potentially fatal cases of rhabdomyolysis, thus rendering the identification of the underlying predisposing factors critical.

The purpose of this review is to summarize the factors that increase the risk of statin-related myopathy. Data from published clinical trials, meta-analyses, postmarketing studies, spontaneous report systems and case reports for rare effects were reviewed. Briefly, the epidemiology, clinical spectrum and molecular mechanisms of statin-associated myopathy are discussed. We further analyse in detail the risk factors that precipitate or increase the likelihood of statin-related myopathy. Individual demographic features, genetic factors and co-morbidities that may account for the significant inter-individual variability in the myopathic risk are presented. Physicochemical properties of statins have been implicated in the differential risk of currently marketed statins. Pharmacokinetic interactions with concomitant medications that interfere with statin metabolism and alter their systemic bioavailability are reviewed. Of particular clinical interest in cases of resistant dyslipidaemia is the interaction of statins with other classes of lipid-lowering agents; current data on the relative safety of available combinations are summarized. Finally, we provide an update of current guidelines for the prevention and management of statin myopathy.

The identification of patients with an increased proclivity to statin-induced myopathy could allow more cost-effective approaches of monitoring and screening, facilitate targeted prevention of potential complications, and further improve the already overwhelmingly positive benefit-risk ratio of statins.

Atherosclerotic cardiovascular disease is the most frequent cause of morbidity and mortality in developed countries. Low-density lipoprotein cholesterol (LDL-C) reduction attenuates the progression of atherosclerosis and reduces the risk of cardiovascular events. Among hypolipidaemic medications, HMG-CoA reductase inhibitors ('statins') have unequivocally revolutionized both primary and secondary prevention of cardiovascular disease, due to their lipid-lowering potential and pleiotropic effects that beneficially affect atherosclerotic plaque stability.<sup>[1]</sup> Statins are competitive inhibitors of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis that converts HMG-CoA into mevalonate. They lower plasma LDL-C through intracellular cholesterol depletion and upregulation of the expression of LDL receptors in hepatocytes.<sup>[2]</sup> The number of patients receiving statins, often in combination with other classes of lipid-lowering

agents, has expanded with the implementation of more aggressive goals for LDL-C lowering,<sup>[3]</sup> while the additional benefit attributed to intensive statin therapy has resulted in higher dose statin regimens.<sup>[4]</sup>

Accumulating evidence from controlled trials and clinical experience demonstrates that statins are well tolerated medicines with a good safety profile.<sup>[5-8]</sup> The major and most common complication to their use is a variety of skeletal muscle-related events, which represent a clinically important cause of statin intolerance and discontinuation. Statins confer a small but definite risk of myopathy, a dose-dependent adverse effect associated with all statins (class effect).<sup>[9]</sup> Muscular adverse effects are usually mild and reversible; however, these adverse effects may be a prelude to rhabdomyolysis, a very rare but potentially serious and even life-threatening clinical condition. The association of statins with cases of

severe myopathic events may have resulted in excessive safety concerns for this revolutionary class of medications.<sup>[10]</sup> Notwithstanding the overall good safety profile, knowledge of the underlying mechanisms and risk factors is required for prompt identification and proper management of adverse muscle events. The purpose of this review is to investigate the risk factors that precipitate statin-induced muscle adverse events, and also to summarize current guidelines on the administration of statins with regard to their potential myotoxicity.

## 1. Definition and Epidemiology of Statin-Induced Myopathy

In the present review the term ‘myopathy’ will be used as a general term to describe all skeletal muscle-related problems.<sup>[11]</sup> Several, often controversial, terms have been used to describe the clinical manifestations and laboratory findings of statin-induced myopathy. The spectrum of myopathy includes asymptomatic increase of creatine kinase (CK), myalgia, myositis and rhabdomyolysis, as summarized in table I. Rhabdomyolysis represents the least frequent, though potentially fatal, complication caused by skeletal muscle breakdown, which leads to the release of toxic intracellular constituents into the blood circulation and eventually causes acute renal failure.

The lack of consensus in the definition of statin-induced muscle events hinders the precise

estimation of their true incidence. Because patients with a considered high susceptibility to statin toxicity are generally excluded from clinical trials of statins, reported adverse event rates from controlled trials may underestimate the true rate of these adverse effects in an unselected patient population. Complaints of muscle symptoms occur in 1.5–3.0% of clinical trial participants, while rates widely range between 0.3% and 33% in routine practice.<sup>[12]</sup> No conclusive evidence supports increased myalgia associated with standard statin doses,<sup>[13]</sup> although this has been reported in patients receiving higher doses.<sup>[14]</sup> The overall excess risk of myopathy attributed to standard statin doses is typically <0.01%.<sup>[13]</sup> According to data from randomized clinical trials and cohort studies, the incidence of myopathy is estimated at 5 patients per 100 000 person-years and rhabdomyolysis at 1.6 patients per 100 000 person-years,<sup>[15]</sup> whereas reporting rates in the US FDA Adverse Event Reporting System database (AERS) are 0.3–2.2 cases of myopathy and 0.3–13.5 cases of rhabdomyolysis per 1 000 000 statin prescriptions.<sup>[16]</sup> A recent, large-scale trial evaluating rosuvastatin 20 mg daily reported comparable rates of myopathy between recipients of drug and placebo (0.1%).<sup>[17]</sup> Regarding higher dose statin regimens, increased risk of myopathy has been reported for simvastatin 80 mg daily<sup>[18]</sup> but not for higher doses of atorvastatin (80 mg).<sup>[4,19,20]</sup>

## 2. Comparison between Statins

Reports associating the use of all marketed statins with the entire spectrum of myopathy suggest that this is a class effect.<sup>[21]</sup> The safety profiles of different statins at standard doses seem comparable but not identical, as indicated by the significantly greater risk and subsequent withdrawal of cerivastatin,<sup>[22,23]</sup> while excess risk seems to be clearly related to increased doses. On the basis of current evidence, and in the absence of randomized trials directly comparing the risk of each available statin in comparable doses and with standard definitions of myopathic events, no definite conclusions on the relative myopathic potential conferred by each of the currently marketed statins can be drawn.<sup>[21]</sup> An overall

**Table I.** The clinical spectrum of statin-induced myopathy<sup>[11]</sup>

| Condition                 | Definition  |
|---------------------------|---|
| Myopathy                  | General term to describe all skeletal muscle-related adverse effects  |
| Asymptomatic CK elevation | CK elevation without muscle symptoms  |
| Myalgia                   | Muscle pain or weakness without CK elevation  |
| Myositis                  | Muscle symptoms with CK elevation typically <10 × ULN   |
| Rhabdomyolysis            | Muscle symptoms with CK elevation typically >10 × ULN, and with creatinine elevation (usually with brown urine and urinary myoglobin) |

**CK** = creatine kinase; **ULN** = upper limit of normal.

higher risk of rhabdomyolysis has been associated with simvastatin 80 mg, whereas the lowest incidence apparently occurs with fluvastatin and pravastatin, presumably associated with their weaker HMG-CoA reductase inhibitor capacity.<sup>[12,15,24,25]</sup> According to a meta-analysis of trials comparing standard doses of all currently marketed statins except rosuvastatin, atorvastatin was associated with the relatively highest risk and fluvastatin with the lowest risk of adverse events in general, and muscular events in particular.<sup>[26]</sup> A recently published meta-analysis of randomized controlled trials comparing different doses of atorvastatin (10–80 mg) and rosuvastatin (5–40 mg) revealed no significant difference in adverse muscular events between these two statins at any dose ratio.<sup>[27]</sup>

### 3. Mechanisms of Statin-Induced Myopathy

The pathogenetic mechanisms of statin-induced myopathy have been thoroughly reviewed by Vaklavas et al.<sup>[28]</sup> and are presented briefly in this review. The interruption of the HMG-CoA reductase biosynthetic pathway and the consequent intracellular depletion of downstream intermediate metabolites (i.e. isopentenylated proteins geranyl pyrophosphatase and farnesyl pyrophosphatase) and end products (i.e. cholesterol, dolichols, ubiquinone) are considered the cornerstone of the myotoxic effects of statins. Reduction of prenylated proteins can result in dysprenylation of proteins, including lamins and small guanosine triphosphatases, thereby causing an imbalance in the intracellular signalling cascades and enhancing apoptosis. Sarcolemmal cholesterol deficiency, as a result of the dynamic equilibrium between membrane and plasma lipids, may adversely modify membrane physical properties, integrity and fluidity, thus resulting in membrane destabilization.<sup>[29]</sup> Inhibition of dolichol synthesis has been implicated in defective N-linked glycosylation of plasma membrane proteins and impaired response to growth factors.<sup>[28]</sup>

Ubiquinone or coenzyme Q10 (CoQ10) is a recognized constituent of oxidative phosphorylation and adenosine triphosphate production in mito-

chondria required to maintain cell integrity.<sup>[30]</sup> Consistently, the decreased CoQ10 biosynthesis and thus energy depletion mediated by statins has been postulated to account for the potential myotoxicity of statins. Statin-mediated reduction of circulating, but not intramuscular,<sup>[31]</sup> CoQ10 levels has been reported, while no direct association between decreased intramuscular CoQ10 levels and mitochondrial myopathy has been established. Accordingly, CoQ10 deficiency may represent a predisposing rather than etiopathogenic factor of statin mediated myopathy, possibly in a synergistic manner with coexisting CoQ10-depleting conditions.<sup>[32]</sup>

The equilibrium between intramuscular statin transport and efflux may be a critical regulator of intramuscular drug concentration and consequently the risk of myopathy. Organic anion transporting polypeptide (OATP) 2B1, a recognized hepatic uptake transporter for statins, has also been identified in skeletal myofibres,<sup>[33]</sup> and the OATP inhibitor estrone sulphate protected the skeletal myofibres against pravastatin- and fluvastatin-induced toxicity. Furthermore, isoforms -1, -4 and -5 of the multidrug resistance-associated protein (MRP), a well characterized statin efflux transporter, are highly expressed in skeletal muscle, and the inhibition of MRP with probenecid precipitates skeletal muscle toxicity in rats treated with rosuvastatin,<sup>[34]</sup> implying that MRP-1 may be involved in statin efflux at the myocyte level.

### 4. Physicochemical and Pharmacokinetic Properties of Statins

The physicochemical properties of statins, which determine their bioavailability and thereby affect the risk of myopathy, are summarized in table II. Water solubility affects statin permeability through cellular membranes of non-hepatic (including muscular) cells and their ability to cross the blood-brain barrier. Pravastatin, rosuvastatin and to some extent fluvastatin exhibit hydrophilic properties, as opposed to the lipophilicity of the other statin molecules (i.e. atorvastatin, simvastatin and lovastatin).<sup>[35]</sup>

**Table II.** Physicochemical and pharmacokinetic properties of statins

| Characteristic                      | Lovastatin           | Simvastatin   | Pravastatin          | Fluvastatin  | Atorvastatin  | Rosuvastatin   |
|-------------------------------------|----------------------|---------------|----------------------|--------------|---------------|----------------|
| Daily dosage (mg)                   | 20–80                | 10–80         | 20–80                | 40–80        | 10–80         | 10–40          |
| Origin                              | Fungi                | Semisynthetic | Fungi                | Synthetic    | Synthetic     | Synthetic      |
| Prodrug                             | Yes                  | Yes           | No                   | No           | No            | No             |
| Solubility                          | Lipophilic           | Lipophilic    | Hydrophilic          | Intermediate | Lipophilic    | Hydrophilic    |
| CNS permeation                      | Yes                  | Yes           | No                   | No           | No            | No             |
| Effect of food intake on absorption | Increased absorption | None          | Decreased absorption | None         | None          | None           |
| First-pass metabolism               | CYP3A4               | CYP3A4        | Multiple ways        | CYP2C9       | CYP3A4        | Limited CYP2C9 |
| Protein binding (%)                 | 95                   | 95            | 50                   | 98           | 90            | 90             |
| Half-life (hours)                   | 2–3                  | 2–3           | 1–2                  | 0.5–2        | 13–16         | 19             |
| Hepatic excretion (%)               | 69                   | 79            | 46                   | >68          | Not available | 63             |
| Renal excretion (%)                 | 30                   | 13            | 60                   | <6           | <2            | 10             |

**CYP** = cytochrome P450 enzyme.

The hepatic cytochrome P450 enzyme (CYP) system is responsible for the metabolism of many drugs, including statins to some extent with the exception of pravastatin.<sup>[36]</sup> Lovastatin, simvastatin and, to a lesser extent, atorvastatin are metabolized by the CYP3A4 isozyme. Coadministration of the previously mentioned statins with medications or food that either inhibit or are substrates of CYP3A4 decreases the statins' first-pass metabolism, thereby resulting in increased bioavailability.<sup>[37]</sup> Fluvastatin is mainly metabolized by CYP2C9, and to a much lesser extent by CYP3A4 and CYP2C8, and consequently does not interact with CYP3A4 inhibitors. Pravastatin is metabolized through several pathways, including isomerization, sulfation, glutathione conjugation and oxidation, and only to a small extent (1%) by the CYP enzyme system; it is the only statin with a significant renal excretion (approximately 60% of the absorbed quantity), in keeping with its hydrophilic nature.<sup>[38]</sup> This theoretically renders it safer as far as its potential drug interactions are concerned.<sup>[9]</sup> Rosuvastatin undergoes minimal metabolism via the CYP2C9 isoenzyme,<sup>[39]</sup> while 90% is eliminated as the parent compound in the faeces.

The systematic bioavailability of statins is quite low. All statins present a high affinity with blood proteins (95%), except pravastatin (approximately 50%). Atorvastatin and rosuvastatin are the two statins with longer half-lives

(13–16 hours) and this property is most probably linked to their higher lipid-lowering efficacy.

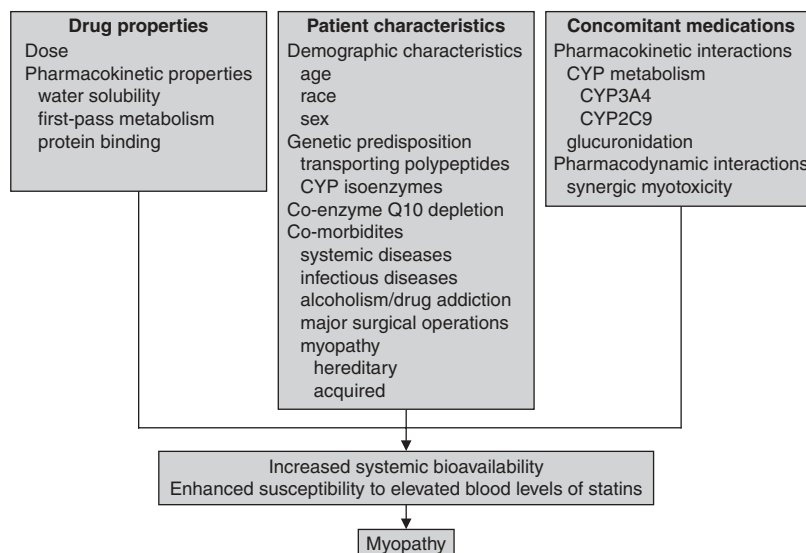
## 5. Risk Factors that Precipitate Statin-Induced Myopathy

When administering statins, physicians should take into consideration a series of factors that potentially increase the risk of myopathic events. As summarized in figure 1, a constellation of factors are associated with the risk of statin-associated myopathy development, including (i) patient characteristics (demographic characteristics, co-morbidities, genetic factors); (ii) drug properties (specific statin molecule, dose, pharmacokinetic properties); and (iii) concomitant interacting medications. Systemic exposure is considered to play a pivotal role in statin-associated myopathy, and risk factors that enhance the respective risk may do so, at least partly, by increasing either statin systemic bioavailability or the sensitivity to increased statin blood levels.

### 5.1 Patient Characteristics

#### 5.1.1 Demographic Characteristics

Certain demographic characteristics have been associated with an increased risk of statin-induced myopathy. It has been observed epidemiologically that advanced age (particularly >80 years), female sex, small body frame and frailty increase the myopathic effect of



**Fig. 1.** Risk factors for statin-induced myopathy. **CYP** = cytochrome P450 enzyme.

statins.<sup>[11,13,40]</sup> Myopathic symptoms may be hard to differentiate from muscular complaints commonly experienced in elderly patients. Polypharmacy and age-related impairment of renal function may in part account for the increased risk of myopathy among elderly individuals. A greater risk has been attributed to Chinese or Japanese descent, although this concept is inadequately supported by current evidence. Typically, Asians achieve similar benefits to Caucasians at lower statin doses. Plasma levels of rosuvastatin in particular have been shown to be 2-fold higher in Asian than in Caucasian individuals receiving similar rosuvastatin doses.<sup>[41]</sup> The smaller body mass index in Asians has been postulated as the underlying cause of the differences in drug response in some<sup>[42,43]</sup> but not all comparable studies.<sup>[44,45]</sup> Genetic differences in statin metabolism involving the CYP450 enzymes and the OATPs are more likely to account for the heightened response to statins in Asians.<sup>[46-48]</sup> Although the increased systemic bioavailability achieved with similar statin doses<sup>[41]</sup> has not been clearly related to a higher myopathic risk in Asians, rosuvastatin is labelled for lower doses in Asians<sup>[49]</sup> and none of the statins are approved in Japan at the highest doses approved in the US.<sup>[50]</sup>

### 5.1.2 Genetic Factors

Genetic predisposition and interindividual variability in susceptibility to statin-induced adverse muscular events have been reported. A number of candidate gene variants that encode statin metabolizing enzymes and receptors,<sup>[51,52]</sup> OATPs<sup>[53]</sup> and CoQ10<sup>[54]</sup> have been implicated.

Genetic polymorphisms may result in variant expression of the CYP isoenzymes both in the liver and small intestine. Low hepatic or intestinal expression of the CYP3A4 isoenzyme ('poor metabolizers') results in decreased first-pass metabolism for lovastatin, simvastatin and atorvastatin, which increases their bioavailability. In a recently published study that performed a genome-wide scan in patients with definite or incipient myopathy receiving simvastatin 80 mg daily, common variants in solute carrier organic anion transporter (SLCO) 1B1 on chromosome 12, which encodes the OATP and thereby the hepatic uptake of most statins, were linked to a substantial excess risk of statin myopathy, with 60% of all myopathy cases attributable to one specific common variant (rs4149056 C). Heterozygotes for this variant displayed a 4-fold increase in the incidence of myopathy, whereas the homozygotes had a 17-fold increase.<sup>[55]</sup> Notably,

these associations were demonstrated among patients receiving high doses of simvastatin (80 mg daily), indicating that genotypic control could optimize tailored therapeutic adjustments in patients under high-dose regimens and with coexisting risk factors.

### 5.1.3 Co-Morbidities

The incidence of statin-induced rhabdomyolysis may be higher in patients with existing myopathies, either hereditary (e.g. carnitine palmityl transferase II deficiency, McArdle's disease and myoadenylate deaminase deficiency) or acquired (e.g. postpolymyelitis syndrome).<sup>[56,57]</sup> Statins have also been implicated in the potential aggravation of myasthenia gravis.<sup>[58]</sup> Furthermore, an underlying metabolic predisposition consisting of biochemical abnormalities in mitochondrial or fatty acid metabolism in myocytes may render some apparently healthy individuals more susceptible to the development of statin-induced myopathic outcomes than others.<sup>[59]</sup>

Underlying chronic systemic diseases may serve as non-modifiable risk factors that decrease statin metabolism and excretion, and thereby increase their systemic bioavailability. These factors render some patients more susceptible to myopathy and increase the probability of adverse muscle events, which may ensue at any time during the administration of a statin. Although limited data suggest a beneficial cardiovascular effect of statins in patients with moderate renal impairment,<sup>[60]</sup> coexisting renal failure increases the risk of statin-induced myopathic events.<sup>[13]</sup> Diabetes mellitus constitutes a further myopathic risk factor in patients receiving statins, particularly combined with advanced age and chronic renal failure,<sup>[11]</sup> although there is no consensus of opinion.<sup>[61]</sup> Enhanced risk of statin-induced myopathy with excessive alcohol consumption cannot be conclusively supported by data from randomized trials as alcoholism is an exclusion criterion in most trials. However, increased alcohol intake *per se* confers a myotoxic potential<sup>[62]</sup> and alcohol abuse could raise the blood levels of statins.<sup>[12]</sup> Untreated hypothyroidism is considered to increase the risk of statin myopathy,<sup>[11,25,63]</sup> and statins may aggravate the

muscle symptoms and CK elevation caused by occult hypothyroidism. Liver dysfunction has been considered a risk factor for statin myopathy,<sup>[11,64-66]</sup> mainly due to the involvement of the hepatobiliary system in the metabolism and excretion of most statins. Although hepatic dysfunction has been associated with statin-induced rhabdomyolysis in reports by regulatory authorities,<sup>[67]</sup> the exclusion of patients with hepatic failure from randomized controlled trials prevents the establishment of a direct link between impaired liver function and heightened risk of myopathy.<sup>[4,6,17]</sup>

Furthermore, acutely acting factors predispose to myopathy independently, and may trigger the development of severe myopathy, even rhabdomyolysis, in statin-receiving individuals. Such precipitating conditions include the use of addictive drugs (e.g. amfetamines, cocaine, heroin, LSD, ecstasy),<sup>[62]</sup> serious viral<sup>[68]</sup> or bacterial infection,<sup>[69,70]</sup> major trauma and intense muscle activity. Statins can exacerbate exercise-induced skeletal muscle injury, as reported in an observational study in patients receiving high-dose statins<sup>[25]</sup> and as suggested by the greater CK response to exercise in statin- compared with placebo-treated patients.<sup>[71]</sup> Statin-related myopathy has been reported in the setting of extensive surgical operations;<sup>[72,73]</sup> therefore, a short-term withdrawal of statins during hospitalization for major surgery is recommended.<sup>[11]</sup> In the case of vascular surgery in particular, including coronary bypass procedures, statins should not be discontinued<sup>[74]</sup> in light of their beneficial plaque-stabilizing effect, with the exception of preoperative muscular symptoms, marked perioperative tissue compression or prolonged postoperative energy deprivation.<sup>[75]</sup>

## 5.2 Statin Properties

### 5.2.1 Dose-Dependent Effects

While the therapeutic benefit from statin therapy is related to the achieved LDL-C reduction,<sup>[76]</sup> the risk of adverse muscular events appears to be a dose-dependent adverse effect<sup>[21]</sup> regardless of the degree of LDL-C decrease.<sup>[15]</sup> However, there does not appear to be a linear

relationship between plasma levels achieved by a certain drug dose and the risk of adverse muscular events. Increased myopathic risk has been demonstrated with higher than currently marketed doses of simvastatin (160 mg)<sup>[76]</sup> and pravastatin (160 mg).<sup>[77]</sup> An increased incidence of myopathy has also been shown in patients with acute coronary syndromes receiving simvastatin 80 mg daily compared with placebo or simvastatin 20 mg.<sup>[18]</sup> A higher incidence of statin-related myalgia was attributed to atorvastatin 80 mg compared with simvastatin 20 mg<sup>[14]</sup> but notably this did not occur when atorvastatin 80 mg was compared with either atorvastatin 10 mg<sup>[19]</sup> or placebo.<sup>[20]</sup>

#### 5.2.2 Physicochemical Properties of Statins: Lipophilicity versus Hydrophilicity

*In vitro* research data indicate that pravastatin, which is water soluble, is less myotoxic in relation to lovastatin and simvastatin.<sup>[78]</sup> Although the inhibition of hepatocellular cholesterol synthesis was comparable between these three statins, the effect of pravastatin was 85 times weaker in rat myocytes. Moreover, pravastatin was 100-200 times (in an inversely dose-dependent mode) less myotoxic.<sup>[78]</sup> Overall, different statins seem to exert diverse dose-dependent effects on the HMG CoA reductase activity of non-hepatic cells *in vitro*. The decreased myotoxicity of pravastatin appears to be related to its decreased penetration of the cell membrane and thus uptake by extra-hepatic tissues, presumably associated with the hydrophilicity of the molecule. Pravastatin is taken up by the hepatic cells via a sodium-independent bile acid transporter, the OATP,<sup>[79]</sup> which, along with sodium-dependent taurocholate cotransporting polypeptide, also mediates the active hepatic uptake of the hydrophilic rosuvastatin molecule. The lipid-rich membranes of non-hepatic cells, such as muscle cells, lack OATP so that they function as a barrier to hydrophilic statins while allowing passive diffusion to lipophilic statins. However, the hydrophilicity of some statins *per se* has not been proven to offer clinically significant muscular protection<sup>[12]</sup> and no clinical evidence supports a direct association between the degree of lipophilicity and the myotoxic potential<sup>[9]</sup> since cases of

rhabdomyolysis have also been attributed to hydrophilic statins.

### 5.3 Statin-Drug Interactions

The interaction of statins with other categories of medications can enhance their myotoxic potential (table III). Indeed, approximately 60% of cases of statin-related rhabdomyolysis are related to drug interactions.<sup>[24]</sup> The underlying mechanism usually has a pharmacokinetic basis involving intestinal absorption, distribution, metabolism, protein binding or excretion of statins. The majority of reported cases pertain to competition at the level of hepatic metabolism,<sup>[80]</sup> considering that over half of currently available drugs are metabolized by the CYP3A4 isoenzyme; inhibition of the CYP activity by coadministered drugs increases the risk of myopathic events. Simvastatin and lovastatin appear to be more susceptible to the inhibiting effect of other CYP3A4 substrates than atorvastatin. Similarly, the interaction between fluvastatin and CYP2C9 inhibitors or competitive substrates may be of clinical importance, whereas CYP450 isoenzymes are minimally involved in rosuvastatin clearance.

**Table III.** Substances that may precipitate statin-induced myopathy

| Non-hypolipidaemic medicines   |
|--|
| Ciclosporin  |
| Macrolide antibacterials (erythromycin, clarithromycin)                |
| Azole antifungals (itraconazole, ketoconazole, fluconazole)            |
| Calcium channel antagonists (diltiazem, verapamil)                     |
| Nefazodone   |
| HIV protease inhibitors (ritonavir, nelfinavir, indinavir)             |
| Warfarin   |
| Histamine H <sub>2</sub> receptor antagonists (cimetidine, ranitidine) |
| Omeprazole   |
| Amiodarone   |
| Hypolipidaemic medicines   |
| Fibrates (gemfibrozil > bezafibrate, clofibrate, fenofibrate)          |
| Niacin   |
| Other substances   |
| Grapefruit juice   |
| Over-the-counter medications (Chinese red rice fungus)                 |



Other sites of potential pharmacokinetic interactions include inhibition of metabolism by intestinal wall isoenzymes of the CYP system, prevention of the OATP-mediated hepatocellular uptake, blocking of biliary excretion and inhibition of the renal elimination of hydrophilic metabolites.<sup>[80]</sup>

Pharmacodynamic interactions involving statins are less common because of the high selectivity of statins as HMG-CoA reductase inhibitors. The concomitant administration of agents with an independent myotoxic effect, such as fibrates, can synergistically increase the risk of statin-associated myopathy. In that case, a pharmacokinetic component may also come into play.

### 5.3.1 Interactions with Non-Hypolipidaemic Agents

#### Pharmacokinetic Interactions with Cytochrome P450 Enzyme (CYP) 3A4 Inhibitors and Competing Substrates

Inhibitors of CYP3A4 isoenzyme decrease statin metabolism and thus increase their serum levels and the likelihood of myopathy. Such enzymatic inhibitors include azole antifungals (itraconazole, ketoconazole, fluconazole),<sup>[37,81,82]</sup> macrolide antibacterials (erythromycin, clarithromycin),<sup>[83,84]</sup> calcium channel antagonists diltiazem<sup>[85,86]</sup> and verapamil, the antidepressant nefazodone and the consumption of grapefruit juice exceeding approximately 1 L daily. Grapefruit juice contains 6',7'-dihydroxybergamottin, which acts as an inhibitor of the intestinal CYP3A4 isoenzyme resulting in decreased metabolism and thereby enhanced bioavailability of statins.<sup>[80]</sup>

HIV protease inhibitors (ritonavir, nelfinavir, indinavir) are recognized CYP3A4 inhibitors and this property renders the myotoxic potential of their combination with statins high risk,<sup>[87]</sup> in particular those statins that rely to a large extent on the CYP3A4 isoform for their metabolism. Of clinical interest is the adverse effect of HIV protease inhibitors on the lipid profile,<sup>[88]</sup> which may increase the risk of cardiovascular disease and pancreatitis and often requires the administration of lipid-lowering agents.<sup>[89]</sup>

Statins are the most effective medicines for the treatment of hypercholesterolaemia in patients who have undergone transplantation,<sup>[90]</sup> and their immunomodulatory properties appear to provide general protection for the graft. However, ciclosporin (cyclosporine) inhibits both intestinal and hepatic CYP3A4 activity and can therefore lead to increased bioavailability of statins metabolized by this cytochrome.<sup>[91]</sup> The more lipophilic the statin and the greater the systemic exposure to unbound active statin compound, the greater the potential for myopathy.<sup>[73,92]</sup> Pravastatin and fluvastatin are less likely to interact with ciclosporin on a pharmacokinetic basis. However, ciclosporin has been reported to increase serum levels of pravastatin.<sup>[93]</sup> Competition at the level of biliary clearance resulting in reduced pravastatin removal through the bile duct and prevention of the P-glycoprotein transfer are considered the main pathomechanisms, indicating that CYP3A4 is not the only site involved in clinically relevant ciclosporin-statin interactions.

The combination of statins with warfarin is likely to increase the serum levels of warfarin, thereby potentiating its anticoagulant effect.<sup>[94]</sup> Regular anticoagulation control and possibly warfarin dose adjustment may thus be required. However, the potentiating effect of warfarin on statin levels has not been studied sufficiently.<sup>[95]</sup> A hypothesis has been articulated that as warfarin constitutes the substrate of CYP2C9, and partly of CYP3A4, it could compete with statins in their enzymatic conversion.

#### Pharmacokinetic Interactions with CYP2C9 Inhibitors and Competing Substrates

Azole antifungal agents are recognized inhibitors of CYP2C9, as well as the previously mentioned CYP3A4. This necessitates a higher index of suspicion when they are administered in patients receiving fluvastatin. For example, fluconazole has been reported to increase fluvastatin bioavailability,<sup>[96]</sup> although no cases of rhabdomyolysis attributable to such a combination are known. Furthermore, histamine H<sub>2</sub> receptor antagonists cimetidine and ranitidine, and the proton pump inhibitor omeprazole, which are

also substrates of CYP2C9, enhance fluvastatin's systemic exposure, but without particular clinical significance. Of note, omeprazole also appears to possess a CYP3A4 induction capacity, potentially increasing the biotransformation and thus decreasing levels of statins that are substrates of the CYP3A4 isoenzyme.<sup>[37]</sup>

### **5.3.2 Interactions with Other Hypolipidaemic Agents**

#### **Fibrates**

In many cases of mixed dyslipidaemia, in diabetic patients or in patients with high triglycerides despite the achievement of the desirable LDL-C goal, the coadministration of statins with fibrates is an attractive therapeutic option. According to data from epidemiological studies and clinical trials, the combination of any statin with fibrates increases the risk of myopathy, which is usually observed within the first 12 weeks by the initiation of treatment. The incidence of myotoxicity with this combination is 0.12%.<sup>[97]</sup> Even if most reports involve gemfibrozil,<sup>[98,99]</sup> other fibrates (bezafibrate, clofibrate, fenofibrate) have also been implicated in cases of rhabdomyolysis when used alone and have an additive myotoxic potential when combined with statins.<sup>[99]</sup> The presence of gemfibrozil in most cases of rhabdomyolysis is partly explained by its wider clinical use than other fibrates; however, the differential safety profile of fibrates seems to remain even after correction for the wider prescription of gemfibrozil.<sup>[100]</sup>

Since fibrates do not interfere with CYP-mediated statin elimination, the additive adverse effect when combined with statins appears to have a predominantly pharmacodynamic basis (synergy). The incidence of hospitalized patients with rhabdomyolysis prescribed fibrate monotherapy has been reported to be more than 5 times higher than with atorvastatin, pravastatin or simvastatin monotherapy.<sup>[101]</sup> Pharmacokinetic parameters are also believed to account to some degree for the observed interactions. Statin glucuronidation is an intermediate step in the conversion of active acid forms to lactones, which in turn are metabolized by the hepatic P450 system.<sup>[102]</sup> The inhibition of statin hydroxy acid

glucoronidation mediated by gemfibrozil<sup>[103]</sup> but not fenofibrate and subsequent increased bioavailability of statins is believed to partly account for the increased myopathic risk associated with the combination of statins with fibrates. Furthermore, statin-fibrate interactions may in part be mediated through the activation of the peroxisome proliferator-activated family of nuclear receptors,<sup>[104]</sup> which have been shown to affect CYP regulation. Moreover, gemfibrozil has been reported to reduce the renal clearance of pravastatin by competitively acting at the transport proteins<sup>[105]</sup> and it increases pravastatin and rosuvastatin concentrations by impeding their biliary excretion.<sup>[37]</sup>

#### **Niacin**

The addition of niacin in a statin-receiving patient can yield complementary benefits in achieving a comprehensive lipid control. The concomitant administration of statins with high doses of niacin has been associated with rhabdomyolysis in a limited number of anecdotal reported cases<sup>[106]</sup> through a mechanism that remains unknown but appears to be unrelated to statin serum levels. Niacin is not implicated as a strong precipitating factor for statin-induced myopathy, and the combination of statin and niacin is considered to carry a lower risk than statin-fibrate coadministration.<sup>[21]</sup> Based on current evidence, no excessive risk of myopathy as a result of a statin-niacin combination, compared with that expected by adding one agent to the other, can be supported.<sup>[107]</sup>

#### **Ezetimibe**

Combined inhibition of intestinal cholesterol absorption mediated by ezetimibe and hepatic cholesterol synthesis via statins has emerged as a challenging therapeutic option. Anecdotal reports of myopathy attributed to the combination of statin plus ezetimibe<sup>[108,109]</sup> have not been confirmed in the setting of randomized controlled trials. An enhanced lipid-lowering effect and comparable safety profile was shown when ezetimibe was added to statins in patients with hypercholesterolaemia.<sup>[110]</sup> The incidence of muscle-related events was not higher in patients taking simvastatin alone than the combination of simvastatin plus

ezetimibe according to pooled data from 17 relative randomized clinical trials.<sup>[111]</sup> In recent studies, the addition of ezetimibe 10 mg resulted in greater lipid-lowering efficacy than, and equal safety and tolerability to, up titration of atorvastatin 20–40 mg in patients at moderately high risk<sup>[112]</sup> and to the doubling of atorvastatin 40–80 mg in patients at high risk for coronary heart disease.<sup>[113]</sup> Overall, current evidence cannot support enhanced risk for statin-related myopathy by the coadministration of ezetimibe.<sup>[21]</sup>

## 6. Recommendations for the Prevention and Management of Statin-Induced Myopathy

### 6.1 Prevention of Statin-Induced Myopathy

Prevention and early recognition are the best approaches to managing statin-related myopathy and averting serious sequelae. Statin treatment should begin with low doses that can be progressively increased; if necessary, the anticipated clinical benefit should be weighed against the increased myopathic risk. Coadministration of interacting medications should be avoided whenever possible. When a high-risk combination is necessary, small doses of the presumably safest statin for any given combination should be prescribed.

Patients should be counselled on the risk and warning signs of myopathy, and on the possibility of drug interactions. Any unexplained muscle symptoms should be reported immediately to the attending physician. Patients at high risk should be followed up clinically, especially during the first months of treatment. When acute clinical conditions that can precipitate rhabdomyolysis coexist, it is advisable to interrupt statins temporarily.

Routine measurement of pretreatment CK levels is not recommended because of the rarity of myopathy when statins are prescribed at usual doses in the general population. However, CK should be measured in patients at high risk for myopathy, at baseline and regularly during the course of statin therapy.<sup>[21]</sup>

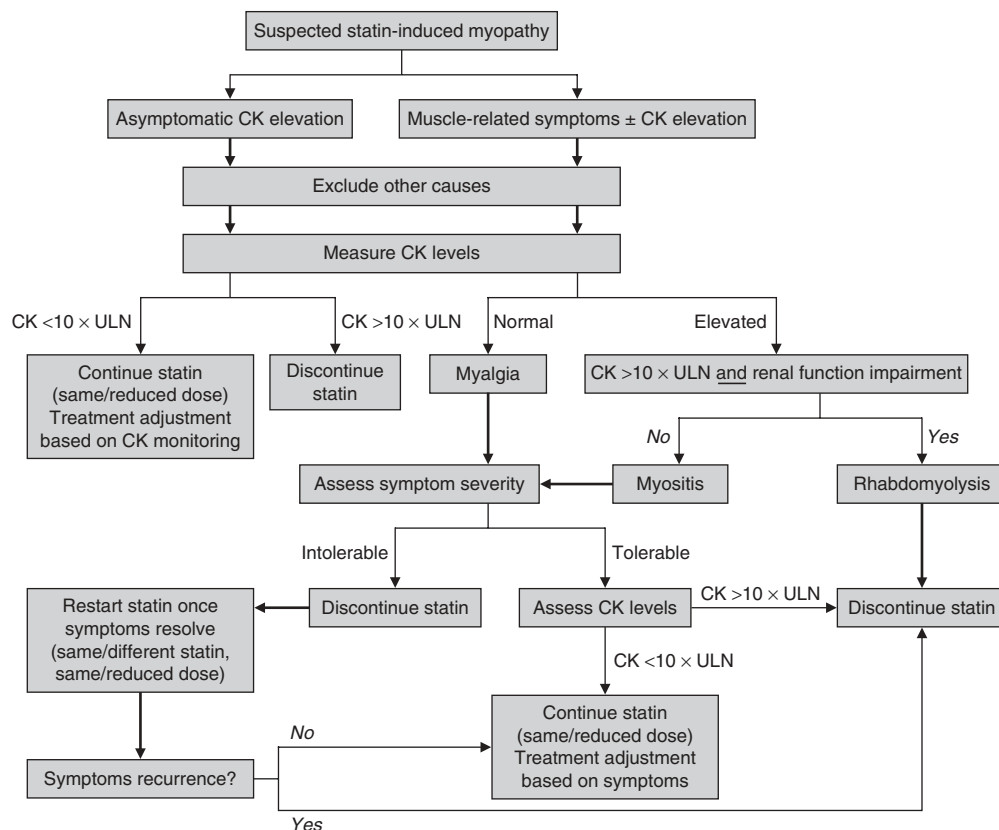
If a statin-fibrate combination is required, fenofibrate is the preferred option over gemfibrozil.<sup>[80,100,114]</sup> The statin doses should remain below the maximal levels. Fluvastatin may be appropriate for combination with gemfibrozil.<sup>[115]</sup> Particular attention is required for patients with increased CK levels, and renal and hepatic dysfunction.

On the basis of current evidence, routine CoQ10 supplementation cannot be recommended to prevent statin-related myopathic events.<sup>[21]</sup> CoQ10 supplementation might be considered in the setting of CoQ10-depleting conditions, such as advanced age or multisystem diseases.<sup>[30]</sup>

### 6.2 Management of Statin-Induced Myopathy

Statin-induced myopathy is usually mild and reversible upon statin discontinuation; however, in very rare cases it may evolve towards severe muscle damage, even rhabdomyolysis. If statin-related myopathy is suspected, more common causes of symptoms and/or CK elevation should be ruled out by thorough history taking, physical examination and laboratory tests. Other etiologies of muscle symptoms include unusual physical activity, trauma, falls, accidents, seizures, alcohol, drugs (corticosteroids, antipsychotics, cocaine, amfetamines), occult hypothyroidism, infections and autoimmune disorders (polymyositis, dermatomyositis, rheumatic polymyalgia).<sup>[116]</sup> Initial tests include CK levels, serum thyroid-stimulating hormone levels, and renal function with urinalysis if rhabdomyolysis is suspected. In rare cases of persistent symptomatology despite statin discontinuation, further investigations including electromyography and muscle biopsy may be required, in consultation with experts in muscle diseases.<sup>[116]</sup>

The intensity of clinical symptoms along with the magnitude of CK elevation should guide clinical management, as summarized in figure 2. In the case of CK levels  $<10\times$  the upper limit of normal, without or with tolerable muscle symptoms, the statin may be continued at the same or a smaller dose.<sup>[116]</sup> In the presence of tolerable symptoms with CK serum elevation  $>10\times$  the



**Fig. 2.** Assessment and management of statin-induced myopathy. **CK**=creatinine kinase; **ULN** = upper limit of normal.

upper limit of normal, or if frank rhabdomyolysis develops, statins should be discontinued. Rhabdomyolysis prompts in-hospital supportive treatment consisting of intravenous hydration and monitoring for potential complications.<sup>[117]</sup> Intolerable muscle symptoms, regardless of CK levels, require temporary statin interruption. Once symptoms resolve, the same or lower dose of the same or a different statin can be restarted. Alternative statin regimens with an ostensibly lower myopathic potential may include fluvastatin extended release,<sup>[118]</sup> low-dose rosuvastatin,<sup>[119]</sup> and non-daily regimens with atorvastatin<sup>[120-122]</sup> or rosuvastatin.<sup>[123-126]</sup> If symptoms reoccur, statin suspension should be permanent. Non-statin lipid-lowering agents that have shown efficacy and safety in patients intolerant to statins

include ezetimibe,<sup>[118,127]</sup> alone or in combination with bile acid-binding resin.<sup>[128]</sup>

## 7. Conclusions

Statins represent the most effective class of medications for reduction of LDL-C and therefore for the prevention of cardiovascular atherosclerotic disease. Although myopathy is their most common adverse effect, severe muscle-related complications are very rare and should not deter physicians from prescribing these generally safe and well tolerated agents. Several factors that may predispose to, or trigger, myopathic events in statin-receiving patients have been well characterized. Individual risk stratification, taking into consideration patient characteristics,

coadministered medications and statin pharmacological properties, should determine clinical decision making. Considering the dose-dependent nature of statin-related myopathy, physicians should start cautiously with lower doses in the presence of predisposing conditions and weigh the benefit of lipid lowering versus the potential of excess risk when uptitrating doses. Combination therapy with other classes of hypolipidaemic agents may be opted for when aggressive lipid-lowering therapy is required. Since most patients eligible for statins receive multiple concomitant medications, often sharing the metabolic pathway of the CYP system, recognition of potential drug interactions is critical. Knowledge of the pharmacokinetic properties of currently available statins may allow the identification of the statin at the presumably lowest risk for drug interactions. In the clinical setting, counselling patients on the risk and warning signs of myopathy will increase awareness and allow prompt recognition and appropriate management of myopathic events. In order to accurately estimate the true incidence of statin-induced myopathy and enhance our understanding of potential risk factors, a more complete and formal reporting of the entire spectrum of muscle-related events attributable to statins is required.

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