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Review

Managing the underestimated risk of statin-associated myopathy

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ABSTRACT

In clinical practice 5–10% of patients receiving statins develop myopathy, a side effect that had been systematically underestimated in the randomized controlled trials with statins. The most common manifestation of myopathy is muscle pain (usually symmetrical, involving proximal muscles) without creatinine kinase (CK) elevation or less frequently with mild CK elevation. Clinically significant rhabdomyolysis (muscle symptoms with CK elevation >10 times the upper limit of normal and with creatinine elevation) is extremely rare. Myopathy complicates the use of all statins (class effect) and is dose-dependent. The pathophysiologic mechanism of statin-associated myopathy is unknown and probably multifactorial. The risk of statin-associated myopathy can be minimized by identifying vulnerable patients (i.e. patients with impaired renal or liver function, advanced age, hypothyroidism, etc.) and/or by eliminating-avoiding statin interactions with specific drugs (cytochrome P-450 3A4 inhibitors, gemfibrozil, etc.). In symptomatic patients, the severity of symptoms, the magnitude of CK elevation and the risk/benefit ratio of statin continuation should be considered before statin treatment is discontinued. Potential strategies are the use of the same statin at a lower dose and if symptoms recur the initiation of fluvastatin XL 80 mg daily or rosuvastatin intermittently in low dose (5–10 mg), combined usually with ezetimibe 10 mg daily. Failure of these approaches necessitates the use of non-statin lipid lowering drugs (ezetimibe, colesevelam). In order to provide evidence based recommendations for the appropriate management of statin-intolerant patients we need randomized clinical trials directly comparing the myopathic potential of different lipid-lowering medications at comparable doses.

1. Introduction

The discovery of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins is one of the most effective pharmaceutical interventions for the confrontation of coronary heart disease (CHD). Benefits from statins have been proved to be great, both in primary as well as in secondary prevention of CHD, irrespective of patients' age or sex. A meta-analysis of 14 randomized trials using statins in 90,056 individuals with or without CHD demonstrated that a mean reduction of low density lipoprotein cholesterol (LDL-C) of 1 mmol/L (39 mg/dL) was accompanied by 12% proportional reduction in all-cause mortality, 19% reduction in CHD deaths and 17% reduction in strokes [1]. Despite the substantial improvement in the proportion of treated patients receiving lipid-lowering medication there is a great therapeutic gap since only half of them are reaching the LDL-C target [2–4]. The therapeutic gap is even more pronounced among very high risk coronary patients where <20% are at the guideline—recommended optional target of LDL-C <1.8 mmol/L (70 mg/dL) [2,5,6]. This failure to achieve the more stringent LDL-C goal is mainly due to the inadequate titration of statin dose till the maximal effect is obtained. One of the reasons of not using statins at high doses is the physician's fear of drug side effects, such as myopathy. The inappropriate assessment of statin-related muscle symptoms usually results in unjustified termination of the drug or its use in low doses, depriving patients of proven clinical benefits. Therefore, there is an urgent need to define the appropriate management of patients who develop myopathy while receiving statins in order to minimize the number of patients who will stay off statins.

2. Defining myopathy: a source of confusion and a cause of underestimation in randomized statin trials

Traditionally, the terminology used to describe muscle toxicity has been imprecise, contributing to the confusion that surrounds the exact incidence of this side effect. The majority of randomized controlled trials with statins defined myopathy as an increase in creatine kinase (CK) >10 times the upper limit of normal (ULN) with [7] or without muscle symptoms [8,9]. In some of them myopathy was defined as a persistent increase in CK >10×ULN on 2 consecutive measurements [10]. Therefore, the reported incidence of myopathy in the Heart Protection Study (HPS) was 0.11% [7], in the West of Scotland Coronary Prevention Study (WOSCOPS) 0.12% [8] and in the Scandinavian Simvastatin Survival Study (4S) 0.27% [9], whereas in the Treating to New Targets (TNT) trial [10] none of the participants fulfilled the criteria for myopathy. Interestingly, this very low incidence of myopathy did not

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Table 1
Manifestations of myopathy according to ACC/AHA/NHLBI clinical advisory on the use and safety of statins [14].

1. Myopathy: a general term referring to any muscle disease
2. Myalgia: muscle pain or weakness with normal CK levels
3. Myositis: "myalgia" with increased CK levels
4. Rhabdomyolysis[a]: muscle symptoms with marked CK elevation (typically >10×ULN) and with creatinine elevation

FDA = Food and Drug Administration, CK = creatine kinase, ULN = upper limit of normal.
[a] According to FDA rhabdomyolysis is defined as muscle symptoms with marked CK elevation (>50×ULN or >10,000 IU/L) with renal compromise.

usually differ from that reported in the placebo group. This lack of association of statins with myopathy was confirmed in a meta-analysis by Kashani et al., which included 35 randomized statin trials and demonstrated that statin monotherapy (after exclusion of cerivastatin trials) was not associated with significant absolute increases in the risk of CK elevations, myalgias or rhabdomyolyses [11]. However, the low incidence of myopathy in randomized trials contrasts with the higher incidence of myopathy seen in observational trials, ranging between 5 and 10% [12,13]. This systematic underestimation of statin-related myopathy in randomized controlled trials may be attributed to the following reasons:

1) Exclusion of patients with risk factors for myopathy, such as patients with a history of muscle symptoms, CK elevations, renal or liver disease, concurrent treatment with cyclosporine, fibrates etc.
2) Failure to systematically document myalgias. In the majority of these studies, patients were not interviewed for mild muscle symptoms which usually represent the commonest manifestation of myopathy
3) Application of strict criteria to define myopathy, such as CK elevations >10×ULN with or without muscle symptoms, which are rare and represent a minority of the spectrum of myopathy
4) The inclusion of a run-in phase in several trials with exclusion of patients experiencing muscle symptoms.

In 2002 the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute Clinical Advisory on the Use and Safety of Statins helped to standardize the terminology on muscle toxicity (Table 1), and despite certain limitations, the proposed set of definitions is currently the most widely used [14]. In 2006, the National Lipid Association's Muscle Safety Expert Panel suggested a slightly different terminology which classifies rhabdomyolysis according to the magnitude of CK increase [15]. However, this proposal has not been widely adopted.

3. Clinical manifestations of statin-associated myopathy

The clinical spectrum of statin-associated myopathy ranges from mild fatigue to fulminant rhabdomyolysis requiring hospitalization.

The rarest type of myopathy is rhabdomyolysis. The incidence of rhabdomyolysis, as this was defined in 2 cohort studies by physicians' diagnosis, hospital admission, muscle symptoms and a serum CK >10,000 U/L was 3.2 per 100.000 patient years [16,17]. The incidence is increased by 12-fold when statins are combined with gemfibrozil. Rhabdomyolysis may present with diffuse muscle pains, weakness, low back pain, proximal muscle pain and aching, or flu-like symptoms [18]. The average length of time on statin therapy before onset of rhabdomyolysis is approximately 1 year but it shortens to 1 month when a statin is combined with gemfibrozil.

The most common type of myopathy (>95%) is muscle pains without (most commonly) or with mild CK elevation [12]. Muscle pains are usually symmetrical and involve large proximal muscle groups. In clinical practice, the incidence of muscle symptoms ranges between 5 and 10% [12,13]. The Prediction of Muscular Risk in Observational conditions (PRIMO) survey [13], a French observational study of 7924 hyperlipidemic patients receiving high statin dose in a usual care, reported an incidence of muscle symptoms of 10.5% However, CK measurements were not performed in this study and therefore it is unknown whether muscle symptoms were associated with CK elevation.

The PRIMO study provided valuable information regarding the characteristics of muscular symptoms (Table 2). Muscle symptoms were usually reported as heaviness, stiffness or cramps, were generalized (60%) and intermittent (75%). One out of 4 patients experienced tendonitis. Muscle symptoms were usually associated with weakness or weakness could be the only presentation. The intensity of the pain was mild or mild to moderate, not interfering with the usual daily activities in 54% while it was moderate or severe in 42% of patients. In 40% of patients there were triggering factors, either excess physical exertion or initiation of a new medication. Muscle symptoms caused the discontinuation of statin treatment in 20% and the reduction in dosage in 17% of patients. The median time of onset of muscle symptoms was 1 month following initiation of statin therapy or titration to a higher dosage. However, in 15% of patients symptoms developed 6 months after treatment initiation. Cham et al. [19] analyzed the characteristics of 354 patients with statin-associated muscle-related adverse effects and reported that the median time of onset of muscle symptoms was 3 months.

4. Pathophysiology of statin-associated myopathy

The underlying mechanisms of statin-associated myopathy are not fully elucidated. Most theories are based on the reduction of important metabolites such as prenylated isoprenoids, ubiquinone or coenzyme Q10 (CoQ10), etc. due to the block of cholesterol synthesis by statins early in its metabolic pathway [20].

One proposed mechanism of myotoxicity is depletion of isoprenoids that control the rate of myofiber apoptosis [21]. Isoprenoids are linked to proteins by either farnesylation or geranylgeranylation. There is evidence that reduction in the farnesylation or geranylgeranylation of proteins increases cytosolic calcium, which in turn activates a cascade of events leading to the activation of caspase-3. The latter is a proteolytic enzyme with a pivotal role in cell death [22]. The apoptosis theory is supported by studies with vascular smooth muscle cells, which demonstrated that statin-induced apoptosis can be prevented with isoprenoids supplementation [23].

Another proposed mechanism of statin associated-myopathy is depletion of sarcolemmal cholesterol, resulting in destabilization of myocyte membrane [24]. However, myotoxicity does not occur in vitro when cholesterol is lowered by inhibiting squalene synthetase [25], a distal enzyme in the cholesterol synthesis cascade. In addition, inherited disorders of the distal cholesterol synthetic pathway result

Table 2
Characteristics of statin-associated muscle symptoms [13].

1. Localization: generalized (60%) or localized to a muscle group. Lower extremities more frequently (25%) affected than upper (8%)
2. Type: heaviness, stiffness, cramps
3. "Equivalent" of muscle pain:
   - weakness, sometimes the only presentation
   - tendonitis (25%)
4. Frequency and duration: usually (75%) intermittent lasting several minutes to several hours
5. Possible triggering factor: present in 40% (usually excess physical activity or initiation of a new drug)
6. Severity: mild–mild to moderate: 54%
   moderate: 38%
   intense: 4% (leading to severe disruption of daily activities)
7. Timing of onset: median time 1 month after initiation of statin

Table 3
Conditions that increase the risk of statin-associated myopathy [14,20,32].

Patient-related risk factors
1. Impaired renal or liver function
2. Hypothyroidism
3. Advanced age (especially >80 years)
4. Female sex
5. Low body mass index
6. Diabetes mellitus
7. Polypharmacy
8. Strenuous exercise
9. Heavy alcohol consumption (alcohol is a direct muscle toxin)
10. Drug abuse (cocaine, amphetamines, heroin)
11. Biliary tract obstruction
12. Inflammatory or inherited metabolic muscle defects (McArdle disease, carnitine palmityl transferase II deficiency)
13. Surgery with high metabolic demands
Risk factors predisposing to statin interactions
1. Co-administration of cytochrome P-450 3A4 inhibitors including:
Macrolide antibiotics: azithromycin, clarithromycin, erythromycin
Cyclosporine
Antifungals: fluconazole[a], itraconazole, ketoconazole[a]
Antivirals (protease inhibitors): amprenavir, indinavir, nelfinavir, ritonavir, saquinavir
Nefazodone (antidepressant)
Amiodarone
Calcium antagonists (diltiazem, verapamil) [weak inhibitors]
Warfarin[a]
Colchicine
Grapefruit juice (if >1 L/day)
2. Co-administration with glucuronidation inhibitors: gemfibrozil
3. Co-administration with nicotinic acid

[a] Also metabolized through cytochrome P-450 2C9.

in reduced cholesterol levels without clinical manifestations of myopathy [26].

The most popular theory for statin myopathy is CoQ10 deficiency. CoQ10 participates in electron transport during oxidative phosphorylation in mitochondria and its depletion results in mitochondrial dysfunction. Serum CoQ10 levels decrease during statin treatment but its myocyte levels are not consistently decreased [27,28]. In addition, CoQ10 supplementation studies failed to prove an etiologic role of CoQ10 deficiency in statin-associated myopathy [29].

Recently, the hypothesis of vitamin E deficiency, secondary to statin treatment, has been proposed as a risk factor in the development of statin-associated myopathy [30].

Finally, individual differences in pain perception due to specific serotonergic gene variants can affect the frequency and severity of statin-associated myopathy [31].

5. Risk factors for statin-associated myopathy

The risk of statin-associated myopathy can be minimized by identifying the vulnerable patients and/or the predisposing conditions to this side effect. Table 3 presents the risk factors associated with the development of statin-induced myotoxicity.

5.1. Patient-related risk factors

Advanced age, small body frame, female gender, hypothyroidism, renal or hepatic disease are associated with a higher risk for statin-induced myopathy due to the increase in statin serum levels [31].

In particular, elderly (especially >80 years), who usually have comorbitities and/or take multiple medications, are at relatively high risk to develop statin-associated myopathy. The fact that most of them have already a decline in muscle strength due to aging, a small compromise in muscle function can cause a much greater functional impairment than in younger subjects [33]. Therefore, in elderly it is prudent to initiate statin at low dose and carefully up-titrate it at moderate doses, if necessary.

The PRIMO survey [13] demonstrated that major risk factors for the development of muscle symptoms during high dose statin treatment were: a history of muscle pain with another lipid-modifying therapy (10-fold higher risk), a history of unexplained cramps (4-fold higher risk) or elevated CK (2-fold higher risk) and a family history of muscle symptoms with or without lipid lowering medication (2-fold higher risk). The latter indicates that a genetic predisposition may determine whether a patient will develop muscle pain and deserves further investigation.

Genetic polymorphism of SLCO1B1 that encodes the organic anion-transporting polypeptide 1B1, which in turn regulates the hepatic uptake of statins, has been found to be associated with statin intolerance [34]. In particular, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH Collaborative Group) [35] reported that the rs4363657 single-nucleotide polymorphism of SLCO1B1 was associated with a 4.5-fold and 17-fold higher risk of myopathy in heterozygotes and homozygotes respectively, when treated with 80 mg simvastatin daily. The Statin Response Examined by Genetic Haplotype Markers (STRENGTH) study [36], reported that carriers of the SLCO1B1*5 allele, were at higher risk of mild statin-induced myopathy, usually associated with normal CK levels, and showed that there was a gene dosage effect with homozygotes having higher risk than heterozygotes.

Although variation in cytochrome P450 (CYP450) isoenzymes activity, where most statins are metabolized, could also affect statin-induced side effects, Zuccaro et al. [37] failed to link CYP450 polymorphisms with tolerability to statins.

Strenuous exercise is associated more frequently with muscular statin related side-effects. In our clinical practice, we recommend a brief discontinuation of statins prior strenuous physical activity i.e. marathon running. Sinzinger et al. [38] who monitored 22 professional athletes with familial hypercholesterolemia on different statins (cerivastatin was not included) reported that 6 athletes (27%) could tolerate statin treatment and only 3 of them continued training performance without any limitation. There were two types of muscle manifestations, usually without CK elevation: muscular ache-like pains during or immediately after exercise or cramp-like symptoms hours or days after physical exercise [39]. These limited data have raised a concern on the use of statins in elite sport performers, however, this issue needs to be further addressed by placebo-controlled trials.

Surgery with high metabolic demands is a risk factor for myopathy [14]. However, several non-randomized studies have shown that perioperative statin therapy in vascular procedures, is associated with lower perioperative morbidity and mortality while discontinuation of pre-existing statin therapy leads to a higher rate of complications in the perioperative period [40,41]. Therefore, statins should be continued through the perioperative period for all vascular procedures, such as cardiac surgery, carotid endarterectomy, abdominal aortic aneurysm repair and lower extremity revascularization. The beneficial effect of statins is due to the combination of their lipid-lowering effect and pleiotropic properties [42]. There are scarce data regarding the safety of statins in non-vascular surgery and discontinuation of statins in the perioperative period in non-vascular prolonged operations might be considered.

5.2. Risk factors related with statin interactions

Statin pharmacologic properties that are associated with a higher risk of statin-induced myopathy include high bioavailability and systemic exposure, lipophilicity, limited protein binding, presence of circulating metabolites and drug interactions via CYP450 isoenzymes (especially CYP3A4, the major CYP450 isoenzyme) or glucuronidation pathways. Table 4 shows the pharmacologic characteristics of statins.

More than half of statin-associated rhabdomyolysis cases involve interactions with agents that affect statin metabolism. Co-administration of a statin with an agent metabolized by the same CYP3A4 isoenzyme

Table 4
Pharmacologic characteristics of statins [20,31,43].

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin XL	Atorvastatin	Rosuvastatin
Primary metabolic pathway	CYP3A4	Sulfation	CYP3A4	CYP2C9	CYP3A4	Minimal (<10%) by CYP2C9
Bioavailability (%)	5	18	5	6	12	20
Absorption (%)	30	34	60–80	95	30	50
Lipophilicity	Yes	No	Yes	Yes	Yes	No
Half-time (h)	2.9	1.3–2.8	2–3	4.7	15–30	20.8
Protein binding (%)	>95	43–55	94–98	>98	80–90	88
Urinary excretion (%)	10	20	13	5	2	10
Fecal excretion (%)	83	70	58	95	98	90

(cyclosporine, macrolide antibiotics, antivirals etc.) can increase statin levels and the risk for myopathy (Table 3). Grapefruit juice consumption >1 L/day increases significantly statin levels by irreversible inhibition of the intestinal CYP3A4 and is associated with a higher risk of statin-related myopathy [44]. Lovastatin, simvastatin and atorvastatin are metabolized by CYP3A4, rosuvastatin minimally by CYP2C9, fluvastatin mainly by CYP2C9 while pravastatin undergoes sulfation. Despite the theoretical advantage of the co-administration of a non-CYP3A4 isoenzyme metabolized statin with CYP3A4 inhibitors, there still remains a low risk of myopathy, possibly due to other metabolic or transporter mechanisms [45].

Pravastatin and rosuvastatin are the most hydrophilic agents and are thought to be less likely to penetrate the myocyte membrane compared to more lipophilic statins. However, the incidence of rhabdomyolysis associated with pravastatin and rosuvastatin does not differ from that of more lipophilic statins [20]. Fluvastatin and atorvastatin are minimally excreted in the urine and may have a safety advantage in patients with chronic kidney disease. Patients with biliary-tract obstruction also have increased risk of myopathy, as bile is the primary route of excretion of statins.

Moreover, gemfibrozil is the concomitant medication most commonly associated with rhabdomyolysis. This is due to the inhibition of glucoronidation of statins, a catabolic pathway of statins, leading to high and potential toxic statin levels. In contrast, fenofibrate is safer when used in combination with statins since it does not affect glucoronidation and therefore has a minimal effect on their metabolism [46].

6. Is there any difference between statins in the risk of myopathy?

Statin-associated myopathy is class effect, dose-dependent and appears independent of LDL-C reduction [20]. There is no conclusive evidence whether there is any difference between different statins in the risk of inducing myopathy. This is mainly due to the lack of well-designed randomized comparative studies of different statins reporting myopathy. In addition, the majority of the randomized statin trials have reported only the incidence of myositis and rhabdomyolysis which are uncommon manifestations of myopathy.

Comparing the maximum approved doses of all statins, 80 mg of simvastatin appears to have the highest rate of myotoxicity [47] while fluvastatin XL 80 mg the lowest. In the PRIMO survey [13] 18.2% of patients on high dose of simvastatin (40 or 80 mg) developed muscle symptoms compared with only 5.1% of those on fluvastatin XL 80 mg, while the incidence with atorvastatin (40 or 80 mg) and pravastatin (40 mg) was intermediate (14.9% and 10.9%, respectively). Recently, the U.S. Food and Drug Administration (FDA) warned about the increased risk of muscle damage from the 80 mg dose of simvastatin and stated that physicians should not be started this high dose in new patients, including patients already taking lower doses of simvastatin [48]. Use of the 80 mg dose of simvastatin should be restricted to patients who have been taking it for ≥12 months without evidence of myopathy. In addition, FDA warned against the co-administration of simvastatin with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. Furthermore, the 10 mg dose of simvastatin should not be exceeded in patients taking amiodarone, verapamil, and diltiazem and the 20 mg in patients on amlodipine and ranolazine. These warnings were mainly based on FDA's review of the SEARCH trial where 0.9% of patients on 80 mg of simvastatin developed myopathy versus 0.02% in the 20 mg group [49].

According to the U.S. cases reported to the FDA before June 2001, the highest rate of fatal rhabdomyolysis was noted with cerivastatin (3.16 per million prescriptions) leading to withdrawal of this statin from the market, while there were no fatal cases with fluvastatin. The rates for other statins were lovastatin 0.19, simvastatin 0.12, atorvastatin 0.04 and pravastatin 0.04 [50]. A meta-analysis of 19 randomized statin trials comparing standard doses of all statins except rosuvastatin, reported that fluvastatin was associated with the lowest rate of myopathy compared to other statins [51].

Therefore, despite the lack of randomized trials directly comparing the myopathic potential of each statin in comparable doses, it appears that simvastatin 80 mg has the highest and fluvastatin XL 80 mg the lowest rate of myopathy. Lovastatin, pravastatin, atorvastatin and rosuvastatin seem to have similar rates of myopathy ranging between those of simvastatin 80 mg and fluvastatin XL 80 mg.

7. Screening and monitoring

7.1. Asymptomatic CK elevation

Pre-treatment screening of CK levels is controversial [14,15] and has not been proven to be cost-effective. However, in our clinical practice we measure baseline CK in all patients since asymptomatic CK elevations are common in the general population (10–20%), especially in certain ethnic groups such as African-Americans, and pre-treatment knowledge may help us to better evaluate future CK elevations. High asymptomatic pre-treatment levels of CK should not discourage the initiation of statin treatment, provided that CK levels are <5×ULN [52].

It should be noted that a common cause of high CK levels (predominantly the MM isoenzyme) is moderate or strenuous exercise due to changes in sarcolemma permeability of skeletal muscles and CK leakage. Post-exercise CK elevations are higher in untrained compared to trained individuals and the highest elevations are seen after marathon running and eccentric exercise such as downhill running. CK elevation usually remains for 1–2 days after exercise with the exception of eccentric exercise where CK elevation persists for several days [53].

Baseline thyroid-stimulating hormone (TSH) is also one of our baseline measurements since subclinical hypothyroidism is known to be a promoting factor of myopathy [54]. Glueck et al. [52] reported that 3% of hyperlipidemic patients referred with asymptomatic high CK had high TSH levels.

Although routine follow-up measurements of CK levels during statin treatment are not recommended, the clinical scenario of an

anxious patient referred to the Lipid Clinic due to asymptomatic CK elevation is not uncommon. In that case, first priority is to exclude other causes of CK elevation such as moderate or intense exercise particularly from untrained subjects, alcohol abuse and latent hypothyroidism. Very rare causes of CK elevations, usually symptomatic, are various myopathies such as polymyositis, dermatomyositis, metabolic myopathy, Duchene and Becker dystrophy, mitochondrial myopathy, etc. Once other causes of asymptomatic CK elevation are excluded, our approach depends on CK levels:

a) If CK >10×ULN, statin treatment should be discontinued
b) If CK <5×ULN, patient should be reassured, continue statin treatment and asked to report symptoms. Although most experts [31,32] do not recommend a repeat CK measurement in asymptomatic patients, in our practice we usually request it in 4–6 weeks, particularly if initial CK >2×ULN.
c) If CK >5×ULN but <10×ULN, statin should be continued with periodic CK checks. The development of symptoms is monitored, and CK measurement is repeated in 2 weeks and then the frequency of repeat measurements depends on the magnitude of CK elevation.

7.2. Muscle symptoms

When patients on statin treatment develop muscle symptoms:

1) exacerbating conditions such as intense exercise, co-administration of CYP3A4 inhibitors, use of alcohol or cocaine (Table 3), should be brought in mind and evaluated accordingly
2) the severity of muscle symptoms should be evaluated. If
   a) symptoms are intolerable, statins should be discontinued and blood should be obtained urgently to determine
      - CK levels to assess the extent of muscle damage
      - creatinine levels to exclude renal involvement
      - TSH levels to exclude hypothyroidism.

      In case of clinically significant rhabdomyolysis patients should be admitted for intravenous hydration and urine alkalinization to prevent precipitation of myoglobin in the renal tubules [20]. After the discontinuation of statins muscle pain usually subsides within 2–3 weeks [38] although sometimes it can take up to 2 months [31].
   b) symptoms are tolerable, statins should be continued (usually at lower doses) if this is justified by the risk/benefit ratio. CK, creatinine and TSH levels should again be obtained. It should be mentioned that CK levels are usually normal but normal CK levels do not rule out structural muscle damage [55]. Mohaupt et al. [56] reported that 25 of 44 (57%) patients with statin-associated muscle symptoms had evidence of structural damage in biopsy samples despite the fact that the majority had normal CK levels and only 4 (9%) had an elevation of CK >5×ULN. When symptoms are associated with CK elevation >10×ULN statins should be stopped.

The Muscle Expert Panel does not recommend muscle biopsy to determine muscle damage in patients with statin-associated myopathy except in patients with persistent symptoms or CK elevations after statin withdrawal [15]. The indication is stronger when neurological symptoms coexist.

8. Lipid lowering strategy in patients intolerant to statin (Fig. 1)

There are only few studies, most of them small and of short duration, evaluating the lipid lowering treatment strategy of statin-intolerant patients. Therefore, the management of these patients cannot be based on evidence-based recommendations but it is mainly based on the experience of experts in this field.

After discontinuation of statin due to intolerable muscle symptoms and/or CK elevation >10×ULN the patient should remain off statin until resolution of symptoms or normalization of CK. When symptoms have been completely resolved and/or CK levels have been normalized, treatment can be restarted with either the same statin at a lower dose (rechallenge) to test reproducibility of symptoms or with a different statin [57].

In our practice we usually restart the same statin at lower dose. If patients can tolerate this treatment we reassess them in 2 months and if they are not at the LDL-C goal which is the most likely scenario for coronary or diabetic patients, we either add ezetimibe 10 mg daily or increase the dose of statin. Combination with ezetimibe provides an additional 15–20% reduction in LDL-C and does not seem to exacerbate statin myopathy in randomized clinical studies [58]. However, the myopathic potential of ezetimibe may have been underestimated in these trials [59]. In a small retrospective study of 12 patients who could not tolerate high statin dose, the addition of ezetimibe to their original low statin dose was not tolerated by 2 (17%) patients who had to discontinue ezetimibe [60]. Although ezetimibe metabolism is independent of CYP450 oxidation, it undergoes glucuronidation, a common metabolic pathway of statins, and this could potentially lead to a pharmacokinetic interaction with statins [59].

If the reinstitution of the offending statin leads to recurrence of symptoms the alternative strategies include the following:

1) Fluvastatin: the extended release fluvastatin 80 mg (fluvastatin XL) is the most widely used formulation of fluvastatin achieving a mean LDL-C reduction of 35% [61]. Fluvastatin has several pharmacokinetic characteristics (high protein binding, not a CYP3A4 nor a glucuronidation substrate), which limits its systemic exposure. Jacobson et al. [57] proposes fluvastatin XL 80 mg daily as the first statin to be used in a patient with statin-associated myopathy. Indeed, Stein et al. [62] tested fluvastatin XL 80 mg for 12 weeks in a randomized controlled study of 199 dyslipidemic patients with a history of muscle-related side effects to other statins and found that the majority of patients (83%) could tolerate it. If the LDL-C target is not achieved, fluvastatin XL 80 mg can be combined with ezetimibe achieving a total LDL-C reduction of 45–50%.
2) Rosuvastatin: rosuvastatin has been used in a low dose regimen (5–10 mg) and various modes of administration: daily, alternate-day or weekly. The intermittent mode of administration is effective due to the long half-time of rosuvastatin. Glueck et al. [63] used low dose (5–10 mg daily) rosuvastatin in 61 patients intolerant to other statins for 12 weeks and found that almost all patients (only one discontinued treatment due to myalgias) tolerated this treatment. In 51 statin-intolerant patients, 37 (72.5%) could tolerate every other day low rosuvastatin dose (average 5.6 mg) achieving a 35% lowering of LDL-C [64]. In 40 statin-intolerant patients in whom rosuvastatin was given twice weekly at a dose of 5 or 10 mg for 8 weeks, 32 (80%) of them could tolerate rosuvastatin with a 26% lowering of LDL-C [65]. Backes et al. [66] examined the response to once-weekly rosuvastatin therapy (5–20 mg) for an average of 4 months in 8 patients intolerant to statin (6 of them had myalgias) and reported a mean LDL-C reduction of 29% and discontinuation of treatment due to reproduction of symptoms in 2 (25%) patients. In another study, rosuvastatin once a week in a dose ranging from 2.5 mg to 20 mg was tolerated by 37 (74%) of the 50 patients previously intolerant of statins and produced a 23% reduction in LDL-C [67]. Finally, non-daily regimens with 10 mg of atorvastatin have been suggested but there are fewer data compared to rosuvastatin [31,68].
3) Red yeast rice: an over-the-counter Chinese herb which has among its ingredients lovastatin. In a dose of 1200–2400 mg (contains approximately 2–4 mg of lovastatin, respectively) twice daily lowers LDL-C by 20–25% [69]. There are data suggesting that

red yeast rice might have a role in statin intolerant patients. Becker et al. [70] randomized 62 statin-intolerant patients to 1800 mg twice daily of red yeast rice or placebo and reported a 22% differential decrease in LDL-C at 12 weeks and 12% at 24 weeks. Interestingly, only 2 of the 31 (6.5%) patients on red yeast rice could not tolerate it due to myalgias. In another study, 20 (95%) of 21 statin-intolerant patients were able to tolerate without muscle problems 2400 mg of red yeast rice twice daily with a 30% lowering of LDL-C after 12 weeks of treatment [71]. A recent retrospective study [72] reported that most (92%) of 25 intolerant to statin patients, of whom 68% had previously experienced myalgias, tolerated red yeast rice at a dose of 1200 mg at bedtime achieving a 21% reduction in LDL-C. Despite these encouraging data there are several concerns, such as the commercial products of red yeast rice have variable amounts of lovastatin, some products may contain toxic components (citrinin), a few cases of myopathy have been reported [73] and most importantly there are no long-term safety data. These concerns led FDA in 2007 to warn consumers against buying red yeast supplements. Until we have safety and effectiveness data from large randomized long-term trials, the use of red yeast rice cannot be recommended as an alternative to statins. However, few experts [31,43] suggest that it can be reserved for some statin-intolerant patients who are unwilling to try a lipid-lowering drug and prefer a natural product. In these cases the patients should be warned about the risks and should be under close monitoring.

4) Ezetimibe: if muscle symptoms reappear with multiple statin trials ezetimibe should be considered. We proceed to ezetimibe when both therapeutic approaches with fluvastatin XL 80 mg daily and intermittent low dose of rosuvastatin fail. As monotherapy ezetimibe decreases LDL-C by 15–20% and does not seem to induce myopathy in randomized clinical trials [59]. However, a few instances of myopathy have been reported [74], the majority of which occurred in patients previously intolerant to statins. The explanation is unclear but a genetic predisposition might play an important role in the development of myopathy in different lipid-lowering medications. There are limited data regarding the administration of ezetimibe in previously statin-induced

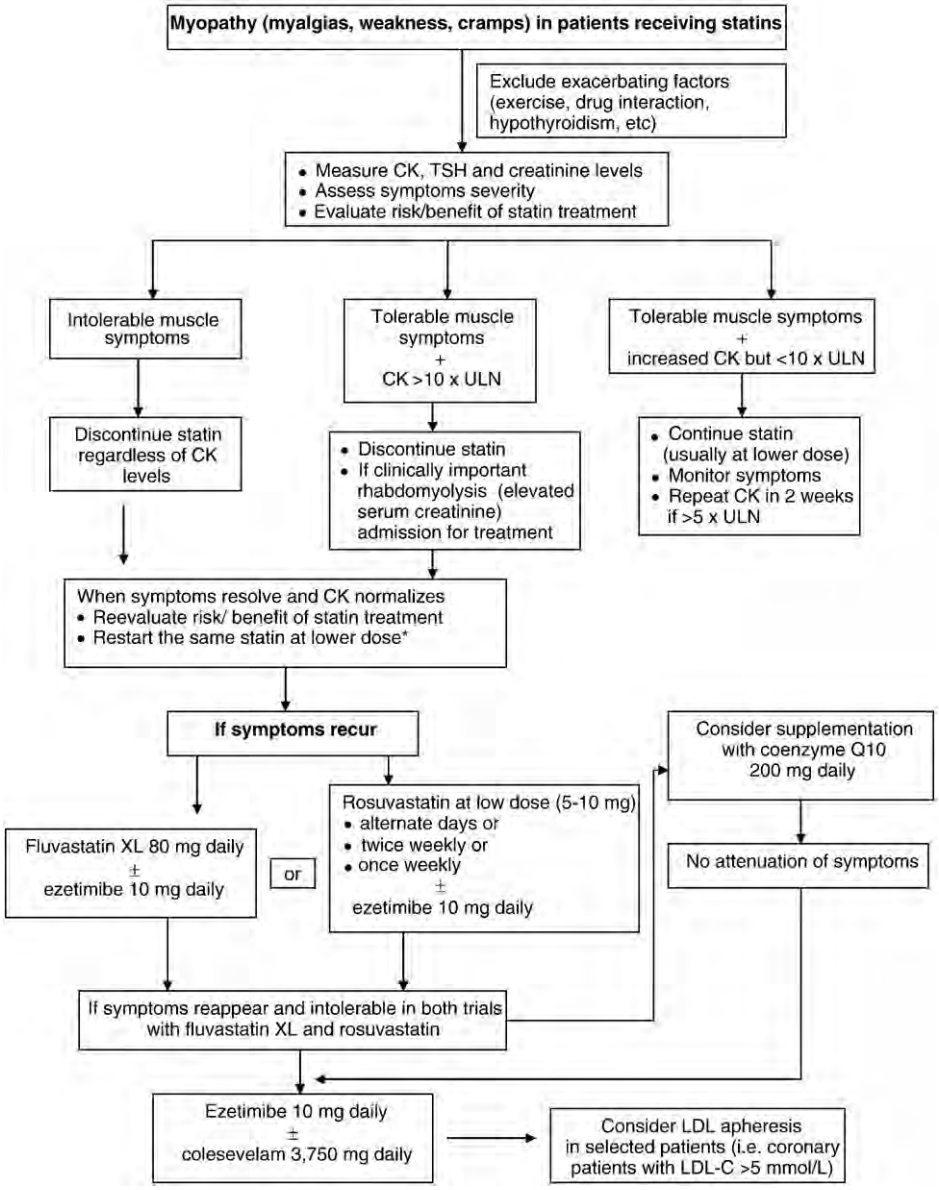

Fig. 1. Algorithm presenting the management strategies in patients with statin-associated myopathy *after rhabdomyolysis avoid the offending statin and give fluvastatin XL 80 mg or rosuvastatin intermittently at low dose. CK = creatinine kinase, LDL-C = low density lipoprotein cholesterol, TSH = thyroid-stimulating hormone, and ULN = upper limit of normal.

myopathy. In 66 dyslipidemic patients with a history of muscle-related side effects to other statins, the administration of ezetimibe 10 mg daily for 12 weeks was associated with recurrence of muscle symptoms in 24% [62]. The two main concerns with ezetimibe treatment are that the majority of patients on ezetimibe monotherapy fail to achieve the LDL-C target and that there are no data regarding the clinical benefits of this intervention.

5) Bile acid sequestrant: colesevelam has a more favorable tolerability and drug interaction profile than cholestyramine and colestipol. Colesevelam is usually combined with ezetimibe in statin-intolerant patients to maximize the cholesterol lowering effect. The maintenance dosage is three 625-mg tablets twice daily or six tablets once daily, taken with meals. Colesevelam lowers LDL-C by 15–19% in monotherapy and 10–16% in combination with various lipid-lowering drugs, such as statins, ezetimibe and fenofibrate [75]. The co-administration of colesevelam 1875 g twice daily with ezetimibe 10 mg daily in 18 statin-intolerant patients for 3 months decreased LDL-C by 42.2% and was well tolerated without reports of myalgias [76].
6) LDL apheresis: this type of LDL-C lowering treatment can be applied in coronary patients intolerant to statins (or any other lipid lowering drug) whose LDL-C levels remain >5 mmol/L (193 mg/dL) despite maximum non-statin lipid-lowering medication [77].

9. Is there any role for coenzyme Q10 administration to attenuate statin-associated myopathy?

Supplementation of CoQ10 increases its blood levels, but whether this has favorable effect on myopathic complaints is unclear [28]. Two small randomized clinical trials [78,79] produced equivocal results regarding the incidence and severity of muscle symptoms when CoQ10 (100–200 mg/day) was given in patients treated with statins. Despite the lack of evidence on its effectiveness, the fact that there are no known risks associated with CoQ10 supplementation up to 600 mg/day, has led some experts [32] to recommend a trial of 200 mg daily of CoQ10 in statin-intolerant patients who cannot be treated satisfactory with other lipid lowering agents.

10. Conclusions

Statins are the most effective cholesterol lowering medications with great benefits both in primary and secondary prevention of CHD. However, their widespread use is partly limited by myopathy, usually presented as myalgias which affect 5–10% of statin-treated patients. Patients receiving statins should be counseled about the increased risk of myopathy and should be instructed on promptly reporting unexpected muscle pain or weakness. The risk of statin-associated myopathy can be minimized by identifying the vulnerable patients and/or by avoiding the predisposing conditions. In symptomatic patients, the severity of symptoms, the magnitude of CK elevation and the risk/benefit ratio of statin continuation must be considered before statin treatment is discontinued. Fluvastatin XL 80 mg daily and rosuvastatin in low dose and intermittent administration can be tried in statin-intolerant patients. Failure of these statins leads to the use of non-statin lipid-lowering drugs. There is a definite need for randomized trials directly comparing the myopathic potential of different lipid-lowering medications at comparable doses in order to provide evidence based recommendations for the management of statin-intolerant patients.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010; 144: 1-2).

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