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An overview of statin-induced myopathy and perspectives for the future

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Abstract

Introduction: Statins remain the most commonly prescribed lipid-lowering drug class for the treatment of atherosclerotic cardiovascular disease. Their well-recognized side effects are known as statin-associated muscle symptom (SAMS). Some advances in this field have been made in recent years, but the understanding of the mechanisms has lagged. Investigating the specific role of the anti-HMGCR autoantibody, pharmacokinetic genetic variants, characterization of the known phenotypes of statin toxicity, in relation to clinical markers of disease, is of high importance.

Areas covered: We summarized currently available findings (on PubMed) related to SAMS and discussed the therapeutic approaches, risk factors, drug interactions, potential novel systems, algorithms and biomarkers for SAMS detection. CoQ10 supplementation has been suggested as a complementary approach to manage SAMS, while vitamin D levels may be useful for both the diagnosis and management.

Expert Opinion/Commentary: Further studies might help to understand the easiest way to diagnose SAMS, suitable prevention and an effective non-statin therapy. This review sheds new light on the future directions in both research and clinical practice, which will help with rapid risk assessment, identification of the SAMS risk factors in order to decrease the incidence of statins' adverse effects, and the most effective therapy.

Keywords: coenzyme Q10, drug interactions, myositis autoantibodies, risk factors, statin-induced myopathy, statin-associated muscle symptoms, therapeutic approaches, underlying mechanisms

Highlights box

1. Statin-associated muscle symptoms (SAMS) represents a spectrum of disorders from myalgia to rhabdomyolysis associated to statin therapy discontinuation.

2. The underlying pathophysiology and mechanisms remain not fully understood.

3. Genetic predispositions, subjects' personal and family histories, including co-existing disorders/risk factors, as well as drug interactions should be carefully considered by clinicians.

4. The use of novel algorithms as well as biomarkers could prevent and/or reduce the incidence of SAMS, including vitamin D supplementation.

5. The risk assessment and diagnosis of SAMS will improve in the next five years, while future genetic research could lead to a personalized therapeutic approach.

1. Introduction

Although several benefits of statins on cardiovascular (CV) health are well documented, statin-associated muscle symptoms (SAMS) remain frequently seen in clinical practice (with the prevalence between 10% and 29%), and they are the most common reason for non-adherence and therapy discontinuation [1-3]. The etiology is complex, with genetic factors likely playing a role. The underlying pathophysiology and mechanisms are currently not fully understood, but statin-induced mitochondrial dysfunction seems to be the most likely cause [2]. It appears to be sex-dependent, as a higher frequency of SAMS was reported in women, while in men, but not in women, the risk of myopathy was dose-dependent [4]. Yet, subjects with SAMS were more susceptible to other statin-induced side effects, as well as adverse effects (AEs) after other drugs, which raises the question about common underlying mechanisms. Besides, it has been suggested that older individuals, especially elderly females, are more likely to experience statin-related muscle disorder compared with younger subjects, although there is no enough evidence to support an increased risk of myopathy in older adults receiving statin therapy [5]. Recently Bharwaj e*t al.* [6] discussed SAMS comprehensively from molecular and genetic aspects, with a particular focus on older women. Identification of strategies to reduce the prevalence of SAMS, especially in this vulnerable group of patients could contribute to a significant reduction in the overall incidence of SAMS and lead to improved global patient compliance, that is further related to increased well-known outcomes associated with the use of statins [6].

Reported rates of muscle symptoms are lower in blinded randomised controlled trials (RCTs) when compared with those in observational studies and registries, with myalgia rates similar in subjects on statin or placebo [7]. Furthermore, dose dependence of muscle symptoms is not evidence based by double-blinded RCTs, in opposite to simvastatin myositis (but not confirmed in cases of atorvastatin or rosuvastatin) [8]. Myalgia has been reported as the most common muscle AEs associated with statin therapy, and excessive alcohol consumption was independently associated with myositis or rhabdomyolysis as suggested by a cross-sectional one-visit, non-interventional study [9]. However, the Heart Protection Study reported no evidence that the people with alcohol intake >21 units per week were at any greater risk of myopathy or of statin-associated excess of raised alanine transaminase [10]. Some studies showed that subjects taking atorvastatin develop myopathy most frequently (even in 12-13%), and it was increased with increase in atorvastatin dose [11]. However, other suggested simvastatin be associated with the highest prevalence of SAMS. It should be emphasized that myalgia and more severe forms have different predisposing factors. For instance, in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, 7% of the participants reported unexplained muscle pain or weakness, but at no time was there any significant difference between the treatment groups, while statin related myopathy increased about 10 times with 80 mg simvastatin daily [12]. Yet, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial [13] medication was discontinued due to a report of myalgias or muscle aches or increased levels of creatine kinase (CK) in 2.7 % of subjects treated with pravastatin, as compared with 3.3 % of those treated with atorvastatin ($p = 0.23$). No cases of rhabdomyolysis were reported in either group. In addition, type 2 diabetes mellitus (T2DM) and atorvastatin may be related to a higher risk of development of myopathy, and some preliminary data indicates that statin-exposed patients with anti- 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies have severe skeletal muscle manifestations, specifically, hip flexor muscle weakness [14]. Besides, a novel association of anti-HMGCR antibodies with muscle weakness in subjects with statin-associated necrotising autoimmune myopathy (SANAM) have been reported when, despite normalisation of muscle strength, functional impairments persist. Although anti-HMGCR antibodies may decrease or even disappear with treatment, further prospective clinical studies are needed to optimise the management of such SAMS [15]. Overall, there are inconsistent findings regarding muscular weakness in individuals with statin-induced myalgia. Results from 3 different investigations indicate that after short-term treatment with a statin, a stringent muscle strength protocol does not demonstrate decrements of muscle strength in

individuals with statin myalgia, although future studies should investigate if the same effects on muscle strength can be expected after of prolonged statin therapy [16]. It should be mentioned that both primary and secondary mitochondrial dysfunction was seen in SAMS subject, but some authors indicate that it is more likely that secondary effects on mitochondrial structure and function have occurred and that only in a small number of cases molecular analysis may be helpful [17]. Yet, recently, the main findings of both diagnosis and the underlying pathogenesis of side effects of statins, with particular focus on SANAM, have been comprehensively summarised [8].

Taking all above into account we aimed to shed some new light on the future directions in both research and clinical practice, which will help in rapidly risk assessment and/or diagnosis, but also prevent and in consequence decrease the incidence of SAMS.

2. Genetic Studies

There are various definitions of SAMS in the literature and the muscle symptoms attributed to the statin use in clinical practice are highly heterogeneous (from aching or muscle pain, tenderness or cramp, stiffness, rhabdomyolysis), usually symmetrical but may be localized, sometimes accompanied by muscle weakness, with or without an elevation of CK [7]. However, they remain one of the main reasons for statin non-adherence and/or discontinuation, which may be associated with adverse CV outcomes. Although the exact mechanism of SAMS is unknown, statins use may lead to the occurrence of previously asymptomatic inherited muscle myopathies [7]. Skin disease, internal organ involvement and muscle weakness, are the main characteristics of the idiopathic inflammatory myopathies. Also, it is known that autoimmunity also has a role in myositis pathogenesis, including myositis-specific autoantibodies, targeting essential intracellular proteins that are recognised as key biomarkers supporting the diagnosis correlated with distinct clinical manifestations. Recently, several novel myositis autoantibodies such as anti-HMGCR, anti-transcription intermediary factor 1 (TIF1), anti- nuclear matrix protein 2 (NXP2), anti- melanoma differentiation-associated gene 5 (MDA5), anti- small ubiquitin-like modifier activating enzyme (SAE), and anti- cytosolic 5'-nucleotidase 1A (cN1A) have been established in both adult and juvenile subjects [18]. Importantly, these autoantibodies were found in inclusion body, statin-induced, clinically amyopathic and juvenile groups of myositis subjects, previously believed to be mainly autoantibody negative. The frequencies of the primary myositis-specific and myositis associated autoantibodies, as well as their associations with different ages and ethnicities, have been described recently [18]. Most of the findings indicate the utility of myositis autoantibodies as both diagnostic and prognostic markers of disease. On the other hand, Keating *et al*. demonstrated the absence of anti-HMGCR autoantibodies in subjects who are intolerant on statins due to self-limiting muscle symptoms and suggested that there is no utility in testing such subjects for the presence of anti-HMGCR autoantibodies [19].

Animal investigation in rats showed that statin-induced skeletal muscle damage is related to the decreasing in resting sarcolemmal chloride conductance (gCl) and muscle chloride channel (ClC-1) expression. Also, the ClC-1 regulation has been affected by statins increasing protein kinase C (PKC) activity, which phosphorylate and close the channel with a simultaneous increase in the intracellular resting calcium (restCa) level. Yet, a higher risk of statin myotoxicity was suggested in aged rats, and all these findings indicate that in the elderly decreased gCl and change in muscle metabolism together with muscle atrophy may be related to the higher risk of SAMS [20]. Besides, when 10 patients, who experienced myalgia and increased CK level after starting statin therapy compared to 9 non-myopathic subjects not using lipid-lowering drugs were examined, results showed a 40% reduction of ClC-1 protein and increased expression of phosphorylated PKC in muscle biopsies of statin-treated subjects, independently from their age and statin type. On the other hand, the ClC-1 mRNA was not reduced significantly, indicating the posttranscriptional modification. Muscle RING-finger protein-1 (MuRF-1) was increased in accord with

muscle atrophy, myocyte enhancer factor 2C (MEF-2), calcineurin (CN) and glucose transporter type 4 (GLUT-4) transporter were reduced, suggesting modified transcription, change of glucose homeostasis and energy deficit. Accordingly, the phosphorylated form of AMPK was increased, suggesting cytoprotective process activation. In parallel, mRNA expression of Notch-1, involved in muscle cell proliferation, was highly expressed in statin-treated patients, suggesting active regeneration. Also, peroxisome proliferator gamma co-activator 1 alpha (PGC-1α) and isocitrate-dehydrogenase increased expression together with increased activity of mitochondrial citrate-synthase, indicates mitochondrial biogenesis. These findings suggest on the importance to avoid statin treatment in conditions characterised by chloride channel malfunction and energy deficit and utility of the measure of ClC-1 expression as a clinical test for assessing the risk of SAMS [21]. However, clinical conclusions still cannot be reached as in the described study [21] non-myopathic statin tolerant controls were not included. Thus, it remains unknown if such controls would have the same regulatory changes induced by statin therapy alone irrespective of the induction of SAMS. Similarly non-human studies indicate that changes in PGC-1α protein and mitochondrial content are related to the statin-induced activation of muscle atrophy genes, while muscle-specific increases in nitric oxide synthase (NOS) expression and possibly NO production, and decreases in fatty acid oxidation, could contribute to the development of the statin-induced muscle damage in fast-twitch muscles [22]. Future prospective randomised controlled trials, including phenotyping, are promising strategies for the risk assessment, prevention, as well as the treatment of this unwanted statins' effects [23].

It is well documented that there is a higher incidence of SAMS in clinical practice than in clinical trials [7,10,24]. In order to answer why there are apparent differences in muscle problems between clinical trials and practice a systematic search and review of statin clinical trials was performed and the results indicate that the percentage of muscle problems tended to be higher with statin compared to placebo group (12.7% vs 12.4%, P = 0.06) [25]. The authors suggest that this small difference may reflect a high background rate of non-specific muscle impairments in both groups that could not be distinguished from statin-associated myalgia, as a majority of included clinical trials did not use a standard definition for statin myalgia. The authors also highlighted that clinical trials have a significantly long run-in period before they actually begin to document SAMS to eliminate participants with early statin intolerance. Further, as SAMS has been partially attributed to deficiency of dolichol and coenzyme Q10 (CoQ10) [26], Latkovskis *et al*. tested the safety and efficacy of plant conifer-tree needle polyprenols (4 mg/day) in combination with CoQ10 (100 mg/day) for alleviation of SAMS in an open-label, one-center prospective pilot study for 8 weeks [27]. Non-significant increase of CK levels was observed, while muscle pain and weakness scores improved considerably ($p<0.001$ and $p=0.018$, respectively) indicating that such combination is generally safe in subjects with SAMS, but caution should be exercised in those with glomerular filtration rate (eGFR) <60 mL/min and monitoring of the liver enzymes and CK is recommended in all subjects [27]. Similarly, a very recent meta-analysis confirmed that CoQ10 supplementation improved SAMS [28], although one previous meta-analysis did not suggest any significant benefit of CoQ10 supplementation in improving SAMS even with the daily doses up to 600 mg [29-31]. Anyhow, more extensive, well-designed trials are necessary to confirm these findings. Taking into account the existing knowledge, it seems that only CoQ10 doses used for some neurological disorders – over 1 g/day are useful in SAMS prevention and treatment. As only it is confirmed, it might be a problem with the adherence and cost-effectiveness of such a treatment, as it would usually mean 5 tables of CoQ10 per day (in most of the countries the highest dose is often 200 mg) [32,33]. However, it should be mentioned that data in studies of CoQ10 are still inconclusive.

The results of a recent systematic review and meta-analysis [34] indicate that statins and exercise combination therapy seem to be more effective than statin monotherapy improving inflammation, insulin sensitivity, and exercise capacity, but without changes in lipid concentrations. However, few studies warrant the need for more randomised controlled trials studying the efficacy and safety of combination therapy.

Some results indicate that true statin-induced myalgia and non-specific myalgia are distinct, with a potential role for the immune system in their development suggesting novel immunogenetic factors associated with statin intolerance, as an essential risk factor for CV outcomes [35]. Moreover, the authors believe that LILRB5 (leukocyte immunoglobulin-like receptor subfamily-B) (rs12975366: T > C: Asp247Gly) genotypes are more likely to be intolerant to the statins.

It should be highlighted that currently, the standard tests for diagnosing SAMS are challenging to interpret. A pharmacogenomics (PGx) test to diagnose SAMS would be highly desirable, and some case-based results show that a PGx test for SAMS in high-risk, secondary prevention patients would be a dominant solution [36]. Some authors, evaluating electrophysiological and histopathological characteristics of statin-induced muscle injury, suggest muscle fibre conduction velocity evaluation as recommended and a relatively simple and reliable test to diagnose SAMS instead of invasive muscle biopsy [37]. However, it should be highlighted that it is not validated, and results were obtained not in statin intolerants. Yet, they confirmed, as mentioned above, that atorvastatin use was associated with increased CK, that statins produce mild muscle injury even in asymptomatic subjects and that statin users with T2DM were more prone to develop muscle injury than others [37]. However, as this study was not a randomised controlled trial, the final conclusion cannot be drawn. Furthermore, a blinded, controlled the Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study indicates that average muscle strength or exercise performance was not decreased after 6 months of a high-dose atorvastatin in healthy, previously untreated subjects [38]. Nevertheless, average CK level increased suggesting a mild muscle injury even among asymptomatic subjects and indicating statin-increased muscle complaints. Such findings remain to be confirmed by studies investigating the effects of prolonged exposure to a high-dose statin therapy.

Genetic variants were used to identify factors contributing to the SAMS suggesting that some subjects are prone to statin intolerance/statin myopathy due to pre-existing inherited muscular disorders, or genetic variation in statin uptake proteins encoded by solute carrier organic anion transporter family member 1B1 (SLCO1B1) or the cytochrome P (CYP) enzyme system [39]. It has been demonstrated that hereditary metabolic diseases are not rare among subjects with drug-induced myopathies and that carrier status alone for either McArdle disease (glycogen storage disease type V) or carnitine palmitoyltransferase (CPT) II deficiency may be associated with an increased risk for myopathic outcomes [40]. Pathogenic variants in the genes causative for malignant hyperthermia (ryanodine receptor 1 (RYR1) and calcium voltage-gated channel subunit alpha1 S (CACNA1S)) were found to be significant potential contributors to risk for severe SAMS [41]. Besides, variations in genes affecting polymorphisms in vascular receptors and pain perception may also contribute to SAMS. It is known that statin-associated AEs might be associated with polymorphisms in several key genes coding for transporters and metabolising enzymes that affect statin pharmacokinetics. The association between the risk of myopathy with cytochrome P450 3A5*3(CYP3A5*3) T>C (rs776746), COQ G>C (rs4693075), and SLCO1B1 T>C (rs4149056) genetic variants were investigated in South Indian patients on statins and the results clearly demonstrate that the frequency of CYP3A5*3 splicing variant is higher in myopathy group than in the tolerant group, while a significant association of genetic polymorphisms in CYP3A5, COQ, and SLCO1B1 with atorvastatin- or rosuvastatin-induced myopathy was not found [42]. The SLCO1B1 521T>C and 388A>G polymorphisms are commonly occurring variants in ethnically diverse populations, and numerous *in vitro* and clinical studies have investigated the consequences of these variants to interindividual differences in drug disposition and response [43]. The potent inhibition of human organic anion transporting polypeptide 1B1 (OATP1B1)/OATP1B3 by fusidic acid could attenuate hepatic uptake of statins, resulting in increased blood and tissue concentrations, potentially manifesting in musculoskeletal toxicity [44]. SLCO1B1 T521C was associated with a higher risk of SAMS, especially for simvastatin, rosuvastatin, and cerivastatin [45]. Future studies should be performed, including subjects receiving specific types of drugs, and any potential adverse events need to be explored.

Similar results have been reported regarding the clinical significance of CYP2D6*4 in atorvastatin-induced myopathy, while the authors did not find sufficient evidence to support the clinical translation of pharmacokinetic genetic variants other than SLCO1B1 for simvastatin [46]. Yet, SLCO1B1 has been suggested to be clinically relevant for pravastatin- and pitavastatin-induced myopathy, although additional mechanistic studies are needed [46]. Moreover, SLCO1B1 521C mutant allele increased the risk of rosuvastatin-associated myotoxicity [47]. In Czech patients who were treated with low statin doses, no association between SLCO1B1 gene polymorphism and the risk of myalgia/myopathy was observed [48]. When the prevalence of SLCO1B1 rs4149056 (521T>C) in the Emirati population was investigating, a lower prevalence of SAMS -linked C allele of rs4149056 in SLCO1B1 gene was found compared to Caucasians and Africans. However, there was a trend of higher glycosylated haemoglobin and body mass index (BMI) associated with good lipid profile in patients having this allele [49].

Interestingly, independently of the 521T>C polymorphism the intronic SNP rs4149081 in SLCO1B1 was linked with the low-density lipoprotein cholesterol (LDL-C) response to statins in Chinese patients [50], while SLCO1B1 (rs4149056, 521T>C) was associated with statin-induced myotoxicity in Chinese patients with coronary artery disease. Although several data indicate the role of SLCO1B1 c.521C>T SNP as a replicable genetic risk factor for SAMS, a very recent study suggests that, aside from SLCO1B1, no other risk loci for SAMS are apparent, and that SAMS risk is likely as a result of non-genetic risk factors or a consequence of rare genetic variants; thus, future translational studies should instead focus on rare analysis and on identifying non-genetic risk factors [51]. Finally, some findings support the role of rare variants and nominate loci for follow-up studies [52]. In details, the authors identified the novel candidate gene chloride voltage-gated channel 1 (CLCN1), a heterozygote truncating mutation p.R894* and detected predictably pathogenic case-specific variants in myotilin (MYOT), CYP3A5, SH3 domain and tetratricopeptide repeats 2 (SH3TC2), F-box protein 32 (FBXO32) and RNA binding motif protein 20 (RBM20). The results from a large, multicenter case-control study of both mild and severe SAMS in *Caucasian participants* do not support an association between the gene encoding glycine amidinotransferase (GATM) rs9806699 and SAMS, as previously documented [53]. However, the authors do not exclude the possibility that such an association might exist in specific conditions, but the potential mechanism between GATM and SAMS remains to be elucidated by future studies.

Finally, it should be highlighted that the SLC1OB1 variant has been found to be associated with SAMS in subjects with high-dose (80 mg) simvastatin and not with lower doses of simvastatin or different statins [54].

Genetic background related to statin intolerance/SAMS is summarized in **Table 1**.

3. Risk factors of SAMS and possible drug interactions with statins

There are almost 300 different recognized statin-drug interactions (see: https://www.drugs.com/drug-interactions) - most of them are minor and moderate, and in the end very rarely are responsible for the statin intolerance, however, at least few groups of drugs need to be remembered. In addition, a very recent paper studied drug interactions in 634 SAMS cases and 114 statin-tolerant controls and compared each participant's medication profile to a key of concomitant medications with known statin drug-drug interactions or independently causative of myopathy without a statin interaction [24]. The authors identified four categories of concomitant medications for each individual: those that can 1) treat symptoms of SAMS; 2) independently cause myopathy; 3) increase statin blood levels and 4) increase statin metabolism and, therefore, potentially decrease statin blood levels. It should be highlighted that this paper assessed the clinical factors associated with SAMS that are further linked with risk to develop SAMS as compared with statin-tolerant controls. For instance, family history of heart disease was the most significant factor, but also obesity, hypertension, history of smoking, and statin type

(those taking rosuvastatin or simvastatin were more likely to be in the SAMS group compared to those who took atorvastatin).

Ranolazine, a drug prescribed for the treatment of chronic angina, has been associated with the development of SAMS because it inhibits CYP3A4, which increases serum statin levels [55]. On the other hand, ranolazine monotherapy was not linked to elevated CK and myalgias. Other drug interactions that increase the risk of SAMS and should be monitored are macrolide antibiotics, calcium channel antagonists and amiodarone [56]. Potential simvastatin-drug interactions (SDIs) (based on the two references: Drug Interaction Facts 2011 and the US Food and Drug Administration (USFDA) safety communication 2011 (http://www.fda.gov/drugs/drugsafety/ucm256581.htm)) have been found in the Thai population, where SDIs were associated with half of the musculoskeletal AEs [57]. After the acute coronary intervention, the combination of the platelet inhibitory drug ticagrelor and a statin is recommended. However, this combination is known to be associated with a risk for rhabdomyolysis (CYP3A4 is metabolising both ticagrelor and simvastatin) even in subjects with normal kidney function [58]. In this case, changes in statin therapy and/or dose adjustments might be required.

The safety and efficacy of statin therapy, as well as dose adjustments required in dialysis patients, have been discussed recently. Interestingly, based on the self-designed questionnaire, statins are considered safe, effective and still widely prescribed in dialysis patients for lowering lipids as well as for secondary prevention of CV events: 65% nephrologists observed SAMS, 61% reported a case of increased liver enzymes, while 51% of nephrologists did not routinely discuss the possible benefits and risks of statin therapy with their patients [59]. Atorvastatin has been suggested as the statin of choice in subjects with chronic kidney disease, including the need for dose adjustment in those with an eGFR < 30 mLs/min/1.73 m^2 [56]. A compelling case on statin-induced rhabdomyolysis with renal failure and previously undiagnosed idiopathic hypothyroidism have been reported recently [60], highlighting the need of the clinicians' attention on this combination, especially with the concomitant thyroid disease, which is recognized to increase the risk of statin intolerance [61]. In addition, even an immune-mediated necrotising myopathy, a relatively novel disease mechanism, which clinically mimics forms of myositis, is rare. Still, awareness and early recognition of this disease are highly recommended in patients who continue to have CK elevation and weakness after discontinuation of statin therapy [62,63]. Several such case reports in the literature offer the "identification patterns" of muscular autoimmune disease, which can be mistakenly associated with the side effect of a drug [64-66]. In this case, an immunosuppressant drug is often required, as well as statin withdrawal [67,68]. Further research is needed to clarify its pathogenesis and provide evidence-based guidelines for management [69]. Finally, some case reports, including a population-based case-control study have suggested a potential link between susceptibility to malignant hyperthermia (MH) and other muscle diseases in subjects with statin-induced muscle toxicity [70].

All the most important drug interactions, as well as identified risk factors/conditions that might increase the risk of statin intolerance/SAMS, are presented in **Table 2**. We would like to highlight that voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis [71], and it is more harmful than fluconazole which does not increase more than 50% of simvastatin or atorvastatin level. Likely prescription and non prescription interactions as well as potential alternatives for special populations were carefully discussed by some experts from the National Lipid Association Statin Safety Taskforce [72].

Schematic representation of the role of genetic predispositions and drug interaction in SAMS is shown in **Figure 1**.

4. Potential molecular mechanisms of SAMS

As mentioned above, the underlying mechanism of SAMS remains enigmatic. In C2C12 myoblasts, several statin lactones reduced respiratory capacity and appeared to be potent inhibitors of mitochondrial complex III (CIII) activity and the lactones were in general three times more potent inducers of cytotoxicity than their corresponding acid forms. Consequently, CIII inhibition was identified as a potential off-target mechanism associated with SAMS [73]. Several studies were performed to explore the downstream effects of the statin-associated inhibition of AKT within the AKT signalling pathway and on myocyte biology and morphology in C2C12 myotubes and in mice *in vivo*. C2C12 myotubes were exposed to 10 µM or 50 µM simvastatin, atorvastatin or rosuvastatin for 24 h. Simvastatin and atorvastatin inhibited AKT phosphorylation. They were cytotoxic starting at 10 µM, whereas similar effects were observed for rosuvastatin at 50 µM. Reduced protein synthesis, accelerated myofibrillar degradation and atrophy of C2C12 myotubes have been attributed to the inhibition of AKT phosphorylation that further led to impaired phosphorylation of S6 kinase, 4E-binding protein 1, FoxO3a and ribosomal protein S6 [74].

Furthermore, impaired AKT phosphorylation was associated with the activation of caspases and poly(ADP-ribose) polymerase (PARP), reflecting the induction of apoptosis. Similar findings were detected in skeletal muscle of mice treated orally with 5 mg/kg/day simvastatin for 3 weeks. These findings indicate the importance of the AKT/the mechanistic target of rapamycin (mTOR) signalling pathway in statin-induced myotoxicity as well as on potential drug targets for the treatment of subjects with SAMS.

It is well known that statins inhibit the biosynthesis of mevalonate, a rate-limiting step of cholesterol synthesis, which is also an essential precursor for producing isoprenoids such as farnesylpyrophosphate and geranylgeranyl pyrophosphate. These isoprenoids are important for anchoring small guanine nucleotide-binding regulatory proteins (GTPases) to the membrane (e.g., Ras GTPases modulate proliferation and apoptosis, Rho GTPases control cytoskeleton formation, and Rab GTPases are essential for intracellular vesicle trafficking). Inactivation of these small GTPases affects cellular functions, and statins induce both depletion of isoprenoids and inactivation of small GTPases, especially Rab, which are critical for statin-induced myotoxicity [75]. Further studies are required in this field, but these findings may contribute to the prevention and novel treatment of statins' AEs on skeletal muscle and the development of safer lipid-lowering drugs.

Cellular stress underpinned by mechanisms of postinflammatory repair and regeneration has been suggested as a potential mechanism of persistent myalgia in response to statins. On the other hand, as discussed in details above, some individuals have a genetic predisposition to develop altered statin metabolism and/or increased susceptibility to SAMS that is further supported by the discovery that a number of single nucleotide polymorphisms (e.g., SLCO1B1, SLCO2B1 and RYR2) associated with statin myalgia and myositis were most frequently seen among subjects with statin myalgia [76,77].

AEs of statins are probably results of decreased antioxidant defences associated with fewer intermediate metabolites in the cholesterol synthesis pathway. Alis *et al.* hypothesised that the simultaneous inhibition of xanthine oxidase via co-administration of allopurinol with statins could diminish reactive oxygen species (ROS)-related muscle damage. This strategy would have, in turn, positive effects on both the incidence of muscle-related AEs and CV outcomes [78]. It is expecting that the proposed approach could have important clinical implications for reducing statin-induced myalgia and rhabdomyolysis. Similarly, very recently, Liu *et al.* [79] summarised the research findings in the last five years regarding the production of ROS, oxidative stress as a result of statin treatments, and their correlation with statin-induced toxicity and metabolism. Statin-induced metabolism involves various CYP450 enzymes, which provide potential sites for statin-induced oxidative stress. Also, the authors discussed the therapeutics of a variety of compounds against statin-induced organ damage based on their anti-oxidative effects to further understand the role of oxidative stress in statin-induced toxicity [79]. The potential mechanisms include also reduced levels of essential mevalonate and cholesterol derivatives as well as the loss of other

antioxidant defences besides CoQ in skeletal muscles which produce a significant amount of ROS [80]. Therefore, a high level of antioxidants is needed for the maintaining of the skeletal muscles function.

To elucidate the mechanisms underlying statin the myotoxicity and HMGCR function in the skeletal muscle, Osaki *et al.* developed the skeletal muscle-specific HMGCR knockout mice. Myopathy in these mice was rescued entirely by the oral administration of mevalonic acid, which further shows that statins may cause skeletal muscle toxicity. It is possibly dependent on the deficiencies of HMGCR enzyme activity and downstream metabolites of the mevalonate pathway in skeletal muscles rather than the liver or other organs [81].

As it has been reported that statins induce endoplasmic reticulum (ER) stress and cell death in immune cells and myoblasts *in vitro*, Kim *et al.* [82] investigated this molecular mechanism. Biochemical data revealed that tauroursodeoxycholic acid (TUDCA), an ER stress inhibitor, inhibited atorvastatin- and simvastatin-induced protein cleavages of PARP-1 and caspase-3, respectively. The statin treatment activated marker proteins of unfolded protein responses (UPR) including activating transcription factor 6 (ATF6), DNA damage-inducible transcript 3 (CHOP), and spliced X-box binding protein 1 (XBP1) and these responses were inhibited by TUDCA. The statin treatment-induced mRNA levels of UPR-marker genes, suggesting that statins activate ER stress in transcriptional regulation. The physiological relevance of ER stress in SAMS as shown in a mouse model of myopathy, in which instillation of simvastatin and atorvastatin led to myopathy.

Interestingly, the reduction of muscular endurance in response to statin instillation was significantly increased in the TUDCA treating group compared to the vehicle control group [82]. Moreover, CHOP deficiency mice showed restoration of statin-induced reduction of muscular endurance, suggesting that SAMS via ER stress and in a CHOP-dependent manner. These findings indicate that statins specifically induce myopathy in an ER stress-dependent manner, suggesting the therapeutic potential of ER stress regulation in preventing AEs of statin [82].

An abnormal relationship in the system of energy synthetic and energy-dependent processes in myocytes has been suggested to serve as the molecular basis for the formation of statin-induced degenerative changes [83]. Such findings may lead to the development of new approaches to metabolic correction with high-dosage statins to maintain skeletal muscle function. The novel system an "*Ecoflex-coupling method*" was created to test the muscle force within a long-term culture, and it opens new possibilities for investigating the mechanical stresses of muscle, which has potential applications in drug screen and multi-organs integration study [84].

Schematic representation of the potential mechanism of SAMS is shown in **Figure 2**. Based on the currently available evidence from pre-clinical and clinical studies we can say that the possible mechanisms include disorders on cellular level (mitochondrial dysfunction, oxidative and ER stress, the loss of the antioxidant defences associated with cholesterol synthesis pathway, inhibition of AKT phosphorylation and mevalonate) that further can lead to the cell apoptosis. Yet, postinflammatory repair and regeneration might underline cellular stress. We believe that a genetic predisposition and immunogenetic factors have an important role in the occurrence of SAMS and that the mechanisms are multifactorial related also to co-existing health disorders (including family history) and concomitant medication as well as subjects' habits. We assume that there is a synergistic interaction between genetic and pharmacologic factors as a trigger to induce SAMS.

5. What can we do to prevent SAMS? How to make better decisions regarding therapy?

Since there is no clear practical consensus on a treatment course of action for SAMS, the investigation into potential confounders to elucidate the dynamics of SAMS is warranted. Frequently the only solution is to either discontinue statin therapy/reduce the dose or attempt intermittent dosing strategies at a low dose or to use of non-statin lipid-lowering therapy [85].

The utility of curcumin in subjects with SAMS only reflects a potential based on the several molecular mechanisms that need to be confirmed in the well-designed randomised controlled studies [86]. There are also other nutraceuticals with the potential to be used in statin intolerance, including red yeast rice, which is a matter of high debate now [87-89]. Interestingly, *Herba Cistanches* (HC, *Cistanchedeserticola* or *Cistanchetubulosa*) is a Chinese herb traditionally used for muscle problems, and previously it has been shown that HC extract could reduce muscle damage and improve ATP storage in post-exercise rats. However, recently, Wat *et al.* [90] demonstrated for the first time that aqueous extract of HC could exert a dose-dependent protective effect on simvastatin-induced toxicity *in vitro*, which was unlikely due to the presence of verbascoside. Of interest, they also suggested the potential use of HC under the situation of simvastatin-induced muscle toxicity.

Song *et al*. [91] investigated the effects of the metabolic modulator trimetazidine on skeletal muscle energy metabolism and statin-associated exercise intolerance. Trimetazidine alleviated statin-related skeletal muscle injury by the restoration of oxidative phenotype and increasing fibre cross-sectional areas in response to exercise training. Correspondingly, the exercise training adaptation was improved in high-fat-fed ApoE/ mice. Moreover, trimetazidine exerted its positive effects without affecting the beneficial lipid-lowering properties of the statins. Thus, trimetazidine was suggested to be prescribed to remedy the undesirable statins-induced exercise intolerance [91]. The results from other study indicate that exercise does not exacerbate SAMS in ApoE-/- mice, yet statin treatment reduces activity in a manner that prevents muscle from mounting a beneficial adaptive response to training [92]. Therefore, further studies, including subjects who take statins with different kinds of exercise, are still warranted [93]. Berent *et al.* aimed to characterise and describe the muscular side effects of statins and create an anatomical frequency mapping [94]. They suggest that physical activity seems to be a key trigger for the onset of statin-induced muscular side effects.

Vitamin D deficiency has been independently associated with muscle weakness and severe myopathy and might be a confounder for SAMS [95]. Vitamin D status may be considered a modifiable risk factor for muscle-related AEs of statins, and supplementation of vitamin D (particularly when ≤20 ng/mL) may improve statin tolerance [96] and can be safely resolved by vitamin D supplementation (50.000-100.000 units /week) in most cases (88-95%) [97]. Interestingly, some authors indicate that baseline low vitamin D, or its deficiency/insufficiency and changes during statin therapy do not predict statin-associated muscle symptoms in subjects already rigorously verified symptoms. However, low vitamin D may exacerbate statin-induced muscle injury and could contribute to statin-associated muscle symptoms development with a longer duration of the statin treatment [98]. Ovesjo *et al.* [99] showed that 25-hydroxyvitamin D (25OHD) levels <50 nmol/L might be a useful marker to predict muscular adverse events during statin treatment. The finding that the vitamin D receptor polymorphism TaqI was associated with myopathy may indicate a causal relationship between vitamin D function and myopathy, but more extensive studies are needed before firm conclusions can be drawn [99].

SAMS is less likely at low doses, and ezetimibe is only rarely reported to induce myopathy. Also, ezetimibe is not usually known to potentiate SAMS. Brahmachari *et al.* [100] reported a case of myalgia with elevated serum creatine phosphokinase in a subject after 2 months of therapy with a fixed-dose combination of atorvastatin and ezetimibe (10 mg each). The subject also was undertaking moderate physical exertion in the form of brisk walking for 30-40 min a day and was detected to have low serum Vitamin D levels [100]. Thus, the authors highlight potential risk factors, such as regular individually intensive (or new) physical exertion and vitamin D deficiency (as well as hypothyroidism, alcohol

consumption and drug interactions) co-existent in dyslipidemic subjects, may exacerbate myopathy potential of statins, and precipitate muscular symptoms even at a low-dose. In that way, vitamin D levels may be useful for both the diagnosis and management of SAMS [101]. Kang *et al.* [102] investigated the effect of replenishing vitamin D on SAMS in veteran patients who failed to maintain statin therapy in a pharmacist-run ambulatory care setting. Also, the authors studied changes in subjects' vitamin D levels, fasting lipid profiles, and achievement of lipid goals after statin rechallenge. All subjects were able to maintain their statin therapy without myalgia after vitamin D supplementation, while about 40 % of them tolerated their previously failed statins. The frequently restarted statins were atorvastatin, pravastatin, and rosuvastatin and the percent of the subjects who achieved the cholesterol goals increased from 22% to 30% after 12-month follow-up [102]. On the other hand, statin discontinuation (or reducing its dosage) is a very relevant clinical issue because it may increase the risk of CV events [103]. Therefore, we need to continue our efforts to provide optimal treatment of hyperlipidaemia while avoiding (or appropriately treating) SAMS [30]. Interestingly, based on the available data, it was shown that even 95% of patients suffering from muscle pain after statins at baseline might be still treated with reduced doses of statins [104]. The use of vitamin D supplementation to relieve SAMS remains controversial as placebo-controlled, double-blinded trials have not been conducted. However, most studies indicate a relationship between vitamin D supplementation and improved tolerance of statin therapy after rechallenge.

The association of lipophilic statins with plasma lipoproteins in the presence of disturbed acid-base balance can modify the pharmacokinetics and tissue distribution of these drugs, resulting in an alteration in their efficacy and toxicity profiles. Taha *et al.* [105] investigated *in vitro* the role of hyperlipidaemic conditions alone or in combination with acidosis/alkalosis in the development and potentiation of statin-induced myotoxicity. Lipophilic simvastatin displayed significant association with triglyceride-rich lipoproteins and LDL, which contributed to increased cellular uptake of simvastatin by C2C12 cells through lipoprotein lipase-mediated process, resulting in enhanced muscle toxicity. Furthermore, a combination of low pH environment (representing acidosis) and hyperlipidaemia increased the association of simvastatin with plasma lipoproteins causing potentiation of cellular uptake and myotoxicity of this drug [105]. Thus, hyperlipidaemia, when coincident with acidosis, can enhance statin-associated muscle toxicity, and therefore require extra caution by prescribing clinicians. Hydrophilic rather than lipophilic statins could be a preferable choice in subjects with such condition (including also patients at the higher risk of statin intolerance, such as elderly ones), although above mentioned PROVE-IT study [13] as well as a randomised controlled, the STAtins in Reducing Events in the Elderly (STAREE) study [106], which was carried out with 40 mg atorvastatin vs. placebo, did not indicate the same preference.

On the other hand, we might sometimes observe that patients that might have SAMS after lipophilic statins might be well-tolerant with hydrophilic ones and opposite; the details of this mechanism are still not well-known. Recent findings indicate that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors such as alirocumab or evolocumab may be an excellent lipid-lowering agent in subjects with statin intolerance and myotonic dystrophy [107]. Some cases from the literature also indicate that creatine administration may prevent SAMS [108].

Chan *et al*. [109] aimed to develop and validate sensitive algorithms to detect hospitalised SAMS cases from electronic medical records (EMRs) [109]. The authors determined the performance of these algorithms against manually curated records and the best algorithm used a combination of elevated CK (> 4X the upper limit of normal (ULN)), discharge summary, diagnosis, and absence of statin in discharge medications. This algorithm achieved a positive predictive value (52-71%) and sensitivity (72-78%) on two validation sets of >30.000 records each. Using this algorithm, the incidence of SAMS was estimated at 0.18% [109]. Similarly, Sai *et al.* [110] aimed to develop a detection algorithm, highly selective for SAMS using EMRs with the combined use of exclusion criteria for a disease, medical practice data and time course of CK values.

6. Conclusions

It is suggested that subjects' personal and family histories, which may be associated with a higher risk for SAMS, should be carefully considered by clinicians. However, further studies are still needed to determine whether some pre-existing adverse health indicators should alter clinicians' treatment decision. In fact, an algorithm/clinical score that would predict the risk of statin intolerance would be much expected by the clinicians. Currently, the effective management options for statin-intolerant subjects are several, and the use of novel algorithms as well as biomarkers could prevent and/or reduce the incidence of AEs of statins, including vitamin D supplementation. The potential for modification and/or prevention of SAMS using personalized medicine is certain. Ongoing genetic researches will contribute to it, elucidating the underlying mechanism and mitigating the risk of statins' AEs, without compromising of statins' CV benefit.

7. Expert opinion

As discussed above, SAMS represents a broad spectrum of disorders from insignificant myalgia to fatal rhabdomyolysis with the frequency ranging from 3-5 % in clinical trials to 15-29 % in daily clinical practice. However, such large variations can be explained by the definition used. Thus, some authors proposed a scoring system to classify SAMS according to clinical and biochemical criteria [111]. The etiology remains still poorly understood, and most probably, an underlying genetic cause is necessary for overt SAMS. Variants in gene groups that encode proteins involved in i) statin metabolism and distribution (membrane transporters and enzymes; OATP1B1, ATP-binding cassette transporter (ABCA1), multidrug resistance protein (MRP), CYP3A4), ii) CoQ10 production (CoQ10A and B), iii) energy metabolism of muscle tissue (glycogen phosphorylase, muscle associated (PYGM), glucosidase alpha, acid (GAA), carnitine palmitoyltransferase 2 (CPT2)) have been proposed as candidates who can predispose to SAMS. On the other hand, pharmacological properties of the statin molecules (lipophilicity, excretion pathways) and patients' characteristics influence the likelihood of SAMS development [111]. All these statements are widely revised in the literature and were summarised above.

Statin specific analyses, multi-variant analyses, as well as a standard definition of SAMS, should be incorporated in the future research that also should be focused on investments in pharmacokinetic genetic variants. Such an important approach could have a profound impact on public health. Among the candidates potentially affecting statin treatment tolerability is the gene CoQ2, encoding 4-hydroxybenzoate-polyprenyltransferase which plays a role in the biosynthesis of CoQ10, which deficiency might be involved in the development of statin-associated muscle symptoms. However, the polymorphisms of the CoQ2 gene do not associate with SAMS in the Czech patients treated with low doses of statins [112]. This is another clue that the CoQ10 pathway is not the most important for the development of SAMS.

There are multiple risk factors for SAMS. These risk factors are both patient-related (age, genetics, co-morbidities) and drug-related (statin metabolism via the CYP system, drug-drug interactions and statin drug transport). Management options for statin-intolerant patients include statin switching, especially to low-dose, intermitted doses of long-acting statins (rosuvastatin and atorvastatin), and other non-statin lipid-lowering agents, such as ezetimibe, colesevelam (as available), PCSK9 inhibitors (as only available and reimbursed), bempedoic acid (a probable effective future statin-intolerant therapy, still before CV outcomes trial results) [113,114] and nutraceuticals [115]. However, SAMS is a significant clinical problem that contributes considerably to statin therapy discontinuation. However, the effective management options for statin-intolerant patients are several, as they have been summarised above. Also, we briefly summarised the potential novel algorithms suggested by the different expert as well as novel biomarkers that could prevent and/or reduce the incidence of this AEs of statins. A future randomized, placebo-controlled studies are needed to confirm the benefits of vitamin D supplementation on SAMS. Based on the

currently available evidence, it may be reasonable to check serum vitamin D level in subjects who have experienced SAMS, and supplement as needed.

Interestingly, Settergren *et al.* [116] investigated the extent to which clinicians avoid well-established drug-drug interactions that cause SAMS. The authors found no evidence for preventing co-prescriptions of statins and antibiotics with an increased risk of statin-induced adverse drug reactions. Paradoxically, co-prescription of statins and gemfibrozil was associated with an increased statin dose, further aggravating the risk for myopathy [116]. It should be highlighted that this investigation was done 6 years ago, and today, scientific evidence is much more substantial, although clinicians should pay attention to these aspects. The identification of subjects with an increased proclivity to SAMS 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 [117].

The research is ongoing to develop a PGx test for SAMS like an alternative to the current diagnosis method that relies on CK levels, although the potential economic value of such analysis is unknown. Mitchell *et al.* [118] developed a lifetime discrete event simulation (DES) model for subjects 65 years old initiating a statin after a first CV event. The authors found that strategy-favouring subjects staying on statin therapy are cost-effective even if subjects maintained on statin are at risk of rhabdomyolysis. The results are explained by the fact that statins are highly effective in reducing the CV risk, and this benefit largely outweighs the risk of rhabdomyolysis [118]. Besides, the same authors recently conducted two economic evaluations of a hypothetical PGx test for SAMS in subjects at high CV risk [119]. They used a broad interpretation of test parameters that reflected physician and subjects' behavioural responses to the test results and accounted for subject adherence to treatment. The findings indicate that a highly accurate PGx test for SAMS would provide a positive incremental net monetary benefit (INMB) for a provincial payer in Canada. However, the value of the test would depend on its ability to accurately diagnose patients when they experience musculoskeletal pain symptoms and guide patients with a test result indicating no SAMS to adhere to treatment. Interestingly, their results showed that a highly inaccurate test would still yield a positive INMB [119].

Given that statin use is increasing in patients at risk for CV disease, and based on recent lipid guidelines, there will be more and more patients at high intensive statin therapy, and consequently rheumatologists and neurologists might see an increasing number of patients with SANAM. We need to propagate knowledge about this disorder to primary care physician and/or cardiologist, as they are the first contact of the patients with SANAM [120]. Given the strong genetic and anti-HMGCR autoantibody association of SANAM, the risk assessment and diagnosis will improve in the next five years. Early recognition and treatment would help in decreasing the morbidity from SANAM in future, although statin is usually not tolerated by these patients and immune-suppressants are supposed to given soon, especially when persistent elevation of CPK is present and diagnosis is confirmed by positive anti-HMG-CoA reductase autoantibody [8,121,122]. In addition, patient-reported functional changes and semi-quantitative muscle strength testing or quantitative dynamometry can be used in therapeutic monitoring of patient with SANAM [121]. Finally, treatment includes steroids, immune-suppressants and discontinuation of statins indefinitely [8,122], but also PCSK9 inhibitors may be an alternative option [8]. Moreover, it is believed that treatment guidelines will get better consolidated in the next 5 years [120]. Finally, it could be very useful to create a team of specialists (GPs + cardiologists/lipidologists + neurologists + rheumatologists + geriatrics, etc.) working together to be effective in the diagnosis, prevention and therapy of a patient with statin intolerance. Also, education on statin efficacy is critical to avoid nocebo or more correctly drucebo effect, introduced by Banach *et al*. within the International Lipid Expert Panel (ILEP) [123].

Statins are general very well tolerated, and even over 95% of patients that suffered from muscle symptoms might still use statins (at reduced dose, alternative-day or twice-weekly dosing strategies, combination therapy), despite methodological limitations (small size, retrospective, open label, or non-

randomized design) [7,124]. However, it needs to be also emphasized that subjects in clinical practice have usually several co-existing disorders/risk factors that all should be always considered by clinicians, as due to this fact they may not tolerate a high-dose statin regimen as seen in some clinical trials [13]. Genetic research in the future could lead to a personalized therapeutic approach. The inherent power of utilizing data and text mining of EMRs to enhance pharmacovigilance activities should not be underestimated. On the other side, it should be kept in mind that CV benefit of statins is much higher than a risk for statin myopathies, including SANAM. It is expecting that in upcoming years, the underlying mechanisms will be understood better that will further lead to more rapidly risk assessment and/or diagnosis as well as to the development of novel preventive and/or treatment options.

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Table 1. Genetic background related to statin intolerance/SAMS

Novel myositis autoantibodies *(8)*	*Clinical signs*
anti-HMGCR anti-TIF1 anti-NXP2 anti-MDA5 anti-SAE anticN1A	↓ ClC-1 protein and ↑ expression of phosphorylated PKC HMGCR → Highly ↑ CK; significantly associated with necrotizing myopathy; TIF1, NXP2, MDA5 and SAE → significantly associated with rush; cN1A → Myositis IBM
Novel immunogenetic factor *(29)*	*Clinical signs*
LILRB5 Asp247 homozygous genotype	presence and rapid accumulation of T regulatory (Treg) cells
Polymorphisms in several key genes coding for transporters and metabolising enzymes that affect statin pharmacokinetics *(33-37,39,42-45)*	*Clinical signs*
cytochrome P450 3A5*3(CYP3A5*3) T>C (rs776746), COQ G>C (rs4693075), and SLCO1B1 T>C (rs4149056)	↑ CK ↑ LDL-C
Disorders providing genetic liability for SAMS *[40-41].*	*Clinical signs*
myophosphorylase deficiency, with a 20-fold increase in disease-causing variants in SAMS (PYGM gene), carnitine palmitoyl transferase deficiency with a 13-fold increase in disease-causing variants in SAMS (CPT2 gene), and dominantly inherited variants in genes causative for	McArdle disease (glycogen storage disease type V) or carnitine palmitoyltransferase (CPT) II deficiency ↑ risk for myopathic outcomes

malignant hyperthermia (RYR1 and CACNA1S)	malignant hyperthermia

ABBREVIATIONS: TIF1: Transcriptional intermediary factor 1; cN1A: Cytosolic 5'nucleotidase 1A; NXP2: Nuclear matrix protein 2; MDA5: Melanoma differentiation associated gene 5; SAE: Small ubiquitin-like modifier activating enzyme; HMGCR : 3-hydroxy-3-methylglutarylcoenzyme A reductase; ClC-1: muscle chloride channel; PKC: protein kinase C; CK: creatine kinase; LDL-C: low-density lipoprotein cholesterol.

Table 2. The most important drug interactions as well as identified risk factors/conditions that might increase the risk of statin intolerance/SAMS

Agents		*Recommendations*
Ranolazine *(48)*	inhibits CYP3A4 ↑ serum statin levels	- Coadministration with rosuvastatin, atorvastatin, pitavastatin, fluvastatin, and pravastatin; simvastatin should be limited to 20 mg/day - might require changes in statin therapy and/or dose adjustments
- macrolide antibiotics (erythromycin, clarithromycin, telithromycin)	inhibits CYP450 ↑ Statin AUC	Contraindicated with simvastatin; atorvastatin maximum 20 mg/day; pravastatin maximum 40 mg/day
- azole antifungals (eg, voriconazole, itraconazole, posaconazole, fluconazole),	↑ plasma statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis	Contraindicated with simvastatin, lovastatin, atorvastatin
- HIV protease inhibitors (eg, nelfinavir, indinavir, ritonavir, tipranavir),		Contraindicated with simvastatin, lovastatin, rosuvastatin
- **other:** nefazodone, ciclosporin, danazol and gemfibrozil		
- calcium channel antagonists (amlodipine, diltiazem, verapamil) and amiodarone *(49)*		Do not exceed 20 mg simvastatin daily in patients also taking amlodipine, diltiazem, verapamil or amiodarone; Caution should be exercised in patients of various ethnic backgrounds, particularly those of Asian descent
Fusidic acid (an orally active bacteriostatic antibiotic for the treatment of methicillin-resistant *Staphylococcus aureus* and multiresistant *Staphylococcus aureus* strains)	could attenuate hepatic uptake of statins, ↑ blood and tissue statin	Patients should be closely monitored

(49)	concentrations, musculoskeletal toxicity	
Platelet inhibitory drug (**ticagrelor**) *(51)*	recommended after the acute coronary intervention; ↑ rhabdomyolysis	might require changes in statin therapy and dose adjustments in order to avoid pharmacological interactions and higher risk for adverse effects; the dose of simvastatin and lovastatin should not exceed 40 mg/day

AUC: the area under the plasma drug concentration-time curve

Figure 1

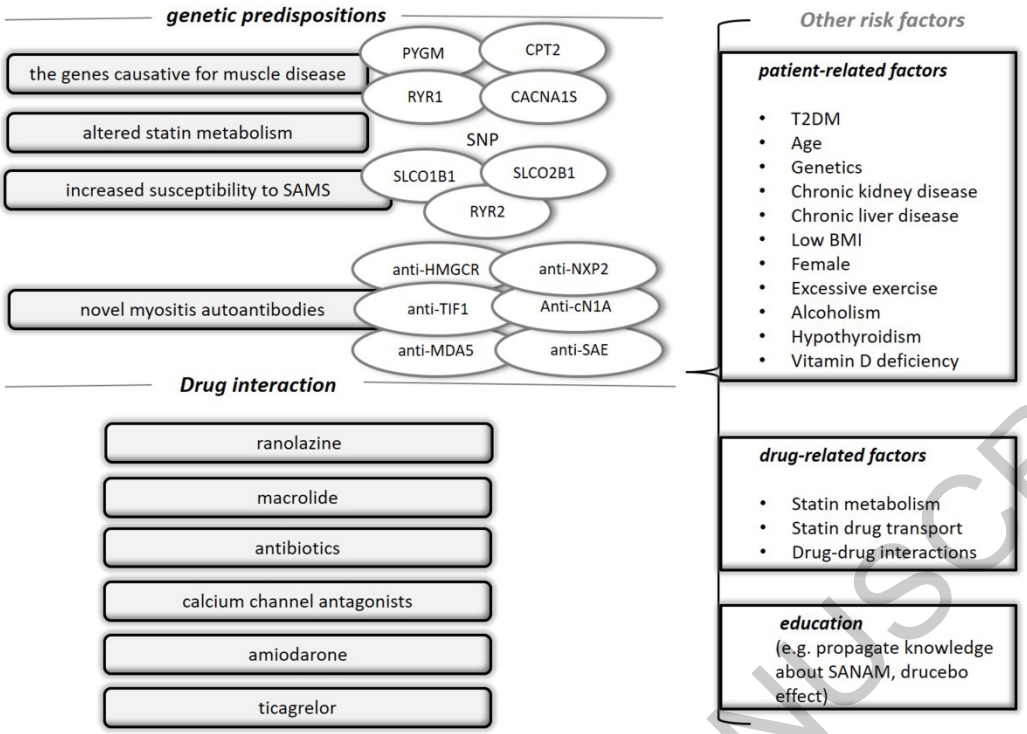

Figure 2