REVIEW ARTICLE

Statin Intolerance: Pathophysiology, Risk Factors, Manifestations, and Management Strategies

ABSTRACT

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality among people across the globe, and the high levels of low-density lipoprotein cholesterol (LDL-C) are one of the main risk factors that can contribute to the occurrence of atherosclerotic cardiovascular disease. The statins, which are 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the mainstay of lipid-lowering therapy and have proven to have a markedly reduced cardiovascular event and mortality. In addition to decreasing LDL-C, statins have pleiotropic actions, such as endothelial repair, vascular inflammation, and atherosclerotic plaque stabilization.

Although statin therapy has been proven to be both effective and safe over time, adherence to statin treatment is often impaired over time because of statin intolerance, which manifests as statin-associated muscle symptoms (SAMS). Statin intolerance is a complex disorder, which depends on the pharmacokinetic features, individual peculiarities of patients, genetic factors, and interactions between drugs. Some of the proposed mechanisms are mitochondrial dysfunction, which is associated with decreased coenzyme Q10 production, impaired calcium homeostasis, immune-mediated muscular damage, and genetic differences related to drug transport and metabolism.

The given review is a comprehensive summary of the pathophysiology, risk factors, clinical manifestations, and evidence-based management of statin intolerance. It also highlights the need to have a systematic diagnostic methodology, which incorporates the temporal association, laboratory analysis, and dechallenge/ rechallenge methods to differentiate between true intolerance and nocebo-based effects. To ensure a sufficient level of cardiovascular risk reduction, it is crucial to optimize therapy with the help of personal dosing, replacement of statins with non-statin agents, ezetimibe, PCSK9 inhibitors and *bempedoic acid*. The adherence to treatment and long-term cardioprotective effects can be improved by better awareness and systematic control of statin intolerance.

Objective of the Review

The purpose of this review is to deliver an in-depth and critical review of statin intolerance, including its underlying pathophysiology, risk factors, clinical presentation, and the current evidence-based approaches to optimize cardiovascular outcomes.

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Keywords: Statin-associated muscle symptoms; Statin intolerance; HMG-CoA reductase inhibitors; Dyslipidemia; Cardiovascular disease; LDL cholesterol; Pharmacogenetics; Lipid-lowering therapy; Drugs safety; Cardiovascular risk management; *PCSK9 inhibitors; Ezetimibe; Bempedoic acid*

1. INTRODUCTION

1.1 Burden of Cardiovascular disease

Cardiovascular disease is the most leading cause of death and morbidity in entire world as nearly a third of total number of deaths worldwide [1]. According to Global Burden of Disease (GBD) 2023 study, CVD killed approximately 19.2 million people in the world where more than 620 million cases of the disease are prevalent, and this amount is quite high in comparison with the numbers in 1990 [1]. Ischemic stroke and heart disease are main causes of death and disability caused by CVDs in the world [1]. The leading contributors to the burden are population ageing, urbanization, and increased proportion of modifiable metabolic risk factors, such as high levels of LDL-C and high blood pressure, obesity and diabetes [1,2]. The fact that high LDL-C is viewed as the most important causal risk factors in the process of the atherosclerotic cardiovascular disease development are worth noting, which is why lipid-lowering instruments are vital in both primary and secondary prevention [2].

1.2 Role and Clinical Importance of Statins in Dyslipidemia

One of the most important risk factors that can be modified in the cardiovascular disease is dyslipidemia, especially raised levels of low-density lipoprotein cholesterol (LDL-C). Statins have been the most prescribed lipid-lowering agent as compared to the other treatment options because they have a solid evidence base, established efficacy, and an excellent safety profile. The mechanism of action of statins is to competitively inhibit the rate-limiting enzyme in the hepatic cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This blockage lowers the levels of cholesterol in the cells, and causes an increase in the number of LDL receptors in hepatocytes, and increases the clearance of the LDL-C in the blood [3].

Besides the main lipid-lowering effect of statins, they also have a number of pleiotropic effects that lead to cardiovascular protection. The experimental and clinical research has shown positive results in endothelial functioning, decrease in vascular inflammation, and stabilization of atherosclerotic plaques. All these mechanisms minimize the risk of thrombotic cardiovascular events [4]. Statin therapy has been demonstrated in large-scale randomized clinical trials and meta-analyses to be associated with significant reduction of the occurrence of myocardial infarction, stroke, and cardiovascular mortality in both primary and secondary prevention. Noticeably, the extent of decrease in cardiovascular risk is directly proportional to the extent of LDL-C reduction, which justifies the present guideline suggestions of intensive statin treatment in suitably chosen high-risk patients [5].

Statins are thus at the forefront of treatment of cardiovascular disease, show consistent and reproducible advantage in a very large patient population [6]. Their role in minimizing significant adverse cardiovascular outcomes, such as myocardial infarction, ischemic stroke, and cardiovascular mortality, has been well-established in extensive clinical research. Interestingly, the clinical effect is directly correlated with the level of LDL-C, which supports the concept of a higher lipid lowering translating to a higher cardiovascular risk lowering [7].

In addition to reducing the occurrence of events, statins also help in stabilizing the plaque, enhancing endothelial performance, and reducing vascular inflammation, which reduces the risk of acute rupture in plaque. These effects are especially significant in people with the high risk of atherosclerotic cardiovascular disease, diabetes mellitus, or significantly high LDL-C levels. As a result, the existing international practice guidelines propose statins as initial therapy to manage lipids in patients with moderate to high cardiovascular risk [8].

Statins remain one of the most widely prescribed drugs across the globe due to their high clinical effectiveness, cost-effectiveness, and the general safety profile. The clinical relevance of lipid reduction is only a part of their clinical relevance, which is significantly lowering the morbidity and mortality of long-term cardiovascular disease in case of proper and regular use.

1.3 Problem of Discontinuation Due to Intolerance

In spite of their good cardiovascular effects, long term compliance with statin therapy is still not optimal in clinical practice daily. Quite a significant percentage of patients either drop statins within a first year of intake, and in most cases, they report muscle-specific symptoms or perceived side effects as the main cause [9]. The evidence on the basis of observation shows that statin withdrawal or subpar adherence correlates with high risk of cardiovascular events and death, especially, in people under secondary prevention [10].

Statin-associated muscle syndrome is the major reported discontinuation cause. Nonetheless, controlled trials indicate that the actual rate of drugs-induced muscle toxicity is significantly lower than the actual cases resulting in routine practice, which is also because of expectation bias and the so-called nocebo effect [11]. False interpretation of nondiscriminate musculoskeletal symptoms to statin therapy tends to result in the untested and untrial discontinuation.

The clinical consequences of statin withdrawal are high. Discontinuation of treatment leads to re-increase of LDL levels, loss of accumulate-stabilizing action, and cardiovascular risk. Hence, distinguishing between actual statin intolerance and supposed intolerance is of paramount importance to guarantee continuity of therapeutic treatment, and to maximize cardiovascular events.

1.4 Need for Proper Evaluation

Stopping of statins in clinical practice can also be done without, though that should not be done, adequate evaluation; in most instances, this is done due to fear of adverse events and not due to intolerance. These decisions may inadvertently put high risk patients at risk of avoidable cardiovascular incidents. Thus, a close and well-organized evaluation is necessary prior to initiating treatment and when side effects are observed.

Premedical examinations (lipid profile, liver, and renal tests, blood glucose, thyroid tests etc.) should be recorded before the commencement. The use of secondary causes of dyslipidemia and attention to preexisting muscle complaints prevents the misdiagnosis of subsequent symptoms of statins [12].

Clinicians must take a methodical approach when adverse effects are reported especially muscle symptoms. Not every symptom is really a statin related symptom. Specific laboratory testing (e.g., creatine kinase in case of clinical necessity), test of drug interaction, and a transient withdrawal and reintroduction to a reduced dose or other statin will help rule out the possibility of true intolerance [13,14]. There has been evidence that most of the patients who were initially intolerant may tolerate statins on reassessment.

Significantly, beneficence, nonmaleficence, and autonomy in risk-benefit analysis can support guided decision-making. The adverse effects of statins are manageable in high cardiovascular risk and therefore its protective effects overrule such effects. Adherence and long-term treatment success will be enhanced through the appropriate counseling and information.

2. LITERATURE SEARCH METHODOLOGY

A thorough and structured literature review was conducted to collect the pertinent scientific information on statin intolerance, its mechanisms, risk factors, clinical presentation, and treatment methods. Several electronic databases, such as PubMed, Scopus, Web of Science, and Google Scholar were searched to locate the studies that were published as late as 2025.

The search strategy was created based on a combination of appropriate keywords with Medical Subject Headings (MeSH), including statin intolerance, statin-associated muscle symptoms, HMG-CoA reductase inhibitors, dyslipidemia, and cardiovascular disease. Search results were narrowed to include only literature related to the topic of interest using the Boolean operators (AND, OR).

To further screen studies that might have been missed in the initial search, the reference lists of the chosen articles and past published reviews were also manually checked to reach out to any other relevant research. As criteria inclusion was limited to studies that were published in English and had human subjects.

The approach to the selection of studies was done stepwise based on the framework of Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA). Following the elimination of duplication records, titles and abstracts were filtered to eliminate studies that did not fit within the scope of this review. Potentially eligible studies were then carefully screened by reading the full-text articles and excluding or including articles according to predetermined inclusion and exclusion criteria.

The studies were incorporated when they contained useful information regarding statin intolerance especially in regard to pathophysiology, clinical presentation, or treatment. The articles that were excluded included editorials, conference abstracts and studies that were not of enough clinical or scientific relevance to retain the quality and reliability of the review. The overall process of study identification, screening, eligibility assessment, and final inclusion is presented in the PRISMA flow diagram (Figure 1) [15].

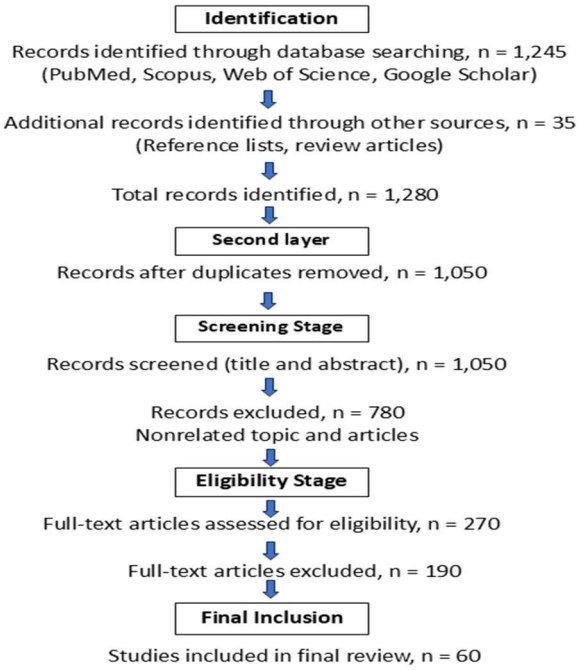

Figure 1: PRISMA flow diagram illustrating the systematic process of identification, screening, eligibility assessment, and inclusion of studies for this review on statin intolerance.

3. OVERVIEW OF STATINS

3.1 Classification: Lipophilic and Hydrophilic Statins

Statins, HMG-CoA reductase inhibitors are a structurally varied group of inhibitors which vary mainly in terms of their lipophilicity. They are categorized as lipophilic and hydrophilic agents based on the solubility properties [16].

Atorvastatin, lovastatin, fluvastatin, simvastatin and pitavastatin are statins which are lipophilic that passively diffuse through cell membranes and show greater tissue distribution. Conversely, hydrophilic statins like rosuvastatin and pravastatin rely mostly on active transport systems to be taken up in the hepatocyte making them more selective in the hepatic tissue [16]. physicochemical differences may affect the tolerability profiles and have an impact on systemic exposure.

Pharmacokinetic analysis reveals that lipophilicity influences tissue penetration, metabolism and their ability to interact [17]. Comparative clinical studies also suggest that despite the both classes being effective in reducing the LDL cholesterol levels, patient specific characteristics tend to dictate the agent to be used [18].

3.2 Commonly Used Statins

The most frequent statins in use.

Atorvastatin

Rosuvastatin

Simvastatin

Pravastatin

Fluvastatin

Pitavastatin

The choice is based on Low density lipid-lowering potency, lipophilicity, metabolic pathway, comorbidities and possible drug-drug interactions [16–18].

3.3 Pleiotropic Effects of Statins

Along with the lipid lowering effect, statins have numerous vascular effects. There is experimental and clinical evidence of enhanced endothelial performance, reduction of oxidative stress, regulation of inflammatory mechanisms and stabilization of atherosclerotic plaques [19]

Partially due to decreased isoprenoid production and the following inhibition of intracellular signaling proteins, i.e., Rho and Rac, these pleiotropic effects can be ascribed [19]. Although LDL lowering is the most common biological protection of the cardiovascular system, these other biological effects can potentially increase the overall therapeutic effect.

3.4 Mechanism of Action: HMG-CoA Reductase Inhibition

The main lipid-lowering activity of all statins is the competitive inhibition of HMG-CoA reductase, the ratelimiting enzyme in the hepatic cholesterol biosynthesis. Based on the effects of the human medication, blocking of the HMG-CoA reductase lowers transformation of HMG-CoA to mevalonate, which results in lower intracellular cholesterol levels in hepatocytes [20]. This decrease causes the sterol regulatory element-binding proteins (SREBPs) to be activated; this leads to the expression of LDL receptor being increased. When LDL receptors are increased in density, it promotes receptor mediated clearance of LDL particles that are in circulation in the plasma [21,22].
This may also be related to cholesterol lowering, but also the blocking of the mevalonate pathway lowers production of isoprenoid intermediates, needed to prenylate small GTP-binding proteins [23]. The mechanism plays roles in some of the non-lipid biological (pleiotropic) effects of statin, such as endothelial and vascular inflammation.

3.5 LDL Reduction and Cardiovascular Impact

The prevention of LDL cholesterol is the primary treatment goal of statin-based treatment. A massive metaanalysis of personal information obtained in 27 randomized trials revealed that every 1 mmol/L decrease in LDL cholesterol is linked to a considerable proportional reduce in major vascular events in even the people whose risk is comparatively low at their baseline [24, 25].

Clinical efficacy is directly proportional to extent of LDL lowering, which supports significance of LDL receptor up-regulation and hepatic clearance increases in the above-described mechanisms [26].

4. DEFINITION AND CLASSIFICATION OF STATIN INTOLERANCE

The inability due to Statin intolerance to tolerate statin therapy at dosages needed to produce apposite lipid lowering because of the occurrence of adverse effects, which are temporary (related to the start of drug therapy), reversible on discontinuation, and repeatable with rechallenge [27,28]. The modern medical opinion defines total and partial intolerance: in the former, no dosage of statin could be tolerated, in the latter, patients can tolerate lower doses or use different statins but cannot meet the target of LDL-C [29].

Statin-associated muscle symptoms a spectrum between mild myalgia and severe rhabdomyolysis is the most reported manifestation [30]. Professional societies such as the National Lipid Association (NLA) and the European Atherosclerosis Society (EAS), point out so to diagnose true statin intolerance, the systematic assessment must be conducted, and, preferably, one should be exposed to minimum two different statins, one among them should be at minimum approved dose [31].

This should be a critical difference between the actual pharmacologic intolerance and the relative perceived intolerance. Quite a number of the symptoms reported can be affected by expectancy effects, which is sometimes termed as the nocebo effect, where expectation of negative effects leads to the occurrence of symptoms regardless of the drug being toxic or

not [32,33]. This difference should be noted to avoid premature withdrawal of treatment and cardiovascular protection. The definition of intolerance gives the basis of studying the biological basis of the same.

5. PATHOPHYSIOLOGY OF STATIN INTOLERANCE

Statin intolerance is a multifactorial process whose mechanisms are not completely understood. It has been supported that the biochemical effects related to the muscles, genetic vulnerability, immune-mediated mechanisms, and pharmacokinetic interactions contribute to it.

5.1 Muscle-Related Mechanisms

Statins prevent the production of HMG-CoA reductase and thus cholesterol production along with intermediates of mevalonate pathway. A postulated model of muscle toxicity is the inhibition of coenzyme Q10 (ubiquinone) production, a vital part of the mitochondrial electron transport. Exhaustion can degrade oxidative phosphorylation and decrease generation of adenosine triphosphates, which predisposes myocytes to the effects of fatigue and damage.
It has been revealed that mitochondrial dysfunction has been implicated among susceptible people and indications have been made that the activity of respiratory sequence is impaired and that oxidative stress is usually elevated. Ca2+ homeostasis breakdown can also have a role since change of intracellular calcium levels can result in the release of proteolytic enzymes and facilitate myocyte damage [34].

In other settings, the apoptotic signalling pathways are triggered, and the cells undergo programmed cell death. Also, a decrease in prenylation of structural proteins and alteration of membrane stability can have an impact on myocyte integrity [35]. All these mechanisms together can offer a biologically plausible explanation of statin-associated muscle symptoms.

5.2 Genetic Susceptibility

A large part of the role of genetic variability in the pharmacokinetics and a toxicity risk of statin plays a role. SLCO1B1 gene is an encoding gene that encodes the hepatic transporter OATP1B1 and may reduce uptake of certain statins by the liver leading to greater levels of the drug in the blood and exposures to the muscle [35]. The same effect may also be produced by cytochrome P450 enzyme variations and particularly the variations in the statins metabolism on the levels of drugs in the body and predisposition to adverse effects [37,38].

These results outline the reality that patient response heterogeneity exists even though genetic screening is not a regular procedure.

5.3 Immune-Mediated Mechanisms

Another rare but severe form of intolerance is immune-mediated necrotizing myopathy which is related to antibodies against HMG-CoA reductase. In contrast to usual SAMS, the symptoms might last even after statin withdrawal and usually involve the need of immunosuppressive treatment [39,40]. This entity is important to take note of because it is an autoimmune process instead of dose-dependent toxicity.

5.4 Mechanisms of Metabolism and Drug-Interaction

Drug-drug interactions have significant influence on the statin tolerability. Some statins increase the risk of muscle toxicity because their plasma concentrations can increase as a result of a CYP3A4 inhibition. Similarly, in case hepatic transporters are impaired, the distribution and excretion of drugs might be distorted [41]. The pharmacokinetic interactions allow one to comprehend the reason why intolerance may be experienced whenever there is an introduction of interacting drugs.

These processes indicate that statin intolerance is not an independent entity but rather a spectrum of biological heterogeneous processes.

6. RISK FACTORS FOR STATIN INTOLERANCE

Statin intolerance is a condition developed under patient-related and drug-related circumstances and that could predispose a particular individual to the adverse effects. The identification of the factors is significant both to determine patients who might be in more danger and to give reasonable therapeutic choices.

A number of patient attributes have been linked with increased risk of intolerance. Age is often cited as a significant risk factor potentially as a result of age-associated alterations in the pharmacokinetics of drugs, the occurrence of various comorbidities, polypharmacy, and decreased muscle mass or reserve [42]. It has also been indicated that female sex and reduced body mass index increases the risk of statin-associated muscle symptoms which could be attributed to dissimilarities in body composition and drug allocation within the body [43]. Moreover, medical pathogenesis can also affect statin metabolism and clearance. Indicatively, renal or hepatic dysfunction can decrease statin clearance, leading to augmented blood exposure and an upsurge in events of adverse reactions. Some endocrine and metabolic diseases, hypothyroidism in particular, and nutritional deficiencies, including vitamin D deficiencies, can also predispose people to muscle-related symptomatic effects of statin therapy [44].

Statin intolerance is also due to drug regulations to a large extent. Adverse effects are more generally related to high-intensity statin regimens since they result in increased systemic exposure to drugs. Besides, lipophilic statins able to enter extrahepatic tissues more easily can contribute to the occurrence of musclerelated symptoms in vulnerable people. The risk may be further increased in the case of administering statins along with drugs with the effect of interfering with the metabolism or of blocking hepatic transport systems, causing an increase in the circulating drug levels. Along with these causes, the genetic variability can also provide the differences in the statin tolerance of individuals. Mutations in the SLCO1B1 gene, which transcodes hepatic transporter OATP1B1, have been implicated in diminished hepatic uptake of some statins as well as an increased propensity to statin-associated muscle toxicity [45].

On the whole, the close evaluation of these risk factors might assist clinicians to predict possible intolerance, introduce preventive measures, and maximize the lipid-lowering treatment and minimize its side effects.

7. CLINICAL MANIFESTATIONS

Statin intolerance is most often manifested by statin-associated muscle symptom, which are a spectrum of skeletal muscle events that may differ in the extent of occurrence in different individuals. The manifestations can also occur in the course of statin treatment and they are one of the most common adverse effects related to such drugs.

Myalgia, or muscle pain, soreness, or stiffness without a marked increase in serum creatine kinase (CK) is the most frequent manifestation. The proximal muscles involved which are normally the thighs, shoulders or the back, and may take weeks or months before the symptoms are realized. Despite the fact that myalgia is mild and reversible in most cases, it has the potential to influence patient compliance with treatment [46].

A severe variant is myopathy in which the symptoms of the muscles are observed along with high-level CK. The patient can develop muscle weakness or fatigue that can disrupt the activities of daily living. In some instances, myositis or inflammation of muscle tissue could also ensue and is usually accompanied with elevated muscle enzyme levels [47].

Rhabdomyolysis is a severe but uncommon complication and is specified by a great destruction of skeletal muscle fibres. It is a condition, which causes significantly high CK and myoglobin release into the circulation, which may cause acute kidney injury when not identified and treated in time [48].

There are rare cases where statins can be linked to immune-mediated necrotizing myopathy which is an autoimmune disease with progressive muscle weakness and significantly increased CK levels. This is an antibody-mediated disorder associated with antibodies against HMG-CoA reductase and may continue to persist despite the withdrawal of statin therapy, commonly necessitating immunosuppressive therapy [49,50].

Statin-associated muscle symptoms (SAMS) represent a spectrum of clinical presentations with varying severity, as summarized in Table 1 [46-50].

Table 1: Statin-Associated Muscle Symptoms (SAMS)

Figure 1: PRISMA assessment, and i **Condition**	**Clinical Features**	**Creatine Kinase (CK) Levels**	**Severity**	**Recommended Management**
Myalgia	Muscle spasms, soreness, tenderness, joint pain	Normal	Mild	Continue statin if tolerable; observe symptoms; consider

				dose reduction or switching statin
Myositis	Dysphagia, pain, muscle inflammation, and weakness	Elevated	Moderate–Severe	Assess underlying cause; stop statin use; rechallenge
Myopathy	Muscle weakness, stiffness	Elevated	Moderate	Dose reduction or discontinue temporarily; assess risk facto; consider switching statin
Immune-mediated necrotizing myopathy (IMNM)	Muscle atrophy, necrosis with minor inflammation; persists after statin withdrawal	Significantly elevated	Severe	Complete discontinuation; immunosuppressive therapy (e.g., corticosteroids)
Rhabdomyolysis	Muscle tenderness, weakness, dark urine; renal failure risk	Markedly elevated	Severe (Life-threatening)	Hospitalization; observe renal function; immediate discontinuation of statin

Other than effects associated with muscle, other patients can have non-muscular adverse reactions such as a mild gastrointestinal adverse reaction or liver enzyme elevations. These effects tend to be rare and tend to disappear upon change in dose or withdrawal of the drug [51-53].
In general, the clinical symptoms of statin intolerance are mild muscle symptoms to uncommon but potentially severe complications. It is significant to detect these signs early so that the cardiovascular advantages of statin treatment are preserved and the signs are properly evaluated and treated.

8. DIAGNOSTIC EVALUATION

The initial phase in examination of suspected statin intolerance is a clinical examination. There is the need to establish the time association between onset of symptoms and initiation of statins or the escalation of dose or drugs interaction [54]. The fact that the symptoms vanish upon withdrawal of the drug and reappear upon trial is of more causality [55,56].

Laboratory assessment of CK should be performed in symptomatic patients. The levels that are significantly high are indicative of the need to explore further and termination, whilst low or normal levels do not exclude SAMS [57,58]. The appropriate test in the given cases can be liver enzyme test.

Even a combination of dechallenge-rechallenge approach is still a systematized method of diagnosis. Discontinuation of statin regime and reinstatement with lower dose or an alternative statin periodically would aid in identifying the true intolerance compared to incidental symptoms [59]. Meanwhile, the clinicians are expected to exclude the secondary causes of muscle symptoms which includes thyroid dysfunction, inflammatory myopathies and interacting medications [60].

To this end, this methodological procedure helps to avoid premature marking of intolerance and in its place, to further reduce cardiovascular risk, where feasible.

9. MANAGEMENT OF STATIN INTOLERANCE

The management of statin intolerance should be patient-centered and systematic to ensure that the patient does not lose cardiovascular protection at the lowest possible cost. Statin therapy should as much as possible not be discontinued especially in individuals at high risk [61,62].

9.1 Dose Modification Strategies

Among the first methods is either lowering the dosage of statins or use of alternate-day dosing schedules. There is evidence to indicate that a low-dose statin therapy can effectively reduce LDL-C levels significantly and increase tolerability [63-65].

9.2 Statin Switching

A change of statin to a different one is a common tactic. Hydrophilic statins like pravastatin or rosuvastatin could be better tolerated in patients with lipophilic intolerance (e.g. simvastatin, atorvastatin) because of reduced muscle tissue penetration. This method has demonstrated a better compliance and symptom remission in a large percentage of patients [66-68].

9.3 Combination Therapy

In patients who are not tolerant to sufficient statin doses, combination therapy is an option. Non-statin agents can be added to meet LDL-C levels at a lower exposure of statin [69-71].

9.4 Non-Statin Lipid-Lowering Therapies

A number of substitute agents are currently available:

Ezetimibe: it inhibits cholesterol absorption in the intestine and it is commonly known as first-line add-on therapy [72].

PCSK9 inhibitors (e.g., evolocumab, alirocumab): Very effective in the reduction of LDL-C and the prevention of cardiovascular events [73].

Bempedoic acid: A new oral antihypertensive that inhibits ATP-citrate lyase and is especially effective in statin-intolerant patients [74].

Such therapies are particularly useful in patients who are fully statin intolerant.

9.5 Coenzyme Q10 Supplementation

The clinical evidence of supplementation is still inconclusive even though decreased levels of coenzyme Q10 have been attributed to statin-associated muscle symptoms. There are studies that indicate small benefit but there are also studies that indicate no significant improvement [75,76].

9.6 Nocebo Effect Management and Patient Education

Patient counseling is very important in enhancing adherence. By overcoming the misinformation surrounding the concept of statin safety and clarifying the nocebo effect, one can reduce the prevalence of symptom reporting by a significant margin and enhance the aspect of tolerance [77,78].

9.7 Rechallenge Strategy

To establish the real intolerance, a systematic dechallenge/rechallenge program is suggested. A great number of patients who are initially described as intolerant could be allowed to tolerate statins through reintroduction with altered dosage regimens [79,80].
Altogether, in order to maximize the long-term outcomes of statin-intolerant patients, the personalized approach that involves pharmacological modifications and patient education is necessary.

10. CONCLUSION

The lipid-lowering therapy has been characterized by statins and it has persistently demonstrated resounding impacts of cardiovascular morbidities and mortalities in their respective customers. They also play a major role in stabilisation of atherosclerotic plaque and decrease in vascular inflammation and this is why they are introduced into the centre of the primary and secondary prevention measures.
Nevertheless, despite the recent trend to discuss the issue of statin intolerance in clinical practice, a more detailed examination of the problem will be predetermined with the fact that the phenomenon of the fullfledged intolerance is not so common. Majority of them are influenced by the changing factors, comorbid, or interaction or expectations of drugs

or effects. The diagnosis system and assessment of time relationships, the special studies of the laboratory and the controlled discontinuations and rechallenge can contribute to manifesting the actual adverse reactions and avoid the unnecessary discontinuations.

It is important to note that the enormous proportion of patients who complain of the lack of tolerance can receive a modified dose in the future, switching to another statin or combination therapy. The furtherreaching none-statin intervention therapies warrant a substitute of lipid repair and heart prophylaxis, which have already been known to be unbearable by the already known intolerant patients.

The concentration on the individual attention, risk-to-benefit ratio, and proper communication with the patient, in its turn, is the widest component of the guarantee of the greatest part of the resulting outcomes. It will in turn empower the clinicians to reinforce the earlier achieved positive effects of the statin treatment besides responding to the safety issues in the timely and evidence-based manner.

11. FUTURE PERSPECTIVES

There are emerging findings that indicate pharmacogenomic profiling could be significant in the prediction of statin intolerance and personalized therapy. The development of lipid-lowering agents, such as RNA-based therapies and new enzyme inhibitors, provides the possible alternatives to patients who have intolerability [81,82].
More studies are required to comprehend better the molecular pathways of statin-associated muscle symptoms and establish some standardized diagnostic criteria. Also, the methods of suppressing the nocebo effect and enhancing patient compliance are an important field of research.

12. LIMITATIONS

There are some limitations of this review. Being a narrative review, it lacks a completely systematic approach to the methodology, which can create a selection bias. Even though an attempt was made to incorporate recent and relevant literature, some of the studies might have been overlooked. Also, differences in study designs and definitions of statin intolerance used in the literature can have an impact on the external validity of the results.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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ABBREVIATIONS

CVD – Cardiovascular disease; LDL-C – Low-density lipoprotein cholesterol; HMG-CoA – 3-hydroxy-3methylglutaryl coenzyme A; SAMS – Statin-associated muscle symptoms; CK – Creatine kinase; NLA – National Lipid Association; EAS – European Atherosclerosis Society; BMI – Body mass index; CYP – Cytochrome P450; OATP1B1 – Organic anion transporting polypeptide 1B1; SLCO1B1 – Solute carrier organic anion transporter family member 1B1; SREBPs – Sterol regulatory element-binding proteins; ATP – Adenosine triphosphate; CoQ10 – Coenzyme Q10.