*Review Article*

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# Statin Intolerance: Update

**Balaraju D[1], Vikram S Patil[2], Satvic CM[3]**

**Authors Affiliation:** [1,2]Assistant Professor [3]Associate Professor, Dept. of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Jayanagar, Bengaluru, Karnataka 560069, India.

**Abstract**

Statins are frequently prescribed drugs in cardiology practice. One of the most important causes of nonadherence is mainly because of muscle-related symptoms. The main adverse reactions due to statins include myalgia, myopathy, and new onset diabetes mellitus. Lipophylic statins are more prone to produce myopathy compared to hydrophilic ones. Statins increase the incidence of new onset DM in patients already having risk factors for DM. Therefore statins to be continued rather than discontinuing, if patients are diagnosed with new onset diabetes mellitus. The benefits of statin therapy outweigh the risk. Statin intolerance can be effectively managed either by reducing the dosage, switching to other statin or alternate day statin regimen with rosuvastatin. Non-statin therapies like PCSK-9 inhibitors evolocumab and alirocumab are also optional in high-risk patients who are intolerant to statins or in whom statins are contraindicated. Inclisiran is a promising drug, however long-term safety data is needed. Nutraceuticals have cholesterol lowering activity however there is insufficient evidence with respect to long-term safety and effectivenes.

**Keywords:** Statin; Side effects; Myopathy; New onset diabetes; Switch therapy; Pcsk 9 inhibitors; Nutraceuticals.

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## Introduction

HMG-COA reductase inhibitors—Statins are frequently prescribed drugs in cardiology practice for both primary and secondary prevention. Statins have proven to have mortality benefits in high-risk patients. They are tolerated well, however muscle related symptoms are one of the cause for nonadherence.[1] This poses a greater challenge to treating physician to decide whether the same drug to be continued or choose other alternative lipid lowering drugs, and this being one of the obstacles in effective management of cardiovascular disease patients.

Statin intolerance is defined as "a clinical syndrome, not caused by drug interactions or risk factors for untreated intolerance and characterized by significant symptoms and/or biomarker abnormalities that prevent the long-term use and adherence to statins documented by challenge/dechallenge/rechallenge, where appropriate, using at least two statins, including atorvastatin and rosuvastatin, and that leads to failure of maintenance of therapeutic goals, as defined by guidelines"[2]

**Corresponding Author: Vikram S Patil,** Assistant Professor, Dept. of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Jayanagar, Bengaluru, Karnataka 560069, India.

**E-mail:** balarajud2000@gmail.com

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Symptoms which are attributed to statin use are significant and seen in 10% or more. Myositis and liver enzyme elevations, which are considered as serious side effects, are seen in another 1–2% of patients.[3,4] In large randomized clinical trials the incidence of statin induced myopathy is 1.5–5%. Compared to real-world data incidence is low because in most trials patients prone for statin intolerance and had history of statin intolerance were not incuded in the trials.[5]

### *Types of statin intolerance*

*Partial*

It is an inability to tolerate a suitable dose of a statin based on patient's CV risk. A patient may not tolerate atorvastatin 40–80 mg or rosuvastatin at 20–40 mg dose which is advised dose in cases of acute coronary syndromes. It's usually seen with increased dose and usually seen within 3–6 months.

*Complete*

Intolerance is when clinically apparent variety of side effects impairing organ function and/or quality of life after intake of any statin at any dose with or without associated laboratory findings.[6]

### *Statin associated side effects [SASE]*

The main adverse reactions due to statins include myopathy, myalgia, myotoxicity, and new onset diabetes mellitus (NOD)[7,8]

*Myopathy:* It includes myalgia, myositis and most severe form — rhabdomyolysis, all three are considered as spectrum of myopathy. In the context of statin use, myopathy is described as myalgia or symptoms which are related to muscles with elevated serum creatine kinase >10 times the UNL.[9]

Statin associated muscle symptoms (SAMS) are classified by the NLA Task Force on Statin Safety into 4 groups.[10]

1. Myalgia: It's only a muscle pain associated with aches or heaviness and have normal creatinine kinase (CK) level. In clinical practice statin-associated muscle complaints varies from 0.3% to 33%[9]. Predominantly proximal muscles are involved. Usually seen in first 6 months of initiating therapy, however late onset of symptoms are not rare. After stopping statins the myalgia symptoms improves within 2 months.[11]
2. Myopathy: Symptoms includes weakness, cramps along with normal or elevated creatinine kinase (CK).[8]
3. Myositis: Its inflammation of muscle associated with muscle tenderness and elevated CK.
4. Myonecrosis (including rhabdomyolysis)[10]: It's rare side effect. It's associated with muscle necrosis and elevated serum CK. The most severe form of myonecrosis is rhabdomyolysis characterized by massive release of serum CK and myoglobin and associated with severe complications like myoglobinuria and acute kidney injury.[8]

The STOMP[12] study included 420 healthy adults randomized into high dose atorvastatin of 80 mg versus placebo and compared muscle symptoms, creatinine kinase, muscle strength, exercise capacity before and after the drug. The study showed, subjects are treated with atorvastatin developed muscle related symptoms with elevated average creatinine kinase compared to placebo. Suggesting that high-dose statins might produce mild muscle injury.[7] The PRIMO survey showed among patients receiving statins, 10.5% have reported muscle symptoms and it varied from statin to statin. Simvastatin had higher rate which is lipophilic compared to fluvastatin which is hydrophilic.[13]

*Diabetes Mellitus:* There has also been research and debate whether statins increase the incidence of diabetes mellitus.

Women's Health Initiative (WHI) study included 153,840 nondiabetic women, 7.04% of the study population was on statin medication at the baseline. Over 1,004,466 person-years of follow-up, 10,242 self-reported cases of diabetes mellitus. The effect was observed across different statins, after adjusting the confounding factors and might be related to a class effect.[14]

The JUPITER trial showed rosuvastatin associated 28% increase in developing DM in patients with 1 or more risk factors. The absolute number of new cases of DM was very small, overall 270 in patients taking rosuvastatin vs 216 taking placebo; hazard ratio, 1.25; 95% CI, 1.05–1.49; P > 0.01.[15]. The prediabetic status, number of metabolic components plays a major role in developing newonset diabetes mellitus along with intensity and duration of statin therapy. The risk of developing new onset diabetes mellitus (NOD) increases with increase in the number of metabolic syndrome components.[16] Therefore, there is evidence to support an association between statin use and an increased incidence of diabetes mellitus. The benefits of statin therapy outweigh the risk of new onset diabetes (NOD) in most patients. If patients develop NOD while on statin therapy, statins should

not be stopped rather statin should be continued along with lifestyle modification. To prevent NOD, treating physicians should emphasize more on weight reduction, regular exercise and reduce caloric intake, avoiding trans fat. Other reported adverse effects are asymptomatic liver transaminase elevation 3x ULN and rarely acute liver failure.

### *Diagnosis*

Statin intolerance is diagnosed when a patient develops symptoms on statin therapy, and resolution or improvement in symptoms when the offending statin is discontinued, and recurrence of symptoms when same or different statins is restarted.

### *Management*

#### *Initial Evaluation*

All attempts should be made not to allow discontinuation of statin in case of side effects. Detailed history of symptoms and complete clinical examination along with assessment of temporal relation with statin use should be a norm. Obtaining a routine CK level is a must, to rule out dangerous complications like rhabdomyolysis.

Patients should be evaluated for predisposing risk factors: history of prior muscle pains, family history of myopathy, renal disease, hypothyroidism, vitamin D deficiency, excessive grapefruit juice consumption, drug-drug interactions like drugs inhibiting CYP3A4 or CYP2C9 (such as amiodarone) should be ruled out. While initiating statins patients should be counseled positively, informing them statins are well tolerated with least side effects. Nocebo effect also plays a role in patient counseling.

***Biomarkers:*** New biomarkers for statin-induced myopathy are emerging. Commonly-used serum marker is the serum CK level,[17] but as a diagnostic marker, it is inadequate and nonspecific. Lactate dehydrogenase may predict and diagnose statin intolerance and myopathy. But validations are required.[18] Some of the newer biomarkers are promising. However they need further research and validation. These include fatty acid-binding protein 3 (FABP3), myosin light chain 1 (MLC1), skeletal muscle troponin I (sTnI), myosin light chain 3.[19,20]

The following strategies can be followed for management of statin intolerance

1. Reduce the dose
2. Switching therapy
3. Alternate day dosing
4. Non-statin lipid-lowering drugs
5. Lipid-lowering nutraceuticals

***Reduce the Dose***: If patient is having incomplete intolerance especially on high dose atorvastatin or rosuvastatin, reducing the 50% dose may lead to improvement of muscle-related symptoms.

***Switching Therapy:*** This strategy is effective in only some group of patients and the criteria are clearly delineated.[21,22] Switching from i) Lipophylic statins to hydrophilic statins ii) switching to a lower dosage of a more potent statin. In one of the open label studies, rosuvastatin in statin intolerant patients, LDL reduced by 42% and 39% with dose of 5 mg and 10 mg respectively after 36 weeks.[23] Pitavastatin is lipophilic statin may be another alternative in patients with statin intolerance due to pharmacokinetic profile. However there is no clinical evidence that it will be tolerated in patients who are already diagnosed to have statin intolerance.[24]

***Alternate Day Dosing***: Statins with longer half-life can be used for alternate day dosing strategy. Rosuvastatin has a long half life of 19 hours. Alternate day dose of rosuvastatin used in patients who were intolerant to daily dose of statin. 72.5% patients tolerated the alternate day dosing, with statistically significant 34.5% reduction in LDL-c. The average dose of rosuvastatin was 5.6 ± 2.9 mg, LDL-c target was met in 50% of study population[25]. Once a week rosuvastatin, with a dose range of 2.5 – 20 mg, Over an average of 4 months, LDL-c was lowered by 23%. This strategy showed statistically significant decrease in total cholesterol and triglycerides, and an increase in HDL-c by 27%.[26] Based on the above studies intermittent rosuvastatin can be used in patients who cannot tolerate daily statin therapy.

### *Non-statin lipid-lowering drugs*

#### *PCSK9 Inhibitors*

These are major breakthrough in cholesterol management especially patients who are statin intolerant or high-risk patients in whom LDL-c is not adequately managed.[27–29] Another approach to PCSK9 inhibition is Inclisiran, it is designed to target PCSK mRNA. It is a chemically synthesized small interfering RNA. In ORION-1 trial inclisiran lowered PCSK9 and LDL-c levels among patients at high CV risk who had elevated LDL-C levels. Two doses of inclisiran 300 mg showed the greatest reduction in LDL-c levels at day 180.

In statin intolerant patients it may be an important therapeutic option, and only few serious adverse events were found in the trial. The drug can be administered every 6 months.[30]

### *Bempedoic Acid*

It's an inhibitor of ATP citrate lyase, reduces levels of low-density lipoprotein (LDL) cholesterol. The Clear harmony trial included patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. The trial showed along with maximally tolerated statin therapy and bempedoic acid there were no higher incidence of overall adverse events than placebo and associated with significantly lower LDL cholesterol levels.[31]

Among nonstatin therapies Ezetimibe is the most frequently used. It lowers LDL-c levels by 13% to 20%. Bile acid sequestrants reduce LDL-c levels by 15% to 30% depending on the dose. They are associated with gastrointestinal complaints (e.g., constipation) and can cause severe hypertriglyceridemia.[32] Side effects and lack of clinical outcome data are the big hindrances to the use of these drugs alone or in combination.

### *Lipid lowering nutraceuticals*

These foods have high viscous fibers and low saturated fats. Examples, oats, barley, soy, and almonds are being used to reduce cholesterol in patients who cannot tolerate statins. These supplements were used as an alternative option due to poor palatability.[33]

*Red yeast rice*: Red yeast rice (RYR) is a dietary supplement. It is produced by fermenting the yeast, Monascus purpureus, over rice. The fermentation process yields monacolins, which have the ability to inhibit HMG-CoA reductase enzyme.[34] Recent trial demonstrated equal efficacy of LDL lowering when comparing RYR to 20 mg of pravastatin daily.[35] There is no standardization in RYR formulations and these products may have significant amounts of monacolin K and toxins like citrinin, which is known to cause nephro toxicity. Until standardization of red yeast rice is implemented, providers and patients should remain cautious when using these products.[36]

*Spirulina*: Spirulina is a filamentous, water blue-green microalga (*Cyanobacterium*). One metanalysis of 7 RCTs showed a significant effect from supplementation with spirulina, with reduced total cholesterol, LDL, triglycerides, and elevated HDL-c levels. The reduction in cholesterol levels was independent of administered dose. Active components responsible for the these hypolidemic effects are not fully understood.[37]

*Curcumin*: A natural dietary polyphenol. It gives yellow color to the Indian spice turmeric (*Curcuma* longa L.), it prevents and reduces muscular fatigue, blocks the inflammatory pathway of the nuclear factor, attenuates muscular atrophy, and improves regeneration of muscle fibers after injuries. Because of its lipid modifying properties, it can be used as an additive to therapy.[38]

## Conclusion

Statins are the most frequently prescribed drugs. This effect of statin is multifactorial and dose related. Myopathy is unrelated to cholesterol reduction. Lipophylic statins are more prone to produce myopathy than to hydrophilic ones which are least prone. Statins increase the incidence of new onset DM in patients who are already having risk factors for DM, but the benefits of statin therapy outweigh the risk. Statins should not be stopped when patients on statins are diagnosed with DM. Instead, statins to be continued along with lifestyle modification. Statin intolerance can be effectively managed either by reducing the dose or switching over statin or alternate day statin regimen with rosuvastatin. Non-statin therapies like Evolocumab and alirocumab can be used in high-risk patients who are intolerant to statins. Inclisiran is a promising drug, however long-term safety data is needed. Nutraceuticals have lipid lowering effects however, there is insufficient evidence with respect to long-term safety and effectiveness.

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