

Management of Statin Intolerance

What is statin intolerance?¹⁻³

- Most often documented as intolerable muscle-associated side effects
- Resolves with discontinuation of therapy and reoccurs with rechallenge
- Intolerant to at least 2 to 3 statins

Decision support tool:

[https://tools.acc.org/
StatinIntolerance](https://tools.acc.org/StatinIntolerance)



Discontinuing statins increases the risk of death and cardiovascular (CV) events. True statin intolerance is uncommon, and thus, evaluation of previous statin use and a retreat should be strongly considered to reduce CV risk (except for patients with life-threatening adverse events, e.g., rhabdomyolysis).^{4,5}

Statin intolerance management pathway

1 Rule out other causes

- Assess for **symmetric, proximal, large muscle group pain/weakness** beginning 2 to 4 weeks after statin initiation and resolving 2 to 4 weeks after discontinuation.
- Obtain thyroid function tests (TFTs) and vitamin D level**; treat if needed.⁶
- Evaluate for drug-drug interactions** (e.g., fibrates, niacin, cyclosporine, protease inhibitors, colchicine, red yeast rice, amiodarone, calcium channel blockers, azole antifungals, macrolides).

2 Evaluate for resolution of muscle symptoms with drug holiday

- Discontinue for 2 to 6 weeks.**⁷ For patients with ASCVD, start ezetimibe while finding an alternative statin.
- Consider obtaining CK** within 48 hours of last dose; intervene if 5 to 10 times above patient's baseline.
- If muscle symptoms resolve**, trial another statin or retreat with a lower dose of the same statin.
If muscle symptoms do not resolve, consider other causes and resume statin at original dose.

3 Rechallenge with 2 to 3 statins

- Hydrophilic statins** (e.g., rosuvastatin, pravastatin) may penetrate the muscle less than lipophilic statins.
- Trial a statin with a **different metabolic pathway**, at the lowest approved dose.
- Try dosing 3x to 1x weekly** instead of daily (use a long half-life statin: atorvastatin or rosuvastatin).^{8,9}

4 Consider non-statin therapies

- Consider non-statin therapy** (e.g., ezetimibe, PCSK9i,* bempedoic acid*) in patients with high ASCVD risk unable to tolerate at least 2 to 3 different statins.

Non-statin therapies have not been shown to decrease mortality and are not suggested unless statin intolerance has been systematically and rigorously evaluated and documented.

Statin selection: Characteristics and dosing chart¹⁰

Agent	Lipophilicity	Major metabolic pathway	Lowest daily dose*	Target dose	Renal dosing
Atorvastatin	Lipophilic	CYP3A4	10 mg	Moderate: 10-20 mg High: 40-80 mg	None required
Fluvastatin (N/F)	Lipophilic	CYP2C9	20 mg	Moderate: 40 mg BID	None required
Lovastatin	Lipophilic	CYP3A4	10 mg	Moderate: 40 mg	CrCl < 30 mL/min: use caution with > 20 mg/day
Pitavastatin (N/F)	Lipophilic	Minimal CYP450	1 mg	Moderate: 1-4 mg	eGFR 15-59 mL/min (non-HD) or ESRD w/HD: 1 mg/day; max 2 mg/day
Pravastatin	Hydrophilic	Hydroxylation, oxidation, and conjugation	10 mg	Moderate: 40-80 mg	Severe renal impairment: 10 mg/day
Rosuvastatin	Hydrophilic	Biliary excretion CYP2C9, CYP2C19	5 mg	Moderate: 5-10 mg High: 20-40 mg	CrCl < 30 mL/min: 5-10 mg/day
Simvastatin	Lipophilic	CYP3A4	5 mg	Moderate: 20-40 mg	Severe renal impairment: 5 mg/day

*Lowest approved daily dose

Statin rechallenge: Leaping into the conversation

L

Listen

- *"Tell me about your symptoms and what they feel like."*

E

Empathize

- *"It can be very frustrating to experience side effects with a new medicine."*
- *"Statins can prevent heart attack and stroke, and are important to take if you can. Let's try to help with the side effects."*

A

Assess

- *"Other things can mimic statin side effects. Has anything changed since you started your statin?"*
- *"How do you feel about temporarily stopping the medicine and drawing some labs to see if there is something else causing these side effects?"*

P

Prevent and Plan

- *"The benefits of statins are too great to give up. If you're ok with it, we can work to find a statin and dose without side effects."*
- *"There are several options. We could try a lower dose of this medicine, switch to a different statin, or try doses only three times per week. Which of these sounds best?"*

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