Updated by Jessica Visentin PharmD
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STATIN INTOLERANCE - MANAGEMENT CONSIDERATIONS

BOTTOM LINE: Practical Recommendations

- **Statins have the best evidence for patient-important outcomes** (↓ MACE & mortality in 1° and 2° prevention)
- **Individuals with statin-related myalgias should be re-challenged, as 80-90% will be able to tolerate a re-challenge**.[51-5]
- In individuals with statin-related AEs, the amount of effort spent in persevering with statin therapy should be related to their level of CV risk.[1] Those at **higher CV risk** stand to benefit more. For statin-intolerant individuals at **low CV risk**, a re-evaluation of need for therapy should precede trial of alternate therapy.[1]
- Having a high risk patient on a statin, irrespective of dose or LDL levels achieved, has shown to decrease CV events (multiple trials[4S, CARDS,HPS 2,3,4,5,6,7,8,9]). Allowing unmet LDL targets to drive therapy toward supratherapeutic unstudied doses &/or combination therapies lacks evidence (unknown net benefit vs harms). *Let the target serve the patient, not the patient the target!*
- CK levels do *not* routinely need to be monitored at baseline or in asymptomatic patients at follow-up. Testing may be appropriate based on symptoms or other risk factors.[40]

MANAGEMENT OF PATIENTS WITH MYOPATHIES

- Muscle symptoms are the most common AE leading to statin discontinuation.
- The incidence of myopathy varies greatly across studies (1-60%) due to differences in study design and patient populations. However, **most muscle symptoms reported in individuals taking a statin are not truly statin-induced, as evidenced by placebo-controlled RCTs that show <1% difference in reported muscle symptoms between statin and placebo groups**.[50]
- **Over-diagnosis of myopathy occurs frequently** & can lead to incorrectly labelling a patient as statin intolerant, therefore, diagnosis should be reserved for patients reporting symptoms which resolve when the statin is stopped.
- Given the comparative CV/mortality benefits of statins vs non-statins, clinicians should re-challenge statin intolerant patients & attempt methods described below before abandoning therapy.
- **80-90% of individuals with statin intolerance are able to tolerate a re-challenge.** [51-53]
- Evidence does not support the use of any one rechallenging strategy over another; patients can be rechallenged with the same or a different statin, at the same or a lower dose. An alternate dosing regimen (e.g. q2days, 1x/week) may also be considered.

MYALGIA
(reported in ~15% of patients; true intolerance in ~1% of patients)

⇨ **Muscle discomfort** (pain, cramping, weakness, soreness, stiffness) that may mimic flu-like symptoms & usually involves bilateral, large muscle groups (CK ≤ ULN) [30-34]

STEP 1: Assess myopathy risk factors (see table below) → *may check CK if concerned re: symptom severity*

STEP 2: Assess & re-emphasize lifestyle measures; re-assess CV risk & statin indication

STEP 3: May stop or continue statin depending on pain severity. If statin stopped, wait 2-4 weeks or until pain resolves before re-initiating [31,32,34]

STEP 4: Consider therapeutic options for management below (not necessarily in order of preference)

A: Consider re-trying the **same statin at the same or a lower dose**.

B: Consider **switching to another statin**.
- Evidence does not suggest any one statin has a lower risk of myalgia; however, some experts agree pravastatin may anecdotally be better tolerated.
- In patients with a history of statin intolerance, ~98% of patients tolerated a switch to rosuvastatin 5-10mg daily and ~96% tolerated a switch to fluvastatin XL 80mg daily. [31,32]

C: If daily dosing is not tolerated, consider **alternate dosing regimens** (allows for at least some statin as opposed to none)
- rosuvastatin 10mg *q2days* was well tolerated by ~75% [31,32]
- atorvastatin 10mg *2x/wk* was well tolerated by ~95% [34]

D: Consider **adding Co-Q10** (200mg/day) to current statin.
- Evidence is limited, however, considered relatively safe[38]. Opinion varies as to the role for Co-Q10.

E: If none of the above are effective, may consider non-statin alternative, however, evidence is lacking [31,32,35]

MYOSITIS (0.1%)

⇨ Myositis involves the same symptoms of myalgia with the **addition of an elevated CK** (>2-4x ULN) in the absence of ↑ SCr & myoglobinuria [31,22,33,34]

STEP 1: Assess & re-emphasize lifestyle measures in lowering CV risk; reassess statin indication

STEP 2: Stop statin until CK ≤ ULN & patient is asymptomatic [31,32,35]

STEP 3: Reassess risk vs benefit & assess for myopathy risk factors (see table below)

STEP 4: Consider options for management as per myalgia

RHABDOMYOLYSIS (0.01%)

⇨ Rhabdomyolysis refers to muscle symptoms consistent with myalgia/ myositis & **significant CK elevation** (>10x ULN) **with potential secondary consequences** (hyperkalemia, hypocalcemia, arrhythmia, AKI) [31,22,33,34]

STEP 1: Stop statin until CK ≤ ULN & patient is asymptomatic [31,32,35]

STEP 2: Reassess risk vs benefit & patients risk factors [33]

STEP 3: If the episode is mild, may consider re-challenge with a low dose of a different statin [31,35]

STEP 4: If episode was moderate-severe, consider specialist referral [31]

MYOPATHY RISK FACTORS

Endogenous Risk Factors	Exogenous Risk Factors
-Age >80 years	-High statin dose
-Female	-Heavy alcohol use
-Asian ethnicity	-Illegal drug use
-Low body mass index	-Antipsychotic use
-History of pre-existing muscle/joint pain	-Surgery with severe metabolic demands
-History of CK elevation	-Heavy &/or unaccustomed exercise (commonly reported symptom trigger)
-Diabetes Mellitus	-DI: amiodarone, azole antifungals, cyclosporine, fibrates, macrolide antibiotics, nicotinic acid, protease inhibitors, tacrolimus, verapamil, warfarin. Grapefruit in large quantities.
-Family history of myopathy with or without statin treatment	
-Metabolic muscle disease	
-Severe renal disease (eGFR ≤ 30 mL/min)	
-Acute/decompensated hepatic disease	
-Hypothyroidism	
-Genetic polymorphisms of CYP enzyme	

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PATIENT-IMPORTANT CLINICAL QUESTIONS:

1. Is the statin indicated in terms of the patient's cardiovascular (CV) risk?

Secondary Prevention

- **Statins lower risk of CV events (NNT=30/5yrs [4S 2,3]) & all-cause mortality (NNT=12/5yrs [4S 2,3]) in patients with history of CV events** [4S, LIPID, HPS 2,3,5,6,7,8,9,10,11]
  - Well designed 5-6 yr RCT data with > 10 yr follow up data
- **High dose statins (e.g. atorvastatin 80mg daily) have evidence of lowering risk of CV events more than low dose (atorvastatin 10mg daily) in select very high-risk patients**
  - Modest benefit post-ACS [TNT, PROVE-IT 12,13]

Comparative Statin Intensity			
	Low	**Moderate**	**High**
Rosuvastatin	2.5 mg	5-10 mg	20-40 mg
Atorvastatin	5 mg	10-20 mg	40-80 mg
Simvastatin	5-10 mg	20-40 mg	-
Pravastatin	10-20 mg	40-80 mg	-

Primary Prevention [CARDS, ASCOT, HPS-subset, JUPITER 5,6,7,8,9,14,15,16,17]

Statins lower risk of CV events in mod-high risk patients without a prior CV event (NNT=32/4yrs [CARDS 15]; NNT= 120/2yrs [JUPITER 18])

- Absolute benefits are modest relative to secondary prevention
- Relative benefit vs harm of high dose statins not studied

- **Assess overall CV risk, not merely LDL levels. Those with lower CV risk have less absolute benefit from a statin which should be weighed against the uncertainties regarding potential benefits versus harms over longer durations**
  - ⇨ Statins may be stopped in patients with statin intolerance who are otherwise at low CV risk
  - ⇨ Although absolute risk of harms (muscle [19], onset of diabetes **NNH=255/4yrs**, ↑ in elderly [20], renal injury [21]) is small, it should not be dismissed in those less likely to benefit where many would be exposed to long term therapy (potentially decades)

2. Why should efforts be made to maintain or re-trial a statin when other lipid lowering drugs are available?

For strategies to overcome statin intolerance, see page 2.

- **Statin therapy is preferred over alternate lipid lowering drugs due to lack of or limited patient-important outcomes for non-statin drugs relative to statins.**

Medication	Primary Prevention	Secondary Prevention
Ezetimibe EZETROL	• **Monotherapy:** some evidence of CV benefit (NNT=38/4 years); however, significant methodological issues limit validity of trial results; no mortality benefit seen [EWTOPIA-75 42] • **Combination with a statin:** lacking evidence of CV/mortality benefit [SEAS 23, ENHANCE 24, 41]	• **Monotherapy:** no evidence • **Combination with a statin:** modest evidence of CV benefit in post-ACS patients (~7% RRR; NNT=50/7 yrs); no mortality benefit seen [IMPROVE-IT 22, 41]
PCSK9i REPATHA PRALUENT	• Data is limited to familial hypercholesterolemia population; no CV outcome data available	• **Monotherapy:** no evidence • **Combination with a statin:** evidence of CV benefit (RRR ~15%; NNT=67/2.2 yrs); no all-cause mortality benefit seen [ODYSSEY OUTOME 43, FOURIER 44]
Fibrates	• Primary & secondary prevention: • **Monotherapy:** evidence mixed for CV benefit; lacking evidence of mortality benefit [26,27,28, 45, 46] • **Combination with a statin:** not more effective than statin monotherapy [ACCORD-Lipid 29, FIELD 47, PROMINENT 48]	
Icosapent ethyl VASCEPA	• Primary & secondary prevention: • **Monotherapy:** no evidence • **Combination with a statin:** evidence of CV benefit in select individuals (RRR ~22%; NNT=21/4.9 yrs); no all-cause mortality benefit seen [REDUCE-IT 49]	

3. In patients who cannot tolerate higher statin doses, what evidence is there for adding a second drug to reduce CV risk?

- **There is no evidence in the primary prevention population.**
- **In secondary prevention, there is limited evidence that adding a second drug may offer benefit:**
  - Moderate-intensity statin + ezetimibe may improve tolerability/adherence vs high-intensity statin monotherapy with similar CV outcomes [RACING 50, 51]
  - Certain combination drug regimens (statin + PCSK9i, statin [ODYSSEY OUTOME 43, FOURIER 44] + icosapent ethyl [REDUCE-IT 49]) may reduce CV risk in select populations (see table above)
  - Other combination drug regimens (statin + niacin [AIM-HIGH 30], statin + fibrate [ACCORD-Lipid 29, FIELD 47, PROMINENT 48]) have failed to show a benefit over statin monotherapy

ACS=acute coronary syndrome **AE**=adverse event **CCS**=Canadian Cardiovascular Society **CK**=creatinine kinase **CKD**=chronic kidney disease **CO-Q10**=coenzyme-Q10 **CV**=cardiovascular **CYP**=cytochrome P450 enzyme **DI**=drug interaction **DIC**=disseminated intravascular coagulation **eGFR**=estimated glomerular filtration rate **IU**=international unit **LDL**=low density lipoprotein **MI**=myocardial infarction **mg**=milligrams **NNT**=number needed to treat **NS**=not significant **RCT**=randomized control trial **SCr**=serum creatinine **ULN**=upper limit of normal **XL**=extended release **yr**=year

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