STATIN INTOLERANCE - MANAGEMENT CONSIDERATIONS

**BOTTOM LINE: PRACTICAL RECOMMENDATIONS**

- Statins are the lipid lowering drugs with the best evidence for outcome benefit! (Non-fatal MI, CV death & stroke & mortality)
- The amount of effort spent in persevering with statin therapy in patients with significant adverse effects should be related to their level of cardiovascular (CV) risk. Those at higher CV risk stand to benefit more!
- For subjects at low risk of CV events who are intolerant to statin therapy, a re-evaluation of need for therapy should precede trial of an alternative therapy.
- CK levels should be monitored at baseline and in those patients who develop myalgia while on a statin.
- Having a high risk patient on a statin, irrespective of LDL levels achieved, has shown a reduction in CV events (multiple trials).
- Allowing unmet LDL targets to drive therapy toward supratherapeutic unstudied doses &/or combination therapies lacks evidence (unknown benefits vs harms). Let the target serve the patient, not the patient the target!

**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 (MI, CV death & stroke) & all-cause mortality in patients with previous history of CV events (e.g. 4S, LIPID, HPS)**
     - well designed 5-6 yr RCT data with >10yr 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
   - Mortality: NNT/~Sr = 30
   - CV events: NNT/~Sr = 12

   **Primary Prevention**
   - **Statins lower risk of CV events in mod-high risk patients without a prior CV event**
     - absolute benefits are modest relative to secondary prevention
     - relative benefit vs harm of high dose statins not studied
   - Those with lower CV risk have less absolute benefit from a statin which must 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 onset of diabetes in elderly renal injury) is small, it should not be dismissed in those less likely to benefit where many would be exposed to long term therapy
     - statins have not been well studied in very elderly patients (>age 82); consider potential for AEs, patient values, etc.

2. **WHY SHOULD EFFORTS BE MADE TO MAINTAIN OR RETRIAL A STATIN WHEN OTHER LIPID LOWERING DRUGS ARE AVAILABLE?**

   [FOR STRATEGIES TO OVERCOME STATIN INTOLERANCE, SEE PAGE 2.]

   **Statin therapy is usually preferred over alternate lipid lowering drugs due to:**
   - lack of, or limited clinical outcome evidence for non-statin drugs relative to statins

   **Ezetimibe EZETROL**
   - no evidence for lowering CV/mortality risk as monotherapy in acute coronary syndrome patients awaiting IMPROVE-IT
   - lacks evidence for lowering CV/mortality risk in combination with a statin compared to a placebo in mild-to-moderate, asymptomatic aortic stenosis patients
   - very limited evidence & surrogate outcome evidence, e.g. intima-media thickness, has been disappointing
   - only when combined with a proven therapy (e.g. simvastatin) in chronic kidney disease & dialysis patients (stage 3-4 CKD patients) was a benefit seen; benefit could have been due to the statin alone

   **Fibrates**
   - monotherapy: evidence mixed or lacking for CV/mortality benefit for fibrates in contrast to statins
   - combination: fenofibrate + simvastatin not more effective than simvastatin monotherapy

3. **WHAT EVIDENCE IS THERE FOR ADDING A 2ND DRUG TO ACHIEVE AN LDL TARGET?**

   There is no evidence that adding a 2nd drug to achieve an LDL target results in more benefit than harm
   - Patients should be informed of the uncertainties surrounding such strategies.
   - Combination drug regimens failed to show a benefit over statin monotherapy in two recent trials
     - 1. Simvastatin +/- Niacin, 2. Simvastatin +/- Fenofibrate
STATIN INTOLERANCE: MANAGEMENT OF PATIENTS WITH MYOPATHIES

- Muscle symptoms (myalgia), signs (CK elevations) or combination (myositis, rhabdomyolysis) are the most prevalent & important AE’s associated with statin therapy discontinuation.

- In statin studies, myopathy incidence varies but is generally thought to occur in 1.5% to 10.5% of patients within the first 6 months; however onset can also be delayed for several years.36

- Over diagnosis of myopathy occurs frequently & can lead to labelling a patient as statin intolerant, therefore, diagnosis should be reserved for patients reporting symptoms associated with use of statin which resolve when the statin is stopped.

- If presented with a true statin intolerant patient there is optimism for use as a recent study found that 9 of 10 patients who stopped taking a statin because of adverse effects are able to restart it or take a different statin & continue therapy for 12 months.

- Considering that the benefits of statins are substantial on reducing CV events & mortality, while non-statin based agents have to date proven no benefit on these hard outcomes, when indicated, should make every effort possible to re-challenge a statin intolerant patient & use all methods described below before abandoning therapy.

- A recent meta-analysis examined the absolute risk versus benefit ratio comparing myopathy related events (myalgia, myopathy, asthenia, rhabdomyolysis) to cardiovascular endpoints (MI, revascularization, stroke, cardiovascular death, or all cause mortality) & determined that there was a 126:1 in favour of statin treatment.37

### Table: Myopathy Risk Factors

<table>
<thead>
<tr>
<th>MYALGIA (occurs in 5-10% of patients)</th>
<th>MYOSITIS (0.1%)</th>
<th>Rhabdomyolysis (0.01%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle discomfort</strong> (pain, cramping, weakness, soreness, aches, tenderness, stiffness) that may mimic flu-like symptoms &amp; usually involves shoulders, pelvic girdle &amp; upper arms or thighs (CK ≤ ULN) 30,31,33,34</td>
<td>Myositis occurs in the presence of the same symptoms of myalgia with the addition of a elevated CK (&gt;2-4 x ULN) in the absence of ↑ SCR &amp; myoglobinuria 31,32,33,34</td>
<td>Rhabdomyolysis refers to muscle symptoms consistent with myalgia/myositis &amp; significant CK elevation (&gt;4-10x ULN) with potential secondary consequences (hyperkalemia, hypocalcemia, cardiac arrhythmia or arrest, DIC, or renal failure) 31,32,33,34</td>
</tr>
<tr>
<td><strong>STEP 1:</strong> Check CK &amp; assess for myopathy risk &amp; etiologic factors (see Myopathy Risk Factors)</td>
<td><strong>STEP 1:</strong> Assess &amp; reemphasize lifestyle measures in lowering CV risk; reassess statin indication</td>
<td><strong>STEP 1:</strong> Stop statin until CK ≤ ULN &amp; patient is asymptomatic 31,32,35</td>
</tr>
<tr>
<td><strong>STEP 2:</strong> Assess &amp; reemphasize lifestyle measures in lowering CV risk</td>
<td><strong>STEP 2:</strong> Stop statin until CK ≤ ULN &amp; patient is asymptomatic 31,32,35</td>
<td><strong>STEP 2:</strong> Reassess risk vs benefit &amp; patients risk factors 33</td>
</tr>
<tr>
<td><strong>STEP 3:</strong> May stop or continue statin depending on pain severity. If statin stopped wait until pain resolves before reinitiating 31,32,34</td>
<td><strong>STEP 3:</strong> Assess the patients’ risk factors for myopathy</td>
<td><strong>STEP 3:</strong> If the episode is mild may consider re-challenge with a low dose of a different statin 31,35</td>
</tr>
<tr>
<td><strong>STEP 4:</strong> Consider therapeutic options for management below (options not necessarily in order of preference)</td>
<td><strong>STEP 4:</strong> Consider options for management as per myalgia (column at left – 4A→4E)</td>
<td><strong>STEP 4:</strong> If the episode was moderate to severe consider referral to specialist to weigh risk vs benefit of statin therapy 31</td>
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<tr>
<td>A: Consider lowering the dose if continuing or re-trialing previous statin, especially if started on high-dose statin. *60% of patients intolerant to a usual dose statin were able to tolerate low dose simvastatin &lt;10 mg daily 31</td>
<td><strong>Step 1:</strong> If the episode is mild may may consider re-challenge with a low dose of a different statin 31,35</td>
<td><strong>STEP 5:</strong> Consider the use of bile acid sequestrant, ezetimibe, nicotinic acid (or possibly combinations) to achieve LDL lowering 31,32,35</td>
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<td>B: Consider switching to another statin.</td>
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<td>• In previously intolerant patients, ~98% were maintained on rosuvastatin 5-10mg daily for 44 weeks and ~96% complied with fluvastatin XL 80mg daily therapy during a 12 week study. 31,32 (However, 71% in a small (n=118 patients) retrospective analysis, were even able to tolerate a same-statin rechallenge. Brennan 17)</td>
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<td>C: If intolerable, consider alternate day dosing regimens (allow for at least some statin as opposed to non-statin)</td>
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<td>• Rosuvastatin 10mg every other day was well tolerated (~ 75%) 31,32</td>
<td>Myophagy occurs in the presence of the same symptoms of myalgia with the addtion of a elevated CK (&gt;2-4 x ULN) in the absence of ↑ SCR &amp; myoglobinuria 31,32,33,34</td>
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<tr>
<td>• Atorvastatin 10mg twice weekly was well tolerated by ~95% 34</td>
<td><strong>STEP 1:</strong> Assess &amp; reemphasize lifestyle measures in lowering CV risk; reassess statin indication</td>
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<tr>
<td>• Rosuvastatin 5-20mg weekly has also been studied</td>
<td><strong>STEP 2:</strong> Stop statin until CK ≤ ULN &amp; patient is asymptomatic 31,32,35</td>
<td>&amp;</td>
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<tr>
<td>D: Consider adding CO-Q10 (200mg/day) or Vit D (400-600 IU daily) to current statin therapy.</td>
<td><strong>STEP 3:</strong> Assess the patients’ risk factors for myopathy</td>
<td><strong>STEP 3:</strong> If the episode is mild may consider re-challenge with a low dose of a different statin 31,35</td>
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<tr>
<td>• Evidence limited, however, considered relatively safe 18</td>
<td><strong>STEP 4:</strong> Consider options for management as per myalgia (column at left – 4A→4E)</td>
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</tr>
<tr>
<td>• E: If none of the above are effective, may consider statin alternative, however, evidence lacking 31,32,35</td>
<td><strong>MYOPATHY RISK FACTORS</strong></td>
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<td></td>
<td><strong>Endogenous Risk Factors</strong></td>
<td><strong>Exogenous Risk Factors</strong></td>
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<td></td>
<td>- Age &gt;80 years</td>
<td>- High statin dose</td>
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<tr>
<td></td>
<td>- Female</td>
<td>- Alcohol abuse</td>
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<tr>
<td></td>
<td>- Asian ethnicity</td>
<td>- Illicit drug use</td>
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<td></td>
<td>- Low body mass index</td>
<td>- Antipsychotic use</td>
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<td></td>
<td>- History of pre-existing muscle/joint/ tendon pain</td>
<td>- Surgery with severe metabolic demands</td>
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<td></td>
<td>- History of CK elevation</td>
<td>- Heavy &amp; or unaccustomed exercise (commonly reported symptom trigger)</td>
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<tr>
<td></td>
<td>- Diabetes Mellitus</td>
<td>- Amiodarone,azole antifungals,</td>
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<td></td>
<td>- Family history of myopathy with or without statin treatment</td>
<td>- Cyclosporine, fibrates, macrolide antibiotics,</td>
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<tr>
<td></td>
<td>- Metabolic muscle disease</td>
<td>- Nefazodone* still available in US, nicotinic acid,</td>
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<td></td>
<td>- Severe renal disease (eGFR ≤ 30 mL/min)</td>
<td>- Protease inhibitors, tacrolimus, verapamil,</td>
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<td></td>
<td>- Acute/decompensated hepatic disease</td>
<td>- Warfarin, Grapefruit in large quantities.</td>
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<td>- Hypothyroidism</td>
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<td></td>
<td>- Genetic polymorphisms of CYP enzyme</td>
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</tbody>
</table>

ACS=acute coronary syndrome AE=adverse event CCS=Canadian Cardiovascular Society CK=creatine 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 controlled trial SCR=serum creatinine ULN=upper limit of normal VIT D=vitamin D XL=extended release yr=year

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4 Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS). Lancet. 2004;364:685-96. Colhoun HM, et al. on behalf of the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia. 2005 Nov 28;12;1-4 [Epub ahead of print] RESULTS: A reduction in the primary endpoint of major CVD events was apparent and statistically significant as after 18 months after treatment initiation. The effect of atorvastatin on CHD events was apparent by 6 months, and at 1 year was similar to the 37% relative risk reduction observed at trial closure (Neil HA, et al. CARDs Study Investigators. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84.

5 Colhoun HM, Betteridge DJ, Durrington PN, et al. Effects of Atorvastatin on Kidney Outcomes and Cardiovascular Disease in Patients With Diabetes: An Analysis From the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009 Jun 18. [Epub ahead of print] A modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria, was observed. Atorvastatin did not influence albuminuria incidence. Atorvastatin was effective at decreasing CVD in those with and without a moderately decreased eGFR and achieved a high absolute benefit.


7 Heart Protection Study Group. MRC/BHF Study of cholesterol lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-12. (269 of 34,135 pts in 4-6 wk run in treatment with simvastatin 40mg were included).


12 LaRosa JC, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease (CARDS). Am J Kidney Dis. 2009 Jun 18. [Epub ahead of print] A modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria, was observed. Atorvastatin did not influence albuminuria incidence. Atorvastatin was effective at decreasing CVD in those with and without a moderately decreased eGFR and achieved a high absolute benefit.


14 Cunningham CP, Braunwald E, McCabe CH, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Am J Cardiol. 2012 Mar 27. [Epub ahead of print] Medication use: The percentage of patients taking aspirin, a non-steroidal anti-inflammatory drug (NSAID), a beta-blocker, a statin, a calcium channel blocker, and a glucocorticoid were 82%, 72%, 84%, 85%, and 14%, respectively. Treatment differences for the primary outcome were consistent across pre-specified subgroups as well as the intention-to-treat population. The median follow-up period was 1.3 years (interquartile range 0.6-2.6). The primary outcome was a composite of the following: death from any cause, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. The proportion of patients with diabetes (41%), those with hypertension (73%), those who were current smokers (26%), and those who were current users of statins (85%) were similar across the two treatment groups. The primary outcome occurred in 231 patients in the placebo group and 205 patients in the atorvastatin group (HR 0.86, 95% CI 0.72 to 1.03, P=0.11). The prevalence of CAD, the percentage of patients who had had previous MI, or the percentage of patients who had had previous PCI were similar between the two groups. The percentage of patients with hypertension, diabetes, and current smokers was also similar. The percentage of patients with a history of MI or PCI was higher in the atorvastatin group (17% vs 14%, P=0.02). The percentage of patients who were current users of statins was higher in the placebo group (13% vs 5%, P=0.01). The percentage of patients who were current users of NSAIDs was similar between the two groups (35% vs 34%, P=0.7).


16 LaRosa JC, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease (CARDS). Am J Kidney Dis. 2009 Jun 18. [Epub ahead of print] A modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria, was observed. Atorvastatin did not influence albuminuria incidence. Atorvastatin was effective at decreasing CVD in those with and without a moderately decreased eGFR and achieved a high absolute benefit.

17 The Prognosis of Recent Onset Stable Angina (PROVE IT-TIMI 22) Investigators. The Prognosis of Recent Onset Stable Angina (PROVE IT-TIMI 22) Investigators. J Am Coll Cardiol. 2008 Jun 24;51(15):1448-54. [PubMed - in process] Aggressive lipid lowering with atorvastatin 80 mg was both safe and effective in reducing the excess of cardiovascular events in a high-risk population with CKD run in treatment with simvastatin 40mg/d


19 Reul JAM, et al.; on behalf of the CARDS Investigators. Rapid emergence of effect of atorvastatin on cardiovascular outcomes in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia. 2005 Nov 28;12;1-4 [Epub ahead of print] RESULTS: A reduction in the primary endpoint of major cardiovascular events was apparent and statistically significant as after 18 months after treatment initiation. The effect of atorvastatin on CHD events was apparent by 6 months, and at 1 year was similar to the 37% relative risk reduction observed at trial closure (Neil HA, et al. CARDs Study Investigators. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84.
