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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.[1(CCS 12)] 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.[1(CCS 12)]
- **CK levels** should be monitored at baseline and in those patients who develop myalgia while on a statin.[1(CCS 12)]
- Having a high risk patient on a statin, irrespective of LDL levels achieved, has shown a reduction in 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 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

i. **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) [2,3,5,6,7,8,9,10,11]
   - well designed 5-6 yr RCT data with > 10yr follow up data

Mortality: NNT/~5yrs = 30 [4S 2,3]
CV events: NNT/~5yrs = 12 [4S 2,3]

ii. **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]

Mortality: NNT/~5yrs = NS [TNT 12]
CV events: NNT/~5yrs = 46 [TNT 12]
NNT/~5yrs = 78 [14(CCT 10)]

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

i. **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

Mortality: NNT/~5yrs = NS
CV events: NNT/~4yrs = 32 [CARDS 15]
NNT/~3.3yrs = 91 [ASCOT 16]
NNT/~2yrs = 120 [JUPITER 18]

ii. **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 [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
   - ⇨ 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 22]
- lacks evidence for lowering CV/mortality risk in combination with a statin compared to a placebo in mild-to-moderate, asymptomatic aortic stenosis patients [SEAS 23]
- very limited evidence & surrogate outcome evidence, e.g. intima-media thickness, has been disappointing [ENHANCE 24]
- 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 [SHARP 25]

Fibrates
- monotherapy: evidence mixed or lacking for CV/mortality benefit for fibrates in contrast to statins [26,27,28]
- combination: fenofibrate + simvastatin not more effective than simvastatin monotherapy [ACCORD-Lipid 29]

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

i. Patients should be informed of the uncertainties surrounding such strategies.
ii. Combination drug regimens failed to show a benefit over statin monotherapy in two recent trials
   - 1. Simvastatin +/- Niacin [NIASPAN AIM-HIGH 30]; 2. Simvastatin +/- Fenofibrate [ACCORD-Lipid 29]

STATIN INTOLERANCE: MANAGEMENT OF PATIENTS WITH MYOPATHIES [31,32,33,34,35]

- 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, clinicians 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]

MYALGIA (occurs in 5-10% of patients)

⇨ **Muscle discomfort** (pain, cramping, weakness, soreness, aches, tenderness, stiffness) that may mimic flu-like symptoms & usually involves shoulders, pelvic girdle & upper arms or thighs (CK ≤ ULN) [30,31,33,34]

STEP 1: **Check CK & assess for myopathy risk & etiologic factors** (see Myopathy Risk Factors)

STEP 2: **Assess & reemphasize lifestyle measures in lowering CV risk**; **reassess statin indication**

STEP 3: **May stop or continue statin depending on pain severity**. If statin stopped wait until pain resolves before reinitiating [31,32,34]

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

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 <10 mg daily [31]

B: Consider **switching to another statin**.
- 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])

C: If intolerable, consider **alternate day dosing regimens** (allow for at least some statin as opposed to non-statin)
- rosuvastatin 10mg *every other day* was well tolerated (~ 75%) [31,32]
- atorvastatin 10mg *twice weekly* was well tolerated by ~95% [34]
- rosuvastatin 5-20mg *weekly* has also been studied

D: Consider **adding CO-Q10** (200mg/day) **or Vit D** (400-600 IU daily) to current statin therapy.
- Evidence limited, however, considered relatively safe[38]. Opinion varies as to the role for these options.

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

MYOSITIS (0.1%)

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

STEP 1: Assess & reemphasize lifestyle measures in lowering CV risk; reassess statin indication

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

STEP 3: Assess the patients' risk factors for myopathy

STEP 4: Consider options for management as per myalgia (column at left – **4A→4E**)

RHABDOMYOLYSIS (0.01%)

⇨ Rhabdomyolysis refers to muscle symptoms consistent with myalgia/ myositis & **significant CK elevation** (>4-10X ULN) **with potential secondary consequences** (hyperkalemia, hypocalcemia, cardiac arrhythmia or arrest, DIC, or renal failure) [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 the episode was moderate to severe consider referral to specialist to weigh risk vs benefit of statin therapy [31]

STEP 5: Consider the use of bile acid sequestrant, ezetimibe, nicotinic acid (or possibly combinations) to achieve LDL lowering [31,32,35]

MYOPATHY RISK FACTORS

Endogenous Risk Factors	**Exogenous** Risk Factors
-Age >80 years	-High statin dose
-Female	-Alcohol abuse
-Asian ethnicity	-Illicit drug use
-Low body mass index	-Antipsychotic use
-History of pre-existing muscle/joint/ tendon 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, nefazodone*still available in USA, 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	

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 limite of normal **Vit D**=vitamin D **XL**=extended release **yr**=year

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