Statins
What a pain!

Eric D. King, DO
9/18/2015
Introduction

• Statins
  • Consistently reduce low-density lipoprotein cholesterol (LDL-C) levels
  • Well tolerated
  • Use has become widespread
  • Awareness of adverse reactions has increased.
    • Myopathy
      • Emerged as the most common complication.
        • Management of myopathy occupies a large proportion of caseloads in specialty lipid clinics, cardiology practices and PC practices.
        • Expected to increase as statin use in primary prevention becomes more widespread and higher statin doses for secondary prevention become standard of care.
Question

• Under which of the following scenarios should statin medications be discontinued and avoided?
  A. Myalgias with mildly elevated LFTs
  B. Myalgias with a CK of 10 times greater than normal.
  C. Myalgias with a CK of 5 times greater than normal.
  D. Unexplained transaminase levels >2 times the upper limit of normal is a contraindication to statin therapy
Diagnosis and Definitions

• Statin intolerance
  • No well-accepted, standardized, or Food and Drug Administration diagnostic criterion exists for statin intolerance.
  • The term typically refers to an inability to use statins because of significant symptoms or elevated CK levels
    • The major diagnostic challenge is to unambiguously link these to statin use.
  • No specific biomarkers exist
Diagnosis and Definitions

• Myopathy
  • Any disease of the muscle including toxic, acquired, and hereditary disorders.

• Statin-induced myopathy
  • Myalgia refers to having myopathy symptoms but no elevation in CK levels.
    • Symptoms include:
      • muscle aches
      • weakness
      • cramps
      • stiffness
      • “heaviness”
      • may mimic flu-like symptoms

• Asymptomatic myopathy
  • No symptoms but a CK elevation that resolves after the statin is stopped.

Definitions adapted from the National Lipid Association, American College of Cardiology/American Heart Association (ACC/AHA), and the Canadian Working Group Consensus.
Diagnosis and Definitions

- **Myositis**
  - Myalgias with CK elevation

- **Rhabdomyolysis**
  - Occurs when muscle fibers break down leading to release of muscle fiber contents (myoglobin) into the bloodstream.
  - Diagnosis involves extreme elevations in CK levels (either CK >10,000 U/L or 10-fold higher than the upper limit of normal) with creatinine elevation
    - Not all definitions require evidence of renal dysfunction.
Diagnosis and Definitions

• “Statin-intolerant” patient
  • No standardized definition.
  • Often divided into:
    • Some investigators, as well as the ACC/AHA Blood Cholesterol Guidelines committee
    • Complete
      • intolerant to any statin at any dose
    • Partial
      • intolerant to some statins at some doses

• Others investigators broadly divide it into severe or mild:
  • Mild - present with aches and pains that resolve with cessation of therapy.
  • Severe - present with incapacitating muscle pain or weakness, rhabdomyolysis, persistent symptoms after therapy, progressive worsening, CK >4 times the upper limit of normal, or an inability to tolerate lower doses of statins;

• For clinical trials, a recently proposed definition involves an inability to tolerate at least 1 statin at the starting daily dose and another statin at any dose (ClinicalTrials.gov identifier: NCT01709513).
Diagnosis and Definitions

• Hepatotoxicity
  • results in cessation of statin therapy (rarely).
  • In clinical trials, transaminitis occurs in 0.5% to 3.0% of patients.
  • Most patients who experience liver injury do so within 3 to 4 months after starting therapy.
  • Measurements of transaminase levels should be performed before initiating statins
    • If normal, do not need to be measured again unless symptoms of hepatotoxicity arise.
    • Unexplained transaminase levels >3 times the upper limit of normal is a contraindication to statin therapy as listed in manufacturer's prescribing information.
      • In such cases, statin therapy should be avoided or discontinued.

Myalgias

• Characteristics of statin-induced myalgias:
  • occur symmetrically
  • involve large and proximal muscle groups
    • especially the legs
  • typically begin within 6 months of drug initiation
    • can occur at any time during the course of statin administration
  • improve promptly after drug termination, but can take up to 3 months to resolve completely.
Myalgias

- Persistence of muscle symptoms/elevated CK after statin discontinuation.
  - Occurs rarely
  - Should prompt further investigation of common myopathies
    - e.g., polymyositis and polymyalgia rheumatic
    - Underlying metabolic muscle disorders
  - Of patients with myopathy severe enough to warrant a muscle biopsy, roughly 10% have genetic variants for triggerable metabolic muscle diseases
    - Heterozygous myophosphorylase deficiency
    - Homozygous myophosphorylase deficiency (McArdle disease)
    - Heterozygous carnitine palmitoyltransferase II (CPT2) deficiency
    - Pompe disease and malignant hyperthermia due to ryanodine receptor (RYR1) mutations

Risk Factors

• Clinical trials and observational studies identify several risk factors for statin-induced myopathy
Risk Factors

- Advanced age (>80 yrs)
- Female sex
- Small body frame and frailty
- Asian ancestry (for rosuvastatin)
- Grapefruit juice consumption (>1 quart/day)
- Excessive physical activity
- History of myopathy while receiving another lipid-lowering therapy
- History of CK elevation, especially >10 times upper limit of normal
- Family history of myopathy
- Family history of statin-induced myopathy
- Co-morbid conditions
- Hypothyroidism
- Chronic kidney disease
- Diabetes mellitus

- Multisystem disease
- Alcoholism
- Major surgery or perioperative period
- Concurrent infection
- Muscle disease (e.g., McArdle disease, myoadenylate deaminase deficiency)
- Genetic
- Polymorphisms of CYP isoenzymes
- Polymorphisms in drug transporter genes such as solute carrier organic anion transporter family member 1B1 (SLCO1B1)
- Use of medications that interact with statins
- Antidepressant or antipsychotic use
- Illicit drug use
- High dose of statins
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Drugs that increase the serum concentration of statins resulting in an increased risk of myopathy or rhabdomyolysis

<table>
<thead>
<tr>
<th>Interacting Drug/Class</th>
<th>Recommendations for Statin Choice and Dosing</th>
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| **Fibrates**           | Fenofibrate: any statin, but monitor for myopathy  
                          Gemfibrozil: Rosuvastatin ≤10 mg/day |
| **Cyclosporine**       | Pravastatin ≤20 mg/day  
                          Fluvastatin ≤20 mg/day  
                          Rosuvastatin ≤5 mg/day |
| **Antifungals (-azole)** | Pravastatin any dose  
                          Fluvastatin ≤20 mg/day  
                          Pitavastatin any dose  
                          Rosuvastatin any dose  
                          Atorvastatin ≤20 mg/day |
| **Macrolide antibiotics** | Pravastatin ≤40 mg/day  
                          Fluvastatin any dose  
                          Pitavastatin ≤1 mg/day  
                          Rosuvastatin any dose  
                          Atorvastatin ≤20 mg/day |

--Adapted from package inserts.
Drugs that increase the serum concentration of statins resulting in an increased risk of myopathy or rhabdomyolysis

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| HIV-1 protease inhibitors                   | Pravastatin any dose  
Fluvastatin any dose  
Pitavastatin any dose  
Rosuvastatin ≤10 mg/day with lopinavir/ritonavir and atazanvir/ritonavir  
Atorvastatin ≤20 mg/day with saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir or fosamprenavir/ritonavir  
Atorvastatin ≤40 mg/day with nelfinavir |
| Other protease inhibitors (boceprevir, telaprevir) | Pravastatin any dose  
Fluvastatin any dose  
Pitavastatin any dose  
Rosuvastatin any dose |
| Nefazodone                                  | Pravastatin any dose  
Fluvastatin any dose  
Pitavastatin any dose  
Rosuvastatin any dose  
Atorvastatin any dose |

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<tbody>
<tr>
<td>Amiodarone</td>
<td>Pravastatin any dose</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin any dose</td>
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<tr>
<td></td>
<td>Pitavastatin any dose</td>
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<tr>
<td></td>
<td>Rosuvastatin any dose</td>
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<tr>
<td></td>
<td>Atorvastatin any dose</td>
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<tr>
<td></td>
<td>Simvastatin ≤20 mg/day</td>
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<tr>
<td></td>
<td>Lovastatin ≤40 mg/day</td>
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<tr>
<td>Calcium antagonists -</td>
<td>Pravastatin any dose</td>
</tr>
<tr>
<td>(Verapamil and diltiazem)</td>
<td>Fluvastatin any dose</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin any dose</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin any dose</td>
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<tr>
<td></td>
<td>Atorvastatin any dose</td>
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<tr>
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| Calcium antagonists - (Amlodipine) | Fluvastatin any dose  
  Pitavastatin any dose  
  Rosuvastatin any dose  
  Atorvastatin any dose  
  Simvastatin ≤20 mg/day  
  Lovastatin any dose |
| Ranolazine             | Pravastatin any dose  
  Fluvastatin any dose  
  Pitavastatin any dose  
  Rosuvastatin any dose  
  Atorvastatin any dose  
  Simvastatin ≤20 mg/day  
  Lovastatin any dose |

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| Danazol                | Pravastatin any dose  
                          Fluvastatin any dose  
                          Pitavastatin any dose  
                          Rosuvastatin any dose  
                          Atorvastatin any dose  
                          Lovastatin ≤20 mg/day |
| Dronedarone            | Pravastatin any dose  
                          Fluvastatin any dose  
                          Pitavastatin any dose  
                          Rosuvastatin any dose  
                          Atorvastatin any dose  
                          Simvastatin ≤10 mg/day  
                          Lovastatin any dose   |
| Colchicine             | Any statin  
                          Monitor for myopathy  
                          Consider statin dose reduction |

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<td>Daptomycin</td>
<td>Any statin, but monitor for myopathy and consider statin dose reduction. Consider temporarily stopping statin therapy before daptomycin initiation</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>Any statin, but monitor for myopathy and consider preventative 50% reduction in statin dose</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Avoid statins</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Any statin, but monitor for myopathy and consider statin dose reduction</td>
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### Drugs that increase the serum concentration of statins resulting in an increased risk of myopathy or rhabdomyolysis

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| Cyproterone            | Pravastatin any dose  
                        | Rosuvastatin any dose  
                        | Pitavastatin any dose |
| Dasatinib              | Any statin, but monitor for myopathy especially with simvastatin, lovastatin, and atorvastatin             |
| Rifampin               | Pravastatin any dose  
                        | Fluvastatin any dose  
                        | Pitavastatin ≤2 mg/day |
|                        | Rosuvastatin any dose  
                        | Atorvastatin any dose  
                        | Simvastatin any dose |
|                        | Lovastatin any dose                                                                                       |
Frequency and Prevalence

- In clinical trials
  - Myopathy
    - rarely occurs
  - Myalgias
    - As few as 2% of clinical trial participants
  - Myositis
    - occur in as few as 0.05%
  - Rhabdomyolysis
    - occur in as few as 0.002%
  - Excluding Cerivastatin
    - the clinical trial frequency of statin-induced myopathy compares favorably with placebo.

Frequency and Prevalence

• PRIMO study - Prediction of Muscular Risk in Observational conditions
  • A survey of muscular side effects in general practice clinics in France
    • Overall, 10.5% of statin users experienced muscular symptoms, with a median time of onset of 1 month after initiation of statin therapy.
    • Patients taking simvastatin 40 to 80 mg/day had the highest prevalence of muscle symptoms (18.2%).

Frequency and Prevalence

• USAGE – Understanding Statin Use in America and Gaps in Education study
  • Survey of >10,000 subjects in the United States who were prescribed statins
    • 12% had discontinued their statin
      • 86% experienced muscle pain or weakness.

Frequency and Prevalence

- **STOMP trial** - Effect of Statin Medications on Muscle Performance trial
  - Double-blinded study
  - Randomized healthy patients to atorvastatin 80 mg or placebo
  - Subjects met the study definition for “myalgia” if all of the following occurred:
    - New or increased muscle pain, cramps, or aching not associated with exercise
    - Symptoms persisted for at least 2 weeks
    - Symptoms resolved within 2 weeks of stopping the study drug
    - Symptoms reoccurred within 4 weeks of restarting the study medication.
  - No statistical difference in myalgias between groups
    - Statin group -- 9%
    - Placebo group -- 5%

Frequency and Prevalence

• 37% of the population of the United States has at least 2 risk factors for coronary heart disease
  • Data from the AHA and Centers for Disease Control and Prevention
  • Therefore potential statin users
  • If 5% to 10% of these subjects experience statin-induced muscular symptoms
    • estimated potential prevalence of statin myopathy is 5 to 10 million in the United States.

Approach to Patients With Statin Intolerance

- No consensus on management of patients with statin-induced myopathy
- Management differs depending on whether the patient has had elevated CK levels
- Most patients have normal CK levels
- Treatment strategies
  - Re-establishing statin use
  - Prescribing non-statin lipid lowering drugs
  - Using LDL-apheresis
  - Maximizing therapeutic lifestyle changes
  - Alternate dosing
  - Red yeast rice
  - Vitamin D
  - Co-enzyme Q10
  - L-carnitine
Patients with elevated CK

- Statins should be avoided for patients with CK elevations >10 times the upper limit of normal
  - Risk of myositis and rhabdomyolysis.
  - Should be prescribed nonstatin LDL-C–lowering agents
    - niacin, ezetimibe, or bile acid sequestrants.
    - The ACC/AHA Blood Cholesterol Guidelines recommend selecting agents that have been shown to reduce CHD events in randomized controlled trials
      - i.e., niacin and the bile acid sequestrant cholestyramine
- Little guidance exists for management of patients with mild elevations in CK (<10 times the upper limit of normal).
- In cases where predisposing factors can be identified and eliminated, statins can be restarted with close monitoring of CK levels.
Patients with normal CK (myalgias)

- Patients with myalgias
  - Need for statin therapy should be reassessed
    - Determine CHD risk per the ACC/AHA Blood Cholesterol Guidelines.
      - Subjects who are low risk for CHD and have experienced statin myopathy may no longer tip the risk-benefit scale toward benefit.
      - Patients who would benefit from statin therapy
        - evaluate factors influencing their adherance to therapy
        - especially because most patients are not attuned to taking drugs every day for a lifetime.
  - Patients stop taking statins for many reasons
    - fear of side effects
    - perceived side effects
    - medication costs
    - lack of insurance coverage
    - misunderstanding of the benefits
    - lack of commitment to treatment
    - loss to follow-up

Statin withdrawal and rechallenge

- Advocated by the ACC/AHA Blood Cholesterol Guidelines committee
  - A way to establish a causal relation between myalgias and statin therapy.
  - Statin held for at least 2 weeks to see if the symptoms go away, then restarting the statin to see if the symptoms return.
    - Some patients require >2 weeks for symptom resolution
      - especially those taking high-potency statins with long half-lives
        - Rosuvastatin and Atorvastatin
  - As long as patients are not under conditions of severe acute vascular stress (e.g., acute coronary syndrome, ischemic stroke or major vascular surgery), short-term withholding of statin therapy is generally regarded as safe.

- Several issues limit widespread use of statin withdrawal and challenge.
  - Health-care providers lack an evidence-based standardized protocol
    - more of an art rather than a science
    - sensitivity and specificity remain unknown
      - in the STOMP trial, even 5% of placebo-treated patients developed myalgias during a controlled withdrawal and rechallenge.

Re-establishing statin use

• Retrospective studies find that 40% to 90% of statin discontinuers can reestablish and maintain use.
  • Accomplished by:
    • adjusting dosages
    • switching agents
    • reducing the frequency of administration.
  • Process of “trial and error”
    • discouraging patients and frustrating providers.

Switching Statins

• Little data exist on which statin to select
  • Identification of risk factors or concomitant medications helps to switch to safer statins

• A few clinical trials explore this topic in statin-intolerant patients.
  • Small studies without standardized definitions of statin intolerance
    • Stein et al found that fluvastatin XL 80 mg/day could be tolerated by 97% of patients
    • Glueck et al found that rosuvastatin 5 or 10 mg/day could be tolerated by 98%

Stein EA, Ballantyne CM, Windler E, Sirnes PA, Sussekov A, Yigit Z, Seper C, Gimpelewicz CR. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. Am J Cardiol 2008;101:490e496.

Reducing the frequency of statin administration

- A few small, short-term, randomized, double-blind, controlled trials have established the efficacy of nondaily dosing.
  - Atorvastatin 10 mg every other day lowered LDL-C by 27%.
  - Rosuvastatin 5 to 10 mg once weekly lowered LDL-C by 12%.
  - Rosuvastatin 80 mg—an unapproved dose—one weekly showed comparable LDL-C lowering (29%) with daily atorvastatin 10 mg.
- Rosuvastatin, atorvastatin and their active metabolites have long half-lives (≈20 hours), which may partially explain their efficacy when given once or twice a week.

Nonstatin lipid-lowering agents

• The ACC/AHA Blood Cholesterol Guidelines Committee recommends:
  • Partially intolerant patients
    • using clinical judgment with regard to the need to add a nonstatin lipid-lowering agent.
  • Completely intolerant patients,
    • monotherapy with nonstatins only if the agent has been shown to reduce CHD events.
      • Niacin and the bile acid sequestrant cholestyramine.


Rifkind BM. Lipid Research Clinics Coronary Primary Prevention Trial: results and implications. Am J Cardiol 1984;54:30Ce34C.
Nonstatin lipid-lowering agents

• Ezetimibe
  • limited by:
    • lack of cardiovascular outcome data and limited efficacy
      • ~15% to 20% LDL-C lowering
      • Rare cases of ezetimibe-induced myopathy and elevated CK levels have been reported.
  • But...
    • both prospective and retrospective data indicate that ezetimibe is well tolerated by statin-intolerant patients and can even be given 3x week.

Nonstatin lipid-lowering agents

• Fibrates and fish oil
  • fail to reduce LDL-C significantly

• Gemfibrozil monotherapy does reduce the incidence of CHD in men with low high-density lipoprotein cholesterol or elevated non–high-density lipoprotein cholesterol.

LDL apheresis

• Option for patients with very high LDL-C who are intolerant to statins

• Indicated if:
  • LDL-C >500 mg/dl in patients with homozygous familial hypercholesterolemia,
  • LDL-C >300 mg/dl in patients without CHD
  • LDL-C >200 mg/dl in patients with CHD.

Harborview Medical Center – Apheresis Department
25 9th Avenue
Seattle, WA 98104  ---------  206-520-5000
www.uwmedicine.org/locations/endocrinology-diabetes-harborview

Therapeutic lifestyle changes

• Should be maximized for every patient
• Include the use of plant sterols and/or stanols as outlined in the National Cholesterol Education Program Adult Treatment Panel III guidelines.
• Can reduce LDL-C by up to 25%
  • similar to the efficacy of low-dose statins
  • depend on baseline saturated fat intake
  • may lack long-term sustainability
Red yeast rice

• Often preferred by patients
  • “natural”
  • available without a prescription
  • In randomized controlled trials of statin-intolerant patients, reduced LDL-C by 21% to 30% at doses of 1,800 to 2,400 mg/day.

• Lowers LDL-C by monacolin K, a natural form of lovastatin.

• Several limitations may prevent health-care providers from routinely recommending:
  • Monacolin K content varies widely among brands
  • Incidence of myopathy at effective doses not statistically different from equally effective statins.
  • Cost often exceeds that of generic statins.

Vitamin D

- Vit D deficiency has been associated with myalgia and poor muscle function
- Supplementation has shown ameliorative effects of myopathy
  - Recent trial demonstrated 92% of patients become symptom free after 3 months of vit D supplementation

Vitamin D

- 146 patients intolerant to > 2 statins and Vit D deficient (<32 ng/mL)
  - Administered Vit D supplementation 50,000-100,000 units/week vs placebo.
  - 88% were free of myalgia, on the re-challenge statin, but 12% still had myalgia and could not tolerate the re-challenge statin
  - The myalgia free group had higher free serum vitamin D levels at 14 months (53 ng/mL vs 36 ng/mL)

Coenzyme Q10

- **CoQ10**
  - An essential co-factor for ATP production
  - Antioxidant activity
  - Reduced muscle pain in statin-treated patients in some, but not all studies
  - Meta-analysis of randomized controlled trials does not suggest any significant reduction in statin-induced myopathy

- Marloff *et al.* randomized 41 patients with statin-induced myalgia to CoQ10 100 mg/day or vitamin E 400 IU/day for 30 days - improvement
- Caso *et al.* randomized 32 patients in a double-blind fashion to CoQ10 100 mg/day (n = 18) patients versus vitamin E 400 IU/day (n = 14) - improvement
- Young *et al.* randomized 44 patients to CoQ10 200 mg/day or placebo for 12 weeks in combination with an upward dose titration of simvastatin, from 10 to 40 mg/day, doubling every 4 weeks if tolerated – no improvement

L-carnitine

• Muscle biopsies and blood samples were tested in 132 patients who developed statin myalgias.

• Patients experiencing muscle pains on statins
  • 11-times more likely to be a heterozygous carrier for the carnitine palmitoyltransferase-2 deficiency
  • 31% of muscle biopsies evaluated had carnitine abnormalities.
  • 20-times more likely to be carriers for McArdle's disease (a glycogen storage disease)
  • 30% had lipid storage problems.

• Suggests that people who experience muscle pains on a statin are more likely to have an underlying metabolic muscle disease with the symptoms of statin muscle pain being brought out in these carriers.

• Almost 50% of the analyzed samples had CoQ10 (ubiquinone) levels that were 2–4 standard deviations below normal.

• Supplementing with both CoQ10 and l-carnitine may be a rationale approach to treating certain statin myalgias.

• Despite the high prevalence of carnitine abnormalities in patients with statin myalgia, there are no randomized controlled trials showing that l-carnitine treats this adverse reaction.

Question

Under which of the following scenarios should statin medications be discontinued and avoided?

(ACC/AHA Blood Cholesterol Guidelines)

A. Myalgias with mildly elevated LFTs
B. Myalgias with a CK of 10 times greater than normal.
C. Myalgias with a CK of 5 times greater than normal.
D. Unexplained transaminase levels >2 times the upper limit of normal is a contraindication to statin therapy
Thank you