Objectives

- Define the role of statins for patients with diabetes
- Recommend appropriate statin therapy with evidence-based indications from recent guidelines
- Adjust statin therapy based on barriers encountered with myopathy and other health concerns
- Describe alternatives to statin therapy
What Does this Mean?
The revocation by these Regulations of a saving on the previous revocation of a provision does not affect the operation of the saving so far as it is not specifically reproduced in these Regulations but remains capable of having effect.


What is Health Literacy (HL)
- Institute of Medicine
  - Degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions

Why Care About HL?
- Obtain health information from multiple resources
- Process information
  - Interpret charts to identify and measure a dose
  - Read medication handouts
- Comprehend the information
  - Follow directions for a medication or device
  - Evaluate and select an over-the-counter medication
  - Medical releases, consents, disease state information

HL Proficiency of Adults
- 36% of the population has limited health literacy skills
- 12% have low health literacy skills
- 12% have very low health literacy skills
- 5% have a severe health literacy problem

90 million adults lack the needed health literacy skills to effectively use the health care system

Why Care About HL?
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  - Evaluate and select an over-the-counter medication
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Poor HL and Diabetes
- 2 times more likely to have worse glycemic control
  - A1c ≥ 9.5%
- 2 times more likely to have retinopathy
- 3 times more likely to have cerebrovascular disease
- 2 times more likely to have nephropathy
- 2.5 times more likely to have a lower extremity amputation
- 2 times more likely to have ischemic heart disease

Poor HL and Diabetes
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Tying it Back to Health Literacy

- Drawing and measuring insulin with a syringe
- Identifying the correct dose on an insulin pen
- Working a glucometer
- Reading and comprehending blood sugars
- Calculating carbohydrates
- Calculating an insulin dose based on carbohydrates
- Understanding nutrition principles
- Understanding the role of exercise
- Medication adherence
- Taking medications appropriately

Why is This Important?

The US Diabetes “Epidemic”

- National prevalence of diabetes (2010)
  - Age ≥ 20 years: 11.3% (25.6 million)
  - Age ≥ 65 years: 26.9% (10.9 million)

- National prevalence of prediabetes (2010)
  - Age ≥ 20 years: 35% (estimated 79 million)
  - Age ≥ 65 years: 50%

Complications of Diabetes

- Macrovascular Complications
  - Heart Disease and Stroke
  
  - Americans with Diabetes ≥ 35 yo (2011)
    - 5 million with heart disease
    - 3.7 million with other heart “condition”
    - 2.1 million with reported stroke
    - 7.6 million with heart disease or stroke

Heart Disease and Stroke

- Diabetes-related death certificates in people ≥ 65 yo (2004)
  - Heart disease noted in 68%
  - Stroke noted in 16%

- Risk
  - Heart disease death rates and risk of stroke are 2 - 4 times higher in adults with diabetes vs. those without diabetes
CHD and Diabetes

- CVD is the major cause of morbidity and mortality in patients with diabetes
- Dyslipidemia and hypertension are clear risk factors
  - Many studies have shown benefit in controlling these to prevent or slow CVD in diabetes

Why We Care About Statins

Lipid Guidelines

- Review of NCEP ATP III
- Highlights of the new 2013 ACC/AHA Blood Cholesterol Guidelines
- ADA Guidelines

NCEP ATP III

- Released: 2001
- Updated: 2004

Prevention of CHD

- Primary Prevention
  - Prevention of 1st cardiovascular event
  - Goal: ↓ long term risk (>10 y) and short term (<10 y)
  - Therapeutic Lifestyle Changes (TLC) are a focus
    - ↓ saturated fat and cholesterol
    - ↓ weight
    - ↑ physical activity

Prevention of CHD

- Secondary Prevention
  - Prevention of subsequent cardiovascular events after a first (MI, CABG, PCI, CVA)
  - Goal: ↓ long term risk (>10 y) and short term (<10 y)
  - TLC remains a focus
  - Drug therapy typically required
  - Higher risk = a stricter goal LDL
Goal Values or Targets

- TC < 200 mg/dL
- HDL > 40 mg/dL (>50 mg/dL for women)
- TG < 150 mg/dL
- LDL goal must be determined based on risk

NCEP ATP III Guidelines

- LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy.
- "This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD."

Risk Category

- CHD and CHD risk equivalents
- Multiple (2+) risk factors
- Zero to one risk factor

LDL Goal (mg/dL)

- <100
- <130
- <160

CHD Risk Equivalents

- Risk for major coronary events equal to that in established CHD
- 10-year risk for CHD event > 20%

Other clinical forms of atherosclerotic disease

- peripheral arterial disease
- abdominal aortic aneurysm
- symptomatic carotid artery disease
- Diabetes
- Multiple risk factors that confer a 10-year risk for CHD > 20%
**Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals**

- Cigarette smoking
- Hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (< 40 mg/dL)
- Family history of premature CHD
  - CHD in male first degree relative < 55 years
  - CHD in female first degree relative < 65 years
- Age (men ≥ 45 years; women ≥ 55 years)

† HDL cholesterol > 60 mg/dL counts as a “negative” risk factor; its presence removes one risk factor from the total count.

**Count major risk factors**

- For patients with multiple (2+) risk factors
  - Perform 10-year risk assessment (Framingham Risk Assessment)
- For patients with 0–1 risk factor
  - 10 year risk assessment not required

Most patients have 10-year risk <10%

**LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)</th>
<th>LDL Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100</td>
<td>≥130</td>
<td>≥160</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≥20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10–20%</td>
</tr>
<tr>
<td>1–1 Risk Factor</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk &lt;10%</td>
</tr>
</tbody>
</table>

**Optional LDL goal < 70 mg/dL**

- Option for patients at “very high risk”
  - Must have established CVD plus any of:
    - Multiple major risk factors (especially diabetes)
    - Severe and poorly controlled risk factors (especially cigarette smoking)
    - Multiple risk factors of Metabolic Syndrome
      - High TG > 200 mg/dL plus
      - Non-HDL ≥ 130 mg/dL with low HDL < 40 mg/dL
    - History of acute coronary syndromes (ACS)

**Algorithm for Lipid-Lowering Medication Therapy**

- Initiate LDL-lowering drug therapy
  - Start statin or bile acid sequestrant
  - If LDL goal not achieved, intensify LDL-lowering therapy
  - First, maximize current statin or BAS dose
  - Second, add ezetimibe, or fibrate, or niacin
  - If LDL goal achieved and TG >200mg/dL, calculate non-HDL
  - Treat other lipid risk factors and metabolic syndrome

- If LDL goal not achieved, intensify drug therapy or refer to a lipid specialist
  - If LDL goal achieved and TG >300mg/dL, calculate non-HDL
  - Treat other lipid risk factors and metabolic syndrome

**Not Good Enough?**

- “Half of all myocardial infarctions and strokes occur despite apparently healthy men and women with LDL levels below currently recommended thresholds for treatment”
  - “Even with adequate LDL lowering, many patients on statin therapy have significant CVD risk”
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Released Mid-November 2013
Journal of the American College of Cardiology

Expert panel for ATP 4
Partnered with ACC/AHA
Focus on ASCVD risk reduction, not comprehensive lipid management
Only used RCT, systematic reviews, meta-analyses of RCT

3 Critical Questions
1. What is the evidence for LDL and non-HDL goals for the secondary prevention of ASCVD?
2. Same as #1, but primary prevention
3. For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

Findings
• “unable to find evidence to support titrating statins to a target LDL or non-HDL goal”
• “extensive evidence that appropriate statin intensity should be used to reduce ASCVD risk”
• “use of non-statin to additionally lower non-HDL once LDL goal achieved. DID NOT further reduce ASCVD outcomes”

Findings
• Non-statin therapies in general have not demonstrated significant ASCVD event reduction.
• Lifestyle modifications remain a critical component of health promotion and ASCVD risk reduction
• Identification of 4 statin benefit groups to focus on ASCVD risk reduction
4 Statin Benefit Groups

- Clinical ASCVD ≤ 75 yo (secondary prevention)
- Primary elevation of LDL ≥ 190 mg/dL
- 40-75 yo with Diabetes and LDL 70-189 mg/dL
- No clinical ASCVD or Diabetes, 40-75 yo and LDL 70-189 mg/dL and 10-year ASCVD risk of 7.5% or higher

Clinical ASCVD ≤ 75 years

- High-intensity statin therapy (1st line)
- If not tolerated, use moderate-intensity
- If > 75 years, consider benefits vs risks and may use moderate- or high-intensity statin

LDL ≥ 190 mg/dL

- High-intensity statin therapy
- If not tolerated, use maximum tolerated intensity
- Once maximum intensity achieved, may consider addition of non-statins to further lower LDL (weak data—expert opinion)

40-75 years with Diabetes and LDL 70-189 mg/dL

- Moderate-intensity statin therapy
- If ASCVD 10-year risk ≥ 7.5%, use high-intensity
- If < 40 or > 75 years, consider benefits vs risks and patient preferences

No clinical ASCVD or Diabetes, 40-75 yo and LDL 70-189 mg/dL and 10-year ASCVD risk of 7.5% or higher

- Moderate-to High-intensity statin therapy
Adults with LDL <190 mg/dL not fitting into a statin benefit group

- Additional factors may be considered to inform treatment decision making
  - LDL ≥ 160 mg/dL
  - Genetic hyperlipidemia
  - Family history of premature ASCVD: ♂ < 55 years or ♀ < 65 years
  - High C-reactive Protein (CRP) > 2 mg/L
  - Coronary artery calcium score ≥ 300 Agatston units or ≥ 75 percentile for age, sex, ethnicity
  - ABI <0.9
  - Lifetime risk of ASCVD

Case Question 1
Patient is a 58 YO male with diabetes and an LDL of 198 mg/dL. Per the 2013 ACC/AHA guidelines, how should he be treated?
A. No statin
B. Low-intensity statin
C. Moderate-intensity statin
D. High-intensity statin

Case Question 2
Patient is a 58 YO male with diabetes and an LDL of 198 mg/dL. Per the 2013 ACC/AHA guidelines, how should he be treated?
A. Pravastatin 80 mg
B. Rosuvastatin 20 mg
C. Atorvastatin 20 mg
D. Fluvastatin 40 mg

Case Question 3
Patient is a 62 YO female with diabetes, an LDL of 82 (on no statin), and an ASCVD 10-year risk of 7.8%. Per 2013 ACC/AHA guidelines, how should she be treated?
A. Atorvastatin 80 mg
B. Pitavastatin 1 mg
C. Lovastatin 20 mg
D. Fluvastatin 80 mg
Calculation of ASCVD 10-year Risk (%)

- Pooled Cohorts Equations
  - Calculates risk of CHD death, fatal or non-fatal MI or stroke
  - Used for "white and black men and women" without clinical ASCVD
  - Controversial calculation
    - This places many more people in higher risk categories than the Framingham Risk tool

Statin Safety Recommendations

- Moderate-intensity statin should be used instead of high-intensity if high risk of statin-associated adverse effects
  - Impaired renal or hepatic function
  - Previous statin intolerances or muscle disorder
  - ALT > 3 times upper limit of normal (CI)
  - On drugs that affect statin metabolism
  - > 75 years of age
  - Possibly history of hemorrhagic stroke
  - Possibly Asian ancestry

Monitoring Statin Therapy

- Initial fasting lipid panel (then start drug)
- Check fasting lipid panel 4-12 weeks (often 6-8 weeks); to check adherence, NOT to achieve a target or goal
- Then check fasting lipid panel 3-12 months

Statin Safety Recommendations

- Monitor creatine kinase (CK or CPK)
  - Baseline and if myopathy symptoms
- Monitor ALT (liver function)
  - Baseline and if hepatotoxic symptoms
- Consider ↓ statin dose if 2 consecutive LDL < 40 mg/dL
- Avoid simvastatin 80 mg
- Evaluate for new onset diabetes

Monitoring Statin Therapy

- Insufficient response to statin dose
  - Reinforce adherence to med and lifestyle
  - Exclude secondary causes
  - If higher-risk ASCVD patients on max statin dose, may consider adding non-statin
    - Clinical ASCVD < 75 years
    - Baseline LDL ≥ 190 mg/dL
    - 40-75 years old with diabetes
Triglycerides > 500 mg/dL
- Risk of pancreatitis
- Treat as a priority over LDL
- Treat with fibrates or niacin
- Once TG < 500, focus on LDL reduction for ASCVD risk reduction (back to statins)

Summary of Lipid Guideline Differences

ATP 3
- Focus on LDL goals
- Use statins or any lipid-lowering drugs to attain goal

2013 ACC/AHA
- Focus on statin intensity
- Use statins almost exclusively

ADA 2014 Standards of Care
- Statin therapy if LDL > 100 mg/dL
- Statin therapy regardless of baseline lipid levels in DM:
  - Without CVD
  - With overt CVD
- If LDL goal of < 100 mg/dL is not reached with optimal statin dosing, an LDL reduction of 30-40% from baseline is an alternative therapeutic goal
- “Combination drug therapy has been shown not to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended”

ADA 2015 Standards of Care
- High-intensity statin
  - All ages with DM and overt CVD
  - 40-75 yo DM with additional CVD risk
- Moderate- or High-Intensity statin
  - <40 yo DM with additional CVD risk
  - >75 yo DM with additional CVD risk
- Moderate-intensity statin
  - 40-75 yo DM without additional CVD risk
  - >75 yo DM without additional CVD risk
- Adjust statin intensity based on patient response (AE, LDL)
- Lipid panel for monitoring adherence
- “Combination therapy has not been shown to provide additional CVD benefit above statin therapy alone and is not generally recommended”

Statin Myopathy
**Statin Mechanism of Action**

Reduces hepatic cholesterol synthesis, lowering intracellular cholesterol, which stimulates upregulation of LDL receptors and increases the uptake of non-HDL particles from the systemic circulation.

**Statin Pharmacotherapy**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lipophilicity</th>
<th>Metabolism</th>
<th>Half-life</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>Hydrophilic</td>
<td>CYP2C9</td>
<td>~21</td>
<td>Minor active metabolite</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Lipophilic</td>
<td>CYP3A4</td>
<td>~15-30</td>
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<td>Sulfation</td>
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<tr>
<td>Fluvastatin</td>
<td>Lipophilic</td>
<td>CYP2C9</td>
<td>~5</td>
<td>No active metabolite</td>
</tr>
</tbody>
</table>

**LDL Lowering Efficacy of Statin**

<table>
<thead>
<tr>
<th>Fluva</th>
<th>Prava</th>
<th>Lova</th>
<th>Pitava</th>
<th>Simva</th>
<th>Atorva</th>
<th>Rosuva</th>
<th>% LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>1 mg</td>
<td>10 mg</td>
<td>--</td>
<td>25 - 30%</td>
<td></td>
</tr>
<tr>
<td>80 mg</td>
<td>40 mg</td>
<td>40/80 mg</td>
<td>2 mg</td>
<td>20 mg</td>
<td>10 mg</td>
<td>--</td>
<td>34 - 33%</td>
</tr>
<tr>
<td>--</td>
<td>80 mg</td>
<td>80 mg</td>
<td>4 mg</td>
<td>40 mg</td>
<td>20 mg</td>
<td>5 mg</td>
<td>40 - 45%</td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>--</td>
<td>80 mg</td>
<td>40 mg</td>
<td>10 mg</td>
<td>45 - 50%</td>
<td></td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>80 mg</td>
<td>20 mg</td>
<td>55 - 60%</td>
<td></td>
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**Definitions of Statin Myopathy**

- **Myopathy**: Any muscle complaint related to statin use
- **Myalgia**: Muscle symptoms without elevated creatine kinase (CK)
- **Myositis**: Elevated serum CK with or without muscle symptoms
- **Rhabdomyolysis**: Severe muscle symptoms with CK elevated > 10 times the upper limit of normal (ULN)

**Characteristics of Statin Myopathy**

- **Localization**: Generalized (60%) or localized to large proximal muscle groups. Lower extremities more frequently (25%) affected than upper (8%)
- **Type**: Heaviness, stiffness, cramps
- **Equivalent of muscle pain**: Weakness, tendinitis
- **Frequency and duration**: Usually intermittent lasting several minutes to hours
- **Timing**: < 1 month to several years

**Statin Myopathy – Randomized Controlled Trials (RCT)**

- Rarely reported in RCTs
  - RCT reported 1-5% of patients experiencing myalgia
  - Patients are carefully selected for RCT
    - Patients with renal or hepatic insufficiency, poorly controlled diabetes, history of muscle complaints, and taking drugs with possible drug interactions usually excluded from trials
    - Most studies focus on reporting rhabdo vs. myalgia
    - Lack of consensus on definitions
Statin Myopathy – Observational Studies Outpatient

- Higher frequency of myopathy
  - 9-20%
- PRIMO Study
  - 10.5%

Bruckert E, et al. Mild to moderate muscular symptoms with dosage statin therapy, PRIMO. Cardiovascular Drugs and Therapy, 2006.

What Causes Statin Myopathy

- Carrier of SLCO1B1 gene polymorphisms
- Drug or food interactions (CYP3A4, CYP2C9, UGT, OAT1B1)

Pharmacotherapy Considerations

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Statin Toxicity

- Simvastatin 40-80mg – 18.2%
- Atorvastatin 40-80mg – 14.9%
- Pravastatin 40mg – 10.9%
- Fluvastatin XL 80mg – 5.1%

Risk Factors for Statin Myopathy

Endogenous Risks
- Advanced age (>65)
- Low BMI and frailty
- Multisystem disease
- Hypothyroidism
- Hypertriglyceridemia
- Metabolic muscle disease
- History of muscular symptoms
- History of elevated CK or muscle symptoms

Exogenous Risks
- Alcohol consumption
- Heavy exercise
- Surgery with severe metabolic demands
- >1 L grapefruit juice daily
- Drug interactions

FIGURE 1

Drugs Affecting CYP450 (3A4)
- Cyclosporine
- Nondihydropyridine Calcium Channel Blockers (i.e. verapamil, diltiazem)
- Amiodarone
- Azole antifungals (i.e. fluconazole)
- Colchicine
- Digoxin
- Protease inhibitors
- Warfarin
- Macrolide antibiotics (i.e. azithromycin)

Drugs Affecting CYP450 (2C9)
- Azole antifungals (i.e. fluconazole)
- H₂ receptor antagonists (i.e. ranitidine)
- Proton pump inhibitors (i.e. omeprazole)
- Warfarin
- NSAIDs
- Sulfonylureas (i.e. glipizide)
- ARBs
- Amiodarone

Gemfibrozil
- Inhibits glucuronidation of UGT
- Inhibits the OATP1B1 transporter
  - Increased levels of statin and increased risk of adverse effects

Simvastatin
- SEARCH trial – 80mg vs. 20mg
  - Major CV events 24.5% vs. 25.7%
  - Myopathy (CK>10x ULN + symptoms)
    - 52 patients on 80mg, 1 patient on 20mg
  - Rhabdomyolysis (CK>40x ULN + symptoms)
    - 22 patients on 80mg, 0 patients on 20mg
  - Risk declines from 5 to 2/1000 person years in the first 12 months, then from 1 to 0.4/1000 per years after 12 months
  - Risk of myopathy found to be 3x higher and risk of fatal rhabdomyolysis higher than with more potent LDL lowering drugs atorvastatin and rosuvastatin

Simvastatin Dosing Restrictions
- 80mg restricted to those taking it >12 months prior to 6/8/2011
- Maximum dose of simvastatin established when used concomitantly with other drugs:
CoEnzyme Q10 Supplementation

- Bookstaver and colleagues
  - CoQ10 60mg twice daily
  - No more effective than placebo in decreasing muscle pain that was presumed to be statin induced
- Kelly and colleagues
  - CoQ10 100mg/day
  - Myopathic pain improved from baseline in treated patients
- Ganesan and colleagues
  - Relationship of GLUT4 protein levels, CoQ10, and statins


CoEnzyme Q10

- Dose: 100-300mg/day in divided doses
- Adverse Effects: (<1%) nausea/vomiting, diarrhea, elevated transaminases (rare)
- Drug Interactions: diminished effect of warfarin
- Rated as ‘Likely Safe’

Managemen of Myopathy

- Muscle symptoms
  - Stop statin (2-6 week drug holiday)
  - Measure CK, serum creatinine and urinalysis
- Symptoms resolve
  - Restart original statin at same or lower dose
  - If recurrence, stop original statin
  - When symptoms resolve, start new statin at a lower dose
- If not resolved > 2 months, likely not statin; resume original dose
- If intolerant of statins, may use non-statin

Alternate Statin Dosing

- Use a lower toxicity statin
  - Fluvastatin XL 80mg (39% LDL lowering potential)
- Use a statin with less CYP450 dependence
  - Pravastatin
- Use alternate day or once/twice weekly dosing with longer acting statins (rosuvastatin, atorvastatin, pitavastatin)
  - 35% LDL lowering with rosuvastatin 5mg every other day
  - 26% LDL lowering with rosuvastatin 5-10mg twice weekly

Statin Discontinuation

- Retrospective cohort study: 107,835 patients over 9 years
- Statin discontinued: 67,292 (53%)
- Statin-related events: 18,778 (17.4%)
- Findings:
  - Of 11,124 who discontinued, 6579 were re-challenged with statin over next 12 months
  - 92.2% were still taking statin after 12 months
  - 2721 who were re-challenged with same statin, 1295 were still taking 12 months later


Bottom Line

- Most patient re-challenged can tolerate statins long-term
  - Statin-related events may have other causes, are tolerable or may be specific to individual statins rather than the entire drug class
- If patients develop muscle symptoms after start
  - Determine likelihood that muscle symptoms are due to the statin
  - Balance of expected statin therapy with the likelihood that muscle symptoms are due to statin
Lab Monitoring

- Obtain baseline CK, liver function test, and lipid panel
  - Naturally elevated CK levels in some populations
- If symptoms develop, check CK, 25-OH vitamin D, thyroid stimulating hormone
  - Other tests as indicated by history and physical
- Recheck lipid panel in 6-8 weeks after initiation or after dose titration
- Annual lipid panel for routine monitoring

Case Question 4

- 45 YO Male with past medical history: hypertension, type 2 diabetes, obesity and smoker complaining of muscle pain
- Labs: ALT/AST WNL and CK 350
- ASCVD risk is 9%
- Medications: Metformin 500 mg 1 tablet twice daily, Lisinopril 40mg daily, HCTZ 25mg daily, amlodipine 10mg, and simvastatin 40mg once daily
  (History of being started on atorvastatin 80mg once daily but complained of muscle pain shortly after. PCP immediately switched to simvastatin 40mg.)

Which of the following is the best recommendation:
A. Change statin therapy to bile acid sequestrant
B. Decrease simvastatin to 20mg once daily
C. Provide a 6-week statin drug holiday and re-challenge with atorvastatin 40mg
D. Discontinue simvastatin and start rosuvastatin 20mg

Other Statin Concerns

Statin and Diabetes

- JUPITER
  - N=17,802
  - 27% increase in risk of diabetes (p=0.01)
  - 39% reduction in primary endpoint (MI, stroke, CV deaths) for patients with diabetes risk factors and 52% reduction in those that with no risk factors
  - 134 vascular deaths avoided for every 54 new cases of diabetes
- Meta-analysis (PROVE IT-TIMI 22, TNT, IDEAL, A to Z, SEARCH)
  - High-dose statins (atorvastatin and simvastatin) increased risk of diabetes (OR 1.12)

Bottom Line

- The cardiovascular benefits of statin therapy outweigh the small absolute risks of developing diabetes

Statins and Cognitive Impairment / Dementia

- Meta-analysis evaluating 16 studies: Without baseline cognitive dysfunction, no effect on cognition
  - Long-term data may support beneficial role for statins in prevention of dementia (HR 0.71, CI 0.61-0.82)
  - 5 studies showed 29% reduction in incidence of dementia
- Prospective study of 6,600 patients: Patients with normal cognitive function or mild cognitive impairment and statin use performed better on attention measures and had slower annual worsening of Clinical Dementia Rating Sum of Boxes (P<0.006)
  - No difference in cognitive decline
**Bottom Line**

- Cardiovascular benefits of statin therapy outweigh the proposed risk of cognitive impairment/dementia
- There may even be a protective role

**Statins and Acute Kidney Injury**

- Retrospective analysis of >2 million patients on moderate to high intensity statins:
  - Rosuvastatin ≥ 10mg
  - Atorvastatin ≥ 20mg
  - Simvastatin ≥ 40mg
- 34% greater risk of hospitalization for acute kidney injury (AKI) in first 120 days of treatment with statin (CI 1.25-1.43)
  - NNH was 1700 for 1 AKI hospitalization within the 120 days
- Retrospective analysis of >3 million patients on statin, no increase in AKI as a whole
  - Simvastatin 40-80mg have increased risk of AKI

**Bottom Line**

- The cardiovascular benefits of statin therapy outweigh the proposed risk of acute kidney injury

**Drug Therapy Options**

**Statin Considerations**

- **Adverse Effects**
  - Myopathy (rhabdomyolysis)
  - Elevated liver transaminases (rare)

- **Contraindications**
  - Pregnancy, active liver disease

- **Monitor**
  - Fasting lipid profile (6-8 weeks)
  - Baseline CPK (CK) and again if muscle pain
  - Baseline LFT and again periodically

**Statin Pearls**

- Dose in evening unless long half-life (atorva-, rosuva-)
- Myopathy - rechallenge with lower dose or different statin
  - Less with prava- (maybe rosuva- and pitava-)
  - CoQ10, alternate dosing with long-half-life statins
- Drug interactions
  - Many (CYP 3A4, 2C9)
  - Less with pravastatin
- Recent label changes:
  - No more simvastatin 80 mg
  - Risk of diabetes, cognitive impairment, less liver monitoring, drug interactions
**Fibrates**

**Mechanism of Action**
- Peroxisome proliferator-activated receptor alpha (PPAR-α)
- Reduced hepatic secretion of VLDL
- Induction of LPL-mediated lipolysis and clearance of TG

**Lipid impact**
- LDL: ↓ 5 - 20% (possible increase if high TG)
- TG: ↓ 20 - 50%
- HDL: ↑ 10 - 20% (possible up to 35%)

**Options**
- Gemfibrozil, Fenofibrate

**Fibrate Considerations**

**Adverse Effects**
- Myopathy (rhabdomyolysis)
- Elevated liver transaminases
- GI upset

**Contraindications**
- Significant renal or hepatic dysfunction, gallbladder disease
  (Canada-pregnancy, breast-feeding)

**Monitor**
- Fasting lipid profile (6 - 8 weeks)
- Baseline CPK (CK) (repeat if muscle pain) and LFT

**Fibrate Pearls**
- Myopathy risk increased with statins
  - Risk is greater with gemfibrozil than fenofibrate
- Reserved for TG > 400 - 500 mg/dL
- Combination with statins may not be more effective for cardiovascular outcomes
  - ACCORD (type 2 DM patients with high CVD risk)
  - Combination of fenofibrate and simvastatin did not reduce rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared to simvastatin alone

**Niacin**

**Mechanism of Action**
- Inhibits hepatic production of VLDL and consequently LDL

**Lipid impact**
- LDL: ↓ 5 - 25%
- TG: ↓ 20 - 50%
- HDL: ↑ 10 - 35%

**Options**
- Immediate-release niacin (OTC)
- Sustained-release niacin (Slo-Niacin) (OTC)
- Extended-release niacin (Niaspan) (Rx)

**Niacin Considerations**

**Adverse Effects**
- Myopathy (especially if combined with statin)
- Elevated LFT (more common with OTC sustained-release)
- Flushing, increased glucose, hyperuricemia

**Contraindications**
- Active hepatic disease, active peptic ulcer

**Monitor**
- Fasting lipid profile (6 - 8 weeks)
- Baseline CPK (CK) and again if muscle pain
- Baseline LFT

**Niacin Pearls**
- Caution in gout - often avoided
- Flushing more common in immediate-release; possible any
  - Lessen if take with food, ASA 30 min prior, titrate slowly, avoid "hot" food/beverage/environment
- More hepatic impact with OTC sustained-release
- Combination with statins may not be more effective for cardiovascular outcomes
  - AIM-HIGH (patients with CVD, TG 150 - 400, low HDL)
  - Halted early; lack of efficacy on CVD outcome and possible increase of ischemic stroke with combo of extended-release niacin and statin
Bile Acid Sequestrants (BAS)

**Mechanism of Action**
- Binds bile acids in the intestine, decreasing biliary cholesterol absorption

**Lipid impact**
- LDL: ↓ 15 - 30%
- TG: no effect or may increase
- HDL: ↑ 3 - 5%

**Options**
- Cholestyramine, Colestipol, Colesevelam

**BAS Considerations**

**Adverse Effects**
- GI (constipation, obstruction)

**Contraindications**
- Complete biliary or bowel obstruction, TG > 500

**Monitor**
- Fasting lipid profile (6 - 8 weeks)

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Ezetimibe

**Mechanism of Action**
- Inhibits absorption of cholesterol in small intestine

**Lipid impact**
- LDL: ↓ 17% (alone) or additional 15 - 20% with statin
- TG: ↓ 5-11% (alone) or additional 29 - 33% with statin
- HDL: ↑ 0-5% (alone) or additional 7 - 9% with statin

**Options**
- Ezetimibe
- Atorvastatin-ezetimibe

**Ezetimibe Pearls**
- Despite further lowering of LDL, lacks clinical outcomes data favoring cardiovascular benefit
  - ENHANCE trial
  - No change in carotid artery intima-media thickness
  - SEAS trial
  - No reduction in aortic stenosis or CV events
  - Simvastatin-ezetimibe
  - Atorvastatin-ezetimibe
Complementary Alternative Medicine Options

- **Cholestoff**: Contains plant stanols and sterols (15 - 20% LDL lowering)
- **Fish oil**: 2000 - 4000 mg/day
- **Soluble fiber**: 10 - 25 g/day
- **Red Yeast Rice**: 1200 - 2400 mg contains lovastatin 2 - 6 mg equivalence (20 - 25% LDL lowering)
- **CoEnzyme Q10**: 100 - 300 mg/day

Patient Education

Health Literacy Sensitive Approaches

- Explain the differences between statins and about medication itself
  - Patients also have fear of perceived adverse effects and have misunderstanding of the benefits
- Use an analogy that the patient can relate to
- Visual aids
- Plain language
- Relate to diabetes and have patient repeat back goals

Motivational Interviewing

- Identify what is important to them (e.g. family, grandkids)
- Involve patient with decision process (shared decision making)
  - Mayo Clinic shared decision making tools

Complex Case 1

- 60 YO Male complaining of general pain with past medication history type 2 diabetes, HTN, dyslipidemia, CAD, MI, CMBS, left carotid endarterectomy

<table>
<thead>
<tr>
<th>Baseline</th>
<th>2 Weeks Later</th>
<th>6 Weeks Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Pravastatin 40mg</td>
<td>None for 4 weeks</td>
</tr>
<tr>
<td>CPK (units/L)</td>
<td>None</td>
<td>563</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>96</td>
<td>122</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>Present</td>
<td>Not Resolved</td>
</tr>
<tr>
<td>Pain</td>
<td>Stop pravastatin</td>
<td>No drug therapy</td>
</tr>
</tbody>
</table>

Which of the following is the best recommendation?

A. Re-challenge statin with rosuvastatin 5mg every other day with coenzyme Q10 supplementation
B. Re-challenge with pravastatin 20mg
C. Re-challenge with atorvastatin 40mg
D. Start bile acid sequestrant

Complex Case 2

- 51 YO Male with past medical history: Dyslipidemia, hypertension, obesity, hypothyroid, coronary artery disease, type 2 diabetes
- Medication intolerances: complaints of myalgias with ALL statins (history of hospital admission in 2013 with AST/ALT 1100/1200, CK 50,000 on atorvastatin 40mg), gemfibrozil, fenofibrate, niacin, ezetimibe
- Not currently on treatment for his dyslipidemia

Which of the following is the best recommendation?

A. Re-challenge statin with rosuvastatin 5mg every other day with coenzyme Q10 supplementation
B. Try Cholestoff
C. Try fish oil
D. Start bile acid sequestrant
The Role and Management of Statins in Dyslipidemia and Addressing Patient Barriers to Use