Update on Lipid Management for the Prevention of Atherosclerotic Disease

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• Review treatment options for lipids in primary and secondary prevention
• Discuss how to overcome statin intolerance
Case 1- Primary Prevention

• 46 y.o man with LDL-C 178 mg/dL, HDL 30 mg/dL, triglycerides 200 mg/dL, total cholesterol 266 mg/dL, no diabetes, no hypertension, nonsmoker, blood pressure 124/76 mm Hg, BMI 23
• Jogs 45 minutes 3 days a week, no ischemic symptoms
• Father had first MI at 52 (nonsmoker), paternal uncle first MI at 44
• 10 year ASCVD risk 5% (1.3% for optimal risk factors) lifetime risk is 50% (5% optimal risk factors)
• What would you advocate for this person?
  A) No medication therapy focus on lifestyle modification and recheck lipids in one year
  B) Start low or moderate dose statin and lifestyle modification
  C) Check hs-crp and start statin if >2 along with lifestyle modification.
  D) A, B and C are all appropriate options
Primary Prevention of ASCVD

• Applies to those with LDL-C <190 mg/dL or those without known atherosclerotic cardiovascular disease (ASCVD)
• LDL-C ≥ 190 mg/dL or established ASCVD - STATIN + lifestyle modification
• Treatment threshold by AHA/ACC 2013 guidelines is ASCVD risk ≥ 7.5%
• Treatment threshold by USPSTF > 10% & ≥ 1 CVD risk factor
  • Gender and race specific (validated in non-Hispanic African Americans and Whites)
  • Validated ages 40 to 79
• Included stroke as outcome
• Can use in other populations but not validated
• May overestimate risk in lower risk populations
Primary Prevention

• If risk remains uncertain:
  • Family history, first degree male relative ≤ 55 or female relative ≤ 65 years
  • Coronary artery calcium ≥ 300 agaston units or ≥ 75% for age and gender
  • hs-crp >2.0
  • ABI <0.9

• Treatment
  • Lifestyle Modification
  • Typically low or moderate dose statin
  • 19 trials evaluated statin therapy in primary prevention
    • Pooled data: 31% reduction in mortality, 36% reduction in MI and 29% reduction in stroke
    • Very safe: Risk of serious adverse events not statistically different between statin and placebo
        AHRQ publication 14-05206-EF-2.
    • Low and moderate dose statin: Atorvastatin 10-20 mg, Fluvastatin 20-80 mg, lovastatin 20 mg to 40 mg, pravastatin 10-80 mg, rosuvastatin 5-10 mg, simvastatin 10-40 mg
Secondary Prevention of ASCVD

- Age <75 years and ASCVD = High dose statin + lifestyle modification
- Rosuvastatin 20 or 40 mg or Atorvastatin 40 mg or 80 mg
  - Drug – drug interactions
  - Comorbid conditions such as ckd, chronic liver disease
- Age ≥75 years and ASCVD= Moderate dose statin +lifestyle modification
  - Secondary prevention trials demonstrate benefit in the elderly
    - Subgroup analyses: LIPID, HPS, CARE, 4S, PROVE-IT, MIRACL, TNT
    - Prosper (ages 70 to 82)15% relative risk reduction in CHD death, non-fatal MI, and fatal and non-fatal stroke with pravastatin vs. placebo
  - Higher risk of adverse events and polypharmacy
PCSK9 Inhibitors

• Proprotein convertase subtilism/kexin 9 Inhibitor
  • Monoclonal antibodies to PCSK9: decrease LDL-R degradation increasing hepatic LDL-R and LDL-C clearance
  • Decrease LDL-C by 39-62% in clinical trials

• Alirocumab (Praluent©) and Evolocumab (Repatha ©) are FDA approved for LDL-C Lowering
  • HeFH/HoFH on appropriate diet and maximally tolerated statin or
  • Clinical atherosclerotic disease (MI or CVA) on appropriate diet and maximally tolerated statin
  • Prior Authorization (tier 5 currently under medicare in Washington state)
PCSK9 Inhibitors

• Recent Outcomes data for Evolocumab
  • 27,564 people with atherosclerosis: MI, stroke, symptomatic PVD + LDL >70 mg/dL (on therapy)
  • 48 weeks
  • Decreased LDL-C by 59% (in addition to statin therapy) compared to placebo
    • Median 92 mg/dL to 30 mg/dL
  • Decreased primary outcome (death, mi, stroke, usa, coronary revascularization)
    • 9.8% vs. 11.3 % HR 0.85 (0.78 to 0.92) p<0.001
  • Decreased secondary outcome (CVD death, mi, stroke)
    • 5.9% vs. 7.4% HR 0.80 (0.73 vs. 0.88) p<0.001
  • No significant difference in AE except injection site reaction
Statin Intolerance

• True statin intolerance 5-20%
• Associated with increased risk of recurrent myocardial infarction and CHD events compared to those with high statin adherence (JACC.2017;69(11):1386-1395)
• Risk Factors
  • Advanced age, Female Sex, Asian Ethnicity
  • Prior hx of neuromuscular syndrome or myopathy, family hx of myopathy
  • Pre-existing liver disease, kidney disease, untreated hypothyroidism
  • Rare genetic polymorphisms involved in drug metabolism (cytochrome enzymes)
  • Excessive etoh intake
  • High intensity exercise
  • Medications: gemfibrozil, antipsychotics, amiodarone, verapamil, cyclosporine, macrolide antibiotics, azole antifungals, protease inhibitors
Statin Intolerance/ Adverse events

- Muscle symptoms 15% patients
  - Measure CK in people with muscle symptoms at baseline
  - Statin related myopathy: CK elevation >10X ULN associated with myalgia or rhabdo
  - Highest incidence of statin related myopathy simvastatin 80 mg dose
- Diabetes may be a real risk but causal relationship has not been shown
  - 9% risk over four years in post hoc analyses
- FDA removed the requirement of periodic monitoring of LFTS in 2012
  - Except in patients with known LFT abnormalities, concern for Rx-Rx interactions
  - Baseline LFTS on everyone
- Memory/cognition
  - Mixed findings but evidence is not consistent
Statin Intolerance: Approach

- **R/O drug interactions:**
  - gemfibrozil, antipsychotics, amiodarone, verapamil, cyclosporine, macrolide antibiotics, azole antifungals, protease inhibitors
  - R/O other etiologies for myopathy: tsh, cpk, b12, vitamin d,
  - Based on history and physical exam: calcium, albumin, cbc, esr, ana, rf
- Stop current statin for two weeks switch to another statin start at low dose and lower frequency
  - Rosuvastatin (2.5 or 5 mg), atorvastatin (5 mg or 10 mg) dosed three times a week
  - If doing well and not at LDL-C goal consider increasing dose first but not frequency
  - Add a nonstatin such as ezetimibe or low dose fibrate or bile acid sequestrant or niacin if needed to attain LDL-C goals but first optimize statin
- Evidence for good LDL-C lowering with these approaches but no evidence yet for CVD risk reduction
- Coenzyme Q-10 (important in mitochondrial function) 100 mg to 200 mg daily
  - Statins deplete coenzyme q-10
  - Evidence is mixed
  - Very safe
  - Vitamin D deficiency
    - Replacing vitamin D may improve statin tolerability in deficient patients
Omega-3 Fatty Acids

- No evidence for benefit in prevention of MI/stroke/death in primary prevention (including diabetes and prediabetes)
- Likely benefit in patients with prevalent coronary heart disease such as recent MI
- Likely benefit in patients with systolic heart failure (HFrEF)
Summary

- Primary prevention: Consider statin (in addition to lifestyle modification) if ASCVD risk is ≥7.5%
  - USPSTF- consider statin if risk >10% + ≥ 1 CVD risk factor
  - If uncertain consider family history, CAC, hs-CRP, ABI
- Secondary Prevention: high dose statin age <75, moderate dose statin age ≥75
- Statin intolerance associated with increased risk of MI and CHD death
- PCSK9 inhibitors FDA approved for LDL-C lowering in (HeFH/HoFH) or CHD on maximally tolerated statin and diet
- Omega-3 fatty acid supplement in CHD or systolic heart failure (HFrEF)
Case 2- Statin Intolerance

• 67 y.o Asian woman, 30 pack-yr prior smoker, BMI 20 kg/m2, 102 pounds, with CAD s/p stent to RCA last year in the setting of NSTEMI. She was put on atorvastatin 80 mg/dL and developed significant myalgias, dose decreased to 20 mg/dL and myalgias did not improve. CPK was 3X ULN. She is afraid of statins based on her experience and her internet searches. No medication interactions. R/o other causes.

• In terms of statin which would be the first approach
  • A) Declare her statin intolerant and focus on lifestyle modification
  • B) Declare her statin intolerant and try ezetimibe
  • C) Try another statin at low dose and dosed less frequently