Cholesterol Screening and Treatment in Adults
Review of the 2013 AHA/ACC Cholesterol Guidelines
(and a bit about kids)

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Cholesterol

* Bad
* Leading cause of morbidity and mortality
* Strong link between higher levels of LDL and disease
  * Good physiologic evidence in plaques
* Strong evidence that lowering LDL reduces disease (secondary prevention and finally primary prevention)
  * ~50% reduction in CHD events since initiation of statin therapies
**Previous Recommendations**

- **NHLBI: Adult Treatment Panel III, 2002**
  - Adopted by USPSTF, AAFP
  - Covered screening and treatment
  - Identified risk factors
  - Treated to specific LDL goals based on risk
    - Noted log-linear relationship between LDL levels and incidence of CHD, rate of atherosclerosis deposits
    - Lower LDL = lower rate of disease
    - Lowering LDL lowered rate of disease along that curve
    - Targets of 160, 130, 100 divided spectrum into quartiles
Figure II.8–1. Relation of CHD Events to LDL Levels in Treatment and Placebo Groups: Statin Trials⁴⁷²
Vascular disease (CHD, Carotids, AAA, PVD) or DM (now considered a CHD equivalent)

Major risk factors
- Smoking
- HTN
- Low HDL
- Family History of Premature Heart Disease
- Age
  - Men > 45
  - Women >55
Vascular disease or DM: LDL <100

Calculate 10 yr. Risk (Framingham tables)
  * 2+ risk factors, >20% risk, LDL goal <100
  * 1-2 risk factors, 10-20% risk, LDL goal <130
  * 0-1 risk factor, <10% risk, LDL goal <160

Initiate TLC

Statins if not brought to goal by TLC
  * Statin for ASCVD/?DM regardless
ATP III: Screen ‘adults.’ Negative ‘risk points’ for age < 40 men, <45 women
Formalized by USPSTF in 2008
Screen men > 35 yo, 20-35 if increased risk
Screen women > 45 yo if at increased risk, and 20-45 if at increased risk
Risk: Diabetes, Vascular disease, Family history early CHD, Tobacco use, HTN, Obesity (BMI >30)
Rescreen every 5 years
4 new guidelines

- Risk Assessment
- Cholesterol Management
- Obesity
- Lifestyle Recommendations
ATP IV (Cholesterol)

- Not the same as ATP III
  - NHLBI stepped out ~ 2013, transitioned the project to AHA/ACA
  - Not a comprehensive reevaluation
  - Asked specific ‘critical questions’
  - Chose only the ‘best’ recent RCT trials
    - Primarily 19 trials for secondary prevention
    - Primarily 6 trials for primary prevention
  - Limited data on women, CHF, dialysis, HDL, DM, elderly
**Critical questions**

- **CQ1:** What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of ASCVD?
  - Only one of the 19 RCTs titrated to a cholesterol goal, and not in enough numbers to establish significance
  - A meta-analysis suggested it was the medication and the resultant amount of LDL drop that was the critical factor
    - High Intensity meds reduced risk further than Medium Intensity meds at similar LDL numbers
  - As a result, LDL numeric goals were dropped
Figure II.8–1. Relation of CHD Events to LDL Levels in Treatment and Placebo Groups: Statin Trials

LDL-C during trial

Major coronary event rate (%)
Streetlight Effect
**Critical questions**

*CQ2: What is the evidence for LDL-C and non-HDL-C goals for the primary prevention of ASVCD?*

* In the 6 RCTs, med doses were fixed, i.e. 20mg or 40mg of lovastatin, 10mg or 20mg of pravastatin. Dosages could be increased if needed, but only by the fixed amounts. Meds were not titrated mg by mg to reach an LDL goal.

* None of the 6 RCTs compared two different LDL goals

* So again, no data supported specific LDL targets
Critical questions

CQ3: 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?

- Studies used statins, fibrates, niacin, bile acid sequestrants, ezetimibe, and omega-3 FA.
- None of the studies showed clinical significance in treatment with non-statin therapies.
ATP IV: Overall Recommendations

* TLC: Still recommended for all patients, prior to and while on statins
  * Heart Healthy diet
  * Regular exercise (40 min, 4 per week)
  * Avoidance of tobacco
  * Maintenance of a healthy weight
  * Control of comorbid HTN and DM
  * See separate report on Lifestyle Recommendations
New Risk Assessment

- Goal is to identify those most likely to benefit
- Includes CVA and TIA as CHD equivalent, and as goal to prevent
- DM no longer CHD equivalent
- Lowers threshold from 10/20% to 5/7.5% to consider or begin treatment
- Family History of early CHD no longer a risk factor
- Factors other than LDL (HDL, Trig, waist circumference, glucose etc.) no longer risk factors
ATP IV: Risk Assessment

- Did not keep ATP III risk tool
  - Derived from all white study population
  - Limited outcome measures (MI/CAD only)
- To be included, a risk factor must have been studied in a RCT with mixed race/gender populations, with minimum 10 yr follow up
- None of the following met criteria: hs-CRP, Apo-B, GFR, microalbumin, Family Hx, ABI, Carotid intima-media thickness, Coronary Artery Calcium score
Screening for adults
- Begin at age 21 for male and female
- Statin for LDL > 190 despite TLC
- Rescreen ‘every 4-6 years’
ATP IV: Overall Recommendations

* Treatment
  * 4 Treatment categories (sort of)
  * Based on history and risk calculator
  * Determines which type/dose of statin to use
  * Not all statins were tested in the 6/19 RCTs
  * Statins divided into Low/Moderate/High Intensity
  * Only Moderate and High Intensity statins recommended for use
## Statin Categories

<table>
<thead>
<tr>
<th>Low Intensity (&lt;30% drop in LDL)</th>
<th>Moderate Intensity (30%-50% drop in LDL)</th>
<th>High Intensity (&gt;50% drop in LDL)</th>
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<td>Pravastatin 10/20</td>
<td>Atorvastatin 10 (20)</td>
<td>Atorvastatin (40) 80</td>
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<td>Lovastatin 10</td>
<td>Rosuvastatin (5) 10</td>
<td>Rosuvastatin 20 (40)</td>
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<td>Simvastatin 20/40</td>
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<td>(Simvastatin 10)</td>
<td>Pravastatin 40 (80)</td>
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<td>(Fluvastatin 20/40)</td>
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<td>(Pitavastatin 1)</td>
<td>Fluvastatin 40 bid</td>
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<td></td>
<td>(Fluvastatin XL 80)</td>
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<tr>
<td></td>
<td>(Pitavastatin 2/4)</td>
<td>(xxx) = not tested but similar effect expected</td>
</tr>
</tbody>
</table>
1) Clinical ASCVD (MI, Angina, TIA, CVA, AAA, PVD, Carotid disease, prior revascularization of any artery)

- Age 75 or younger with no statin related safety concerns: HIGH Intensity Statin (1,A)
- Age greater than 75 or with safety concerns: MODERATE Intensity Statin (1,A) (few subjects >75 in studies on HIGH)
  - If already tolerating High Intensity statin can consider keeping them on it
- Safety Concerns: Liver or Renal dz, prior intolerance or reaction, muscle disease, other meds, multiple comorbidities
  - Then ‘consider risks vs. benefits’
2) LDL >190 (despite TLC and negative workup for secondary causes (1,B))

- HIGH intensity statin (1,B)
- ....that’s it
3) Diabetics, age 40-75, not in group 1 or 2

- 10 year ASCVD risk 7.5% or more: HIGH Intensity statin (2a,B)
- 10 year ASCVD risk < 7.5%: Moderate Intensity statin (1,A)

Under 40 or over 75? Not adequately studied in the RCTs selected for the guidelines to make a recommendation.

“...statin therapy should be individualized based on considerations of ASCVD risk reduction benefits, the potential for adverse effects and drug-drug interactions, and patient preferences.”
4) Patients ages 40-75, not in groups 1,2,3
   * 10 year ASCVD risk 7.5% or greater: MODERATE or HIGH Intensity Statin (1,B)
   * My gestalt
     * Smoker? HIGH. Worse risk factor than HTN or DM. Quit smoking, might not need a statin
     * Early Family History? HIGH
     * Healthy 76 y.o., can keep on HIGH if tolerating
     * Otherwise MODERATE
   * 10 year ASCVD risk 5-7.5%: benefit of statins is difficult to prove. Wait long enough, they will hit 7.5% (~age 68)
Other groups

- CHF NY Class II-IV: If this is the only dx, i.e. non ischemic disease, then statins not indicated
- Dialysis: If this is the only dx, then statins not indicated
  - Talk with your friendly neighborhood nephrologist
Initiating Statins

- TLC before, and during (1,A)
- No need to check CK prior, only if symptoms develop
  - Do ask about muscle pain prior to statin therapy and at each f/u visit
  - Can consider baseline CK if history of muscle problems or statin related muscle pain
- Check ALT prior, 3x normal precludes tx, needs workup
  - ALT surveillance no longer recommended (2a,C)
  - ALT changes no different from placebo groups
  - Check ALT if sx of liver disease
Ongoing Surveillance

- Fasting lipid panel 4-12 weeks after starting statin (1,A)
  - CK, ALT not needed (2a,C)
  - To check for effectiveness (expected drop in LDL)
  - To check for compliance (LDL didn’t drop as expected)
- Assess compliance (1,A)
- Reinforce TLC (1,A)
- Assess for side effects at each visit (1,A)
- Consider increase dosage if LDL drop not adequate (E)
- “LDL-C levels and percents reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.” (E)
- Repeat fasting lipids “every 3-12 months thereafter.”
Statins and DM

- Did address the small risk of developing DM as a result of statin therapy.
- Absolute and relative risk reduction in ASCVD events from statins outweigh increase in ASCVD events from increase in DM from statins for all groups using the 7.5% 10 year risk cutoff. At 5%, benefit disappears.
Assess compliance
Assess TLC
Exclude secondary causes
  * Thyroid, nephrotic syndrome, drugs
“In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of non-statin cholesterol-lowering drugs may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.”
Statin Intolerance

* Rates of CK elevation, ALT elevation, muscle pain similar in treatment and placebo groups in all the studies
* Use the highest dose tolerated by the patient
* Consider additional medications
Transition ATP III to ATP IV

- Not addressed in ATP IV
- Clinical ASCVD: Easy. Just make sure on appropriate medication
- Other groups, not so easy.
  - Need record/documentation of LDL >190
  - Need record/documentation of baseline lipid profile, i.e. off meds, to calculate risk level
- Consider taking off current meds and rechecking baseline lipid profile to calculate risk. Oy
Not full reevaluation of the data
Data incomplete due to limited RCTs reviewed
  * DM before 40
  * Age 75 and older (highest risk group)
Transition from ATP III to ATP IV
Risk tool and cut off at 7.5%
  * Various millions estimated to now need meds
  * Shifted to elderly men (68 yo male = 8% risk, female only 4.8%)
  * May take younger non-smokers, women, off meds
Other groups/organizations: USPSTF,
Controversies

* **AAFP: Endorses but with Qualifications**
  * “The guideline uses a CVD risk assessment tool that has not been validated and may overestimate risk. The risk cut-off of 7.5%, rather than 10%, will significantly increase the number of individuals on statins.
  * Many of the recommendations were based on expert opinion, although the key points are evidence based.
  * Seven of the 15 members of the guideline panel had conflicts of interest”


Suggests new risk calculator more sensitive and specific than old one, but used CAC as an endpoint.
Upcoming Changes

* USPSTF statement on adults: 2015
  * Likely in response to ATP IV
  * Unclear if will follow the same recommendations
    * ATP IV very limited in scope
      * DM under 40
      * DM and ASCVD after 75
      * Etc.
Upcoming Changes

* (ATP IV)... “is not and was never intended to be a comprehensive approach to lipid management.”
* Future ‘CQs’ to be addressed
  * Triglycerides
  * Other markers of risk
  * Lifetime risk vs 10 year risk
  * Non invasive imaging (CAC, carotid) or testing to assess risk
  * Long term effects of statin associated DM
  * Pharmagenetic testing
  * Statins in excluded groups (CHF, dialysis, HIV regimen, Organ transplant regimen)
* NHLBI Recommendations, published in Pediatrics, December 2011
* AAP endorses
  * Fasting Lipids age 1-4
    * If Family Hx positive for HL or CAD
    * Any other risk factors
  * Fasting Lipids age 9 to 11
    * All
* Statins now prescribable for age > 10
Children

* USPSTF
  * July 2007, “I” recommendation (Insufficient evidence)
  * Currently being updated
  * Anticipated release 2016

* AAFP: “Similarly, evidence is lacking that lowering cholesterol levels with lifestyle changes or medications improves cardiovascular outcomes, and long-term statin use is associated with rare but serious harms.16,17”
  * http://www.aafp.org/afp/2015/0315/p362.html
Questions and Discussion

* I assume there will be several....