The New Lipid Guidelines: A Practical Guide

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Disclosures

- None
Goals

- Introduce the 2013 ACC/AHA Cholesterol Guidelines
- Review differences between the “old” guidelines (ATP III) and the “new”
- Highlight the areas of controversy, particularly in the area of primary prevention
Schedule of Events

• Historical perspective and review of ATP III (old guidelines)
• Some new definitions
• Synopsis of the 2013 Cholesterol Guidelines
• The “big fight” about the risk prediction model
Evolution of Cholesterol Management

ATP I Guidelines 1988
- LDL level linearly related to CHD risk. LDL of 160 selected as abnormal

ATP II Guidelines 1993
- Started to give recommendations for clinical practice

ATP III Guidelines 2001
- Recommended all the major lipid lowering drug classes

ATP III Guidelines Revised 2004
- LDL lowering still the goal. Extrapolated from statins to other drug therapies
## ATP III (revised)

<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, consider &lt;70 (-30-40%)</td>
<td>≥100</td>
<td>≥100 &lt;100 consider drug</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≤20%)</td>
<td>&lt;130 Consider &lt;100</td>
<td>≥130</td>
<td>10-year risk 10–20%: ≥130 Consider drug 100-130</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190 (160–189: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>
### Framingham Point Scores in Men

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 34</td>
<td>-9</td>
</tr>
<tr>
<td>35 to 39</td>
<td>-4</td>
</tr>
<tr>
<td>40 to 44</td>
<td>0</td>
</tr>
<tr>
<td>45 to 49</td>
<td>3</td>
</tr>
<tr>
<td>50 to 54</td>
<td>6</td>
</tr>
<tr>
<td>55 to 59</td>
<td>8</td>
</tr>
<tr>
<td>60 to 64</td>
<td>10</td>
</tr>
<tr>
<td>65 to 69</td>
<td>11</td>
</tr>
<tr>
<td>70 to 74</td>
<td>12</td>
</tr>
<tr>
<td>75 to 79</td>
<td>13</td>
</tr>
</tbody>
</table>

**NOTE:** These risk estimates for the development of coronary heart disease do not account for all important cardiovascular risk factors. Not included are diabetes mellitus (which is considered a CHD-equivalent), family history of CHD, alcohol intake, and the serum C-reactive protein concentration.

<table>
<thead>
<tr>
<th>Total cholesterol mg/dL (mmol/L)</th>
<th>Age 20 to 39</th>
<th>Age 40 to 49</th>
<th>Age 50 to 59</th>
<th>Age 60 to 69</th>
<th>Age 70 to 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;160 (5.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>160 to 199 (3.4 to 5.15)</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>200 to 239 (5.17 to 6.18)</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>240 to 279 (6.2 to 7.21)</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>≥280 (7.24)</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 39</td>
<td>0</td>
</tr>
<tr>
<td>40 to 49</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL cholesterol mg/dL (mmol/L)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 (1.55)</td>
<td>-1</td>
</tr>
<tr>
<td>50 to 59 (1.29 to 1.53)</td>
<td>0</td>
</tr>
<tr>
<td>40 to 49 (1.05 to 1.27)</td>
<td>1</td>
</tr>
<tr>
<td>&lt;40 (1.03)</td>
<td>2</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Systolic blood pressure, mmHg</th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120 to 129</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>130 to 139</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>140 to 159</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>≥160</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Point total</th>
<th>10-year risk, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
<td>1</td>
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<td>3</td>
<td>1</td>
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<td>4</td>
<td>1</td>
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<td>2</td>
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<td>6</td>
<td>2</td>
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<td>4</td>
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<td>10</td>
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<td>20</td>
<td>24</td>
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<tr>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>23</td>
<td>30</td>
</tr>
</tbody>
</table>

The point total is determined in each category and the 10-year risk determined in the bottom row.
## Classification of Serum Triglycerides

<table>
<thead>
<tr>
<th>Category</th>
<th>mg/dl</th>
<th>mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;150</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td>Borderline high</td>
<td>150–199</td>
<td>1.7–2.2</td>
</tr>
<tr>
<td>High</td>
<td>200–499</td>
<td>4.5–5.6</td>
</tr>
<tr>
<td>Very high</td>
<td>≥500</td>
<td>&gt; 5.6</td>
</tr>
</tbody>
</table>
Treating Elevated Triglycerides

- Primary aim of therapy is to reach LDL goal.
- Intensify weight management; Increase physical activity.
- If triglycerides are 200 mg/dL after LDL goal is reached….

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>Non-HDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>2+ Risk Factor</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>0-1 Risk Factor</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
</tbody>
</table>

- If triglycerides 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal.
Treating Elevated Triglycerides

If triglycerides 500 mg/dL, first lower triglycerides to prevent pancreatitis:

- very low-fat diet (15% of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid
ATP III: Low HDL Cholesterol

Management of Low HDL Cholesterol

• First reach LDL goal, then:
• Intensify weight management and increase physical activity.
• If triglycerides 200-499 mg/dL, achieve non-HDL goal.
• If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent, consider nicotinic acid or fibrate.
The New Guidelines: What are they all about?
First, some definitions

- Atherosclerotic Cardiovascular Disease (ASCVD) refers to
  - Acute coronary syndromes
  - Myocardial infarctions
  - Stable angina
  - Coronary or other arterial revascularization
  - Stroke
  - TIA
  - Peripheral arterial disease of atherosclerotic origin
### Table 2. High-, Moderate-, and Low-Intensity Statin Therapy*

<table>
<thead>
<tr>
<th>Statin Therapy</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Intensity†</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20 (40) mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>–</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>–</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>–</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>–</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>–</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>–</td>
</tr>
</tbody>
</table>

FDA = U.S. Food and Drug Administration; LDL-C = low-density lipoprotein cholesterol; XL = extended-release.

* Individual responses to statin therapy varied in randomized, controlled trials and vary in clinical practice. A less-than-average response may have a biologic basis. Statins and dosages in bold were reduced in major cardiovascular events in randomized, controlled trials. Statins and doses in italics were approved by the FDA but were not tested in randomized, controlled trials.

† Daily dose decreases LDL-C levels by an average of ≥50%.
‡ Daily dose decreases LDL-C levels by an average of 30% to <50%.
§ Daily dose decreases LDL-C levels by an average of <30%.
¶ Evidence from 1 randomized, controlled trial only; down-titration if patient is unable to tolerate atorvastatin, 80 mg.
** Although simvastatin, 80 mg, was evaluated in randomized, controlled trials, the FDA recommends against initiation of or titration to 80 mg of simvastatin because of increased risk for myopathy and rhabdomyolysis.

** Twice daily.

The New ATP IV

• Began in 2008 (considered RCT and meta analyses 1995 through July 2013)
• Created in an era when there are now guidelines for the development of guidelines
• Questions Posed
  – What are the optimal LDL and HDL cholesterol goals of treatment?
  – What are the risk-benefit profiles of specific drug treatments to lower cholesterol?

• **Question:** What are the optimal LDL and HDL cholesterol goals of treatment?

• **Answer:** Task force found no scientific evidence to supposed specific treatment goals for either LDL or HDL cholesterol

Question: What are the risk-benefit profiles of specific drug treatments to lower cholesterol?

Answer: New Guidelines separate patients into risk categories, usually with a clear relationship between the risk groups and eligibility criteria of major clinical trials.

Efficacy and safety of various drugs is focused on health outcomes (disease endpoints) rather than surrogate end point of LDL cholesterol.

The Recommendations…

Encourage Adherence to a Healthy Lifestyle

Statin therapy is recommended for adults in groups demonstrated to benefit.

- Clinical ASCVD
- Primary LDL cholesterol of >190 mg/dL
- Diabetes, age 40-75 and LDL >69 mg/dL
- Age 40-75, no diabetes, and ASCVD risk of 7.5% or more (consider in those with risk of >5%)
What Intensity of Statin Should I use?

Clinical ASCVD (of age >21) → **High**
Unless Age <75 with safety concerns, or >75 → **Moderate**

LDL >190 mg/dL (of age >21) → **High**

DM, age 40-75 and LDL >69 mg/dL → **Moderate**

Age 40-75, ASCVD risk of 7.5% or more
Discussion with patient, if statin chosen, **Moderate/High**
Group 1: Clinical ASCVD

- Strong clinical evidence
- High intensity statin in patients <75 will reduce events more than moderate intensity statin
- Most trials including patients >75 used moderate intensity statins and pts had a reduction in events
- Still need to individualize in older patients
Group 2: LDL >190

- If LDL >190 OR triglycerides >500: evaluate for secondary causes of hyperlipidemia

- Moderate evidence to use high intensity statin (unless contraindicated) in patients >21

- For triglycerides >500: addressed in an alternate set of guidelines
<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Sat. or trans fat, weight gain</td>
<td>Weight gain, very low-fat diets, refined carbs, excessive alcohol</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic synd.</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hypothyroidism, obesity, pregnancy</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy</td>
</tr>
</tbody>
</table>
Group 3: Diabetics (age 40-75)

- Strong clinical trial evidence that moderate intensity statin will lower ASCVD risk in Diabetics (age 40-75)
- If 10 year risk is >7.5%, consider high intensity statin (expert opinion)
- Age <40 or >75: Individualize
  - ASCVD risk reduction
  - Potential for adverse events, drug-drug interaction
  - Patient preference
Group 4: 10 year risk >7.5%

- Age 40-75 (no DM, LDL 70-189)
- Calculate 10 year risk
- If Risk >7.5% use moderate to high dose statin (strong evidence)
- If Risk is 5-7.5%, it is reasonable to offer treatment (weak evidence)

DISCUSS
How do I estimate risk?

The Pooled Cohort Equations Risk Calculator

• Made with data from 5 trials of African American and white men and women
• ARIC (Atherosclerotic Risk in Communities)
• CHS (Cardiovascular Health Study)
• CARDIA ( Coronary Artery Risk Development in Young Adults)
• Original Framingham Heart Study
• FHS Offspring Cohorts
2013 Prevention Guidelines Tools

CV RISK CALCULATOR

The American Heart Association and the American College of Cardiology are excited to provide a series of new cardiovascular prevention guidelines for the assessment of cardiovascular risk, lifestyle modifications that reduce risk, management of elevated blood cholesterol, and management of increased body weight in adults. To support the implementation of these guidelines, the new Pooled Cohort Equations CV Risk Calculator and additional Prevention Guideline Tools are available below. Others may be developed and available in the near future.

DOWNLOAD CV RISK CALCULATOR
Inputs

- Sex
- Age
- Race (AA or non-AA)
- Total Cholesterol
- HDL
- Systolic Blood Pressure
- Treatment for High Blood Pressure (Y/N)
- Diabetes
- Smoker
10-year risk of atherosclerotic cardiovascular disease

11.3% 🔴

10-year risk in a similar patient with optimal risk factors

3.7%

Lifetime risk of atherosclerotic cardiovascular disease

69% (62% to 73%)

Lifetime risk for a 50-year-old with optimal risk factors

5% (0% to 12%)
Live Demo

• http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
How was it tested?

• Validated in 2 cohorts
  – MESA (Multi-Ethnic Study of Atherosclerosis)
  – REGARDS (Reasons for Geographic and Racial Differences in Stroke)
• Some overestimation of ASCVD risk observed (primarily in higher-risk individuals)
• According to guidelines writers, modest overestimation of risk in those with >7.5% 10-year risk does not change management (still >5%)
Additional Useful Information

• Monitoring of statins
  – Advise baseline fasting (preferred) lipid panel CK and ALT prior to initiating statin
  – Routine monitoring of ALT or CK is not recommended unless clinically indicated by symptoms
  – Fasting lipid panel is recommended after initiation of therapy or changes of therapy to assess and provide feedback to the patient (not to check the “LDL goal”)
  – Allows for opportunity to promote adherence to lifestyle measures and statin therapy
Additional Useful Information

• Individual Risk of Adverse Effects
  – Advanced age (>75)
  – Small body frame and frailty
  – Multi-system disease (Impaired renal or hepatic function)
  – History of previous statin intolerance or muscle disorders
  – Medication interaction
  – Unexplained ALT>3 x upper limit of normal
What Was NOT Covered?
There are no recommendations

- In adults with NYHA heart failure class II-IV
- In adults receiving maintenance hemodialysis

- Subgroups may benefit

- Not currently enough evidence to make a recommendation one way or another
HDL and triglycerides

- Panel did not find any randomized control trials that supported addressing a low HDL or high triglycerides to prevent ASCVD
- AIM-HIGH: futility of adding niacin to a statin in patients with low HDL and high triglycerides
- ACCORD: futility of adding fenofibrate to statin in patients with diabetes
- Important question requiring further study
- Management of triglycerides >500 are addressed in a different paper
Patients over 75

- RCT support continuation of statins in pts over 75 years if already taking and tolerating these drugs
- Limited data indicate an ASCVD event reduction benefit in primary prevention
- Consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care.
- Risk equation works up to 80 years of age
Controversy?
• Argue that there is no need for a risk stratification model to allocate statin therapy
  – Many primary prevention trials published, why not use those inclusion criteria?
  – No trial of statins has ever used a risk model as an enrollment criterion
Ridker and Cook (cont)

• Question the validity of the risk prediction tool

• Compared the tool with observed event rates in primary prevention cohorts
  – Women’s health study
  – Physicians health study
  – Women’s health initiative observational study
Algorithm overestimated observed risks by 75-150%
The News Media Coverage

Does calculator overstate heart attack risk?

Risk calculator for cholesterol appears flawed

Cholesterol Controversy
The Response from ACC/AHA

- Clinical trial criteria are too complicated
- Three studies mentioned had abnormally low event rates
- Committee took some overestimation into account

Guideline Summary

Patients >21 yr of age without heart failure (NYHA class II, III, or IV) or end-stage renal disease (undergoing hemodialysis)
Screen for cardiovascular risk factors
Measure LDL cholesterol

Clinical atherosclerotic CVD
High-intensity statin therapy

Diabetes mellitus (type 1 or type 2) and age of 40–75 yr and LDL cholesterol 70–189 mg/dl
Calculate 10-yr risk of atherosclerotic CVD
If risk <7.5%, moderate-intensity statin therapy
If risk ≥7.5%, high-intensity statin therapy

No diabetes mellitus and age of 40–75 yr and LDL cholesterol 70–189 mg/dl
Calculate 10-yr risk of atherosclerotic CVD
If risk ≥7.5%, moderate-to-high-intensity statin therapy

LDL cholesterol ≥190 mg/dl
High-intensity statin therapy

Keaney et al. A pragmatic view of the new cholesterol treatment guidelines. NEJM. January 16, 2014
Vignette 1

- A 44-year-old woman has a 10-year history of type 2 diabetes. She is a nonsmoker with well-controlled hypertension and microalbuminuria. She is on dietary management, metformin, and takes one omega-3 fatty acid capsule with 840 mg of EPA and DHA. She also takes lisinopril/hydrochlorothiazide for her blood pressure. She has a family history of diabetes, but not premature ASCVD. She has a BP 134/78 and a BMI of 36.0. Her fasting lipid panel reveals an LDL–C 95 mg/dL, triglycerides 350 mg/dL, and HDL–C 38 mg/dL. Her hemoglobin A1c is 7.5%.
I. Which of the following statements is the best answer?

• a. Her LDL–C is under 100 mg/dL so she is at “goal” and does not require a statin.
• b. She should start simvastatin 20 mg and fenofibrate 160 mg daily.
• c. To reduce her risk of an ASCVD event, the dose of omega-3 fatty acid should be increased to 4 capsules daily to lower her triglycerides.
• d. If she does not want to start a statin, a bile acid sequestrant is the next best choice for her.
• e. Her 10-year ASCVD risk should be calculated to determine if she needs a high- or moderate-intensity statin.
A 63-year-old man is seen in the office 2 weeks after a STEMI. A former smoker with hypertension, he was discharged on atorvastatin 80mg daily, dual anti-platelet therapy, long-acting metoprolol, and an ACE inhibitor. One year before the acute MI, he was prescribed simvastatin 40 mg which was then increased to simvastatin 80 mg. He stopped the simvastatin 80 mg 2 weeks later after developing muscle cramps in his legs. Although he has no muscle symptoms since he started the atorvastatin 80 mg, he is concerned about having had muscle cramps in the past on a statin and would like to decrease the atorvastatin to 20 mg daily.
Question 2

I. Which of the following statements is the best answer?

a. Randomized trials of high intensity statin therapy versus moderate intensity statin therapy have not shown a significant difference in outcomes. He should decrease the atorvastatin to 20 mg to minimize adverse effects.

b. Systematic meta-analyses of randomized clinical trials support using an intensive statin dose such as atorvastatin 80 mg/day over a moderate intensity statin. He should stay on atorvastatin 80 mg.

c. He should be followed with creatine kinase (CK) values when his lipids are checked at each visit for the first year.

d. Although his liver panel was normal in the hospital, he should have an alanine aminotransferase (ALT) done at each subsequent visit.
Vignette 3

- A 60-year-old African-American woman has asked whether she should be taking a statin to reduce her risk of stroke, but is worried about the statin causing diabetes. Her mother had diabetes and had a stroke at age 62. She is a nonsmoker. Blood pressure is 142/88 mm Hg on 2 antihypertensive medications and BMI is 31. Her fasting lipid panel reveals a total cholesterol 200 mg/dL, HDL–C 55 mg/dL, triglyceride 100 mg/dL, and LDL–C 125 mg/dL. Her fasting blood sugar is 109 mm/dL and hemoglobin A1c is 5.9%. According to the Pooled Cohort Equation for African-American Women, her estimated 10-year ASCVD risk is 8.7 %.
Question 3

I. Which of the following statements is the best answer?

a. She should focus on lifestyle change to improve her risk factors because lifestyle has been shown to reduce ASCVD events more than statin therapy.

b. The risk of progression to diabetes with a statin outweighs any ASCVD risk reduction benefits from statin therapy. The decision about a statin to be deferred.

c. She should start a moderate or high intensity statin.

d. A high-sensitivity C-reactive protein (hs-CRP) >2 would be needed before the decision can be made whether to start a statin.
• Prevention Guidelines Clinical Vignettes, Cardiosource.org