Update on Cholesterol Management: The 2013 ACC/AHA Guidelines

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11th Annual National Summit on Healthcare Disparities
Disclosure: Conflict of Interest

Speaker

Arbor Pharmaceuticals
Takeda Pharmaceuticals
Forest Laboratories

Some slides provided by Stephen L Kopecky MD
Historical Perspective

Previous lipid guidelines:

ATP 1 to ATP 3
LDL-centric (LDL levels assumed to determine levels of cardiovascular risk)
LDL : primary target of therapy
Historical Perspective

- Blood Cholesterol expert panel evolved from ATP (IV) panel (NHLBI)
- Focus on RCT and meta-analysis of RCTs
- Limited expert opinions
What has been the endpoint for statin studies?

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Comparison</th>
<th># Pts</th>
<th>n=80473</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Simva 20-40</td>
<td>P</td>
<td>4,444</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Prava 40</td>
<td>P</td>
<td>6,595</td>
</tr>
<tr>
<td>CARE</td>
<td>Prava 40</td>
<td>P</td>
<td>4,159</td>
</tr>
<tr>
<td>Post CABG</td>
<td>Lova 40-80</td>
<td>Lo 2.5-5</td>
<td>1,351</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>Lova 20-40</td>
<td>P</td>
<td>6,605</td>
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<tr>
<td>LIPID</td>
<td>Prava 40</td>
<td>P</td>
<td>9,014</td>
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<tr>
<td>GISSI Prevenzione</td>
<td>Prava 20</td>
<td>No Rx</td>
<td>4,271</td>
</tr>
<tr>
<td>HPS</td>
<td>Simva 40</td>
<td>P</td>
<td>20,536</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Prava 40</td>
<td>Us Care</td>
<td>10,355</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Atorva 10</td>
<td>P</td>
<td>10,305</td>
</tr>
<tr>
<td>CARDS</td>
<td>Atorva 10</td>
<td>P</td>
<td>2,838</td>
</tr>
</tbody>
</table>

Lancet 2005: 366;1267

P=Placebo
Lipid Trials

• The randomized intervention was statin use not LDL levels.
## Known Lipid-Independent Effects of Statins*

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased synthesis of nitric oxide</td>
</tr>
<tr>
<td>Inhibition of free radical release</td>
</tr>
<tr>
<td>Decreased synthesis of endothelin-1</td>
</tr>
<tr>
<td>Inhibition of low-density lipoprotein cholesterol oxidation</td>
</tr>
<tr>
<td>Upregulation of endothelial progenitor cells</td>
</tr>
<tr>
<td>Reduced number and activity of inflammatory cells</td>
</tr>
<tr>
<td>Reduced levels of C-reactive protein</td>
</tr>
<tr>
<td>Reduced macrophage cholesterol accumulation</td>
</tr>
<tr>
<td>Reduced production of metalloproteininases</td>
</tr>
<tr>
<td>Inhibition of platelet adhesion or aggregation</td>
</tr>
<tr>
<td>Reduced fibrinogen concentration</td>
</tr>
<tr>
<td>Reduced blood viscosity</td>
</tr>
</tbody>
</table>

*These effects have been reported to have molecular mechanisms that are independent of statins' effect on low-density lipoprotein cholesterol (18).
Why not continue to Treat to LDL Target?

Major difficulties:

1) Current RCT data do not indicate what the target should be.
2) Unknown magnitude of additional ASCVD risk reduction with one target vs. another.
3) Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal.
4) Therefore, unknown net benefit from treat-to-target approach.

ASCVD=atherosclerotic cardiovascular disease
LDL HOUSE OF CARDS
1) Clinical ASCVD

2) LDL >190 mg/dL (4.9 mmol/l)

3) Diabetic 40-75 years, w/ LDL 70-189 mg/dL (1.8-4.9 mmol/l)

4) Others 40-75 years, w/ LDL 70-189 mg/dL (1.8-4.9 mmol/l) and 10-year ASCVD risk >7.5%.

Age >21 yrs and statin candidate
NOT Heart Failure Class 2-4; NOT on dialysis
CHECK YOUR PULSE. IF YOU HAVE ONE, YOU SHOULD BE TAKING STATIN DRUGS.
Pt > 21 yrs of Age

Screen for CV Risk Factors & Measure LDL

AtheroCVD

DM 1 OR 2
Age 40-75
LDL 70-189

10 yr Risk

< 7.5%, Mod Dose Statin
≥7.5%, High dose Statin

No DM
Age 40-75
LDL 70-189

10 yr Risk

≥7.5% Mod-Hi Dose

LDL ≥ 190

High Dose Statin

Not for patients w/ Heart (NYHA 2-4) or Renal Failure (dialysis)

LDL = Low Density Lipoprotein mg/dL (to convert to mmol/L, multiply by 0.0259)
AtheroCVD = Known atherosclerotic cardiovascular disease

A Pragmatic View of the New Cholesterol Treatment Guidelines Keaney et al November 27, 2013 NEJM
<table>
<thead>
<tr>
<th>LDL ↓</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>≥50%</td>
<td>30%-%&lt;50%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>At (40*)-80</td>
<td>At 10 (20)</td>
<td>Si 10</td>
<td></td>
</tr>
<tr>
<td>Ro 20 (40)</td>
<td>Ro (5) 10</td>
<td>Pr 10–20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Si 20–40</td>
<td>Lo 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pr 40 (80)</td>
<td>Fl 20–40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lo 40</td>
<td>Pi 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fl XL 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fl 40 bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pi 2–4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All doses in mg per day
*If unable to tolerate 80 mg

Ro=Rosuvastatin At=Atorvastatin Si=Simvastatin Pr=Pravastatin
Lo=Lovastatin Fl=Fluvastatin Pi=Pitavastatin

**Yellow:** Evaluated in RCTs and Chol Treatment Trialists Meta-analysis of 170,000 participants Lancet 2010;376:1670–1681; All demonstrated reduction in major CV events
Welcome to ClinCalc.com

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Clinical Calculators

By Category  A to Z  By Date

Cardiology

- CHADS2 Calculator for Atrial Fibrillation
- CHADS2-VASc Calculator for Atrial Fibrillation
- Digoxin calculator for heart failure and atrial fibrillation
- HAS-BLED Calculator for Atrial Fibrillation
- Pooled Cohort 10-Year Risk Assessment Equations
# Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

## Risk Factors for ASCVD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/Female</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
</tr>
<tr>
<td>Race</td>
<td>White/other</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>mmHg</td>
</tr>
<tr>
<td>Receiving treatment</td>
<td>Yes/No</td>
</tr>
<tr>
<td>for high blood pressure</td>
<td></td>
</tr>
<tr>
<td>(if SBP &gt; 120 mmHg)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Smoker</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

## Calculations

- [Reset](#) [Calculate](#)
Clinical ASCVD
Initiating Statin Therapy

Defined as: ACS, Hx of MI, Angina, Revasc, CVA, TIA or PAD

Clinicians should engage in discussion of:
1. ASCVD Risk Reduction Benefits
2. Adverse Effects
3. Drug-drug interactions
4. Patient preferences

Re-emphasize healthy lifestyle habits
lifestyle modification (i.e., adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol-lowering drug therapies
Case Vignettes

• 45 year old white female
• Malpractice attorney
• No prior history of ASCVD
• Father died at the age of 52 from a massive heart attack
• No other risk factor
• BP 140/70
• Tc = 275, LDL = 188, HDL = 52, Trig = 175
• Calc 10-year risk = 1.8%
Who else to consider for statins?
Individuals with additional risk factors

- LDL ≥160 mg/dL (4.14 mmol/l) or other evidence of genetic hyperlipidemias,
- Family History: <55 yrs 1st degree male relative or <65 years 1st degree female relative
- hs-CRP: >2 mg/L,
- CAC: ≥300 Agatston u or ≥75 %tile age, sex, race
- Ankle-brachial index <0.9
- Elevated lifetime risk of ASCVD
What are you going to see more of?

- **Patients on statins** – expands indications from current 43 million to 56 million (mainly for primary prevention)
- **Statin Intolerance**
- **Less Rx for LDL ≥ 190**

Pencina et al NEJM 2014
370;15:1422
The Strip by Brian McFadden

STATINS SHOULD BE RECLASSIFIED AS A SCHEDULE 1 CONDIMENT.
Case Vignette

- 68 year old AA male
- No hx of ASCVD
- Asymptomatic
- No modifiable risk factor for CAD
- Tc = 162, LDL = 79, HDL= 52, Trig = 156
- Calc 10-year risk = 11%
What are the gaps?

- Maybe too age dependent
- Treating Risk $\geq 7.5\%$ not validated
- Residual on-statin risk
- Ignores HDL
Key Points: New Lipid Guidelines

- **Assess patient for RISK indication** (Known ASCVD, LDL>190, DM Age 40-75, 10 Yr Risk > 7.5%)
- **Should be Age > 21, Statin Candidate**
  - NOT Heart Failure Class 2-4; NOT on Dialysis
- Assess 10-year pooled risk
- **Lifestyle always key 1st step**
- **Dosing**: Low – Si 10; Mod-At 10-20; Hi- At 40-80
- **Goal** is dose of statin, not LDL
- **Consider additional risk stratifiers** (Lifetime risk, CT Cor Cal ≥ 300, LDL ≥ 160, FH, hs-CRP ≥ 2.0, ABI ≤ 0.90)
Thank you for your attention!
ASCVD Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention.

In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL–C 70-189 mg/dL.
Who Should Get a Statin
Dr. Akinboboye’s approach?

- **CVD** (age > 75 : Mod statin, < 75 : High Statin)
- **Is**
- **Super High** (LDL >190 (High statin))
- **In**
- **40 to 75 year old diabetic** with LDL = 70-189) (calc risk for intensity
- **40 to 75 year old non-diabetic** with LDL 70-189 and Calc risk >= 7.5 (mod or high statin)
Who Should Get a Statin
Dr. Akinboboye’s approach?

- LDL 70 to 189
- and
- Age : 40-75
- and
- Calc 10 year risk >= 7.5
LDL Exposure Over Time: Equivalent to Other Disease States?

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>LDL Exposure</th>
<th>SBP</th>
<th>FBS</th>
<th>PPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>180 mmHg</td>
<td>100</td>
<td>140 mg/dl</td>
<td>2 PPD</td>
</tr>
<tr>
<td>30</td>
<td>130 mg/dl</td>
<td>100</td>
<td>140 mg/dl</td>
<td>2 PPD</td>
</tr>
<tr>
<td>40</td>
<td>160 mg/dl</td>
<td>100</td>
<td>140 mg/dl</td>
<td>2 PPD</td>
</tr>
<tr>
<td>50</td>
<td>200 mg/dl</td>
<td>100</td>
<td>140 mg/dl</td>
<td>2 PPD</td>
</tr>
<tr>
<td>60</td>
<td>250 mg/dl</td>
<td>100</td>
<td>140 mg/dl</td>
<td>2 PPD</td>
</tr>
<tr>
<td>70</td>
<td>300 mg/dl</td>
<td>100</td>
<td>140 mg/dl</td>
<td>2 PPD</td>
</tr>
</tbody>
</table>

Myocardial Infarction
Primary Prevention: *Crucial Opportunity to Reduce the Burden of CHD*

Results for the Heart Protection Study. No statistically or clinically significant difference was seen in relative benefit of statin therapy by low-density lipoprotein (LDL) cholesterol level at baseline or prerandomization LDL response. To convert LDL cholesterol values to mg/dL, divide by 0.02586.

Figure Legend:
## Classification of Recommendation and Level of Evidence

### Size of Treatment Effect

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Class I | Benefit >>> Risk  
Procedure/Treatment SHOULD be performed/administered | A     | Multiple populations evaluated*  
Data derived from multiple randomized clinical trials or meta-analyses |
| Class IIa | Benefit >>> Risk  
Additional studies with focused objectives needed  
It is reasonable to perform procedure/administer treatment | A     | Limited populations evaluated*  
Data derived from a single randomized trial or nonrandomized studies |
| Class IIb | Benefit ≥ Risk  
Additional studies with broad objectives needed; additional registry data would be helpful  
Procedure/Treatment MAY BE CONSIDERED | A     | Very limited populations evaluated*  
Only consensus opinion of experts, case studies, or standard of care |
| Class III | No Benefit  
or Class III Harm | B     | No benefit  
Not Helpful  
No Proven Benefit |
| Class III | Excess Cost  
Without Benefit or Harmful to Patients | B     | Recommendation that procedure or treatment is not useful/effective and may be harmful  
Sufficient evidence from multiple randomized trials or meta-analyses |
| Class III | Excess Cost  
Harmful to Patients |

### Level of Evidence

<table>
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<th>Level</th>
<th>Description</th>
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| A     | Recommendation that procedure or treatment is useful/effective  
Sufficient evidence from multiple randomized trials or meta-analyses |
| B     | Recommendation that procedure or treatment is useful/effective  
Evidence from single randomized trial or nonrandomized studies |
| C     | Recommendation that procedure or treatment is useful/effective  
Only expert opinion, case studies, or standard of care |
Summary of lipid studies. Top. Event rate assuming a single association between low-density lipoprotein (LDL) cholesterol and outcome. Bottom. The LDL–outcome associations found within each study. 4S= Scandinavian Simvastatin Survival Study; CARE= Cholesterol and Recurrent Events Study; HPS= Heart Protection Study; LIPID= Long-Term Intervention with Pravastatin in Ischemic Disease Study; TNT= Treating to New Targets Study. To convert LDL cholesterol values to mmol/L, multiply by 0.02586.

Figure Legend:

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Pooled Cohort Risk Assessment Equations
Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

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</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>59 years</td>
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<tr>
<td><strong>Race</strong></td>
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<tr>
<td>White or other</td>
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<tr>
<td><strong>Total Cholesterol</strong></td>
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<tr>
<td>220 mg/dL</td>
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<tr>
<td><strong>HDL Cholesterol</strong></td>
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<tr>
<td>46 mg/dL</td>
</tr>
<tr>
<td><strong>Systolic BP</strong></td>
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<tr>
<td>119 mmHg</td>
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<tr>
<td><strong>Receiving treatment for high blood pressure (if SBP &gt; 120 mmHg)</strong></td>
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<tr>
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<tr>
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</tr>
<tr>
<td><strong>Smoker</strong></td>
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<tr>
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<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

**Reset  Calculate**
Clinical ASCVD
Initiating Statin Therapy

Evaluation prior to statin:
- Fasting lipids
- ALT
- CK (if indicated)
- Secondary Causes
- Statin Safety

Evaluate and Treat Lab Abnormalities:
1) TG’s ≥ 500 mg/dl
2) LDL > 190mg/dl
   • Secondary Causes
   • Screen family for FH

Monitor cholesterol levels to track adherence
Who Should Get a Statin?

My Approach

• CVD
• Is
• Super High
• In
• 40-75 year old diabetics with LDL:70-189 mg/dL
• and
• Others: 40-75 year old with LDL:70-189 and risk score of >=7.5
ASCVD Risk Evaluation

10-year risk of atherosclerotic cardiovascular disease: 8.2%

10-year risk in a similar patient with optimal risk factors: 5.2%

Lifetime risk of atherosclerotic cardiovascular disease: 46% (95% CI 38% to 53%)

Lifetime risk for a 50-year-old with optimal risk factors: 5% (95% CI 0% to 12%)
ASCVD Risk Interpretation

- This patient is at ELEVATED 10-year risk (≥ 7.5%) for atherosclerotic cardiovascular disease (ASCVD)

- Consider a moderate-to-high intensity statin in patients with a 10-year ASCVD risk of 7.5% or higher (assuming no clinical ASCVD or diabetes, aged 40 to 75 years, and LDL 70 to 189 mg/dL)

- In individuals not receiving cholesterol-lowering drug therapy, recalculate the 10-year ASCVD risk every 4 to 6 years (assuming age 40-75 years, no clinical ASCVD or diabetes, and LDL 70-189 mg/dL)
ASCVD Risk Evaluation

10-year risk of atherosclerotic cardiovascular disease: 8.2%

10-year risk in a similar patient with optimal risk factors: 5.2%

Optimal risk factors include:
- Total cholesterol of 170 mg/dL
- HDL cholesterol of 50 mg/dL
- Systolic BP of 110 mmHg
- Not taking medications for hypertension
- Not a diabetic
- Not a smoker

Lifetime risk of atherosclerotic cardiovascular disease: 46%
(95% CI 38% to 53%)

Lifetime risk for a 50-year-old with optimal risk factors: 5%
(95% CI 0% to 12%)