New Cholesterol Guidelines

What the LDL are we supposed to do now?!

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2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association and WomenHeart: The National Coalition for Women With Heart Disease

NHLBI Charge to the Expert Panel

- Evaluate higher-quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk
  - Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
  - RCTs and systematic reviews/meta-analyses of RCTs independently assessed for quality
  - Independent contractors performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel

NHLBI Charge to the Expert Panel

- Guidelines included RCTs with major ASCVD outcomes through July 2013
- Less expert opinion than in prior guidelines
- All 16 members of the NHLBI ATP IV Panel transitioned to the ACC/AHA guideline Expert Panel
The Expert Panel constructed CQs relevant to clinical practice.

The Expert Panel identified (a priori) inclusion/exclusion (I/E) criteria for each CQ

An independent contractor developed a literature-search strategy, based on I/E criteria, for published clinical trial reports for each CQ

An independent contractor executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ

The date range for the overall literature search was from January 1, 1995 through December 1, 2009

However, RCTs with the ASCVD outcomes of MI, stroke, and cardiovascular death published after that date were eligible for consideration until July 2013

Systematic Review Process

Synopsis of Recommendations

1. Encourage adherence to a healthy lifestyle
2. Statin therapy recommended for adult groups demonstrated to benefit
3. Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored
4. Engage in a clinician-patient discussion before initiating statin therapy — especially for primary prevention in patients with lower ASCVD risk


Synopsis of Recommendations

5. Use the newly developed pooled cohort equations to estimate 10-year ASCVD risk
6. Initiate proper intensity of statin therapy
7. Evidence is inadequate to support treatment to specific LDL-C or non-HDL-C goals
8. Regularly monitor patients for adherence to lifestyle and statin therapy


Well-patient visit

- A 68 year old African American man who is proud of his good health takes amlodipine for elevated blood pressure and is otherwise well. BP is 120/80

  He has these labs:
  Total Chol 200
  HDL-C 40
  LDL-C 113

Clinical Questions:
1) Does this patient belong on a statin?
2) Really?!!
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk

Four Statin Benefit Groups

1. Individuals with clinical atherosclerotic cardiovascular disease (ASCVD) – acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

2. Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL.

3. Individuals 40–75 years of age with diabetes, and LDL-C 70–189 mg/dL without clinical ASCVD.

4. Individuals without clinical ASCVD or diabetes, who are 40–75 years of age with LDL-C 70–189 mg/dL, and have an estimated 10-year ASCVD risk of 7.5% or higher.

Overview: Statin Benefit Groups

High Risk Groups

Secondary Prevention
Diabetes
40 to 75 yrs
LDL-C 70-189 mg/dL
LDL-C ≥ 190 mg/dL

Primary Prevention
40 to 75 yrs
LDL-C 70-189 mg/dL
ASCVD Risk ≥ 7.5%

Rx: Moderate- or high-intensity (dependent on clinical context)
Statin Rx not automatic, requires clinician-patient discussion

Intensity of Statin Therapy

High-, Moderate- and Low-Intensity Statin Therapy (used in the RCTs reviewed by the Expert Panel)*

<table>
<thead>
<tr>
<th>Statin</th>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10-40 mg</td>
<td>Daily dose lowers LDL-C, on average, by approximately ≥ 50%</td>
<td>Daily dose lowers LDL-C, on average, by approximately 30% to &lt; 50%</td>
<td>Daily dose lowers LDL-C, on average, by &lt; 30%</td>
</tr>
<tr>
<td>Rosuvastatin 10-20 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin 10-80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 20-40 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitavastatin 2-4 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** In bold are agents with benefit demonstrated in RCTs
**Exceptions/contraindications to high-dose**  
*(Choose moderate-intensity instead)*

- Age >75 (ASCVD)
- Lower ASCVD risk
- Multiple or serious comorbidities, ↓ renal or hepatic function
- Side effects
- Muscle disorders
- Anticipated drug interactions  
  - (P450, HIV meds, immunosuppressives)
- History of hemorrhagic stroke
- Asian ancestry

**Excluded from Guideline**

Consider using no statin: unlikely to benefit despite high ASCVD risk –

- ESRD on maintenance dialysis
- Higher NYHA classes (II-IV) of heart failure

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**What Does the Clinician-Patient Discussion Before Statin Therapy Look Like?**

<table>
<thead>
<tr>
<th>Estimate 10-yr ASCVD risk</th>
<th>Review potential for benefit from heart-healthy lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review other risk factors and risk factor control</td>
<td>Include informed patient preferences to facilitate shared decision making</td>
</tr>
</tbody>
</table>

| Review potential for - benefit from statins and potential for adverse effects and drug-drug interactions |  |

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**Additional Factors when Risk Decision is Uncertain**

- LDL-C ≥ 160
- Family history of premature ASCVD
- Increased lifetime risk
- CAC score ≥ 300 or ≥ 75th percentile
- hs-CRP ≥ 2
- ABI < 0.9
Monitoring and Follow-up

Adherence to a heart-healthy lifestyle
- Optimal adherence to improve lipid profile

Measure lipids regularly; 3-12 weeks after start, then 4-12 months as appropriate to check adequacy of statin Rx
- If high risk and inadequate response, consider nonstatin Rx
- Consider secondary causes

Review safety issues at each visit
Maximally tolerated statin intensity to keep LDL-C low

- For example, some may require CK, FBS, HbA1C

Lifetime risk estimator

- For those 20-59 years, it provides lifetime risk estimate
- This is intended to drive discussions of greater adherence to heart-healthy lifestyle
- Part of risk discussion

Areas of Controversy

- Pooled cohort equation
- Significantly lower threshold to consider initiation of statin in primary prevention
- Emphasis on intensive statin therapy
- No cholesterol treatment target goals
- Emphasis on importance of chronologic age
### Eligibility for statin

**Age 60-75 without ASCVD, currently not on statin:**

- **Men:** 87.4%
- **Women:** 53.6%

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**Pooled Cohort Equation**

<table>
<thead>
<tr>
<th></th>
<th>Sex: Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated or Untreated BP Reading?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker?</td>
<td>Non-Smoker</td>
<td>Smoker</td>
</tr>
<tr>
<td>Diabetic?</td>
<td>Non-Diabetic</td>
<td>Diabetic</td>
</tr>
<tr>
<td>10 Year Risk of ASCVD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Application of New Cholesterol Guidelines to a Population-Based Sample**

Michael J. Pencina, Ph.D., Ann Marie New-Bergen, M.D., Ph.D., Ralph S. D’Agostino, Sr., Ph.D., Jon Williams, M.S., Benjamin H. Levy, M.D., Allen D. Siscovick, M.D., and Eric D. Peterson, M.D., M.P.H.

**ABSTRACT**

**BACKGROUND:**

The 2013 guidelines of the American College of Cardiology and the American Heart Association (AHA) allow for the treatment of individuals based on the indications for the prevention of cardiovascular disease.

**METHODS:**

Using data from the National Health and Nutrition Examination Surveys of 2005 to 2010, we calculated the numbers and characteristics of individuals who would be recommended for treatment based on the new AHA guidelines, as compared to the guidelines of the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program, and compared the results to a population of 157,4 million U.S. adults between the ages of 40 and 75 years.

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**Pencina et al., NEJM, March 19, 2014**
Initial doubts

“The AHA/ACC prediction algorithm systematically overestimates the risk as compared to the observed event rates in these cohorts”…

*Primary prevention patient cohorts:
  --Women’s Health Study
  --Women’s Health Initiative
  --Physician’s Health Study

Primary Prevention Statin Therapy

- Thresholds for initiating statin therapy derived from 3 exclusively primary prevention RCTs
  - JUPITER, MEGA, AFCAPS-TEXCAPS
- Benefit of statin was seen down to risk of 5%
- Committee chose 7.5% cutoff instead so if overestimation, patient still in a statin benefit group

Pooled Cohort Equation

- Data from 5 population based NHLBI cohort studies and heart and stroke risk
  - ARIC, CARDIA, CHS, Framingham, FOS
- Includes African American status an input
- The previous ATP-III FRS for 10-yr CHD risk was based on older data
  - Higher estimate of CHD risk in many cases than the more recent Pooled Cohort Equation
- The Pooled Cohort Equation was recently validated in the REGARDS study of 30,000 black and white Americans from a contemporary population-based sample

REGARDS

- Observed and predicted 5-year ASCVD risk estimates were similar indicating that these risk equations were well calibrated
- Discrimination was moderate/good
  - Previous results of overestimation of ASCVD risk are likely due to incomplete capture of ASCVD events and inclusion of participants taking statins
- REGARDS supports the validity of the Pooled Cohort risk equations

Ridker P et al. Lancet 2013

Muntner P et al. JAMA 2014;311:1406-1415
# Observed and Predicted ASCVD Risk Among REGARDS Participants

Muntner P et al. JAMA 2014;311:1406-1415

## ASCVD Risk Calculator Pooled Cohort Equations

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Value</th>
<th>Acceptable Range of Values</th>
<th>Optimal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M or F</td>
<td>F</td>
<td>M or F</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>55</td>
<td>20-79</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>AA or WH</td>
<td>AA</td>
<td>AA or WH</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>mg/dL</td>
<td>210</td>
<td>130-320</td>
<td>170</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>mg/dL</td>
<td>56</td>
<td>20-100</td>
<td>50</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>mm Hg</td>
<td>145</td>
<td>90-200</td>
<td>110</td>
</tr>
<tr>
<td>Treatment for high blood pressure</td>
<td>Y or N</td>
<td>Y</td>
<td>Y or N</td>
<td>N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y or N</td>
<td>N</td>
<td>Y or N</td>
<td>N</td>
</tr>
<tr>
<td>Smoker</td>
<td>Y or N</td>
<td>N</td>
<td>Y or N</td>
<td>N</td>
</tr>
</tbody>
</table>

## ASCVD Risk Calculator 55-Year-Old AA and White Women

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Value</th>
<th>Acceptable Range of Values</th>
<th>Optimal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American Women</td>
<td>7.7</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Women</td>
<td>3.6</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Is threshold of 7.5% really a problem?

- About one-third of US adults 40-79 (~32M) will have risk >7.5% and merit risk discussion and statin consideration for primary prevention
- **Context**
  - One-third of Americans die from heart disease and stroke
  - 60% have a major vascular event during life
  - ~70M US adults qualify for BP-lowering therapy
  - Other tests may be considered when risk-based treatment is uncertain

### Why Not Continue to Treat to 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 compared to 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

### Focus on Appropriate Intensity of Statin Therapy to Reduce ASCVD Risk

- Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL-C goals
- Strong evidence that **appropriate intensity of statin therapy** should be used to reduce ASCVD risk in those most likely to benefit
- RCT data allows quantitative comparison of statin benefits with statin adverse effects
  - Important in discussions re: benefit of statin vs risk of diabetes
- Nonstatin therapies did not provide ASCVD risk-reduction benefits or safety profiles comparable to statin therapy

### Statin-Treated Individuals

**Nonstatin Therapy Considerations**

- Use the maximum-tolerated intensity of statin
- Consider the addition of nonstatin cholesterol-lowering drug
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - Clinical ASCVD < 75 years of age
    - Baseline LDL-C ≥ 190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Preference is given to non-statin drugs that have demonstrated reduction in ASCVD events in RCTs

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<table>
<thead>
<tr>
<th>Statin-Treated Individuals</th>
<th>Nonstatin Therapy Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use the maximum-tolerated intensity of statin</td>
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</tr>
<tr>
<td>• Consider the addition of nonstatin cholesterol-lowering drug</td>
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</tr>
<tr>
<td>– If a less-than-anticipated therapeutic response persists</td>
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</tr>
<tr>
<td>• Clinical ASCVD &lt; 75 years of age</td>
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</tr>
<tr>
<td>• Baseline LDL-C ≥ 190 mg/dL</td>
<td>• Baseline LDL-C ≥ 190 mg/dL</td>
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</tr>
</tbody>
</table>
Areas of Controversy

Response to the Critics

<table>
<thead>
<tr>
<th>Accuracy of ASCVD Risk Estimator</th>
<th>Faulty assumption that ASCVD risk ≥ 7.5% means automatic statin Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial concerns not supported by new data from REGARDS</td>
<td>No statin Rx without clinician-patient discussion!</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No LDL-C/non-HDL-C goals</th>
<th>Confusion regarding the role of nonstatin Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didn’t find evidence for or against...</td>
<td>Nonstatins may be used in high-risk patients to further reduce LDL-C levels per clinician judgment</td>
</tr>
</tbody>
</table>

The Risk Decision in Young Adults

- 41 yo white man with FHx of premature CAD and LDL-C 180 mg/dl
  - At 41, he has a low 10 year ASCVD risk, but still would qualify for Rx
  - Guidelines state that premature CHD and LDL-C ≥ 160 mg/dl may inform the treatment decision
  - Statin therapy would be reasonable in this situation after a risk discussion reviewing potential for benefit, potential for adverse effects, drug-drug interaction and patient preference

The Risk Decision in Older Adults

- 68 yo white man with average risk factors and estimated 10 year ASCVD risk of ≥ 7.5%
  - Merits a risk discussion to consider adherence to optimal lifestyle, potential for benefit, potential for adverse effects, drug-drug interactions, and informed patient preference
  - If clinician or patient felt risk decision uncertain, could order CACS, hs-CRP, or ABI

The Risk Decision in Older Adults

Follow-up lipid panel—see if anticipated response

- Reinforce adherence
- Follow-up 4-12 wk
- If intolerance:
  - Increase statin intensity
  - OR
  - Consider addition of nonstatin drug therapy

Follow-up medical adherence
- Reinforce adherence to recommended lifestyle changes
- Exclude secondary causes of hypercholesterolemia (Table 6)

Follow-up 4-12 wk
Management of Muscle Symptoms on Statin Therapy

- It is reasonable to evaluate and treat muscle symptoms including pain, cramping, weakness or fatigue in statin-treated patients according to the management algorithm.

- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy.

- If mild-to-moderate muscle symptoms develop during statin therapy:
  - Discontinue the statin until the symptoms are evaluated.
  - Evaluate the patient for other conditions* that might increase the risk of muscle symptoms.
  - If, after 2 months without statin Rx, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms.

*Hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency or primary muscle diseases.

Management of Muscle Symptoms on Statin Therapy

- If unexplained severe muscle symptoms or fatigue develop during statin therapy:
  - Promptly discontinue the statin.
  - Address possibility of rhabdomyolysis with:
    - CK
    - Creatinine
    - Urine analysis for myoglobinuria.

Risk of New Diagnosis of DM with Statins

- Statin intensity:
  - 1 in 1000 cases for moderate
  - 3 in 1000 cases for high intensity

- Number of DM risk factors:
  - 4 diabetes risk factors: BMI ≥ 30; FBS ≥ 100; A1c ≥ 6.0%, Metabolic risk factors
  - New onset DM (NOD) risk - atorva 80 mg v less intense statin
    - No increase if 0 to 1 NOD risk factors
    - 24% increase if 2 to 4 NOD risk factors
    - number of CV events significantly reduced with atorva 80 mg in both NOD risk groups.

Waters et al J Am Coll Cardiol 2013
Accuracy of Statin Assignment Using the 2013 AHA/ACC Cholesterol Guideline Versus the 2001 NCEP-ATP III Guideline

CONCLUSIONS: The new American Heart Association/American College of Cardiology guideline matches statin assignment to total plaque burden better than the older guidelines, with only a modest increase in the number of patients who were assigned rosuvastatin. 

IMPROVE-IT Study Design

Patients stabilized post ACS ≤ 10 days:

- LDL-C 50–125 mg/dL, or 50–100 mg/dL, if prior lipid-lowering Rx

N=18,144

1. Standard Medical & Interventional Therapy

2. Simvastatin 40 mg

3. Ezetimibe/Simvastatin 10/40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

LDL-C and Lipid Changes

1. Year Mean LDL-C (mg/dL)

<table>
<thead>
<tr>
<th>Group</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvast</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.6</td>
</tr>
<tr>
<td>EZ/Simv</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Δ in mg/dL: -16.7 -19.3 -19.7 -16.6 -0.5

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥ 30 days), or stroke

HR 0.936 CI (0.887, 0.988) p=0.016

Simvastin — 34.7% 2742 events

EZ/Simvastin — 32.7% 2572 events

NNT=50
Four Principles

1. Focus on proven therapy for those shown to benefit

2. To reduce ASCVD, statins are drugs of choice; most are inexpensive and safe when taken as tolerated

3. Focus on proper intensity of statin therapy and monitor for adherence to optimal lifestyle and statin Rx

4. A clinician-patient discussion in primary prevention:
   a. Discuss a global risk-reduction strategy
   b. Discuss potential for benefit and adverse effects of statin therapy including drug-drug interactions
   c. Patient preferences (shared decision making)