THE 2103 ACC/AHA GUIDELINES ON THE TREATMENT OF BLOOD CHOLESTEROL

Anne Carol Goldberg, MD, FACP, FAHA, FNLA
Associate Professor of Medicine
Washington University School of Medicine
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2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

• J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934.
• Also see full paper (electronic supplement only) at ACC or AHA websites
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
  • Cholesterol Panel: 3 CQs
  • Risk Assessment Work Group: 2 CQs
  • Lifestyle Management Work Group: 3 CQs
• RCTs and systematic reviews/meta-analyses of RCTs independently assessed as fair-to-good quality
• Develop recommendations based on RCT evidence
• Less expert opinion than in prior guidelines

Systematic Review Process

The Expert Panel constructed Critical Questions relevant to clinical practice.

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

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

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

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

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

Process

• Started 2008
• Critical questions developed and 5 chosen (later cut to 3)
• Evidence review
• Evidence tables
• Evidence statements
• Recommendations
• Writing
• Multiple reviews—NHLBI, other agencies, outside reviewers, etc.—every single comment was answered
• Waiting (NHLBI announced June 2013—not doing guidelines)
• Work with ACC and AHA—remapping the grades
• Presentation and on-line publication—November 2013
• Print—early July 2014
Evidence included randomized controlled clinical trials and meta-analyses such as those by the Cholesterol Treatment Trialists' Collaborators.

Overview of 2013 ACC/AHA cholesterol guideline
1. Treat blood cholesterol to reduce ASCVD risk
2. Healthy lifestyle is the foundation for ASCVD risk reduction
   • Background therapy for all randomized controlled trials
   • ACC/AHA 2013 Lifestyle and Obesity Guidelines
3. Use appropriate intensity of statin therapy to reduce ASCVD risk in those most likely to benefit
   • Quantitative comparison of statin ASCVD risk reduction versus adverse effects
   • Emphasis on 4 statin benefit groups (Strong evidence)
   • Other groups may benefit from statins (Less evidence)
4. Only consider nonstatin therapy for additional LDL-C lowering after maximizing lifestyle & statin therapy in high risk patients

Emphasis on healthy lifestyle
• Initial treatment for everyone
• Risk estimator provides lifetime risk estimate for patients 20 to 59
• This helps to drive discussions of greater adherence to heart-healthy lifestyle and improved risk factors
• Can be helpful in the decision process in people with lower short-term risk but high lifetime risks
**Lifestyle Recommendations Include:**

Advise Adults Who Would Benefit from LDL-Cholesterol Lowering to:

- Consume a dietary pattern that emphasizes:
  - Intake of vegetables, fruits, and whole grains
  - Includes low-fat dairy products, poultry, fish, legumes
  - Non-tropical vegetable oils and nuts
  And limits intake of:
  - sweets, sugar-sweetened beverages & red meats.

- Aim for a dietary pattern that achieves 5%–6% of calories from saturated fat.


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### 4 Statin Benefit Groups

- **Clinical atherosclerotic cardiovascular disease**
- LDL–C ≥ 190 mg/dL, Age ≥ 21 years
- **Primary prevention – Diabetes**: Age 40-75 years, LDL–C 70-189 mg/dL

- **Primary prevention - No Diabetes**: ≥7.5%† 10-year ASCVD risk, Age 40-75 years, LDL–C 70-189 mg/dL

†Requires risk discussion between clinician and patient before statin initiation.

Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator.

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### Statin Benefit Groups

- **Secondary Prevention**: Clinical atherosclerotic cardiovascular disease (ASCVD)
- **Primary prevention**: LDL–C ≥190 mg/dL, Age ≥21 years
- **Primary prevention: Diabetes**: Age 40-75 years, LDL–C 70-189 mg/dL + ASCVD risk ≥7.5%
  - In these groups—Optimal benefit with high intensity statins (lower LDL-C ≥ 50%)
  - Diabetes + risk < 7.5%; moderate intensity statin
    - Age over 75 or can’t tolerate high intensity statin: use moderate intensity

- **Primary prevention - Risk discussion between clinician and patient before starting medication**
  - Age 40 to 75; No Diabetes; LDL-C 70-189
  - 10-year ASCVD risk ≥ 7.5%

Consider statin therapy if risk decision is uncertain after use of ASCVD risk estimator

Moderate or high intensity statin
Clinician – Patient Discussion before Statin Therapy

- Estimate 10-year ASCVD risk
- Review other risk factors and risk factor control
- Review potential for benefit from heart-healthy lifestyle
- Review potential for benefit from statins and potential for adverse effects and drug-drug interactions
- Consider patient preferences
Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>Intensity of Statin Therapy</th>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C, on average, by approximately ≥50%</td>
<td>Atorvastatin (40)≥80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 40 (80) mg</td>
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<td></td>
<td></td>
<td>Simvastatin 20–40 mg</td>
<td>Lovastatin 40 mg</td>
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<tr>
<td></td>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 40 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pritavastatin 2–4 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Goals versus Intensity of Therapy

- Lack of randomized trial 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
- Randomized trial data allows quantitative comparison of statin benefits with statin adverse effects
  - Important in discussions regarding benefit/risk of diabetes with statin therapy
  - Number-needed-to-treat compared with number-needed-to-harm

Safety

- Randomized clinical trials and meta-analyses of randomized clinical trials used to identify important safety considerations
- Allow estimation of net benefit from statin therapy
  - ASCVD risk reduction versus adverse effects
- Expert guidance on management of statin-associated adverse effects, including muscle symptoms
- Recommendations on non-statin safety issues
- Advise use of additional information including pharmacists, manufacturers prescribing information, and drug information centers for complex cases
Additional factors to consider when evaluating risk

- For those patients where a risk decision is uncertain, these factors may inform clinical decision making in the context of the clinician-patient discussion:
  - LDL-C ≥ 160 mg/dL
  - Family history of premature ASCVD
  - Increased lifetime risk
  - Hs-CRP ≥ 2
  - Coronary calcium score ≥ 300
  - Ankle-brachial index < 0.9

NOTE: Guidelines do not supersede clinical judgment. Treatment thresholds and goals without consideration of risk makes less sense than personalizing therapy to the patient’s risks and preferences.

Monitoring and follow up

- Adherence to a heart healthy lifestyle
  - Optimal adherence to help improve lipids, affect other risk factors
- Each visit review adherence to statin
  - Maximally tolerated statin intensity and lifestyle to keep LDL-C low
- Measure lipids regularly
  - 3-12 weeks after start, then 4-12 months as appropriate to check adequacy of statin therapy
  - If not taking statin—why?
  - Consider secondary causes of LDL-C elevation (e.g. hypothyroidism)
  - If high risk and inadequate response, consider non-statin therapy
  - There are biologic differences in response (e.g. FH patients)
  - Review safety issues at each visit with history, and labs if appropriate
  - For example: some may need CK, fasting glucose, hemoglobin A1c

Lipid measurements required for follow up

Response needs to be monitored = checking lipid panel

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL-C ≥300 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.
Some of the controversies

- Accuracy of ASCVD risk estimator
  - Initial concerns not supported by new data from REGARDS
  - Over-estimates occur if populations using statins are used
  - Faulty assumption that ASCVD risk ≥ 7.5% means automatic statin therapy
    - The clinician-patient discussion comes first
  - No LDL-C/non HDL-C goals
    - Panel did not find evidence for or against
    - Lipids followed regularly to assess therapeutic response and adherence
  - Confusion regarding role for non-statins treatment
    - Non-statin treatments may be used in high risk patients to further reduce LDL-C levels per clinician judgment (e.g., familial hypercholesterolemia, statin intolerant patients)
Support for 2013 ACC/AHA cholesterol guideline

- 2013 ACC/AHA risk-based/statin intensity approach better than ATP 3 risk factor/LDL-C approach
- Will prevent more CVD events – Dallas Heart Study
- Better identifies those with subclinical atherosclerosis

Pooled Cohort Equations

- Data from 5 population-based NHLBI cohort studies on heart and stroke risk
- Includes African American status as an input
- ATP 3 Framingham Score evaluated 10-year risk of fatal and non-fatal MI—older data, less diverse population, does not include stroke risk
- The Pooled Cohort equations were validated in a subset of the REGARDS study of 30,000 black and white Americans from a contemporary population-based sample. (Muntner P, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA. 2014 Apr 9;311(14):1406-15)

Why not continue to treat to target?

1. Current randomized clinical trial 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

Cholesterol Treatment Trialists meta-analyses suggest greater reductions lead to greater risk reduction, but where that number should be is not clear. Even treating people with lower baseline LDL cholesterol levels shows benefit. Should someone with LDL cholesterol 65 mg/dl, diabetes, and CAD, not be treated with a statin?
Statin-Treated Individuals
Non-statin Therapy Considerations
- Use the maximum tolerated intensity of statin
- Consider addition of a non-statin cholesterol-lowering drug(s)
  - 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
- Non-statin cholesterol-lowering drugs shown to reduce ASCVD events in randomized trials are preferred (bile-acid sequestrants, niacin, and now ezetimibe)

Lifetime risk
- Risk estimator provides lifetime risk estimate for patients 20 to 59
- This helps to drive discussions of greater adherence to heart-healthy lifestyle and improved risk factors
- Can be helpful in decision process in people with lower short term risk but high lifetime risks

Future Updates to the Blood Cholesterol Guideline
- These guidelines represent a change from previous guidelines. They align recommendations more closely to the evidence.
- For primary prevention, they focus on shared decision making
- Guidelines will be improved by future high-quality research
Complex Lipid Disorders

“For the many questions about complex lipid disorders that are beyond the scope of our systematic evidence review, or for which little or no RCT data are available, it is anticipated that clinicians with lipid expertise can contribute to their management.”


Evidence gaps and future research needs

1. Outcomes of RCTs to evaluate statins for the primary prevention of ASCVD in adults > 75 years of age.
2. Outcomes of RCTs to evaluate alternative treatment strategies for ASCVD risk reduction. These RCTs may compare titration to specific cholesterol or apolipoprotein goals versus fixed-dose statin therapy in high-risk patients.
3. RCTs to determine whether submaximal statin doses, combined with non-statin therapies, reduce ASCVD risk in statin-intolerant patients.
4. Evaluation of the incidence, pathophysiology, clinical course, and clinical outcomes of new-onset diabetes associated with statin therapy.
5. Outcomes of RCTs of new lipid-modifying agents to determine the incremental ASCVD event-reduction benefits when added to evidence-based statin therapy.


Synopsis of recommendations

1. Encourage adherence to a healthy lifestyle
2. Statin therapy recommended for adults in 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 pooled cohort equations for estimating 10-Year ASCVD risk
6. Initiate the appropriate 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


“These guidelines are meant to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient. As a result, situations might arise in which deviations from these guidelines may be appropriate. These considerations notwithstanding, in caring for most patients, clinicians can employ the recommendations confidently to reduce the risks of atherosclerotic cardiovascular disease (ASCVD) events.”


Thank you!