How Do the 2013 Cholesterol Guidelines Compare With Previous Cholesterol Guideline Reports?

Cynthia A. Jackevicius, BScPhm, PharmD, MSc, BCPS

The American College of Cardiology and American Heart Association released the Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults on November 12, 2013. Are these new cholesterol guidelines perfect? No. Are they an improvement for the decade old guidelines? Yes. Much has happened in the field of cholesterol lowering for the purposes of reducing cardiovascular risk in the past decade. Given that the previous version of cholesterol guidelines were published 13 years ago as the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) in May 2001, with a final report in December 2002 and an update published 9 years ago as the article Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines in July 2004, it has been long overdue to update the cholesterol guidelines to reflect contemporary clinical trial evidence.

These new guidelines are opening an important dialogue about the evidence that supports how we approach cardiovascular risk reduction in the context of dyslipidemia. There are many advances that are now in line with the current clinical trial evidence in the new guidelines, including no longer aiming for a specific low-density lipoprotein target, except as a measure of monitoring patient adherence, and focusing on statins, the most proven agents for cardiovascular risk reduction, as the mainstay of lipid-lowering therapy.

However, there are areas of uncertainty and controversy, in particular, the accuracy of prediction of the new risk calculator for identifying patients for primary prevention, which will require further dialogue in the medical community. In addition, although shared patient decision making is emphasized in the new guidelines, no specific tools or instruments are suggested to guide the recommended shared decision making. Some resources for shared decision making that clinicians may wish to consider are presented in this Website: http://www.informedmedicaldecisions.org/what-is-shared-decision-making/shared-decision-making-resources/. Also, the Mayo Clinic Shared Decision Making National Resource Center has a statin decision aid available online (http://statindecisionaid.mayoclinic.org/). However, at present it calculates cardiovascular risk according to the Framingham, Reynolds, and United Kingdom Prospective Diabetes Study (UKPDS) scores, rather than the new Pooled Cohort Equation that is now used in the new cholesterol guidelines.

Continuous updates of these guidelines are most certainly necessary—and sooner than another 13 years. For now, a first step in appreciating the new cholesterol guidelines is to understand how the new guidelines compare with the previous guidelines. As such, a comparative summary of the 2001 guidelines, the 2002 final report, the 2004 update, and the 2013 guidelines in some key areas is presented in Tables 1 to 3.

Disclosures

None.

References


Key Words: cholesterol ▪ guideline ▪ lipids
Table 1.  Risk Estimation, Target Groups, and Target Levels

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<tr>
<td>Evidence grading</td>
<td>NCEP III 2001, 2002, and update²⁻⁴: Evidence is graded according to the standard ACC/AHA classification and levels of evidence (class I–III and levels A–C) for the NCEP full report in 2002. Recommendations are not graded. An evidence grading system is not used or provided for the initial 2001 NCEP report or the 2004 update</td>
<td>Recommendations are graded according to the standard ACC/AHA classification and levels of evidence (class I–III and levels A–C).</td>
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<td>Risk estimation</td>
<td>NCEP III 2001, 2002, and update²⁻⁴: FRS equation used to calculate 10-year risk of coronary heart disease</td>
<td>Use of the new pooled cohort equations to estimate 10-year ASCVD risk</td>
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<td>Target groups</td>
<td>NCEP III 2001, 2002, and update²⁻⁴:†</td>
<td>Identified 4 principal statin benefit groups:‡</td>
</tr>
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<td>LDL or other lipid targets</td>
<td>NCEP III 2001 and 2002²⁻⁵:</td>
<td>The guidelines state that there is no evidence to support continued use of specific LDL-C and non-HDL-C treatment targets. LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards (IIaB)‡</td>
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<td>HDL target (2002):</td>
<td>NCEP has the following evidence statement on HDL target and therapy: clinical trials provide suggestive evidence that raising HDL-C levels will reduce risk for CHD (A2). However, it remains uncertain whether raising HDL-C levels per se, independent of other changes in lipid and or nonlipid risk factors, will reduce risk for CHD. It also gives an encouraging recommendation about targeting treatment to HDL lowering: a specific HDL-C goal level to reach with HDL-raising therapy is not identified. However, nondrug and drug therapies that raise HDL-C levels and are part of management of other lipid and nonlipid risk factors should be encouraged. NCEP III update⁵:</td>
<td>It recommends using the maximum tolerated statin intensity in those groups shown to benefit‡</td>
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**ACC/AHA** indicates American College of Cardiology and American Heart Association; **ASCVD**, atherosclerotic cardiovascular disease; **ATP**, Adult Treatment Panel; **CHD**, coronary heart disease; **FRS**, Framingham Risk Score; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **MI**, myocardial infarction; **NCEP**, National Cholesterol Education Program; and **TIA**, transient ischemic attack.

*At which to initiate lipid-lowering drug therapy in addition to lifestyle modification.
†Adapted with permission from Grundy et al.⁴
‡This information represents the interpretation of the author and the author takes responsibility for any misstatements or errors.
Table 2. Statin Dosing and Nonstatin Therapy

<table>
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<tr>
<td>Dosing of statins</td>
<td>NCEP III 20012: Table 7 footnote provides range of usual doses of statins. In the primary prevention section it states “In most cases, the statin should be started at a moderate dose. In many patients, the LDL cholesterol goal will be achieved, and higher doses will not be necessary” NCEP 20022: In the text, it states “The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. The starting dose of statin will depend on the baseline LDL-C level” NCEP III update4:* There is a section that discusses standard-dose statins to achieve 30%–40% LDL reduction, including the below table that provides statin doses that generally achieve this effect. However, the update specifically states “these comments must not be taken to mean that NCEP is recommending a 30%–40% reduction of LDL levels as a goal of therapy”</td>
<td>Appropriate intensity of statin therapy:† Secondary prevention: High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD, unless contraindicated (IA) In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when either high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Table 8 for Safety of Statins, Recommendation 1; IA) In individuals with clinical ASCVD &gt;75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it (IIaB). In the text and figure, it recommends moderate intensity in those &gt;75 y. Primary prevention:‡ LDL-C &gt;190 mg/dL Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-y ASCVD risk estimation is not required): Use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity (IB) It is reasonable to intensity statin therapy to achieve at least a 50% LDL-C reduction (IIaB) After the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to lower LDL-C further. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug–drug interactions, and consider patient preferences (IIbC) LDL-C 70–189 mg/dL‡ Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes mellitus and an estimated 10-y ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy (IA) It is reasonable to offer treatment with a moderate-intensity statin to adults 40–75 years of age, with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes mellitus and an estimated 10-y ASCVD risk of 5% to &lt;7.5% (IIaB) Diabetes mellitus:† Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus (A) High-intensity statin therapy is reasonable for adults 40–75 years of age with diabetes mellitus with a ≥7.5% estimated 10-y ASCVD risk unless contraindicated (IIaB)</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose, mg/day</td>
<td>% LDL reduction</td>
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<tr>
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</tr>
<tr>
<td>Atorvastatin</td>
<td>10</td>
<td>39</td>
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<tr>
<td>Lovastatin</td>
<td>40</td>
<td>31</td>
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<tr>
<td>Pravastatin</td>
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<td>34</td>
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<tr>
<td>Simvastatin</td>
<td>20–40</td>
<td>35–41</td>
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<tr>
<td>Fluvastatin</td>
<td>40–80</td>
<td>25–35</td>
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<tr>
<td>Rosuvastatin</td>
<td>5–10</td>
<td>39–45</td>
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(Continued)
Table 2. Continued

|------------|--------------------------------------------------------------------------------|----------------------|
| Nonstatin therapy | Table 7 lists drugs that affect lipoprotein metabolism with lipid profile changes that can be expected. It also lists clinical trial results summarized briefly without reference to specific trials, evidence or percent risk reduction. Figure 2, Progression of Drug Therapy in Primary Prevention, suggests to start LDL-lowering therapy with any of the following lipid-lowering agents: statin, bile acid sequestrant, or nicotinic acid. In the text, it states that the usual drug will be a statin. And in most cases, a moderate dose should be started (moderate dose not defined). **NCEP 2002²⁻**: Figure VI.1-1, Progression of Drug Therapy, suggests to start LDL-lowering therapy with any of the following lipid-lowering agents: statin, bile acid sequestrant, or nicotinic acid. In the text, it states "The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. The starting dose of statin will depend on the baseline LDL-C level" In conflict with this statement, a subsequent recommendation states “Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals” The full NCEP 2002 report includes a section onatherogenic dyslipidemia characterized by high TG, low HDL, and small LDL particles. It includes a specific recommendation that encourages the use of nonstatin therapies: Consideration should be given to treatment of atherogenic dyslipidemia with specific drug therapy, (ie, fibrates or nicotinic acid, in higher risk patients) **NCEP III update⁴**: The update uses the term LDL-lowering drugs in general in the summary recommendations contained in Table 3 rather than referring to or recommending statins specifically. Other relevant wording related to nonstatin therapies in the update includes: Although the evidence base to support fibrate therapy is not as strong as that for statins, fibrates may have an adjunctive role in the treatment of patients with high TG/low HDL, especially in combination with statins. Several clinical trials support the efficacy of nicotinic acid for reduction of CHD risk, both when used alone and in combination with statins. The update also notes: To attain an LDL-C <100 mg/dL in the remaining patients, either the statin dose must be increased or a second LDL-lowering drug must be added to therapy. For LDL-C >100 mg/dL, other lipid-lowering drugs (eg, fibrates, nicotinic acid) can be considered for patients with elevated TG and low HDL-C; these drugs can be used, either as alternatives to statin therapy, as shown by the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), 40 or in combination with statins The guidelines state that nonstatin therapies do not provide acceptable ASCVD risk-reduction benefits in relation to safety. In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-desired therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher risk individuals include: Individuals with clinical ASCVD <75 years of age. Individuals with baseline LDL-C ≥190 mg/dL. Individuals 40–75 years of age with diabetes mellitus. Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs (IIbC) In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in randomized, controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects (IIaB) ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; and TG, triglycerides. *Adapted with permission from Grundy et al.⁴ †Reproduced from Stone et al.¹ ‡This information represents the interpretation of the author and the author takes responsibility for any misstatements or errors.
### Safety of Lipid-Lowering Agents and Patient Values

|-----------------------------|--------------------------------------------------------------------------|-----------------------|
| Safety of lipid-lowering agents | NCEP III 2001²: Table 7 lists common or important side effects. Specific rates or risk factors are not mentioned. NCEP III 2002²: In the drug therapy section, it reviews statin myopathy in general but does not consider specific risk factors for myopathy. NCEP III update³: General statements are made about considering safety in making decisions. ACC/AHA/NHLBI Clinical Advisory on Statines⁴: A separate publication focused on statin safety was published in August 2002 from some of the members of the previous NCEP committee after the August 2001 withdrawal of cerivastatin from the US market. It reviewed the incidence of myopathy, its prevention and management, and recommended monitoring. | The guidelines emphasize the use of randomized, controlled trials to identify important safety considerations in individuals receiving treatment of blood cholesterol.* Moderate-intensity statin therapy should be used in individuals with characteristics predisposing them to statin-associated adverse effects, and in whom high-intensity statin therapy would otherwise be recommended (IA)* Characteristics predisposing individuals to statin adverse effects include, but are not limited to:†  
  - Multiple or serious comorbidities, including impaired renal or hepatic function.  
  - History of previous statin intolerance or muscle disorders.  
  - Unexplained alanine transaminase elevations >3× upper limit of normal  
  - Patient characteristics or concomitant use of drugs affecting statin metabolism  
  - >75 y of age  
  Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:  
  - History of hemorrhagic alanine transaminase stroke  
  - Asian ancestry  
  Baseline creatine kinase is recommended based on expert opinion (IIaC)* Baseline alanine transaminase is recommended for baseline assessment of liver function (IIbC)* The guidelines recommend to consider decreasing the statin dose when 2 consecutive values of LDL-C levels are <40 mg/dL based on opinion (IIbC)* There is a recommendation that it may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily (IIaA)† A new monitoring recommendation includes: individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes mellitus screening guidelines (B7) (IIb)† |
| Management of statin side effects | NCEP III²: There are no specifics stated about management or prevention of statin side effects NCEP III update³: There is nothing specific stated about statin side effects except to state that combining fenofibrate plus a statin is better at avoiding drug interactions and myopathy than older fibrates | Expert guidance on management of statin-associated adverse effects, including muscle symptoms are recommended to be followed: It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm:†  
  - To avoid unnecessary discontinuation of statins, obtain a history of previous or current muscle symptoms to establish a baseline before initiating statin therapy.  
  - If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatine kinase, creatinine, and a urinalysis for myoglobinuria.  
  - If mild to moderate muscle symptoms develop during statin therapy:  
    - Discontinue the statin until the symptoms can be evaluated  
    - Evaluate the patient for other conditions that might increase the risk for muscle symptoms (eg, hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases)  
    - If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy  
    - If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.  
    - Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.  
    - If, after 2 months without statin treatment, muscle symptoms or elevated creatine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above.  
    - If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose (IIaB) |
| Patient values and preferences | Not explicitly considered | Consideration of patients’ values and preferences are explicitly incorporated into the text and algorithms on treatment recommendations, particularly with regard to the intensity of dosing and use of statins in primary prevention. No specific tools or instruments are suggested to guide the recommended shared decision making |

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ACC/AHA indicates American College of Cardiology and American Heart Association; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; and NHLBI, National Heart, Lung, and Blood Institute.

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†Reproduced from Stone et al."
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