A Summary and Critical Assessment of the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults: Filling the Gaps

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Abstract

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines has recently released the new cholesterol treatment guideline. This update was based on a systematic review of the evidence and replaces the previous guidelines from 2002 that were widely accepted and implemented in clinical practice. The new cholesterol treatment guideline emphasizes matching the intensity of statin treatment to the level of atherosclerotic cardiovascular disease (ASCVD) risk and replaces the old paradigm of pursuing low-density lipoprotein cholesterol targets. The new guideline also emphasizes the primacy of the evidence base for statin therapy for ASCVD risk reduction and lists several patient groups that will not benefit from statin treatment despite their high cardiovascular risk, such as those with heart failure (New York Heart Association class II-IV) and patients undergoing hemodialysis. The guideline has been received with mixed reviews and significant controversy. Because of the evidence-based nature of the guideline, there is room for several questions and uncertainties on when and how to use lipid-lowering therapy in clinical practice. The goal of the Mayo Clinic Task Force in the assessment, interpretation, and expansion of the ACC/AHA cholesterol treatment guideline is to address gaps in information and some of the controversial aspects of the newly released cholesterol management guideline using additional sources of evidence and expert opinion as needed to guide clinicians on key aspects of ASCVD risk reduction.

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Affiliations continued at the end of this article.
TABLE 1. Critical Questions Set by the Expert Panel

<table>
<thead>
<tr>
<th>Critical question</th>
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<td>What is the evidence for LDL-C and non–HDL-C goals for the secondary prevention of ASCVD?</td>
<td>Of 19 RCTs examined, only 1 had a treatment titration strategy to achieve a cholesterol goal (the 4S study; titration of simvastatin from 20-40 mg to achieve a total cholesterol level &lt;200 mg/dL, but only 37% of participants followed this course of therapy). No RCTs were identified that compared outcomes based on different LDL-C or non–HDL-C treatment goals.</td>
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<td>What is the evidence for LDL-C and non–HDL-C goals for the primary prevention of ASCVD?</td>
<td>4 of 6 RCTs of primary prevention of ASCVD with statin therapy were examined. In 2 studies, treatment targets were included but were not used as a firm strategy in the intervention arms of the studies (AFCAPS-TEXCAPS: lovastatin, 20-24 mg, to achieve LDL-C levels &lt;110 mg/dL, 40% of the treatment group followed this course; MEGA trial: pravastatin, 10-20 mg, to achieve total cholesterol levels &lt;220 mg/dL). No RCTs were identified that compared treatment strategies based on differing LDL-C or non–HDL-C targets.</td>
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For primary and secondary prevention, what is the effect on the lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups? RCTs involving available lipid-lowering drugs were included for consideration. Plant stanols and sterylols were not included because no ASCVD outcome studies were identified. Red yeast rice was not evaluated because it was not available for use during most of the period under consideration.

AFCAPS-TEXCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; RCT = randomized controlled trial; 4S = Scandinavian Simvastatin Survival Study.

likely to benefit from statin therapy. These classes include patients with established ASCVD, patients with low-density lipoprotein cholesterol (LDL-C) levels greater than 190 mg/dL, (to convert to mmol/L, multiply by 0.0259) (likely familial hypercholesterolemia), diabetic patients aged 40 to 75 years with LDL-C levels of 70 to 189 mg/dL, and those aged 40 to 75 years without diabetes mellitus (DM) or ASCVD but with an estimated 10-year ASCVD risk of at least 7.5%. Furthermore, the panel found no evidence for treating to a particular goal LDL-C or non–high-density lipoprotein cholesterol (HDL-C) level but accepts the practice of

TABLE 2. Summary of the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD

1. Persons $\geq 21$ y who fall into any of the following 4 at-risk groups are to be considered for statin therapy to reduce ASCVD risk:
   a. Known ASCVD
   b. LDL-C level $>190$ mg/dL
   c. Diabetes, aged 40-75 y, with LDL-C levels of 70-189 mg/dL
   d. 10-y risk of cardiac event or stroke $>7.5\%$ (by the Pooled Cohort Risk Calculator)

2. Lipid-lowering statin therapy should be based on the degree of ASCVD risk and the intensity of the statin. High-intensity statin therapy is recommended for patients with known ASCVD, LDL-C levels $>190$ mg/dL, and DM, with 10-y risk $>7.5\%$. Moderate-dose statin therapy is recommended for the other treatment groups (patients with DM but with 10-y risk $<7.5\%$ and those without DM who have a 10-y risk $<7.5\%)$.

3. The expert panel did not recommend for or against LDL-C goals or targets but rather recommends that lipids be checked at baseline and then 4-12 wk after initiating statin therapy to assess adherence and response to therapy. Individuals receiving high-dose statin therapy would be expected to lower their LDL-C level by $>50\%$ from their baseline level, and those receiving moderate-dose statin therapy would be expected to lower their LDL-C level by $30\%-49\%$.

4. Consider rechecking lipid levels every 3-12 mo as clinically indicated. Reassess lifestyle therapy on a regular basis.

5. Shared decision making should be performed between providers and patients when considering the use of statin therapy for ASCVD risk reduction. (See the section on shared decision making.)

6. The expert panel notes that these clinical guidelines, although based on evidence, should not replace clinical judgment, particularly in patients who fall outside of the 4 categories listed in item 1 but who still may be at elevated ASCVD risk (eg, patients with a family history of early ASCVD).

7. These guidelines are not meant to be inclusive of all types of hyperlipidemia. Patients with complex hyperlipidemias should be referred to a lipid specialist for evaluation and treatment recommendations.

ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol.

High-intensity therapy (25%-50% LDL-C reduction): atorvastatin, 40-80 mg; rosuvastatin, 20-40 mg

Moderate-intensity therapy (30%-49% LDL-C reduction): atorvastatin, 10-20 mg; rosuvastatin, 5-10 mg; simvastatin, 20-40 mg; pravastatin, 40-80 mg; lovastatin, 40 mg; fluvastatin XL, 80 mg; fluvastatin, 40 mg twice daily; pitavastatin, 2-4 mg.
up-titrating doses when there is a less-than-anticipated response to statin therapy. Broad adoption of this guideline should aid in the appropriate tailoring of the intensity of statin therapy relative to baseline risk and should help limit the use of unnecessary and unproven add-on therapies. The panel also found no evidence to support initiation of lipid-lowering treatment in patients with heart failure (HF) with a New York Heart Association (NYHA) functional class II to IV or in patients with chronic kidney disease (CKD) undergoing hemodialysis. The panel also introduced the idea of sharing the decision-making process with the patient and incorporating patient preferences and values.

PITFALLS WITH RANDOMIZED CLINICAL TRIALS AS THE ONLY SOURCE OF EVIDENCE

Clinical trials generally define a somewhat narrow study population and have entry criteria that exclude many patients who might be seen in a typical clinic and who would be most likely to benefit from the drug under study. Industry-sponsored trials do not generally address questions of broad interest, and neither do they usually include medications that are off patent. For example, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial assessed the benefit of using moderate- to high-intensity rosuvastatin, a relatively new, nongeneric statin, in patients with elevated high-sensitivity C-reactive protein (hsCRP) levels.6 Patients with normal LDL-C levels, multiple nonlipid risk factors, but normal hsCRP levels were not included in the trial. In the end, the trial assessed the impact of a patented test to screen patients and a patented statin to treat them.

Although published randomized clinical trials generally represent “scientific truth”, it is important to recognize that in reality truth is not simply the sum of published randomized clinical trials. Randomized clinical trials exclude many patients who need and might benefit from therapy; exclusion criteria and run-in periods often ensure that a study drug will have the greatest potential for impact, whereas it leaves many unanswered questions regarding the potential benefit or even harm for the excluded groups. In general, randomized clinical trials could end up representing a fraction of individuals affected by the condition being studied. Furthermore, there is a significant bias, either intentional or unintentional, toward publishing and publicizing a positive study, whereas negative trials might not get published (except as a brief report in the ClinicalTrials.gov database [http://www.clinicaltrials.gov]) or publicized.7 The time horizon is also an issue. Clinical trials rarely assess outcomes in a timeframe beyond 4 or 5 years. Some analyses extend outcome assessment several years longer but rarely provide effectiveness data beyond 10 years. This shortcoming, along with the fact that the 10-year horizon is typically used in ASCVD risk assessment, leads to the erroneous conclusion that only outcomes that occur or may be prevented within a 10-year timeframe matter.

It may also be worth commenting, in the spirit of basing recommendations on evidence, that no randomized clinical trial has used the Framingham or another risk factor score to select patients for statin therapy. It is equally true that none of the randomized clinical trials of statin vs placebo targeted a specific percentage of LDL-C level lowering, and neither did any of the statin comparison trials intentionally compare 2 prespecified degrees of LDL-C level lowering.

FILLING THE GAPS

The new guideline represents a major step forward by the ACC/AHA to produce evidence-based clinical recommendations. However, the same approach that enhances the scientific validity of the recommendations and the panel decision to focus on cholesterol treatment also allows for many unanswered questions, leaving clinicians with multiple uncertainties about when and how to use lipid-lowering therapy in clinical practice. The following sections review some of the controversies of the new guideline using additional sources of evidence and address gaps in information primarily based on expert opinion to guide clinicians on key aspects of cardiovascular risk reduction. Table 3 compares the ACC/AHA GTBC and the Mayo Clinic Task Force recommendations, and the Figure summarizes the recommendations with an algorithm.

Role of Therapeutic Lifestyle Changes Before Starting Statin Therapy in Patients Without ASCVD

When people are identified as being at high risk for ASCVD using the Pooled Cohort Risk
### TABLE 3. Comparison Between the ACC/AHA Guideline on the Treatment of Blood Cholesterol and the Mayo Clinic Task Force Recommendations

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACC/AHA Guideline on the Treatment of Blood Cholesterol</th>
<th>Mayo Clinic position</th>
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<tbody>
<tr>
<td>Pretreatment evaluation</td>
<td>Obtaining a fasting lipid panel, ALT, and hemoglobin A1c if diabetes status is unknown, and CK level if indicated. Consider evaluation of secondary causes of hyperlipidemia or conditions that may influence statin safety.</td>
<td>Measuring fasting blood glucose levels would also be reasonable if diabetes status is unknown. Consider measuring CK levels at baseline in African American patients.</td>
</tr>
<tr>
<td>Focus on statin treatment</td>
<td>Statins should be the cornerstone of lipid treatment for the reduction of ASCVD risk, but other medications might be considered in special circumstances, such as statin intolerance or when patients do not achieve the anticipated cholesterol reduction.</td>
<td>Statins should be the cornerstone of lipid treatment for the reduction of ASCVD risk. Nonstatin drugs, such as niacin, ezetimibe, and bile acid binding resins, may also be considered in statin-intolerant patients, patients who do not get the anticipated response to statin monotherapy, or patients with an LDL-C level at baseline &gt; 190 mg/dL. We recommend considering fibrate with statin therapy in patients with high triglyceride and low HDL-C levels.</td>
</tr>
<tr>
<td>Statin therapy matching intensity to ASCVD risk, not based on lipid thresholds or targets</td>
<td>The decision to initiate statin therapy and its intensity are based on underlying ASCVD risk and not on lipid thresholds or targets.</td>
<td>We agree that the decision to initiate statin therapy and its intensity should be based on underlying ASCVD risk and not on lipid thresholds or targets, despite the fact that such a strategy has not been studied widely in randomized clinical trials. Statin RCTs have targeted patient populations with a particular ASCVD risk factor(s) and not according to a specific risk threshold. In patients who are currently taking low-dose statins, would not recommend increasing the dose if the LDL-C level has already decreased by 30%-50% from baseline. In patients who are currently taking low-dose statins but with unknown baseline LDL-C levels, would not recommend increasing the dose if the LDL-C level is &lt; 70 mg in the presence of ASCVD or &lt; 100 mg without ASCVD.</td>
</tr>
<tr>
<td>Role of therapeutic lifestyle changes</td>
<td>Physicians should emphasize healthy lifestyle habits and address other risk factors when initiating statin therapy for the primary prevention of ASCVD.</td>
<td>When considering the initiation of statin therapy for the primary prevention of ASCVD in patients with elevated risk, it is reasonable to attempt therapeutic lifestyle changes in highly motivated individuals for whom ASCVD risk could reasonably be decreased to below the statin treatment threshold (&lt; 7.5% 10-y risk of an ASCVD event). ASCVD risk should be reevaluated in 3-6 mo. If 10-y estimated risk is still &gt; 7.5%, the provider and patient should discuss the possible addition of statin therapy.</td>
</tr>
<tr>
<td>Lipid management in the elderly</td>
<td>Initiate moderate-intensity statin therapy in persons aged &gt; 75 y in the presence of clinical ASCVD. Recommend the continuation of statin therapy beyond age 75 y in persons who are already taking and tolerating statins. Recommend consideration of additional factors before initiating statin therapy for the primary prevention of ASCVD in individuals aged &gt; 75 y, including potential benefit, risk of adverse effects, increasing comorbidities, drug-drug interaction, and patient preferences.</td>
<td>Same general recommendations. Also, clinicians should highlight the scarcity of evidence to support statin treatment for the primary prevention of ASCVD in individuals aged &gt; 75 y or who have comorbidities that may limit life expectancy. We recommend having a low threshold to discontinue statin treatment in these patients if there are any safety concerns.</td>
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**TABLE 3. Continued**

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<tr>
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<tr>
<td>Lipid management in people with diabetes mellitus aged (&lt;40) y and with an LDL-C level of (70-189) mg/dL</td>
<td>Statin therapy may be considered in selected persons. Other factors that might influence the decision will be an LDL-C level (\geq 160) mg/dL, a family history of early-onset CAD, coronary calcification, an elevated high-sensitivity C-reactive protein level, an abnormal ankle-brachial index, or a high lifetime ASCVD risk. No details of these recommendations are provided.</td>
<td>An initial lifestyle approach is particularly advisable in this age group because there are no safety data with very-long-term statin therapy. We recommend moderate-intensity statin treatment for individuals aged (21-39) y with moderate hypercholesterolemia (LDL-C level of (160-189) mg/dL) or with a (30)-y ASCVD risk (&gt;30)% or a family history of premature ASCVD if the LDL-C level is (&gt;100) mg/dL. There is no role for coronary calcium computed tomography or ankle-brachial index in this age group because sensitivity is low in this age group.</td>
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<tr>
<td>Lipid management in those without clinical ASCVD aged (\geq 40) y who are free of diabetes and have an LDL-C level of (70-189) mg/dL</td>
<td>To estimate the 10-y ASCVD risk and determine whether risk is (\geq 7.5)% to initiate moderate- or high-intensity statin therapy, and whether risk is (&lt;5)% to (\geq 7.5)% to consider moderate-intensity statin therapy. In the process, to engage in a clinician-patient discussion of the potential for ASCVD risk reduction, adverse effects, drug-drug interactions, and patient preferences.</td>
<td>Estimate the 10-y ASCVD risk. Then use shared decision making with or without tools or decision aids to display and discuss risks, benefits, and costs. If risk is (\geq 7.5)% recommend therapeutic lifestyle changes if the patient is motivated and the ASCVD risk could be reasonably reduced with lifestyle changes to (&lt;7.5)% Consider moderate-intensity statin therapy in patients with an ASCVD risk (&gt;7.5)% particularly if the LDL-C level is (&gt;100) mg/dL or the non-HDL-C level is (&gt;130) mg/dL, if risk cannot be reasonably reduced with therapeutic lifestyle change. We recommend that in patients at high risk for ASCVD but with LDL-C levels (&lt;100) mg/dL to focus on improvement of nonlipid risk factors for the primary prevention of ASCVD.</td>
</tr>
<tr>
<td>Persons aged (\leq 75) y with clinical ASCVD</td>
<td>If no safety concerns, recommend high-intensity statin therapy regardless of the baseline LDL-C level.</td>
<td>For persons without safety concerns, recommend high-intensity statin therapy if the LDL-C level is (\geq 70) mg/dL. We do not recommend for or against high-intensity statin treatment for persons with LDL-C levels (&lt;70) mg/dL not already taking a lipid-lowering medication. The decision to start moderate-intensity statin treatment when the LDL-C level is (&lt;70) mg/dL can be considered and discussed with the patient, recognizing the lack of evidence for such therapy in this population.</td>
</tr>
<tr>
<td>Role of shared decision making with the patient</td>
<td>Engage in clinician-patient discussions of potential ASCVD risk reduction, adverse effects, drug-drug interactions, and patient preferences when considering the initiation of statin treatment for primary prevention.</td>
<td>We recommend exercising shared decision making between the patient and the clinician. Strongly consider using tools or decision aids to help improve patient understanding of individualized risks, benefits, and costs of treatment. This applies not only to situations in which a specific cutoff value of risk is proposed to determine the initiation of statin therapy but also when deciding to use high-intensity statin therapy in patients with established ASCVD or diabetes mellitus.</td>
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### TABLE 3. Continued

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<tbody>
<tr>
<td>Role of statin treatment in people with evidence of subclinical ASCVD</td>
<td>Statins may be considered in individuals with an abnormal ankle-brachial index or with a coronary artery calcification Agatston score ≥300 or ≥75th percentile for age and sex.</td>
<td>We recommend the initiation of statin treatment in patients with subclinical ASCVD, especially if the disease is extensive (eg, a coronary calcium score ≥75th percentile for age and sex), absolute score is ≥300, or a computed tomographic angiogram shows evidence of obstructive disease (&gt;60% stenosis), even in the absence of ischemia or cardiovascular symptoms, or if multiple small plaques (&lt;30% stenosis) are present. Patients with other manifestations of subclinical atherosclerosis, such as carotid plaque or asymptomatic peripheral vascular disease, may also benefit from statin therapy.</td>
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<tr>
<td>Lipid-lowering treatment in statin-intolerant patients</td>
<td>If muscle or other symptoms occur, establish their relationship to statin therapy. If symptoms develop during statin therapy, discontinue the therapy. If mild to moderate symptoms resolve, rechallenge the patient with the same or a lower dose of statin. If muscle symptoms recur, discontinue statin therapy and rechallenge with progressively lower doses of the same or a different statin. Consider nonstatin cholesterol-lowering therapy in high-risk individuals (with ASCVD, diabetes, or LDL-C levels ≥190 mg/dL), preferentially drugs that have been found in RCTs to provide ASCVD risk reduction. No details provided.</td>
<td>If muscle or other symptoms occur, establish their relationship to statin therapy. If symptoms develop during statin therapy, discontinue the therapy. If mild to moderate symptoms resolve, rechallenge with a different statin. If muscle symptoms recur, consider rechallenge with a third statin or use either 5 mg of rosuvastatin or 10 mg of atorvastatin every other day, twice a week, or once a week, recognizing that limited evidence exists to prove a reduction in ASCVD events using this approach. Consider the use of ezetimibe, niacin, or bile acid sequestrants in individuals with elevated LDL-C and fibrate levels if the non–HDL-C level is elevated and at high risk for ASCVD events. Consider these options as monotherapy for totally statin-intolerant patients, but preferably in addition to a low dose of statin.</td>
</tr>
<tr>
<td>Lipid-lowering treatment in patients with chronic kidney disease</td>
<td>Initiation of statin therapy is not routinely recommended for patients who are receiving maintenance hemodialysis. No specific recommendations are given for patients with chronic kidney disease not undergoing hemodialysis.</td>
<td>Continue statin treatment in patients receiving maintenance hemodialysis if a statin has been well tolerated and there is no evidence of CK elevation. Do not initiate statin treatment in patients undergoing maintenance hemodialysis.</td>
</tr>
<tr>
<td>Lipid-lowering treatment in patients with NYHA class II-IV HF</td>
<td>Statin initiation is not routinely recommended for patients with NYHA class II-IV HF. Continue statin therapy for patients with HF who are taking statins that have been well tolerated.</td>
<td>Statin therapy initiation is not routinely recommended for patients with NYHA class II-IV HF. Continue statin therapy for patients with HF who are taking statins and are free of adverse effects. We recommend considering initiation of statin therapy in patients with HF who meet all 4 of the following criteria: (1) HF is well-controlled and with a projection of good survival (life expectancy &gt;2 y); (2) ASCVD is the underlying cause of HF; (3) the baseline LDL-C level is ≥130 mg/dL; and (4) age is &lt;75 y.</td>
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<td>Patients with chronic rheumatologic/inflammatory diseases or HIV+ patients receiving antiretroviral therapy</td>
<td>Clinician judgment is especially important for these patient groups for whom RCT evidence is insufficient for guiding clinical recommendations.</td>
<td>It seems prudent to initiate statin therapy for primary ASCVD prevention in patients whose estimated 10-y risk for ASCVD is &gt;5% or 30-y risk is &gt;20%, particularly if their LDL-C level is &gt;130 mg/dL. Consider subclinical disease assessment in patients whose risk is &lt;5%.</td>
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<tr>
<td>Patients with solid organ transplant</td>
<td>Clinician judgment is especially important for these patient groups for whom the RCT evidence is insufficient for guiding clinical recommendations.</td>
<td>We recommend starting all cardiac and renal transplant recipients on low-to-moderate-intensity statin therapy (other than simvastatin) after careful consideration of drug-drug interactions.</td>
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Equation 4 (i.e., >7.5% risk of an ASCVD event in 10 years), the new guideline recommends the initiation of statin therapy along with therapeutic lifestyle change. Some patients, however, could potentially lower their cardiovascular risk to less than the statin treatment threshold with therapeutic lifestyle change alone and may not technically qualify for statin treatment. For example, a 55-year-old man who smokes and has mildly elevated blood pressure (135/80 mm Hg), an elevated non-HDL-C level (175 mg/dL [to convert to mmol/L, multiply by 0.0259]), a suboptimal diet, a sedentary lifestyle, and an estimated 10-year risk of 13.8% might be able to reduce his cardiovascular risk to 5% if he can quit smoking and improve his blood pressure and HDL-C level by means of exercise training and healthy dietary habits. Clinicians need to assess the likelihood that such a significant lifestyle change will occur and also need to calculate the ASCVD risk assuming realistic goals to determine whether the risk can be decreased low enough so that the patient would not qualify for statin treatment in the near future. This point illustrates that a major risk of emphasizing the primary value of statin treatment is that patients might overlook the importance of lifestyle changes in cardiovascular risk reduction.

Mayo Clinic Task Force Recommendations. When considering the initiation of statin treatment for the primary prevention of ASCVD in patients with elevated risk, it is reasonable to attempt therapeutic lifestyle changes in highly motivated individuals for whom ASCVD risk could reasonably be decreased to below the statin treatment threshold (<7.5% 10-year risk of an ASCVD event). Risk of ASCVD should be reevaluated in 3 to 6 months. If 10-year estimated risk is still greater than 7.5%, the provider and patient should discuss the possible addition of statin therapy.

Use of Non-HDL-C Level as a Criterion for Initiation of Treatment

The new guideline does not recommend treatment to reach a particular LDL-C or non-HDL-C level, which is understandable because the panel did not find any evidence of treating to a target. However, they still use LDL-C levels to assess baseline risk and do not make any recommendations about using non-HDL-C levels as point-of-care criteria, despite a wealth of epidemiologic studies showing non-HDL-C level to be a superior marker of cardiovascular risk than LDL-C level.8-11 Indeed, the Pooled Cohort Risk Calculator inputs total cholesterol and HDL-C (hence, non-HDL-C) levels, not LDL-C levels, into the equation to calculate risk. This is especially true in patients with DM, as evidenced by a post hoc meta-analysis of 4 large longitudinal studies that found increased coronary
heart disease (CHD) risk with increasing non–HDL-C levels but not LDL-C levels. Furthermore, changes in non–HDL-C levels have been found to better explain the treatment effect of statins than changes in LDL-C levels.

The ATP III had recommended non–HDL-C as a secondary target in patients with hypertriglyceridemia, and many other organizations, such as the National Lipid Association, the American Diabetes Association, and the ACC, also strongly support the use of non–HDL-C level to assess cardiovascular risk. Many patients with metabolic syndrome or DM and dyslipidemia have elevated non–HDL-C levels despite normal to low LDL-C levels. Offering therapy to patients with elevated non–HDL-C levels is clearly more judicious and is a must for patients with DM and hypertriglyceridemia. Although the ATP III had made such recommendations, its importance was not appreciated, and anecdotal evidence suggests that few practitioners focused their attention on this "secondary" target.

**Mayo Clinic Task Force Recommendations.** To avoid confusion, it would be reasonable to recommend using non–HDL-C level...
as the sole lipid parameter to assess baseline risk in all patients. It can be easily measured in a nonfasting sample using current robust analytical methods without any additional costs. Because it is an integrated measure of all atherogenic lipoproteins, including LDL-C, changing from LDL-C to non—HDL-C thresholds will not miss any high-risk patients, such as those with familial hypercholesterolemia, but will better identify other high-risk patients, such as those with diabetic dyslipidemia. Restricting statin therapy for primary prevention to patients with non—HDL-C levels greater than 130 mg/dL would be a prudent option.

Lipid Management for ASCVD Risk Reduction in People With DM
The recommendation to initiate moderate- or moderate- to high-dose statin therapy in all patients with DM aged 40 to 75 years with LDL-C levels greater than 70 mg/dL, regardless of their level of risk is not entirely supported by published randomized clinical trial evidence. First, contemporary cohort studies and 1 meta-analysis have debunked the assumption that DM is an ASCVD risk equivalent.17,18 For individuals with type 2 DM without a history of myocardial infarction (MI), their ASCVD risk is approximately 30% of the ASCVD for nondiabetic patients with a history of MI and only approximately 50% in patients with a history of DM, whether the diagnosis of DM was incidental or prevalent.17 Second, there are no large randomized clinical trials in the primary prevention of ASCVD involving people with DM that have compared high- versus low-intensity statin therapy or that have used high-dose statin therapy alone (Supplemental Table 1; available online at http://www.mayoclinicproceedings.org). Third, the benefits of statin therapy in the primary prevention of ASCVD events in individuals with type 2 DM, as shown by the results of the Collaborative Atorvastatin Diabetes Study (CARDS), the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA), and the Heart Protection Study (HPS),19-21 may be applicable only to patients with an ASCVD risk similar to that in participants enrolled in these trials. The CARDS enrolled patients with DM with an LDL-C level less than 160 mg/dL and the presence of at least 1 other cardiovascular risk factor, such as smoking or hypertension, or other risk indicators, such as retinopathy or albuminuria. All the patients in the ASCOT-ALL were hypertensive and had to have several major risk factors for ASCVD to be enrolled in the trial. In the HPS, 51% of participants had cardiovascular disease (CVD). The 10-year ASCVD risk, estimated by the event rate in the placebo group, was well above 20% in all studies assessing the effect of statin therapy in patients with DM. This level of risk is significantly higher than what has been reported in population-based cohort studies, with reported 10-year risk for fatal or nonfatal CHD of approximately 11%.22 Fourth, the subgroup analyses grouped by LDL-C level that were performed in these trials used LDL-C cutoff values from 115 to 135 mg/dL. No results were reported on the subgroups with LDL-C levels less than 100 mg/dL. Indirect estimates using baseline mean values and standard deviations suggest that there were few individuals with LDL-C levels less than 90 mg/dL in these trials. Fifth, several studies, such as the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non—Insulin-Dependent Diabetes Mellitus (ASPEN) and ASCOT, did not find a significant benefit for primary prevention of MI or ischemic heart disease mortality in people with DM. Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) shows the inclusion criteria, intervention tested, mean LDL-C level at baseline, percentage of patients who developed the primary outcome in the placebo group, and other information of the main randomized clinical trials testing the effect of statin therapy in people with DM. The table illustrates that the evidence justifying statin therapy in patients with DM may not apply to all patients with DM in the general population. Patients with DM in the general population, who have no other comorbidities, particularly if they are men or women younger than 50 years, may be found to have a relatively low 10-year ASCVD risk, as measured by the Pooled Cohort Risk Calculator. The cholesterol management guideline, in this case, is somewhat inconsistent in that it recommends the use of a statin treatment threshold of 7.5% or greater for individuals without DM while it recommends statin therapy in patients with type 2 DM aged 40 to 75 years even if their calculated risk is less than 7.5%.

Another issue to consider in the treatment of diabetic dyslipidemia is that many patients with DM have hypertriglyceridemia and are likely to
benefit from combination therapy with statin and fibrate. The ACC/AHA panel acknowledges the evidence of benefit of such treatment from a subgroup analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial but stops short of recommending combination therapy. Because multiple fibrate trials besides ACCORD have consistently reported better outcomes in the subgroup of patients with high triglyceride and low HDL-C levels, it is important to consider statin-fibrate combination therapy in this select group of patients, keeping in mind that combining fibrates with statins can increase the risk of adverse effects and that no trial using fibrates has found a reduction in mortality.

Mayo Clinic Task Force Recommendations. For the primary prevention of ASCVD, patients with DM aged 21 to 75 years identified as being at high risk for ASCVD (10-year risk ≥7.5% or 30-year risk ≥30%) should receive statin treatment and could consider intensive therapy if tolerated, particularly if the LDL-C level is greater than 70 mg/dL or the non–HDL-C level is greater than 100 mg/dL. We recommend that patients with DM with an intermediate risk of ASCVD (5%-7.5% risk at 10 years or 20%-30% at 30 years if aged 21-50 years) should be offered statin treatment, using shared decision-making methods with his or her provider, recognizing the lack of evidence in DM with this level of ASCVD risk. There is no evidence to recommend statin treatment in patients with DM and low ASCVD risk (<5% at 10 years and <20% at 30 years).

Lipid Management for Primary Prevention in Individuals Aged 40 to 75 Years Identified as Being at High Risk but With a Low LDL-C Level (<100 mg/dL)

One of the most controversial aspects of the GTBC pertains to primary prevention in patients without ASCVD, DM, or severe hypercholesterolemia. Statin therapy is recommended in those aged 40 to 75 years with LDL-C levels of 70 to 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or greater. Because the calculated risk of almost all patients older than 65 years would be greater than 7.5% irrespective of their lipid levels, adherence to this guideline would likely lead to initiation of statin therapy in many patients. It is especially difficult to justify statin therapy for primary prevention in patients with baseline LDL-C levels in the 70- to 100-mg/dL range when their sole determinant of risk is their age. Of the 5 major primary prevention trials that were not exclusive for diabetic patients, 3 did not include patients with LDL-C values less than 130 mg/dL or total cholesterol levels less than 220 mg/dL. The mean baseline LDL-C levels in those 3 trials ranged from 150 to 192 mg/dL. In the remaining 2 trials, the ASCOT-ALL required participants to have hypertension and at least 3 additional risk factors, and the JUPITER trial required an elevated C-reactive protein level. Evidence is limited on the potential impact of statin therapy for ASCVD primary prevention in patients with LDL-C levels less than 100 mg/dL. (See Supplemental Table 2 [available online at http://www.mayoclinicproceedings.org] for highlights of the main randomized clinical trials for primary prevention of ASCVD.) The panelists acknowledged this limitation but pointed to the Cholesterol Treatment Trialists’ Collaborators (CTTC) meta-analysis data showing similar benefits of LDL-C reduction with statin therapy in patients with lower baseline LDL-C levels (≤70 mg/dL). However, the results were not reported based on treatment strategy but as risk reduction per millimole reduction in LDL-C level. In addition, this analysis included data from multiple clinical trials of patients with stable CHD or acute coronary syndrome and not only patients studied for primary prevention. In fact, in the latter group, the relative risk reduction in the subgroup of patients with baseline LDL-C levels less than 77 mg/dL was not significant (relative risk = 0.87; 95% confidence interval = 0.6-1.28). A subgroup analysis of the JUPITER trial did not find a statistically significant benefit with high-dose statin treatment in patients with baseline LDL-C levels less than 90 mg/dL. Similarly, in the MEGA trial (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) testing statins for the primary prevention of ASCVD, there was no event reduction in patients with baseline LDL-C levels less than 155 mg/dL.

Mayo Clinic Task Force Recommendations. Consider statin therapy for primary ASCVD prevention only in patients with baseline LDL-C levels of 100 mg/dL or greater or non–HDL-C levels of 130 mg/dL or greater, unless they have evidence of subclinical ASCVD or have elevated hsCRP levels, until more data in
patients with LDL-C levels less than 100 mg/dL are available. The Mayo Clinic Task Force also recommends that for the primary prevention of ASCVD in individuals with a high estimated ASCVD risk but an LDL-C level less than 100 mg/dL, one should focus on nonlipid risk factors for ASCVD.

Very Low LDL-C Levels in Patients With ASCVD

The ACC/AHA GTBC recommends high-intensity statin therapy in patients with clinical ASCVD regardless of their LDL-C levels. The assumption is that statins will reduce outcomes irrespective of baseline LDL-C levels. Although 3 of the 5 randomized clinical trials that compared high-intensity and low- to standard-intensity statin treatment in patients with CHD did not have a lower LDL-C cutoff limit to enter the trial, the studies likely ended up with few patients with very low LDL-C levels (<70 mg/dL).36-41 Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org) shows the highlights of the randomized clinical trials comparing high and low doses of statins in people with ASCVD. Mean LDL-C levels at baseline ranged from 97 to 121 mg/dL, although 2 trials reported baseline LDL-C values tested after the run-in period for statin therapy. In addition, the evidence supporting the use of high-intensity vs low- to standard-intensity treatment is probably not as robust as has been promulgated, so it is difficult to extrapolate any presumed benefit to individuals with very low LDL-C levels. To illustrate this point, only 2 of the 3 clinical trials using high-intensity statin treatment reached statistical significance for the primary (composite) outcome and none for total mortality. There was significant heterogeneity in the effect of high-intensity statin treatment regarding individual outcome end points. For example, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial38 primarily reduced the rate of revascularizations with no effect on MI or coronary artery disease (CAD) mortality, whereas the Treating to New Targets (TNT) trial did reduce the rates of nonfatal MI. Furthermore, the results from the CTTC meta-analysis using individual data from the 5 trials testing 2 different intensities of statin therapy showed a 4% absolute risk reduction for the primary outcome, no reduction in CHD mortality, and modest 1.5% and 1% absolute risk reductions in coronary events and nonfatal MI, respectively, at 5 years.34 In addition, subgroup analyses of patients with low LDL-C levels were not statistically significant. The PROVE-IT trial clearly showed an effect modification, meaning that baseline LDL-C levels influenced the results, with benefit limited to those with LDL-C levels greater than 125 mg/dL. The CTTC meta-analysis did not show a subgroup analysis on the basis of baseline LDL-C level according to treatment allocation. The CTTC investigators concluded, however, that high-intensity therapy was beneficial regardless of the LDL-C level based on the interpretation of data analyzed by level of LDL-C reduction, not by treatment allocation. Furthermore, they found a statistically significant reduction in the primary outcome in individuals with an LDL-C level less than 70 mg/dL who achieved an LDL-C reduction of 1 mmol compared with those who did not. However, they did not show an analysis comparing outcomes according to treatment allocation. As mentioned previously herein, the pooled baseline LDL-C values were not exactly baseline for all patients because 12,604 patients from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial had their LDL-C levels measured after a run-in period with 20 mg of simvastatin. They concluded, however, that high-intensity therapy was beneficial regardless of the LDL-C level based on the interpretation of these observational, not experimental, analyses. Studies of statins vs placebo in secondary prevention, in fact, excluded patients with low LDL-C levels at baseline, so it is unclear whether such patients would benefit from any statin use. Although very few patients with established ASCVD would have a very low LDL-C level in the absence of lipid-lowering treatment, those few patients may be exposed to unnecessary harm and a questionable clinical benefit with a high-intensity statin regimen.

Mayo Clinic Task Force Recommendations. High-dose statin therapy, if tolerated, is recommended for patients with established ASCVD, particularly after MI and stroke, recognizing the modest incremental benefit of high-intensity over moderate-intensity treatment. We do not recommend for or against high-intensity statin treatment for persons with LDL-C levels less than 70 mg/dL not already taking lipid-lowering medication. The decision
to start moderate-intensity statin therapy as opposed to high-intensity therapy can be considered and discussed with the patient, recognizing the lack of evidence for such therapy in this population.

**Individuals Younger Than 40 Years With a High Lifetime or 30-Year ASCVD Risk With LDL-C Levels of 160 to 189 mg/dL or Elevated Non–HDL-C Levels (>190 mg/dL)**

The newly published cholesterol management guideline does not give specific recommendations for statin treatment for individuals with mild hypercholesterolemia and multiple risk factors if they are younger than 40 years. In this age group, the 10-year calculated ASCVD risk will nearly always be less than the treatment threshold of 7.5%. In fact, it is nearly impossible for a patient younger than 40 years to have a high risk using the Pooled Cohort Risk Calculator. Although the GTBC suggests using the 30-year and lifetime cardiovascular risk calculators, they fall short of encouraging the initiation of statin treatment on the basis of long-term risk estimates. The problem with this approach is assuming that the only outcomes that matter for patients are those that fall within a 10-year horizon. When dealing with other cardiovascular risk factors, risk reduction treatment is not withheld in individuals with a relatively low short-term risk of ASCVD. For example, providers would generally consider recommending that a 25-year-old smoker quit smoking, would refer him or her to a smoking cessation clinic, or would even prescribe pharmacologic treatment to help him or her quit smoking. Likewise, providers would not withhold treatment for a 41-year-old woman with a persistent blood pressure greater than 160/95 mm Hg just because her risk of cardiovascular events in the next 10 years is low. Still, the limited evidence on the risk and benefit of long-term treatment with statins seems to make policy makers and some providers hesitant when recommending statin therapy in young adults. Therefore, a discussion of statin therapy, with the younger patient in particular, should include the limitations in evidence for or against long-term statin use and the assumption that treatment of younger patients with ASCVD risk factors will prevent the initiation or progression of atherosclerosis and thereby reduce the risk of ASCVD events in the longer-term, ie, more than 10 years into the future.

Individuals younger than 40 years may be treated with low- to intermediate-intensity statins with minimal or negligible risk of complications and at a very low cost. However, women who are younger than 40 years should be advised that the safety of statin therapy during pregnancy has not been established. Studies are limited that have assessed the cost-effectiveness of long-term statin therapy initiated at younger ages. Despite this fact, the cost-effectiveness of shorter-term statin therapy seems favorable and is likely to be even more favorable in the era of generic statin medications. The final decision should be based on a shared decision-making process with the patient understanding the uncertainties around this decision.

**Mayo Clinic Task Force Recommendations.** Lifestyle therapy is recommended as a first-line therapy in individuals younger than 40 years because there are no safety data with very long-term statin therapy. The Task Force also recommends moderate-intensity statin treatment for individuals 21 to 39 years of age with moderate hypercholesterolemia (LDL-C level of 160-189 mg/dL) or a non–HDL-C level greater than 190 mg/dL, likely polygenic in nature, with a 30-year ASCVD risk greater than 30% or a family history of premature ASCVD if the LDL-C level is greater than 100 mg/dL. There is no role for coronary calcium computed tomography (CT), ankle-brachial index measurement, or searching for carotid artery plaque in this age group because the yield to identify atherosclerotic plaque or subclinical peripheral vascular disease is very low in this age group. The potential role of other measures, such as lipoprotein(a), for risk stratification is discussed in a companion article addressing the Guideline on the Assessment of Cardiovascular Risk.

**Troubles With a Specific Risk Cutoff Point to Define High Cardiovascular Risk**

The new definition of high risk (≥7.5% 10-year risk of ASCVD events) is based on a significantly lower value than the 20% used in the previous guideline. This new definition, although somewhat arbitrary, is more aligned with other preventive recommendations in other areas of medicine, such as recommendations for the ideal target population and frequency of colonoscopy to screen for colon cancer. Currently, guidelines...
recommend that individuals older than 50 years (who are at <5% 10-year risk of colon cancer) undergo a screening colonoscopy every 10 years, whereas individuals with a strong family history of colon cancer (who have a 10-year risk >10%) be considered for more frequent screening examinations.

The treatment threshold of 7.5% or greater in the new guideline was derived considering the threshold at which the benefit of taking statins would be higher than the risk of developing type 2 DM from statin use. The benefit was calculated as the rate of primary prevention of ASCVD hard outcomes using data from exclusively primary prevention trials, and the risk of DM was estimated to be approximately 1 in 1000 per year for low-intensity statin therapy and 3 in 1000 per year for high-intensity treatment. This approach has 2 main limitations. The first is that a mathematical model giving a similar clinical value to an incidental diagnosis of DM and to a cardiovascular event is questionable, even assuming that those who will develop DM as a consequence of the use of statins will have an increased cardiovascular risk. Another limitation of the fixed cutoff value to define high risk is neglecting patient preferences and values. Extensive research has found that patients can and should participate in difficult clinical decisions through the process of shared decision making. The risks and benefits of a treatment according to guidelines, developers, and researchers may be very different from how patients interpret their own personal risk. Effective tools are available to help providers and patients assess the risks and expected benefits from statin therapy using shared decision-making techniques. In this setting, some patients might decide that taking a pill every day for the next 10 years might not be desirable to them if only 2 or 3 patients of 100 will actually benefit from 10 years of statin treatment (ie, a 2%-3% absolute risk reduction in people with a 10-year risk of an ASCVD event of 10%) (Statin/Aspirin Choice Decision Aid, http://statindecisionaid.mayoclinic.org). This concept is also applicable when deciding to use high-vs moderate-intensity statin treatment in patients with ASCVD. It is possible that after learning that it would take 100 patients to be on the high-intensity statin regimen for 5 years to prevent 1 recurrent nonfatal MI with no reduction in total or CVD mortality and that 1 or 2 patients will become diabetic because of the statin therapy in the same period, some patients would prefer to take a moderate-intensity statin regimen instead. The new guideline recommends that we “engage in a clinician-patient discussion of potential for ASCVD risk reduction, adverse effects, drug-drug interactions, and patient preferences,” but the fact that a cutoff value to define high risk has already been established without patient input can be an impediment to the shared decision-making process, potentially making the provider-patient decision making less patient centered and, ultimately, making the patient feel less involved in the decision-making process.

Mayo Clinic Task Force Recommendations. Use shared decision making between the patient and the clinician when discussing lipid-lowering drug therapy for ASCVD risk reduction. Strongly consider using tools or decision aids to help improve patient understanding of individualized risks, benefits, and costs of treatment. This applies not only to situations in which a specific cutoff value for risk is proposed to determine the initiation of statin therapy but also when deciding to use high-intensity statin therapy in patients with established ASCVD or DM.

Statin Treatment in People With Subclinical ASCVD

The guideline gives clear recommendations for people with clinical ASCVD but does not provide specific recommendations for individuals who are found to have subclinical ASCVD and who are labeled as low risk by the Pooled Cohort Risk Calculator. The use of CT coronary angiograms, the incidental finding during regular chest CT showing coronary calcification, and the implementation of coronary calcium CT screening programs have increased the prevalence of patients aware of having coronary atherosclerosis, and clinicians face uncertainty on how to manage their lipids. The incorporation of coronary calcium information into the cardiovascular risk assessment is more straightforward than estimating the added prognostic value of incidental findings using other radiographic techniques because of the paucity of data assessing incremental risk in the presence of calcification during noncardiac CT. In an individual who will otherwise be labeled as low risk according to the Pooled Cohort Risk Calculator but is found to have subclinical ASCVD, it would
be reasonable to start statin treatment under the general assumption that in a patient who has subclinical ASCVD, statins may halt the progression of the disease. The choice between moderate- or high-intensity statin therapy in those individuals would depend on the presence of other risk factors, the estimated 10-year ASCVD risk, and patient preferences.

**Mayo Clinic Task Force Recommendations.** Initiate statin treatment in patients with subclinical ASCVD, especially if the disease is extensive (eg, a coronary calcium score ≥75th percentile for age and sex) or an absolute Agatston score of 300 or greater, or if a CT angiogram shows evidence of obstructive disease (>60% stenosis), even in the absence of ischemia or cardiovascular symptoms or if multiple small plaques (<30% stenosis) are present. Patients with other manifestations of subclinical atherosclerosis, such as carotid plaque or asymptomatic peripheral vascular disease, may also benefit from statin therapy.

**Lipid-Lowering Treatment in Statin-Intolerant Patients**

The GTBC recognizes the vacuum of information regarding cholesterol treatment in people who are intolerant to statins, recommends monitoring of muscle symptoms after initiation of statin therapy, and provides an excellent stepwise approach in how to address muscle symptoms that may or may not be related to statin therapy. The guideline also includes a comprehensive review of the safety of nonstatin lipid-lowering options, but it falls short of giving specific recommendations on what medications to use in people with statin intolerance.

The most important step in the management of patients with presumed statin intolerance is to assess the “intolerance” itself, as some patients may have been labeled as statin intolerant on the basis of an isolated event of muscle discomfort that was attributed to but in reality not related to the use of statins. The diagnosis of statin intolerance goes beyond the scope of this article, but in the situation in which a patient declines statin therapy owing to clear evidence that he or she has developed adverse symptoms from multiple statins, it would be reasonable to consider the use of other, nonstatin medications for cholesterol lowering. The guideline rightfully recognizes the lack of evidence regarding nonstatin lipid-lowering therapies to reduce cardiovascular events. However, the lack of evidence of benefit does not equal evidence of no benefit. In the absence of clinical trials to address this issue, it is reasonable to recommend alternative cholesterol-lowering treatment in statin-intolerant individuals. Such treatment could include therapeutic lifestyle changes and the use of ezetimibe, fibrates, bile acid sequestrants, or other newer treatment alternatives, if tolerated. This recommendation is based on the extensive epidemiologic data showing that the lower the cholesterol level, the lower the rate of ASCVD events. Some studies have found a modest to moderate LDL-C level reduction in people with statin intolerance when using extremely low doses of certain statins, such as rosvastatin, 5 mg once or twice a week.43-46

Patients need to be informed that these alternative therapeutic options have not been fully tested in clinical trials and may not prevent or reduce the risk of ASCVD. However, theoretically, these treatments could potentially have clinical benefit.

**Mayo Clinic Task Force Recommendations.** If statin intolerance is not manifested with severe symptoms or life-threatening conditions, consider attempting an alternative statin or a very low-dose statin approach, such as with 5 mg of rosvastatin either every other day or as infrequently as once or twice a week. If this approach fails, we recommend alternative cholesterol-lowering treatment, including therapeutic lifestyle change and the use of ezetimibe, fibrates, or bile acid sequestrants, if tolerated. Other newer treatment alternatives, such as evolocumab, lomitapide, and mipomersen, could be considered for people intolerant to statins once they become available in clinical practice.

**Statin Treatment for Individuals Older Than 75 Years**

There is evidence suggesting that statins might not be effective in lowering ASCVD events in the elderly, particularly for primary prevention. As people age, the added risk attributed to LDL-C level is marginal, and, in addition, lower LDL-C levels have been associated with increased mortality.47-49 It is not valid to assume that because elderly patients have an increased absolute risk of CAD that they will automatically benefit from statin treatment because studies in...
some patients known to be at high risk for ASCVD have failed to prove any benefit, as was the case in patients undergoing hemodialysis or who have HF. This is particularly relevant because age is the main driver of cardiovascular risk using the Pooled Cohort Risk Equation.

The guideline supports the use of moderate-intensity statin therapy for the secondary prevention of ASCVD in individuals who are 75 years or older but highlight the limited evidence in primary prevention in this age group. We concur with the newly published guideline that high-intensity statin treatment in the elderly should be used only with great caution.

There is some evidence suggesting that cholesterol level reduction could be beneficial for secondary prevention in people older than 75 years based on analysis of pooled data from 26 randomized controlled trials. Although the analysis did not separate patients by age groups and presence or absence of ASCVD, the pooled data included primarily people with ASCVD.

The only randomized clinical trial specifically testing statins in the elderly with and without CAD reported no benefit in the primary prevention of CAD. Neither the composite end point of CHD death, nonfatal MI, or stroke nor any other prespecified outcome was statistically significant. A recent meta-analysis of statin trials assessing the effect of statins in primary prevention in people 65 years or older using data from 8 randomized clinical trials testing statins found a reduction in stroke and MI but not in cardiovascular or total mortality. However, most of those trials, except the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), had an upper age limit of 70 to 75 years. Therefore, the meta-analysis does not add more information than was recommended in the guideline for primary prevention with statins in people 75 years or older. In addition, a sex-based subanalysis of the PROSPER study found that women did not benefit from statin treatment, suggesting that the benefit of statin therapy in women older than 70 years is limited regardless of the presence of CAD. The meta-analysis assessing the effect of statin therapy in primary prevention in the elderly did not report data by sex to answer the question of whether statin therapy in elderly women provides any clinical benefit. Thus, the limited evidence in primary prevention in people older than 75 years does not support the use of statins for the primary prevention of ASCVD.

Mayo Clinic Task Force Recommendations. Clinicians can consider the theoretical benefit with statin therapy that patients older than 75 years at very high risk for ASCVD could get, especially if they have elevated cholesterol values. Patients in this age group need to know that evidence is extremely limited in people older than 80 years and should also be made aware that the scientific evidence for such treatment has shown no mortality benefit. Clinicians need to keep in mind that the Pooled Cohort Equations developed in this age group to guide treatment is limited to people younger than 80 years and that the calculation of risk in this age group will be high in most patients.

Lipid Management in Patients With CKD

The expert panel states that statin initiation is not routinely recommended in persons undergoing maintenance hemodialysis. There are also no guidelines to treat patients with CKD who are not receiving renal replacement therapies. It is well-known that patients with CKD are at high cardiovascular risk, and LDL-C is not a robust indicator of the risk, particularly with advancing renal insufficiency. Patients with CKD are at high risk for cardiovascular events even when the LDL-C level is low and may benefit from aggressive risk reduction strategies, including statin therapy. Indeed, post hoc subgroup analyses of large statin trials do show risk reduction in patients with CKD, and a recent large-scale randomized controlled trial (the Study of Heart and Renal Protection) reported a significant reduction in atherosclerotic events in patients with CKD with estimated glomerular filtration rates (eGFRs) of 60 mL/min/1.73 m² or less who were treated with a combination of simvastatin and ezetimibe compared with placebo. However, this trial, and 2 other large randomized trials did not find any benefit in patients undergoing maintenance hemodialysis.

Mayo Clinic Task Force Recommendations. We recommend statin therapy for cardiovascular risk reduction in all patients 40 years or older with eGFRs of 60 mL/min/1.73 m² or less except those undergoing hemodialysis. Younger patients with CKD may also benefit from statin therapy, especially if they have an...
Lipid Management in Patients With NYHA Class II to IV HF

Despite the apparently favorable effects of statin therapy in preventing HF and HF outcomes from observational data, small trials, and post hoc analyses of statin trials in patients not initially selected for HF, the results of 2 large randomized clinical trials in patients with HF found no benefit of statin therapy on total mortality in patients with class II to IV HF. The Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) did report a benefit in terms of reducing hospitalization for cardiac causes, but that was not seen in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico Heart Failure (GISSI-HF) trial. There seemed to be no benefit in either trial in particular subgroups defined by age older than 70 years, DM, severity of HF, left ventricular ejection fraction higher or lower, ischemic vs nonischemic cause, or baseline lipid levels. Statins (specifically 10 mg of rosuvastatin, which was the active agent used in both trials) seemed safe.

Placebo-controlled statin trials, including the Cardiac Angiography in Renally Impaired Patients (CARE) study, the Scandinavian Simvastatin Survival Study (4S), and the HPS reported a reduced incidence of HF in statin-treated patients. The differences were statistically significant in the HPS and the 4S, but there was only a trend in the CARE study. All of these trials were composed either exclusively (CARE or 4S) or primarily (HPS) of patients with ASCVD. However, the ASCOT was a trial of statin therapy in hypertensive patients, with patients with ASCVD largely excluded, that found no benefit in terms of reduced HF incidence. A meta-analysis of 4 statin comparison trials (PROVE-IT, Aggrastat to Zocor [A to Z], TNT, and Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering [IDEAL]) found that hospitalization for HF was significantly reduced by 27% with intensive statin therapy (80 mg of atorvastatin in the PROVE-IT, TNT, and IDEAL trials; 80 mg of simvastatin in the A to Z trial) in patients with CAD compared with the lower-dose arms of the studies. These results are based on relatively small numbers, but they do suggest that the development of HF could be prevented with high-dose statin therapy in patients with baseline ASCVD.

Regarding these findings, the new guideline states: “the Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic HF or in patients on maintenance hemodialysis.”

In clinical practice, the issue of statin therapy in patients with HF will likely be addressed in 1 of 2 ways. First, should a patient who is taking a statin for the primary or secondary prevention of ASCVD but subsequently develops HF now discontinue statin therapy? Second, should a patient who presents with HF and otherwise qualifies for statin therapy for the primary or secondary prevention of ASCVD be excluded from statin therapy? To make recommendations for action in these 2 scenarios, it will be helpful to closely examine

estimated 30-year ASCVD risk greater than 30%. Because they are at higher risk for statin-induced myositis, it would be prudent to use only low- to moderate-intensity statin therapy or a combination of a statin and ezetimibe if they cannot tolerate even moderate doses of statins. We would not recommend discontinuation of statin therapy in patients undergoing hemodialysis who are already taking statins that they are tolerating well or in patients starting renal replacement therapies when receiving statin therapy. In the Study of Heart and Renal Protection, approximately a third of the patients who were previously not undergoing hemodialysis went on to require hemodialysis, generally within a year of starting the trial, and yet seemed to benefit regarding cardiovascular risk reduction. Furthermore, none of these studies have found an increased risk of rhabdomyolysis in patients undergoing hemodialysis and receiving statin therapy, and there would be no reason to deny them any minimal benefit that they may get from statin therapy. In patients with eGFRs of 60 mL/min/1.73 m² or greater, we recommend an approach similar to the general population. These recommendations are largely congruent with those issued recently by the Kidney Disease: Improving Global Outcomes organization.

We recommend the continuation of statin therapy in patients with CKD undergoing hemodialysis if the treatment has been well tolerated. We recommend against high-intensity statin therapy and against the initiation of statin therapy in patients undergoing long-term hemodialysis.
the methods of the 2 randomized clinical trials CORONA and GISSI-HF.

Both trials were similar in including patients with NYHA class II to IV HF. In the GISSI-HF trial, ischemic cardiomypathy was listed as the cause of HF in approximately 40% of patients, whereas all patients in the CORONA had ischemic cardiomypathy and all were required to have a left ventricular ejection fraction of 40% or less. In the GISSI-HF trial, patients taking a statin or having a history of or risk factors for statin intolerance were excluded. The statin exclusion criterion for the CORONA was slightly different: patients could be considered only if “the investigator thought they did not need treatment with a cholesterol-lowering drug.” Baseline lipid levels seemed slightly higher in the CORONA vs the GISSI-HF trial (average LDL-C level of 137 mg/dL vs 122 mg/dL). According to the new guideline, most patients with ischemic heart disease in both trials probably should have been receiving statin therapy before the development of HF. Both trials also used 10 mg of rosuvastatin as the active agent. This would be considered a moderate statin dose under the new guideline, whereas patients with ASCVD should be treated with high-dose statin according to that same guideline.

What the GISSI-HF and CORONA trials likely tell us is that patients with existing HF that is not due to an ischemic event and who have relatively low lipid levels will not benefit from statin therapy. In other words, statins do not treat HF independently of treating risk factors for CAD. The question of statin treatment in CAD is likewise pretty clear in terms of preventing cardiovascular events, perhaps even HF, as the post hoc analyses of the statin-placebo and statin-comparison studies suggest. We, therefore, suggest that it would be prudent to continue statin therapy in already treated patients with ASCVD after they develop HF, assuming that the HF is younger than 75 years. The exact cutoff point for when to consider starting or continuing statin therapy is, of course, arbitrary, but expected survival of less than 2 years certainly brings into question the likelihood that statin therapy will be of significant benefit.

For the second group of patients, those who have developed HF, especially from an ischemic cause, and are not currently taking a statin but otherwise fall into 1 of the 4 groups that qualify for statin therapy under the new guideline, the 2 statin in HF trials do not provide much support for initiating statins. Outcomes were not better in patients with higher baseline lipid levels, which might be expected if lipid lowering did play a positive role. Similarly, stratification for hsCRP level, which is favorably affected by statin therapy, did not affect results. Death from all causes within 3 years of randomization was greater than 20% in the GISSI-HF trial and greater than 30% in the CORONA (patients were an average of 5 years older at baseline than in the GISSI-HF trial), whereas mortality at 5 years in the “high-risk” cohort of the HPS was only 3% in simvastatin-treated patients and 4% in the placebo group. High background mortality from the combination of advanced age and HF was probably a major factor in the lack of efficacy in the 2 statin in HF trials and would limit efficacy in clinical practice also.

**Mayo Clinic Task Force Recommendations.** Initiation of statin therapy is not routinely recommended for patients with NYHA class II to IV HF. Continue statin therapy for patients with HF who are taking statins and are free of adverse effects. We recommend considering initiation of statin therapy in patients with HF who meet all 4 of the following criteria: (1) HF is well-controlled and with a projection of good survival (life expectancy >2 years); (2) ASCVD is the underlying cause of HF; (3) the baseline non–HDL-C level is 160 mg/dL or greater or the LDL-C level is 130 mg/dL or greater; and (4) age is younger than 75 years.
Lipid Management in Patients With Rheumatologic Inflammatory Disease

Patients with rheumatoid arthritis and other connective tissue diseases are known to be at increased risk for CAD. Both increased prevalence of traditional risk factors and nontraditional risk factors related to chronic systemic inflammation are thought to contribute to this increased risk. The European Society of Cardiology/European Atherosclerosis Society Guidelines recognize the increased risk of ASCVD in these patients but discourage the preventive use of lipid-lowering drugs on the basis of the presence of autoimmune diseases. The European League Against Rheumatism has issued recommendations to help clinicians identify and manage cardiovascular risk in these patients and suggest that in certain patients with a high burden of inflammatory disease, there should be a reduced threshold to start statin therapy. Although there are no intervention trials looking at cardiovascular outcomes in patients with connective tissue disease treated with statins, post hoc subgroup analyses of the TNT and IDEAL studies suggest that lipid lowering and risk reduction in patients with inflammatory joint disease are similar to those without. The Trial of Atorvastatin for the Primary Prevention of Cardiovascular Disease in Rheumatoid Arthritis Patients was stopped prematurely because of low primary event rates. Whether the advent of more effective disease-modifying therapies will also reduce the prevalence of CAD in patients with rheumatologic disease needs to be investigated.

Mayo Clinic Task Force Recommendations. At this time, it seems prudent to initiate statin therapy for primary prevention in patients with connective tissue disease whose estimated 10-year risk for ASCVD is greater than 5% or 30-year risk is greater than 20% under the assumption that inflammatory connective tissue diseases increase the risk for ASCVD approximately 1.5- to 2-fold, independent of traditional ASCVD risk factors, particularly if the non–HDL-C level is greater than 130 to 160 mg/dL or the LDL-C level is greater than 100 to 130 mg/dL. This should be combined with the implementation of healthy lifestyle changes and effective management of other risk factors, such as hypertension and smoking, and of the primary rheumatologic process.

Lipid Management in Patients With Human Immunodeficiency Virus

Increased cardiovascular risk has also been noted in human immunodeficiency virus—infected patients, and a large 10-year observational study reported a high proportion of cardiovascular deaths in this patient cohort despite their relatively young age and low prevalence of other traditional risk factors except smoking. Dyslipidemia and body fat changes may result from antiretroviral therapy and may contribute to the increased risk. There are no trials examining the benefit of lipid-lowering therapies on cardiovascular end points in these patients, but small studies have reported the safety and efficacy of statins, fibrates, fish oil, and niacin in improving lipid parameters.

Mayo Clinic Task Force Recommendations. In the absence of clinical trial data, it would be reasonable to start statin therapy in patients with human immunodeficiency virus receiving antiretroviral therapy when their estimated 10-year risk of ASCVD is greater than 5% or their 30-year risk is greater than 20%, assuming that human immunodeficiency virus while receiving antiretroviral therapy increases the risk of ASCVD approximately 1.5-fold independent of traditional ASCVD risk factors, particularly if their non–HDL-C level is greater than 160 mg/dL or their LDL-C level is greater than 130 mg/dL.

Pravastatin, which is not metabolized to a substantial extent by the cytochrome P450 enzymes, is the statin of choice to avoid drug interactions with protease inhibitors and other antiretroviral agents. Coadministration of simvastatin and protease inhibitors should be avoided, and if other statins, such as rosvuavastatin, atorvastatin, pitavastatin, and fluvastatin, are used, therapy should commence with a low dose. Combination therapy with fibrates, niacin, or fish oil is often required, especially in those with hypertriglyceridemia, and a careful consideration of drug-drug interactions must be undertaken in all patients.

Lipid Management in Patients With Solid Organ Transplants

Another group of patients who are likely to benefit from statin therapy are recipients of solid organ transplants, especially kidney and heart. The 10-year risk of cardiovascular events in renal
transplant recipients is greater than 20%, and statin therapy has been found to reduce the risk of cardiac death or nonfatal MI by 35%. Similarly, improved survival and less cardiac allograft vasculopathy has been reported in patients after cardiac transplant treated with statins and current guidelines recommend initiation of statin therapy in all cardiac transplant recipients irrespective of cholesterol levels. Although there are some limited data to suggest benefits of early, aggressive statin therapy over titrated dosing, it is important to consider the increased risk of adverse effects due to concomitant medications, such as cyclosporine.

**Mayo Clinic Task Force Recommendations.** We recommend starting all cardiac and renal transplant recipients on low- to moderate-intensity statin therapy after careful consideration of drug-drug interactions. Pravastatin and fluvastatin would be the first choice because of their safety data in transplant patients.

**ADDITIONAL RESEARCH NEEDED**

Statins are one of the most studied drugs in randomized clinical trials in the history of medicine. However, there are still several relevant questions that have not been answered in those trials that merit future investigation. A key question to be answered is whether pursuing a specific LDL-C or non−HDL-C target will lead to better clinical outcomes than a fixed statin dose. There is ample observational evidence that the lower the LDL-C level, the better the clinical outcomes, but this has not been tested in clinical trials. A clinical trial testing the “threshold” hypothesis would determine whether the target LDL-C approach, either with statins alone or with the addition of nonstatin drugs, leads to better risk reduction than matching risk level to intensity of statin therapy without specific LDL-C goals.

There is little experimental evidence supporting the recommendation to give statins to people without DM or ASCVD but with elevated ASCVD risk and LDL-C levels less than 130 mg/dL, particularly in the absence of subclinical atherosclerosis or inflammation. A trial enrolling individuals with a high ASCVD risk and a normal or low LDL-C level will answer this question. Furthermore, there are no clinical trials proving that high-intensity statin treatment will benefit patients at very high risk for ASCVD compared with moderate- or lower-intensity statin treatment. Although ample evidence suggests that the intensity of the statin treatment should match the risk of ASCVD, no trial in primary prevention has been performed to prove this.

Clinical trials testing the efficacy of statins in patients with DM for primary prevention have all used relatively low doses of statins, and they all had very high rates of CVD outcomes, much higher than the average rates observed in patients with DM in the community. Therefore, it would be desirable to have clinical trials proving that patients with DM with a low ASCVD risk using the Pooled Cohort Risk Calculator will benefit from statin treatment, and also trials comparing high- vs low-intensity statin therapy in diabetic patients with elevated ASCVD risk. The dose-dependent statin-related risk of insulin resistance and DM adds urgency for such trials.

There is scant evidence from clinical trials using statins in the elderly. Because elderly people represent a large and growing number of patients who qualify for statin treatment according to current guidelines, clinical trials need to demonstrate that statins are safe and effective to prevent ASCVD events in people older than 75 years.

Statin use seems to be safe in the long-term, but more data are needed confirming the safety of statin therapy in the very long—term. Because most statin clinical trials had a run-in period during which patients who did not tolerate the drug or for other unknown reasons declined to enter into the randomized portion of those trials, the real incidence of statin intolerance in the population is still yet to be determined. Prospective series of patients newly prescribed statins and particularly clinical trials without a run-in period will help answer this question.

Finally, there is a need for clinical trials testing the efficacy and safety of statins for the primary prevention of ASCVD in special populations at increased risk for ASCVD and in which case series and small trials suggest some benefit from using statins even when the LDL-C level is not elevated.

**CONCLUSION**

The new ACC/AHA cholesterol guideline represents an important step forward in the management of ASCVD by giving evidence-based recommendations and focusing on specific clinical questions. Although helpful and important, this guideline has gap areas that involve clinical scenarios, subgroups, and situations that are not covered fully by the
guideline. This article addresses some of the clinical questions that relate to these gap areas. The decision regarding when to prescribe statins will ultimately rely on clinical judgment and shared decision making between the provider and the patient. There is a need for more randomized clinical trials to address some gaps in knowledge.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: A to Z = Aggrastat to Zocor; ABI = ankle-brachial index; ACC/AHA = American College of Cardiology/American Heart Association; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACCOS-TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALT = alanine aminotransferase; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm; ASCVD = atherosclerotic cardiovascular disease; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non—Insulin-Dependent Diabetes Mellitus; ATP III = Adult Treatment Panel III; CAD = coronary artery disease; CARDs = Collaborative Atorvastatin Diabetic Study; CARE = Cardiac Angiography in Renally Impaired Patients; CHD = coronary heart disease; CK = creatine kinase; CKD = chronic kidney disease; CORONA = Controlled Rosuvastatin in Multinational Trial in Heart Failure; CT = computed tomography; CTTC = Cholesterol Treatment Trials’ Collaborators; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GISSI-HF = Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico—Heart Failure; GTBC = Guideline on the Treatment of Blood Cholesterol; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HIV = human immunodeficiency virus; HPS = Heart Protection Study; hsCRP = high-sensitivity C-reactive protein; IDEAL = Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NYHA = New York Heart Association; PROSPECT = Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infarction Therapy; Rx = treatment; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TLC = therapeutic lifestyle change; TNT = Treating to New Targets; 4S = Scandinavian Simvastatin Survival Study

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