

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

2013 ACC/AHA Guideline Recommends Fixed-Dose Strategies Instead of Targeted Goals to Lower Blood Cholesterol



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ABSTRACT

The American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines recently issued the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. This new guideline endorses a paradigm shift in strategies for reducing atherosclerotic cardiovascular disease (ASCVD) events by lowering blood cholesterol. Whereas previous guidelines focused on therapy to decrease low-density lipoprotein and non-high-density lipoprotein cholesterol to specific target levels, the new guideline instead proposes implementation of cholesterol-lowering treatment using evidenced-based intensity of statin therapy without such targets. The guideline also provides a new risk estimator for primary prevention decisions, including stroke outcomes and data on African Americans, which will significantly increase the number of patients recommended for outcome-related benefits of cholesterol-lowering therapy. The first section of this paper reviews the process by which the task force developed the new evidence-based guideline, the major findings and recommendations, and their implications. The second section primarily focuses on the question of how much low-density lipoprotein cholesterol should be lowered and on additional considerations in risk assessment. (J Am Coll Cardiol 2014;64:601-12) © 2014 by the American College of Cardiology Foundation.

CHOLESTEROL GUIDELINES: FOLLOWING THE EVIDENCE

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BACKGROUND. Almost one-third of the population in the United States will die as a result of heart attack or stroke associated with atherosclerotic cardiovascular disease (ASCVD), the leading cause of death and disability in our country today (1). The major treatable causes of ASCVD include hypercholesterolemia, hypertension, diabetes, and an unhealthy lifestyle associated with tobacco consumption, poor diet, lack of exercise, and obesity. Over the past 3 decades, on

the basis of observational studies and some randomized controlled trials (RCTs), guideline recommendations have been developed focusing on treatment strategies to reduce these risk factors. A primary strategy in these efforts has been lowering of blood cholesterol in at-risk populations. To update the previous guideline recommendations issued by the Adult Treatment Panel III in 2001 (2), the National Heart, Lung, and Blood Institute (NHLBI) convened a panel in 2008 to review the evolving evidence base from RCTs regarding treatment of blood cholesterol. The report from the work of this panel, the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ACC = American College of Cardiology

AHA = American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CQ = critical question

FH = familial hypercholesterolemia

HDL-C = high-density lipoprotein cholesterol

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

NHLBI = National Heart, Lung, and Blood Institute

RCT = randomized controlled trial

of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2), is strongly focused on RCT-related evidence. This has resulted not only in a new perspective on treatment strategies, but also in a new paradigm focusing on proven therapy, rather than arbitrary low-density lipoprotein cholesterol (LDL-C) and/or non-high-density lipoprotein cholesterol (HDL-C) targets.

PROCESS. These new guidelines for the treatment of blood cholesterol are distinguished by: 1) an exclusive focus on evidence derived from the systematic review of RCTs; 2) a guideline panel with broad expertise appointed by the NHLBI, composed of 13 members and 3 ex-officio members from primary care, cardiology, epidemiology, clinical lipidology, and endocrinology; and 3) a restriction to develop guideline recommendations on the basis of evidence review from 3 critical questions (CQs) developed by the guideline committee.

The guideline process was conducted along lines consistent with recommendations made by the Institute of Medicine (3). Indeed, an analysis of the durability of ACC/AHA Class I recommendations indicates that downgrades, reversals, and omissions were more likely among recommendations not supported by multiple RCTs (4). For each of the 3 CQs, an independent contractor performed a systematic review of the published data restricted to RCTs published in English from January 1, 1995, through December 1, 2009. Major RCTs and meta-analyses of RCTs published through July 2013 were included in the expert panel's discussion of recommendations.

This process differs significantly from that associated with previous guideline recommendations in that no observational studies are included and hard clinical endpoints of ASCVD are required for an RCT to be considered in the evidence base. For this report, ASCVD included coronary heart disease, stroke, and peripheral arterial disease of presumed atherosclerotic origin. Importantly, studies with outcomes of surrogate markers, such as LDL-C, other lipids, or biomarkers, were not included for consideration. **Only RCTs with hard clinical outcomes were used as evidence for recommendations in the new guidelines.**

Evidence tables were developed and evidence statements were decided upon by the expert panel and rated according to strength of evidence. On the basis of the evidence tables, the panel made guideline

recommendations, graded according to strength of evidence. The panel was limited to the 3 CQs considered of the greatest importance to the development of guidelines for the treatment of blood cholesterol. This was also true of the Risk Assessment (5) and Lifestyle Guideline Panels (6) that were part of the same process. The CQs that governed the systematic review upon which the guideline recommendations are as follows:

CQ1: What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of ASCVD? In a review of 19 RCTs, no data supporting treatment or titration of cholesterol-lowering therapy to a specific LDL-C or non-HDL-C goal in adults with clinical ASCVD were found. Fixed-dose strategies using statin therapy were used in the majority of trials showing improved clinical outcomes. Specifically, the expert panel was unable to find any RCTs that evaluated treatment of all patients in a treatment group to specific treatment goals of <100 or <70 mg/dl.

CQ2: What is the evidence for LDL-C and non-HDL-C goals for the primary prevention of ASCVD? In a review of 6 RCTs in patients without clinical ASCVD, fixed-dose strategies, rather than a treat-to-target strategy, were used to confirm the efficacy of cholesterol-lowering therapy to prevent ASCVD. None of the RCTs considered for CQ1 and CQ2 compared statin therapy titrated to 1 or another LDL-C or non-HDL-C goal.

CQ3: For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups? Therapeutic interventions reviewed involved single-dose or combination therapies for lowering cholesterol including statins, fibrates, nicotinic acid, bile acid sequestrants, ezetimibe, and omega-3 fatty acids. Information from CQ3 was included with that from CQ1 and CQ2 for recommendations regarding cholesterol-lowering drugs for primary and secondary prevention of ASCVD.

A thorough review of the methods and results of the evidence reviewed may be found in the guideline (2) and in the NHLBI evidence report (7).

MAJOR FINDINGS AND RECOMMENDATIONS. To develop guideline recommendations, the results from the systematic review conducted by this panel were supplemented by those from the Risk Assessment Working Group (5) and the Lifestyle Management Panel (6), initially in a format developed by the NHLBI

(2). After the NHLBI announced its intent to publish the guidelines via a collaborative arrangement with the ACC and the AHA (8), the guideline recommendations were translated into the ACC/AHA guideline recommendation format (2). This process also occurred with the Risk Assessment and Lifestyle Guidelines, published at the same time. A list of the major guideline recommendations may be found in Figure 1, and a complete summary has been published as the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2).

The major findings and recommendations in the new guideline are as follows:

Adherence to a healthy lifestyle. The panel unanimously endorsed the report of the 2013 ACC/AHA Lifestyle Management Guideline (6), which endorses a DASH (Dietary Approaches to Stop Hypertension) or Mediterranean-style diet (A diet high in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, and nuts; and low in sweets, sugar-sweetened beverages, and red meats. Also, it includes foods that are low in saturated fat, total fat, and cholesterol but rich in potassium, magnesium, and calcium as well as protein and fiber.) The guideline also stresses the importance of daily aerobic physical activity, avoidance of the use of tobacco products, and maintenance of a healthy body weight. Patients should be checked periodically for hypertension and diabetes and be treated appropriately. The importance of a healthy lifestyle cannot be overemphasized, and its benefits should be stressed to all patients being seen for both primary and secondary prevention during their regular visits.

Benefits of statin therapy for 4 patient groups. The systematic review of RCTs found *strong evidence* for the benefits of statin therapy to reduce cardiovascular events and improve outcomes in 4 patient groups (Central Illustration), which included those with:

- Established clinical ASCVD (secondary prevention);
- Primary elevation of LDL-C levels ≥ 190 mg/dl;
- diabetes, age 40 to 75 years, who have LDL-C levels 70 to 189 mg/dl; and
- primary prevention without diabetes, age 40 to 75 years, with an estimated 10-year risk $\geq 7.5\%$.

Evidence of moderate strength was found to support statin therapy for primary prevention when the 10-year ASCVD risk was $\geq 5\%$ to 7.5% .

Review of evidence from RCTs failed to show consistent benefit when statin therapy was started in:

- Patients undergoing maintenance hemodialysis; or
- Patients in New York Heart Association functional classes II to IV.

Thus, no recommendation was made regarding the initiation or continuation of statin therapy in these patients.

Use of risk estimator for primary prevention.

The Framingham risk assessment tool did not include stroke as an endpoint and did not have a separate risk equation for African-American men and women. A new pooled cohort risk estimator was developed to assist with decisions regarding lowering blood cholesterol for primary prevention by the Risk Assessment Work Group (5). This risk estimator for 10-year ASCVD events has been expanded from the previous endpoint of hard congenital heart disease (nonfatal myocardial infarction and congenital heart disease) recommended by the Adult Treatment Panel III to include first occurrence of stroke (nonfatal and fatal) along with myocardial infarction (nonfatal and fatal). Pooled cohort equations for the risk estimator were developed from 5 NHLBI-sponsored longitudinal population-based cohorts of African-American and white men and women (ARIC [Atherosclerotic Risk in Communities]), CHS [Cardiovascular Health Study], CARDIA [Coronary Artery Risk Development in Young Adults], and the original Framingham Heart Study and its offspring cohorts). These pooled cohort equations were then validated in the contemporary cohorts of MESA (Multi-Ethnic Study of Atherosclerosis) and REGARDS (Reasons for Geographic and Racial Differences in Stroke). The equations are applicable to non-Hispanic, white, and African-American men and women age 40 to 79 years with LDL-C levels of 70 to 189 mg/dl. Data from the REGARDS study (9) are especially important because it is a community-based study appropriate to the United States population. It confirms the use of these pooled risk equations in the populations for which they are designed.

It is important to emphasize that this risk estimator should be used as part of the patient-clinician discussion regarding the potential benefits of statin therapy and not the sole determinant of whether a prescription is written. The use of the risk estimator serves as the beginning of such a discussion, not the end. It should be noted that the risk estimator may overpredict events in Hispanic and East-Asian men and women. Clinical judgment is particularly important for patients where the RCT evidence is insufficient for guiding clinical recommendations. These patients may be younger adults (<40 years of age) who have a low estimated 10-year ASCVD risk, but

Recommendations	ACC/AHA COR	ACC/AHA LOE
A. Heart-healthy lifestyle habits should be encouraged for all individuals		
B. The appropriate intensity of statin therapy should be initiated or continued:		
1. Clinical ASCVD*		
a. Age ≤ 75 y and no safety concerns: High-intensity statin	I	A
b. Age > 75 y or safety concerns: Moderate-intensity statin	I	A
2. Primary prevention – Primary LDL-C ≥ 190 mg/dL		
a. Rule out secondary causes of hyperlipidemia (Table 6)	I	B
b. Age ≥ 21 y: High-intensity statin	I	B
c. Achieve at least a 50% reduction in LDL-C	IIa	B
d. LDL-C lowering nonstatin therapy may be considered to further reduce LDL-C	IIb	C
3. Primary prevention—Diabetes 40–75 years of age and LDL-C 70–189 mg/dL		
a. Moderate-intensity statin	I	A
b. Consider high-intensity statin when $\geq 7.5\%$ 10-y ASCVD risk using the Pooled Cohort Equations [†]	IIa	B
4. Primary prevention – No diabetes 40–75 years of age and LDL-C 70–189 mg/dL		
a. Estimate 10-y ASCVD risk using the Risk Calculator based on the Pooled Cohort Equations [†] in those NOT receiving a statin; estimate risk every 4–6 y	I	B
b. To determine whether to initiate a statin, engage in a clinician-patient discussion of the potential for ASCVD risk reduction, adverse effects, drug-drug interactions, and patient preferences	IIa	C
c. Re-emphasize heart-healthy lifestyle habits and address other risk factors		
i. $\geq 7.5\%$ 10-y ASCVD risk: Moderate- or high-intensity statin	I	A
ii. 5 to $< 7.5\%$ 10-y ASCVD risk: Consider moderate-intensity statin	IIa	B
iii. Other factors may be considered [‡] : LDL-C ≥ 160 mg/dL, family history of premature ASCVD, hs-CRP ≥ 2.0 mg/L, CAC score ≥ 300 Agatston units, ABI < 0.9 , or lifetime ASCVD risk	IIb	C
5. Primary prevention when LDL-C < 190 mg/dL and age < 40 or > 75 y, or $< 5\%$ 10-y ASCVD risk	IIb	C
a. Statin therapy may be considered in selected individuals [§]		
6. Statin therapy is not routinely recommended for individuals with NYHA class II-IV heart failure or who are receiving maintenance hemodialysis		
C. Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments		
1. Assess adherence, response to therapy, and adverse effects within 4–12 wk following statin initiation or change in therapy	I	A
a. Measure a fasting lipid panel	I	A
b. Do not routinely monitor ALT or CK unless symptomatic	IIa	C
c. Screen and treat type 2 diabetes according to current practice guidelines. Heart-healthy lifestyle habits should be encouraged to prevent progression to diabetes	I	B
d. Anticipated therapeutic response: approximately $\geq 50\%$ reduction in LDL-C from baseline for high-intensity statin and 30% to $< 50\%$ for moderate-intensity statin	IIa	B
i. Insufficient evidence for LDL-C or non-HDL-C treatment targets from RCTs		
ii. For those with unknown baseline LDL-C, an LDL-C < 100 mg/dL was observed in RCTs of high-intensity statin therapy		
e. Less than anticipated therapeutic response:		
i. Reinforce improved adherence to lifestyle and drug therapy	I	A
ii. Evaluate for secondary causes of hyperlipidemia if indicated [¶]	I	A
iii. Increase statin intensity, or if on maximally-tolerated statin intensity, consider addition of nonstatin therapy in selected high-risk individuals [§]	IIb	C
f. Regularly monitor adherence to lifestyle and drug therapy every 3–12 mo once adherence has been established. Continue assessment of adherence for optimal ASCVD risk reduction and safety	I	A
D. In individuals intolerant of the recommended intensity of statin therapy, use the maximally tolerated intensity of statin.		
1. If there are muscle or other symptoms, establish that they are related to the statin	I	B
2. For specific recommendations on managing muscle symptoms [¶]	IIa	B

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

[†]Estimated 10-year or “hard” ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations (<http://my.americanheart.org/cvriskscalculator> and <http://www.cardiosource.org/en/ScienceAndQuality/PracticeGuidelines-and-QualityStandards/2013PreventionGuidelineTools.aspx>).

[‡]These factors may include primary LDL-C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset < 55 years of age in a first-degree male relative or < 65 years of age in a first-degree female relative; hs-CRP ≥ 2 mg/L; CAC score ≥ 300 Agatston units or ≥ 75 th percentile for age, sex, and ethnicity (for additional information, see <http://www.mesa-nhlbi.org/CACReference.aspx>); ABI < 0.9 ; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

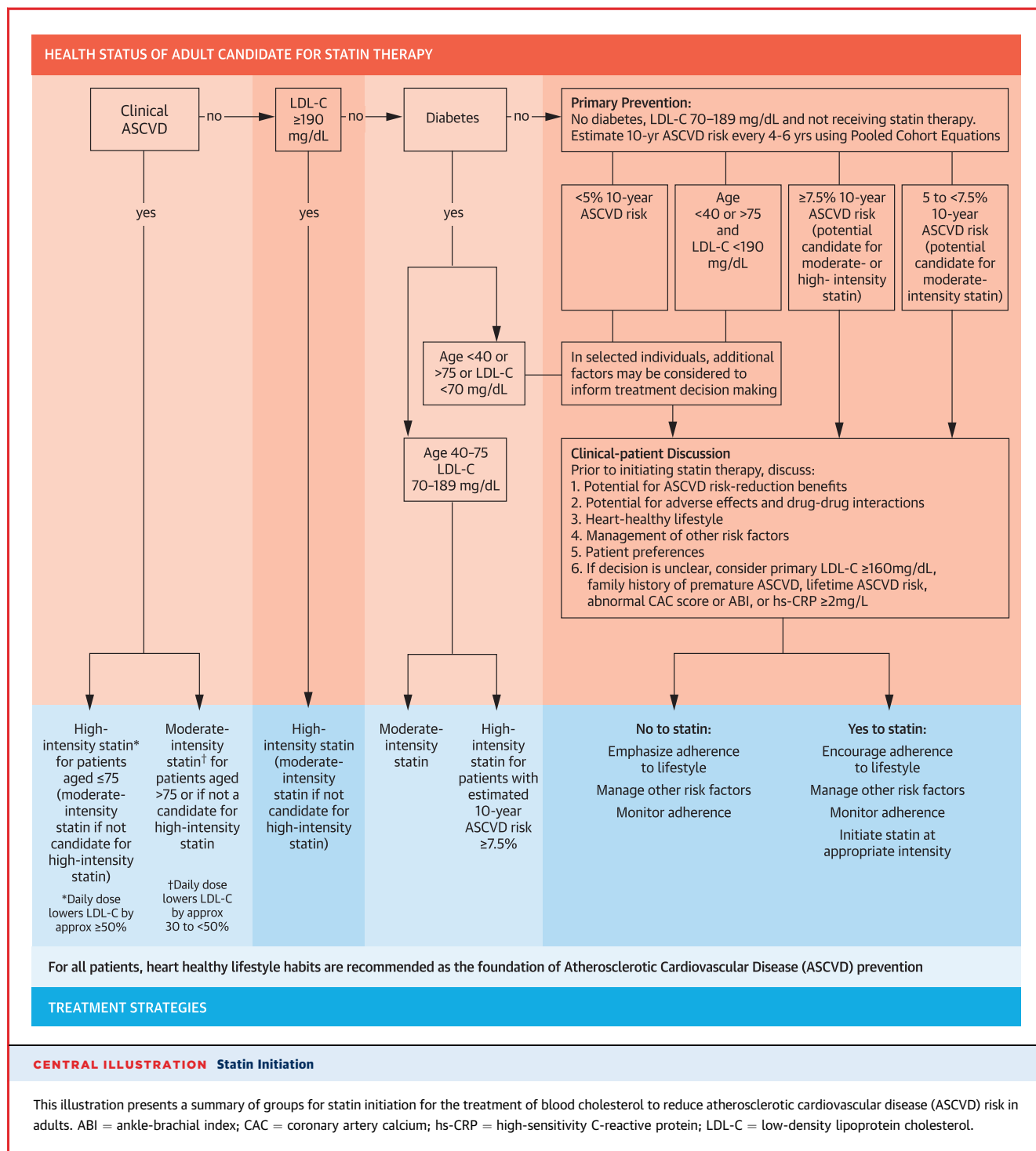
[§]High-risk individuals include those with clinical ASCVD, an untreated LDL-C ≥ 190 mg/dL suggesting genetic hypercholesterolemia, or individuals with diabetes 40 to 75 years of age and LDL-C 70 to 189 mg/dL.

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ALT, alanine aminotransferase, a test of hepatic function; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CK, creatine kinase, a test of muscle injury; COR, Class of Recommendation; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; and TIA, transient ischemic attack.

[¶]See reference 2 for tables 6 and 8.

FIGURE 1 Summary of Recommendations

Key recommendations for the treatment of blood cholesterol to reduce ASCVD risk in adults. Reprinted with permission from Stone et al. (2)



a high lifetime ASCVD risk on the basis of a single strong factor or multiple risk factors. Other groups that deserve consideration include those with serious comorbidities and increased ASCVD risk. Examples include those patients with human

immunodeficiency virus, with rheumatologic or inflammatory diseases, or who have undergone solid organ transplantation. Here, the elements of the clinician-patient discussion weighing treatment of all risk factors, adherence to an optimal lifestyle, the

potential for benefit with statin therapy weighed against the potential for adverse effects and drug-drug interactions, and informed patient preference can guide therapeutic decisions.

When a quantitative risk decision regarding the initiation of therapy is uncertain, the expert panel recommends that other factors be considered. These additional factors include: family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; low-density lipoprotein (LDL) ≥ 160 mg/dl; coronary artery calcium (CAC) score ≥ 300 Agatston units or >75th percentile for age, sex, and ethnicity (10); high-sensitivity C-reactive protein (hsCRP) ≥ 2.0 mg/l; or ankle-brachial index (ABI) <0.90. A family history of ASCVD or LDL ≥ 160 mg/dl is most useful in younger individuals, whereas the ABI, hsCRP, and CAC are generally useful in older individuals. A 30-year or lifetime risk estimation in those individuals 20 to 59 years of age is especially useful for emphasizing lifestyle change. The ACC/AHA risk estimator can be downloaded from either the ACC (11) or from the AHA website (12).

The risk estimator includes information on the lifestyle and obesity guidelines and provides decision support after data are entered. This allows for more informed patient preference in primary prevention. Thus, the clinician-patient discussion embraces 4 areas: 1) estimation of 10-year risk (or lifetime risk, if appropriate) and review of treatable risk factors such as hypertension and cigarette smoking; 2) need for adherence to an improved

healthy lifestyle; 3) the potential for benefit in contrast to the potential for adverse effects and/or drug-drug interactions of statin therapy; and 4) informed patient preference.

No evidence from RCTs to support the use of LDL-C or non-HDL-C goals. As noted earlier, CQ1 focused on RCT evidence supporting the use of LDL-C goals to guide cholesterol-lowering therapy. Whereas this approach is supported conceptually by extrapolation of data from observational studies and RCTs, there are no direct data from RCTs that confirm the efficacy of using LDL-C or non-HDL-C goals for therapy. For example, there is no RCT evidence to support that titrating to a goal of LDL-C <70 mg/dl improves outcomes over treating to a goal of LDL-C <80 mg/dl. Furthermore, no evidence was found from RCTs to support improved clinical outcomes resulting from the addition of a nonstatin drug to a statin to further lower LDL-C to an arbitrary target goal. Thus, the expert panel was unable to make any evidence-based recommendations about the use of treatment goals to guide therapy.

Appropriate dose and recommendations for statin therapy. Review of evidence from RCTs confirmed a strong and consistent reduction in ASCVD clinical events for those patients who were treated with 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statin) therapy. Improved clinical outcomes occurred when statin therapy was started at LDL-C levels as low 70 mg/dl for both primary and secondary prevention of ASCVD. Two meta-analyses of large studies (13,14) published after completion of

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately $\geq 50\%$	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg	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 BID Pitavastatin 2–4 mg	<i>Simvastatin 10 mg</i> Pravastatin 10–20 mg Lovastatin 20 mg <i>Fluvastatin 20–40 mg</i> <i>Pitavastatin 1 mg</i>

Boldface type indicates specific statins and doses that were evaluated in RCTs (16–18,46–49,64–75,77) included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

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

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study (47).

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

BID indicates twice daily; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

FIGURE 2 High-, Moderate-, and Low-Intensity Statin Therapy

The therapies were used in the RCTs reviewed by the expert panel. Reprinted with permission from Stone et al. (2).

the expert panel's systematic review further confirm these outcomes and the benefits of statin therapy. The results of RCTs show that statin therapy can be categorized on the basis of the dose and specific statin as high intensity, moderate intensity, or low intensity (Fig. 2). The RCT evidence demonstrates that, for patients <75 years of age, high-intensity statin therapy consistently reduces ASCVD events more than moderate-intensity statin therapy. Fewer patients >75 years of age were included in the RCTs. For these patients, although there was evidence of an additional reduction of ASCVD events from high- versus moderate-intensity statin therapy, for safety reasons (including increased comorbidities and potential for side effects in the elderly) the expert panel recommended that moderate-intensity statin therapy be considered for patients >75 years of age with clinical ASCVD. In essence, the expert panel acknowledges that "lower is better" but recommends proven therapy that is both tolerated and safe. The expert panel recommendations for treatment are summarized in Figure 1 and the Central Illustration.

Monitoring and safety of statin therapy. The evidence from RCTs supporting the safety of statin use was judged to be strong when used as recommended in properly-selected patients with regular follow-up assessments. Patient characteristics identified from RCTs that may influence statin safety include: multiple or serious comorbidities, such as impaired renal or hepatic function; a history of previous statin intolerance or muscle disorders; concomitant use of drugs affecting statin metabolism; a history of hemorrhagic stroke; and age >75 years. Myopathy (0.01 excess cases per 100) and hemorrhagic stroke (0.01 excess cases per 100) make minimal contributions to excess risk from statin therapy (13). The expert panel did not find evidence from RCTs that statins adversely affect either cognitive changes or risk of dementia. It was noted that Asian ancestry might be a consideration in the initial choice of statin intensity.

Routine measurement of creatine kinase is not recommended. It is recommended that creatine kinase be obtained as a baseline test in those at increased risk of adverse of muscle events and in those on statin therapy who develop muscle symptoms (12). Patients should be asked about muscle symptoms when starting statin therapy and at each subsequent visit. Baseline measurement of transaminase (alanine transaminase) levels should be performed before initiation of statin therapy and measured during therapy if symptoms suggestive of hepatotoxicity develop, but should not be measured routinely.

Although treatment to a target LDL-C goal is not given a recommendation, a fasting lipid panel is recommended prior to starting and 4 to 12 weeks after initiating therapy. The percent reduction in LDL-C should not be used as a treatment goal or a performance measure, but can provide useful information about a patient's adherence to medical therapy and lifestyle recommendations. If LDL-C is <40 mg/dl on 2 consecutive measurements, decreasing the dose of statin therapy may be considered. This recommendation is derived from the protocol for 2 RCTs, although it should be noted that no data have been identified to suggest that adverse events occurred when LDL-C was <40 mg/dl.

Review of the RCT evidence base indicates that statin therapy modestly increases the risk for developing type 2 diabetes. However, in patients taking high-intensity statins for secondary prevention or for primary prevention with a 10-year ASCVD risk $\geq 7.5\%$, the reduction in risk for ASCVD far outweighs the risk of diabetes. For patients on moderate-intensity statins, the risk reduction benefits outweigh the excess risk of diabetes even down to a 10-year ASCVD risk $\geq 5\%$. The rate of excess diabetes generally occurs in those with diabetes risk factors and varies by statin intensity. The risk is lower for moderate-intensity statins (approximately 0.1 excess case of diabetes per 100 statin-treated patients/year) than for high-intensity statins (approximately 0.3 excess case of diabetes per 100 statin-treated patients/year).

IMPLICATIONS AND OBSERVATIONS. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2) represents a significant paradigm change in the treatment of blood cholesterol to reduce ASCVD events in both secondary prevention and in carefully-selected primary prevention patients. A systematic review of the RCT evidence base clearly establishes patient benefits on the basis of hard ASCVD clinical outcomes that result from varying intensities of statin therapy. The panel did recommend nonstatin therapies of proven benefit in the 3 high-risk groups if optimal statin therapy was not tolerated or if it resulted in lipid lowering less than the recommended statin class would indicate. The use of nonstatin medical therapies without RCT evidence of improved clinical outcomes to achieve target LDL-C treatment goals cannot be recommended using the current RCT evidence base. Further research is needed to confirm the incremental benefits of nonstatin therapies and the value of specific LDL-C or non HDL-C goals for patient care.

The RCT systematic review provides strong evidence that additional patients benefit from statin

therapies beyond those previously recommended for primary prevention. To assist in identifying these additional patients, a new risk estimator, which includes stroke (nonfatal and fatal) and African-American patients, has been developed. If a quantitative risk decision cannot be made, additional factors may be considered, including family history of premature ASCVD; LDL-C ≥ 160 mg/dl; hsCRP ≥ 2.0 mg/l; CAC score ≥ 300 Agatston units or 75th percentile on the basis of race, age, and sex; and ABI < 0.9 . A 30-year or lifetime risk estimation in those patients 20 to 59 years of age is especially useful for emphasizing lifestyle change. ***A heart-healthy lifestyle remains the foundation for preventing ASCVD and must be part of all efforts to improve ASCVD risk factors and outcomes.***

There is a need for additional RCT evidence regarding effective strategies to reduce ASCVD risk in women, in patients > 75 and < 40 years of age, and in those of additional ethnic groups (e.g., East Asian, South Asian and Hispanic). RCTs are needed to confirm hard clinical outcomes for nonstatin therapies. RCT confirmation of the efficacy of the new risk estimator and associated primary prevention strategies is needed to provide a foundation for future treatment strategies.

Guidelines, including the new 2013 ACC/AHA Blood Cholesterol Treatment Guideline, inform, but do not replace, clinical judgment. The current evidence base must be combined with clinical judgment and patient preference to achieve optimal care and reduce ASCVD risk.

CHOLESTEROL GUIDELINES: NEGOTIATING THE UNCERTAINTIES

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Three leading causes of ASCVD are hypercholesterolemia, hypertension, and cigarette smoking. Over 3 decades ago, demonstration of risk reduction through RCTs led the NHLBI to initiate national education programs for high blood cholesterol and high blood pressure. Many subsequent RCTs have confirmed clinical benefits from the lowering of these 2 risk factors (15,16). Other factors associated with ASCVD risk are diabetes, obesity, physical inactivity, family history of ASCVD, and various proinflammatory and prothrombotic factors. Although all of these factors are risk-associated, prevention of ASCVD through therapeutic intervention has yet to be shown.

LDL is the dominant cholesterol-carrying lipoprotein. It is measured routinely as LDL-C. The most

dramatic demonstration of atherogenicity of LDL comes from familial hypercholesterolemia (FH). Elevated LDL-C results from a deficiency in hepatic LDL receptors (17). In heterozygous FH, serum LDL-C is elevated about 2-fold; with homozygous FH, LDL-C is at least 4 times increased. FH patients commonly develop premature ASCVD, which can occur even without concomitant risk factors.

In population studies, it is apparent that elevated LDL-C (typically reflected in high total cholesterol) underlies ASCVD. Cross-country comparisons show that populations with relatively elevated LDL-C manifest higher rates of ASCVD than do those with lower concentrations (18). Within populations, patients with higher cholesterol levels have greater ASCVD rates than those with lower concentrations, even after adjusting for other factors (18,19).

Concurrently, over the past 4 decades, numerous RCTs have documented a reduction of ASCVD from cholesterol-lowering therapies (20,21). Earlier RCTs utilized nonstatin treatment. The more robust of these demonstrated benefit, but stronger evidence of benefit was uncovered through meta-analysis of all trials (20). Subsequently, single RCTs with statins and meta-analysis of multiple-statin trials confirmed a marked reduction of ASCVD from highly efficacious cholesterol lowering (21).

Although LDL is the dominant atherogenic lipoprotein, very-low-density lipoproteins seem to also promote atherosclerosis. Combining LDL-C and very-low-density lipoprotein cholesterol into a single target (non-HDL-C) may thus be preferable to targeting LDL-C alone. In support, a recent meta-analysis of statin trials found that non-HDL-C is more closely correlated with ASCVD risk than LDL-C (22). Hence, “cholesterol-lowering therapy” can apply to both LDL-C and/or non-HDL-C.

Epidemiological studies demonstrate a continuous relationship between cholesterol levels and ASCVD risk, from low to high (18). RCTs show the reverse: the more LDL-C is lowered, the greater the risk reduction (23,24). These findings imply “the more, the better” is true for cholesterol lowering. Furthermore, there appears to be no limit beneath which a lower LDL-C fails to reduce risk (25). Meta-analysis of statin trials show that risk reduction extends into the very low range for LDL-C. Thus, it can be said that “the lower, the better” is true for cholesterol reduction. Genetic epidemiology adds another dimension; persons having a lifetime of low cholesterol levels manifest a particularly low prevalence of ASCVD (26). This finding indicates that “the longer, the better” is true for cholesterol

TABLE 1 Categories of LDL-C and Non-HDL-C

Cholesterol Category	LDL-C Level, mg/dl	Non-HDL-C Level, mg/dl
Very high	≥175	≥200
High	150-174	175-199
Borderline high	125-149	150-174
Borderline low	100-124	125-149
Low	75-99	100-124
Very low	50-74	75-99

Range of cholesterol categories, on the basis of the guidelines.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

lowering. **Table 1** gives a suggested classification of LDL-C and non-HDL-C ranges according to relative risk for ASCVD. These ranges come from a meta-analysis of statin trials (25).

RCTs reveal that, regardless of the modality of cholesterol lowering, ASCVD risk is diminished. This is true for diet, bile acid resins, ileal-exclusion operation, fibrates, nicotinic acid, and statins (15,20,21). The degree of risk reduction depends on the extent of lowering, not on the therapeutic modality. Statins lower LDL-C by 35% to 55%, depending on the type and dose; ileal exclusion, which is rarely used, reduces LDL-C by 30% to 35%; and bile acid resins, nicotinic acid, and fibrates decrease LDL-C by 10% to 20%. A newer drug, ezetimibe, lowers LDL-C by 15% to 20%. Dietary therapy adds an additional 5% to 15% lowering. Because of high efficacy and tolerability, statins have emerged as first-line therapies. Other cholesterol-lowering drugs are generally reserved for patients who are statin-intolerant or as add-ons to statins to enhance cholesterol reduction. Unfortunately, the clinical benefit from combined drug therapy has not been adequately explored through RCTs.

Because FH patients can develop full-blown ASCVD in the absence of other risk factors, there is little doubt that elevated LDL-C is atherogenic. Population and genetic studies further disclose that without some elevation of LDL-C, cigarette smoking, hypertension, and diabetes cause little coronary heart disease (26,27). We might conclude, therefore, that elevated LDL is the prime driver of atherogenesis, whereas other risk factors worsen atherosclerosis or precipitate its complications. If true, treatment of these accelerating risk factors should probably be accompanied by cholesterol-lowering therapy.

There is almost universal agreement that patients with established ASCVD should receive cholesterol-lowering drugs. This consensus is supported by

single RCTs and by meta-analysis (23-25). High doses of statins usually are required for maximized cholesterol lowering. Ideally, LDL-C and non-HDL-C should be reduced to very low levels (**Table 1**). Yet, many patients cannot achieve these very low levels, even with high doses of powerful statins (25). Should a second cholesterol-lowering drug be added in such patients? One clinical trial failed to demonstrate added efficacy when niacin was combined with maximal statin therapy (28). Additional LDL-C lowering with niacin was modest. Another secondary prevention study is currently comparing high-dose simvastatin with the same drug plus ezetimibe. The latter agent is expected to add another 15% to 20% of LDL-C lowering. Whether ezetimibe plus high-dose statin is more efficacious than the high-dose statin alone remains to be seen. A newer class of drugs, called PCSK9 inhibitors, powerfully reduces LDL-C; PCSK9 inhibitors are currently being tested to determine how much additional risk reduction occurs when combined with high doses of statins (29).

Primary prevention with cholesterol-lowering drugs is a more complex issue than secondary prevention. A few examples can be considered.

Most researchers support intensive cholesterol lowering in patients with type 2 diabetes, even in the absence of ASCVD (2). These patients carry a high risk for future ASCVD, and risk reduction with statin therapy has been clearly documented. Furthermore, when patients with diabetes have concomitant metabolic syndrome, their ASCVD risk is substantially raised (30). Consequently, it is reasonable to lower LDL-C in patients with metabolic syndrome, as well as in those with diabetes.

Cigarette smoking is another factor that confers high lifetime risk for ASCVD. That statins reduce cardiovascular events in smokers has been amply documented (21). Thus, middle-aged and older smokers are good candidates for statin treatment. The same can be said for older persons with poorly-controlled hypertension. Whether to utilize a statin in patients with well-controlled hypertension as the only risk factor is a matter of clinical judgment. For persons who are smokers only or who only have hypertension, reducing LDL-C levels to a low range may be sufficient (**Table 1**). But, for those with both risk factors, lowering LDL-C to a very low range is reasonable (31).

The ACC/AHA (5) recently published a 10-year risk algorithm for ASCVD on the basis of major risk factors. At the same time, the ACC/AHA (26) recommended that statin therapy be instituted in persons with a 10-year risk for ASCVD ≥7.5%. Older persons

(i.e., men age >60 years and women age >70 years) mostly exceed the treatment threshold, and accordingly, are recommended for statin treatment. In this age range, the presence of a single risk factor confers a 10-year risk of approximately 15% by the algorithm (5). Here statins seem reasonable. A 10-year risk of $\geq 15\%$ because of multiple borderline risk factors is equivalent to a single major risk factor; likewise, at this level of risk, statin therapy in older persons is sound.

Whether to initiate statin therapy in older persons whose calculated 10-year risk for ASCVD is 7.5% to 15% is a matter of clinical judgment. This is particularly true in the light of the claim that the ACC/AHA algorithm substantially overestimates the 10-year risk for the current U.S. population (32).

An underused modality for risk assessment in older persons is the CAC score. ACC/AHA guidelines contend that a high CAC score (e.g., ≥ 300 Agatston units) confers a high-enough risk to initiate statin therapy (2). Persons with low CAC and a paucity of major risk factors are at low risk and are not good candidates for cholesterol-lowering drugs (33). CAC measurement is a more reliable indicator of risk than chronological age (34). Older patients with a 10-year risk of 7.5% to 15% who have CAC scores in the range of 100 to 299 are in a borderline zone, making cholesterol-lowering drugs optional. In this range, additional risk indicators may be useful for guidance of therapy. At lower CAC scores in otherwise low-risk individuals, 10-year risk is low and statin therapy is not necessary.

For 2 reasons, the AHA/ACC algorithm should be more reliable in middle-aged adults (age 40 to 65 years) than in older persons. First, in this age range, estimated risk depends more on major risk factors than on age; and second, for any estimated risk, lifetime risk is higher in middle-aged adults than in elderly patients. Therefore, using a 7.5% risk threshold for initiating statin therapy is more reasonable for middle-aged adults than for older persons. But, lifestyle intervention should not be ignored; it has greater potential for long-term risk reduction when started at a younger age. Indeed, for younger people (age <40 years), priorities for prevention should be given to lifestyle change.

The ACC/AHA (2) recommended starting statin therapy in anyone with an LDL-C ≥ 190 mg/dl, even in the absence of other risk factors. Because a lifetime of elevated LDL-C carried a high risk, the use of statins in patients whose LDL-C is consistently over 160 mg/dl seems reasonable.

CRITIQUE OF THE ACC/AHA GUIDELINES. The ACC/AHA guidelines describe themselves as an effort to

apply strict “evidence-based” rules to the complex topic of cholesterol management. The cholesterol panel adhered more rigidly to perceived rules than did the blood pressure panel working under the same mandate. For example, the cholesterol panel could identify no therapeutic goals for cholesterol lowering, whereas the blood pressure panel was able to set goals even though the strength of the evidence was similar for the 2 risk factors. A lack of cholesterol goals leaves the physician in the dark for setting an individualized statin dose and evaluating the adequacy of the risk reduction from therapy. This is less helpful than the approach taken by the blood pressure panel.

The cholesterol panel stressed restriction of guideline development to data from RCTs. Still, they resorted to epidemiological data when establishing the all-important basis for who should be treated with cholesterol-lowering drugs, namely, global risk assessment. In middle-aged individuals, a mix of major risk factors is required to justify statin therapy. Importantly, age is generally not the dominant risk factor. But in older populations, age becomes the dominant risk factor; at the same time, age loses its reliability as a risk factor when applied to patients. The most problematic result of deriving a uniform risk threshold for drug treatment from population-based data, regardless of age, is that almost all older people will require statin therapy, even though a significant number of them are virtually free of major risk factors and underlying atherosclerosis. Consequently, a high number of very low-risk persons of advancing age will be treated unnecessarily. To avoid overtreatment of older persons, either a higher risk threshold must be set or imaging modalities must be used to distinguish between higher- and lower-risk patients.

The cholesterol panel was left in the awkward position of having to relegate cholesterol-lowering lifestyle therapies to another panel, which did not use the same “evidence-based” approach. RCT evidence for lifestyle intervention is largely lacking, but epidemiological evidence of the benefit of certain lifestyle patterns is strong. Previous cholesterol guidelines stressed lifestyle intervention as the foundation of cholesterol management. By removing this priority from the cholesterol guidelines, they are transformed largely into statin treatment guidelines. This conveys an unfortunate message to caregivers, particularly in the area of primary prevention.

It is curious that the new guidelines failed to discuss the metabolic syndrome, even though the AHA and NHLBI have placed great emphasis on this syndrome as a major multiplex risk factor for ASCVD. Thanks in no small part to these 2 organizations, the

metabolic syndrome has gained traction in the cardiovascular community and has enhanced the opportunity to highlight lifestyle intervention in the prevention of ASCVD.

Finally, the purpose of cholesterol guidelines is to assist physicians in the management of patients at risk. However, the guidelines, as written, effectively apply a public health strategy rather than a clinical strategy by recommending standard doses of statins using evidence derived from RCTs, in which the average participant had a risk similar to the patient's risk. This shortcoming appears to be an unfortunate result of the panel's misapplication of the so-called evidence-based approach. Almost as an afterthought, the concluding statement of the first section

of this article states: "The current evidence base must be combined with clinical judgment and patient preference to achieve optimal care and reduce ASCVD risk." However, virtually no guidance is provided to the caregiver for how to adjust the guidelines to best fit the patient.

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