Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death, decreased quality of life, and medical costs in the United States. Nearly 1 in 3 Americans die of heart disease and stroke (1). Most ASCVD is preventable through a healthy lifestyle and effective treatment of cholesterol and blood pressure. The 2013 “Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults” from the American College of Cardiology and American Heart Association (ACC/AHA) provides an evidence-based approach to reducing ASCVD risk (2).

**Guideline Development Process**

In 2008, the National Heart, Lung, and Blood Institute (NHLBI) convened the Adult Treatment Panel (ATP) IV to update the 2001 ATP-III cholesterol guidelines using a rigorous systematic process to identify and review randomized, controlled trials (RCTs) with cardiovascular outcomes and meta-analyses of these RCTs. The panel comprised experts and clinicians from the fields of cardiology, epidemiology, primary care, and endocrinology (2) and received support from the Lifestyle Management and Risk Assessment Work Groups (3, 4).

Systematic evidence reviews conducted according to principles recommended by the Institute of Medicine (5) were performed to answer 3 questions relevant to clinical care. Two questions focused on the evidence supporting low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) levels as targets of treatment. One question examined the reduction in ASCVD events and adverse effects for each cholesterol-lowering drug class. The panel synthesized the evidence from these 3 reviews as well as from Lifestyle Management and Risk Assessment Work Groups reviews (3, 4) that addressed 5 additional critical questions.

Systematic electronic searches of relevant databases of the peer-reviewed English-language literature published from 1 January 1995 through 1 December 2009 for each critical question were conducted by an NHLBI-selected independent contractor and focused on RCTs and systematic reviews and meta-analyses of RCTs assessed as fair to good quality. In addition, RCTs with ASCVD outcomes that included coronary heart disease, stroke, and cardiovascular deaths published after that date were eligible for consideration through July 2013. Evidence tables were constructed, and the strength of evidence was rated according to the NHLBI (Table 1 of the Supplement, available at www.annals.org). Recommendations were graded accord-
Synopsis of the 2013 ACC/AHA Cholesterol Guideline

The guideline focuses on treatment of blood cholesterol to reduce ASCVD risk in adults. Major recommendations are summarized here and in Table 1. The guideline report provides a complete listing of recommendations and supporting evidence behind each recommendation (2).

1. Encourage Adherence to a Healthy Lifestyle
   A healthy lifestyle is the foundation for cardiovascular health. The panel endorsed the 2013 ACC/AHA Lifestyle Management Guideline (3) for a diet that is low in saturated fat, trans fat, and sodium; emphasizes vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts; and limits sweets, sugar-sweetened beverages, and red meats and engage in regular aerobic physical activity. Adults also should maintain a healthy body weight, avoid smoking, and control hypertension and diabetes when present.

2. Statin Therapy Is Recommended for Adults in Groups Demonstrated to Benefit
   Strong RCT evidence shows that reduction in ASCVD events from statin therapy exceeds adverse events for 4 patient groups: those with clinical ASCVD (acute coronary syndromes, myocardial infarction, stable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin) when statins are used for secondary prevention, and those with LDL-C levels ≥190 mg/dL; those aged 40 to 75 years with diabetes and LDL-C levels 70 to 189 mg/dL; and those aged 40 to 75 years without diabetes and with a 10-year ASCVD risk ≥7.5% when statins are used for primary prevention. Moderate evidence supports consideration of statin therapy for primary prevention in individuals with a 10-year ASCVD risk of 5% to <7.5%. Routine initiation of statin therapy is not recommended in adults with New York Heart Association heart failure class II to IV or those receiving maintenance hemodialysis. Randomized, controlled trials in these groups showed no reduction in ASCVD.

3. Statins have an Acceptable Margin of Safety When Used in Properly Selected Individuals and Appropriately Monitored
   Strong RCT evidence supports safety of statins when they are used as directed in conjunction with regular follow-up assessments in properly selected patients. Adjustment of statin intensity is recommended in individuals older than 75 years with a history of statin intolerance or other characteristics (2) or those receiving drug therapy that may increase statin adverse events.

   Routine monitoring of hepatic aminotransferase level or creatine kinase level is not recommended unless clinically indicated by symptoms suggesting hepatotoxicity or myopathy. Given the potential for decreasing ASCVD events and death, the relationship of muscle and other symptoms to statin treatment must be confirmed. Therefore, eliciting a history of muscle symptoms before statin initiation and carefully monitoring symptoms during statin discontinuation and rechallenge is recommended. Severe myopathy, rhabdomyolysis, and possibly hemorrhagic stroke are rare complications of statin therapy.

   Although statin therapy modestly increases the risk for type 2 diabetes, ASCVD risk reduction outweighs the excess risk for diabetes for high-intensity statins in secondary prevention or for 10-year ASCVD risk ≥7.5%. Similarly, ASCVD risk reduction outweighs the excess risk for diabetes for moderate-intensity statin therapy in adults with a 10-year ASCVD risk ≥5%.

4. Engage in a Clinician–Patient Discussion Before Initiating Statin Therapy, Especially for Primary Prevention in Patients With Lower ASCVD Risk
   Decisions to initiate statin therapy in primary prevention should be based on clinical judgment and preferences of informed patients. In adults without clinical ASCVD or...
Synopsis of the 2013 ACC/AHA Cholesterol Guideline

**Clinical Guideline**

**Table 1. Major Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults**

Healthy lifestyle habits should be encouraged for all persons.

The appropriate intensity of statin therapy should be initiated or continued:

1. Clinical ASCVD†
   a. Persons aged ≤75 y with no safety concerns: high-intensity statin (class I, level A)
   b. Persons aged >75 y or with safety concerns: moderate-intensity statin (class I, level A)
2. Primary prevention: primary LDL-C level ≥190 mg/dL
   a. Rule out secondary causes of hypercholesterolemia
   b. Persons aged ≥21 y: high-intensity statin (class I, level B)
   c. Achieve ≥50% reduction in LDL-C level (class Ia, level B)
   d. May consider LDL-C-lowering nonstatin therapy to further reduce LDL-C levels (class IIb, level C)
3. Primary prevention: persons with diabetes aged 40–75 y with an LDL-C level of 70–189 mg/dL
   a. Moderate-intensity statin (class I, level A)
   b. Consider high-intensity statin when 10-y ASCVD risk is ≥7.5% (class IIa, level B)
4. Primary prevention: persons aged 40–75 y without diabetes with an LDL-C level of 70–189 mg/dL
   a. Estimate 10-y ASCVD risk (risk calculator based on Pooled Cohort Equations recommended)§ in those not receiving a statin; estimate risk every 4–6 y (class I, level B)
   b. To determine whether to initiate a statin, engage in clinician-patient discussion of potential for ASCVD risk reduction, adverse effects, drug-drug interactions, and patient preferences (class IIa, level C). Reemphasize healthy lifestyle habits and address other risk factors. If statin therapy is chosen:
      i. Persons with ≥7.5% 10-y ASCVD risk: moderate- or high-intensity statin (class I, level A)
      ii. Persons with ≤7.5% 10-y ASCVD risk: consider moderate-intensity statin (class IIa, level B)
      iii. Other factors may be considered: LDL-C level ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, high-sensitivity C-reactive protein level of ≥2.0 mg/L, coronary artery calcification score ≥300 Agatston units, or ankle–brachial index <0.9 (class IIb, level C)
5. Primary prevention when LDL-C level is ≤190 mg/dL and person is aged <40 y or >75 y or has <5% 10-y ASCVD risk
   a. Statin therapy may be considered in selected persons (class IIb, level C)
   b. Statin initiation is not routinely recommended for persons with NYHA class II–IV heart failure or those who are receiving maintenance hemodialysis.

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments. Nonstatin therapy can be considered in selected persons.

Assess adherence, response to therapy, and adverse effects within 4–12 wk after statin initiation or change in therapy (class I, level A)

a. Measure fasting lipid panel (class I, level A)
   b. Do not routinely monitor hepatic function with ALT levels or muscle injury with CK levels unless patient is symptomatic (class IIa, level C).
   c. Screen and treat type 2 diabetes mellitus according to current practice guidelines. Healthy lifestyle habits should be encouraged to prevent progression to diabetes (class I, level B)
   d. Anticipated therapeutic response: approximately ≥50% reduction in LDL-C level from baseline for high-intensity statin and 30% to <50% for moderate-intensity statin (class IIa, level B)
      i. Insufficient evidence from RCTs for LDL-C or non–HDL-C treatment goals
      ii. For guidance in persons with unknown baseline LDL-C level, a level of <100 mg/dL was observed in RCTs about high-intensity statin therapy.
   e. Less-than-anticipated therapeutic response:
      i. Reinforce improved adherence to lifestyle and drug therapy (class I, level A)
      ii. Evaluate for secondary causes of hypercholesterolemia if indicated† (class I, level A)
      iii. Increase statin intensity, or if patient is receiving maximally tolerated statin intensity, consider addition of nonstatin therapy shown in RCT to reduce ASCVD events in selected high-risk persons** (class IIb, level C)
   f. Regularly monitor adherence to lifestyle and drug therapy every 3–12 mo once statin adherence has been established. Continue to assess adherence for optimum ASCVD risk reduction and safety (class I, level A)

In persons unable to tolerate the recommended intensity of statin therapy, use the maximally tolerated intensity of statin.

If there are muscle or other symptoms, establish their relationship to statin therapy (class IIa, level B)

a. Obtain a history of muscle symptoms before initiating statin therapy.
   b. If muscle or other symptoms develop during statin therapy, discontinue the statin.
   c. Once mild to moderate muscle or other symptoms resolve, rechallenge with the same dose of statin or lower; if muscle symptoms recur, discontinue statin and rechallenge with progressively lower doses of the same or a different statin.
   d. If muscle symptoms persist >2 mo after statin discontinuation, consider other conditions that may increase the risk for muscle symptoms††

ALT = alanine aminotransferase; ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NYHA = New York Heart Association; RCT = randomized, controlled trial.

* Adapted from reference 2. Reprinted with permission.
† For information about class and level, please see Table 3 of the Supplement.
‡ Clinical ASCVD is defined as acute coronary syndrome or a history of myocardial infarction, stable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.
§ Estimated 10-y “hard” ASCVD risk includes first occurrence of nonfatal myocardial infarction, death from coronary heart disease, and nonfatal and fatal stroke as used in the Pooled Cohort Equations on the basis of age, sex, smoking status, total cholesterol level, HDL-C level, systolic blood pressure, and the use of antihypertensive therapy.
¶ Other factors that may influence ASCVD risk include primary LDL-C level ≥160 mg/dL, or other evidence of genetic hyperlipidemia; family history of premature ASCVD with onset before age 55 y in a first-degree male relative or before age 65 y in a first-degree female relative; high-sensitivity C-reactive protein level of ≥2.0 mg/L; coronary artery calcification score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see www.mesa-nhlbi.org/CACReference.aspx); or ankle–brachial index <0.9 or lifetime ASCVD.
¶¶ Common causes of muscle ache, pain, or fatigue include hypothyroidism, reduced renal or hepatic function, rheumatologic disorders (especially polymyalgia rheumatica), steroid myopathy, vitamin D deficiency, or primary muscle diseases.

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diabetes whose LDL-C level is <190 mg/dL, calculating the estimated 10-year ASCVD risk should be the start of the clinician–patient discussion and should not automatically lead to statin initiation. As the absolute risk for ASCVD events decreases, so does the net benefit of the intervention. Therefore, discussion of the potential for ASCVD event reduction, adverse effects, drug–drug interactions, and patient preferences is especially important for lower-risk primary prevention. The discussion provides the opportunity to encourage healthy lifestyle habits and control other risk factors.

Additional factors may be considered when a risk-based decision is uncertain, including LDL-C levels ≥160 mg/dL, family history of premature ASCVD, elevated lifetime ASCVD risk, high-sensitivity C-reactive protein level ≥2.0 mg/L, coronary artery calcification score >300 Agatston units, and ankle–brachial index <0.9. After age 75 years, comorbid conditions, anticipated longevity, safety considerations, and patient preferences should play a large role in decision making.

5. Use the Newly Developed Pooled Cohort Equations for Estimating 10-Year ASCVD Risk

The Pooled Cohort Equations are currently the best available method for estimating 10-year ASCVD risk to guide statin initiation (4, 6). Application of the inclusion and exclusion criteria from RCTs is cumbersome and results in underidentifying high-risk and overidentifying low-risk individuals for statin treatment.

The Pooled Cohort Equations were developed using recent data 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). When the Pooled Cohort Equations were validated in 2 independent contemporary cohorts (MESA [Multi-Ethnic Study of Atherosclerosis] and REGARDS [Reasons for Geographic and Racial Differences in Stroke]), discrimination and calibration ranged from “good” to “fair.” Some overestimation of ASCVD risk was observed, primarily in higher-risk individuals, perhaps due to high rates of statin initiation after baseline examinations in these cohorts and limited duration of follow-up. Modest overestimation of ASCVD risk generally will not affect most decisions to recommend statin treatment for adults with a 10-year ASCVD risk ≥7.5% because ASCVD event reduction exceeds adverse effects in the 10-year ASCVD risk range of 5% to <7.5%.

Although overprediction was reported by 1 group for 3 other cohorts (7), these cohorts of health professionals and women screened for a clinical trial are not representative of the U.S. population (the reason the risk assessment panel decided not to use them for derivation or validation) and may have been subject to high rates of statin use during the follow-up period (8).

6. Initiate the Appropriate Intensity of Statin Therapy

The appropriate intensity of statin therapy should be used to reduce ASCVD risk and minimize adverse effects (Table 2). On the basis of strong RCT evidence, high-intensity statin therapy (LDL-C level decreased by ≥50%) is preferentially recommended for adults aged 75 years or younger who have clinical ASCVD and no safety concerns. Moderate-intensity statins (LDL-C level decreased by 30% to <50%) are recommended for adults aged 75 years or younger who have clinical ASCVD and safety concerns and in those older than 75 years with clinical ASCVD.

High-intensity statin therapy is also recommended for individuals with LDL-C levels ≥190 mg/dL. In primary prevention in patients with LDL-C levels <190 mg/dL, moderate-intensity statin therapy is recommended, although high-intensity statin therapy also can be considered for individuals with or without diabetes who have a 10-year ASCVD risk ≥7.5%. When choosing the intensity of statin therapy for primary prevention, consideration may be given to a high estimated 10-year ASCVD risk, an LDL-C level of 160 to 189 mg/dL, or additional factors that may influence ASCVD risk. Low-intensity statin therapy may be used when high- or moderate-intensity statins are not tolerated.

7. Evidence Is Inadequate to Support Treatment to Specific LDL-C or Non–HDL-C Goals

Randomized, controlled trials of statins, nonstatin drugs, or both did not compare titration to different LDL-C goals. Thus, the panel was unable to make any
evidence-based recommendations about use of treatment goals for guiding therapy. “Treating to goal” may result in treatment with suboptimum statin intensity or adding nonstatin therapy in the absence of RCT evidence that combination therapy improves outcomes.

8. Regularly Monitor Patients for Adherence to Lifestyle and Statin Therapy

Randomized, controlled trials of statins regularly assessed adherence and safety. A fasting lipid panel is needed after initiation of or changes in statin or other drug therapy. Percentage reductions in LDL-C level should not be used as treatment goals or performance measures but should be used to assess and provide feedback to promote adherence to healthy lifestyle behaviors and statin therapy. Safety measurements should be assessed as clinically indicated.

In patients with a less-than-anticipated therapeutic response or intolerance of recommended statin therapy intensity, adherence to healthy lifestyle behaviors and medications should be reemphasized and secondary causes of hyperlipidemia excluded. A nonstatin LDL-C-lowering drug, preferably one that reduced ASCVD events in RCTs, can be considered in higher-risk adults, including those with genetic dyslipidemias, such as familial hypercholesterolemia, if the potential for additional ASCVD risk reduction outweighs the potential for adverse effects.

SUMMARY

Millions of U.S. adults are at increased ASCVD risk—some because they have had an ASCVD event, others because of ASCVD risk factors. Adherence to healthy lifestyle behaviors, control of blood pressure and diabetes, and avoidance of smoking is recommended for all adults. Statin therapy should be used to reduce ASCVD risk in individuals likely to have a clear net benefit (those with clinical ASCVD) or in primary prevention for adults with LDL-C levels ≥190 mg/dL, those aged 40 to 75 years with diabetes, and those with a 10-year ASCVD risk ≥7.5% without diabetes. A clinician–patient discussion that considers potential ASCVD risk reduction, adverse effects, and patient preferences is needed to decide whether to initiate statin therapy, especially in lower-risk primary prevention.

Appropriate intensity of statin therapy based on ASCVD risk and potential for adverse effects is recommended rather than focusing on specific LDL-C or non-HDL-C goals. Five of the 7 statins marketed in the United States, including a high-intensity statin, are available as low-cost generics.

The Pooled Risk Equations, which were developed in a geographically diverse sample of African Americans and non-Hispanic whites, identify adults at increased risk for an ASCVD event (including stroke as well as heart disease). They represent important steps forward in the ability to match intensity of preventive treatment to level of ASCVD risk. These risk equations will be reevaluated and revised as additional information becomes available, including research assessing other potentially useful markers of ASCVD risk and data required to develop equations specific to other ethnic groups.

Until heart-healthy lifestyles are adopted throughout the lifespan, the need for preventive measures using evidence-based drug therapy will remain high. As with all clinical guidelines, the 2013 ACC/AHA cholesterol guidelines must be implemented in conjunction with sound clinical judgment. These evidence-based recommendations focus statin treatment on patients likely to obtain the greatest benefit, thereby reducing the ASCVD burden in adults.

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APPENDIX: 2013 ACC/AHA CHOLESTEROL GUIDELINE PANEL

The members of the 2013 ACC/AHA Cholesterol Guideline Panel are Neil J. Stone, MD (Chair); Jennifer G. Robinson, MD, MPH (Vice-Chair); Alice H. Lichtenstein, ScD (Vice-Chair); Donald M. Lloyd-Jones, MD, ScM (Co-Chair, ASCVD Risk Assessment Expert Work Group); Robert H. Eckel, MD (Co-Chair, Lifestyle Management Expert Work Group); C. Noel Bairey Merz, MD; Conrad B. Bloom, MD; Anne C. Goldberg, MD; David Gordon, MD; Daniel Levy, MD; Patrick McBride, MD, MPH; J. Sanford Schwartz, MD; Susan T. Shero, MS, RN; Karol Watson, PhD; and Peter W.F. Wilson, MD. Although he is not a member of the ACC/AHA Cholesterol Guideline Panel, David C. Goff Jr., MD, PhD, is Co-Chair of the ASCVD Risk Assessment Expert Work Group.