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CLINICAL GUIDELINE

2018 Cholesterol Clinical Practice Guidelines: Synopsis of the 2018 American Heart Association/American College of Cardiology/ Multisociety Cholesterol Guideline*

Scott M. Grundy, MD, PhD, and Neil J. Stone, MD; for the Guideline Writing Committee for the 2018 Cholesterol Guidelines†

Description: In November 2018, the American Heart Association and American College of Cardiology (AHA/ACC) released a new clinical practice guideline on cholesterol management. It was accompanied by a risk assessment report on primary prevention of atherosclerotic cardiovascular disease (ASCVD).

Methods: A panel of experts free of recent and relevant industry-related conflicts was chosen to carry out systematic reviews and meta-analyses of randomized controlled trials (RCTs) that examined cardiovascular outcomes. High-quality observational studies were used for estimation of ASCVD risk. An independent panel systematically reviewed RCT evidence about the benefits and risks of adding nonstatin medications to statin therapy compared with receiving statin therapy alone in persons who have or are at high risk for ASCVD.

Recommendation: The guideline endorses a heart-healthy lifestyle beginning in childhood to reduce lifetime risk for ASCVD. It contains several new features compared with the 2013 guideline. For secondary prevention, patients at very high risk may be candidates for adding nonstatin medications (ezetimibe or proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) to statin therapy. In primary prevention, a clinician–patient risk discussion is still strongly recommended before a decision is made about statin treatment. The AHA/ACC risk calculator first triages patients into 4 risk categories. Those at intermediate risk deserve a focused clinician–patient discussion before initiation of statin therapy. Among intermediate-risk patients, identification of risk-enhancing factors and coronary artery calcium testing can assist in the decision to use a statin. Compared with the 2013 guideline, the new guideline gives more attention to percentage reduction in low-density lipoprotein cholesterol as a treatment goal and to long-term monitoring of therapeutic efficacy. To simplify monitoring, nonfasting lipid measurements are allowed.

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According to the Centers for Disease Control and Prevention, heart disease is the leading cause of death in the United States, including for African American, Hispanic, and white persons (1) and for both women and men. The leading cause of death attributable to cardiovascular disease (CVD) in the United States is coronary heart disease (43.8%), followed by stroke (16.8%)–the 2 components of fatal atherosclerotic CVD (ASCVD) (2). The economic impact of ASCVD is large: It accounted for 14% of total health expenditures in 2013 to 2014, more than any major diagnostic group.

The American Heart Association and American College of Cardiology (AHA/ACC), with the support of 10 collaborating organizations, have recently released their 2018 cholesterol guideline (3). In addition, they have released a companion special report on the use of risk assessment tools to guide decision making in primary prevention of ASCVD (4).

Guideline Development Process

The writing committees of both documents represented various areas of expertise, and all members were free of recent and relevant industry-related conflicts. New since the 2013 guideline are 3 randomized controlled trials (RCTs) that support the use of nonstatin lipid-modifying medications to reduce ASCVD events in patients at highest risk. The AHA/ACC commissioned an independent panel to systematically review evidence and assess the magnitude of benefits and harms from the addition of nonstatin medications to statin therapy in ASCVD (5). Their report was used by the guideline panel for the secondary prevention recommendations. An extensive evidence review covering May 1980 to July 2017 was also done initially. The writing committee considered additional relevant studies published through August 2018 during the guideline-writing process and added them to the evidence tables when appropriate.

Synopsis of Recommendations

1. Healthy lifestyle over the lifespan. A healthy lifestyle reduces ASCVD risk at all ages. In younger persons, healthy lifestyle can reduce development of risk factors, can prevent the need for subsequent statin use,

See also:

Web-Only
CME/MOC activity

* Collaborating organizations were the American Heart Association, American College of Cardiology, American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Physician Assistants, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association.

† For members of the 2018 Cholesterol Guideline Panel, see the **Appendix** (available at Annals.org).

and is foundational therapy for ASCVD risk reduction. In young adults aged 20 to 39 years, an assessment of lifetime risk facilitates the clinician–patient risk discussion and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

2. Use of maximally tolerated doses of statins in secondary prevention of ASCVD. In patients with clinical ASCVD, the guideline recommends reduction of low-density lipoprotein cholesterol (LDL-C) levels with high-intensity or maximally tolerated statin therapy. The more LDL-C is reduced during statin therapy, the greater the subsequent risk reduction will be. High-intensity statins typically reduce LDL-C levels by an average of at least 50%, which is an attainable goal in most patients with ASCVD.

3. Use of nonstatin medications in addition to statin therapy for patients at very high risk for ASCVD. Very high risk is defined as a history of multiple major ASCVD events, or 1 major ASCVD event and multiple other high-risk conditions. In very-high-risk ASCVD, the guideline recommends an LDL-C threshold of 1.8 mmol/L (70 mg/dL) as reasonable for adding a nonstatin medication (ezetimibe or proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) to maximally tolerated statin therapy. In patients who had very high risk, had a baseline LDL-C level of approximately 1.8 mmol/L (70 mg/dL), and were receiving statin therapy, addition of ezetimibe reduced risk for major events by 2 percentage points (6). Two RCTs recruited patients at very high risk who were receiving maximally tolerated doses of statins, had LDL-C levels greater than 1.8 mmol/L (70 mg/dL) (average, about 2.3 mmol/L [90 mg/dL]), and were treated with PCSK9 inhibitors for approximately 3 years (7, 8). Addition of PCSK9 inhibitors reduced risk for subsequent ASCVD events by about 15%. On the basis of these RCTs, the guideline states that addition of ezetimibe to maximally tolerated statin therapy is reasonable when LDL-C levels are 1.8 mmol/L (70 mg/dL) or higher. In patients at very high risk whose LDL-C levels remain above this threshold while they receive maximally tolerated statin and ezetimibe therapy, the guideline suggests that a PCSK9 inhibitor is a reasonable addition, although long-term safety (>3 years) is uncertain and cost-effectiveness was low at mid-2018 list prices. Some prescription programs have recently been initiated to reduce the cost of PCSK9 inhibitors. As cost decreases, cost-effectiveness will increase (9).

4. Severe primary hypercholesterolemia, often starting in childhood. In patients with primary, severe hypercholesterolemia (LDL-C level ≥4.9 mmol/L [≥190 mg/dL]), calculating 10-year ASCVD risk is not necessary. Maximally tolerated statin therapy is required to reduce LDL-C levels toward a lower risk range. If the LDL-C level remains at or above 2.6 mmol/L (100 mg/dL), adding ezetimibe is reasonable. If the patient still has an LDL-C level above this threshold while receiving a statin plus ezetimibe and has multiple factors that increase subsequent risk for ASCVD events, a PCSK9 inhibitor may be considered, although long-term safety (>3 years) is uncertain and economic value is low based on list prices from mid-2018.

5. Adults aged 40 to 75 years with diabetes mellitus and an LDL-C level of 1.8 mmol/L (70 mg/dL) or higher. In these patients, the guidelines recommend starting moderate-intensity statin therapy without the need to calculate 10-year ASCVD risk. In patients with diabetes and higher risk, especially those who have multiple risk factors or are aged 50 to 75 years, use of a high-intensity statin is reasonable to reduce the LDL-C level by at least 50%.

6. Clinician–patient risk discussion. In adults aged 40 to 75 years who are evaluated for primary ASCVD prevention, the guidelines continue to recommend a clinician–patient risk discussion before statin therapy is started. Risk discussion should include review of major risk factors (such as cigarette smoking and elevated levels of blood pressure, LDL-C, hemoglobin A_{1c} level [if indicated], or calculated 10-year risk for ASCVD), risk-enhancing factors (see recommendation 8), the potential benefits of lifestyle and statin therapies, the potential for adverse effects and drug–drug interactions, consideration of costs of statin therapy, and patient preferences and values in shared decision making.

7. Adults aged 40 to 75 years without diabetes mellitus who have LDL-C levels of at least 1.8 mmol/L (70 mg/dL), and a 10-year ASCVD risk of 7.5% or higher. In this population, the guidelines recommend moderate-intensity statin therapy if a discussion of treatment options favors statins. Patients without ASCVD are categorized and stratified for risk by age, coexisting conditions, and risk factors (**Figure**). When those with diabetes or LDL-C levels above 4.9 mmol/L (190 mg/dL) are excluded, RCT evidence for the benefit of statin therapy in persons aged 40 to 75 years continues to accumulate (10). Patients in this age range are triaged into 4 categories of 10-year risk for ASCVD: low (<5%), borderline (5% to 7.4%), intermediate (7.5% to 19.9%), and high (≥20%). In the latter category, the guideline recommends high-intensity statin therapy because of its proven benefit. Evidence from RCTs supports the efficacy of statin therapy for patients whose 10-year risk is 5% or higher. Nonetheless, in those with borderline or intermediate risk, clinical judgment is required to initiate statin treatment on the basis of risk–benefit considerations and patient preferences.

8. Decision making in primary prevention in adults aged 40 to 75 years. The guideline endorses a 3-tiered decision process for treatment in adults aged 40 to 75 years with borderline (5% to 7.4%) or intermediate (7.5% to 19.9%) risk for ASCVD. The decision process *begins* with estimation of 10-year risk. As in prior guidelines, 10-year risk of 7.5% or higher does not result in automatic statin assignment. To personalize risk, the current guideline recommends evaluation of risk-enhancing factors—that is, stable factors that associate with ASCVD beyond the major risk factors incorporated into the risk calculator. These include family history of premature ASCVD; LDL-C levels of 4.1 mmol/L (160 mg/dL) or higher; metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (in women); chronic inflammatory disorders; high-risk ethnicity, such as South Asian ancestry; triglyceride levels persistently elevated above 2.0 mmol/L (175 mg/dL); and, if measured, elevations in apolipoprotein B (may be especially useful if hypertriglyc-

eridemia >2.3 mmol/L [>200 mg/dL] persists), high-sensitivity C-reactive protein levels of 19.0476 nmol/L (2.0 mg/L) or higher, lipoprotein(a) levels with elevations above 125 nmol/L (50 mg/dL) (especially useful in those with a family history of premature ASCVD), or reduced ankle–brachial index. Presence of risk-enhancing factors in patients at intermediate risk favors statin therapy. In addition, if risk status remains uncertain, measurement of coronary artery calcium (CAC) can be considered.

9. CAC scoring to improve risk stratification. In adults who do not have diabetes, are aged 40 to 75 years, have LDL-C levels of 1.8 to 4.9 mmol/L (70 to 189 mg/dL), and have a 10-year risk of 7.5% to 19.9% as estimated by the pooled cohort equations (PCEs), but who are uncertain about statin benefit, CAC scoring may help resolve the uncertainty. If the CAC score is 0 Agatston units, statin therapy may be withheld or delayed, except in cigarette smokers and those with a strong family history of premature ASCVD or diabetes. A CAC score of 1 to 99 units favors statin therapy, especially in patients older than 55 years. For any patient, if the CAC score is at least 100 Agatston units or is at or above the 75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of a clinician–patient risk discussion.

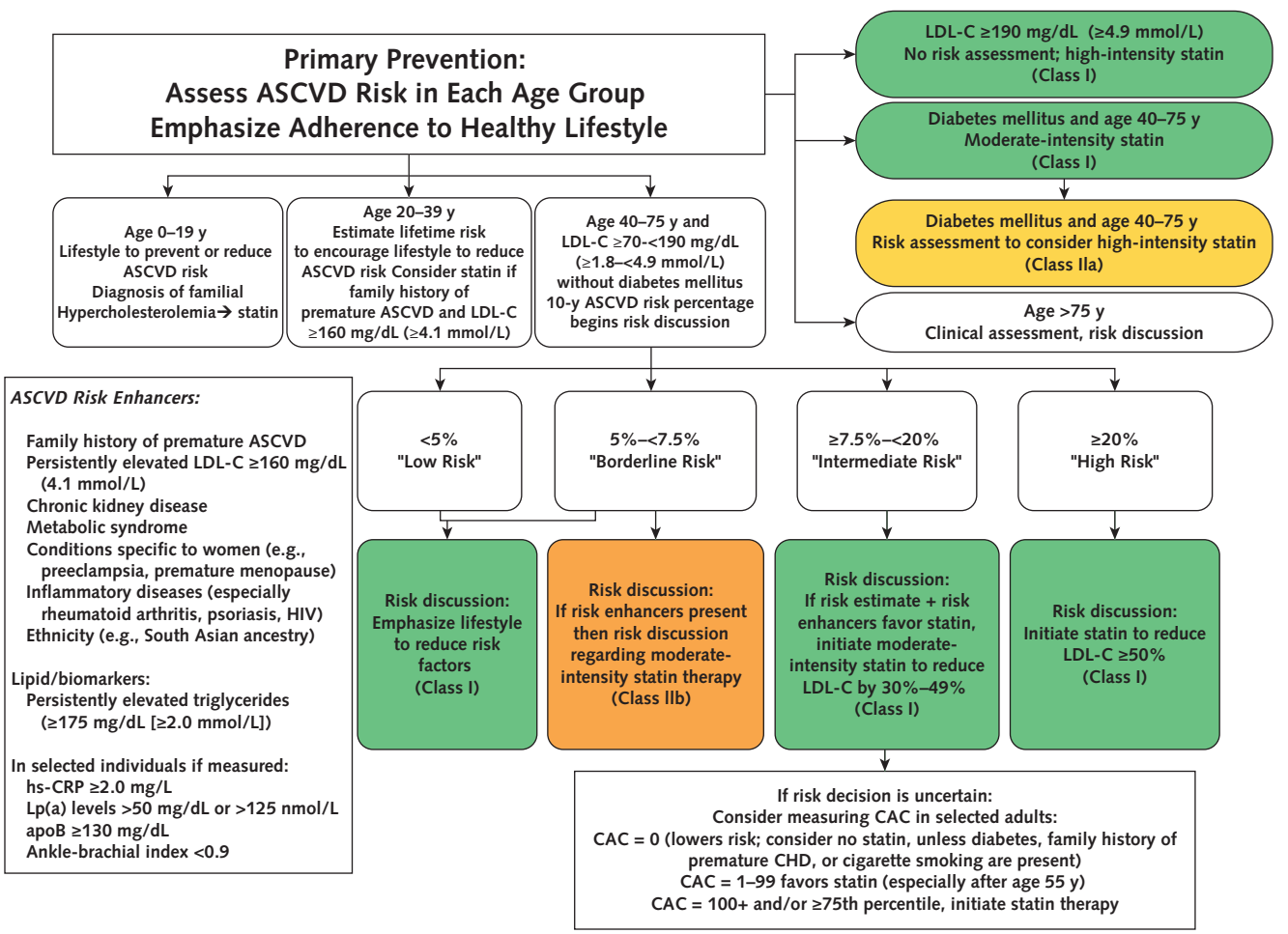
10. Follow-up for adherence and adequacy of response. The current guideline continues to recommend assessment of adherence to medications and lifestyle and percentage change in LDL-C level at 4 to 12 weeks after statin initiation or dosage adjustment; this assessment should be repeated every 3 to 12 months as needed. Clinicians may often underestimate adherence unless specific questions are asked (11).

SPECIAL TOPICS

Statin Safety

The 2018 guideline offers guidance to clinicians for their patients who develop symptoms while receiving statin therapy. It prefers to designate such symptoms as

Figure. Flow diagram for primary prevention of ASCVD.



Color corresponds to class of recommendation; green = Class I (strong); yellow = Class IIa (moderate); orange = Class IIb (weak). apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a). (Reproduced from Grundy and colleagues [3] with permission of the American Heart Association/American College of Cardiology.).

"statin-associated side effects." This acknowledges that blinded, placebo-controlled trials of patients recruited with statin-associated muscle symptoms saw a clinically significant percentage of symptoms while participants received only placebo and not statins (12, 13). Thus, many patients with statin-associated muscular symptoms are able to tolerate statin rechallenge—after a dechallenge period for symptom resolution—with an alternative statin or alternative regimen, such as a reduced dosage or a statin in combination with nonstatin medications. Because statin-associated muscular symptoms may result in nonadherence that can adversely affect ASCVD outcomes (14), a helpful initial approach to these symptoms is to reassess, rediscuss, and encourage rechallenge, unless side effects are severe. Statins modestly increase risk for incident diabetes mellitus in susceptible persons (15). Metabolic abnormalities that increase risk for diabetes include body mass index of 30 kg/m^2 or higher, elevated glucose and hemoglobin A_{1c} levels in the prediabetes range, and risk factors for metabolic syndrome (16). The more metabolic risk factors, the greater the chance of new-onset diabetes during statin therapy. The guideline cautions that new-onset diabetes should not be cause for discontinuation of statin treatment because ASCVD risk reduction can be greater in this higher-risk group.

Risk Stratification for Primary Prevention

For screening, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C level. The 2013 guidelines for risk assessment introduced risk estimation by the PCEs for patients aged 40 to 75 years. These equations were derived from several populations that are representative of U.S. residents and were validated by a natural history study in a large U.S. cohort (17). Other reports have indicated that in some populations, the PCEs overpredicted ASCVD risk (18). Regardless, risk equations predict average population risk and alone cannot personalize the risk decision for an individual. Because patient characteristics (such as ethnicity and long-term exposure to risk factors, as reflected by socioeconomic status and health behaviors) will modify population risk estimates, these must be considered when evaluating individual risk. A companion document to the 2018 cholesterol guideline summarizes the rationale and evidence base for quantitative risk assessment in general and reviews strengths and limitations of existing risk scores (4). Of note, it discusses approaches for refining individual risk estimates to personalize risk assessment. It gives practical advice that is useful in implementing risk assessment and offers decision-making strategies for clinical practice consistent with current guidelines.

In summary, the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol uses an evidence-based approach to guide cholesterol management over the lifespan. The goal is to reduce risk for heart attack and stroke. Careful adherence to lifestyle recommendations at an early age could reduce risk factor burden over the lifespan and decrease the need for preventive drug therapies later in life. Thus, improved lifestyle is stressed throughout the document. For persons at increased risk for ASCVD who belong to groups shown to benefit from cholesterol-lowering drug therapy added to a heart-healthy lifestyle, as well as to those persons who present with ASCVD, these guidelines represent an evidence-based approach to ASCVD preventive efforts (**Table**).

Table. Brief Summary of the 2018 AHA/ACC/Multisociety Cholesterol Guideline

- Assess ASCVD risk and emphasize adherence to heart-healthy lifestyle.
- In patients with clinical ASCVD, guidelines recommend lowering LDL-C levels with high-intensity statin therapy or using maximally tolerated statin therapy to lower LDL-C levels ≥50%.
- In patients with very high risk (a history of multiple major ASCVD events or 1 major ASCVD event and multiple other high-risk conditions) who are receiving maximally tolerated statin therapy, consider nonstatin (ezetimibe or PCSK9 inhibitor) therapy above an LDL-C threshold of 1.8 mmol/L (70 mg/dL).
- In those with a primary elevation of LDL-C ≥4.9 mmol/L (≥190 mg/dL), quantitative risk assessment is not needed; start high-intensity statin therapy. Starting in childhood, familial hypercholesterolemia should be detected and treated.
- In adults aged 40–75 y with diabetes, quantitative risk assessment is not needed. Start moderate-intensity statin therapy. If high-risk features are present, high-intensity statin therapy is appropriate.
- In adults, a clinician–patient risk discussion continues to be recommended for decision making *before* statin therapy. Tools for the risk discussion include:
  - *10-y ASCVD risk estimation.* This begins the risk discussion. Categories of 10-y ASCVD risk are low (<5%), borderline (5%–7.4%), intermediate (7.5%–19.9%), and high (≥20%). Statins are clinically efficacious in the latter 3 categories, but the higher the risk, the stronger the statin indication.
  - *Risk-enhancing factors: stable factors that favor initiation of statin therapy* "stable factors that favor initiation of statin therapy", especially after intermediate risk. These include family history of premature ASCVD; persistently elevated LDL-C levels ≥4.1 mmol/L (≥160 mg/dL); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 y); chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of triglyceride levels ≥1.97 mmol/L (≥175 mg/dL); and, if measured in selected individuals, apolipoprotein B levels ≥1.30 g/L, high-sensitivity C-reactive protein levels ≥19.05 nmol/L (≥2.0 mg/L), ankle–brachial index <0.9, and lipoprotein(a) levels ≥125 nmol/L (≥50 mg/dL), especially at higher values of lipoprotein(a).
  - *CAC scoring.* Use this if a risk decision is still uncertain in patients at intermediate risk (7.5%–19.9%) to improve specificity of the risk decision. A CAC score of 0 Agatston units may allow for statin therapy to be postponed or deferred, except in those with diabetes, current cigarette smoking, or a strong family history of premature ASCVD. A CAC score of 1–99 Agatston units favors statin therapy, especially in those aged >55 y. For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile,* statin therapy is indicated unless otherwise deferred by the outcome of a clinician–patient risk discussion.

AHA/ACC = American Heart Association/American College of Cardiology; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
* See www.mesa-nhlbi.org/Calcium/input.aspx.

From University of Texas Southwestern Medical Center, Dallas, Texas (S.M.G.); and Northwestern University Feinberg School of Medicine, Chicago, Illinois (N.J.S.).

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Corresponding Author: Neil J. Stone, MD, 676 North St. Clair Street, Suite 600 (Cardiology), Chicago, IL 60611; e-mail, n-stone@northwestern.edu.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Grundy: 5323 Harry Hines Boulevard, Suite Y3.206, Dallas, TX 75390.
Dr. Stone: 676 North St. Clair Street, Suite 600 (Cardiology), Chicago, IL 60611.

Author Contributions: Conception and design: S.M. Grundy, N.J. Stone.
Analysis and interpretation of the data: N.J. Stone.
Drafting of the article: N.J. Stone.
Critical revision of the article for important intellectual content: S.M. Grundy, N.J. Stone.
Final approval of the article: S.M. Grundy, N.J. Stone.
Statistical expertise: S.M. Grundy.
Collection and assembly of data: N.J. Stone.

Appendix: Members of the Guideline Writing Committee for the 2018 Cholesterol Guidelines

Members of the Guideline Writing Committee who authored this work are Scott M. Grundy, MD, PhD (AHA/ACC representative), and Neil J. Stone, MD (AHA/ACC representative).

Members of the Guideline Writing Committee who contributed to this work but did not author it are Alison L. Bailey, MD (American Association of Cardiovascular and Pulmonary Rehabilitation representative); Craig Beam, CRE (AHA/ACC representative); Kim K. Birtcher, MS, PharmD (AHA/ACC Task Force on Clinical Practice Guidelines liaison); Roger S. Blumenthal, MD (prevention subcommittee liaison); Lynne T. Braun, PhD, CNP (Preventive Cardiovascular Nurses Association representative); Sarah de Ferranti, MD, MPH (AHA/ACC representative); Joseph Faiella-Tommasino, PhD, PA-C (American Academy of Physician Assistants representative); Daniel E. Forman, MD (American Geriatrics Society representative); Ronald Goldberg, MD (American Diabetes Association representative); Paul A. Heidenreich, MD, MS (American College of Preventive Medicine representative); Mark A. Hlatky, MD (AHA/ACC representative); Daniel W. Jones, MD (prevention subcommittee liaison); Donald Lloyd-Jones, MD, ScM (AHA/ACC representative); Nuria Lopez-Pajares, MD, MPH (American College of Preventive Medicine representative); Chiadi E. Ndumele, MD, PhD (AHA/ACC representative); Carl E. Orringer, MD (National Lipid Association representative); Carmen A. Peralta, MD, MAS (AHA/ACC representative); Joseph J. Saseen, PharmD (American Pharmacists Association representative); Sidney C. Smith Jr., MD (AHA/ACC representative); Laurence Sperling, MD (American Society for Preventive Cardiology representative); Salim S. Virani, MD, PhD (AHA/ACC representative); and Joseph Yeboah, MD, MS (Association of Black Cardiologists representative).