

# 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

## A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

*Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Geriatrics Society, the American Society of Preventive Cardiology, and the Preventive Cardiovascular Nurses Association*

### WRITING COMMITTEE MEMBERS

Donna K. Arnett, PhD, MSPH, FAHA, *Co-Chair*

Roger S. Blumenthal, MD, FACC, FAHA, *Co-Chair*

Michelle A. Albert, MD, MPH, FAHA\*

Andrew B. Buroker, Esq†

Zachary D. Goldberger, MD, MS, FACC, FAHA‡

Ellen J. Hahn, PhD, RN\*

Cheryl D. Himmelfarb, PhD, RN, ANP, FAHA\*

Amit Khera, MD, MSc, FACC, FAHA\*

Donald Lloyd-Jones, MD, SCM, FACC, FAHA\*

J. William McEvoy, MBBCh, MEd, MHS\*

Erin D. Michos, MD, MHS, FACC, FAHA\*

Michael D. Miedema, MD, MPH\*

Daniel Muñoz, MD, MPA, FACC\*

Sidney C. Smith, Jr, MD, MACC, FAHA\*

Salim S. Virani, MD, PhD, FACC, FAHA\*

Kim A. Williams, Sr, MD, MACC, FAHA\*

Joseph Yeboah, MD, MS, FACC, FAHA\*

Boback Ziaieian, MD, PhD, FACC, FAHA§

### ACC/AHA TASK FORCE MEMBERS

Patrick T. O'Gara, MD, MACC, FAHA, *Chair*

Joshua A. Beckman, MD, MS, FAHA, *Chair-Elect*

Glenn N. Levine, MD, FACC, FAHA, *Immediate Past Chair*||

Sana M. Al-Khatib, MD, MHS, FACC, FAHA

Kim K. Birtcher, PharmD, MS, AACC

Joaquin E. Cigarroa, MD, FACC

Anita Deswal, MD, MPH, FACC, FAHA

Lee A. Fleisher, MD, FACC, FAHA

Federico Gentile, MD, FACC

Zachary D. Goldberger, MD, MS, FACC, FAHA‡

Mark A. Hlatky, MD, FACC, FAHA

John Ikonidis, MD, PhD, FAHA||

José A. Joglar, MD, FACC, FAHA

Laura Mauri, MD, MSc, FAHA||

Mariann R. Piano, RN, PhD, FAHA

Barbara Riegel, PhD, RN, FAHA||

Duminda N. Wijeyesundera, MD, PhD

\*ACC/AHA Representative. †Lay Representative. ‡ACC/AHA Task Force on Clinical Practice Guidelines Liaison. §Task Force Performance Measures Representative. || Former Task Force member; current member during the writing effort.

This document was approved by the American College of Cardiology Clinical Policy Approval Committee, the American Heart Association Science Advisory and Coordinating Committee, and the American Heart Association Executive Committee in February 2019.

Supplemental materials are available with this article at

<https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000678>

Arnett et al.

## 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

The American Heart Association requests that this document be cited as follows: Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;000:e000–e000. DOI: 10.1161/CIR.0000000000000678

This article has been copublished in the *Journal of the American College of Cardiology*.

Copies: This document is available on the websites of the American College of Cardiology ([www.acc.org](http://www.acc.org)) and the American Heart Association ([professional.heart.org/](http://professional.heart.org/)). A copy of the document is also available at <https://professional.heart.org/statements> by selecting the “Guidelines & Statements” button. To purchase additional reprints, call 843-216-2533 or e-mail [kelle.amsay@wolterskluwer.com](mailto:kelle.amsay@wolterskluwer.com).

The expert peer review of AHA-commissioned documents (e.g., scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <https://professional.heart.org/statements>. Select the “Guidelines & Statements” drop-down menu near the top of the webpage, then click “Publication Development.”

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the “Copyright Permissions Request Form” appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).

(*Circulation*. 2019;000:e000–e000. DOI: 10.1161/CIR.0000000000000678)



© 2019 by the American College of Cardiology Foundation and the American Heart Association, Inc.

*Circulation* is available at <https://www.ahajournals.org/journal/circ>

*Circulation*

## Table of Contents

Top 10 Take-Home Messages for the Primary Prevention of Cardiovascular Disease.....	4
Preamble.....	5
1. Introduction .....	6
1.1. Methodology and Evidence Review.....	6
1.2. Organization of the Writing Committee .....	7
1.3. Document Review and Approval .....	8
1.4. Scope of the Guideline .....	8
1.5. Class of Recommendation and Level of Evidence.....	8
1.6. Abbreviations .....	10
2. Overarching Recommendations for ASCVD Prevention Efforts.....	11
2.1. Patient-Centered Approaches to Comprehensive ASCVD Prevention .....	11
2.2. Assessment of Cardiovascular Risk .....	14
3. Lifestyle Factors Affecting Cardiovascular Risk.....	18
3.1. Nutrition and Diet .....	18
3.2. Exercise and Physical Activity .....	21
4. Other Factors Affecting Cardiovascular Risk.....	24
4.1. Adults with Overweight and Obesity .....	24
4.2. Adults with Type 2 Diabetes Mellitus .....	26
4.3. Adults with High Blood Cholesterol .....	29
4.4. Adults with High Blood Pressure or Hypertension .....	35
4.5. Treatment of Tobacco Use.....	41
4.6. Aspirin Use .....	45
5. Cost and Value Considerations .....	47
6. Conclusion.....	48
Appendix 1. Search Criteria .....	50
Appendix 2. Author Relationships With Industry and Other Entities (Relevant) .....	58
Appendix 3. Reviewer Relationships With Industry and Other Entities (Comprehensive).....	63
References .....	75



## Top 10 Take-Home Messages for the Primary Prevention of Cardiovascular Disease

1. The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life.
2. A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions.
3. Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning.
4. All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of *trans* fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss.
5. Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity.
6. For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist.
7. All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit.
8. Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit.
9. Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels ( $\geq 190$  mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion.
10. Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be  $<130/80$  mm Hg.

## Preamble

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts.

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease (CVD). The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the goals are to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most but not all circumstances and should not replace clinical judgment.

Recommendations for guideline-directed management and therapy, which encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments, are effective only when adopted by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

The ACC/AHA Task Force on Clinical Practice Guidelines strives to ensure that the guideline writing committee includes requisite expertise and is representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and scopes of clinical practice. The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found at: <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy>.

Beginning in 2017, numerous modifications to the guidelines have been and continue to be implemented to make guidelines shorter and enhance "user friendliness." Guidelines are written and presented in a modular knowledge chunk format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. More structured guidelines—including word limits ("targets") and a web guideline supplement for useful but noncritical tables and figures—are 2 such changes. This Preamble is an abbreviated version, with the detailed version available at: <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000678>

*Patrick T. O'Gara, MD, MACC, FAHA*

*Chair, ACC/AHA Task Force on Clinical Practice Guidelines*

## 1. Introduction

Although there has been substantial improvement in atherosclerotic cardiovascular disease (ASCVD) outcomes in recent decades, ASCVD remains the leading cause of morbidity and mortality globally (S1-1–S1-3). In the United States, it is also the leading cause of death for people of most racial/ethnic groups, with an estimated cost of >\$200 billion annually in healthcare services, medications, and lost productivity. Much of this is attributable to suboptimal implementation of prevention strategies and uncontrolled ASCVD risk factors in many adults (S1-2).

Most Americans who have had a myocardial infarction (MI) had unfavorable levels of at least 1 cardiovascular risk factor before their ASCVD event (S1-4). In 2010, the AHA defined a new model of “ideal cardiovascular health,” referred to as Life’s Simple 7 (S1-5). Clinicians will find the 2018 Journal of American College of Cardiology (JACC) Cardiovascular Health Promotion Series very helpful in approaching the various aspects of prevention with patients (S1-6). An increasing number of ideal cardiovascular health factors have been associated with a lower prevalence and incidence of ASCVD events, heart failure, atrial fibrillation, cancer, depression, and cognitive impairment (S1-7). Therefore, moving individuals toward ideal cardiovascular health is critically important for prevention of many important health conditions.

The ACC/AHA Task Force on Clinical Practice Guidelines has commissioned this guideline to consolidate existing recommendations and various recent scientific statements, expert consensus documents, and clinical practice guidelines into a single guidance document focused on the primary prevention of ASCVD. However, this guideline also includes newly generated recommendations for aspirin use, exercise and physical activity, and tobacco use, in addition to recommendations related to team-based care, shared decision-making, and assessment of social determinants of health, to create a comprehensive yet targeted ACC/AHA guideline on the prevention of ASCVD. This guideline has been formatted in the modular chunk format to facilitate readability and future updating.

Prevention strategies occur at the population level but must also engage individual adults to slow the development of ASCVD. The most important way to prevent ASCVD is to promote a healthy lifestyle throughout life. Prevention strategies must include a strong focus on lifestyle optimization (improvements in diet, physical activity, and avoidance of tobacco use and exposure to secondhand smoke) to minimize the risk of future ASCVD events.

A comprehensive patient-centered approach that addresses all aspects of a patient’s lifestyle habits and estimated risk of a future ASCVD event is the first step in deciding on where there may be a need for pharmacotherapy. Even if a blood pressure (BP)–reducing medication, lipid-lowering medication, or diabetes medication is ultimately prescribed, lifestyle goals should be emphasized on a regular basis. Only when a person’s risk is sufficiently high should medications to reduce ASCVD risk be considered as part of a shared decision-making process for optimal treatment. In summary, clinicians and individuals should focus attention on living a healthy lifestyle by referring to these evidence-based recommendations to help prevent ASCVD.

### 1.1. Methodology and Evidence Review

This guideline continues the ACC and AHA effort to design a comprehensive yet succinct compilation of practical guidance for the primary prevention of ASCVD and to promote optimal dissemination of information by using concise language and formatting. The recommendations listed in this guideline are evidence based and supported by an extensive evidence review. A search for literature derived from research involving human subjects, published in English, and indexed in Ovid MEDLINE, PubMed,

Cochrane Library, National Institute for Health and Care Excellence (NICE), and other selected databases relevant to this guideline, was conducted between May and July 2018. For specific search terms used and years searched per section, please see Appendix 1.

Randomized controlled trials (RCTs), systematic reviews of RCTs, meta-analyses, and large, United States–based, high-quality cohort studies, as well as observational studies and systematic reviews of observational studies, were evaluated for their content on the prevention of ASCVD outcomes related to the following 9 topic areas: risk assessment, diet, exercise/physical activity, obesity and weight loss, type 2 diabetes mellitus (T2DM), blood cholesterol, hypertension, smoking cessation, and aspirin use. Previous ACC/AHA guidelines, as well as U.S. Preventive Services Task Force (USPSTF) reviews and other guidance relevant to this guideline, were also assessed. The final evidence tables included in the Online Data Supplement (<https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000678>) summarize the evidence used to formulate recommendations. References selected and published in this document are representative and not all-inclusive.

Avalere Health, a healthcare advisory services firm contracted by ACC/AHA, served as the document manager for this guideline to facilitate its development process. Avalere Health commissioned the Pacific Northwest Evidence-based Practice Center at Oregon Health and Science University to perform rapid systematic evidence reviews for 5 of the key topics: aspirin use, T2DM, nutrition and diet, obesity and weight loss, and tobacco use. In parallel, an independent health data and epidemiology expert, Lee Ann Prebil, conducted a systematic evidence review for the key topic of exercise and physical activity and conducted targeted literature searches to support this document's discussion of patient-centered approaches, including team-based care, shared decision-making, and assessment of social determinants of health. A targeted literature search was also conducted for this guideline's cost and value considerations.

Recommendations and supportive text relevant to cardiovascular risk, blood cholesterol, and high BP were taken directly from 2 recently released ACC/AHA guidelines, the 2017 Hypertension Clinical Practice Guidelines (S1.1-1) and the 2018 Cholesterol Clinical Practice Guideline (S1.1-2), and were adapted for the present guideline, which aims to provide an overview of the primary prevention of ASCVD among adults. Recommendations that were adapted from previous publications are noted in the recommendation tables, and both the original published recommendation and the adapted version are provided in the guideline.

The results of these evidence reviews were evaluated by the writing committee for incorporation into the present guideline. (See Table S1 in the Web Supplement for a list of relevant publications and statements used in support of the guideline's recommendations.) Each topic area was assigned a primary writer, as well as a primary, and sometimes secondary, reviewer. These assignments were based on areas of particular expertise of writing committee members. All recommendations were fully reviewed and discussed among the full committee to allow for diverse perspectives and considerations for this guideline. Recommendations were then voted upon, with a modified Delphi process used to reach consensus.

## 1.2. Organization of the Writing Committee

The writing committee consisted of clinicians, cardiologists, health services researchers, epidemiologists, internists, nurses, and a lay representative. The writing committee included representatives from the ACC and AHA. Appendix 2 of the present document lists writing committee members' relevant RWI. For the purposes of full transparency, the writing committee members' comprehensive disclosure information is available online (<https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000678>).

### 1.3. Document Review and Approval

This document was reviewed by 5 official reviewers nominated by the ACC and AHA (1 reviewer from the ACC/AHA Task Force for Practice Guidelines, 2 reviewers from the AHA, and 2 reviewers from the ACC); 3 reviewers on behalf of the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Society for Nutrition, and the American Society of Preventive Medicine; and 23 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 3). This document was approved for publication by the governing bodies of the ACC and AHA.

### 1.4. Scope of the Guideline

This guideline is intended to be a resource for the clinical and public health practice communities. It addresses the primary prevention of CVD in adults ( $\geq 18$  years of age), focused on outcomes of ASCVD (i.e., acute coronary syndromes, MI, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin), as well as heart failure and atrial fibrillation. The guideline presents recommendations to prevent CVD that are related to lifestyle factors (e.g., diet and exercise or physical activity), other factors affecting CVD risk (e.g., obesity, diabetes, blood cholesterol, high BP, smoking, aspirin use), patient-centered approaches (e.g., team-based care, shared decision-making, assessment of social determinants of health), and considerations of the cost and value of primary prevention.

### 1.5. Class of Recommendation and Level of Evidence

Recommendations are designated with both a Class of Recommendation (COR) and a Level of Evidence (LOE). The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1) (S1.5-1).





**Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated August 2015)**

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE†
<b>CLASS I (STRONG)</b> <span style="float: right;">Benefit &gt;&gt;&gt; Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is recommended</li> <li>■ Is indicated/useful/effective/beneficial</li> <li>■ Should be performed/administered/other</li> <li>■ Comparative-Effectiveness Phrases‡:               <ul style="list-style-type: none"> <li>○ Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>○ Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<b>LEVEL A</b> <ul style="list-style-type: none"> <li>■ High-quality evidence‡ from more than 1 RCT</li> <li>■ Meta-analyses of high-quality RCTs</li> <li>■ One or more RCTs corroborated by high-quality registry studies</li> </ul>
<b>CLASS IIa (MODERATE)</b> <span style="float: right;">Benefit &gt;&gt; Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is reasonable</li> <li>■ Can be useful/effective/beneficial</li> <li>■ Comparative-Effectiveness Phrases‡:               <ul style="list-style-type: none"> <li>○ Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>○ It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<b>LEVEL B-R</b> <span style="float: right;">(Randomized)</span> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more RCTs</li> <li>■ Meta-analyses of moderate-quality RCTs</li> </ul>
<b>CLASS IIb (WEAK)</b> <span style="float: right;">Benefit ≥ Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ May/might be reasonable</li> <li>■ May/might be considered</li> <li>■ Usefulness/effectiveness is unknown/unclear/uncertain or not well established</li> </ul>	<b>LEVEL B-NR</b> <span style="float: right;">(Nonrandomized)</span> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>■ Meta-analyses of such studies</li> </ul>
<b>CLASS III: No Benefit (MODERATE)</b> <span style="float: right;">Benefit = Risk</span> <i>(Generally, LOE A or B use only)</i> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is not recommended</li> <li>■ Is not indicated/useful/effective/beneficial</li> <li>■ Should not be performed/administered/other</li> </ul>	<b>LEVEL C-LD</b> <span style="float: right;">(Limited Data)</span> <ul style="list-style-type: none"> <li>■ Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>■ Meta-analyses of such studies</li> <li>■ Physiologic or mechanistic studies in human subjects</li> </ul>
<b>CLASS III: Harm (STRONG)</b> <span style="float: right;">Risk &gt; Benefit</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Potentially harmful</li> <li>■ Causes harm</li> <li>■ Associated with excess morbidity/mortality</li> <li>■ Should not be performed/administered/other</li> </ul>	<b>LEVEL C-EO</b> <span style="float: right;">(Expert Opinion)</span> Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

## 1.6. Abbreviations

Abbreviation	Meaning/Phrase
ASCVD	atherosclerotic cardiovascular disease
AU	Agatston units
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CKD	chronic kidney disease
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DM	diabetes mellitus
ENDS	electronic nicotine delivery systems
FDA	U.S. Food and Drug Administration
GLP-1R	glucagon-like peptide-1 receptor
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HbA1c	hemoglobin A1c
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction
PCE	pooled cohort equations
RCT	randomized controlled trial
SBP	systolic blood pressure
SGLT-2	sodium-glucose cotransporter 2
T2DM	type 2 diabetes mellitus
USPSTF	U.S. Preventive Services Task Force



## 2. Overarching Recommendations for ASCVD Prevention Efforts

### 2.1. Patient-Centered Approaches to Comprehensive ASCVD Prevention

Recommendations for Patient-Centered Approaches to Comprehensive ASCVD Prevention		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 1 and 2</a> .		
COR	LOE	Recommendations
I	A	1. A team-based care approach is recommended for the control of risk factors associated with ASCVD (S2.1-1–S2.1-14).
I	B-R	2. Shared decision-making should guide discussions about the best strategies to reduce ASCVD risk (S2.1-15–S2.1-18).
I	B-NR	3. Social determinants of health should inform optimal implementation of treatment recommendations for the prevention of ASCVD (S2.1-19–S2.1-25).

#### Synopsis

This 2019 ACC/AHA Guideline on the Primary Prevention of CVD aims to promote the delivery of patient-centered care, which the writing committee felt was foundational to the guidance provided throughout. These patient-centered recommendations emphasize the importance of team-based care delivery, shared decision-making, and the evaluation of social determinants of health in ASCVD prevention efforts. These recommendations apply to all aspects of clinical practice for the primary prevention of ASCVD.

#### Recommendation-Specific Supportive Text

1. Team-based care makes use of multidisciplinary health professionals to improve the quality and maintenance of ASCVD prevention. It is a multifaceted approach that supports clinical decision-making (i.e., treatment algorithms), collaboration among different clinicians, and patient and family member participation to facilitate the treatment goals of patients (S2.1-26). RCTs and systematic reviews with meta-analyses demonstrated greater reduction of ASCVD risk with team-based care than with usual care in patients with hypertension, diabetes, and hyperlipidemia (S2.1-1–S2.1-14). A team-based approach to ASCVD prevention may result in significant improvements in patient outcomes (S2.1-27) and often meets patient needs better than standard care, especially in low-resource settings and among vulnerable populations. In a team-based care model that compared patients enrolled in a preventive cardiology clinic staffed by advanced practice providers with a propensity-matched cohort of patients enrolled in primary care clinics, a reduction in cardiovascular risk was demonstrated through effective risk stratification and preventive management (S2.1-28). Other successful interventions that have used team-based care include telehealth monitoring, follow-up support aids, and patient education (S2.1-27).
2. Decisions about primary prevention should be collaborative between a clinician and a patient. Shared decision-making occurs when practitioners engage patients in discussions about personalized ASCVD risk estimates and their implications for the perceived benefits of preventive strategies, including lifestyle habits, goals, and medical therapies. Collaborative decisions are more likely to address potential barriers to treatment options, compared with treatment and guidance offered without patient input (S2.1-15–S2.1-18).
3. Socioeconomic inequalities are strong determinants of CVD risk internationally (S2.1-21, S2.1-24). Therefore, the clinician should tailor advice to a patient's socioeconomic and educational status, as well as cultural, work, and home environments (S2.1-23). The Centers for Medicare & Medicaid

Services has developed a screening tool (<https://nam.edu/standardized-screening-for-health-related-social-needs-in-clinical-settings-the-accountable-health-communities-screening-tool/>) to assess 5 domains of non–health-related measures that affect health outcomes: housing instability, food insecurity, transportation difficulties, utility assistance needs, and interpersonal safety (S2.1-29). ASCVD prevention could benefit from such screening. ASCVD risk begins early in life, with heightened susceptibility tied to low socioeconomic status (S2.1-25). Examples of upstream social determinants of health that affect treatment adherence and ASCVD health outcomes include comorbid mental illness, lack of health literacy, exposure to adversity (e.g., home/community violence, trauma exposures, safety concerns), financial strain, inadequate housing conditions, lack of food security (i.e., access to affordable and nutritious food), and inadequate social support (S2.1-30). Systems of care should evaluate social determinants of health that affect care delivery for the primary prevention of ASCVD (e.g., transportation barriers, the availability of health services).

Important considerations related to socioeconomic disadvantage are not captured by existing CVD risk equations (S2.1-31). Addressing unmet social needs improves management of BP and lipids (S2.1-32), which highlights the importance of dietary counseling and encouraging physical activity (S2.1-19). More time may be required to address ASCVD prevention with adults of low health literacy or disadvantaged educational backgrounds.

Differential cardiovascular outcomes persist by important sociodemographic characteristics that include but are not limited to age, sex, and race/ethnicity (S2.1-22, S2.1-33–S2.1-35). Failure to address the impact of social determinants of health impedes efficacy of proven prevention recommendations. Table 2 outlines key considerations related to social determinants of health and ASCVD prevention.

**Table 2. Example Considerations for Addressing Social Determinants of Health to Help Prevent ASCVD Events**

Topic/Domain	Example Considerations
Cardiovascular risk	<ul style="list-style-type: none"> <li>Adults should be routinely assessed for psychosocial stressors and provided with appropriate counseling (S2.1-31).</li> <li>Health literacy should be assessed every 4 to 6 y to maximize recommendation effectiveness (S2.1-36).</li> </ul>
Diet	<ul style="list-style-type: none"> <li>In addition to the prescription of diet modifications, body size perception, as well as social and cultural influences, should be assessed (S2.1-37, S2.1-38).</li> <li>Potential barriers to adhering to a heart-healthy diet should be assessed, including food access and economic factors; these factors may be particularly relevant to persons from vulnerable populations, such as individuals residing in either inner-city or rural environments, those at socioeconomic disadvantage, and those of advanced age* (S2.1-39).</li> </ul>
Exercise and physical activity	<ul style="list-style-type: none"> <li>In addition to the prescription of exercise, neighborhood environment and access to facilities for physical activity should be assessed (S2.1-30, S2.1-40, S2.1-41).</li> </ul>
Obesity and weight loss	<ul style="list-style-type: none"> <li>Lifestyle counseling for weight loss should include assessment of and interventional recommendations for psychosocial stressors, sleep hygiene, and other individualized barriers (S2.1-42–S2.1-44).</li> </ul>

Topic/Domain	Example Considerations
	<ul style="list-style-type: none"> <li>Weight maintenance should be promoted in patients with overweight/obesity who are unable to achieve recommended weight loss.</li> </ul>
Diabetes mellitus	<ul style="list-style-type: none"> <li>In addition to the prescription of type 2 diabetes mellitus interventions, environmental and psychosocial factors, including depression, stress, self-efficacy, and social support, should be assessed to improve achievement of glycemic control and adherence to treatment (S2.1-45–S2.1-48).</li> </ul>
High blood pressure	<ul style="list-style-type: none"> <li>Short sleep duration (&lt;6 h) and poor-quality sleep are associated with high blood pressure and should be considered (S2.1-49). Because other lifestyle habits can impact blood pressure, access to a healthy, low-sodium diet and viable exercise options should also be considered.</li> </ul>
Tobacco treatment	<ul style="list-style-type: none"> <li>Social support is another potential determinant of tobacco use. Therefore, in adults who use tobacco, assistance and arrangement for individualized and group social support counseling are recommended (S2.1-50, S2.1-51).</li> </ul>

\*Advanced age generally refers to age  $\geq 75$  years.

ASCVD indicates atherosclerotic cardiovascular disease.



# Circulation



## 2.2. Assessment of Cardiovascular Risk

Recommendations for Assessment of Cardiovascular Risk		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplement 3</a> .		
COR	LOE	Recommendations
I	B-NR	1. For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using the pooled cohort equations (PCE) (S2.2-1, S2.2-2).
IIa	B-NR	2. For adults 20 to 39 years of age, it is reasonable to assess traditional ASCVD risk factors at least every 4 to 6 years (S2.2-1–S2.2-3).
IIa	B-NR	3. In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk ( $\geq 7.5\%$ to <20% 10-year ASCVD risk), it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions (e.g., statin therapy) (S2.2-4–S2.2-14).
IIa	B-NR	4. In adults at intermediate risk ( $\geq 7.5\%$ to <20% 10-year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10-year ASCVD risk), if risk-based decisions for preventive interventions (e.g., statin therapy) remain uncertain, it is reasonable to measure a coronary artery calcium score to guide clinician–patient risk discussion (S2.2-15–S2.2-31).
IIb	B-NR	5. For adults 20 to 39 years of age and for those 40 to 59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered (S2.2-1, S2.2-2, S2.2-32–S2.2-35).

### Synopsis

Assessment of ASCVD risk remains the foundation of primary prevention. Although all individuals should be encouraged to follow a heart-healthy lifestyle, estimating an individual's 10-year absolute ASCVD risk enables matching the intensity of preventive interventions to the patient's absolute risk, to maximize anticipated benefit and minimize potential harm from overtreatment. The 10-year ASCVD risk estimate is used to guide decision-making for many preventive interventions, including lipid management (S2.2-4, S2.2-36) and BP management (S2.2-37); it should be the start of a conversation with the patient about risk-reducing strategies (the "clinician–patient discussion") and not the sole decision factor for the initiation of pharmacotherapy (S2.2-4, S2.2-36, S2.2-38). All risk estimation tools have inherent limitations, and population-based risk scores must be interpreted in light of specific circumstances for individual patients. The PCE have been shown to overestimate (S2.2-15, S2.2-39–S2.2-47) or underestimate (S2.2-12, S2.2-48–S2.2-51) ASCVD risk for certain subgroups. Thus, after calculation of the PCE, it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions for borderline- or intermediate-risk adults (S2.2-4–S2.2-14). However, the value of preventive therapy may remain uncertain for many individuals with borderline or intermediate estimated 10-year risk, and some patients may be reluctant to take medical therapy without clearer evidence of increased ASCVD risk. For these individuals, the assessment of coronary artery calcium is a reasonable tool to reclassify risk either upward or downward, as part of shared decision-making. For younger adults 20 to 59 years of age, estimation of lifetime risk may be considered. For adults >75 years of age, the clinician and patient should engage in a discussion about the possible benefits of preventive therapies appropriate to the age group in the context of comorbidities and life expectancy.

**Recommendation-Specific Supportive Text**

1. To facilitate decisions about preventive interventions, it is recommended to screen for traditional ASCVD risk factors and apply the race- and sex-specific PCE (ASCVD Risk Estimator: [http://tools.acc.org/Idl/ascvd\\_risk\\_estimator/index.html#!/calculate/estimator/](http://tools.acc.org/Idl/ascvd_risk_estimator/index.html#!/calculate/estimator/)) to estimate 10-year ASCVD risk for asymptomatic adults 40 to 75 years of age (S2.2.1, S2.2.2). For management of stage 1 hypertension (BP 130–139 / 80–89 mm Hg), adults should be categorized as <10% or >10% 10-year ASCVD risk for therapeutic decisions (see Section 4.4 Figure 4). For management of blood cholesterol, adults should be categorized as having low (<5%), borderline (5% to <7.5%), intermediate ( $\geq 7.5\%$  to <20%), or high ( $\geq 20\%$ ) 10-year risk (S2.2-4). The PCE are best validated among non-Hispanic whites and non-Hispanic blacks living in the United States (S2.2-1, S2.2-39, S2.2-48, S2.2-49, S2.2-52). In other racial/ethnic groups (S2.2-53, S2.2-54) or in some non-U.S. populations (S2.2-40, S2.2-41, S2.2-53, S2.2-54), the PCE may overestimate or underestimate risk. Therefore, clinicians may consider the use of another risk prediction tool as an alternative to the PCE if the tool was validated in a population with characteristics similar to those of the evaluated patient. Examples include the general Framingham CVD risk score (S2.2-55), the Reynolds risk scores (S2.2-56, S2.2-57), SCORE (Systematic COronary Risk Evaluation) (S2.2-58), and the QRISK/JBS3 (S2.2-59) tools. Other professional societies have incorporated some of these alternative validated risk scores into their lipid management guidelines or have considered different risk thresholds for preventive interventions (S2.2-58–S2.2-63). Although slight differences exist across organizational guidelines, they are all very similar in their overarching goal of matching the intensity of preventive therapies to the absolute (generally 10-year) risk of the patient (S2.2-58–S2.2-63).
2. After age 20 years, it is reasonable to measure traditional risk factors at least every 4 to 6 years (S2.2-1, S2.2-3). For adults 20 to 39 years of age, limited data exist on the performance and utility of 10-year risk estimation tools (S2.2-64). Because age is a major driver of risk, most in this age range (<40 years) are unlikely to have a sufficiently elevated 10-year risk to warrant pharmacological therapy with a statin (with some exceptions, such as in familial hypercholesterolemia). Nevertheless, periodic assessment of risk factors (e.g., at least every 4 to 6 years in younger adults 20 to 39 years of age) is important to guide discussions about intensity of lifestyle interventions, frequency of risk factor monitoring, treatment of nonlipid risk factors, and consideration of 30-year or lifetime risk estimation (S2.2-1–S2.2-3).
3. No single risk calculator is appropriate for all patients. In certain populations, the PCE have reasonable calibration (S2.2-1, S2.2-65–S2.2-67). However, some studies have found *underestimation* of risk (and potential for undertreatment) among individuals with chronic inflammatory conditions (e.g., autoimmune disease (S2.2-50), HIV infection (S2.2-12)) or socioeconomic disadvantage (S2.2-48, S2.2-49, S2.2-51) not captured in current risk scoring models. Patients with familial hypercholesterolemia are at significant risk of having an early ASCVD event, and the use of risk calculators is not applicable to these patients. In contrast, other studies have found *overestimation* of risk with the PCE, particularly among those with higher socioeconomic position and those with continual access to care and preventive services, which could lead to overtreatment of individuals less likely to receive net benefit from preventive pharmacotherapies over the next decade (S2.2-15, S2.2-39–S2.2-47). The PCE may be suboptimally calibrated in more modern populations as compared with the older cohorts from which they were derived (S2.2-68). Therefore, among adults at borderline (5% to <7.5%) and intermediate ( $\geq 7.5\%$  to <20%) risk, one may consider additional individual risk-enhancing clinical factors (Table 3) that can be used to revise the 10-year ASCVD risk estimate (S2.2-4). These factors may include having a family history of premature ASCVD (S2.2-5), chronic inflammatory disease [rheumatoid arthritis (S2.2-6), lupus (S2.2-7), or HIV infection (S2.2-12)], South Asian ancestry (S2.2-13), a history of preeclampsia (S2.2-8) or preterm delivery (S2.2-9), early menopause (S2.2-10),

erectile dysfunction (S2.2-11), chronic kidney disease (CKD), metabolic syndrome, persistently elevated inflammatory markers (S2.2-14), or elevated lipid biomarkers (S2.2-4). After these clinically available risk-enhancing factors have been considered, if there is still uncertainty about the reliability of the risk estimate for individuals in the borderline- or intermediate-risk categories, further testing to document subclinical coronary atherosclerosis is reasonable to more accurately reclassify the risk estimate upward or downward (S2.2-17–S2.2-19, S2.2-69).

4. For individuals with intermediate predicted risk ( $\geq 7.5\%$  to  $< 20\%$ ) by the PCE or for select adults with borderline ( $5\%$  to  $< 7.5\%$ ) predicted risk, coronary artery calcium measurement can be a useful tool in refining risk assessment for preventive interventions (e.g., statin therapy) (S2.2-4). In these groups, coronary artery calcium measurement can reclassify risk upward (particularly if coronary artery calcium score is  $\geq 100$  Agatston units (AU) or  $\geq 75$ th age/sex/race percentile) or downward (if coronary artery calcium is zero) in a significant proportion of individuals (S2.2-15). The extent of reclassification is sufficient to provide confidence that borderline- or intermediate-risk patients with elevated coronary artery calcium will have event rates that clearly exceed benefit thresholds (i.e.,  $\geq 7.5\%$  in 10 years) and those with coronary artery calcium scores of zero will have event rates  $< 7.5\%$ , which can help guide shared decision-making about statins (S2.2-15, S2.2-16, S2.2-21) or potentially even aspirin (S2.2-70). In observational data, the presence and severity of coronary artery calcium have been shown to be associated with the likelihood of benefit from statin therapy for ASCVD risk reduction (S2.2-71). Coronary artery calcium scoring has superior discrimination and risk reclassification as compared with other subclinical imaging markers or biomarkers (S2.2-22, S2.2-27). In the MESA (Multi-Ethnic Study of Atherosclerosis) trial, the coronary artery calcium score was strongly associated with 10-year ASCVD risk in a graded manner across age, sex, and racial/ethnic groups, independent of traditional risk factors (S2.2-17). Coronary artery calcium may even refine ASCVD risk estimates among lower-risk women ( $< 7.5\%$  10-year risk) (S2.2-7), younger adults ( $< 45$  years of age) (S2.2-20), and older adults ( $\geq 75$  years of age) (S2.2-26), but more data are needed to support its use in these subgroups. A coronary artery calcium score of zero identifies individuals at lower risk of ASCVD events and death over a  $\geq 10$ -year period (S2.2-15, S2.2-17, S2.2-25), who appear to derive little or no benefit from statins for ASCVD risk reduction (S2.2-71). Thus, the absence of coronary artery calcium could reclassify a patient downward into a lower risk group in which preventive interventions (e.g., statins) could be postponed (S2.2-22). Note that the absence of coronary artery calcium does not rule out noncalcified plaque, and clinical judgment about risk should prevail. Coronary artery calcium might also be considered in refining risk for selected low-risk adults ( $< 5\%$  10-year risk), such as those with a strong family history of premature coronary heart disease (CHD) (S2.2-23). MESA (S2.2-28) and Astro-CHARM (Astronaut Cardiovascular Health and Risk Modification) (S2.2-29) are risk estimation tools that incorporate both risk factors and coronary artery calcium for estimating 10-year CHD and ASCVD risk, respectively. Coronary artery calcium measurement is not intended as a “screening” test for all but rather may be used as a decision aid in select adults to facilitate the clinician–patient risk discussion.
5. For adults 20 to 39 years of age (who are not included in the PCE) and those 40 to 59 years of age who are not already at elevated ( $\geq 7.5\%$ ) 10-year risk, estimating a lifetime or 30-year risk of ASCVD may be considered (ASCVD Risk Estimator: [http://tools.acc.org/ldl/ascvd\\_risk\\_estimator/index.html#!/calculate/estimator/](http://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calculate/estimator/)) (S2.2-2). Younger individuals often have low estimated 10-year risk, but the presence of at least 1 major risk factor by middle age is associated with increased lifetime ASCVD risk and reduced survival free of morbidity compared with those with optimal risk factors (S2.2-32–S2.2-34). Calculation of lifetime risk with the ACC/AHA 30-year/lifetime risk estimator for those 20 to 59 years of age (not at high short-term risk)



may be reasonable to consider as a communication strategy for reinforcing adherence to lifestyle recommendations (S2.2-2).

**Table 3. Risk-Enhancing Factors for Clinician–Patient Risk Discussion**

Risk-Enhancing Factors
<ul style="list-style-type: none"> <li>• <b>Family history of premature ASCVD</b> (males, age &lt;55 y; females, age &lt;65 y)</li> <li>• <b>Primary hypercholesterolemia</b> (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non-HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*</li> <li>• <b>Metabolic syndrome</b> (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [&gt;150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)</li> <li>• <b>Chronic kidney disease</b> (eGFR 15–59 mL/min/1.73 m<sup>2</sup> with or without albuminuria; not treated with dialysis or kidney transplantation)</li> <li>• <b>Chronic inflammatory conditions</b>, such as psoriasis, RA, lupus, or HIV/AIDS</li> <li>• <b>History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia</b></li> <li>• <b>High-risk race/ethnicity</b> (e.g., South Asian ancestry)</li> <li>• <b>Lipids/biomarkers:</b> associated with increased ASCVD risk             <ul style="list-style-type: none"> <li>○ Persistently elevated* primary hypertriglyceridemia (≥175 mg/dL, nonfasting)</li> <li>○ If measured:                 <ul style="list-style-type: none"> <li>▪ <b>Elevated high-sensitivity C-reactive protein</b> (≥2.0 mg/L)</li> <li>▪ <b>Elevated Lp(a):</b> A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).</li> <li>▪ <b>Elevated apoB</b> (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C &gt;160 mg/dL and constitutes a risk-enhancing factor</li> <li>▪ <b>ABI</b> (&lt;0.9)</li> </ul> </li> </ul> </li> </ul>



\*Optimally, 3 determinations.

ABI indicates ankle-brachial index; AIDS, acquired immunodeficiency syndrome; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); and RA, rheumatoid arthritis.

Reproduced with permission from Grundy et al. (S2.2-4). Copyright © 2018, American Heart Association, Inc., and American College of Cardiology Foundation.

### 3. Lifestyle Factors Affecting Cardiovascular Risk

#### 3.1. Nutrition and Diet

Recommendations for Nutrition and Diet		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 4 and 5</a> .		
COR	LOE	Recommendations
I	B-R	1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors (S3.1-1–S3.1-11).
IIa	B-NR	2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce ASCVD risk (S3.1-12, S3.1-13).
IIa	B-NR	3. A diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease ASCVD risk (S3.1-9, S3.1-14–S3.1-16).
IIa	B-NR	4. As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk (S3.1-17–S3.1-24).
III: Harm	B-NR	5. As a part of a healthy diet, the intake of <i>trans</i> fats should be avoided to reduce ASCVD risk (S3.1-12, S3.1-17, S3.1-25–S3.1-27).

#### Synopsis

Approximately 630,000 Americans died from heart disease in 2015, of whom 366,000 died from coronary artery disease. After 4 decades of decline, heart disease deaths rose in 2015 by 1% (S3.1-28). This trend has been attributed to the obesity epidemic. Healthy nutrition has an important impact on ASCVD and its risk factors (see recommendations in the individual sections), potentially reversing or reducing obesity, high cholesterol, diabetes, and hypertension. The cardiovascular nutrition literature is limited by the paucity of large-scale prospective randomized trials with ASCVD outcomes. Although RCTs focused on hard endpoints are limited, multiple observational studies have focused on the association of CVD mortality with dietary patterns—specifically, sugar, low-calorie sweeteners, high-carbohydrate diets, low-carbohydrate diets, refined grains, *trans* fat, saturated fat, sodium, red meat, and processed red meat (e.g., bacon, salami, ham, hot dogs, sausage) (S3.1-1–S3.1-24).

#### Recommendation-Specific Supportive Text

1. Plant-based and Mediterranean diets, along with increased fruit, nut, vegetable, legume, and lean vegetable or animal protein (preferably fish) consumption, with the inherent soluble and insoluble vegetable fiber, have consistently been associated with lower risk of all-cause mortality than control or standard diets (S3.1-1–S3.1-10, S3.1-29, S3.1-30) in observational studies. The PREDIMED (Prevención con Dieta Mediterránea) trial randomized participants to a Mediterranean diet supplemented with either extra-virgin olive oil or nuts and demonstrated 30% and 28% reductions, respectively, in the combined endpoint (MI, stroke, or cardiovascular mortality), but the improved outcome was driven largely by the reduction in stroke, with no significant improvement over the control diet for mortality or MI (S3.1-1). When the PREDIMED cohort was reanalyzed post hoc for the

“provegetarian” food pattern (more vegetable consumption versus animal, egg, fish, dairy, or meat product consumption), a significant mortality rate reduction (41%) was noted in the 2 quintiles with the highest vegetarian score (S3.1-11). A comparison of plant and animal protein from the Adventist Health Study-2 cohort (S3.1-10) similarly indicated that using meat for protein was associated with a 61% increase in mortality rate, whereas replacing meat with nuts and seeds was associated with a 40% reduction in mortality rate. Similarly, the graded risk published by Song et al. indicated that lower mortality rate was associated with replacing animal protein of different origins with plant protein (S3.1-9). The evidence is mixed with regard to the effectiveness of dairy intake to reduce ASCVD risk factors, which is why it is not included in the listed foods for this recommendation. Although the DASH (Dietary Approaches to Stop Hypertension) diet, which includes low-fat dairy products, was shown to reduce BP (S3.1-14), and the PURE (Prospective Urban Rural Epidemiology) study indicated that dairy intake was associated with a 23% lower mortality rate (S3.1-31), Song et al. indicated an 11% increase in cardiovascular mortality rate with dairy consumption as compared with vegetable protein (S3.1-9).

2. *Trans* and saturated fats have been associated with a higher risk of total and cause-specific death (S3.1-12). However, observational data from the PURE trial suggested that, when used instead of refined carbohydrates, saturated and unsaturated fats were associated with reduced stroke and mortality (S3.1-13).
3. Dietary sodium reduction was found to reduce BP and cardiovascular events in the DASH trial and in TOHP (Trials of Hypertension Prevention) (S3.1-14, S3.1-15). Data from NHANES (National Health and Nutrition Examination Surveys) (S3.1-16) suggest that high consumption of sodium (>2,000 mg daily), red meat (>14 g/d), and sugar-sweetened beverages and processed red meat consumption were associated with cardiovascular death. A prospective cohort study of U.S. healthcare professionals (S3.1-9) with at least 1 risk factor indicated that replacement of animal protein (sources of cholesterol, saturated fat, heme iron and precursors of trimethylamine-N-oxide) with plant protein was associated with reduced cardiovascular mortality rate. In that study, compared with plant protein, poultry and fish were associated with a 6% higher mortality rate, dairy with an 8% higher mortality rate, unprocessed red meat with a 12% higher mortality rate, eggs with a 19% higher mortality rate, and processed red meat with a 34% higher mortality rate. Overall, plant protein was associated with a reduction in mortality rate of 10% for every 3% energy increment replacement of animal protein.
4. Intake of several food products has been shown to be potentially harmful or increase risk of ASCVD. Sugar-sweetened and artificially sweetened beverages have been correlated with increasing the development of T2DM and with ASCVD risk, with a 20% increase in the frequency of diabetes mellitus with 1 daily serving of these sweetened beverages (S3.1-18). In large cohort studies, consumption of added sugar at >10% of daily calories has been associated with increased mortality rate (S3.1-19). However, adults who are habitually high consumers of sugar-sweetened beverages and utilize low calorie sweetened beverages as a replacement strategy that provides a sweet taste while reducing caloric intake may find this useful in the transition to water (S3.1-20). In REGARDS (REasons for Geographic and Racial Differences in Stroke) (S3.1-21), the Southern dietary pattern was identified as substantially increasing health risks, including a 56% higher risk of heart disease and a 30% higher risk of stroke. This pattern consisted of more fried food, added fats, organ and processed meats, and sugar-sweetened beverages. Consuming a diet (S3.1-4) with juices and sweetened beverages, refined grains, potatoes/fries, and sweets resulted in a greater increase in coronary events than the increase seen with consumption of animal products. Given the additional risk associated with intake of these various food products, clinicians would do well to counsel individuals about their associated harm and advise them to avoid these foods when possible. Furthermore, longstanding dietary patterns that focus on low intake of carbohydrates and a high intake of animal fat and protein are associated with increased cardiac and noncardiac mortality rate (S3.1-22–S3.1-24). In 1 meta-analysis (S3.1-23), low-

carbohydrate diets were associated with a 31% higher risk of all-cause death, with increased cardiac mortality rate. Population data from the ARIC (Atherosclerosis Risk in Communities) study indicated an 18% increase in mortality rate with low-carbohydrate diets using animal-derived protein and fat sources (e.g., lamb, beef, pork, chicken) (S3.1-22), but plant sources (e.g., vegetables, nuts, peanut butter, whole-grain breads) were associated with lower mortality rate. In addition, the ARIC investigators noted a 23% increase in mortality rate associated with high-carbohydrate diets, with the optimal carbohydrate intake observed to be 50% to 55%.

5. Intake of *trans* fat has been shown to be harmful and increase risk of ASCVD. *Trans* fat was associated with higher all-cause mortality rate in the REGARDS U.S. healthcare professionals cohort studies (S3.1-12, S3.1-17). Additionally, regulations to curb use of *trans* fat in the food industry have been associated with a decrease in stroke and MI (S3.1-25). *Trans* fats have adverse effects on lipid and lipoproteins and promote endothelial dysfunction, insulin resistance, inflammation, and arrhythmias (S3.1-26). Since partially hydrogenated oils are optional food additives, their elimination has been a public health priority (S3.1-27).



# Circulation

## 3.2. Exercise and Physical Activity

Recommendations for Exercise and Physical Activity		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 6 and 7</a> .		
COR	LOE	Recommendations
I	B-R	1. Adults should be routinely counseled in healthcare visits to optimize a physically active lifestyle (S3.2-1, S3.2-2).
I	B-NR	2. Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk (S3.2-3–S3.2-8).
IIa	B-NR	3. For adults unable to meet the minimum physical activity recommendations (at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity), engaging in some moderate- or vigorous-intensity physical activity, even if less than this recommended amount, can be beneficial to reduce ASCVD risk (S3.2-5, S3.2-6).
IIb	C-LD	4. Decreasing sedentary behavior in adults may be reasonable to reduce ASCVD risk (S3.2-3, S3.2-9–S3.2-11).



### Synopsis

The numerous health benefits of regular physical activity have been well established (S3.2-12–S3.2-15), and physical activity is a cornerstone of maintaining and improving cardiovascular health (S3.2-6). Nevertheless, approximately half of adults in the United States do not meet the minimum physical activity recommendations (S3.2-12). Strategies are needed to increase physical activity at both the individual and the population levels (S3.2-16, S3.2-17).

Extensive observational data from meta-analyses and systematic reviews support recommendations for aerobic physical activity to lower ASCVD risk (S3.2-3–S3.2-8, S3.2-12, S3.2-18, S3.2-19). Resistance exercise should also be encouraged because of its several health benefits, including improving physical functioning (S3.2-20), improving glycemic control in individuals with diabetes (S3.2-21), and possibly BP lowering (S3.2-22). Whether resistance exercise lowers ASCVD risk is unclear (S3.2-12).

Aerobic physical activity is generally very safe (S3.2-23). However, sedentary individuals starting an exercise program should initiate exercise at a lower intensity (e.g., slow walking) and duration and progress gradually to recommended levels (S3.2-24). It is uncertain whether an upper limit of habitual exercise, either in amount or intensity, may have adverse cardiovascular consequences (S3.2-25). But, in discussions with patients, it should be mentioned that these very high levels of physical activity (i.e., >10 times the minimum recommended amount) pertain to only a small fraction of the population (S3.2-12). Individuals with significant functional impairments may need modifications to and more specific guidance on the type, duration, and intensity of physical activity.

### Recommendation-Specific Supportive Text

1. Physical activity assessment and counseling in the healthcare setting have important complementary roles in promoting increased physical activity (S3.2-16). Ascertaining physical activity patterns during a standard clinical visit is the first step toward effective counseling and can be accomplished through several available simple assessment tools (S3.2-16). The results of these tools can be recorded in the electronic health record, along with parameters such as weight and BP (S3.2-16). Physical activity

counseling by clinicians can result in modest improvements in physical activity levels, with a number needed to counsel as low as 12 for an individual to achieve recommended physical activity levels (S3.2-1, S3.2-2). This counseling might include an exercise prescription that consists of recommended frequency, intensity, time (duration), and type of exercise.

2. There is a consistent, strong, inverse dose–response relationship between the amount of moderate to vigorous physical activity and incident ASCVD events and death (S3.2-3–S3.2-8, S3.2-12). The shape of the dose–response relationship is curvilinear, with significant benefit observed when comparing those engaging in little or no physical activity with those performing moderate amounts (S3.2-5, S3.2-6, S3.2-12). All adults should engage in at least 150 minutes per week of accumulated moderate-intensity aerobic physical activity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to lower ASCVD risk (Table 4). These recommendations are in line with those of other health organizations (S3.2-26). Shorter durations of exercise seem to be as beneficial as longer ones (e.g., ≥10-minute bouts) (S3.2-27, S3.2-28), and thus the focus of physical activity counseling should be on the total accumulated amount. Additional reduction in ASCVD risk is seen in those achieving higher amounts of aerobic physical activity (>300 minutes per week of moderate-intensity aerobic physical activity or 150 minutes per week of vigorous-intensity aerobic physical activity) (S3.2-5, S3.2-6, S3.2-12, S3.2-14). There is a continued but diminishing additive benefit of further increasing physical activity to very high levels (S3.2-5, S3.2-6, S3.2-12). Specific exercise recommendations for the prevention of heart failure may differ slightly because the dose–response relationship with increasing physical activity levels may be linear (S3.2-29).
3. There is likely no lower limit on the quantity of moderate-to-vigorous physical activity at which benefits for ASCVD risk start to accrue (S3.2-6). All efforts should be made to promote achievement of the minimum recommended amount of physical activity by all adults. However, for individuals unable to achieve this minimum, encouraging at least some moderate-to-vigorous physical activity among those who are inactive (i.e., no moderate-to-vigorous physical activity) or increasing the amount in those who are insufficiently active is still likely beneficial to reduce ASCVD risk (S3.2-6). Strategies to further increase physical activity in those achieving less than targeted amounts should be implemented.
4. Despite the focus on moderate- and vigorous-intensity physical activity, such activity accounts for a small proportion of individuals' daily time as compared with other forms of activity. Other activity states that comprise a 24-hour period for an average individual include sleep, light-intensity physical activity, and sedentary behavior (Figure 1). *Sedentary behavior* refers to waking behavior with an energy expenditure of ≤1.5 metabolic equivalents while in a sitting or reclining posture (Table 4) (S3.2-30). Increased sedentary behavior is associated with worse health parameters, including cardiometabolic risk factors (S3.2-3, S3.2-9–S3.2-11). Sedentary behavior may be most deleterious to ASCVD risk for individuals who engage in the least amount of moderate to vigorous physical activity (S3.2-3, S3.2-10, S3.2-12). Thus, strategies to reduce sedentary behavior, particularly in those not achieving current recommended physical activity levels, may be beneficial for lowering ASCVD risk. However, data on the value of reducing or modifying sedentary behavior over time to reduce ASCVD risk are sparse, and whether replacing sedentary behavior with light-intensity activity (e.g., slow walking, light work) is beneficial for ASCVD prevention is unclear (S3.2-31). The strength and specificity of the recommendation to reduce sedentary behavior are limited by uncertainty about the appropriate limits of and optimal approach to modifying sedentary behavior (S3.2-30).



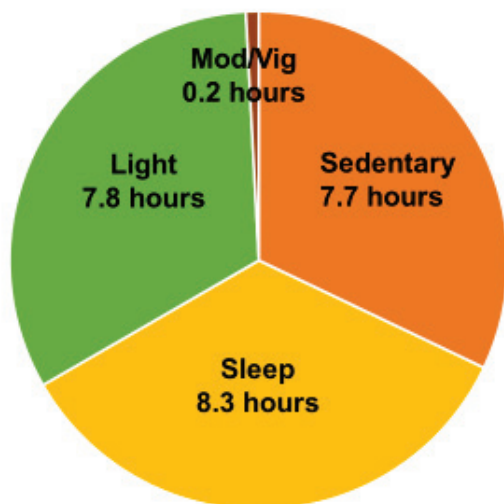
**Table 4. Definitions and Examples of Different Intensities of Physical Activity**

Intensity	METs	Examples
Sedentary behavior*	1–1.5	Sitting, reclining, or lying; watching television
Light	1.6–2.9	Walking slowly, cooking, light housework
Moderate	3.0 –5.9	Brisk walking (2.4–4 mph), biking (5–9 mph), ballroom dancing, active yoga, recreational swimming
Vigorous	≥6	Jogging/running, biking (≥10 mph), singles tennis, swimming laps

\**Sedentary behavior* is defined as any waking behavior characterized by an energy expenditure  $\leq 1.5$  METs while in a sitting, reclining, or lying posture. Standing is a sedentary activity in that it involves  $\leq 1.5$  METs, but it is not considered a component of sedentary behavior.

MET indicates metabolic equivalent; and mph, miles per hour.

**Figure 1. Hours Per Day Spent in Various States of Activity**



U.S. adults spend >7 h/d on average in sedentary activities. Replacing sedentary time with other physical activity involves increasing either moderate- to vigorous-intensity physical activity or light-intensity physical activity.  
Data modified from Young et al. (S3.2-30).

## 4. Other Factors Affecting Cardiovascular Risk

### 4.1. Adults With Overweight and Obesity

Recommendations for Adults With Overweight and Obesity		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 8 and 9</a> .		
COR	LOE	Recommendations
I	B-R	1. In individuals with overweight and obesity, weight loss is recommended to improve the ASCVD risk factor profile (S4.1-1).
I	B-R	2. Counseling and comprehensive lifestyle interventions, including calorie restriction, are recommended for achieving and maintaining weight loss in adults with overweight and obesity (S4.1-1, S4.1-2).
I	C-EO	3. Calculating body mass index (BMI) is recommended annually or more frequently to identify adults with overweight and obesity for weight loss considerations.
Ila	B-NR	4. It is reasonable to measure waist circumference to identify those at higher cardiometabolic risk (S4.1-3–S4.1-6).

#### Synopsis

The increased availability of affordable, palatable, and high-calorie foods and the decreased physical demands of many jobs have fueled the epidemic of obesity and the consequent increases in hypertension and T2DM (S4.1-7). Adults diagnosed as obese (BMI  $\geq 30$  kg/m<sup>2</sup>) or overweight (BMI = 25 to 29.9 kg/m<sup>2</sup>) are at increased risk of ASCVD, heart failure, and atrial fibrillation, compared with those of a normal weight (S4.1-8, S4.1-9). The nutritional aspects of obesity revolve around the principle of balancing caloric intake with caloric expenditure. Following the 2013 Guideline for the Management of Overweight and Obesity in Adults from the AHA, ACC, and The Obesity Society (TOS), adults with overweight/obesity are advised to participate in comprehensive lifestyle programs of  $\geq 6$  months' duration that assist participants in adhering to a low-calorie diet (800 to 1,500 kcal/day) and increased physical activity. Existing clinical guidance strongly recommends face-to-face or telephone-delivered weight-loss maintenance programs that provide regular contact (at least monthly) with a trained interventionist to help participants engage in high levels of physical activity (200 to 300 minutes/week), monitor body weight regularly (at least weekly), and consume a reduced-calorie diet (S4.1-10).

U.S. Food and Drug Administration (FDA)–approved pharmacological therapies (S4.1-1, S4.1-11) and bariatric surgery (S4.1-12), adjunctive to complementary lifestyle interventions, additionally reduce weight and may have a role in weight loss for select patients. The present guideline document focuses primarily on lifestyle interventions for overweight and obesity, as outlined in the 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (S4.1-10). Weight loss interventions should be cautiously implemented and individualized, especially in older adults, to avoid detrimental effects, such as loss of lean body/muscle mass and nutritional deficiencies (S4.1-13–S4.1-15).

#### Recommendation-Specific Supportive Text

1. Clinically meaningful weight loss ( $\geq 5\%$  initial weight) is associated with moderate improvement in BP, low-density lipoprotein cholesterol (LDL-C), triglyceride, and glucose levels among individuals with overweight/obesity (S4.1-1). Weight loss reduces or delays the development of T2DM in persons with obesity (S4.1-1, S4.1-16, S4.1-17). High-intensity ( $\geq 14$  sessions in 6 months) comprehensive weight-loss interventions provided by a trained interventionist work best (S4.1-10). However, other



modalities, such as electronically delivered weight-loss programs with personalized feedback and some commercial-based programs, have also shown moderate results.

2. Comprehensive lifestyle intervention consists of a structured program, which includes regular self-monitoring of food intake, physical activity, and weight. Increased physical activity, preferably aerobic physical activity (e.g., brisk walking) for  $\geq 150$  minutes/week (equal to  $\geq 30$  minutes/day on most days of the week), is recommended for initial weight loss (S4.1-10). Higher levels of physical activity, approximately 200 to 300 minutes/week, are recommended to maintain weight loss or minimize weight regain after 1 year. Adults with obesity are also typically prescribed a diet designed to reduce caloric intake by  $\geq 500$  kcal/day from baseline, which often can be attained by limiting women to 1,200 to 1,500 kcal/day and men to 1,500 to 1,800 kcal/day (S4.1-10). A very-low-calorie diet (defined as  $< 800$  kcal/day) should be prescribed only in limited circumstances and only by trained clinicians in a medical care setting with the patient under medical supervision (S4.1-10). Comprehensive lifestyle intervention has been shown to produce on average 8 kg of weight loss (5% to 10% of initial body weight) in the short term ( $\leq 6$  months) and intermediate term (6 to 12 months), compared with usual care (S4.1-1, S4.1-10). However, longer interventions after 1 year are associated with gradual weight gain of 1 or 2 kg/year (on average), compared with usual care. Weight loss of 5% to 10% of initial weight, achieved through comprehensive lifestyle intervention, has been shown to improve BP, delay the onset of T2DM, improve glycemic control in T2DM, and improve lipid profile (S4.1-1, S4.1-2).
3. Measures used to estimate body fat and quantify the associated health risks include BMI, waist circumference, waist-hip ratio, bioimpedance, and dual-energy X-ray absorptiometry (DXA) (S4.1-18). BMI, waist circumference, and waist-hip ratio are easily measured and therefore are the most widely used in clinical practice. A USPSTF document found good evidence supporting the use of BMI to identify adults at increased risk of future morbidity and mortality (S4.1-18). Because obesity/overweight defined by BMI is the most studied and standardized approach, we recommend its measurement for primary screening of individuals needing weight loss. BMI should be interpreted with caution in persons of Asian ancestry, older adults, and muscular adults (S4.1-19, S4.1-20).
4. Increased waist circumference has been associated with increased cardiometabolic and ASCVD risk (S4.1-3–S4.1-6). Central adiposity, captured by using waist circumference, has been associated with ASCVD risk and may be missed when BMI is used as the only measure of obesity (S4.1-21, S4.1-22). Waist circumference measurement is recommended in all patients with BMI  $< 35$  kg/m<sup>2</sup> (S4.1-9, S4.1-19, S4.1-23). Ethnic differences in waist circumference thresholds associated with cardiometabolic risk have been reported. Waist circumference may be more useful than BMI in persons with abdominal obesity (central adiposity) (S4.1-24). Definitions of elevated waist circumference as  $\geq 40$  inches ( $\geq 102$  cm) in men and  $\geq 35$  inches ( $\geq 88$  cm) in women were recommended by the 1998 National Heart, Lung, and Blood Institute Obesity Initiative Expert Panel (S4.1-25) and were adopted by the 2013 AHA/ACC/TOS writing committee (S4.1-1). Furthermore, waist circumference assessment is needed for the diagnosis of metabolic syndrome. Thus, combining waist circumference and BMI may be the best approach for assessing obesity-related risk. Counseling and comprehensive lifestyle interventions, including calorie restriction and adjunctive therapies (e.g., FDA-approved drugs, bariatric surgery), have all been associated with significant reductions in waist circumference and improvement in cardiometabolic risk profiles (S4.1-1).

## 4.2. Adults With Type 2 Diabetes Mellitus

See Figure 2 for an algorithm for treatment of T2DM for primary prevention of cardiovascular disease.

Recommendations for Adults With Type 2 Diabetes Mellitus		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplement 10</a> .		
COR	LOE	Recommendations
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).
I	A	2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).
IIa	B-R	3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk (S4.2-5–S4.2-8).
IIb	B-R	4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk (S4.2-9–S4.2-14).

### Synopsis

T2DM, defined as a hemoglobin A1c (HbA1c)  $\geq 6.5\%$ , is a metabolic disorder characterized by insulin resistance leading to hyperglycemia. Unlike type 1 diabetes mellitus (an autoimmune condition largely unrelated to lifestyle factors), the development and progression of T2DM are heavily influenced by dietary pattern, physical activity, and body weight. Approximately 12% of U.S. adults have diabetes, 90% to 95% of whom have T2DM, with significant heterogeneity according to age, sex, race/ethnicity, and socioeconomic status (S4.2-15). Alarming, more than one-third of U.S. adults ( $\approx 80$  million adults) have prediabetes and are at risk of developing T2DM (S4.2-15).\*

Although contemporary data have shown a significant decrease in ASCVD rates in individuals with T2DM (S4.2-15), T2DM remains a highly prevalent disease and a major ASCVD risk factor. An aggressive, comprehensive approach to ASCVD risk factor treatment in adults with T2DM reduces ASCVD events (S4.2-16). Management of cholesterol and hypertension in adults with T2DM is discussed in the relevant sections of the present guideline (see Sections 4.3. and 4.4.).

### Recommendation-Specific Supportive Text

1. A heart-healthy dietary pattern is a key intervention in the treatment of T2DM. The Mediterranean, DASH, and vegetarian/vegan diets have all been shown to help in the achievement of weight loss and improve glycemic control in T2DM (S4.2-1, S4.2-2). Prospective cohorts have demonstrated a significantly lower likelihood of CVD events and CVD death in adults with T2DM who follow a healthy

\*An HbA1c is the optimal screening method, with a level  $\geq 6.5\%$  indicating T2DM.

dietary pattern (S4.2-17). However, an RCT targeting aggressive lifestyle interventions in T2DM was unable to show a reduction in ASCVD events despite early success in achieving weight loss (S4.2-18).

The quality of carbohydrate intake is especially important for control of T2DM, and focus should be placed on the intake of fiber-rich whole grains and avoidance of refined carbohydrates (S4.2-19). Additionally, red meat consumption has been shown to increase the risk of T2DM, and decreasing intake of red meat can improve glycemic control (S4.2-20, S4.2-21). Weight loss is an essential treatment component for T2DM, and dietary recommendations should be adjusted to achieve meaningful weight loss, if needed. Establishing an appropriate nutrition plan requires time and effort and is best accomplished with assistance from a registered dietitian-nutritionist or a diabetes education program.

2. Initiation of an exercise program for those with T2DM has been shown to improve glycemic control, with a prior meta-analysis showing a significant reduction in mean HbA1c (7.65% versus 8.31%) in individuals assigned to an exercise program versus control groups (S4.2-22). The combination of aerobic and resistance training further improves glycemic control and facilitates weight loss more than either type of exercise alone (S4.2-3, S4.2-4). Prospective cohort studies have provided supportive data for the benefits of physical activity in individuals with T2DM, with increased levels of physical activity associated with lower rates of CVD events and CVD death (S4.2-17).

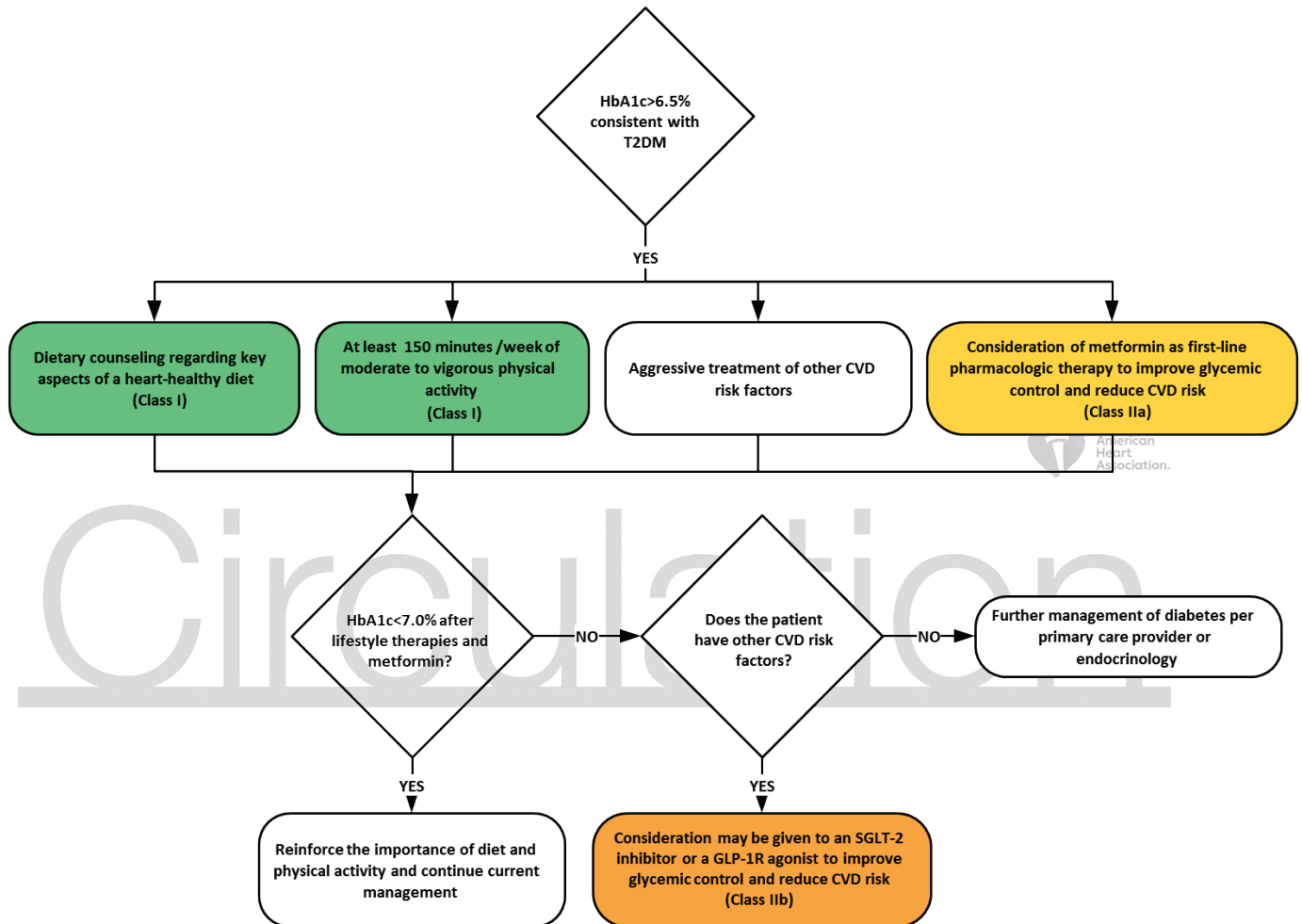
How to best promote physical activity in individuals with T2DM remains unclear. For older individuals with other comorbidities, a simple walking program may be ideal, whereas for younger, healthier individuals, a variety of activities should be encouraged. In addition to a structured exercise program, a general increase in physical activity throughout the day (e.g., taking the stairs, walking or biking to work, avoiding prolonged periods of sitting) should be encouraged.

3. Metformin decreases hepatic glucose production and increases peripheral insulin sensitivity, leading to a reduction in hyperglycemia in adults with T2DM. In a substudy of the UKPDS (United Kingdom Prospective Diabetes Study), metformin, compared with conventional therapy (i.e., lifestyle modifications alone), resulted in a 32% reduction in microvascular and macrovascular diabetes-related outcomes, a 39% reduction in MI, and a 36% reduction in all-cause mortality rate (S4.2-5). A 2016 systematic review and meta-analysis of glucose-lowering therapies for T2DM supported the use of metformin as first-line therapy for T2DM because of its beneficial effects on HbA1c, weight, and improved ASCVD outcomes (compared with sulfonylureas), as well as its acceptable safety profile and low cost. However, a separate systematic review found no evidence of reduced CVD events or CVD deaths with metformin (S4.2-8). Metformin carries a small risk of lactic acidosis and must be used with caution in patients with CKD. For younger individuals or those with a mildly elevated HbA1c at the time of diagnosis of T2DM, clinicians can consider a trial of lifestyle therapies for 3 to 6 months before reconsideration of metformin.
4. Several classes of medications have been shown to effectively lower blood glucose but may or may not affect ASCVD risk (S4.2-23–S4.2-26). However, 2 classes of glucose-lowering medications have recently been demonstrated to reduce CVD events in adults with T2DM and high ASCVD risk. SGLT-2 inhibitors act in the proximal tubule to increase urinary excretion of glucose and sodium, leading to a reduction in HbA1c, body weight, and BP. Three RCTs have shown a significant reduction in ASCVD events and heart failure with use of an SGLT-2 inhibitor (S4.2-9, S4.2-10, S4.2-12). Although most patients studied had established CVD at baseline, the reduction in heart failure has been shown to extend to primary prevention populations (S4.2-12, S4.2-27). The GLP-1R agonists increase insulin and glucagon production in the liver, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. Three GLP-1R agonists have been found to significantly reduce the risk of ASCVD in adults with T2DM who are at high ASCVD risk (S4.2-11, S4.2-13, S4.2-14). As opposed to a

reduction in heart failure with SGLT-2 inhibitors, the benefit of the GLP-1R agonists has been a reduction in ASCVD events though the majority of patients studied had established CVD.

In patients with T2DM and additional risk factors for CVD, it may be reasonable to initiate these 2 classes of medications for primary prevention of CVD.

Figure 2. Treatment of T2DM for Primary Prevention of Cardiovascular Disease



CVD indicates cardiovascular disease; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, hemoglobin A1c; SGLT-2, sodium-glucose cotransporter 2; and T2DM, type 2 diabetes mellitus.

### 4.3. Adults With High Blood Cholesterol

Recommendations from the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1) are included and adapted below.

Recommendations for Adults With High Blood Cholesterol		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 11 and 12</a> .		
COR	LOE	Recommendations
I	A	<p>1. In adults at intermediate risk (<math>\geq 7.5\%</math> to <math>&lt; 20\%</math> 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended (S4.3-2–S4.3-9).</p> <p>Adapted from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>
I	A	<p>2. In intermediate risk (<math>\geq 7.5\%</math> to <math>&lt; 20\%</math> 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (<math>\geq 20\%</math> 10-year ASCVD risk), levels should be reduced by 50% or more (S4.3-2, S4.3-5–S4.3-10).</p> <p>Adapted from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>
I	A	<p>3. In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated (S4.3-11–S4.3-19).</p> <p>Included from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>
I	B-R	<p>4. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (<math>\geq 4.9</math> mmol/L) or higher, maximally tolerated statin therapy is recommended (S4.3-2, S4.3-20–S4.3-25).</p> <p>Included from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>
IIa	B-R	<p>5. In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more (S4.3-2, S4.3-7).</p> <p>Included from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>
IIa	B-R	<p>6. In intermediate-risk (<math>\geq 7.5\%</math> to <math>&lt; 20\%</math> 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy (S4.3-7, S4.3-26–S4.3-33).</p> <p>Adapted from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>

IIa	B-NR	<p>7. In intermediate-risk (<math>\geq 7.5\%</math> to <math>&lt; 20\%</math> 10-year ASCVD risk) adults or selected borderline-risk (<math>5\%</math> to <math>&lt; 7.5\%</math> 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND</p> <ul style="list-style-type: none"> <li>• If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking);</li> <li>• If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients <math>\geq 55</math> years of age;</li> <li>• If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy (S4.3-28, S4.3-34).</li> </ul> <p>Adapted from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>
IIb	B-R	<p>8. In patients at borderline risk (<math>5\%</math> to <math>&lt; 7.5\%</math> 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy (S4.3-28, S4.3-35).</p> <p>Adapted from recommendations in the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).</p>

### Synopsis

Primary ASCVD prevention requires attention to ASCVD risk factors beginning early in life (Figure 3). This guideline addresses major issues related to cholesterol management and primary ASCVD prevention, which are also addressed in the recently published 2018 Cholesterol Clinical Practice Guidelines (S4.3-1). Therefore, the relevant subset of those recommendations is presented here, along with its accompanying supportive text. This writing committee agrees that for young adults (20 to 39 years of age), priority should be given to estimating lifetime risk and promoting a healthy lifestyle. Only in select patients with moderately high LDL-C ( $\geq 160$  mg/dL) or those with very high LDL-C ( $\geq 190$  mg/dL) is drug therapy indicated. In adults 40 to 75 years of age, 10-year ASCVD risk should guide therapeutic considerations. The higher the estimated risk, the more likely the patient is to benefit from statin treatment. For patients  $> 75$  years of age, assessment of risk status and a clinician patient risk discussion are needed to decide whether to continue or initiate statin treatment. For a detailed discussion of statin safety and management of statin-associated side effects, please refer to Section 5 of the 2018 Cholesterol Clinical Practice Guidelines (S4.3-1).

### Recommendation-Specific Supportive Text

1. Large-scale RCTs in primary prevention demonstrated ASCVD risk reduction with moderate-intensity (S4.3-6, S4.3-36) and high-intensity statin therapy (S4.3-7) that outweighed the observable risks. Subsequently, a large-scale RCT in an ethnically and racially diverse population confirmed statin benefit from a moderate-intensity statin therapy, as compared with placebo, in intermediate-risk patients. That RCT enrolled men  $\geq 55$  years of age and women  $\geq 65$  years of age with at least 1 cardiovascular risk factor. In the placebo group, the 10-year risk of "hard ASCVD" was 8.7%, and the risk of the expanded ASCVD endpoint that included coronary revascularization was 10% (S4.3-9). After 5.6 years, those assigned to rosuvastatin 10 mg per day showed significant absolute risk reduction in both co-primary endpoints, with an acceptable safety record. By comparison, after a median follow-

up of 1.9 years, those assigned to a high-intensity statin dose of rosuvastatin in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) RCT achieved greater LDL-C lowering and greater reductions in ASCVD outcomes (S4.3-7). This corroborates meta-analyses demonstrating that in those at risk, net benefit of LDL-C-lowering therapy is greater with greater reductions in LDL-C (S4.3-2, S4.3-10).

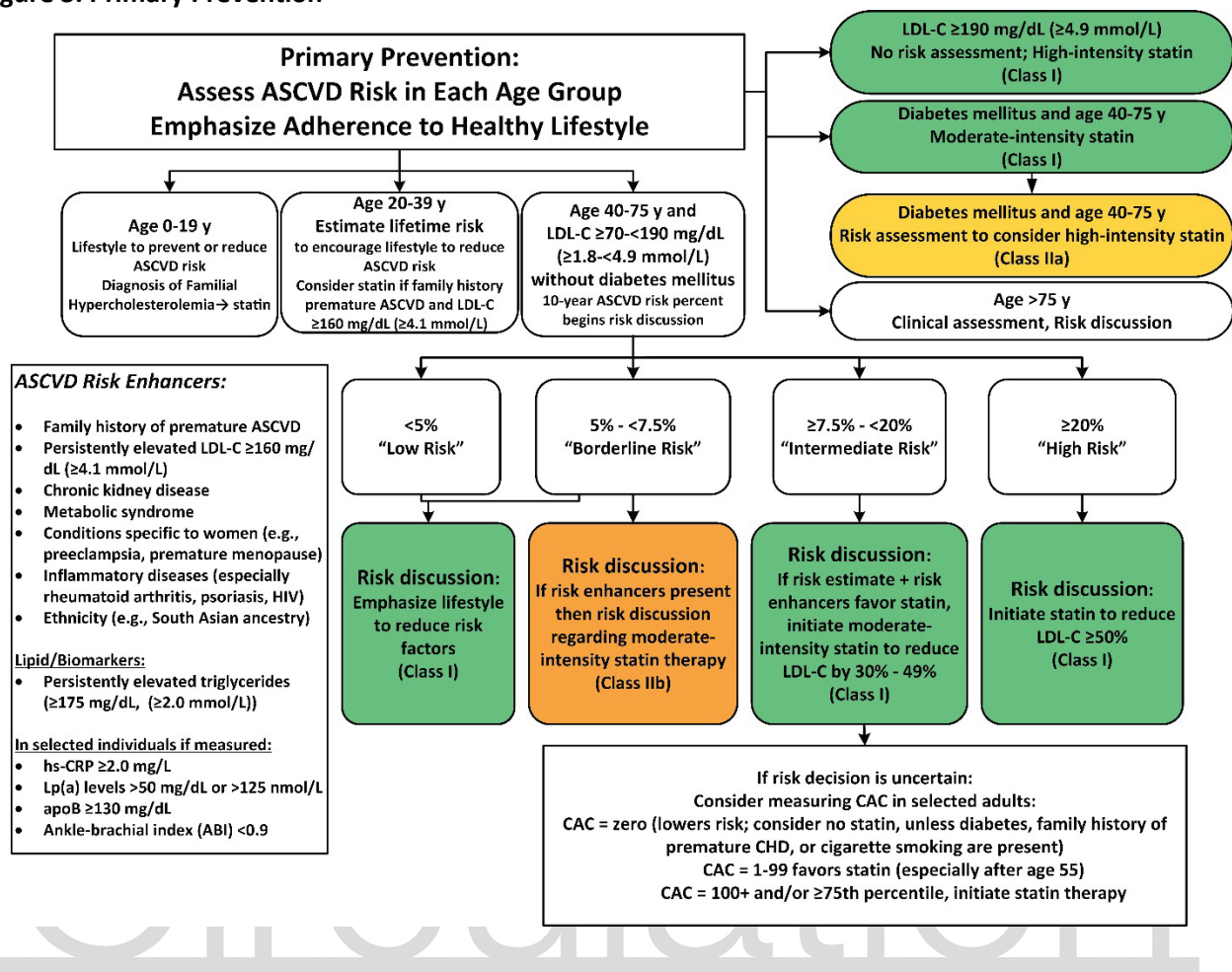
2. If in the context of a risk discussion, maximal ASCVD risk reduction is desired, it is reasonable to use a high-intensity statin to lower LDL-C by  $\geq 50\%$ . This provides increased benefit, especially when 10-year ASCVD risk is  $\geq 20\%$ . JUPITER enrolled men  $\geq 50$  years of age and women  $\geq 60$  years of age with high-sensitivity C-reactive protein values  $\geq 2.0$  mg/L and LDL-C  $< 130$  mg/dL. Participants randomly assigned to 20 mg per day of rosuvastatin achieved a median LDL-C reduction of 50% and a highly significant ASCVD risk reduction at 1.9 years (S4.3-7). Importantly, the magnitude of the percent LDL-C reduction achieved determined benefit (S4.3-29). The USPSTF systematic review of statin therapy in primary prevention showed a reduced risk of all-cause and cardiovascular mortality and ASCVD events and noted greater absolute benefits in those at greater baseline risk (S4.3-5), consistent with other high-quality systematic reviews and meta-analyses (S4.3-2, S4.3-8, S4.3-35). This underscores the need for aggressive and safe risk reduction in the highest-risk groups and the need for follow-up LDL-C testing to determine adherence and adequacy of effect of the statin prescribed (S4.3-1).
3. Most patients 40 to 75 years of age with diabetes are at intermediate or high risk (PCE  $\geq 7.5\%$  10-year risk) of ASCVD events (S4.3-15, S4.3-16, S4.3-18). Three of 4 double-blinded primary-prevention RCTs of moderate statin therapy in large cohorts with diabetes in this age range showed significant reductions in ASCVD events (S4.3-11, S4.3-12, S4.3-14, S4.3-17). A meta-analysis of these trials found that moderate-intensity statin therapy was associated with a risk reduction of 25% (S4.3-13), similar to people without diabetes and with no apparent difference in benefit between type 1 diabetes mellitus and T2DM. Therefore, moderate-intensity statin therapy is indicated for primary prevention in patients 40 to 75 years of age with diabetes.
4. Patients with primary severe hypercholesterolemia (LDL-C  $\geq 190$  mg/dL [ $\geq 4.9$  mmol/L]) have a high risk of ASCVD (S4.3-23) and premature and recurrent coronary events. Although no randomized, placebo-controlled trials of statin therapy have been done exclusively in subjects with LDL-C  $\geq 190$  mg/dL, a placebo-controlled primary-prevention study performed in men with a mean baseline LDL-C of  $192 \pm 17$  mg/dL demonstrated a reduced incidence of MI and cardiovascular death in those receiving pravastatin 40 mg daily (S4.3-24). These findings were extended in a post hoc analysis of 2,560 exclusively primary-prevention subjects in that RCT and in a 20-year observational post-trial long-term follow-up study (S4.3-37). Because moderate- or high-intensity statins have been shown to reduce ASCVD risk and because high-intensity statins provide greater ASCVD risk reduction than do moderate-intensity statins or placebo (S4.3-2), maximally tolerated statin therapy should be administered to patients with LDL-C  $\geq 190$  mg/dL. Please refer to the 2018 cholesterol guideline (S4.3-1) for recommendations on the use of non-statin therapies in these patients.
5. The occurrence of a first ASCVD event in patients 40 to 75 years of age with diabetes is associated with increased morbidity and mortality compared with those without diabetes, which places a particularly high premium on primary prevention in individuals with diabetes in that age range. Although trials using moderate-intensity statin therapy have demonstrated significant benefit in such individuals, the residual risk in the statin treatment groups in these trials remained high. (e.g., 8.5% had major cardiovascular events in 3.8 years) (S4.3-13). The benefit from statin therapy is related to both global risk and intensity of treatment (S4.3-2), and no RCTs of high-intensity statin therapy have been carried out in cohorts of patients exclusively with diabetes. On the basis of these considerations and the fact that patients with diabetes have a higher trajectory of lifetime risk than do those without

diabetes, high-intensity statin therapy is preferred in patients with diabetes as they develop risk modifiers (Table 5).

6. Knowledge of risk-enhancing factors (Table 3 in Section 2.2.) is useful for all individuals but particularly for those at intermediate risk (ASCVD risk of 7.5% to  $\leq 20\%$ ). For example, in an RCT (S4.3-38), a family history of premature ASCVD identified women  $\geq 60$  years of age with elevated hsCRP and without ASCVD who benefitted from high-intensity statin therapy. Those with primary LDL-C elevations of  $\geq 160$  mg/dL ( $\geq 4.1$  mmol/L) have elevated lifetime ASCVD risk and benefit from statin therapy (S4.3-33, S4.3-36). Increased ASCVD risk is seen with metabolic syndrome (S4.3-31); inflammatory diseases, including psoriasis (S4.3-39) and rheumatoid arthritis; and HIV when treated with protease inhibitors (S4.3-40). The presence of risk-enhancing factors may affect the threshold for statin initiation or intensification. Lipoprotein (a) levels, especially in those with a family history of premature ASCVD, can increase risk (S4.3-27). However, no available RCT evidence supports lipoprotein (a) levels as a target of therapy. Moderate primary elevations of triglycerides, non-HDL-C (total cholesterol – HDL-C), and, if measured, apolipoprotein B can improve selection of those at increased ASCVD risk (S4.3-33).
7. In adults at intermediate risk, coronary artery calcium measurement can be effective for meaningfully reclassifying risk in a large proportion of individuals (S4.3-41–S4.3-55). In such intermediate-risk adults, those with coronary artery calcium  $\geq 100$  AU or coronary artery calcium  $\geq 75$ th percentile have ASCVD event rates for which initiation of statin therapy is reasonable (S4.3-41). Those with coronary artery calcium scores of zero appear to have 10-year event rates in a lower range for which statin therapy may be of limited value. For those with coronary artery calcium scores of 1 to 99 AU, 10-year ASCVD event rates are 3.8%, 6.5%, and 8.3% for adults 45 to 54, 55 to 64, and 65 to 74 years of age, respectively (S4.3-34), indicating that risk reclassification is modest for individuals with coronary artery calcium scores of 1 to 99. Therefore, for patients with coronary artery calcium scores of 1 to 99, it is reasonable to repeat the risk discussion. If these patients remain untreated, repeat coronary artery calcium measurement in 5 years may have some value, but data are limited (S4.3-56, S4.3-57). Selected examples of candidates who might benefit from knowing that their coronary artery calcium scores are zero are listed in Table 6. Clinicians should not downclassify risk in patients who have coronary artery calcium scores of zero but who are persistent cigarette smokers, have diabetes, have a family history of ASCVD, or, possibly, have chronic inflammatory conditions. In the presence of these conditions, a coronary artery calcium of zero does not rule out risk from noncalcified plaque or increased risk of thrombosis (S4.3-58).
8. Benefit from statin therapy is also seen in lower-risk individuals (S4.3-35). For those in the 5% to  $< 7.5\%$  risk range, available generic statins are cost-effective (S4.3-59). Nonetheless, the challenge among those in a lower ASCVD risk category is to include those who would benefit, yet avoid casting too wide a net, to minimize treating those who would derive little benefit from statins. This risk group benefits greatly from a clinician–patient risk discussion. Clinicians should assess priorities for health care, perceived ASCVD risk, and prior risk reduction experiences and should use best practices for communicating risk to arrive at a shared risk decision. The presence of risk-enhancing factors is probably the best indicator favoring initiation of statin therapy (Table 3 in Section 2.2.) (S4.3-60). Although a coronary artery calcium score can be useful in select individuals, it will be positive less often in this lower-risk group than in those with higher levels of ASCVD risk and is not recommended routinely (S4.3-41).



Figure 3. Primary Prevention



Colors correspond to Class of Recommendation in Table 1.

ABI indicates ankle-brachial index; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a).

Reproduced with permission from Grundy et al. (S4.3-1). Copyright © 2018, American Heart Association, Inc., and American College of Cardiology Foundation.

**Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus**

Risk Enhancers in Diabetic Patients
<ul style="list-style-type: none"> <li>• Long duration (<math>\geq 10</math> years for T2DM (S4.3-61) or <math>\geq 20</math> years for type 1 diabetes mellitus (S4.3-16))</li> <li>• Albuminuria <math>\geq 30</math> mcg albumin/mg creatinine (S4.3-62)</li> <li>• eGFR <math>&lt; 60</math> mL/min/1.73 m<sup>2</sup> (S4.3-62)</li> <li>• Retinopathy (S4.3-63)</li> <li>• Neuropathy (S4.3-64)</li> <li>• ABI <math>&lt; 0.9</math> (S4.3-65, S4.3-66)</li> </ul>

ABI indicates ankle-brachial index; eGFR, estimated glomerular filtration rate; and T2DM, type 2 diabetes mellitus. Reproduced with permission from Grundy et al. (S4.3-1). Copyright © 2018, American Heart Association, Inc., and American College of Cardiology Foundation.

**Table 6. Selected Examples of Candidates for Coronary Artery Calcium Measurement Who Might Benefit From Knowing Their Coronary Artery Calcium Score Is Zero**

Coronary Artery Calcium Measurement Candidates Who Might Benefit from Knowing Their Coronary Artery Calcium Score Is Zero
<ul style="list-style-type: none"> <li>• Patients reluctant to initiate statin who wish to understand their risk and potential for benefit more precisely</li> <li>• Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms</li> <li>• Older patients (men 55–80 y of age; women 60–80 y of age) with low burden of risk factors (S4.3-53) who question whether they would benefit from statin therapy</li> <li>• Middle-aged adults (40–55 y of age) with PCE-calculated 10-year risk of ASCVD 5% to <math>&lt; 7.5\%</math> with factors that increase their ASCVD risk, although they are in a borderline risk group.</li> </ul>

Caveats: If patient is at intermediate risk and if a risk decision is uncertain and a coronary artery calcium score is obtained, it is reasonable to withhold statin therapy unless higher-risk conditions, such as cigarette smoking, family history of premature ASCVD, or diabetes mellitus, are present and to reassess coronary artery calcium score in 5 to 10 years. Moreover, if coronary artery calcium scoring is recommended, it should be performed in facilities that have current technology and expertise to deliver the lowest radiation possible.

ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and PCE, pooled cohort equations.

Reproduced with permission from Grundy et al. (S4.3-1). Copyright © 2018, American Heart Association, Inc., and American College of Cardiology Foundation.

#### 4.4. Adults With High Blood Pressure or Hypertension

Recommendations from the 2017 Hypertension Clinical Practice Guidelines (S4.4-1) are adapted below.

Recommendations for Adults With High Blood Pressure or Hypertension		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 13 and 14</a> .		
COR	LOE	Recommendations
I	A	<p><b>1. In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include:</b></p> <ul style="list-style-type: none"> <li>• weight loss (S4.4-2–S4.4-5);</li> <li>• a heart-healthy dietary pattern (S4.4-6–S4.4-8);</li> <li>• sodium reduction (S4.4-9–S4.4-13);</li> <li>• dietary potassium supplementation (S4.4-14–S4.4-18);</li> <li>• increased physical activity with a structured exercise program (S4.4-3, S4.4-5, S4.4-11, S4.4-19–S4.4-23); and</li> <li>• limited alcohol (S4.4-24–S4.4-29).</li> </ul> <p>Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines (S4.4-1).</p>
	SBP: A	<p><b>2. In adults with an estimated 10-year ASCVD risk* of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD (S4.4-30–S4.4-38).</b></p> <p>Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines (S4.4-1).</p>
	DBP: C-EO	
	SBP: B-R <sup>SR</sup>	<p><b>3. In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended (S4.4-33, S4.4-39–S4.4-42).</b></p> <p>Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines (S4.4-1).</p>
	DBP: C-EO	
	SBP: B-R <sup>SR</sup>	<p><b>4. In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended (S4.4-43–S4.4-48).</b></p> <p>Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines (S4.4-1).</p>
	DBP: C-EO	
I	SBP: B-R <sup>SR</sup>	<p><b>5. In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg (S4.4-33, S4.4-47, S4.4-49–S4.4-54).</b></p> <p>Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines (S4.4-1).</p>
	DBP: C-EO	

I	C-LD	<p><b>6. In adults with an estimated 10-year ASCVD risk &lt;10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended (S4.4-36, S4.4-55–S4.4-58).</b></p> <p>Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines (S4.4-1).</p>
IIb	SBP: B-NR	<p><b>7. In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable (S4.4-59–S4.4-62).</b></p>
	DBP: C-EO	<p>Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines (S4.4-1).</p>

\*ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD.

### Synopsis

In the United States, hypertension accounts for more ASCVD deaths than any other modifiable ASCVD risk factor (S4.4-63). The prevalence of hypertension (defined as systolic blood pressure [SBP]  $\geq 130$  mm Hg or diastolic blood pressure [DBP]  $\geq 80$  mm Hg) among U.S. adults is 46%; is higher in blacks than in whites, Asians, and Hispanic Americans; and increases dramatically with increasing age (S4.4-64). In a meta-analysis of 61 prospective studies, a log-linear association was observed between SBP levels <115 to >180 mm Hg and DBP levels <75 to 105 mm Hg and risk of ASCVD (S4.4-55). In that analysis, 20-mm Hg higher SBP and 10-mm Hg higher DBP were each associated with a doubling in the risk of death from stroke, heart disease, or other vascular disease. An increased risk of ASCVD associated with higher SBP and DBP has been reported across a broad age spectrum, from 30 to >80 years of age. Although the relative risk of incident CVD associated with higher SBP and DBP is smaller at older ages, the corresponding high BP-related increase in absolute risk is larger in older persons ( $\geq 65$  years) given the higher absolute risk of CVD at an older age (S4.4-55). See Figure 4 for the BP thresholds and treatment recommendations algorithm and refer to the 2017 Hypertension Clinical Practice Guidelines for comprehensive details (S4.4-1).

### Recommendation-Specific Supportive Text

1. Nonpharmacological interventions are effective in lowering BP and may be sufficient to prevent hypertension and to achieve goal BP in some individuals with hypertension, and they are integral in the management of those on antihypertensive medication (S4.4-2, S4.4-3, S4.4-6, S4.4-7, S4.4-9–S4.4-11, S4.4-14, S4.4-15, S4.4-19, S4.4-20, S4.4-24). Furthermore, combining recommended nonpharmacological interventions has been shown to increase impact on BP reduction (S4.4-65). Nonpharmacological intervention is the preferred therapy for adults with elevated BP and an appropriate first-line therapy for adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of <10%. Adherence to and impact of nonpharmacological therapy should be assessed within 3 to 6 months. See Table 7 for recommended goals and approximate impact on SBP.
2. Meta-analyses and RCTs provide evidence for the benefit of BP-lowering medications on ASCVD prevention in adults with moderate to high ASCVD risk and SBP  $\geq 130$  mm Hg or DBP  $\geq 80$  mm Hg (S4.4-32, S4.4-33, S4.4-36, S4.4-37, S4.4-66), with significant outcome reductions demonstrated in stroke, heart failure, coronary events, and death. Significant reductions were seen in stroke and all-cause death at SBP <130 mm Hg and in stroke at DBP <80 mm Hg (S4.4-37). SPRINT (Systolic Blood Pressure Intervention Trial) provides additional support for the use of BP-lowering medications in patients without CVD at SBP levels  $\geq 130$  mm Hg (S4.4-34).

Antihypertensive drug treatment that is based on overall ASCVD risk assessment combined with BP levels may prevent more CVD events than treatment that is based on BP levels alone (S4.4-67–S4.4-70). These meta-analyses are consistent in concluding that lowering of BP results in larger absolute risk reduction in higher-risk individuals, regardless of baseline treated or untreated BP  $\geq 130/80$  mm Hg and irrespective of the specific cause of elevated risk. These analyses indicate that the benefit of treatment outweighs the potential harm at threshold BP  $\geq 130/80$  mm Hg.

3. Meta-analyses and systematic reviews of trials that compare more intensive BP reduction to standard BP reduction report that more intense BP lowering significantly reduces the risk of stroke, coronary events, major cardiovascular events, and cardiovascular mortality (S4.4-33, S4.4-39, S4.4-47, S4.4-71). Achieving an additional 10-mm Hg reduction in SBP reduced CVD risk when compared with an average BP of 158/82 to 143/76 mm Hg, 144/85 to 137/81 mm Hg, and 134/79 to 125/76 mm Hg. Patients with diabetes mellitus and CKD were included in the analyses (S4.4-39).
4. Most patients with CKD have a 10-year ASCVD risk  $\geq 10\%$ , requiring initiation of antihypertensive drug therapy at BP  $\geq 130/80$  mm Hg. In SPRINT, the participants with CKD who were randomized to intensive therapy (SBP target  $< 120$  mm Hg) derived the same beneficial reduction in CVD events and all-cause mortality that was seen among in their counterparts without CKD, with no difference seen in the principal renal outcome (S4.4-34). Other RCTs (S4.4-43, S4.4-44) that evaluated the effect of differing BP goals on CKD progression in patients with CKD demonstrated no benefit for more intensive BP reduction, although post hoc follow-up analyses favored lower targets in patients with more severe proteinuria (S4.4-72). These trials were underpowered to detect differences in CVD event rates. Several meta-analyses and systematic reviews support more intensive BP treatment to reduce cardiovascular events but do not demonstrate a reduction in the rate of progression of kidney disease (S4.4-31, S4.4-33, S4.4-39). More intensive BP treatment may result in a modest reduction in glomerular filtration rate, which is thought to be primarily attributable to a hemodynamic effect and may be reversible. Electrolyte abnormalities are also more likely during intensive BP treatment.
5. Most adults with diabetes mellitus a 10-year ASCVD risk  $\geq 10\%$ , requiring initiation of antihypertensive drug therapy at BP  $\geq 130/80$  mm Hg and a treatment goal of  $< 130/80$  mm Hg (S4.4-73). Several meta-analyses of RCTs included all trials with a difference in BP levels (S4.4-31, S4.4-71) and supported lowering BP to  $< 130/80$  mm Hg among those with diabetes mellitus. Two meta-analyses addressing target BP in adults with diabetes mellitus restricted the analysis to RCTs that randomized patients to different BP levels (S4.4-33, S4.4-47). Target BP of 133/76 mm Hg provided significant benefit compared with that of 140/81 mm Hg for major cardiovascular events, MI, stroke, albuminuria, and retinopathy progression (S4.4-33).

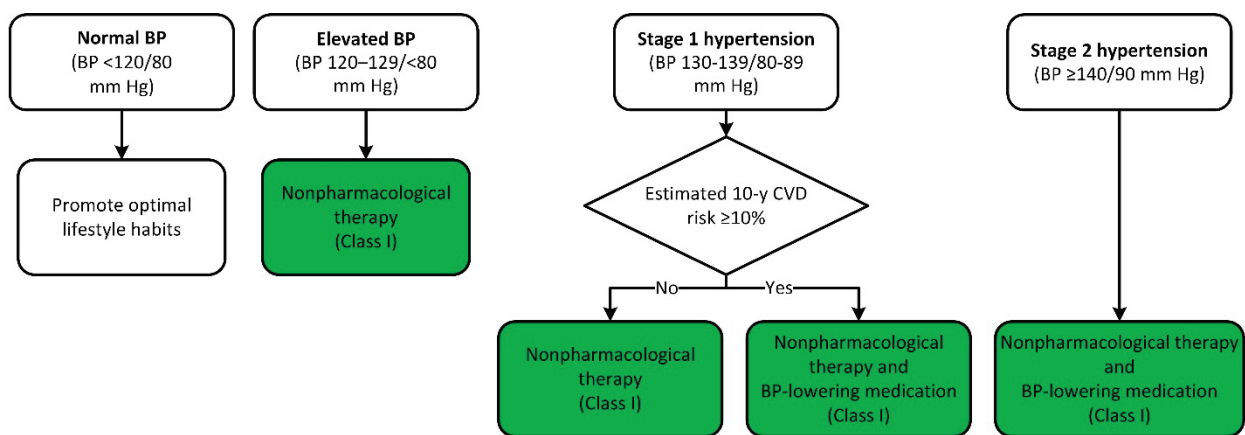
In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (S4.4-51), lowering the BP target (SBP  $< 120$  mm Hg) did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events and was associated with greater risk of adverse events, such as self-reported hypotension and a reduction in estimated glomerular filtration rate. Secondary analyses of the ACCORD trial demonstrated a significant outcome benefit of stroke risk reduction in the intensive BP/ standard glycemic group (S4.4-74).

6. The relationship of SBP with CVD risk is continuous across levels of SBP and similar across groups that differ in level of absolute risk (S4.4-55). The relative risk reduction attributable to BP-lowering medication therapy is consistent across the range of absolute risk observed in trials (S4.4-36), suggesting that relative risk reduction may be similar at lower levels of absolute risk. Indirect support is also provided by evidence from trials using BP-lowering medications to reduce the risk of developing higher levels of BP (S4.4-75, S4.4-76). In the HOPE-3 (Heart Outcomes Prevention Evaluation-3) BP Trial, there was no evidence of short-term benefit during treatment of adults (average age 66 years) with a relatively low risk of CVD (3.8% CVD event rate during 5.6 years of follow-up). However,

subgroup analysis suggested benefit in those with an average SBP >140 mm Hg (and a CVD risk of 6.5% during the 5.6 years of follow-up) (S4.4-59).

7. The treatment of patients with hypertension without elevated risk has been systematically understudied because lower-risk groups would require prolonged follow-up to have a sufficient number of clinical events to provide useful outcomes data. Although there is clinical trial evidence that both drug and nondrug therapy will interrupt the progressive course of hypertension, there is no trial evidence that this treatment decreases CVD morbidity and mortality. The clinical trial evidence is strongest for a target BP of 140/90 mm Hg in this population. However, observational studies suggest that these individuals often have a high lifetime risk and would benefit from BP control earlier in life (S4.4-77).

**Figure 4. BP Thresholds and Recommendations for Treatment**



Colors correspond to Class of Recommendation in Table 1.

BP indicates blood pressure; and CVD, cardiovascular disease.

Adapted with permission from Whelton et al. (S4.4-1). Copyright © 2017, American College of Cardiology Foundation and the American Heart Association, Inc.

**Table 7. Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension\***

	Nonpharmacological Intervention	Goal	Approximate Impact on SBP		
			Hypertension	Normotension	Reference
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	-5 mm Hg	-2/3 mm Hg	(S4.4-2)
Healthy diet	DASH dietary pattern <sup>†</sup>	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	-11 mm Hg	-3 mm Hg	(S4.4-7, S4.4-8)
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.	-5/6 mm Hg	-2/3 mm Hg	(S4.4-10, S4.4-12)
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	-4/5 mm Hg	-2 mm Hg	(S4.4-14)





Physical activity	Aerobic	<ul style="list-style-type: none"> <li>90–150 min/wk</li> <li>65%–75% heart rate reserve</li> </ul>	-5/8 mm Hg	-2/4 mm Hg	(S4.4-19, S4.4-20)
	Dynamic resistance	<ul style="list-style-type: none"> <li>90–150 min/wk</li> <li>50%–80% 1 rep maximum</li> <li>6 exercises, 3 sets/exercise, 10 repetitions/set</li> </ul>	-4 mm Hg	-2 mm Hg	(S4.4-19)
	Isometric resistance	<ul style="list-style-type: none"> <li>4 × 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk</li> <li>8–10 wk</li> </ul>	-5 mm Hg	-4 mm Hg	(S4.4-21, S4.4-78)
Moderation in alcohol intake	Alcohol consumption	<p>In individuals who drink alcohol, reduce alcohol† to:</p> <ul style="list-style-type: none"> <li>Men: ≤2 drinks daily</li> <li>Women: ≤1 drink daily</li> </ul>	-4 mm Hg	-3 mm Hg	(S4.4-20, S4.4-24, S4.4-25)

\*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.

†Detailed information about the DASH diet is available via the NHLBI (S4.4-81) and Dashdiet.org (S4.4-82).

‡In the United States, 1 “standard” drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol) (S4.4-80).

BP indicates blood pressure; DASH, Dietary Approaches to Stop Hypertension; NHLBI, National Heart, Lung, and Blood Institute; and SBP, systolic blood pressure.

Reproduced with permission from Whelton et al. (S4.4-1). Copyright © 2017, American College of Cardiology Foundation and the American Heart Association, Inc.





## 4.5. Treatment of Tobacco Use

Recommendations for Treatment of Tobacco Use		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 15</a> and <a href="#">16</a> .		
COR	LOE	Recommendations
I	A	1. All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation (S4.5-1).
I	A	2. To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit (S4.5-2).
I	A	3. In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates (S4.5-2, S4.5-3).
I	B-NR	4. In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk (S4.5-4, S4.5-5).
IIa	B-R	5. To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system (S4.5-1).
III: Harm	B-NR	6. All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk (S4.5-6).

### Synopsis

Tobacco use is the leading preventable cause of disease, disability, and death in the United States (S4.5-7). Smoking and smokeless tobacco (e.g., chewing tobacco) use increases the risk of all-cause mortality and is a cause of ASCVD (S4.5-4, S4.5-5). Secondhand smoke is a cause of ASCVD and stroke (S4.5-6), and almost one-third of CHD deaths are attributable to smoking and exposure to secondhand smoke. Even low levels of smoking increase risks of acute MI; thus, reducing the number of cigarettes per day does not totally eliminate risk (S4.5-8). Healthy People 2020 recommends that cessation treatment in clinical care settings be expanded, with access to proven cessation treatment provided to all tobacco users (S4.5-9). Electronic Nicotine Delivery Systems (ENDS), often called e-cigarettes (S4.5-10), are a new class of tobacco product that emit aerosol containing fine and ultrafine particulates, nicotine, and toxic gases that may increase risk of cardiovascular and pulmonary diseases (S4.5-11). Arrhythmias and hypertension with e-cigarette use have also been reported (S4.5-12). Chronic use is associated with persistent increases in oxidative stress and sympathetic stimulation in young, healthy subjects (S4.5-13).

### Recommendation-Specific Supportive Text

1. On the basis of on the U.S. Public Health Service's Clinical Practice Guideline for Treating Tobacco Use and Dependence (S4.5-14, S4.5-15), the USPSTF recommended (Grade A) in 2003 and reaffirmed in 2009 that clinicians ask all adults about tobacco use (S4.5-2). Treating tobacco use status as a vital sign and recording tobacco use status in the health record at every healthcare visit not only increases the rate of tobacco treatment but also improves tobacco abstinence (S4.5-15, S4.5-16). Office-wide screening systems (e.g., chart stickers, computer prompts) that expand the vital signs to include tobacco use status (current, former, never) can facilitate tobacco cessation (S4.5-15). Because many people who use tobacco do not report it, using multiple questions to assess tobacco use status may improve accuracy and disclosure. For example, clinicians *should ask*, "Have you smoked any tobacco product in the past 30 days, even a puff?" "Have you vaped or 'juuled' in the past 30 days, even a puff?" "Have you used any other tobacco product in the past 30 days?" If these questions are answered with "yes," the patient is considered a current smoker. Clinicians should *avoid asking* "Are

you a smoker?” or “Do you smoke?” because people are less likely to report tobacco use when asked in this way (S4.5-17).

2. Tobacco users are more likely to quit after 6 months when clinicians strongly advise adults to quit using tobacco than when clinicians give no advice or usual care (S4.5-2). To help patients quit, it is critically important to use language that is clear and strong, yet compassionate, nonjudgmental, and personalized, to urge every tobacco user to quit (S4.5-15). For example, “The most important thing you can do for your health is to quit tobacco use. I (we) can help.” The ASCVD benefits of quitting are immediate (S4.5-18). The best and most effective treatments are those that are acceptable to and feasible for an individual patient; clinicians should consider the patient’s specific medical history and preferences and offer to provide tailored strategies that work best for the patient (S4.5-3, S4.5-19).
3. In alignment with previous expert consensus regarding strategies for tobacco cessation (S4.5-19), Table 8 summarizes recommended behavioral interventions and pharmacotherapy for tobacco treatment. There are 7 FDA-approved cessation medications, including 5 forms of nicotine replacement. *Note that the black box warnings about neuropsychiatric events have been removed by the FDA* (S4.5-20, 4.5-21). The net benefit of FDA-approved tobacco-cessation pharmacotherapy and behavioral interventions (even just 3 minutes of practical advice), alone or combined, in nonpregnant adults ( $\geq 18$  years of age) who smoke is substantial. The net benefit of behavioral interventions for tobacco cessation on perinatal outcomes and smoking abstinence in pregnant women who smoke is substantial. However, the evidence on pharmacotherapy for tobacco cessation in pregnant women is insufficient; the balance of benefits and harms cannot be determined. Among hospitalized adults who use tobacco, intensive counseling with continued supportive follow-up contacts for at least one month after discharge is recommended (S4.5-22).

ENDS are not recommended as a tobacco treatment method. The evidence is unclear about whether ENDS are useful or effective for tobacco treatment, and they may be potentially harmful. The evidence on the use of ENDS as a smoking-cessation tool in adults (including pregnant women) and adolescents is insufficient (S4.5-23) or limited (S4.5-24). The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety.

4. Cigarette smoking remains a strong, independent risk factor for ASCVD events and premature death (S4.5-4). Even among older adults, tobacco cessation is beneficial in reducing excess risk (S4.5-5). The risk of heart failure and death for most former smokers is similar to that of never smokers after  $>15$  years of tobacco cessation (S4.5-25). In the National Health Interview Survey, smoking was strongly associated with ASCVD in young people after adjustment for multiple risk factors (S4.5-26), which is why abstinence from an early age is recommended.
5. Tobacco use dependence is a chronic disease that requires highly skilled chronic disease management. It is a reasonable expectation that every health system or practice should dedicate trained staff to tobacco treatment. Healthcare professionals who receive training in tobacco treatment are more likely to ask about tobacco use, offer advice to quit, provide behavioral interventions, follow up with individuals, and increase the number of tobacco users who quit (S4.5-1). Participants who earn a certificate in tobacco treatment practice demonstrate a nationally recognized level of training and skill acquisition in treating tobacco dependence (S4.5-27). A Tobacco Treatment Specialist is a professional who possesses the skills, knowledge, and training to provide effective, evidence-based interventions for tobacco dependence across a range of intensities (S4.5-28). A list of accredited Tobacco Treatment Specialist programs is available here: <http://cttpp.org/accredited-programs> (S4.5-29).
6. Secondhand smoke exposure is known to cause CVD (S4.5-6) and stroke (S4.5-16) in nonsmokers, and it can lead to immediate adverse events (S4.5-30). There is no safe lower limit of exposure to

secondhand smoke (S4.5-31). Even brief exposure to secondhand smoke can trigger an MI (S4.5-30, S4.5-32). Even though exposure to secondhand smoke has steadily decreased over time, certain subgroups remain exposed to secondhand smoke in homes, vehicles, public places, and workplaces. It is estimated that 41,000 preventable deaths per year occur in adult nonsmokers as a result of exposure to secondhand smoke (S4.5-33). The U.S. Department of Housing and Urban Development prohibited the use of combustible tobacco products in all public housing living units, indoor common areas, and public housing agency administrative office buildings, extending to all outdoor areas up to 25 feet from public housing buildings (S4.5-34). Therefore, the present writing committee recommends that clinicians advise patients to take precautions against exposure to secondhand smoke and aerosol from all tobacco products, such as by instituting smoking restrictions (including ENDS) inside all homes and vehicles and within 25 feet from all entryways, windows, and building vents.



# Circulation

**Table 8. Highlights of Recommended Behavioral and Pharmacotherapy Tobacco Treatment Modalities for Prescribers\***

Timing of Behavioral Interventions†			
<3 min of tobacco status assessment with cessation counseling at each clinic encounter		>3-10 min of tobacco status assessment with cessation counseling at each clinic encounter	>10 min of tobacco status assessment with cessation counseling at each clinic encounter
Treatment		Dosing‡	Precautions
NRT*			
Patch	21 mg, 14 mg, or 7 mg	Starting dose: 21 mg for >10 CPD; 14 mg for <10 CPD	Local irritation possible; avoid with skin disorders; may remove for sleep if needed
Gum	2 mg or 4 mg	Starting dose: 4 mg if first tobacco use is ≤30 min after waking; 2 mg if first tobacco use is >30 min after waking; maximum of 20 lozenges or 24 pieces of gum/d. Chew and park gum*	Hiccups/dyspepsia possible; avoid food or beverages 15 min before and after use
Lozenge	2 mg or 4 mg		
Nasal spray	10 mg/mL	Starting dose: 1-2 doses/h (1 dose=2 sprays); maximum of 40 doses/d	Local irritation possible; avoid with nasal or reactive airway disorders
Oral inhaler	10, 10-mg cartridge	Starting dose: Puff for 20 min/cartridge every 1-2 h; maximum 6-16 cartridges/d; taper over 3-6 mo§	Cough possible; avoid with reactive airway disorders
Other			
Bupropion (Zyban [GlaxoSmithKline], Wellbutrin SR [GlaxoSmithKline])	150 mg SR	150 mg once daily (am) for 3 d; then 150 mg twice daily; may use in combination with NRT (S4.5-21)	Avoid with history/risk of seizures, eating disorders, MAO inhibitors, or CYP 2D6 inhibitor
Varenicline (Chantix [Pfizer])	0.5 mg or 1 mg	0.5 mg once daily (am) for 3 d; then 0.5 mg twice daily for 4 d; then 1 mg twice daily (use start pack followed by continuation pack) for 3-6 mo	Nausea common; take with food. Renal dosing required. Very limited drug interactions; near-exclusive renal clearance.

\*CPD can guide dosing. 1 CPD is ≈1-2 mg of nicotine. *Note: Use caution with all NRT products for patients with recent (≤2 wk) MI, serious arrhythmia, or angina; patients who are pregnant or breastfeeding; and adolescents.*

†Timing of assessment relates to ICD-10 coding.

‡Dose and duration can be titrated on the basis of response (S4.5-21).

§See Rx for Change for greater detail: <http://rxforchange.ucsf.edu> (S4.5-35).

|| The FDA has issued a removal of black box warnings about neuropsychiatric events (S4.5-20, S4.5-21).

am indicates morning; CPD, cigarettes smoked per day; FDA, U.S. Food and Drug Administration; ICD-10, *International Classification of Diseases, Tenth Revision*; MAO, monoamine oxidase; NRT, nicotine replacement; and SR, sustained release.

## 4.6. Aspirin Use

Recommendations for Aspirin Use		
Referenced studies that support recommendations are summarized in <a href="#">Online Data Supplements 17</a> and <a href="#">18</a> .		
COR	LOE	Recommendations
<b>IIb</b>	<b>A</b>	1. <b>Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (S4.6-1–S4.6-8).</b>
<b>III: Harm</b>	<b>B-R</b>	2. <b>Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults &gt;70 years of age (S4.6-9).</b>
<b>III: Harm</b>	<b>C-LD</b>	3. <b>Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (S4.6-10).</b>

### Synopsis

For decades, aspirin has been widely administered for ASCVD prevention. By irreversibly inhibiting platelet function, aspirin reduces risk of atherothrombosis but also increases risk of bleeding, particularly in the gastrointestinal tract (S4.6-11). Aspirin is well established for secondary prevention of ASCVD (S4.6-12) and is widely recommended for this indication (S4.6-13). However, in primary prevention, aspirin use is more controversial. Because persons without prior ASCVD are inherently less likely to have future ASCVD events than are those with a prior history, it is more challenging for clinicians and patients to balance benefits and harms of prophylactic aspirin for primary prevention. This uncertainty is reflected in international guidelines, where, for example, aspirin is not recommended in European guidelines for primary ASCVD prevention (S4.6-13) but is recommended in prior U.S. guidelines for selected primary prevention for adults who have elevated risk of ASCVD based on traditional risk factors (S4.6-14, S4.6-15). Adding to this controversy are more recently conducted primary-prevention trials that, in contrast to older trials (S4.6-12), have shown less overall benefit of prophylactic aspirin alongside coadministration of contemporary ASCVD preventive treatments, such as evidence-based hypertension and cholesterol therapies (S4.6-5–S4.6-9, S4.6-16, S4.6-17).

### Recommendation-Specific Supportive Text

1. To balance the benefits and risks, prior U.S. guidelines have recommended prophylactic aspirin only in the setting of elevated ASCVD risk (e.g., as calculated by risk estimators like the PCE or based on the presence of specific ASCVD risk factors) (S4.6-14, S4.6-18). Meta-regression analyses of historical trials show that observed ASCVD risk tracks reasonably well with baseline-estimated ASCVD risk (S4.6-19). In contrast, observed bleeding risk on aspirin is less well correlated with baseline-estimated ASCVD risk (S4.6-19). (A nonexhaustive list of scenarios associated with increased risk of bleeding includes: a history of previous gastrointestinal bleeding or peptic ulcer disease or bleeding from other sites, age >70 years, thrombocytopenia, coagulopathy, CKD, and concurrent use of other medications that increase bleeding risk, such as nonsteroidal anti-inflammatory drugs, steroids, direct oral anticoagulants, and warfarin.) In this context, post hoc study of older trials suggests that the benefit–risk ratio for prophylactic aspirin generally becomes more favorable at >10% estimated 10-year ASCVD risk (S4.6-15, S4.6-19). However, the relative benefits of aspirin, specifically in preventing nonfatal MI and perhaps stroke (with a trend to lower mortality) have been less evident in more recent trials (S4.6-9, S4.6-16, S4.6-17, S4.6-20). Similarly, in these recent trials, the estimated ASCVD risk has generally exceeded the actual risk observed during follow-up (S4.6-17). These recent data are the rationale for

the lower COR for prophylactic aspirin in the present guideline (Class IIb) and the removal of a specific PCE risk threshold as an inclusion criterion for aspirin consideration. These changes reflect the need to instead consider the totality of available evidence for ASCVD risk [inclusive, where appropriate, of risk-enhancing factors, such as strong family history of premature MI, inability to achieve lipid or BP or glucose targets, or significant elevation in coronary artery calcium score (S4.6-21)] and to also tailor decisions about prophylactic aspirin to patient and clinician preferences. Depending on risk factors present, a given patient and his/her clinician may decide that lowering the risk of MI (which has potentially serious long-term consequences not captured by clinical trials of 5 to 10 years' duration) is worth a slight excess risk of serious bleeding. Recent trials show that absolute risk for ASCVD events typically exceeds that of bleeding and, although the gap of relative benefit to relative harm for aspirin has narrowed, the number needed to treat to prevent an ASCVD event remains lower than the number needed to harm to cause bleeding. Others may feel that the benefit of prophylactic aspirin is comparable to the risk and may instead choose to focus on optimal control of other modifiable ASCVD risk factors. Therefore, a Class IIb recommendation remains more suitable than a Class III recommendation for adults 40 to 70 years of age. Given the narrow overall balance between benefits and harms of prophylactic aspirin, there is limited justification to use aspirin at doses >100 mg daily for primary prevention. Indeed, meta-analyses suggest that the ASCVD risk benefit for low-dose aspirin is equivalent to that for high-dose aspirin, but the bleeding risk is higher with high-dose aspirin. Recent observational studies motivate future research on the personalization of prophylactic aspirin dose according to patient-specific factors (e.g., weight) (S4.6-22), though we note that, regarding weight specifically, there was no evidence low-dose aspirin was any more effective in low-weight individuals than in high-weight individuals in the more recently published ASCEND (A Study of Cardiovascular Events in Diabetes) trial (S4.6-16), trial. Most importantly, recent clinical trials also teach us that low-dose prophylactic aspirin may be best justified among persons at high ASCVD risk who cannot achieve optimal control of other ASCVD risk factors (S4.6-23).

2. Prophylactic aspirin in primary-prevention adults >70 years of age is potentially harmful and, given the higher risk of bleeding in this age group, difficult to justify for routine use (S4.6-9). In addition, for adults <40 years of age, there is insufficient evidence to judge the risk–benefit ratio of routine aspirin for the primary prevention of ASCVD. However, one caveat is that, although routine use is not recommended in these settings, there is also insufficient evidence to comment on whether there may be select circumstances in which physicians might discuss prophylactic aspirin with adults <40 years of age or >70 years of age in the context of other known ASCVD risk factors (e.g., strong family history of premature MI, inability to achieve lipid or BP or glucose targets, or significant elevation in coronary artery calcium score). As inferred from the first recommendation, there is also no justification for the routine administration of low-dose aspirin for the primary prevention of ASCVD among adults at low estimated ASCVD risk. For example, in the recent ARRIVE (A Randomized Trial of Induction Versus Expectant Management) trial, observed average 10-year ASCVD risk was <10%, and the overall benefits of prophylactic aspirin by intention-to-treat were negligible (S4.6-17).
3. The accumulated trial and observational data to date support avoiding prophylactic aspirin in the setting of known risk factors for increased bleeding outcomes (S4.6-10). A nonexhaustive list of conditions associated with increased bleeding risk includes: a history of previous gastrointestinal bleeding or peptic ulcer disease or bleeding at other sites, age >70 years, thrombocytopenia, coagulopathy, CKD, and concurrent use of other medications that increase bleeding risk, such as nonsteroidal anti-inflammatory drugs, steroids, direct oral anticoagulants, and warfarin (S4.6-10).

## 5. Cost and Value Considerations

The growing need to consider value stems directly from the goal of achieving the best possible health outcomes with finite healthcare resources in the primary prevention of CVD (S5-1). *Value* in health care can be defined as the incremental health benefits of a therapy or procedure relative to its incremental net long-term costs. The consideration of cost and value in the guideline development process supports key goals, including: 1) enhancing overall value in the delivery of cardiovascular care and 2) involving healthcare professionals in the challenging care decisions that must be made to increase value in the U.S. healthcare system (S5-2).

The integration of value assessments into our national guidelines involves inherent methodological challenges, including: 1) variability in costs across different healthcare settings, 2) variability in costs and benefits across different patient subgroups, 3) variability over time, 4) variability in who bears the burden of the health outcome (i.e., typically the individual patient) versus who bears the burden of the healthcare cost (e.g., often spread beyond the individual to third-party payers, taxpayers), and 5) an inadequate literature base on which to render a sound, evidence-based assessment of certain specific therapies (S5-1, S5-2).

There are additional challenges specific to the prevention realm. As described in the 2011 AHA policy statement, “Value of Primordial and Primary Prevention in CVD” (S5-1):

*“Assessing the value of prevention in apparently healthy patients is generally more difficult than evaluating therapy for established disease because the time horizon to the clinical manifestation of disease is generally long—many decades in the young. Thus, it is difficult, perhaps impossible, to assess long-term effectiveness in terms of survival or quality-adjusted life-years (QALYs) or associated costs because of increasing uncertainty about outcome the further one tries to look into the future.”*



Furthermore, the principle of *discounting*, which places relative emphasis on current costs and benefits while deemphasizing downstream costs and benefits, creates disadvantages for prevention because costs often accrue in the present while the benefit may only be fully realized long into the future. These methodological challenges notwithstanding, prior AHA statements have highlighted the public policies, community efforts, and pharmacological interventions that are likely to be cost-effective and, at times, cost-saving prevention tactics compared with common benchmarks. For example, robust evidence suggests that both antihypertensive therapy (S5-3–S5-6) and statin therapy (S5-7–S5-9), particularly with low-cost generic drug formulations, are high-value interventions across a wide spectrum of risk and age strata.

The incorporation of the value category into clinical practice guidelines is one of several considerations in medical decision-making and resource allocation. Clinicians, researchers, and policymakers must continue to place cost-effective analyses in the proper context, extracting key value determinations while acknowledging the challenges in fully characterizing and incorporating the downstream benefits of a given therapeutic prevention tactic. Further research and methodological advances are needed to comprehensively characterize the full spectrum of benefits produced by the prevention approach, thereby rendering cost-effectiveness assessments more consequential to clinical practice.



## 6. Conclusion

Most ASCVD events are avoidable through primordial prevention (i.e., the prevention of risk factor development) and control of traditional cardiovascular risk factors. Tobacco avoidance is critically important for ASCVD prevention, and all adults should strive to engage in regular brisk physical activity most days of the week and adhere to a healthy dietary pattern to help lower future ASCVD risk. A diet high in fruits, vegetables, and whole grains is best. Fish, legumes, and poultry are the preferred sources of protein. Minimizing the consumption of *trans* fats, added sugars (including sugar-sweetened beverages), red meats, sodium, and saturated fats is also important. Clinicians should work in partnership with patients to assess their readiness for sustained lifestyle improvements, identify potential barriers to change, and encourage them to try to achieve measurable goals and continue to monitor their progress (S6-1). Finally, social determinants of ASCVD risk—and their impact on the patient's ability to prevent or treat risk factors—must be taken into account. Clinicians need to consider patients' health literacy and education levels and assess patients' motivation to improve their lifestyle habits.

The goal of the clinician is to match the intensity of preventive efforts with an individual's absolute risk of a future ASCVD event and with the individual's willingness and capacity to implement preventive strategies. Risk estimation is imperfect and based on group averages that are then applied to individual patients. The clinician must balance an understanding of a patient's estimated ASCVD risk with potential benefits and adverse risk from pharmacological therapy in the context of a risk discussion. To determine the appropriateness of pharmacological therapy after quantitative risk estimation in cases that are unclear, risk-enhancing factors or selective use of a coronary artery calcium measurement can inform decision-making for cholesterol-lowering or antihypertensive medication use in intermediate-risk individuals.

This primary-prevention guideline strives to provide clinicians with the information they need to help their patients reduce their risk of ASCVD and encourage them to make healthier lifestyle changes when needed.

**Presidents and Staff**

***American College of Cardiology***

C. Michael Valentine, MD, FACC, President

Timothy W. Attebery, MBA, FACHE, Chief Executive Officer

William J. Oetgen, MD, MBA, FACC, Executive Vice President, Science, Education, Quality, and Publishing

MaryAnne Elma, MPH, Senior Director, Science, Education, Quality, and Publishing

Amelia Scholtz, PhD, Publications Manager, Science, Education, Quality, and Publishing

***American College of Cardiology/American Heart Association***

Katherine A. Sheehan, PhD, Director, Guideline Strategy and Operations

Abdul R. Abdullah, MD, Senior Manager, Guideline Science

Thomas S.D. Getchius, Manager, Guideline Operations

***American Heart Association***

Ivor Benjamin, MD, FAHA, President

Nancy Brown, Chief Executive Officer

Rose Marie Robertson, MD, FAHA, Chief Science and Medicine Officer

Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations

Cammie Marti, PhD, MPH, RN, Science and Medicine Advisor, Office of Science Operations

Jody Hundley, Production and Operations Manager, Scientific Publications, Office of Science Operations

**Key Words:** ACC/AHA Clinical Practice Guidelines ■ guidelines ■ antihypertensive agents ■ aspirin ■ atherosclerosis ■ atherosclerotic cardiovascular disease ■ atrial fibrillation ■ behavior modification ■ behavior therapy ■ blood cholesterol ■ blood pressure ■ body mass ■ index ■ cardiovascular team-based care ■ cardiovascular ■ cardiovascular disease ■ cholesterol ■ chronic kidney disease ■ coronary artery calcium score ■ coronary disease ■ coronary heart disease ■ cost ■ diet ■ dietary patterns ■ dietary fats ■ dietary sodium ■ dyslipidemia ■ e-cigarettes ■ exercise ■ healthcare disparities ■ health services accessibility ■ heart failure ■ hypertension ■ LDL-cholesterol ■ diabetes mellitus ■ lifestyle ■ lipids ■ measurement ■ myocardial infarction ■ nicotine ■ nonpharmacological treatment ■ nutrition ■ physical activity ■ prejudice ■ primary prevention ■ psychosocial deprivation ■ public health ■ quality indicators ■ quality measurement ■ risk assessment ■ risk-enhancing factors ■ risk factors ■ risk reduction ■ risk reduction discussion ■ risk treatment discussion ■ secondhand smoke ■ sleep ■ smoking ■ smoking cessation ■ social determinants of health ■ socioeconomic factors ■ statin therapy ■ systems of care ■ tobacco ■ tobacco smoke pollution ■ treatment adherence ■ treatment outcomes ■ type 2 diabetes mellitus ■ waist circumference ■ weight loss

## Appendix 1. Search Criteria

The rapid review conducted by the Evidence-based Practice Center to complete this literature search, in the limited timeframe provided, built on existing systematic reviews conducted on behalf of the USPSTF.

Medical Subject Headings (MeSH) Terms	Key Words
<b><i>Nutrition and Diet</i></b>	
Search since the 2017 review (1)	
exp Diet/	diet*
exp Diet Therapy/	cardiovascular
Healthy Diet	coronary
Primary Prevention/	heart
	myocardial infarction
	MI
	CVD
	CHD
	cerebrovascular
	stroke
	microvascular
	mortality
	prevent*
<b><i>Obesity and Weight Loss</i></b>	
Search since the 2018 review (2)	
exp Obesity/	obes*
exp Weight Loss	overweight
Primary Prevention/	weight
	cardiovascular
	coronary
	heart
	myocardial infarction
	MI
	CVD
	CHD
	cerebrovascular
	stroke
	microvascular
	mortality
	prevent*
<b><i>Type 2 Diabetes Mellitus</i></b>	
Search since the 2015 review (3)	
exp Diabetes Mellitus, Type 2/	impaired fasting glucose
Prediabetic State/	impaired glucose tolerance
Glucose Intolerance/	lfg
Primary Prevention/	lgt
	prediabetes*
	type 2 diabet*



Medical Subject Headings (MeSH) Terms	Key Words
	DM
	cardiovascular
	coronary
	heart
	myocardial infarction
	MI
	CVD
	CHD
	cerebrovascular
	stroke
	microvascular
	mortality
	prevent*
<b>Tobacco Use</b>	
Search since the 2015 review (4)	
Smoking/	smoking
exp "Tobacco Use Cessation"/	cigarette*
"Tobacco Use Disorder"/	tobacco
Electronic Cigarettes/	nicotine
Primary Prevention/	vape
	vaping
	e-cigarette
	electronic cigarette
	electronic nicotine delivery system*
	ENDS
	cardiovascular
	coronary
	heart
	myocardial infarction
	MI
	CVD
	CHD
	cerebrovascular
	stroke
	microvascular
	mortality
	prevent*
<b>Aspirin Use</b>	
Search since the 2016 review (5)	
Aspirin	aspirin
exp Cerebrovascular Disorders/	acetylsalicylic acid
exp Cardiovascular Diseases/	clopidogrel
Primary Prevention/	cardiovascular
	coronary



Medical Subject Headings (MeSH) Terms	Key Words
	heart
	myocardial infarction
	MI
	CVD
	CHD
	cerebrovascular
	stroke
	microvascular
	mortality
	prevent*
Medical Subject Headings (MeSH) Terms	Key Words
<b><i>Social Determinants of Health</i></b>	
Search limited to English. No date restrictions (conducted 7/11/2018) Similar articles searches were also conducted where potentially highly relevant papers were found	
NONE SPECIFIED, BUT DUE TO AUTOMATIC TERM MAPPING IN PUBMED, SOME MeSH TERMS MAY HAVE BEEN EMPLOYED	Social determinants of health
	Equity
	Social status
	Social deprivation
	Neighborhood
	Neighborhood conditions
	Uninsured
	Housing
	Immigration
	Adverse childhood events
	Social gradient
	Educational status
	Inequalities
	Sexuality
	Atherosclerosis
	cardiovascular
<b><i>Team Based Care</i></b>	
Search limited to English, 1/1/2010-10/14/2018 (though earlier articles may have been identified through related articles search) Related articles searches were also conducted where potentially highly relevant papers were found	
NONE SPECIFIED, BUT DUE TO AUTOMATIC TERM MAPPING IN PUBMED, SOME MeSH	team



Medical Subject Headings (MeSH) Terms	Key Words
TERMS MAY HAVE BEEN EMPLOYED	
	Team care
	Collaborative care
	Multidisciplinary
	“team based”
	“team approach”
	prevention
	Primary prevention
	Cardiovascular disease,
	Cholesterol
	Aspirin
	Smoking
	Obesity
	Heart disease
	Atherosclerosis
	stroke
<b>Shared Decision Making</b>	
Search limited to English, 1/1/2010-10/24/2018 (though earlier articles may have been identified through related articles search) Related articles searches were also conducted where potentially highly relevant papers were found	
NONE SPECIFIED, BUT DUE TO AUTOMATIC TERM MAPPING IN PUBMED, SOME MeSH TERMS MAY HAVE BEEN AUTOMATICALLY EMPLOYED	Shared decision making
	Prevention
	Cardiovascular
	Atherosclerosis
	Stroke
	Heart
	Hypertension
	Lipids
	Cholesterol
	diabetes
<b>Exercise &amp; Physical Activity</b>	
Search limits: Not ACP Journal Club OR Summaries for patients OR Editorial OR case-report OR letter OR letter OR abstract OR newspaper article OR comment OR baseline characteristics OR study design OR methodology Terms to identify clinical trials/SRs/Mas:	



Medical Subject Headings (MeSH) Terms	Key Words
Filters: Meta-Analysis, Systematic Reviews, Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial, From 2011/01/01 to 2018/05/25, Humans, English, Adult: 19+ years Terms to identify observational studies: 2011/01/01 to 2018/12/31, Humans, English, Epidemiologic Studies, Case-Control Studies, Cohort Studies, Cross-Sectional Studies, epidemiolog* AND stud*, case control, cohort stud*, cross sectional, cohort analys*, follow up stud*, longitudinal, retrospective, prospective, observational AND stud* Filters: Adult: 19+ years	
<b>Waist Circumference</b>	
Search limited to adult populations, 01/01/2010-10/3/18, English language	
Acute Coronary Syndrome	Acute coronary syndromes
Angina Unstable	Unstable angina?, "Angina Unstable"
Myocardial infarction	Myocardial infarctions
Shock cardiogenic	"shock cardiogenic"
Myocardial Stunning	"myocardial stunning"
No Reflow Phenomenon	
Heart Arrest	
St elevation myocardial infarction	STEMI
Non-st elevated myocardial infarction	NSTEMI
	"death/sudden cardiac"
<b>Stroke</b>	
Brain Infarction	
Brain Stem Infarctions	
Lateral Medullary Syndrome	
Cerebral Infarction	
	Myocardial ischemia
	"Dementia Multi infarct"
	"infarction anterior cerebral artery"
	"infarction middle cerebral artery"
	"infarction posterior cerebral artery"
Myocardial revascularization	
Coronary artery bypass	
Internal mammary coronary artery anastomosis	
Angioplasty	"angioplasty transluminal percutaneous coronary"
Heart failure	





Medical Subject Headings (MeSH) Terms	Key Words
Hospitalization	Hospitalization? OR rehospitalization?
	“atherectomy coronary”
	Coronary stent
	CABG
	“bypass grafts”
	“Carotid”
	pathology
	physiopathology
	Non-coronary revascularization procedure
	Carotid revascularization?
	Lower extremity revascularization?
	Percutaneous transluminal angioplast?
	Stent placement?
	Abdominal aortic aneurysm repair?
	AAA repair?
	complications
	Event? OR outcome? OR episode?
	Risk score
	Coronary risk modification
Cardiovascular diseases	Cardiovascular OR CVD
Cardiovascular disease	
Coronary disease	coronary
Coronary artery disease	
Myocardial infarction	
Heart failure	CHF OR CHD
Cerebrovascular disorders	
	“dyspnea paroxysmal”
	“edema cardiac”
Physical fitness	
Motor activity	
Exercise tolerance	
Metabolic equivalent	Metabolic equivalent
Exercise test	Graded exercise test OR gxt
Life style or lifestyle	
Exercise	
Training	
Walking	
	Vo2
	Maximal met



Medical Subject Headings (MeSH) Terms	Key Words
	Mets
	Physical activity
	Maximal metabolic?
Acute Coronary Syndrome	Acute coronary syndromes
Angina Unstable	Unstable angina?, "Angina Unstable"
Myocardial infarction	Myocardial infarctions
Shock cardiogenic	"shock cardiogenic"
Myocardial Stunning	"myocardial stunning"
No Reflow Phenomenon	
Heart Arrest	
St elevation myocardial infarction	STEMI
Non-st elevated myocardial infarction	NSTEMI
	"death/sudden cardiac"
Stroke	
Brain Infarction	
Brain Stem Infarctions	
Lateral Medullary Syndrome	
Cerebral Infarction	
	Myocardial ischemia
	"Dementia Multi infarct"
	"infarction anterior cerebral artery"
	"infarction middle cerebral artery"
	"infarction posterior cerebral artery"
Myocardial revascularization	
Coronary artery bypass	
Internal mammary coronary artery anastomosis	
Angioplasty	"angioplasty transluminal percutaneous coronary"
Heart failure	
Hospitalization	Hospitalization? OR rehospitalization?
	"atherectomy coronary"
	Coronary stent
	CABG
	"bypass grafts"
	"Carotid"
	pathology
	physiopathology
	Non-coronary revascularization procedure



Medical Subject Headings (MeSH) Terms	Key Words
	Carotid revascularization?
	Lower extremity revascularization?
	Percutaneous transluminal angioplast?
	Stent placement?
	Abdominal aortic aneurysm repair?
	AAA repair?
	complications
	Event? OR outcome? OR episode?
	Risk score
	Coronary risk modification
Cardiovascular diseases	Cardiovascular OR CVD
Cardiovascular disease	
Coronary disease	coronary
Coronary artery disease	
Myocardial infarction	
Heart failure	CHF OR CHD
Cerebrovascular disorders	
	"dyspnea paroxysmal"
	"edema cardiac"

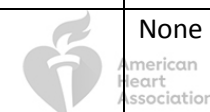
Because of automatic term mapping in PubMed, some MeSH terms may have been used even when not explicitly specified.



## Appendix 2. Author Relationships With Industry and Other Entities (Relevant)—2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Donna K. Arnett ( <i>Co-Chair</i> )	University of Kentucky College of Public Health—Dean and Professor of Epidemiology	None	None	None	None	None	None
Roger S. Blumenthal ( <i>Co-Chair</i> )	Johns Hopkins University—Professor of Medicine and Director, Ciccarone Center for the Prevention of Heart Disease	None	None	None	None	None	None
Michelle A. Albert	UCSF School of Medicine—Professor of Medicine and Director, UCSF NURTURE Center	None	None	None	None	None	None
Andrew B. Buroker	Faegre Baker Daniels LLP, Partner	None	None	None	None	None	None
Zachary D. Goldberger	University of Wisconsin School of Medicine and Public Health—Associate Professor of Medicine, Division of Cardiology	None	None	None	None	None	None

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ellen J. Hahn	University of Kentucky College of Nursing—Professor & Director, BREATHE, Deputy Director, UK-CARES & Leader, and Community Engagement Core; Marcia A. Dake Professor of Nursing	None	None	None	None	None	None
Cheryl D. Himmelfarb	Johns Hopkins School of Nursing—Professor; Associate Dean Research, Office for Science and Innovation; and Deputy Director, Johns Hopkins Institute for Clinical and Translational Research	None	None	None	None	None	None
Amit Khera	UT Southwestern School of Medicine—Professor of Internal Medicine and Director, Preventive Cardiology Program	None	None	None	None	None	None
Donald Lloyd-Jones	Northwestern University—Eileen M. Foell Professor; Senior Associate Dean for Clinical and Translational Research; Chair, Department of Preventive Medicine; and Director, Clinical and Translational Sciences Institute	None	None	None	None	None	None



Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
J. William McEvoy	National University of Ireland, Galway Campus—Professor of Preventive Cardiology; National Institute for Preventive Cardiology, Galway—Medical and Research Director; and University Hospital Galway, Ireland—Consultant Cardiologist.	None	None	None	None	None	None
Erin D. Michos	Johns Hopkins School of Medicine—Associate Professor of Medicine and Associate Director of Preventive Cardiology, Ciccarone Center for the Prevention of Heart Disease; Johns Hopkins Bloomberg School of Public Health—Associate Professor of Epidemiology	None	None	None	None	None	None
Michael D. Miedema	Minneapolis Heart Institute—Director of Cardiovascular Prevention	None	None	None	None	None	None
Daniel Muñoz	Vanderbilt University Medical Center—Assistant Professor of Medicine, Division of Cardiology, Medical Director for Quality, Vanderbilt Heart & Vascular Institute, and Associate Medical Director, Cardiovascular ICU	None	None	None	None	None	None

Arnett et al.  
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

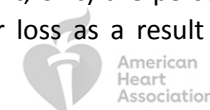
Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Sidney C. Smith, Jr	University of North Carolina, Chapel Hill—Professor of Medicine, Division of Cardiology	None	None	None	None	None	None
Salim S. Virani	Baylor College of Medicine—Professor, Section of Cardiovascular Research and Director for Research, Cardiology Fellowship Training Program; Michael E. DeBakey VA Medical Center—Staff Cardiologist and Investigator, Health Policy, Quality & Informatics Program, Center for Innovations in Quality, Effectiveness and Safety	None	None	None	None	None	None
Kim A. Williams, Sr	Rush Medical College—James B. Herrick Professor and Chief, Division of Cardiology, Department of Internal Medicine	None	None	None	None	None	None
Joseph Yeboah	Wake Forest Baptist Health—Associate Professor, Internal Medicine, Cardiovascular	None	None	None	None	None	None
Boback Ziaeian	University of California at Los Angeles, David Geffen School of Medicine—Clinical Instructor, Division of Cardiology	None	None	None	None	None	None





This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5,000$  of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a relevant relationship IF: a) the relationship or interest relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the company/entity (with whom the relationship exists) makes a drug, drug class, or device addressed in the document or makes a competing drug or device addressed in the document; or c) the person or a member of the person's household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.



ACC indicated American College of Cardiology; AHA, American Heart Association; ICU, Intensive Care Unit; LLP, Limited Liability Partnership; UCSF, University of California, San Francisco; UT, University of Texas; and VA, Veterans Affairs.

Circulation

### Appendix 3. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Amy Peterson	Official Reviewer—AHA	Hospital Affiliations: American Family Children's Hospital; UnityPoint Health—Meriter; UW School of Medicine and Public Health Department of Pediatrics	None	None	None	None	None	None	None
Kim K. Birtcher	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines Lead Reviewer	University of Houston, College of Pharmacy, Clinical Professor	<ul style="list-style-type: none"> <li>Jones &amp; Bartlett Learning</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>Accreditation Council for Clinical Lipidology (Other category)<sup>†</sup></li> </ul>	None	None
Sanjay Gandhi	Official Reviewer—ACC	Metro Health Medical Center Cleveland, Associate Professor, Case Western Reserve University School of Medicine	None	None	None	<ul style="list-style-type: none"> <li>Cleveland Heart Lab</li> <li>Juventas</li> </ul>	<ul style="list-style-type: none"> <li>Athersys (Data Safety Monitoring Board)</li> <li>Tendyne (Other category)</li> </ul>	None	None



**Arnett et al.**  
**2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease**

Andrea Price	Official Reviewer—ACC Science and Quality Committee	Quality Databases at Indiana University Health, Director	None	None	None	None	• ACC*	None	None
Jennifer E. Sanner Beauchamp	Content Reviewer—AHA	University of Texas Health Science Center, Cizik School of Nursing, Associate Professor	None	None	None	None	None	None	None
Glenn N. Levine	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Professor of Medicine at Baylor College of Medicine in Houston, Texas	None	None	None	None	None	<ul style="list-style-type: none"> <li>• Out of hospital cardiopulmonary arrest 2017 (Defendant)*</li> <li>• Out of hospital death 2018 (Defendant)*</li> </ul>	None
Patrick T. O’Gara	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Director of Strategic Planning for the Cardiovascular Division at Brigham and Women’s Hospital, the Watkins Family Distinguished Chair in Cardiology and Professor of Medicine at Harvard Medical School	None	None	None	None	<ul style="list-style-type: none"> <li>• Edwards Scientific (Other)†</li> <li>• Medtronic (Other)</li> <li>• NIH (Other)*</li> </ul>	None	None

**Arnett et al.**  
**2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease**

Joshua A. Beckman	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Director, Vascular Medicine; Professor of Medicine at Vanderbilt University	<ul style="list-style-type: none"> <li>• Aralez Pharmaceuticals*</li> <li>• Astra Zeneca Pharmaceuticals*</li> <li>• Janssen Scientific Affairs*</li> <li>• ER Squibb &amp; Sons</li> <li>• Boehringer Ingelheim Pharmaceuticals*</li> <li>• Merck</li> <li>• Sanofi</li> </ul>	<ul style="list-style-type: none"> <li>• AstraZeneca Pharmaceuticals</li> </ul>	None	<ul style="list-style-type: none"> <li>• Bristol-Myers Squibb*</li> </ul>	<ul style="list-style-type: none"> <li>• Bayer (Data Safety Monitoring Board)*</li> <li>• Novartis Corporation (Data Safety Monitoring Board)</li> <li>• Vascular Interventional Advances (Officer, Director, Trustee, or other Fiduciary Role)*</li> <li>• EMX†</li> <li>• JanaCare†</li> </ul>	None	None
-------------------	---	---	---	---	------	---	--	------	------



Circulation

**Arnett et al.**  
**2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease**

Anita Deswal	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Chief, Cardiology, Michael E. DeBakey VA Medical Center & Baylor College of Medicine, Professor, Baylor College of Medicine	None	None	None	• NIH*	<ul style="list-style-type: none"> <li>• ACC/AHA (Other)</li> <li>• Novartis Corporation (Other)†</li> <li>• AHA Get With The Guidelines Steering Committee (Other)†</li> <li>• Heart Failure Society of America (Other)†</li> <li>• Immediate Past Chair and Member, AHA Committee on Heart Failure and Transplantation (Other)†</li> <li>• NIH (Other)†</li> </ul>	None	None
Federico Gentile	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Centro Medico Diagnostico—Director, Cardiovascular Disease	None	None	None	None	None	None	None
José A. Joglar	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Program Director, Clinical Cardiac Electrophysiology Fellowship Program; Professor, UT Southwestern Medical Center	None	None	None	None	None	None	None



**Arnett et al.**  
**2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease**

Duminda N. Wijeyesundera	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Associate Professor Anesthesia, University of Toronto	None	None	None	<ul style="list-style-type: none"> <li>• Canadian Institutes of Health Research*</li> <li>• Ministry of Health and Longterm Care of Ontario (Canada)*</li> <li>• NIH*</li> </ul>	<ul style="list-style-type: none"> <li>• PCORI (Data Safety Monitoring Board)†</li> </ul>	None	<ul style="list-style-type: none"> <li>• Canadian Institutes of Health Research (Ottawa, Ontario, Canada)*</li> </ul>
--------------------------	---	---	------	------	------	--	---	------	---



Circulation

Arnett et al.  
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease


Eileen M. Handberg	Content Reviewer—ACC	Research Professor of Medicine; Director, Clinical Trials Program; Program Director, Florida CARES, UF Health	<ul style="list-style-type: none"> <li>• Bristol-Myers Squibb Company</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Aastrom Biosciences*</li> <li>• Amorceye, Inc*</li> <li>• Biocardia, Inc*</li> <li>• Brigham and Women's Hospital*</li> <li>• Capricor*</li> <li>• Cytori Therapeutics, Inc*</li> <li>• Department of Defense*</li> <li>• Direct Flow Medical*</li> <li>• Duke Clinical Research Institute*</li> <li>• East Carolina University*</li> <li>• Everyfit Inc*</li> <li>• MEDTRONIC*</li> <li>• Merck &amp; Co., Inc.*</li> <li>• Mesoblast Inc*</li> <li>• NIH*</li> <li>• PCORI*</li> <li>• Sanofi Aventis*</li> </ul>	<ul style="list-style-type: none"> <li>• Amgen (Other)</li> <li>• AstraZeneca (Other)</li> <li>• Boehringer Ingelheim (Other)</li> <li>• Daiichi Sankyo (Other)</li> <li>• Gilead Sciences, Inc. (Other)</li> <li>• Ionis (Other)</li> <li>• Relysa (Other)</li> </ul>	None	None
Prem Soman	Content Reviewer—ACC	Associate Professor of Medicine (Cardiology), Director, Nuclear Cardiology, UPMC	<ul style="list-style-type: none"> <li>• Alnylam Pharma</li> </ul>	None	<ul style="list-style-type: none"> <li>• American Society of Nuclear Cardiology*</li> </ul>	<ul style="list-style-type: none"> <li>• Astellas Pharma US*</li> </ul>	None	None	None




Circulation



**Arnett et al.**  
**2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease**

Eric Stecker	Content Reviewer—ACC	Associate Professor of Medicine, Division of Cardiovascular Medicine School of Medicine, OHSU	None	None	<ul style="list-style-type: none"> <li>• Hygeia / Desi MD*</li> </ul>	<ul style="list-style-type: none"> <li>• American Heart Association*</li> <li>• Medical Research Foundation of Oregon*</li> </ul>	None	None	None
Pamela Morris	Content Reviewer—ACC	Professor, Medical University of South Carolina	<ul style="list-style-type: none"> <li>• Amgen Inc.</li> <li>• Sanofi</li> <li>• Regeneron</li> </ul>	None	None	None	None	None	None
Andrew Freeman	Content Reviewer—ACC	Director, Clinical Cardiology and Operations; Co-Director, Nuclear Cardiology, National Jewish Health	None	<ul style="list-style-type: none"> <li>• Boehringer Ingelheim*</li> </ul>	None	None	None		None
Carl J. Lavie	Content Reviewer—ACC	Medical Director, Cardiac Rehabilitation and Prevention, Ochsner Clinic Foundation	None	<ul style="list-style-type: none"> <li>• Amgen*</li> <li>• ER Squibb &amp; Sons</li> <li>• Pfizer*</li> <li>• Aralez Pharmaceuticals</li> <li>• Amarin Pharma</li> <li>• Sanofi Aventis*</li> </ul>	None	None	None	None	None
James Stein	Content Reviewer—ACC	Director, UW Health Preventive Cardiology Program, Robert Turell Professor in Cardiovascular Research, UW School of Medicine and Public Health	<ul style="list-style-type: none"> <li>• Eli Lilly and Company (DSMB)</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• Up To Date (Other)</li> <li>• Wisconsin Alumni Research Foundation (Other)</li> </ul>	None	None

Arnett et al.  
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Heather Johnson	Content Reviewer—ACC	Associate Professor in the Division of Cardiovascular Medicine at the University of Wisconsin School of Medicine and Public Health	None	None	None	None	• Pfizer	None	None
Nanette Wenger	Content Reviewer—AHA	Professor of Medicine, Division of Cardiology, Emory University School of Medicine.	<ul style="list-style-type: none"> <li>• Janssen Pharmaceuticals, Inc*</li> <li>• Amgen</li> <li>• AstraZeneca</li> <li>• Gilead Sciences</li> <li>• Merck</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Gilead Sciences*</li> <li>• NHLBI*</li> <li>• Pfizer*</li> <li>• Society for Women's Health Research*</li> </ul>	None		None
Michael Blaha	Content Reviewer—AHA	Director of Clinical Research, Ciccarone Center for the Prevention of Heart Disease Associate Professor of Medicine, Johns Hopkins Medicine	<ul style="list-style-type: none"> <li>• Ferring Pharmaceuticals</li> <li>• Regeneron Pharmaceuticals</li> <li>• Sanofi-Aventis*</li> <li>• Amgen</li> <li>• Akcea</li> <li>• MedImmune</li> <li>• Novartis</li> <li>• Novo Nordisk</li> <li>• Siemens*</li> <li>• ACC</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Aetna†</li> <li>• Amgen†</li> <li>• AHA†</li> <li>• FDA†</li> <li>• NIH†</li> </ul>	None	None	None

**Arnett et al.**  
**2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease**

Laurence Sperling	Content Reviewer—ACC/AHA	Founder and Director of Preventive Cardiology at the Emory Clinic, Co-Director of the Cardiovascular Disease Fellowship Program at Emory, Professor of Medicine (Cardiology) at the Emory University School of Medicine	None	None	None	None	None	None	None
Seth Martin	Content Reviewer—ACC/AHA	Director, Advanced Lipid Disorders Program of the Ciccarone Center; Associate Professor of Medicine at Johns Hopkins Medicine	<ul style="list-style-type: none"> <li>• Amgen</li> <li>• Akcea Therapeutics</li> <li>• Quest Diagnostics</li> <li>• Sanofi-Regeneron</li> <li>• Esperion</li> <li>• Novo Nordisk</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Aetna Foundation*</li> <li>• Apple*</li> <li>• Google*</li> <li>• iHealth*</li> <li>• Maryland Innovation Initiative*</li> <li>• AHA*</li> </ul>	<ul style="list-style-type: none"> <li>• Corrie Health (Officer, Director, Trustee, or other Fiduciary Role)†</li> <li>• Co-inventor on pending patent filed by Johns Hopkins University for method of LDL-C estimation (Other)†</li> </ul>	None	None




Arnett et al.  
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Samia Mora	Content Reviewer—ACC/AHA	Associate Professor of Medicine, Harvard Medicine School Director, Center for Lipid Metabolomics, Brigham and Women's Hospital	<ul style="list-style-type: none"> <li>• Pri-Med*</li> <li>• Pfizer</li> <li>• Quest Diagnostics</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• C3 Conference (Other)</li> <li>• European Atherosclerosis Society (Other)</li> <li>• FEBS Congress (Other)</li> <li>• Oregon Health &amp; Science University (Other)</li> <li>• Vascular Biology Working Group Meeting (Other)</li> <li>• Atherotech Diagnostics*</li> <li>• Pfizer*</li> <li>• Quest Diagnostics*</li> <li>• NHLBI*</li> <li>• NIDDK*</li> </ul>	None	None
Clyde Yancy	Content Reviewer—ACC/AHA	Chief of Cardiology in the Department of Medicine, Northwestern Medicine	None	None	None	None	<ul style="list-style-type: none"> <li>• JAMA Cardiology (Other)*</li> </ul>	None	None
Quinn Pack	AACVPR	Assistant Professor of Medicine at University of Massachusetts Medical School	None	None	None	None	None	None	None



Arnett et al.  
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Frank Sacks	ASN	Professor of Cardiovascular Disease Prevention, Harvard School of Public Health	<ul style="list-style-type: none"> <li>• Amgen</li> <li>• Pfizer*</li> <li>• AstraZeneca*</li> </ul>	None	None	None	None	None	None
Salvatore Lacagnina	ACPM	System Medical Director of Wellness & Employee Health, Lee Health	None	None	None	None	None	None	None
Ron Blankstein	ASPC	Co-Director, Cardiovascular Imaging Training Program, Associate Physician, Preventive Cardiology, Director, Cardiac Computed Tomography, Brigham Health, Associate Professor in Medicine and Radiology, Harvard Medical School	<ul style="list-style-type: none"> <li>• Ekos Corporation</li> <li>• Amgen</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Amgen†</li> <li>• Astellas†</li> <li>• Sanofi-Aventis†</li> </ul>	<ul style="list-style-type: none"> <li>• American Society of Nuclear Cardiology (Officer, Director, Trustee, or other Fiduciary Role)†</li> <li>• Intersocietal Accreditation Commission for Computed Tomography (Officer, Director, Trustee, or other Fiduciary Role)†</li> <li>• Society of Cardiovascular Computed Tomography (Officer, Director, Trustee, or other Fiduciary Role)†</li> </ul>	 None	None

Arnett et al.  
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Jo-Ann Eastwood	PCNA	Associate Professor, UCLA School of Nursing	None	None	None	None	None	None	None
Stuart Haines	Content Reviewer—ACC/AHA	Professor of Pharmacy Practice, University of Mississippi	None	None	• Rx Instructional Systems*	None	• American Association of Colleges of Pharmacy (Officer, Director, Trustee, or other Fiduciary Role)†	None	None
Michael Rich	AGS	Professor of Medicine, Washington University School of Medicine in St. Louis	None	None	None	None	None	None	None

This table represents all relationships of reviewers with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5,000$  of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. Please refer to <http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

\*Significant relationship.

†No financial benefit.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; AGS, American Geriatrics Society; AHA, American Heart Association; ASN, American Society for Nutrition; American Society of Preventive Cardiology; DSMB, Data and Safety Monitoring Board; FDA, U.S. Food and Drug Administration; FEBS, Federation of European Biochemical Societies; *JAMA*, *Journal of the American Medical Association*; LDL-C, low-density lipoprotein cholesterol; NHLBI, National Heart, Lung, and Blood Institute; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; OHSU, Oregon Health & Science University; PCNA, Preventive Cardiovascular Nurses Association; PCORI, Patient-Centered Outcomes Research Institute; UCLA, University of California, Los Angeles; UF, University of Florida; UPMC, University of Pittsburgh Medical Center; UT, University of Texas; UW, University of Wisconsin; and VA, Veterans Affairs.

## References

### 1. Introduction

- S1-1. Weir HK, Anderson RN, Coleman King SM, et al. Heart disease and cancer deaths—trends and projections in the United States, 1969-2020. *Prev Chronic Dis*. 2016;13:E157.
- S1-2. Johnson NB, Hayes LD, Brown K, et al. CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors—United States, 2005-2013. *MMWR Suppl*. 2014;63:3-27.
- S1-3. Xu J, Murphy SL, Kochanek KD, et al. Mortality in the United States, 2015. *NCHS Data Brief*. 2016;1-8.
- S1-4. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290:891-7.
- S1-5. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586-613.
- S1-6. Turco JV, Inal-Veith A, Fuster V. Cardiovascular health promotion: an issue that can no longer wait. *J Am Coll Cardiol*. 2018;72:908-13.
- S1-7. Younus A, Aneni EC, Spatz ES, et al. A systematic review of the prevalence and outcomes of ideal cardiovascular health in US and non-US populations. *Mayo Clin Proc*. 2016;91:649-70.

### 1.1. Methodology and Evidence Review

- S1.1-1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13-115.
- S1.1-2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online ahead of print November 10, 2018]. *Circulation*. doi: 10.1161/CIR.0000000000000625

### 1.5. Class of Recommendation and Level of Evidence

- S1.5-1. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016;133:1426-8.

### 2.1. Patient-Centered Approaches for Providing Comprehensive ASCVD Prevention

- S2.1-1. Carter BL, Rogers M, Daly J, et al. The potency of team-based care interventions for hypertension: a meta-analysis. *Arch Intern Med*. 2009;169:1748-55.
- S2.1-2. Chisholm-Burns MA, Kim Lee J, Spivey CA, et al. US pharmacists' effect as team members on patient care: systematic review and meta-analyses. *Med Care*. 2010;48:923-33.
- S2.1-3. Fazel MT, Bagalagel A, Lee JK, et al. Impact of diabetes care by pharmacists as part of health care team in ambulatory settings: a systematic review and meta-analysis. *Ann Pharmacother*. 2017;51:890-907.
- S2.1-4. Mills KT, Obst KM, Shen W, et al. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: a systematic review and meta-analysis. *Ann Intern Med*. 2018;168:110-20.
- S2.1-5. Proia KK, Thota AB, Njie GJ, et al. Team-based care and improved blood pressure control: a community guide systematic review. *Am J Prev Med*. 2014;47:86-99.
- S2.1-6. Chen Z, Ernst ME, Ardery G, et al. Physician-pharmacist co-management and 24-hour blood pressure

- control. *J Clin Hypertens* (Greenwich). 2013;15:337-43.
- S2.1-7. Hirsch JD, Steers N, Adler DS, et al. Primary care-based, pharmacist-physician collaborative medication-therapy management of hypertension: a randomized, pragmatic trial. *Clin Ther*. 2014;36:1244-54.
- S2.1-8. Hunt JS, Siemieniczuk J, Pape G, et al. A randomized controlled trial of team-based care: impact of physician-pharmacist collaboration on uncontrolled hypertension. *J Gen Intern Med*. 2008;23:1966-72.
- S2.1-9. Isetts BJ, Buffington DE, Carter BL, et al. Evaluation of pharmacists' work in a physician-pharmacist collaborative model for the management of hypertension. *Pharmacotherapy*. 2016;36:374-84.
- S2.1-10. McLean DL, McAlister FA, Johnson JA, et al. A randomized trial of the effect of community pharmacist and nurse care on improving blood pressure management in patients with diabetes mellitus: study of cardiovascular risk intervention by pharmacists-hypertension (SCRIP-HTN). *Arch Intern Med*. 2008;168:2355-61.
- S2.1-11. Polgreen LA, Han J, Carter BL, et al. Cost-effectiveness of a physician-pharmacist collaboration intervention to improve blood pressure control. *Hypertension*. 2015;66:1145-51.
- S2.1-12. Chen EH, Thom DH, Hessler DM, et al. Using the Teamlet Model to improve chronic care in an academic primary care practice. *J Gen Intern Med*. 2010;25(suppl 4):S610-4.
- S2.1-13. Kravetz JD, Walsh RF. Team-based hypertension management to improve blood pressure control. *J Prim Care Community Health*. 2016;7:272-5.
- S2.1-14. Wan EYF, Fung CSC, Jiao FF, et al. Five-year effectiveness of the Multidisciplinary Risk Assessment and Management Programme-Diabetes Mellitus (RAMP-DM) on diabetes-related complications and health service uses—a population-based and propensity-matched cohort study. *Diabetes Care*. 2018;41:49-59.
- S2.1-15. Buhse S, Mühlhauser I, Heller T, et al. Informed shared decision-making programme on the prevention of myocardial infarction in type 2 diabetes: a randomised controlled trial. *BMJ Open*. 2015;5:e009116.
- S2.1-16. Cooper LA, Roter DL, Carson KA, et al. A randomized trial to improve patient-centered care and hypertension control in underserved primary care patients. *J Gen Intern Med*. 2011;26:1297-304.
- S2.1-17. Olomu A, Hart-Davidson W, Luo Z, et al. Implementing shared decision making in federally qualified health centers, a quasi-experimental design study: the Office-Guidelines Applied to Practice (Office-GAP) program. *BMC Health Serv Res*. 2016;16:334.
- S2.1-18. Parchman ML, Zeber JE, Palmer RF. Participatory decision making, patient activation, medication adherence, and intermediate clinical outcomes in type 2 diabetes: a STARNet study. *Ann Fam Med*. 2010;8:410-7.
- S2.1-19. Havranek EP, Mujahid MS, Barr DA, et al. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132:873-98.
- S2.1-20. Vilhelmsson A, Östergren P-O. Reducing health inequalities with interventions targeting behavioral factors among individuals with low levels of education—a rapid review. *PLoS ONE*. 2018;13:e0195774.
- S2.1-21. Schultz WM, Kelli HM, Lisko JC, et al. Socioeconomic status and cardiovascular outcomes: challenges and interventions. *Circulation*. 2018;137:2166-78.
- S2.1-22. Backholer K, Peters SAE, Bots SH, et al. Sex differences in the relationship between socioeconomic status and cardiovascular disease: a systematic review and meta-analysis. *J Epidemiol Community Health*. 2017;71:550-7.
- S2.1-23. Beauchamp A, Peeters A, Tonkin A, et al. Best practice for prevention and treatment of cardiovascular disease through an equity lens: a review. *Eur J Cardiovasc Prev Rehabil*. 2010;17:599-606.
- S2.1-24. Khaing W, Vallibhakara SA, Attia J, et al. Effects of education and income on cardiovascular outcomes: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24:1032-42.
- S2.1-25. Pollitt RA, Rose KM, Kaufman JS. Evaluating the evidence for models of life course socioeconomic factors and cardiovascular outcomes: a systematic review. *BMC Public Health*. 2005;5:7.
- S2.1-26. Schottenfeld L, Petersen D, Peikes D, et al. Creating Patient-centered Team-based Primary Care. AHRQ Publication No. 16-0002-EF. Rockville, MD: Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services; 2016. Available at: <https://pcmh.ahrq.gov/page/creating-patient-centered-team-based-primary-care>. Accessed January 3, 2019.
- S2.1-27. Brush JE Jr, Handberg EM, Biga C, et al. 2015 ACC health policy statement on cardiovascular team-based care and the role of advanced practice providers. *J Am Coll Cardiol*. 2015;65:2118-36.
- S2.1-28. Fentanes E, Vande Hei AG, Holuby RS, et al. Treatment in a preventive cardiology clinic utilizing



- advanced practice providers effectively closes atherosclerotic cardiovascular disease risk-management gaps among a primary-prevention population compared with a propensity-matched primary-care cohort: a team-based care model and its impact on lipid and blood pressure management. *Clin Cardiol*. 2018;41:817-24.
- S2.1-29. Billioux A, Verlander K, Anthony S, et al. Standardized Screening for Health-Related Social Needs in Clinical Settings: The Accountable Health Communities Screening Tool. Available at: <https://nam.edu/wp-content/uploads/2017/05/Standardized-Screening-for-Health-Related-Social-Needs-in-Clinical-Settings.pdf>. Accessed January 5, 2019.
- S2.1-30. Malambo P, Kengne AP, De Villiers A, et al. Built environment, selected risk factors and major cardiovascular disease outcomes: a systematic review. *PLoS ONE*. 2016;11:e0166846.
- S2.1-31. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. *Eur Heart J*. 2017;38:598-608.
- S2.1-32. Berkowitz SA, Hulberg AC, Standish S, et al. Addressing unmet basic resource needs as part of chronic cardiometabolic disease management. *JAMA Intern Med*. 2017;177:244-52.
- S2.1-33. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e393-423.
- S2.1-34. Rodriguez CJ, Allison M, Daviglus ML, et al. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. *Circulation*. 2014;130:593-625.
- S2.1-35. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e1-34.
- S2.1-36. Magnani JW, Mujahid MS, Aronow HD, et al. Health literacy and cardiovascular disease: fundamental relevance to primary and secondary prevention: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e48-74.
- S2.1-37. Powell TM, de Lemos JA, Banks K, et al. Body size misperception: a novel determinant in the obesity epidemic. *Arch Intern Med*. 2010;170:1695-7.
- S2.1-38. Padgett J, Biro FM. Different shapes in different cultures: body dissatisfaction, overweight, and obesity in African-American and caucasian females. *J Pediatr Adolesc Gynecol*. 2003;16:349-54.
- S2.1-39. U.S. Department of Health and Human Services. Healthy People 2020. Washington, DC: 2010. Available at: <https://www.healthypeople.gov>. Accessed January 3, 2019.
- S2.1-40. Bird EL, Ige JO, Pilkington P, et al. Built and natural environment planning principles for promoting health: an umbrella review. *BMC Public Health*. 2018;18:930.
- S2.1-41. Kaiser P, Diez Roux AV, Mujahid M, et al. Neighborhood environments and incident hypertension in the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2016;183:988-97.
- S2.1-42. Kumanyika SK, Gary TL, Lancaster KJ, et al. Achieving healthy weight in African-American communities: research perspectives and priorities. *Obes Res*. 2005;13:2037-47.
- S2.1-43. Grandner MA. Addressing sleep disturbances: an opportunity to prevent cardiometabolic disease? *Int Rev Psychiatry*. 2014;26:155-76.
- S2.1-44. Knutson KL. Sociodemographic and cultural determinants of sleep deficiency: implications for cardiometabolic disease risk. *Soc Sci Med*. 2013;79:7-15.
- S2.1-45. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. *Lancet*. 2004;363:1589-97.
- S2.1-46. Alam R, Sturt J, Lall R, et al. An updated meta-analysis to assess the effectiveness of psychological interventions delivered by psychological specialists and generalist clinicians on glycaemic control and on psychological status. *Patient Educ Couns*. 2009;75:25-36.
- S2.1-47. Bolen SD, Chandar A, Falck-Ytter C, et al. Effectiveness and safety of patient activation interventions for adults with type 2 diabetes: systematic review, meta-analysis, and meta-regression. *J Gen Intern Med*. 2014;29:1166-76.

- S2.1-48. Gonzalez JS, Tanenbaum ML, Commissariat PV. Psychosocial factors in medication adherence and diabetes self-management: Implications for research and practice. *Am Psychol*. 2016;71:539-51.
- S2.1-49. Javaheri S, Redline S. Insomnia and risk of cardiovascular disease. *Chest*. 2017;152:435-44.
- S2.1-50. Samuel LJ, Dennison Himmelfarb CR, Szklo M, et al. Social engagement and chronic disease risk behaviors: the Multi-Ethnic Study of Atherosclerosis. *Prev Med*. 2015;71:61-6.
- S2.1-51. Verbiest M, Brakema E, van der Kleij R, et al. National guidelines for smoking cessation in primary care: a literature review and evidence analysis. *NPJ Prim Care Respir Med*. 2017;27:2.

## 2.2. Assessment of Cardiovascular Risk

- S2.2-1. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2935-59.
- S2.2-2. American College of Cardiology, American Heart Association. ASCVD Risk Estimator. Available at: [https://tools.acc.org/ldl/ascvd\\_risk\\_estimator/index.html#/calculate/estimator](https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#/calculate/estimator). Accessed September 21, 2018.
- S2.2-3. Ference BA, Graham I, Tokgozoglu L, et al. Impact of lipids on cardiovascular health: JACC Health Promotion Series. *J Am Coll Cardiol*. 2018;72:1141-56.
- S2.2-4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online ahead of print November 10, 2018]. *Circulation*. doi: 10.1161/CIR.0000000000000625
- S2.2-5. Patel J, Al Rifai M, Scheuner MT, et al. Basic vs more complex definitions of family history in the prediction of coronary heart disease: the Multi-Ethnic Study of Atherosclerosis. *Mayo Clin Proc*. 2018;93:1213-23.
- S2.2-6. del Rincón ID, Williams K, Stern MP, et al. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum*. 2001;44:2737-45.
- S2.2-7. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol*. 1997;145:408-15.
- S2.2-8. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003497.
- S2.2-9. Tanz LJ, Stuart JJ, Williams PL, et al. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. *Circulation*. 2017;135:578-89.
- S2.2-10. Wellons M, Ouyang P, Schreiner PJ, et al. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. *Menopause*. 2012;19:1081-7.
- S2.2-11. Uddin SMI, Mirbolouk M, Dardari Z, et al. Erectile dysfunction as an independent predictor of future cardiovascular events. *Circulation*. 2018;138:540-2.
- S2.2-12. Triant VA, Perez J, Regan S, et al. Cardiovascular risk prediction functions underestimate risk in HIV infection. *Circulation*. 2018;137:2203-14.
- S2.2-13. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e1-34.
- S2.2-14. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-207.
- S2.2-15. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015;162:266-75.
- S2.2-16. Mahabadi AA, Möhlenkamp S, Lehmann N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. *JACC Cardiovasc Imaging*. 2017;10:143-53.
- S2.2-17. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the Multi-Ethnic Study of Atherosclerosis (MESA). *Eur Heart J*.

- 2018;39:2401-8.
- S2.2-18. McClelland RL, Jorgensen NW, Budoff M, et al. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) study and the DHS (Dallas Heart Study). *J Am Coll Cardiol*. 2015;66:1643-53.
- S2.2-19. Kavousi M, Desai CS, Ayers C, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. *JAMA*. 2016;316:2126-34.
- S2.2-20. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. *JAMA Cardiol*. 2017;2:391-9.
- S2.2-21. Mortensen MB, Fuster V, Muntendam P, et al. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people: the BioImage Study. *J Am Coll Cardiol*. 2016;68:881-91.
- S2.2-22. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2016;133:849-58.
- S2.2-23. Patel J, Al Rifai M, Blaha MJ, et al. Coronary artery calcium improves risk assessment in adults with a family history of premature coronary heart disease: results from the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e003186.
- S2.2-24. Pursnani A, Massaro JM, D'Agostino RB Sr, et al. Guideline-based statin eligibility, coronary artery calcification, and cardiovascular events. *JAMA*. 2015;314:134-41.
- S2.2-25. Valenti V, Ó Hartaigh B, Heo R, et al. A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9,715 individuals. *JACC Cardiovasc Imaging*. 2015;8:900-9.
- S2.2-26. Yano Y, O'Donnell CJ, Kuller L, et al. Association of coronary artery calcium score vs age with cardiovascular risk in older adults: an analysis of pooled population-based studies. *JAMA Cardiol*. 2017;2:986-94.
- S2.2-27. Yeboah J, Young R, McClelland RL, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. *J Am Coll Cardiol*. 2016;67:139-47.
- S2.2-28. Multi-Ethnic Study of Atherosclerosis. MESA 10-Year CHD Risk with Coronary Artery Calcification. Available at: <https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx>. Accessed September 21, 2018.
- S2.2-29. Astronaut Cardiovascular Health and Risk Modification (Astro-CHARM). 10-Year ASCVD Risk Calculator with Coronary Artery Calcium. Available at: <http://astrocharm.org/calculator-working>. Accessed September 21, 2018.
- S2.2-30. Gupta A, Lau E, Varshney R, et al. The identification of calcified coronary plaque is associated with initiation and continuation of pharmacological and lifestyle preventive therapies: a systematic review and meta-analysis. *JACC Cardiovasc Imaging*. 2017;10:833-42.
- S2.2-31. Shah RV, Spahillari A, Mwasongwe S, et al. Subclinical atherosclerosis, statin eligibility, and outcomes in African American individuals: the Jackson Heart Study. *JAMA Cardiol*. 2017;2:644-52.
- S2.2-32. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791-8.
- S2.2-33. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321-9.
- S2.2-34. Wilkins JT, Ning H, Berry J, et al. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795-801.
- S2.2-35. Pencina MJ, D'Agostino RB Sr, Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:3078-84.
- S2.2-36. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1-45.
- S2.2-37. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of



- Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:e13-115.
- S2.2-38. Pender A, Lloyd-Jones DM, Stone NJ, et al. Refining statin prescribing in lower-risk individuals: informing risk/benefit decisions. *J Am Coll Cardiol*. 2016;68:1690-7.
- S2.2-39. Andersson C, Enserro D, Larson MG, et al. Implications of the US cholesterol guidelines on eligibility for statin therapy in the community: comparison of observed and predicted risks in the Framingham Heart Study Offspring Cohort. *J Am Heart Assoc*. 2015;4:e001888.
- S2.2-40. Kavousi M, Leening MJG, Nanchen D, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA*. 2014;311:1416-23.
- S2.2-41. Pylypchuk R, Wells S, Kerr A, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. *Lancet*. 2018;391:1897-907.
- S2.2-42. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. *Eur Heart J*. 2017;38:598-608.
- S2.2-43. Emdin CA, Khera AV, Natarajan P, et al. Evaluation of the pooled cohort equations for prediction of cardiovascular risk in a contemporary prospective cohort. *Am J Cardiol*. 2017;119:881-5.
- S2.2-44. Rana JS, Tabada GH, Solomon MD, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. *J Am Coll Cardiol*. 2016;67:2118-30.
- S2.2-45. Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. *JAMA Intern Med*. 2014;174:1964-71.
- S2.2-46. Sussman JB, Wiitala WL, Zawistowski M, et al. The veterans affairs cardiac risk score: recalibrating the atherosclerotic cardiovascular disease score for applied use. *Med Care*. 2017;55:864-70.
- S2.2-47. Wolfson J, Vock DM, Bandyopadhyay S, et al. Use and customization of risk scores for predicting cardiovascular events using electronic health record data. *J Am Heart Assoc*. 2017;6:e003670.
- S2.2-48. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. *JAMA*. 2014;311:1406-15.
- S2.2-49. Colantonio LD, Richman JS, Carson AP, et al. Performance of the atherosclerotic cardiovascular disease pooled cohort risk equations by social deprivation status. *J Am Heart Assoc*. 2017;6:e005676.
- S2.2-50. Crowson CS, Gabriel SE, Semb AG, et al. Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. *Rheumatology (Oxford)*. 2017;56:1102-10.
- S2.2-51. Dalton JE, Perzynski AT, Zidar DA, et al. Accuracy of cardiovascular risk prediction varies by neighborhood socioeconomic position: a retrospective cohort study. *Ann Intern Med*. 2017;167:456-64.
- S2.2-52. Mora S, Wenger NK, Cook NR, et al. Evaluation of the pooled cohort risk equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. *JAMA Intern Med*. 2018;178:1231-40.
- S2.2-53. Yang X, Li J, Hu D, et al. Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese population: the China-PAR project (Prediction for ASCVD Risk in China). *Circulation*. 2016;134:1430-40.
- S2.2-54. Jung KJ, Jang Y, Oh DJ, et al. The ACC/AHA 2013 pooled cohort equations compared to a Korean Risk Prediction Model for atherosclerotic cardiovascular disease. *Atherosclerosis*. 2015;242:367-75.
- S2.2-55. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743-53.
- S2.2-56. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297:611-9.
- S2.2-57. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation*. 2008;118:2243-51, 4p following 2251.
- S2.2-58. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999-3058.

- S2.2-59. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart*. 2014;100(suppl 2):ii1-ii67.
- S2.2-60. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2016;32:1263-82.
- S2.2-61. Downs JR, O'Malley PG. Management of dyslipidemia for cardiovascular disease risk reduction: synopsis of the 2014 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. *Ann Intern Med*. 2015;163:291-7.
- S2.2-62. Bibbins-Domingo K, U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2016;164:836-45.
- S2.2-63. U.S. Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Statin use for the primary prevention of cardiovascular disease in adults: U.S. Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;316:1997-2007.
- S2.2-64. Karmali KN, Goff DC Jr, Ning H, et al. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2014;64:959-68.
- S2.2-65. Mortensen MB, Nordestgaard BG, Afzal S, et al. ACC/AHA guidelines superior to ESC/EAS guidelines for primary prevention with statins in non-diabetic Europeans: the Copenhagen General Population Study. *Eur Heart J*. 2017;38:586-94.
- S2.2-66. Mortensen MB, Afzal S, Nordestgaard BG, et al. Primary prevention with statins: ACC/AHA risk-based approach versus trial-based approaches to guide statin therapy. *J Am Coll Cardiol*. 2015;66:2699-709.
- S2.2-67. Loprinzi PD, Addoh O. Predictive validity of the American College of Cardiology/American Heart Association pooled cohort equations in predicting all-cause and cardiovascular disease-specific mortality in a national prospective cohort study of adults in the United States. *Mayo Clin Proc*. 2016;91:763-9.
- S2.2-68. Yadlowsky S, Hayward RA, Sussman JB, et al. Clinical implications of revised pooled cohort equations for estimating atherosclerotic cardiovascular disease risk. *Ann Intern Med*. 2018;169:20-9.
- S2.2-69. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2015;66:1657-68.
- S2.2-70. Miedema MD, Duprez DA, Misialek JR, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Qual Outcomes*. 2014;7:453-60.
- S2.2-71. Mitchell JD, Fergestrom N, Gage BF, et al. Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. *J Am Coll Cardiol*. 2018;72:3233-42.

### 3.1. Nutrition and Diet

- S3.1-1. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378:e34.
- S3.1-2. Kim H, Caulfield LE, Rebholz CM. Healthy plant-based diets are associated with lower risk of all-cause mortality in US adults. *J Nutr*. 2018;148:624-31.
- S3.1-3. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr*. 2014;144:881-9.
- S3.1-4. Satija A, Bhupathiraju SN, Spiegelman D, et al. Healthful and unhealthful plant-based diets and the risk of coronary heart disease in US adults. *J Am Coll Cardiol*. 2017;70:411-22.
- S3.1-5. Sotos-Prieto M, Bhupathiraju SN, Mattei J, et al. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med*. 2017;377:143-53.
- S3.1-6. Whalen KA, Judd S, McCullough ML, et al. Paleolithic and Mediterranean diet pattern scores are inversely associated with all-cause and cause-specific mortality in adults. *J Nutr*. 2017;147:612-20.
- S3.1-7. Bao Y, Han J, Hu FB, et al. Association of nut consumption with total and cause-specific mortality. *N Engl J Med*. 2013;369:2001-11.

- S3.1-8. Bernstein AM, Sun Q, Hu FB, et al. Major dietary protein sources and risk of coronary heart disease in women. *Circulation*. 2010;122:876-83.
- S3.1-9. Song M, Fung TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. *JAMA Intern Med*. 2016;176:1453-63.
- S3.1-10. Tharrey M, Mariotti F, Mashchak A, et al. Patterns of plant and animal protein intake are strongly associated with cardiovascular mortality: the Adventist Health Study-2 cohort. *Int J Epidemiol*. 2018;47:1603-12.
- S3.1-11. Martínez-González MA, Sánchez-Tainta A, Corella D, et al. A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. *Am J Clin Nutr*. 2014;100(suppl 1):320S-8S.
- S3.1-12. Wang DD, Li Y, Chiuve SE, et al. Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med*. 2016;176:1134-45.
- S3.1-13. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2017;390:2050-62.
- S3.1-14. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3-10.
- S3.1-15. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ*. 2007;334:885-8.
- S3.1-16. Micha R, Peñalvo JL, Cudhea F, et al. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA*. 2017;317:912-24.
- S3.1-17. Kiage JN, Merrill PD, Robinson CJ, et al. Intake of trans fat and all-cause mortality in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) cohort. *Am J Clin Nutr*. 2013;97:1121-8.
- S3.1-18. Löfvenborg JE, Andersson T, Carlsson P-O, et al. Sweetened beverage intake and risk of latent autoimmune diabetes in adults (LADA) and type 2 diabetes. *Eur J Endocrinol*. 2016;175:605-14.
- S3.1-19. Yang Q, Zhang Z, Gregg EW, et al. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Intern Med*. 2014;174:516-24.
- S3.1-20. Johnson RK, Lichtenstein AH, Anderson CAM, et al. Low-calorie sweetened beverages and cardiometabolic health: a science advisory from the American Heart Association. *Circulation*. 2018;138:e126-40.
- S3.1-21. Shikany JM, Safford MM, Newby PK, et al. Southern dietary pattern is associated with hazard of acute coronary heart disease in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Circulation*. 2015;132:804-14.
- S3.1-22. Seidemann SB, Claggett B, Cheng S, et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health*. 2018;3:e419-28.
- S3.1-23. Trichopoulou A, Psaltopoulou T, Orfanos P, et al. Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. *Eur J Clin Nutr*. 2007;61:575-81.
- S3.1-24. Noto H, Goto A, Tsujimoto T, et al. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. *PLoS ONE*. 2013;8:e55030.
- S3.1-25. Brandt EJ, Myerson R, Perrillon MC, et al. Hospital admissions for myocardial infarction and stroke before and after the trans-fatty acid restrictions in New York. *JAMA Cardiol*. 2017;2:627-34.
- S3.1-26. Micha R, Mozaffarian D. Trans fatty acids: effects on metabolic syndrome, heart disease and diabetes. *Nat Rev Endocrinol*. 2009;5:335-44.
- S3.1-27. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation*. 2016;133:187-225.
- S3.1-28. Weir HK, Anderson RN, Coleman King SM, et al. Heart disease and cancer deaths—trends and projections in the United States, 1969-2020. *Prev Chronic Dis*. 2016;13:E157.
- S3.1-29. Van Horn L, Carson JAS, Appel LJ, et al. Recommended dietary pattern to achieve adherence to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e505-29.

- S3.1-30. Rimm EB, Appel LJ, Chiuve SE, et al. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2018;138:e35-47.
- S3.1-31. Dehghan M, Mente A, Rangarajan S, et al. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2018;392:2288-97.

### 3.2. Exercise and Physical Activity

- S3.2-1. Orrow G, Kinmonth A-L, Sanderson S, et al. Effectiveness of physical activity promotion based in primary care: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2012;344:e1389.
- S3.2-2. Sanchez A, Bully P, Martinez C, et al. Effectiveness of physical activity promotion interventions in primary care: a review of reviews. *Prev Med*. 2015;76(suppl):S56-67.
- S3.2-3. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet*. 2016;388:1302-10.
- S3.2-4. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. *Br J Sports Med*. 2008;42:238-43.
- S3.2-5. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ*. 2016;354:i3857.
- S3.2-6. Sattelmair J, Pertman J, Ding EL, et al. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation*. 2011;124:789-95.
- S3.2-7. Zheng H, Orsini N, Amin J, et al. Quantifying the dose-response of walking in reducing coronary heart disease risk: meta-analysis. *Eur J Epidemiol*. 2009;24:181-92.
- S3.2-8. Wahid A, Manek N, Nichols M, et al. Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and meta-analysis. *J Am Heart Assoc*. 2016;5:e002495.
- S3.2-9. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med*. 2015;162:123-32.
- S3.2-10. Chomistek AK, Manson JE, Stefanick ML, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. *J Am Coll Cardiol*. 2013;61:2346-54.
- S3.2-11. Patterson R, McNamara E, Tainio M, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol*. 2018;33:811-29.
- S3.2-12. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services; 2018. Available at: <https://health.gov/paguidelines/second-edition/report>. Accessed January 3, 2019.
- S3.2-13. Lee I-M, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380:219-29.
- S3.2-14. Physical Activity Guidelines Steering Committee. 2008 Physical Activity Guidelines for Americans. Available at: <https://health.gov/paguidelines/2008/>. Accessed January 5, 2019.
- S3.2-15. Milton K, Macniven R, Bauman A. Review of the epidemiological evidence for physical activity and health from low- and middle-income countries. *Glob Public Health*. 2014;9:369-81.
- S3.2-16. Lobelo F, Rohm Young D, Sallis R, et al. Routine assessment and promotion of physical activity in healthcare settings: a scientific statement from the American Heart Association. *Circulation*. 2018;137:e495-522.
- S3.2-17. Kraus WE, Bittner V, Appel L, et al. The National Physical Activity Plan: a call to action from the American Heart Association: a science advisory from the American Heart Association. *Circulation*. 2015;131:1932-40.

- S3.2-18. Diep L, Kwagyan J, Kurantsin-Mills J, et al. Association of physical activity level and stroke outcomes in men and women: a meta-analysis. *J Womens Health (Larchmt)*. 2010;19:1815-22.
- S3.2-19. Sofi F, Capalbo A, Cesari F, et al. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil*. 2008;15:247-57.
- S3.2-20. Liu C-J, Latham NK. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst Rev*. 2009;CD002759.
- S3.2-21. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147:357-69.
- S3.2-22. Carlson DJ, Dieberg G, Hess NC, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. *Mayo Clin Proc*. 2014;89:327-34.
- S3.2-23. Goodman JM, Burr JF, Banks L, et al. The acute risks of exercise in apparently healthy adults and relevance for prevention of cardiovascular events. *Can J Cardiol*. 2016;32:523-32.
- S3.2-24. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation*. 2007;115:2358-68.
- S3.2-25. Merghani A, Maestrini V, Rosmini S, et al. Prevalence of subclinical coronary artery disease in masters endurance athletes with a low atherosclerotic risk profile. *Circulation*. 2017;136:126-37.
- S3.2-26. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315-81.
- S3.2-27. Saint-Maurice PF, Troiano RP, Matthews CE, et al. Moderate-to-vigorous physical activity and all-cause mortality: do bouts matter? *J Am Heart Assoc*. 2018;7:e007678.
- S3.2-28. Vasankari V, Husu P, Vähä-Ypyä H, et al. Association of objectively measured sedentary behaviour and physical activity with cardiovascular disease risk. *Eur J Prev Cardiol*. 2017;24:1311-8.
- S3.2-29. Pandey A, Garg S, Khunger M, et al. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation*. 2015;132:1786-94.
- S3.2-30. Young DR, Hivert M-F, Alhassan S, et al. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262-79.
- S3.2-31. Chastin SFM, De Craemer M, De Cocker K, et al. How does light-intensity physical activity associate with adult cardiometabolic health and mortality? Systematic review with meta-analysis of experimental and observational studies. *Br J Sports Med*. 2018 Apr 25 [Epub ahead of print].

#### 4.1. Obesity and Being Overweight

- S4.1-1. LeBlanc EL, Patnode CD, Webber EM, et al. Draft evidence review for weight loss to prevent obesity-related morbidity and mortality in adults: behavioral interventions. Kaiser Permanente Research Affiliates Evidence-based Practice Center, Kaiser Permanente Center for Health Research: Portland, OR; 2018. AHRQ Publication No. 18-05239-EF-1. Available at: <https://www.uspreventiveservicestaskforce.org/Page/Document/draft-evidence-review/obesity-in-adults-interventions1>. Accessed January 5, 2019.
- S4.1-2. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849.
- S4.1-3. Canoy D, Cairns BJ, Balkwill A, et al. Coronary heart disease incidence in women by waist circumference within categories of body mass index. *Eur J Prev Cardiol*. 2013;20:759-62.
- S4.1-4. Warren TY, Wilcox S, Dowda M, et al. Independent association of waist circumference with hypertension and diabetes in African American women, South Carolina, 2007-2009. *Prev Chronic Dis*. 2012;9:E105.
- S4.1-5. Czernichow S, Kengne A-P, Stamatakis E, et al. Body mass index, waist circumference and waist-hip



- ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. *Obes Rev*. 2011;12:680-7.
- S4.1-6. Flint AJ, Rexrode KM, Hu FB, et al. Body mass index, waist circumference, and risk of coronary heart disease: a prospective study among men and women. *Obes Res Clin Pract*. 2010;4:e171-81.
- S4.1-7. American Heart Association. Extreme Obesity, And What You Can Do. Available at: <https://www.heart.org/en/healthy-living/healthy-eating/losing-weight/extreme-obesity-and-what-you-can-do>. Accessed January 5, 2019.
- S4.1-8. Hales CM, Carroll MD, Fryar CD, et al. Prevalence of obesity among adults and youth: United States, 2015-2016. *NCHS Data Brief*. 2017;1-8.
- S4.1-9. Asad Z, Abbas M, Javed I, et al. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. *J Cardiovasc Electrophysiol*. 2018;29:725-32.
- S4.1-10. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63:2985-3023.
- S4.1-11. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311:74-86.
- S4.1-12. Golzarand M, Toolabi K, Farid R. The bariatric surgery and weight losing: a meta-analysis in the long- and very long-term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults. *Surg Endosc*. 2017;31:4331-45.
- S4.1-13. Newman AB, Lee JS, Visser M, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr*. 2005;82:872-8; quiz 915-6.
- S4.1-14. Zamboni M, Mazzali G, Zoico E, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond)*. 2005;29:1011-29.
- S4.1-15. Miller SL, Wolfe RR. The danger of weight loss in the elderly. *J Nutr Health Aging*. 2008;12:487-91.
- S4.1-16. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
- S4.1-17. Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145-54.
- S4.1-18. McTigue KM, Harris R, Hemphill B, et al. Screening and interventions for obesity in adults: summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2003;139:933-49.
- S4.1-19. Stegenga H, Haines A, Jones K, et al. Identification, assessment, and management of overweight and obesity: summary of updated NICE guidance. *BMJ*. 2014;349:g6608.
- S4.1-20. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363:157-63.
- S4.1-21. Zhang P, Wang R, Gao C, et al. Prevalence of central obesity among adults with normal BMI and its association with metabolic diseases in northeast China. *PLoS ONE*. 2016;11:e0160402.
- S4.1-22. Sharma S, Batsis JA, Coutinho T, et al. Normal-weight central obesity and mortality risk in older adults with coronary artery disease. *Mayo Clin Proc*. 2016;91:343-51.
- S4.1-23. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3):1-203.
- S4.1-24. Balkau B, Deanfield JE, Després J-P, et al. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation*. 2007;116:1942-51.
- S4.1-25. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD: National Heart, Lung, and Blood Institute; 1998. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK2003/>. Accessed January 5, 2019.

## 4.2. Type 2 Diabetes Mellitus

- S4.2-1. Huo R, Du T, Xu Y, et al. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. *Eur J Clin Nutr*. 2015;69:1200-8.
- S4.2-2. Azadbakht L, Fard NRP, Karimi M, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. *Diabetes Care*. 2011;34:55-7.
- S4.2-3. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care*. 2006;29:2518-27.
- S4.2-4. Church TS, Blair SN, Cocroham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010;304:2253-62.
- S4.2-5. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-65.
- S4.2-6. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2016;164:740-51.
- S4.2-7. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care*. 2013;36:1304-11.
- S4.2-8. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia*. 2017;60:1620-9.
- S4.2-9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117-28.
- S4.2-10. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644-57.
- S4.2-11. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-22.
- S4.2-12. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1812389.
- S4.2-13. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392:1519-29.
- S4.2-14. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834-44.
- S4.2-15. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67-492.
- S4.2-16. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-93.
- S4.2-17. Liu G, Li Y, Hu Y, et al. Influence of lifestyle on incident cardiovascular disease and mortality in patients with diabetes mellitus. *J Am Coll Cardiol*. 2018;71:2867-76.
- S4.2-18. Rejeski WJ, Ip EH, Bertoni AG, et al. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med*. 2012;366:1209-17.
- S4.2-19. Burger KNJ, Beulens JWJ, van der Schouw YT, et al. Dietary fiber, carbohydrate quality and quantity, and mortality risk of individuals with diabetes mellitus. *PLoS ONE*. 2012;7:e43127.
- S4.2-20. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation*. 2010;121:2271-83.
- S4.2-21. Pan A, Sun Q, Bernstein AM, et al. Changes in red meat consumption and subsequent risk of type 2 diabetes mellitus: three cohorts of US men and women. *JAMA Intern Med*. 2013;173:1328-35.
- S4.2-22. Boulé NG, Haddad E, Kenny GP, et al. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA*. 2001;286:1218-27.
- S4.2-23. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in



- insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-86.
- S4.2-24. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-53.
- S4.2-25. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360:129-39.
- S4.2-26. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet.* 2009;373:1765-72.
- S4.2-27. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet.* 2018. doi:10.1016/S0140-6736(18)32590-X

### 4.3. High Blood Cholesterol

- S4.3-1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online ahead of print November 10, 2018]. *Circulation.* doi: 10.1161/CIR.0000000000000625
- S4.3-2. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376:1670-81.
- S4.3-3. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011;377:2181-92.
- S4.3-4. Cholesterol Treatment Trialists' (CTT) Collaboration, Herrington W, Emberson J, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol.* 2016;4:829-39.
- S4.3-5. Chou R, Dana T, Blazina I, et al. Statin use for the prevention of cardiovascular disease in adults: a systematic review for the U.S. Preventive Services Task Force. Report No. 14-05206-EF-2. Rockville, MD: U.S. Agency for Healthcare Research and Quality; 2016. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK396415>. Accessed January 5, 2019.
- S4.3-6. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA.* 1998;279:1615-22.
- S4.3-7. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195-207.
- S4.3-8. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2013;CD004816.
- S4.3-9. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med.* 2016;374:2021-31.
- S4.3-10. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA.* 2016;316:1289-97.
- S4.3-11. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364:685-96.
- S4.3-12. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 2003;361:2005-16.
- S4.3-13. de Vries FM, Denig P, Pouwels KB, et al. Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta-analysis. *Drugs.* 2012;72:2365-73.

- S4.3-14. Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care*. 2006;29:1478-85.
- S4.3-15. Mulnier HE, Seaman HE, Raleigh VS, et al. Risk of myocardial infarction in men and women with type 2 diabetes in the UK: a cohort study using the General Practice Research Database. *Diabetologia*. 2008;51:1639-45.
- S4.3-16. Rana JS, Liu JY, Moffet HH, et al. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. *J Gen Intern Med*. 2016;31:387-93.
- S4.3-17. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm (ASCOT-LLA). *Diabetes Care*. 2005;28:1151-7.
- S4.3-18. Soedamah-Muthu SS, Fuller JH, Mulnier HE, et al. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. *Diabetes Care*. 2006;29:798-804.
- S4.3-19. Wong ND, Glovaci D, Wong K, et al. Global cardiovascular disease risk assessment in United States adults with diabetes. *Diab Vasc Dis Res*. 2012;9:146-52.
- S4.3-20. Besseling J, Hovingh GK, Huijgen R, et al. Statins in familial hypercholesterolemia: consequences for coronary artery disease and all-cause mortality. *J Am Coll Cardiol*. 2016;68:252-60.
- S4.3-21. Khera AV, Won H-H, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578-89.
- S4.3-22. Nanchen D, Gencer B, Muller O, et al. Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. *Circulation*. 2016;134:698-709.
- S4.3-23. Perak AM, Ning H, de Ferranti SD, et al. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. *Circulation*. 2016;134:9-19.
- S4.3-24. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301-7.
- S4.3-25. Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolemia: a long term cohort study. *BMJ*. 2008;337:a2423.
- S4.3-26. Mortensen MB, Fuster V, Muntendam P, et al. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people: the BioImage Study. *J Am Coll Cardiol*. 2016;68:881-91.
- S4.3-27. Willeit P, Kiechl S, Kronenberg F, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. *J Am Coll Cardiol*. 2014;64:851-60.
- S4.3-28. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2015;66:1657-68.
- S4.3-29. Ridker PM, Mora S, Rose L, et al. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. *Eur Heart J*. 2016;37:1373-9.
- S4.3-30. Yano Y, O'Donnell CJ, Kuller L, et al. Association of coronary artery calcium score vs age with cardiovascular risk in older adults: an analysis of pooled population-based studies. *JAMA Cardiol*. 2017;2:986-94.
- S4.3-31. Malik S, Zhao Y, Budoff M, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-Ethnic Study of Atherosclerosis. *JAMA Cardiol*. 2017;2:1332-40.
- S4.3-32. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. *J Am Coll Cardiol*. 2014;63:1935-47.
- S4.3-33. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol,

- non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes*. 2011;4:337-45.
- S4.3-34. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J*. 2018;39:2401-8.
- S4.3-35. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581-90.
- S4.3-36. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet*. 2006;368:1155-63.
- S4.3-37. Vallejo-Vaz AJ, Robertson M, Catapano AL, et al. Low-density lipoprotein cholesterol lowering for the primary prevention of cardiovascular disease among men with primary elevations of low-density lipoprotein cholesterol levels of 190 mg/dL or above: analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) 5-year randomized trial and 20-year observational follow-up. *Circulation*. 2017;136:1878-91.
- S4.3-38. Mora S, Glynn RJ, Hsia J, et al. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation*. 2010;121:1069-77.
- S4.3-39. Samarasekera EJ, Neilson JM, Warren RB, et al. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. *J Invest Dermatol*. 2013;133:2340-6.
- S4.3-40. Feinstein MJ, Nance RM, Drozd DR, et al. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the Centers for AIDS Research Network of Integrated Clinical Systems. *JAMA Cardiol*. 2017;2:155-62.
- S4.3-41. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015;162:266-75.
- S4.3-42. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. *JAMA Cardiol*. 2017;2:391-9.
- S4.3-43. Fudim M, Zalawadiya S, Patel DK, et al. Data on coronary artery calcium score performance and cardiovascular risk reclassification across gender and ethnicities. *Data Brief*. 2016;6:578-81.
- S4.3-44. Gupta A, Lau E, Varshney R, et al. The identification of calcified coronary plaque is associated with initiation and continuation of pharmacological and lifestyle preventive therapies: a systematic review and meta-analysis. *JACC Cardiovasc Imaging*. 2017;10:833-42.
- S4.3-45. Han D, Ó Hartaigh B, Lee JH, et al. Assessment of coronary artery calcium scoring for statin treatment strategy according to ACC/AHA guidelines in asymptomatic Korean adults. *Yonsei Med J*. 2017;58:82-9.
- S4.3-46. Hong JC, Blankstein R, Shaw LJ, et al. Implications of coronary artery calcium testing for treatment decisions among statin candidates according to the ACC/AHA cholesterol management guidelines: a cost-effectiveness analysis. *JACC Cardiovasc Imaging*. 2017;10:938-52.
- S4.3-47. Kavousi M, Desai CS, Ayers C, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. *JAMA*. 2016;316:2126-34.
- S4.3-48. Mahabadi AA, Möhlenkamp S, Lehmann N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. *JACC Cardiovasc Imaging*. 2017;10:143-53.
- S4.3-49. McClelland RL, Jorgensen NW, Budoff M, et al. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) study and the DHS (Dallas Heart Study). *J Am Coll Cardiol*. 2015;66:1643-53.
- S4.3-50. Pursnani A, Massaro JM, D'Agostino RB Sr, et al. Guideline-based statin eligibility, coronary artery calcification, and cardiovascular events. *JAMA*. 2015;314:134-41.
- S4.3-51. Qureshi WT, Rana JS, Yeboah J, et al. Risk stratification for primary prevention of coronary artery disease: roles of C-reactive protein and coronary artery calcium. *Curr Cardiol Rep*. 2015;17:110.
- S4.3-52. Shah RV, Spahillari A, Mwasongwe S, et al. Subclinical atherosclerosis, statin eligibility, and outcomes in

- African American individuals: the Jackson Heart Study. *JAMA Cardiol.* 2017;2:644-52.
- S4.3-53. Waheed S, Pollack S, Roth M, et al. Collective impact of conventional cardiovascular risk factors and coronary calcium score on clinical outcomes with or without statin therapy: The St Francis Heart Study. *Atherosclerosis.* 2016;255:193-9.
- S4.3-54. Yeboah J, Polonsky TS, Young R, et al. Utility of nontraditional risk markers in individuals ineligible for statin therapy according to the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. *Circulation.* 2015;132:916-22.
- S4.3-55. Yeboah J, Young R, McClelland RL, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. *J Am Coll Cardiol.* 2016;67:139-47.
- S4.3-56. Krumholz HM. Treatment of cholesterol in 2017. *JAMA.* 2017;318:417-8.
- S4.3-57. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA guidelines. *J Am Coll Cardiol.* 2015;65:1361-8.
- S4.3-58. Cohen R, Budoff M, McClelland RL, et al. Significance of a positive family history for coronary heart disease in patients with a zero coronary artery calcium score (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol.* 2014;114:1210-4.
- S4.3-59. Pandya A, Sy S, Cho S, et al. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. *JAMA.* 2015;314:142-50.
- S4.3-60. Singh A, Collins BL, Gupta A, et al. Cardiovascular risk and statin eligibility of young adults after an MI: Partners YOUNG-MI Registry. *J Am Coll Cardiol.* 2018;71:292-302.
- S4.3-61. Huo X, Gao L, Guo L, et al. Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study. *Lancet Diabetes Endocrinol.* 2016;4:115-24.
- S4.3-62. Svensson MK, Cederholm J, Eliasson B, et al. Albuminuria and renal function as predictors of cardiovascular events and mortality in a general population of patients with type 2 diabetes: a nationwide observational study from the Swedish National Diabetes Register. *Diab Vasc Dis Res.* 2013;10:520-9.
- S4.3-63. Guo VY, Cao B, Wu X, et al. Prospective association between diabetic retinopathy and cardiovascular disease—a systematic review and meta-analysis of cohort studies. *J Stroke Cerebrovasc Dis.* 2016;25:1688-95.
- S4.3-64. Brownrigg JRW, de Lusignan S, McGovern A, et al. Peripheral neuropathy and the risk of cardiovascular events in type 2 diabetes mellitus. *Heart.* 2014;100:1837-43.
- S4.3-65. Ogren M, Hedblad B, Engström G, et al. Prevalence and prognostic significance of asymptomatic peripheral arterial disease in 68-year-old men with diabetes. Results from the population study “Men born in 1914” from Malmö, Sweden. *Eur J Vasc Endovasc Surg.* 2005;29:182-9.
- S4.3-66. Pang X-H, Han J, Ye W-L, et al. Lower extremity peripheral arterial disease is an independent predictor of coronary heart disease and stroke risks in patients with type 2 diabetes mellitus in China. *Int J Endocrinol.* 2017;2017:9620513.

#### 4.4. High Blood Pressure or Hypertension

- S4.4-1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018;71:e127-248.
- S4.4-2. Neter JE, Stam BE, Kok FJ, et al. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension.* 2003;42:878-84.
- S4.4-3. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA.* 1992;267:1213-20.
- S4.4-4. Whelton PK, Kumanyika SK, Cook NR, et al. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. *Trials of Hypertension Prevention Collaborative Research Group. Am J Clin Nutr.* 1997;65:652S-660S.
- S4.4-5. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence

- in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. *Arch Intern Med.* 1997;157:657-67.
- S4.4-6. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344:3-10.
- S4.4-7. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med.* 1997;336:1117-24.
- S4.4-8. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA.* 2003;289:2083-93.
- S4.4-9. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. *N Engl J Med.* 2014;371:624-34.
- S4.4-10. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ.* 2013;346:f1325.
- S4.4-11. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA.* 1998;279:839-46.
- S4.4-12. Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ.* 2013;346:f1326.
- S4.4-13. Graudal NA, Hubeck-Graudal T, Jürgens G. Effects of low-sodium diet vs. high-sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride (Cochrane Review). *Am J Hypertens.* 2012;25:1-15.
- S4.4-14. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA.* 1997;277:1624-32.
- S4.4-15. Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ.* 2013;346:f1378.
- S4.4-16. Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. *J Hum Hypertens.* 2003;17:471-80.
- S4.4-17. World Health Association. Guideline: Potassium Intake for Adults and Children. Geneva, Switzerland: World Health Organization, Department of Nutrition for Health and Development; 2012.
- S4.4-18. Whelton PK, He J. Health effects of sodium and potassium in humans. *Curr Opin Lipidol.* 2014;25:75-9.
- S4.4-19. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc.* 2013;2:e004473.
- S4.4-20. Whelton SP, Chin A, Xin X, et al. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 2002;136:493-503.
- S4.4-21. Carlson DJ, Dieberg G, Hess NC, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. *Mayo Clin Proc.* 2014;89:327-34.
- S4.4-22. García-Hermoso A, Saavedra JM, Escalante Y. Effects of exercise on resting blood pressure in obese children: a meta-analysis of randomized controlled trials. *Obes Rev.* 2013;14:919-28.
- S4.4-23. Rossi AM, Moullec G, Lavoie KL, et al. The evolution of a Canadian Hypertension Education Program recommendation: the impact of resistance training on resting blood pressure in adults as an example. *Can J Cardiol.* 2013;29:622-7.
- S4.4-24. Roerecke M, Kaczorowski J, Tobe SW, et al. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. *Lancet Public Health.* 2017;2:e108-20.
- S4.4-25. Xin X, He J, Frontini MG, et al. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension.* 2001;38:1112-7.
- S4.4-26. Stewart SH, Latham PK, Miller PM, et al. Blood pressure reduction during treatment for alcohol dependence: results from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. *Addiction.* 2008;103:1622-8.
- S4.4-27. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens.* 2006;24:215-33.
- S4.4-28. Wallace P, Cutler S, Haines A. Randomised controlled trial of general practitioner intervention in



- patients with excessive alcohol consumption. *BMJ*. 1988;297:663-8.
- S4.4-29. Lang T, Nicaud V, Darné B, et al. Improving hypertension control among excessive alcohol drinkers: a randomised controlled trial in France. The WALPA Group. *J Epidemiol Community Health*. 1995;49:610-6.
- S4.4-30. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
- S4.4-31. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957-67.
- S4.4-32. Sundström J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. *Ann Intern Med*. 2015;162:184-91.
- S4.4-33. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016;387:435-43.
- S4.4-34. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-16.
- S4.4-35. Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. *J Hypertens*. 2011;29:4-16.
- S4.4-36. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet*. 2014;384:591-8.
- S4.4-37. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels—overview and meta-analyses of randomized trials. *J Hypertens*. 2014;32:2296-304.
- S4.4-38. Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. *JAMA*. 2011;305:913-22.
- S4.4-39. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels—updated overview and meta-analyses of randomized trials. *J Hypertens*. 2016;34:613-22.
- S4.4-40. Verdecchia P, Angeli F, Gentile G, et al. More versus less intensive blood pressure-lowering strategy: cumulative evidence and trial sequential analysis. *Hypertension*. 2016;68:642-53.
- S4.4-41. Bangalore S, Toklu B, Gianos E, et al. Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. *Am J Med*. 2017;130:707-19.e8.
- S4.4-42. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol*. 2017;2:775-81.
- S4.4-43. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005;365:939-46.
- S4.4-44. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421-31.
- S4.4-45. Upadhyay A, Earley A, Haynes SM, et al. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med*. 2011;154:541-8.
- S4.4-46. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med*. 2003;139:244-52.
- S4.4-47. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ*. 2013;185:949-57.
- S4.4-48. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330:877-84.
- S4.4-49. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and



- meta-analysis. *JAMA*. 2015;313:603-15.
- S4.4-50. Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2013;CD008277.
- S4.4-51. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. *Diabetes Care*. 2014;37:1721-8.
- S4.4-52. Bress AP, Bellows BK, King JB, et al. Cost-effectiveness of intensive versus standard blood-pressure control. *N Engl J Med*. 2017;377:745-55.
- S4.4-53. Soliman EZ, Byington RP, Bigger JT, et al. Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with diabetes mellitus: Action to Control Cardiovascular Risk in Diabetes blood pressure trial. *Hypertension*. 2015;66:1123-9.
- S4.4-54. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575-85.
- S4.4-55. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-13.
- S4.4-56. Kassai B, Boissel J-P, Cucherat M, et al. Treatment of high blood pressure and gain in event-free life expectancy. *Vasc Health Risk Manag*. 2005;1:163-9.
- S4.4-57. van Dieren S, Kengne AP, Chalmers J, et al. Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes. *Diabetes Res Clin Pract*. 2012;98:83-90.
- S4.4-58. Montgomery AA, Fahey T, Ben-Shlomo Y, et al. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: a Markov decision analysis. *J Hypertens*. 2003;21:1753-9.
- S4.4-59. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2009-20.
- S4.4-60. Neaton JD, Grimm RH Jr, Prineas RJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *JAMA*. 1993;270:713-24.
- S4.4-61. Julius S, Nesbitt SD, Egan BM, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med*. 2006;354:1685-97.
- S4.4-62. Lawes CMM, Bennett DA, Lewington S, et al. Blood pressure and coronary heart disease: a review of the evidence. *Semin Vasc Med*. 2002;2:355-68.
- S4.4-63. Danaei G, Ding EL, Mozaffarian D, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med*. 2009;6:e1000058.
- S4.4-64. Muntner P, Carey RM, Gidding S, et al. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation*. 2018;137:109-18.
- S4.4-65. Blumenthal JA, Babyak MA, Hinderliter A, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med*. 2010;170:126-35.
- S4.4-66. Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:2176-98.
- S4.4-67. Baker S, Priest P, Jackson R. Using thresholds based on risk of cardiovascular disease to target treatment for hypertension: modelling events averted and number treated. *BMJ*. 2000;320:680-5.
- S4.4-68. Eddy DM, Adler J, Patterson B, et al. Individualized guidelines: the potential for increasing quality and reducing costs. *Ann Intern Med*. 2011;154:627-34.
- S4.4-69. Karmali KN, Lloyd-Jones DM. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. *Hypertension*. 2017;69:e2-9.
- S4.4-70. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure

- to guide antihypertensive medication treatment. *J Am Coll Cardiol*. 2017;69:2446-56.
- S4.4-71. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ*. 2016;352:i717.
- S4.4-72. Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010;363:918-29.
- S4.4-73. Reboli G, Gentile G, Angeli F, et al. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. *J Hypertens*. 2011;29:1253-69.
- S4.4-74. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-59.
- S4.4-75. Julius S, Kaciroti N, Egan BM, et al. TROPHY study: Outcomes based on the Seventh Report of the Joint National Committee on Hypertension definition of hypertension. *J Am Soc Hypertens*. 2008;2:39-43.
- S4.4-76. Lüders S, Schrader J, Berger J, et al. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens*. 2008;26:1487-96.
- S4.4-77. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA*. 2014;311:490-7.
- S4.4-78. Inder JD, Carlson DJ, Dieberg G, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. *Hypertens Res*. 2016;39:88-94.
- S4.4-79. Roerecke M, Kaczorowski J, Tobe SW, et al. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2:e108-20.
- S4.4-80. National Institute on Alcohol Abuse and Alcoholism. What Is A Standard Drink? Available at: <https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink>. Accessed August 16, 2017.
- S4.4-81. National Heart, Lung, and Blood Institute. Your Guide to Lowering Your Blood Pressure With DASH—How Do I Make the DASH? Available at: [https://health.gov/dietaryguidelines/dga2005/toolkit/DASH/how\\_make\\_dash.htm](https://health.gov/dietaryguidelines/dga2005/toolkit/DASH/how_make_dash.htm). Accessed January 6, 2019.
- S4.4-82. Top 10 Dash Diet Tips. Available at: <http://dashdiet.org/dash-diet-tips.html>. Accessed January 6, 2019.

## 4.5. Tobacco Use

- S4.5-1. Carson KV, Verbiest MEA, Crone MR, et al. Training health professionals in smoking cessation. *Cochrane Database Syst Rev*. 2012;CD000214.
- S4.5-2. Patnode CD, Henderson JT, Thompson JH, et al. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015;163:608-21.
- S4.5-3. Stead LF, Koilpillai P, Fanshawe TR1, et al. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2016;3:CD008286.
- S4.5-4. Pan A, Wang Y, Talaei M, et al. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: a meta-analysis and systematic review. *Circulation*. 2015;132:1795-804.
- S4.5-5. Mons U, Muezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ*. 2015;350:h1551.
- S4.5-6. Lv X, Sun J, Bi Y, et al. Risk of all-cause mortality and cardiovascular disease associated with secondhand smoke exposure: a systematic review and meta-analysis. *Int J Cardiol*. 2015;199:106-15.
- S4.5-7. U.S. National Center for Chronic Disease Prevention and Health Promotion Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Centers for Disease Control and Prevention; 2014. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK179276>. Accessed January 5, 2019.
- S4.5-8. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet*. 2006;368:647-58.

- S4.5-9. U.S. Department of Health and Human Services. Healthy People 2020. Washington, DC: 2010. Available at: <https://www.healthypeople.gov>. Accessed January 3, 2019.
- S4.5-10. Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*. 2014;130:1418-36.
- S4.5-11. Bhatnagar A. cardiovascular perspective of the promises and perils of e-cigarettes. *Circ Res*. 2016;118:1872-5.
- S4.5-12. Lippi G, Favaloro EJ, Meschi T, et al. E-cigarettes and cardiovascular risk: beyond science and mysticism. *Semin Thromb Hemost*. 2014;40:60-5.
- S4.5-13. Moheimani RS, Bhetraratana M, Yin F, et al. Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: implications for cardiovascular risk. *JAMA Cardiol*. 2017;2:278-84.
- S4.5-14. A clinical practice guideline for treating tobacco use and dependence: a US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline panel, staff, and consortium representatives. *JAMA*. 2000;283:3244-54.
- S4.5-15. Tobacco Use and Dependence Guideline Panel. Treating Tobacco Use and Dependence: 2008 Update. Washington, DC: U.S. Department of Health and Human Services; 2008.
- S4.5-16. Pbert L, Fletcher KE, Flint AJ, et al. Smoking prevention and cessation intervention delivery by pediatric providers, as assessed with patient exit interviews. *Pediatrics*. 2006;118:e810-24.
- S4.5-17. Wang M, Wang J-W, Cao S-S, et al. Cigarette smoking and electronic cigarettes use: a meta-analysis. *Int J Environ Res Public Health*. 2016;13:120. doi: 10.3390/ijerph13010120
- S4.5-18. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013;368:341-50.
- S4.5-19. Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2018;72:3332-65.
- S4.5-20. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387:2507-20.
- S4.5-21. Prochaska JJ, Benowitz NL. The past, present, and future of nicotine addiction therapy. *Annu Rev Med*. 2016;67:467-86.
- S4.5-22. Rigotti NA, Clair C, Munafo MR, et al. Interventions for smoking cessation in hospitalised patients. *Cochrane Database Syst Rev*. 2012;CD001837.
- S4.5-23. U.S. Preventive Services Task Force. Final Recommendation Statement: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. 2017. Available at: <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1>. Accessed January 5, 2019.
- S4.5-24. Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine. Public Health Consequences of E-Cigarettes. 2018. Available at: <http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx>. Accessed January 5, 2019.
- S4.5-25. Ahmed AA, Patel K, Nyaku MA, et al. Risk of heart failure and death after prolonged smoking cessation: role of amount and duration of prior smoking. *Circ Heart Fail*. 2015;8:694-701.
- S4.5-26. Khan RJ, Stewart CP, Davis SK, et al. The risk and burden of smoking related heart disease mortality among young people in the United States. *Tob Induc Dis*. 2015;13:16.
- S4.5-27. NAADAC, the Association for Addiction Professionals. National Certificate in Tobacco Treatment Practice (NCTTP). Available at: <https://www.naadac.org/NCTTP>. Accessed January 5, 2019.
- S4.5-28. Association for the Treatment of Tobacco Use and Dependence (ATTUD). Available at: <http://www.attud.org>. Accessed January 5, 2019.
- S4.5-29. Council for Tobacco Treatment Training Programs. Accredited programs. Available at: <http://ctttp.org/accredited-programs>. Accessed January 30, 2019.
- S4.5-30. Otsuka R, Watanabe H, Hirata K, et al. Acute effects of passive smoking on the coronary circulation in healthy young adults. *JAMA*. 2001;286:436-41.
- S4.5-31. Oono IP, Mackay DF, Pell JP. Meta-analysis of the association between secondhand smoke exposure

- and stroke. *J Public Health (Oxf)*. 2011;33:496-502.
- S4.5-32. U.S. Institute of Medicine Committee on Secondhand Smoke Exposure and Acute Coronary Events. *Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence*. Washington, DC: National Academies Press; 2010. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK219565>. Accessed January 5, 2019.
- S4.5-33. U.S. Department of Health and Human Services. *The health consequences of smoking--50 years of progress: A report of the Surgeon General*. ed. Atlanta, GA: 2014.
- S4.5-34. Tobacco Control Legal Consortium, Public Health Law Center. *HUD's rule to restrict smoking in public housing: an overview*. 2017. Available at: <https://publichealthlawcenter.org/sites/default/files/resources/HUD-Final-Rule-Smoke-Free-Public-Housing-2016.pdf>. Accessed January 5, 2019.
- S4.5-35. University of Southern California. *Rx for change: clinician-assisted tobacco cessation*. Available at: <http://rxforchange.ucsf.edu/>. Accessed January 30, 2019.

#### 4.6. Aspirin Use

- S4.6-1. Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164:804-13.
- S4.6-2. Whitlock EP, Burda BU, Williams SB, et al. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164:826-35.
- S4.6-3. Lotrionte M, Biasucci LM, Peruzzi M, et al. Which aspirin dose and preparation is best for the long-term prevention of cardiovascular disease and cancer? Evidence from a systematic review and network meta-analysis. *Prog Cardiovasc Dis*. 2016;58:495-504.
- S4.6-4. Raju N, Sobieraj-Teague M, Bosch J, et al. Updated meta-analysis of aspirin in primary prevention of cardiovascular disease. *Am J Med*. 2016;129:e35-6.
- S4.6-5. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;300:2134-41.
- S4.6-6. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.
- S4.6-7. Fowkes FGR, Price JF, Stewart MCW, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA*. 2010;303:841-8.
- S4.6-8. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA*. 2014;312:2510-20.
- S4.6-9. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med*. 2018;379:1509-18.
- S4.6-10. García Rodríguez LA, Martín-Pérez M, Hennekens CH, et al. Bleeding risk with long-term low-dose aspirin: a systematic review of observational studies. *PLoS ONE*. 2016;11:e0160046.
- S4.6-11. Capodanno D, Angiolillo DJ. Aspirin for primary cardiovascular risk prevention and beyond in diabetes mellitus. *Circulation*. 2016;134:1579-94.
- S4.6-12. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849-60.
- S4.6-13. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315-81.
- S4.6-14. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease

- and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation*. 2002;106:388-91.
- S4.6-15. Bibbins-Domingo K, U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164:836-45.
- S4.6-16. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379:1529-39.
- S4.6-17. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;392:1036-46.
- S4.6-18. Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Circulation*. 2010;121:2694-701.
- S4.6-19. Halvorsen S, Andreotti F, ten Berg JM, et al. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol*. 2014;64:319-27.
- S4.6-20. Mora S, Manson JE. Aspirin for primary prevention of atherosclerotic cardiovascular disease: advances in diagnosis and treatment. *JAMA Intern Med*. 2016;176:1195-204.
- S4.6-21. Miedema MD, Duprez DA, Misialek JR, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Qual Outcomes*. 2014;7:453-60.
- S4.6-22. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet*. 2018;392:387-99.
- S4.6-23. Ridker PM. Should aspirin be used for primary prevention in the post-statin Era? *N Engl J Med*. 2018;379:1572-4.

## 5. Cost and Value Considerations

- S5-1. Weintraub WS, Daniels SR, Burke LE, et al. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation*. 2011;124:967-90.
- S5-2. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2304-22.
- S5-3. Bress AP, Bellows BK, King JB, et al. Cost-effectiveness of intensive versus standard blood-pressure control. *N Engl J Med*. 2017;377:745-55.
- S5-4. Moran AE, Odden MC, Thanataveerat A, et al. Cost-effectiveness of hypertension therapy according to 2014 guidelines. *N Engl J Med*. 2015;372:447-55.
- S5-5. Park C, Wang G, Durthaler JM, et al. Cost-effectiveness analyses of antihypertensive medicines: a systematic review. *Am J Prev Med*. 2017;53:S131-42.
- S5-6. Richman IB, Fairley M, Jørgensen ME, et al. Cost-effectiveness of intensive blood pressure management. *JAMA Cardiol*. 2016;1:872-9.
- S5-7. Heller DJ, Coxson PG, Penko J, et al. Evaluating the impact and cost-effectiveness of statin use guidelines for primary prevention of coronary heart disease and stroke. *Circulation*. 2017;136:1087-98.
- S5-8. Odden MC, Pletcher MJ, Coxson PG, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. *Ann Intern Med*. 2015;162:533-41.
- S5-9. Heart Protection Study Collaborative Group. Statin cost-effectiveness in the United States for people at different vascular risk levels. *Circ Cardiovasc Qual Outcomes*. 2009;2:65-72.

## 6. Conclusion

S6-1. Lehr AL, Driver SL, Stone NJ. The ABCDs of lifestyle counseling. *JAMA Cardiol.* 2016;1:505-6.

### Appendix 1. Search Criteria

1. Patnode CD, Evans CV, Senger CA, et al. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults without known cardiovascular disease risk factors: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2017;318:175-93.
2. LeBlanc ES, Patnode CD, Webber EM, et al. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2018;320:1172-91.
3. Selph S, Dana T, Bougatsos C, et al. Screening for abnormal glucose and type 2 diabetes mellitus: a systematic review to update the 2008 U.S. Preventive Services Task Force Recommendation. Report No. 13-05190-EF-1. Rockville, MD: U.S. Agency for Healthcare Research and Quality; 2015. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK293871>. Accessed January 5, 2019.
4. Patnode CD, Henderson JT, Thompson JH, et al. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2015;163:608-21.
5. Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2016;164:804-13.



# Circulation