

CLINICAL PRACTICE GUIDELINE

# 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease



A Report of the American Heart Association/American College of Cardiology  
Joint Committee on Clinical Practice Guidelines

*Developed in Collaboration With and Endorsed by the American College of Clinical Pharmacy,  
American Society for Preventive Cardiology, National Lipid Association, and  
Preventive Cardiovascular Nurses Association*

*Endorsed by the Society for Cardiovascular Angiography and Interventions*

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**ABSTRACT**

**AIM** The “2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease” provides an update to and consolidates new evidence since the “2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease” and the corresponding “2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease.”

**METHODS** A comprehensive literature search was conducted from September 2021 to May 2022. Clinical studies, systematic reviews and meta-analyses, and other evidence conducted on human participants were identified that were published in English from MEDLINE (through PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline.

**STRUCTURE** This guideline provides an evidenced-based and patient-centered approach to management of patients with chronic coronary disease, considering social determinants of health and incorporating the principles of shared decision-making and team-based care. Relevant topics include general approaches to treatment decisions, guideline-directed management and therapy to reduce symptoms and future cardiovascular events, decision-making pertaining to revascularization in patients with chronic coronary disease, recommendations for management in special populations, patient follow-up and monitoring, evidence gaps, and areas in need of future research. Where applicable, and based on availability of cost-effectiveness data, cost-value recommendations are also provided for clinicians. Many recommendations from previously published guidelines have been updated with new evidence, and new recommendations have been created when supported by published data.

This document was approved by the American College of Cardiology Clinical Policy Approval Committee and the American Heart Association Science Advisory and Coordinating Committee in January 2023, and the American College of Cardiology Science and Quality Committee and the American Heart Association Executive Committee in April 2023.

The American College of Cardiology requests that this document be cited as follows: Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, Dixon DL, Fearon WF, Hess B, Johnson HM, Kazi DS, Kolte D, Kumbhani DJ, LoFaso J, Mahtta D, Mark DB, Minissian M, Navar AM, Patel AR, Piano MR, Rodriguez F, Talbot AW, Taqueti VR, Thomas RJ, van Diepen S, Wiggins B, Williams MS. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2023;82:833–955.

This article has been copublished in *Circulation*.

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)). For copies of this document, please contact the Elsevier Inc. Reprint Department via fax (212-633-3820) or e-mail ([reprints@elsevier.com](mailto:reprints@elsevier.com)).

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**TOP 10 TAKE-HOME MESSAGES FOR CHRONIC CORONARY DISEASE**

1. Emphasis is on team-based, patient-centered care that considers social determinants of health along with associated costs while incorporating shared decision-making in risk assessment, testing, and treatment.
2. Nonpharmacologic therapies, including healthy dietary habits and exercise, are recommended for all patients with chronic coronary disease (CCD).
3. Patients with CCD who are free from contraindications are encouraged to participate in habitual physical activity, including activities to reduce sitting time and to increase aerobic and resistance exercise. Cardiac rehabilitation for eligible patients provides significant cardiovascular benefits, including decreased morbidity and mortality outcomes.
4. Use of sodium glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists are recommended for select groups of patients with CCD, including groups without diabetes.
5. New recommendations for beta-blocker use in patients with CCD: (a) Long-term beta-blocker therapy is not recommended to improve outcomes in patients with CCD in the absence of myocardial infarction in the past year, left ventricular ejection fraction  $\leq 50\%$ , or another primary indication for beta-blocker therapy; and (b) Either a calcium channel blocker or beta blocker is recommended as first-line antianginal therapy.
6. Statins remain first line therapy for lipid lowering in patients with CCD. Several adjunctive therapies (eg, ezetimibe, PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitors, inclisiran, bempedoic acid) may be used in select populations, although clinical outcomes data are unavailable for novel agents such as inclisiran.
7. Shorter durations of dual antiplatelet therapy are safe and effective in many circumstances, particularly when the risk of bleeding is high and the ischemic risk is low to moderate.
8. The use of nonprescription or dietary supplements, including fish oil and omega-3 fatty acids or vitamins, is not recommended in patients with CCD given the lack of benefit in reducing cardiovascular events.

9. Routine periodic anatomic or ischemic testing without a change in clinical or functional status is not recommended for risk stratification or to guide therapeutic decision-making in patients with CCD.

10. Although e-cigarettes increase the likelihood of successful smoking cessation compared with nicotine replacement therapy, because of the lack of long-term safety data and risks of sustained use, e-cigarettes are not recommended as first-line therapy for smoking cessation.

**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. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA collaborate with other organizations.

**Intended Use**

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 intent is 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.

**Clinical Implementation**

Management, in accordance with guideline recommendations, is effective only when followed 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.

**Methodology and Modernization**

The AHA/ACC Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of

published standards from organizations, including the National Academy of Medicine (formerly the Institute of Medicine),<sup>1,2</sup> and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to health care professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them 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.

In recognition of the importance of cost-value considerations, in certain guidelines, when appropriate and feasible, an assessment of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.<sup>3</sup>

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. When applicable, recommendations will be updated with new evidence or new recommendations will be created when supported by published evidence-based data. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of “full revision” and “focused update” will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual<sup>4</sup> and other methodology articles.<sup>5–7</sup>

### Selection of Writing Committee Members

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as collaborators.

### Relationships With Industry and Other Entities

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 [online](#). Appendix 1 of the guideline lists writing committee members’ comprehensive and relevant RWI; for the purposes of full transparency, comprehensive and relevant disclosure information for the Joint Committee is also available [online](#).

### Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.<sup>4,5</sup> Literature searches focus on randomized controlled trials (RCTs) but also include registries, non-randomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there are  $\geq 1$  questions deemed of utmost clinical importance and merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked “SR”.

### Guideline-Directed Management and Therapy

The term guideline-directed management and therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

*Joshua A. Beckman, MD, MS, FACC, FAHA  
Chair, AHA/ACC Joint Committee on  
Clinical Practice Guidelines*

## 1. INTRODUCTION

### 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review—which included literature derived from research involving human subjects, published in English,

and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline—was conducted from September 24, 2021, to May 2022. Key search words included but were not limited to the following: *AHA/ACC Clinical Practice Guidelines; acute coronary syndrome; angina; cardiac rehabilitation; cardiovascular diseases; coronary artery disease; coronary disease; diabetes; type 2 diabetes; diet; diet therapy; dietary supplements; drug therapy; dual antiplatelet therapy; factor Xa inhibitors; hypertension; outcomes; quality of life; secondary prevention; therapy.*

Additional relevant studies, which were published through November 2022 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the *Online Data Supplement* and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

The ACC and AHA have acknowledged the importance of value in health care to include development of cost-value statements for clinical practice recommendations. Available cost-effectiveness data were determined to be sufficient to support 9 specific recommendations in this guideline (*Section 4.2.6*, “Lipid Management”; *Section 4.2.8*, “SGLT2 Inhibitors and GLP-1 Receptor Agonists”; *Section 5.1*, “Revascularization”; and *Section 8.1*, “Cost and Value Considerations”). As a result, a Level of Value was assigned to those recommendations on the basis of the “ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures,”<sup>1</sup> as shown in **Table 1**. Available quality-of-life (QOL) data were deemed to be insufficient to support specific recommendations in this guideline.

**TABLE 1** **Level of Value for Clinical Guideline Recommendations\***

<b>Level of Value for Clinical Guideline Recommendations*</b>	
Level of Value	
<b>High value:</b> Better outcomes at lower cost or ICER <\$50,000 per QALY gained	
<b>Intermediate value:</b> \$50,000 to <\$150,000 per QALY gained	
<b>Low value:</b> ≥\$150,000 per QALY gained	
<b>Uncertain value:</b> Value examined but data are insufficient to draw a conclusion because of no studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant	
<b>Not assessed:</b> Value not assessed by the writing committee	
Proposed abbreviations for each value recommendation: <i>H</i> indicates high value; <i>I</i> , intermediate value; <i>L</i> , low value; <i>U</i> , uncertain value; and <i>NA</i> , value not assessed.	

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\*Figures used in this table are based on U.S. GDP data from 2012 and were obtained from WHO-CHOICE Cost-Effectiveness Thresholds.<sup>2</sup>

GDP indicates gross domestic product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; and WHO-CHOICE, World Health Organization Choosing Interventions that are Cost-Effective.

## 1.2. Organization of the Writing Committee

The writing committee consisted of general cardiologists, interventional cardiologists, cardiovascular surgeons, cardiac imaging experts, advance practice nurses, clinical pharmacists, health economists, and lay/patient representatives. The writing committee included representatives from the AHA, ACC, American College of Clinical Pharmacy (ACCP), American Society for Preventive Cardiology (ASPC), National Lipid Association (NLA), and Preventive Cardiovascular Nurses Association (PCNA). *Appendix 1* of the current document lists writing committee members’ comprehensive and relevant RWI.

## 1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC and AHA; 1 reviewer each from the ACCP, ASPC, NLA, PCNA, and 6 individual content reviewers. Reviewers’ RWI information was distributed to the writing committee and is published in this document (*Appendix 2*).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the ACCP, ASPC, NLA, PCNA, and Society for Cardiovascular Angiography and Interventions.

## 1.4. Scope of the Guideline

The scope of the “2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease” (referred to hereafter as the “2023 CCD guideline”) is to provide an update to and consolidate new evidence since the publication of the “2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease”<sup>3</sup> and the “2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease”<sup>4</sup> and will replace these prior guidelines.<sup>4</sup> This current document provides a patient-centered approach to management of chronic coronary disease (CCD) incorporating the principles of shared decision-making, social determinants of health (SDOH), and team-based care. Where applicable and based on availability of cost-effectiveness data, value recommendations are also provided for clinicians.

The writing committee acknowledges that care of patients with CCD is a continuum from postacute care in patients presenting with chest pain, acute coronary syndromes (ACS), or both to outpatient CCD-related management. The primary intended audience for this guideline is clinicians in primary care and cardiology specialty who care for patients with CCD in the outpatient setting. It aims to provide succinct recommendations in the domains of diagnostic evaluation, symptom relief, improvement in QOL, and reduction of future

atherosclerotic cardiovascular disease (ASCVD)-related events and heart failure (HF) in patients with CCD. The recommendations provided in this guideline pertain to the chronic outpatient care of patients with CCD. Clinicians are referred to the relevant guidelines when evaluating patients with acute chest pain, ACS, or both.<sup>5–9</sup> See **Table 2** for other relevant guidelines.

#### 1.4.1. CCD Definition

This guideline is intended to apply to the following categories of patients in the outpatient setting:

- Patients discharged after admission for an ACS event or after coronary revascularization procedure and after stabilization of all acute cardiovascular issues.
- Patients with left ventricular (LV) systolic dysfunction and known or suspected coronary artery disease (CAD) or those with established cardiomyopathy deemed to be of ischemic origin.
- Patients with stable angina symptoms (or ischemic equivalents such as dyspnea or arm pain with exertion) medically managed with or without positive results of an imaging test.
- Patients with angina symptoms and evidence of coronary vasospasm or microvascular angina.
- Patients diagnosed with CCD based solely on the results of a screening study (stress test, coronary computed tomography angiography [CTA]), and the treating clinician concludes that the patient has coronary disease.

This guideline is structured to address epidemiology and general principles in the management and transition of care in patients with CCD (**Section 2**, “Epidemiology/General Principles”). This is followed by evaluation of patients with CCD presenting with angina symptoms and risk stratification for future CVD events in patients with CCD (**Section 3**, “Evaluation, Diagnosis, and Risk Stratification”). **Section 4**, “Treatment” focuses on guiding principles in the management of patients with CCD (**Section 4.1**, “General Approach to Treatment Decisions”), overview of lifestyle and medical therapy (**Section 4.2**, “Guideline-Directed Management and Therapy”), and medical therapies to reduce cardiovascular events and manage symptoms (**Section 4.3**, “Medical Therapy to Prevent Cardiovascular Events and Manage Symptoms”) in patients with CCD. This is followed by key considerations in decision-making related to revascularization in patients with CCD (**Section 5**, “Revascularization”). Special populations with key considerations are discussed next (**Section 6**, “Special Populations”), followed by recommendations related to follow-up and monitoring of patients with CCD (**Section 7**, “Patient Follow-up: Monitoring and Managing Symptoms”). Cost and value considerations while treating patients with CCD and future research needs in patients with CCD are covered in **Section 8** (“Other Important Considerations”). Where applicable, key

recommendations from ACC/AHA guidelines and other scientific statements (**Table 2**) pertinent to outpatient management of patients with CCD are referenced and discussed. Readers should refer to these ACC/AHA guidelines and scientific statements for further details.

The writing committee acknowledges several principles while managing patients with CCD. First, the population of patients with CCD is heterogeneous, and the risk of future cardiovascular events is not uniform across this patient population. Therefore, clinicians should prioritize therapies based on a patient’s future risk of CVD-related events. Second, symptom relief and improvement in QOL are extremely important considerations in patients with CCD. In several circumstances and after shared decision-making, clinicians may, as a first step, recommend therapies that improve symptom relief without necessarily improving cardiovascular outcomes. Third, several domains in the management of patients with CCD (eg, lifestyle, medical therapy, management of symptoms, and initial work-up) can be effectively performed by primary care clinicians. Therefore, this guideline acknowledges the principle of collaboration between clinicians in primary care and cardiology specialties. Lastly, the writing committee acknowledges that asymptomatic patients with significant coronary artery calcium noted on cardiac computed tomography (CT) or chest CT performed for noncardiac indications showing extensive coronary artery calcifications without history of a previous ASCVD event, have a high risk of future ASCVD events. Although this guideline does not address those patients, aggressive lifestyle management and the use of evidence-based medical therapies to prevent further progression of atherosclerosis and to reduce the risk of future cardiovascular events remain important considerations in such patients. Readers are referred to the appropriate ACC/AHA guidelines that address ASCVD risk reduction in this patient phenotype.<sup>7,10</sup>

In developing the 2023 CCD guideline, the writing committee reviewed previously published guidelines and related scientific statements. **Table 2** contains a list of these publications deemed pertinent to this writing effort. It is intended for use as a resource, obviating the need to repeat existing guideline recommendations. Some recommendations have been carried forward from previously published guidelines. If unchanged, those recommendations remain current. Any changes to the formatting or content of these recommendations are defined as:

- Modified: formatting changes (eg, minor modifications such as PICO[TS] structure)
- Adapted: substantive changes (eg, major adaptations, such as a change in COR, LOE, drug or device classification).

Changes are depicted in a footnote below the recommendation tables.

**TABLE 2** Associated AHA/ACC Guidelines

Title	Organization	Publication Year (Reference)
<b>Guidelines</b>		
Secondary prevention and risk reduction therapy in coronary and other atherosclerotic disease	AHA/ACCF	2011 <sup>11</sup>
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/SCAI/STS	2012 <sup>3</sup>
Overweight and obesity in adults	AHA/ACC/TOS	2013 <sup>12</sup>
Focused update on stable ischemic heart disease	ACC/AHA	2014 <sup>4</sup>
Focused update on DAPT with coronary artery disease	ACC/AHA	2016 <sup>13</sup>
Ventricular arrhythmias and the prevention of sudden cardiac death	AHA/ACC/HRS	2017 <sup>14</sup>
Management of blood cholesterol	AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA	2018 <sup>10</sup>
Prevention, detection, evaluation, and management of high blood pressure in adults	ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA	2018 <sup>15</sup>
Focused update on patients with atrial fibrillation	AHA/ACC/HRS	2019 <sup>16</sup>
Primary prevention of CVD	ACC/AHA	2019 <sup>7</sup>
Valvular heart disease	ACC/AHA	2021 <sup>17</sup>
Coronary artery revascularization	ACC/AHA/AATS/STS/SCAI	2021 <sup>8</sup>
Evaluation and diagnosis of chest pain	AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR	2021 <sup>6</sup>
Management of heart failure	AHA/ACC/HFSA	2022 <sup>18</sup>
<b>Scientific Statements</b>		
Core components of cardiac rehabilitation and secondary prevention programs	AHA	2007 <sup>19</sup>
Sexual activity and CVD	AHA	2012 <sup>20</sup>
Depression and poor prognosis among patients with CHD	AHA	2014 <sup>21</sup>
Hypertension in patients with CAD	AHA	2015 <sup>22</sup>
Management of clinically significant drug-drug interactions with statins and select agents used in patients with CVD	AHA	2016 <sup>23</sup>
Dietary pattern to achieve adherence to AHA/ACC guidelines	AHA/ACC	2016 <sup>24</sup>
Spontaneous coronary artery dissection	AHA	2018 <sup>25</sup>
CVD in people living with HIV	AHA	2019 <sup>26</sup>
Cardiovascular considerations and pregnant patients	AHA	2020 <sup>27</sup>
Clinical management of stable CAD and type 2 diabetes	AHA	2020 <sup>28</sup>
Psychological health, well-being, and the mind-heart-body connection	AHA	2021 <sup>29</sup>
Air pollution and the impact on CVD	ACC/AHA/ESC	2021 <sup>30</sup>
Cardio-oncology drug interactions	AHA	2022 <sup>31</sup>
<b>Consensus Document/Reports/Presidential Advisory</b>		
Hypertension in elderly	ACCF/AHA	2011 <sup>32</sup>
Diagnostic catheterization	ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS	2012 <sup>33</sup>
Tobacco cessation treatment	ACC	2018 <sup>34</sup>
Novel therapies for cardiovascular risk reduction in patients with type 2 diabetes	ACC	2020 <sup>35</sup>
ASCVD risk reduction in patients with persistent hypertriglyceridemia	ACC	2021 <sup>36</sup>
Anticoagulant and antiplatelet therapy in patients with AF or VT undergoing PCI or with ASCVD	ACC	2021 <sup>37</sup>
Life's Essential 8 and cardiovascular health	AHA	2022 <sup>38</sup>

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Associates (formerly American Academy of Physician Assistants); AATS, American Association for Thoracic Surgery; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACP, American College of Chest Physicians; ACM, American College of Preventive Medicine; ADA, American Diabetes Association; AF, atrial fibrillation; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASCVD, atherosclerotic cardiovascular disease; ASE, American Society of Echocardiography; ASH, American Society of Hypertension; ASNC, American Society of Nuclear Cardiology; ASPC, American Society for Preventive Cardiology; CAD, coronary artery disease; CHD, coronary heart disease; CHEST, American College of Chest Physicians; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; NLA, National Lipid Association; NMA, National Medical Association; PCI, percutaneous coronary intervention; PCNA, Preventive Cardiovascular Nurses Association; SAEM, Society for Academic Emergency Medicine; SCAI, Society for Coronary Angiography and Interventions; SCCM, Society of Critical Care Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCAI, Society for Cardiovascular Angiography and Interventions; SCMR, Society for Cardiovascular Magnetic Resonance; STS, Society of Thoracic Surgery; TOS, The Obesity Society; and VT, venous thromboembolism.

**1.5. Class of Recommendations and Level of Evidence**

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to

risk. The Level of Evidence (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 3).<sup>1</sup>

**TABLE 3 Applying the American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated May 2019)**

CLASS (STRENGTH) OF RECOMMENDATION		LEVEL (QUALITY) OF EVIDENCE†
CLASS 1 (STRONG)	Benefit >> Risk	LEVEL A
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>	<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>	
CLASS 2a (MODERATE)	Benefit >> Risk	LEVEL B-R (Randomized)
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>	<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>	
CLASS 2b (WEAK)	Benefit ≥ Risk	LEVEL B-NR (Nonrandomized)
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>	<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>	
CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only)	Benefit = Risk	LEVEL C-LD (Limited Data)
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>	<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>• Physiological or mechanistic studies in human subjects</li> </ul>	
CLASS 3: Harm (STRONG)	Risk > Benefit	LEVEL C-EO (Expert Opinion)
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>	<ul style="list-style-type: none"> <li>• Consensus of expert opinion based on clinical experience</li> </ul>	

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 1 and 2a; 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
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AF	atrial fibrillation
ARB	angiotensin-receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blocker
CCD	chronic coronary disease
CHD	coronary heart disease
CKD	chronic kidney disease
CMR	cardiovascular magnetic resonance
COVID-19	coronavirus disease 2019
CR	cardiac rehabilitation
CVD	cardiovascular disease
CTA	computed tomography angiography
CCTA	coronary CT angiography
DAPT	dual antiplatelet therapy
DOAC	direct oral anticoagulant
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
FH	familial hypercholesterolemia
FFR	fractional flow reserve
GDMT	guideline-directed management and therapy
GLP-1	glucagon-like peptide-1
HDL	high-density lipoprotein
HF	heart failure
HIV	human immunodeficiency virus
iFR	instantaneous wave-free ratio
INOCA	ischemia with nonobstructive coronary artery
LDL	low-density lipoprotein
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
MBFR	myocardial blood flow reserve
MPI	myocardial perfusion imaging
MI	myocardial infarction
NRT	nicotine replacement therapy
P2Y12	platelet adenosine diphosphate receptor
PET	positron emission tomography
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PPI	proton pump inhibitor

Continued in the next column

Abbreviation	Meaning/Phrase
QOL	quality of life
RAASi	renin-angiotensin-aldosterone system inhibitor
RCT	randomized controlled trial
SAPT	single antiplatelet therapy
SCAD	spontaneous coronary artery dissection
SDOH	social determinants of health
SGLT2	sodium glucose cotransporter 2
SPECT	single-photon emission computed tomography
TIA	transient ischemic attack

## 2. EPIDEMIOLOGY AND GENERAL PRINCIPLES

CCD is a heterogeneous group of conditions that includes obstructive and nonobstructive CAD with or without previous myocardial infarction (MI) or revascularization, ischemic heart disease diagnosed only by noninvasive testing, and chronic angina syndromes with varying underlying causes. Approximately 20.1 million persons in the United States live with CCD, 11.1 million Americans have chronic stable angina pectoris, and approximately one-quarter ( $n=200,000$ ) of all MIs in the United States occur among the 8.8 million persons with CCD who have had a previous MI (Table 4).<sup>1</sup> Despite an approximate 25% overall relative decline in death from coronary heart disease (CHD) over the past decade, it remains the leading cause of death in the United States and worldwide and is associated with substantial individual, economic, and societal burdens.<sup>1</sup> Within the United States (Figures 1 and 2, Table 4) and worldwide (Figure 3), the prevalence of CCD and chronic stable angina vary by age, sex, race, ethnicity, and geographic region, and the role of SDOH in both risk for and outcomes from CCD is increasingly recognized.<sup>1</sup>

Since the publication of the “2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease,”<sup>2</sup> not only have health care expenditures for CCD remained high, but also the number and complexity of comorbid conditions and concurrent treatments for those conditions among patients with CCD have increased. For example, older age and chronic kidney disease (CKD) commonly coexist with CCD and independently and together raise unique considerations for diagnosis, risk stratification, and treatment. At the intersection between CCD and atrial fibrillation (AF), new information informs the use of antiplatelet therapy and anticoagulation in patients with CCD and atrial fibrillation. Additionally, as the population ages and both CCD and cancer survival improve, concurrent CCD and cancer more often coexist, and the field of cardio-oncology has emerged to address the challenges of these intersecting chronic conditions.

**TABLE 4 U.S. Heart Disease Prevalence, by Age, Race, Ethnicity, and Sex, 2015 to 2018**

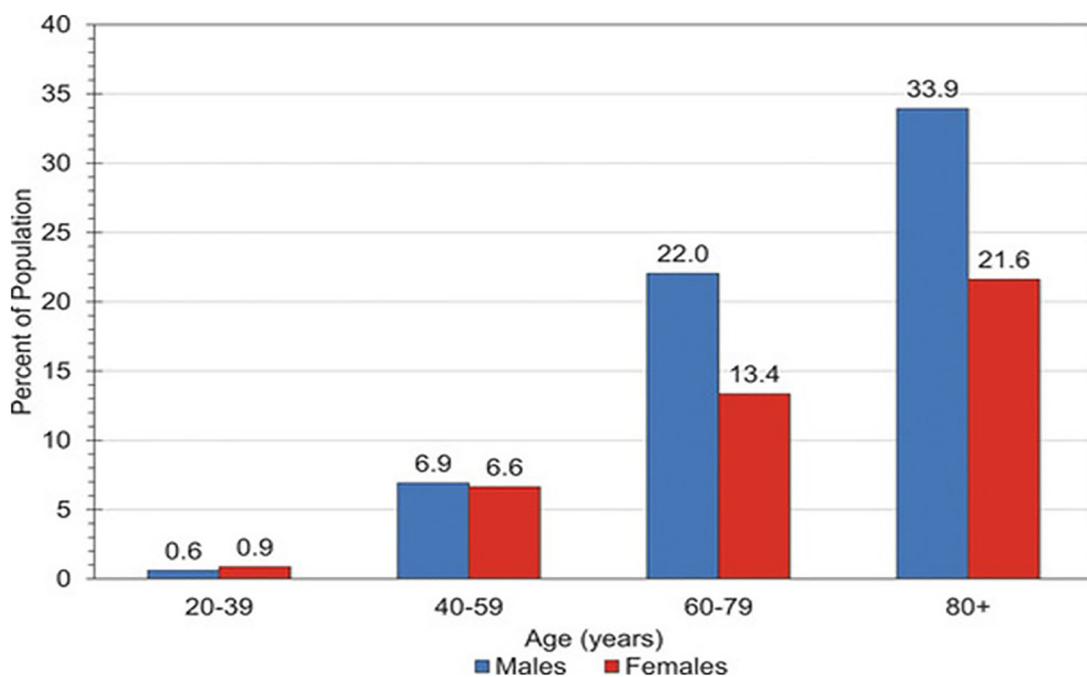
Population Group	Prevalence, CHD, 2015-2018, Age $\geq 20$ y	Prevalence, MI, 2015-2018, Age $\geq 20$ y	Prevalence, AP,* 2015-2018, Age $\geq 20$ y
Both sexes	20.1 million (7.2% [95% CI, 6.5-7.9])	8.8 million (3.1% [95% CI, 2.7-3.6])	11 million (4.1%)
Men	11 million (8.3%)	5.8 million (4.3%)	5.3 million (4.2%)
Women	9.1 million (6.2%)	3 million (2.1%)	5.7 million (4.0%)
NH White men	8.7%	4.4%	4.5%
NH White women	6.0%	2.0%	4.0%
NH Black men	6.7%	3.9%	3.3%
NH Black women	7.2%	2.3%	4.7%
Hispanic men	6.8%	3.7%	3.5%
Hispanic women	6.4%	2.1%	4.3%
NH Asian men	5.0%	2.7%	2.1%
NH Asian women	3.2%	0.7%	2.2%
NH Native American/Alaska Native	—	—	—

CHD includes people who responded "yes" to at least 1 of the questions in "Has a doctor or other health professional ever told you that you had CHD, angina or angina pectoris, heart attack, or MI?" Those who answered "no" but were diagnosed with Rose angina are also included (the Rose questionnaire is administered only to survey participants  $>40$  y of age). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading. Source: Prevalence of CHD: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey and Behavioral Risk Factor Surveillance System data.<sup>3,4</sup> Percentages for racial and ethnic groups are age adjusted for Americans  $\geq 20$  y of age. Age-specific percentages are extrapolated to the 2018 U.S. population estimates. These data, based on self-reports, include people who either answered "yes" to the question of ever having angina or angina pectoris or were diagnosed with Rose angina (the Rose questionnaire is administered only to survey participants  $>40$  y of age). Percentages for racial and ethnic groups are age adjusted for U.S. adults  $\geq 20$  y of age. Estimates from NHANES 2015 to 2018 were applied to 2018 population estimates ( $\geq 20$  y of age).

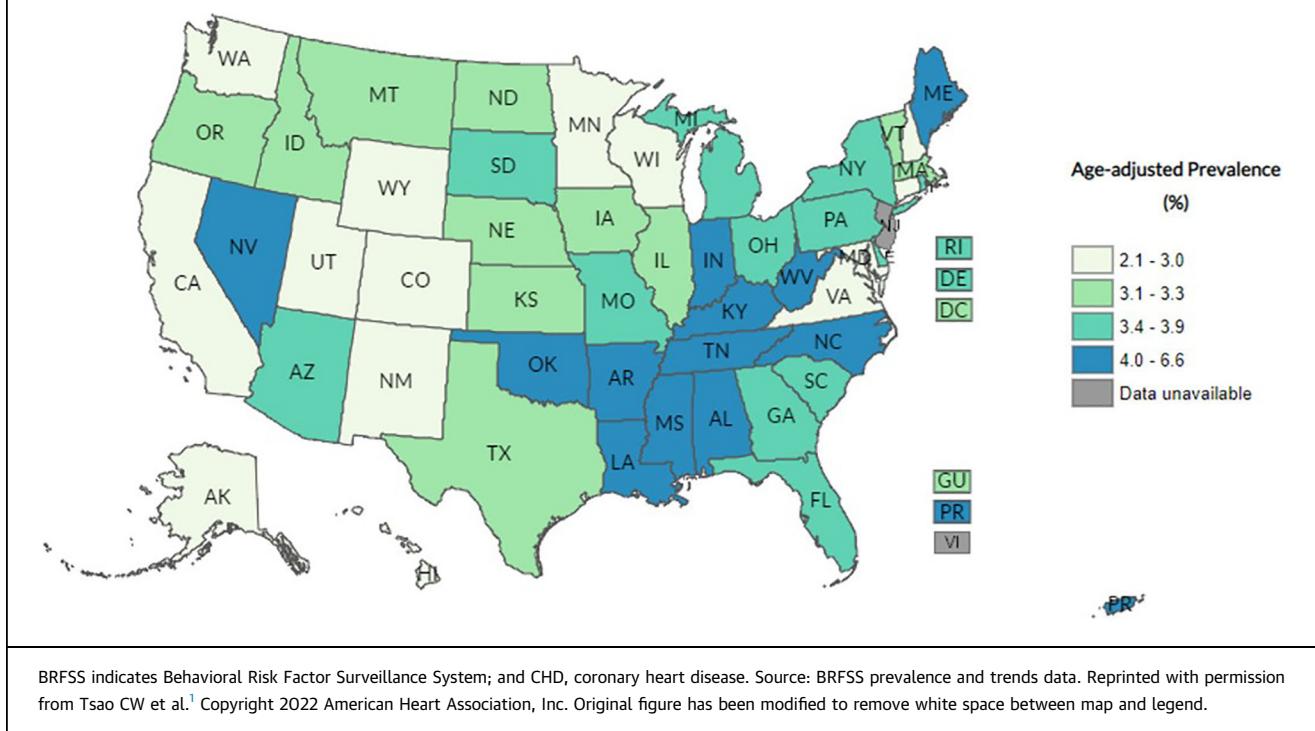
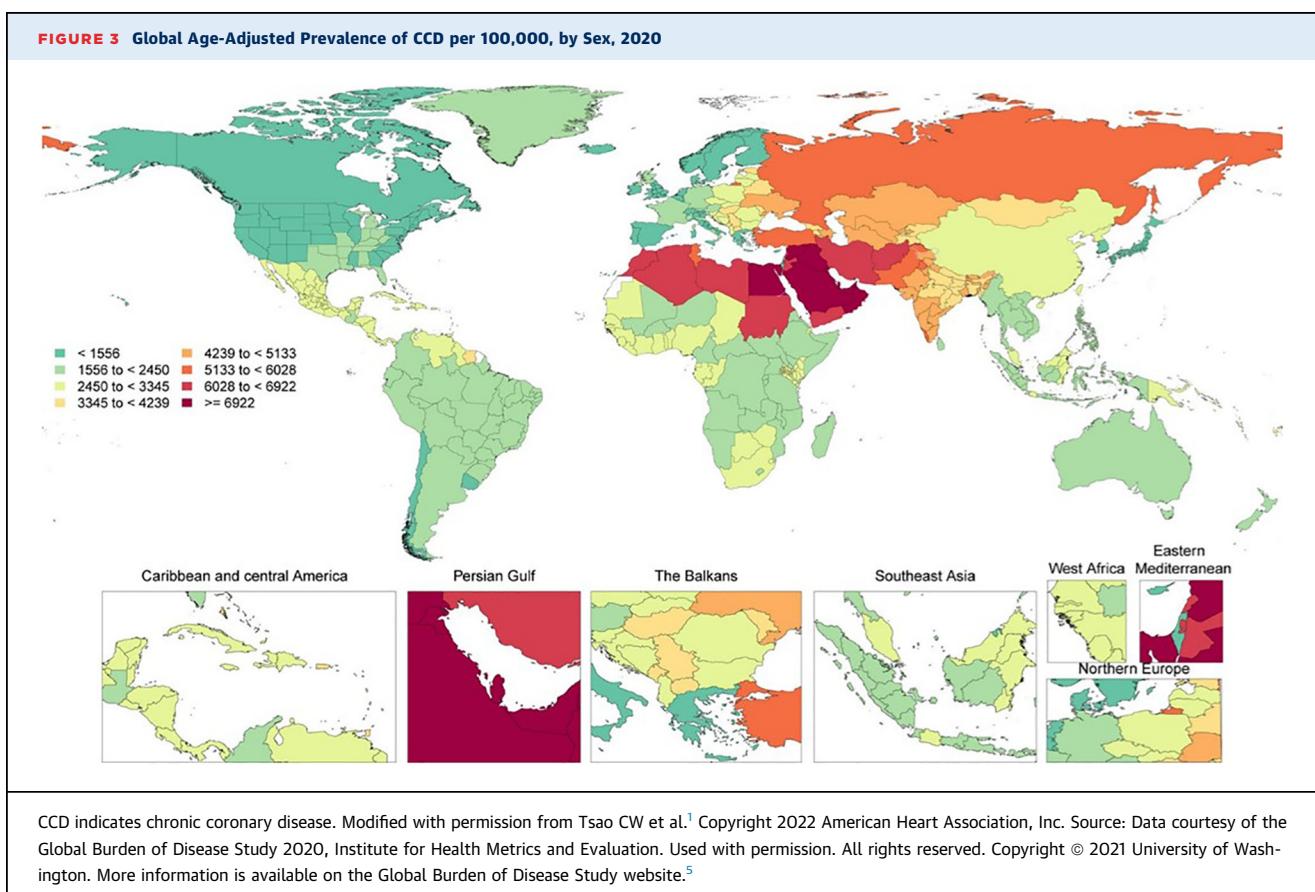
\*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without MI.

AP indicates angina pectoris; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; and NH, non-Hispanic.

Adapted with permission from Tsao CW, et al.<sup>1</sup> Copyright 2022 American Heart Association, Inc.

**FIGURE 1 U.S. Prevalence of CHD per 100,000, by Age and Sex (NHANES 2015 to 2018)**

CHD indicates coronary heart disease. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 15, 2021. <https://www.cdc.gov/nchs/nhanes/>. Reprinted with permission from Tsao CW et al.<sup>1</sup> Copyright 2022 American Heart Association, Inc.

**FIGURE 2** "Ever Told You Had Angina or CHD?" Age-Adjusted U.S. Prevalence, by State (BRFSS Prevalence and Trends Data, 2019)**FIGURE 3** Global Age-Adjusted Prevalence of CCD per 100,000, by Sex, 2020

Further, the fields of diabetes and lipid management have evolved rapidly with multiple new therapies (eg, sodium glucose cotransporter 2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, bempedoic acid, and inclisiran) emerging in these areas, and the range of diagnostic and interventional procedures available for use in patients with CCD has expanded. Thus, this guideline will address established diagnostic, risk stratification, and treatment approaches in a

contemporary context, new therapies, and the intersection between CCD and other comorbid diseases in a framework that recognizes the importance of shared decision-making, team-based care, and cost and value.

### 3. EVALUATION, DIAGNOSIS, AND RISK STRATIFICATION

#### 3.1. Diagnostic Evaluation

##### Recommendations for Diagnostic Evaluation

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	B-NR	<ol style="list-style-type: none"><li>In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, stress positron emission tomography/single photon emission CT myocardial perfusion imaging (PET/SPECT MPI), cardiovascular magnetic resonance (CMR) imaging, or stress echocardiography is recommended to detect the presence and extent of myocardial ischemia, estimate risk of major adverse cardiovascular events (MACE), and guide therapeutic decision-making.*<sup>1-23</sup></li></ol>
1	B-R	<ol style="list-style-type: none"><li>In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, invasive coronary angiography (ICA) is recommended for guiding therapeutic decision-making with the goal of improving anginal symptoms.*<sup>24-28</sup></li></ol>
2a	B-R	<ol style="list-style-type: none"><li>In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, when selected for rest/stress nuclear MPI, PET is reasonable in preference to SPECT, if available, to improve diagnostic accuracy and decrease the rate of nondiagnostic test results.*<sup>29</sup></li></ol>
2a	B-NR	<ol style="list-style-type: none"><li>In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, exercise treadmill testing can be useful to determine whether the symptoms are consistent with angina pectoris, assess the severity of symptoms, evaluate functional capacity, and guide management.*<sup>26,30-32</sup></li></ol>
2a	B-NR	<ol style="list-style-type: none"><li>In patients with CCD undergoing stress PET MPI or stress CMR imaging, the addition of myocardial blood flow reserve (MBFR) can be useful to improve diagnostic accuracy and enhance risk stratification.*<sup>18-23</sup></li></ol>
2a	B-NR	<ol style="list-style-type: none"><li>In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, and who have had previous coronary revascularization, coronary CT angiography (CCTA) is reasonable to evaluate bypass graft or stent patency (for stents ≥3 mm).*<sup>33-37</sup></li></ol>

\*Modified from the 2021 AHA/ACC/Multisociety Guideline for the Evaluation and Diagnosis of Chest Pain.<sup>38</sup>

#### Synopsis

In patients with CCD, if there is an opportunity to do so, clinicians should first intensify GDMT and defer testing. In patients with CCD, assessing the severity of ischemia may be useful to guide clinical decision-making regarding the use of ICA and for intensification of preventive and anti-ischemic therapy. Imaging should be considered in those with new-onset or persistent stable chest pain. In patients with CCD and frequent angina or severe stress-induced ischemia, referral to ICA or CCTA is an option.<sup>26</sup> For additional recommendations about known obstructive and nonobstructive CAD, suspected ischemia, ischemia with nonobstructive coronary arteries (INOCA), role of invasive testing, and revascularization, refer to the 2021

AHA/ACC chest pain guideline,<sup>38</sup> the 2021 ACC/AHA/SCAI revascularization guideline,<sup>39</sup> as well as Section 6.1.2 (“Ischemia With Nonobstructive Coronary Arteries”) of this guideline. Additionally, cost-value considerations for diagnostic testing contained within the 2021 AHA/ACC chest pain guideline, Section 5.3, should be considered.<sup>38</sup>

#### Recommendation-Specific Supportive Text

- Observational studies reveal that patients with moderate to severe ischemia on PET and SPECT MPI have an improved outcome with early coronary revascularization.<sup>7,21,40-43</sup> Clinical trials of CMR imaging that included subgroups of patients with obstructive CAD, showed comparable diagnostic accuracy to stress

SPECT MPI.<sup>10,11</sup> Several large, multicenter registries revealed that stress CMR imaging effectively risk stratifies patients with known CAD.<sup>14–17</sup> In a multi-center registry of 2,496 patients with a history of CAD, an abnormal stress CMR image was associated with a nearly 2-fold increased mortality hazard.<sup>14</sup> Registry data also reported that patients with chest pain syndrome with ischemia by MPI and scarring by late gadolinium enhancement had a relative hazard of 1.5 to 2.1 for cardiovascular death or nonfatal MI.<sup>17</sup> Prognosis worsens for patients by the extent and severity of inducible wall motion abnormalities on stress echocardiography.<sup>44,45</sup> Recent randomized trial evidence supports the role of stress echocardiography to guide clinical decision-making. From the ORBITA (Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial, a secondary outcome was a greater reduction in the stress echocardiographic wall motion score among patients with single-vessel CAD treated with percutaneous coronary intervention (PCI) compared with placebo ( $P<0.0001$ ).<sup>46</sup> Patients with PCI and who have a wall motion score  $\geq 1$  were more often angina-free compared with those in the placebo arm.

2. Randomized trials of patients with CCD reveal a pattern that ischemia-guided PCI results in an improvement in angina when compared with medical therapy alone.<sup>24–26,47,48</sup> In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical & Invasive Approaches) trial, 5,179 patients with stable CAD and site-determined moderate-severe ischemia on stress testing (patients with  $\geq 50\%$  left main stenosis on CCTA, left ventricular ejection fraction [LVEF]  $<35\%$ , and unacceptable angina on medical therapy were excluded) were randomized to invasive versus conservative care strategies.<sup>26</sup> No difference in the composite primary MACE (cardiovascular death, MI, hospitalization for unstable angina, HF, or resuscitated cardiac arrest) endpoint was observed at  $\sim 3.3$  years of follow-up. Angina symptoms improved in both the conservative and invasive treatment arms, although improvements were larger in the invasive arm, particularly with more frequent angina at baseline.<sup>48</sup>

Therefore, in patients with CCD with known anatomy and ongoing angina despite GDMT, early invasive angiography and revascularization should be considered to improve symptoms. Notably, secondary analyses of RCTs have reported no differences in major adverse cardiovascular outcomes in medical versus invasive medical treatment strategies in patient with CCD<sup>49</sup> when stratified by ischemia severity on noninvasive testing.

3. The improved diagnostic accuracy of PET MPI is helpful in patients with known CAD. In a randomized trial of 322 symptomatic patients with known CAD, the presence of low- and high-risk stress PET findings was associated with lower and higher rates of ICA when compared with SPECT MPI ( $P=0.001$ ).<sup>29</sup>
4. Observational studies of patients with CAD and stable chest pain have shown that exercise treadmill testing can be useful by evaluating the relation of symptoms to graded stress testing, thereby helping to confirm the diagnosis of angina pectoris; assessing symptom severity; and selecting appropriate management (eg, medical therapy, revascularization, cardiac rehabilitation [CR]).<sup>26,30–32</sup>
5. Reduced MBFR reflects abnormalities of flow within the epicardial coronary arteries, microvasculature, or both, and independently predicts risk of major CAD events. Measurement of MBFR can be effectively accomplished using PET<sup>18,50,51</sup> or CMR.<sup>15</sup> Normal MBFR may be helpful in excluding high-risk anatomy, although global reduced levels ( $<2$ ) may provide a better estimate of disease extent and severity. Non-obstructive CAD with reduced MBFR is more frequently observed in women.<sup>50</sup>
6. CCTA is accurate for the assessment of native vessel CAD and bypass graft patency with high accuracy ( $\sim 96\%$ ) and concordance (82% to  $>93\%$ ) to ICA. It may also be useful to assess patency of proximal large stents ( $\geq 3$  mm) if such information is known at the time of presentation.<sup>33–37</sup> Other modalities may be considered in patients with CCD with smaller or more distal stents. Several controlled clinical trials have evaluated the concordance of fractional flow reserve (FFR)-CT with invasive FFR.<sup>52–55</sup> Diagnostic sensitivity of FFR-CT compared with invasive FFR is high.<sup>19,53</sup>

### 3.2. Risk Stratification and Relationship to Treatment Selection

**Recommendations for Risk Stratification and Relationship to Treatment Selection**  
Referenced studies that support the recommendations are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATIONS
<b>Risk Stratification and Prognosis</b>		
1	B-NR	1. In patients with CCD, it is recommended that risk stratification incorporate all available information, including noninvasive, invasive, or both cardiovascular diagnostic testing results or use validated risk scores to classify patients as low (<1%), intermediate (1%-3%), or high (>3%) yearly risk for cardiovascular death or nonfatal MI. <sup>1-4</sup>
<b>Relationship to Treatment</b>		
1	A	2. In patients with CCD, optimization of GDMT is recommended to reduce MACE.* <sup>5-7</sup>
1	A	3. In patients with CCD with newly reduced LV systolic function, clinical heart failure, or both, ICA is recommended to assess coronary anatomy and guide potential revascularization. <sup>8,9</sup>
3: No benefit	A	4. In patients with CCD, ICA for risk stratification is not routinely recommended in patients without LV systolic dysfunction, heart failure, stable chest pain refractory to GDMT, and/or noninvasive testing suggestive of significant (>50%) left main disease. <sup>5-7,10,11</sup>

\*Modified from the 2021 AHA/ACC/Multisociety Guideline for the Evaluation and Diagnosis of Chest Pain.<sup>12</sup>

#### Synopsis

In patients with CCD, the results of noninvasive or invasive testing alone are insufficient to accurately risk stratify an individual's annual future risk of future cardiovascular death or nonfatal MI.<sup>13</sup> Clinicians should integrate cardiovascular test results with demographic, social, and medical variables (Table 5) and use validated risk prediction models (where available) to estimate the annual cardiovascular risk. Although multiple randomized trials have shown that routine revascularization does not lead to a reduction in MACE, a symptom and integrated risk assessment may help identify subsets of patients, such as those with persistent angina, reduced LV function or HF, who may benefit from routine revascularization.<sup>5-8,14</sup>

#### Recommendation-Specific Supportive Test

1. Noninvasive test results alone are insufficient to adequately risk stratify patients with CCD, and the additional information improves risk prediction.<sup>4</sup> In an externally validated study of patients who underwent an exercise stress testing, the Duke Treadmill Score alone had a c-index of 0.62 for all-cause death, but the addition of clinical variables into an integrated risk score improved discrimination (c-index=0.83) and reclassified 64% of low-risk Duke Treadmill Score scores to intermediate or high risk.<sup>1</sup> Externally validated risk scores lack some functional and anatomic testing modalities, but observational studies and secondary analyses from randomized trials consistently

**TABLE 5** Potential Features Associated With a Higher Risk of MACE Among Patients With Established CCD

**Demographics and Socioeconomic Status (also see Section 4.1.4, "Social Determinants of Health")**

Age

Male sex

Poor social support

Poverty or lack of health care access

**Past or Concurrent Medical, Mental Health Conditions**

Elevated body mass index

Previous MI, PCI, or CABG

HF

Atrial fibrillation or flutter

Diabetes

Dyslipidemia

Chronic kidney disease

Current or former smoker

Peripheral artery disease

Depression

Poor adherence with goal-directed pharmacotherapy

**Ancillary Cardiac Testing or Imaging**

Inability to exercise

Angina with stress

ECG: left bundle branch block, left ventricular hypertrophy, higher resting heart rate

Echocardiography: reduced left ventricular ejection fraction, left ventricular hypertrophy

*Continued on the next page*

**TABLE 5** Continued

EST: higher DTS, higher resting heart rate, achieved heart rate <85% predicted
Exercise or dobutamine stress echocardiography: higher DTS, lower exercise workload, peak rate-pressure product <15,000, coronary flow reserve <2, no change or increase in left ventricular end-systolic volume, reduced ejection fraction, ischemic electrocardiographic changes with stress
SPECT or PET: Percentage fixed myocardium on SPECT, transient ischemic dilation with stress, reduced coronary flow reserve, ischemic electrocardiographic changes with stress
Higher calcium score: alone and in addition to functional imaging
CCTA: total plaque burden, high-risk plaque (positive remodeling [remodeling index >1.1], low attenuation [mean CT number <30 HU], or napkin-ring sign), reduced CT-fractional flow reserve
CMR: reduced left and/or right ventricular ejection fraction, left ventricular hypertrophy, scar or infarct, reduced myocardial perfusion reserve, myocardial blood flow at stress
<b>Biomarkers</b>
High-sensitivity troponin, B-type natriuretic peptide

CABG indicates coronary artery bypass graft; CCD, chronic coronary disease; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; DTS, Duke Treadmill Score; ECG, electrocardiogram; EST, exercise stress test; HF, heart failure; HU, Hounsfield units; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PET, positron emission tomography; and SPECT, single-photon emission computed tomography.

report that the addition of clinical and ancillary imaging variables are associated with improved risk prediction (Table 5).<sup>3,4,15–44</sup> A meta-analysis of 165 studies reported that in patients with a normal functional test for CCD, a negative study did not uniformly predict a <1% annual risk of cardiovascular death or nonfatal MI, suggesting that population and patient differences may be associated with prognosis.<sup>13</sup> The lone exception is a normal CCTA.<sup>45,46</sup> Previous AHA/ACC guidelines have recommended stratifying patients with CCD as low (<1% annual risk), intermediate (1%–3% annual risk), or high (>3% annual risk) risk for MACE.<sup>47,48</sup> Although these cutoffs are somewhat arbitrary and may be grounded in historical Bethesda Conference recommendations based on Duke Treadmill Score risk tertiles, we suggest maintaining these categorizations for annual cardiovascular death or nonfatal MI.<sup>47,49,50</sup>

2. The 2021 AHA/ACC chest pain guideline recommends the optimization of anti-ischemic and preventive therapies with the goal to reduce the patient's angina burden and improve clinical outcomes.<sup>12</sup> Three major RCTs including COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), ISCHEMIA, and BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) have shown that there is no reduction in MACE with routine cardiovascular revascularization.<sup>5–7</sup> The COURAGE trial, which included patients with stabilized Canadian Cardiovascular Society class IV angina and at least a 70% stenosis in at least 1 coronary artery with evidence of ischemia, reported no difference in all-cause death or

nonfatal MI between revascularization with PCI and optimal medical therapy. The BARI-2D trial randomized patients with type 2 diabetes and CCD ( $\geq 70\%$  stenosis of a major coronary artery and angina or  $\geq 50\%$  stenosis of a major coronary artery with a positive stress test) to revascularization or medical therapy and reported no difference in survival.

3. The STICH (Surgical Treatment for Ischemic Heart Failure) trial randomized 1,212 patients with an ejection fraction  $\leq 35\%$  with coronary disease amenable to coronary artery bypass grafting (CABG) to either medical therapy alone or medical therapy and CABG. After a median follow-up of 56 months, no significant difference was observed in the primary outcomes of all-cause death (41% versus 36%;  $P=0.12$ ), but cardiovascular death (33% versus 28%;  $P=0.05$ ) and all-cause death or cardiovascular hospitalization (68% versus 58%;  $P<0.001$ ) were lower in the CABG arm.<sup>9</sup> In a secondary analysis of the ISCHEMIA trial, 398 participants had HF or an LVEF <45%. Both the 4-year primary composite endpoint (17.2% versus 29.3%; event rate difference,  $-12.1\%$  [95% CI,  $-22.6$  to  $-1.6$ ]) and cardiovascular death or MI (14.6% versus 25.9%; event rate difference  $-11.4\%$  [95% CI,  $-21.4$  to  $-1.4$ ]) were lower in the invasive treatment arm.<sup>8</sup> The REVIVED-BCIS2 trial randomized 700 patients with and LVEF  $\leq 35\%$  with CCD amenable to PCI to either medical therapy or PCI plus medical therapy and reported no difference all-cause death or health failure hospitalization (38.0% versus 37.2%).<sup>51</sup> In addition to revascularization, ICA can also help diagnose the cause of HF and help direct medical therapies (eg, lipid lowering). We acknowledge the data are less robust for patient with HF with preserved ejection fraction.<sup>9</sup> Noninvasive modalities may be appropriate to evaluate for coronary ischemia in some circumstances. Alternatively, CCTA may be considered as an initial diagnostic strategy in selected patients with suspected nonischemic cardiomyopathy.<sup>52</sup>
4. Three multicenter trials (COURAGE, BARI 2D, ISCHEMIA) showed no improvement in clinical endpoints in patients with CCD randomized to routine revascularization plus GMDT or initial GMDT; although 21% to 42% of patients randomized to GMDT eventually underwent revascularization.<sup>5–7</sup> In a secondary analysis of the ISCHEMIA trial, although ischemia severity on noninvasive testing was associated with all-cause death, no treatment interaction was observed when participants were stratified by mild, moderate, or severe ischemia.<sup>10</sup> Similarly, in a secondary analysis of the COURAGE trial limited to the 60% of patients with stress perfusion imaging and coronary angiography information available, there was no interaction between therapeutic strategy and either severity of ischemia or coronary anatomy.<sup>11</sup>

## 4. TREATMENT

### 4.1. General Approach to Treatment Decisions

#### Recommendations for General Approach to Treatment Decisions

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	C-LD	1. In patients with CCD, clinical follow-up at least annually is recommended to assess for symptoms, <sup>1-12</sup> change in functional status, adherence to and adequacy of lifestyle and medical interventions, <sup>13-15</sup> and monitoring for complications of CCD and its treatments. <sup>16-18</sup>
2b	B-NR	2. In patients with CCD, use of a validated CCD-specific patient-reported health status measure may be reasonable to assess symptoms, functional status, and QOL. <sup>19-23</sup>

#### Synopsis

The ultimate goals for treatment of CCD are to prolong survival and improve QOL. To do this, treatments should target a reduction in (1) cardiac death, (2) nonfatal ischemic events, (3) progression of atherosclerosis, and (4) symptoms and functional limitations of CCD while considering patient preferences, potential complications of procedures/medications, and costs to the health care system. When engaging patients in shared decision-making (Section 4.1.3), clinicians should clearly identify that some therapies may improve patient's symptoms whereas other therapies may reduce the risk of ischemic events. To optimize treatment for each patient, several factors should be considered (Figure 4).<sup>24,25</sup>

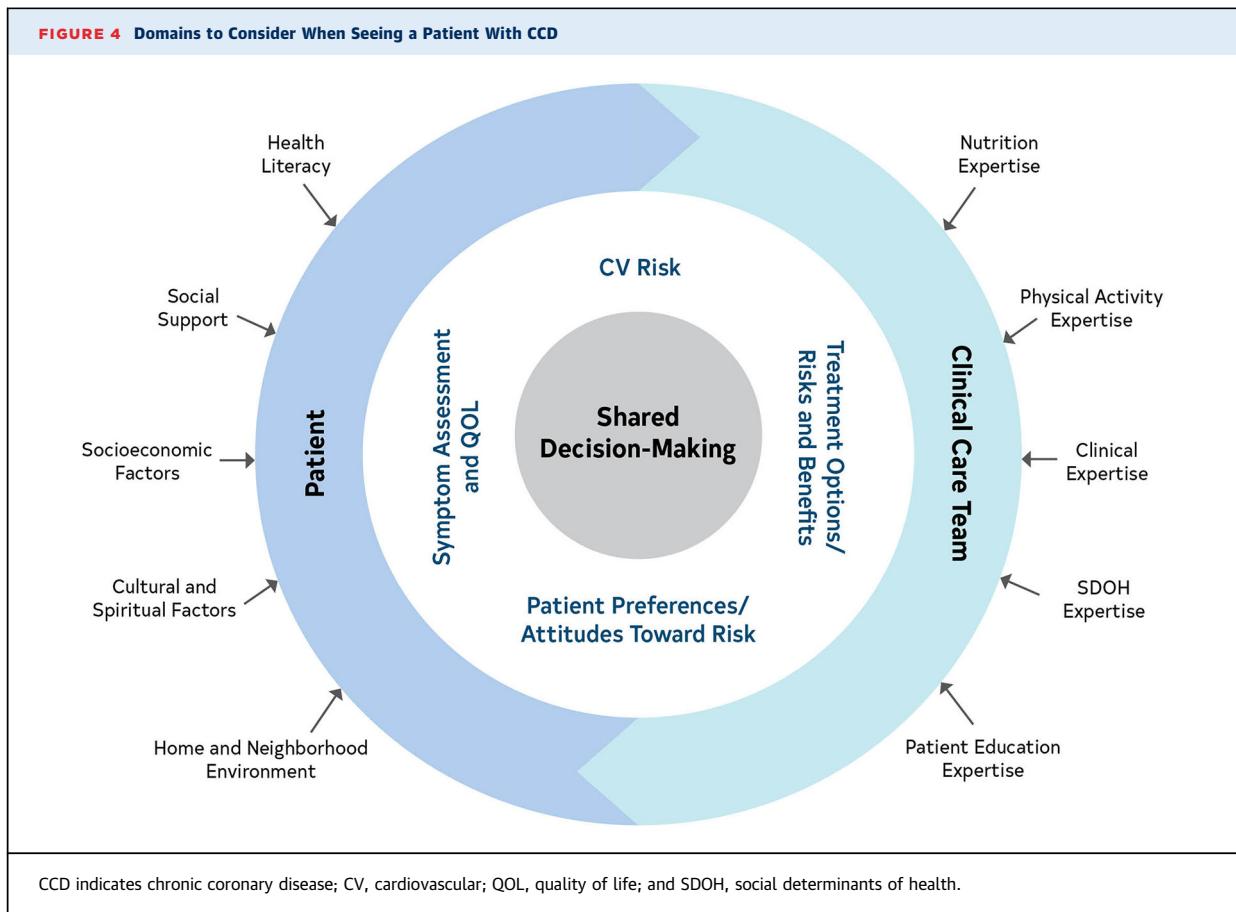
First, a global assessment of the risk of the patient is needed (Section 3), including both the risk of ischemic events and complications of potential treatment options. Second, obtaining a careful assessment of symptoms of CCD, functional limitations, and QOL is important. Third, SDOH (Section 4.1.4) must be considered. Fourth, the patient must be educated (Section 4.1.2) so they can actively participate in shared decision-making (Section 4.1.3). Finally, a team-based approach (Section 4.1.1) can help patients and clinicians navigate this process.

#### Recommendation-Specific Supportive Text

1. Patients with CCD comprise a heterogeneous group that includes those with or without angina, a history of coronary revascularization, and previous ACS. The goals of routine clinical follow-up in these patients include: (a) to assess for new or worsened symptoms, change in functional status, or decline in QOL; (b) to assess for adherence to and adequacy of recommended lifestyle and medical interventions, including physical

activity, nutrition, weight management, stress reduction, smoking cessation, immunization status, blood pressure (BP) and glycemic control, and antianginal, antithrombotic, and lipid-lowering therapies<sup>13-15</sup>; and (c) to monitor for complications of disease or adverse effects related to therapy.<sup>16,17</sup> Although there are insufficient data on which to base a definitive recommendation regarding frequency, clinical follow-up evaluation at least annually is recommended and may be sufficient if the patient is stable on optimized GDMT and reliable enough to seek care with a change in symptoms or functional capacity. For select individuals, an annual in-person evaluation may be supplemented with telehealth visits when clinically appropriate.<sup>26</sup> Implementation of remote, algorithmically driven-disease management programs may provide a useful adjunctive strategy to achieve GDMT optimization in eligible patients.<sup>27</sup>

2. Revascularization<sup>1-3,12</sup> and antianginal medications<sup>4-7</sup> primarily reduce the symptoms of CCD. The factor most strongly associated with improvement in symptoms and QOL after revascularization is the burden of ischemic symptoms before intervention.<sup>8-12,28-30</sup> Thus, assessment of symptoms at each clinic visit is important to identify times when additional interventions could be useful, as well as to quantify the symptomatic response to interventions. Observational studies suggest that clinicians may inaccurately estimate the burden of ischemic symptoms,<sup>19-21</sup> which can lead to under-<sup>22</sup> or overtreatment.<sup>21</sup> Validated patient-reported disease-specific health status measures (eg, 7-item Seattle Angina Questionnaire<sup>31</sup>) may help to reliably quantify the burden of CCD symptoms and reduce variation in assessment among clinicians.<sup>23</sup> Furthermore, patient-reported disease-specific health



status instruments also measure how the patient's angina affects their QOL, which should be an important component of the treatment decision process. Although several studies showed deficiencies with clinician estimation of patient's symptoms, no studies

show an improvement in quality of care or outcomes with routine use of patient-reported measures in clinical care.

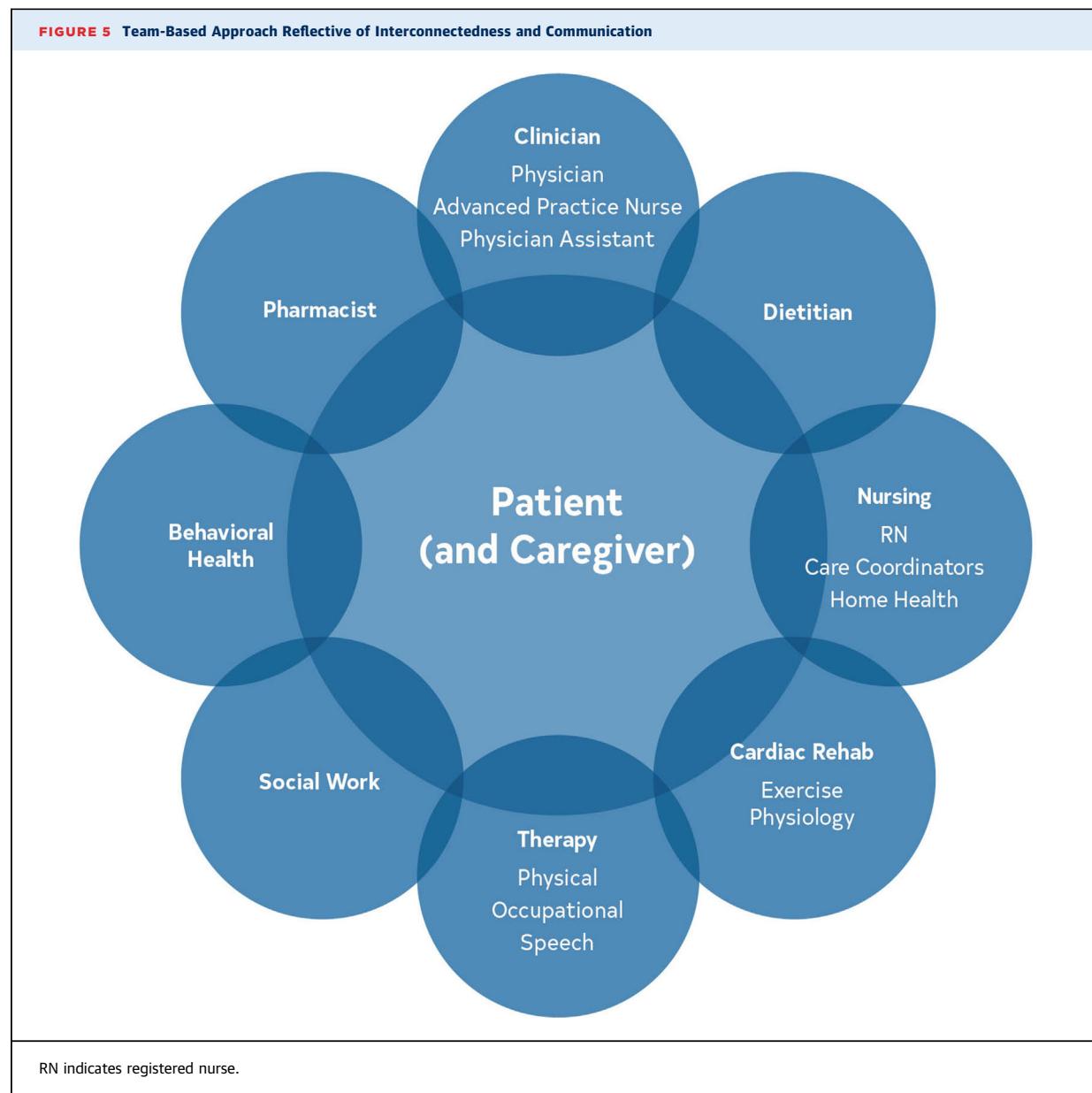
#### 4.1.1. Team-Based Approach

##### Recommendation for Team-Based Approach

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
1	A	1. In patients with CCD, a multidisciplinary team-based approach is recommended to improve health outcomes, facilitate modification of ASCVD risk factors, and improve health service utilization.* <sup>1-13</sup>

\*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.<sup>14</sup>



### Synopsis

A patient-centered, team-based approach that focuses on shared decision-making is essential to monitoring and managing patients' CCD symptoms throughout their disease course. These recommendations apply to all aspects of clinical practice for long-term management of CCD. A team-based approach can effectively be applied to nearly all aspects of CCD management and care. Continuous

communication among the care team, the patient, and any caregivers is essential to optimize outcomes and meet patient needs. **Figure 5** reflects the interconnectedness of the patient and caregiver to the care team and the care team members to each other. Components of the health care team include but are not limited to: physicians; nurse practitioners; physician assistants; nurses and nursing assistants; pharmacists; dietitians; exercise physiologists;

physical, occupational, and speech therapists; psychologists; and social workers.

#### **Recommendation-Specific Supportive Text**

1. RCTs and systematic reviews with meta-analysis show that a patient-centered, multidisciplinary, team-based approach can improve patient self-efficacy, health-related QOL, and ASCVD risk factor management compared with usual care in patients with CCD who also may have hypertension, diabetes, or hyperlipidemia.<sup>1–8,11–13,15–34</sup> Patients actively involved in their care with the medical team tend to have greater knowledge and confidence in self-management, which improves health-related QOL.<sup>1,21,32</sup> Team-based care also facilitates behavior change and promotes weight loss, tobacco cessation, and reduces depression.<sup>8,12,16,31,33,35</sup> A team-based approach may be more cost-effective and cost-efficient compared with usual care and

reduces emergency department visits, unplanned health service utilization, cardiovascular complications in patients with diabetes, and readmission costs.<sup>6,7,9,10,20–22,27,28,31,32,34</sup> A large cohort study comparing health care resource utilization of >1 million patients with either diabetes or ASCVD found that, overall, health care resource utilization was comparable among patients receiving care from physicians compared with advanced practice providers, although physicians work with larger patient panels.<sup>9</sup> Communication through telehealth, patient education sessions, specialty clinics, medication therapy management, and patient decision support aids are appropriate and useful methods for providing patient care.<sup>36</sup> Refer to Sections 4.1, 4.2, 4.3, and 7 for management.

#### **4.1.2. Patient Education**

##### **Recommendations for Patient Education**

Referenced studies that support the recommendations are summarized in [Online Data Supplement](#).

COR	LOE	RECOMMENDATIONS
1	C-LD	1. Patients with CCD should receive ongoing individualized education on symptom management, lifestyle changes, and SDOH risk factors to improve knowledge and facilitate behavior change. <sup>1</sup>
1	C-LD	2. Patients with CCD should receive ongoing individualized education on medication adherence to improve knowledge and facilitate behavior change. <sup>2–4</sup>

#### **Synopsis**

Patient education is defined as “the process by which health professionals and others impart information to patients that will alter their health behaviors or improve their health status.”<sup>1,5</sup> Systematic reviews of studies using educational interventions suggest they improve patient knowledge and facilitate behavior change,<sup>1</sup> although impact on sustained lifestyle change, cholesterol and BP levels, and morbidity and mortality rates are less clear.<sup>5–7</sup> A meta-analysis of secondary prevention programs suggested education and counseling after MI reduced mortality but not recurrent MI.<sup>6</sup> In contrast, a review of RCTs on educational interventions among patients with various manifestations of coronary disease concluded that education had no effect on total mortality, recurrent MI, or hospitalizations.<sup>5</sup> Yet, Swedish registry data suggest that the education component of CR is strongly linked to cardiovascular and total mortality.<sup>7</sup> Published studies of educational interventions for patients with CCD, whether provided in person or by Internet, are heterogeneous, often incompletely described, many are short-term, and outcomes assessment varies. At this time, there are insufficient comparative data to provide clinicians and their care teams assistance when choosing among

interventions, a gap that should be addressed in future research studies.

#### **Recommendation-Specific Supportive Text**

1. A systematic review of the effect of patient education reported improvement in knowledge about medications and appropriate responses to symptoms,<sup>1</sup> as well as improvements in physical activity, dietary habits, and smoking cessation rates, but no convincing evidence of improvement in response to cardiac symptoms or psychosocial well-being was observed.<sup>1</sup> A review of 7 RCTs of Internet-based education and support found there was some supportive evidence for these interventions, but the overall effectiveness could not be determined.<sup>8</sup> Education should be tailored to individual patients and their caregivers, reinforced at regular intervals, and modified as the patient’s circumstances change. Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”<sup>9</sup> Verbal and written communications should be designed at the appropriate reading level, preferably in a patient’s native language, and culturally and contextually appropriate. The

Agency for Healthcare Research and Quality has created a toolkit with detailed guidance on improving written and spoken communication, self-management and empowerment, and improving supportive systems.<sup>10</sup> Internet-based self-management programs to improve access to ongoing support have been developed, but data on their efficacy are limited.<sup>8</sup>

2. Of the 68 trials and 20 intervention approaches in an Agency for Healthcare Research and Quality comparative effectiveness analysis, only 1 trial enrolled patients with CCD (those with recent MI).<sup>4</sup> In that trial, patients in the treatment arm had 1.3 extra days of medication coverage per month over 9 months of follow-up and were 17% more likely to have >80% adherence compared with patients in the control arm. No significant difference in persistence of medication use was observed.<sup>11</sup> Another systematic review found no convincing evidence of improved medication adherence with educational interventions.<sup>1</sup> A 2020 systematic re-

view of pharmacist-based patient education for patients on cardiovascular medications (only some with CCD) concluded that the interventions improved medication adherence but not necessarily clinical outcomes.<sup>2</sup> Another systematic review with the goal of comparing outcomes of different types of educational interventions targeting medication adherence found interventions delivered by pharmacists and nurses had the most favorable outcomes, although results were very heterogeneous.<sup>12</sup> A recent RCT of a pharmacist-administered intervention that used motivational interviewing to improve medication adherence among CCD patients improved medication adherence but had no effect on low-density lipoprotein cholesterol (LDL-C) levels, systolic BP, unplanned health care contact, or physical or emotional scores of the Heart Quality of Life Instrument.<sup>3</sup>

#### 4.1.3. Shared Decision-Making

##### Recommendations for Shared Decision-Making

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	C-LD	<ol style="list-style-type: none"><li>1. Patients with CCD and their clinicians should engage in shared decision-making particularly when evidence is unclear on the optimal diagnostic or treatment strategy, or when a significant risk or benefit tradeoff exists.<sup>1-3</sup></li></ol>
2b	B-R	<ol style="list-style-type: none"><li>2. For patients with CCD and angina on GDMT who are engaged in shared decision-making regarding revascularization, a validated decision aid may be considered to improve patient understanding and knowledge about treatment options.<sup>4</sup></li></ol>

#### Synopsis

Shared decision-making is a collaborative decision-making process that includes patient education about risks, benefits, alternatives to treatment and testing options, and clinician ascertainment of patient values and goals. Shared decision-making helps to maximize patient engagement in medical decision-making, increase patient knowledge about their care, and align treatment decisions with patient preferences. Even when evidence suggests one treatment or testing modality compared with another may lead to improved cardiovascular outcomes at a population level, the optimal treatment or testing choice for an individual patient may vary based on patient values and preferences, as well as the financial implications of the choice to the patient. Decision aids can improve knowledge and reduce decisional conflict in shared decision-making, but few validated decision aids are available for patients with CCD. Clinician-patient conversations, as well as corresponding educational materials, should be tailored to the patient's preferred language, reading level, health literacy, and visual acuity.

#### Recommendation-Specific Supportive Text

1. Most patients prefer to have an active role in their treatment decisions.<sup>1-3,5</sup> The right to information includes patients without decision-making capacity or who have chosen to defer treatment decisions to a designated caregiver. In shared decision-making, clinicians inform patients of the availability, risks, benefits, and alternatives of all medically appropriate testing or treatment options (which may include no testing or treatment), confirm patient understanding, assess patient values and treatment goals, and collaborate with patients to decide about their care. Patients may choose to include others in the shared decision-making process. Patient choices can include a treatment or therapeutic decision, an active choice to defer the decision, or a delegation of that decision to their care team or other designated individual. Patients and clinicians should engage in shared decision-making particularly when multiple medically appropriate options are available, when treatments or testing options confer increased risks, or when evidence is unclear on the

- optimal treatment strategy or when a risk:benefit tradeoff exists between different options. In patients with CCD, example areas for shared decision-making include duration, dose, and choice of antithrombotic therapy for secondary prevention and revascularization or medical therapy for stable angina.
2. Decision aids can increase patient knowledge, accuracy of risk perception, and agreement between patient values and care choices made, and may reduce decisional conflict for patients, but aids have not been developed and validated for many decisions made by

patients with CCD.<sup>6</sup> Before implementation of any decision aid, the decision aid should be developed according to best practice and validated in the target population.<sup>7–9</sup> Decision aids should augment, not replace, conversations between clinicians and patients. The decision aid PCI Choice was shown to increase knowledge about therapy options among patients with CCD choosing between optimal medical therapy alone or with PCI.<sup>4</sup>

#### 4.1.4. Social Determinants of Health

##### Recommendation for SDOH

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
1	B-R	1. In patients with CCD, routine assessment by clinicians and the care team for SDOH is recommended to inform patient-centered treatment decisions and lifestyle change recommendations.* <sup>1–8</sup>

\*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.<sup>9</sup>

#### Synopsis

SDOH, such as health care access, economic stability, and social context are key drivers of persistent health disparities and health inequities.<sup>1,10–13</sup> SDOH have profound influences on the health and well-being of patients with CCD and have become increasingly recognized in cardiovascular medicine.<sup>2,9,10,14–18</sup> There is an intersection of SDOH with sex, socioeconomic class, race, ethnicity, sexual orientation, and social vulnerabilities.<sup>12,19–21</sup> SDOH impact all stages of CCD management, including secondary prevention, treatment, access to care, and patient follow-up ([Section 7.1](#), “Follow-Up Plan and Testing”) and self-management.<sup>14</sup> Clinicians should ensure health equity in cardiovascular care by viewing each patient through an SDOH lens with cultural humility to formulate comprehensive care plans ([Figure 6](#)). Brief, evidence-based screening tools are available to support clinicians in identifying SDOH that may negatively affect health outcomes and health care utilization.<sup>4,13,22–24</sup> Routine SDOH screening in patients with CCD by clinicians or front-line staff should encompass assessment of mental health ([Section 4.2.2](#)), psychosocial stressors, health literacy, sociocultural influences (language, religious affiliation, body image), financial strain, transportation, insurance status, barriers to adherence to a heart healthy diet (food security) ([Section 4.2.1](#), “Nutrition, Including Supplements”), neighborhood or environmental exposures ([Section 4.2.11](#)), and viable options for regular physical activity ([Section 4.2.10](#), “Cardiac Rehabilitation”) and social support.<sup>1,2,25</sup> Based on identified barriers or

needs, collaborative cardiovascular care teams can provide tangible and practical community-based resources and services to patients.<sup>2,26–28</sup> Operationalization of guidelines on addressing SDOH requires embedding health equity into clinical practice, team-based care, patient education, and shared decision-making tools ([Sections 4.1.1, 4.1.2, and 4.1.3](#)).<sup>13,14,17,19,29–33</sup>

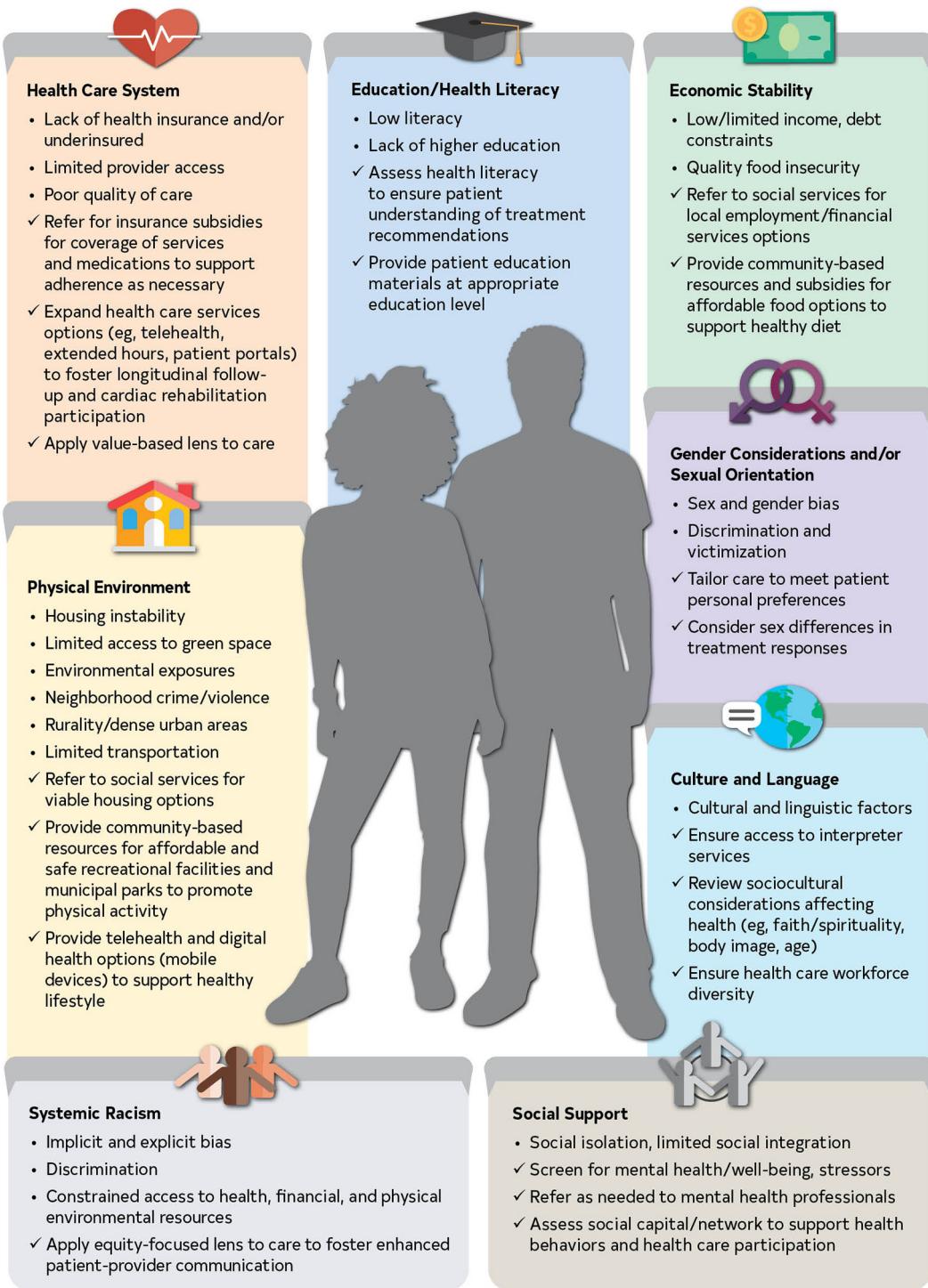
#### Recommendation-Specific Supportive Text

1. Integration of SDOH is based on evidence showing the effect of SDOH on long-term cardiovascular outcomes.<sup>9,10</sup> Patients experiencing an MI at a young age had higher neighborhood disadvantage that was associated with 57% higher cardiovascular mortality after an 11-year period.<sup>34</sup> Women in the lower-income bracket were more likely to be under- or uninsured and had higher medication costs and higher 5-year rehospitalization rates compared with higher-income women.<sup>35</sup> Lower education and income levels were associated with lower prescribing of GDMT, as well as outcomes post-MI.<sup>2,36–39</sup> Further, there are disparities in CR ([Section 4.2.10](#)) referral and completion among racial and ethnic minorities, women, according to socioeconomic status, and across those living in rural and dense urban areas.<sup>2,40–42</sup> Neighborhood environment influences healthy lifestyle promotion and maintenance, management of traditional and nontraditional cardiovascular risk factors, and outcomes.<sup>43–48</sup> Telehealth and digital interventions are promising strategies to improve access to health care, management and health

**FIGURE 6** Social Determinants of Health and Cardiovascular Care for Patients With CCD

## Social Determinants of Health and Cardiovascular Care for Patients With CCD

### Actionable Steps for Clinicians and Care Teams



• Identifies SDOH issue. ✓ Considerations for clinicians and care teams. CCD indicates chronic coronary disease, and SDOH, social determinants of health.  
Adapted with permission from Lindley KJ et al.<sup>3</sup> Copyright 2021 American College of Cardiology Foundation.

behaviors; however, consideration of SDOH influences is warranted.<sup>3,29,49–51</sup> Empirical evidence supports the use of screening tools in patients with multiple chronic diseases to efficiently assess SDOH in the clinical setting, facilitate tailoring of individualized care plans, and improve quality of care and outcomes.<sup>4,22,30,31,52–54</sup> Collaborative partnerships between health care systems and community-based organizations can assist

clinicians, patients, and their families in meeting unmet social needs as an extension of standard cardiovascular care for health equity.<sup>3,55</sup>

## 4.2. Guideline-Directed Management and Therapy

### 4.2.1. Nutrition, Including Supplements

#### Recommendations for Nutrition, Including Supplements

Referenced studies that support the recommendations are summarized in [Online Data Supplement](#).

		RECOMMENDATIONS
COR	LOE	Nutrition
1	B-R	1. In patients with CCD, a diet emphasizing vegetables, fruits, legumes, nuts, whole grains, and lean protein is recommended to reduce the risk of CVD events.* <sup>1–4</sup>
2a	B-NR	2. In patients with CCD, reducing the percentage of calories from saturated fat (<6% of total calories) and replacing with dietary monounsaturated and polyunsaturated fat, complex carbohydrates, and dietary fiber can be beneficial to reduce the risk of CVD events.* <sup>1–6</sup>
2a	B-NR	3. In patients with CCD, minimization of sodium (<2,300 mg/d; optimally 1,500 mg/d) and minimization of processed meats (eg, cured bacon, hot dogs) can be beneficial to reduce the risk of CVD events.* <sup>2,3,6,7</sup>
2a	B-NR	4. In patients with CCD, limiting refined carbohydrates (eg, containing <25% whole grain by weight, including refined cold ready-to-eat breakfast cereal, white bread, white rice), and sugar-sweetened beverages (eg, soft drinks, energy drinks, fruit drinks with added sugars) can be beneficial to reduce the risk of CVD events.* <sup>2–4,6,8</sup>
3: Harm	B-NR	5. In patients with CCD, the intake of <i>trans</i> fat should be avoided because <i>trans</i> fat is associated with increased morbidity and mortality rates.* <sup>9,10</sup>
		Nutrition Supplements
3: No Benefit	B-NR	6. In patients with CCD, the use of nonprescription or dietary supplements, including omega-3 fatty acid, vitamins C, D, E, beta-carotene, and calcium, is not beneficial to reduce the risk of acute CVD events. <sup>11–22</sup>

\*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.<sup>23</sup>

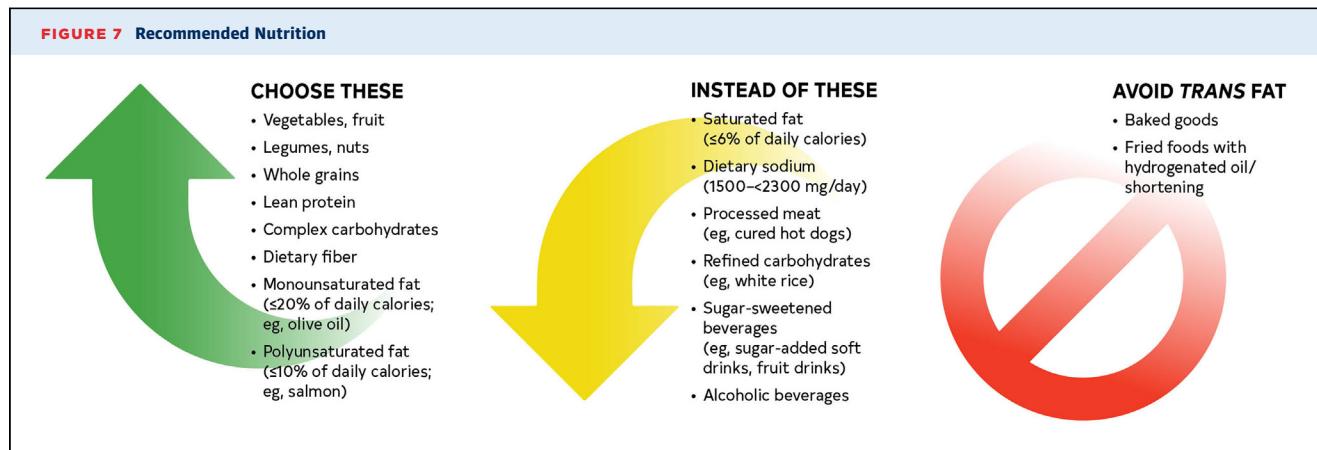
#### Synopsis

Among patients with CCD, dietary behavior changes along with GDMT are important to reduce the risk of acute CVD events including ASCVD, and outcomes related to HF, stroke, and CVD-related deaths.<sup>1,2,24</sup> Among patients with CCD, it is well established that healthy dietary choices improve management of CVD risk factors and target pathophysiologic mechanisms contributing to acute CVD events.<sup>25,26</sup> Studies across diverse populations support the health benefits of a higher intake of whole grains and fiber, with lower intake of saturated fat, sodium, refined carbohydrates, and sweetened beverages<sup>23,27,28</sup> (Figure 7). Healthy dietary choices combined with caloric reduction will support weight loss goals and improve cardiometabolic health for overweight and obese patients.<sup>29,30</sup> In contrast, nonprescription nutrition or dietary supplements<sup>28</sup> have insufficient evidence to

support their use to reduce the risk of acute CVD events in patients with CCD.<sup>18,31</sup> For this guideline, nutrition supplements is defined by the National Institutes of Health – Office of Dietary Supplements as nonprescription, dietary supplements that contain minerals (eg, calcium), herbs, amino acids, and vitamins across all dosage forms (eg, tablets, gummies).<sup>32</sup>

#### Recommendation-Specific Supportive Text

1. Mediterranean-type dietary plans with higher intake of healthy plant-based foods and lean protein (eg, fish), with lower quantities of saturated fat (eg, red meat) help reduce cardiovascular risk factors, including insulin resistance, diabetes, dyslipidemia, hypertension, and obesity.<sup>1,2,30,33–35</sup> Multiple secondary CVD prevention studies showed lower risk of subsequent CVD events and total mortality rate with higher intake of



healthy plant-based diets, including Mediterranean diets.<sup>1-3,33</sup> The Lyon Diet Heart Study randomized participants hospitalized with their first MI to a Mediterranean diet intervention or usual care.<sup>2</sup> After a mean intervention follow-up of 44.9 months, the Mediterranean diet showed up to a 65% reduction in composite CVD outcomes (cardiac death and nonfatal MI).<sup>2</sup> Additionally, multiple prospective cohorts showed an inverse relationship between lower all-cause death, greater adherence across multiple components of the Mediterranean diet (including fish),<sup>36</sup> and higher intake of healthier plant-based options.<sup>37</sup> Specific dietary components and serving sizes have varied across studies<sup>1</sup>; the AHA has previously published recommendations according to energy needs and weight loss goals.<sup>30</sup> However, additional research is needed on mechanisms associated with Mediterranean-diet patterns, CVD death, and all-cause death.<sup>1</sup>

2. Implementation of healthy plant-based and Mediterranean-based diets includes reducing saturated fat and optimizing caloric intake to include higher intake of monounsaturated fats, polyunsaturated fats, and complex carbohydrates.<sup>2,34,35,38</sup> Higher dietary fiber intake is associated with improvement in CVD risk factors, including lower BP, improved insulin sensitivity, and support of weight loss goals,<sup>3,5</sup> in addition to a lower risk of CVD events and all-cause death in patients with CCD.<sup>3</sup> A meta-analysis of prospective cohorts and randomized clinical trials supports a dose-response relationship of higher quality carbohydrate intake and lower CVD-related morbidity and mortality rates.<sup>5,39</sup> For patients at higher CVD risk, the AHA recommends lowering saturated fatty acids to  $<6\%$  of total caloric intake.<sup>30</sup> Reduction in saturated fatty acids, with healthier fat and carbohydrate intake, lowers LDL-C, which is associated with lower CVD morbidity and mortality rates.<sup>3,30,38-40</sup> A recent Cochrane review of randomized trials that reduced saturated fat intake, altered dietary

fats, or both highlighted a 17% reduction of CVD events in patients with CCD.<sup>6</sup> Among secondary prevention trials, the number needed to treat for an additional benefit was 53, by lowering saturated fat  $>4$  years.<sup>6,29</sup>

3. Dietary sodium reduction to  $<2,300\text{ mg/d}$  (optimal target of  $1,500\text{ mg/d}$ ) is important to lower BP.<sup>8,41</sup> Sodium reduction with a healthy diet reduces the risk of future CVD events, even in patients with CCD.<sup>3,7</sup> Recent analysis of the DASH (Dietary Approaches to Stop Hypertension)-Sodium study showed that sodium reduction may improve biomarkers of cardiac injury, inflammation, and cardiac strain.<sup>42</sup> Dietary education should highlight potential sources of dietary sodium, including processed meat, which is a significant contributor to dietary sodium in the United States.<sup>43,44</sup> According to the AHA, processed meats include smoked, cured, salted meats, and/or meats with chemical preservatives.<sup>23</sup> Although the DASH diet supports higher potassium intake,<sup>8</sup> insufficient data are available in populations with CCD to provide specific potassium recommendations.

4. The consumption of simple carbohydrates (eg, high-fructose corn syrup) and refined grains (eg, containing  $<25\%$  whole grain by weight, including some refined cold ready-to-eat breakfast cereal, white bread, white rice)<sup>4</sup> has adverse effects on lipoproteins, including LDL-C, apolipoprotein B, and plasma triglycerides.<sup>6,38</sup> Minimizing intake of simple carbohydrates and refined grains supports a healthier cardiometabolic profile.<sup>4,6,39</sup> Sugar-sweetened beverages are defined by the AHA as “manufactured carbonated and noncarbonated beverages containing caloric sweeteners or syrups and include caloric soft drinks (ie, not sugar-free), fruit drinks, sports and energy drinks, sweetened waters, and tea and coffee beverages with added sugars.”<sup>45</sup> Sugar-sweetened beverage consumption is associated with an increased risk of CVD events, including in patients with CCD,<sup>3</sup> and associated with chronic conditions including diabetes, CKD, and

- obesity.<sup>23,46</sup> Overall, multiple healthy dietary components, including reduction in dietary sodium, sugar-sweetened beverages, and saturated fat reduces all-cause death among secondary prevention cohorts.<sup>3</sup> Recommendations are unavailable for artificial sweeteners because of limited data in populations with CCD.
5. Consumption of *trans* fat has been associated with an increased risk of CVD events, including CVD mortality rate, and all-cause death in primary prevention populations and among individuals with CCD.<sup>9,10,23,47</sup> This association has been primarily attributed to industrially processed hydrogenated vegetable oils (eg, baked goods, fried foods), and less from ruminant *trans* fats (eg, meat and milk from ruminant animals, including cattle and sheep),<sup>40,47</sup> resulting in a higher risk of CHD.<sup>9,10,23,47</sup>
6. In patients at high risk for CCD, nonprescription dietary omega-3 fatty acid supplements (eg, capsules, oil, soft gels) do not reduce CVD events or all-cause death<sup>12,13</sup>; a Cochrane meta-analysis including 86 RCTs showed “little or no effect.”<sup>11</sup> See [Section 4.2.6](#) (“Lipid Management”) on the role of prescription icosapent ethyl (highly purified eicosapentaenoic acid ethyl ester).<sup>48</sup> Despite observational studies,<sup>49,50</sup>

#### Recommendations for Mental Health Conditions

Referenced studies that support the recommendations are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATIONS
2a	B-R	1. In patients with CCD, targeted discussions and screening for mental health is reasonable for clinicians to assess and to refer for additional mental health evaluation and management. <sup>1-4</sup>
2a	B-R	2. In patients with CCD, treatment for mental health conditions with either pharmacologic or non-pharmacologic therapies, or both, is reasonable to improve cardiovascular outcomes. <sup>2,4-6</sup>

#### Synopsis

Mental health has a major role in overall cardiovascular health and well-being in patients with CCD.<sup>7</sup> Mental health is defined as “a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community.”<sup>8</sup> Mental health can have positive or negative effects on cardiovascular risk factors and outcomes.<sup>7,9</sup> It is estimated that 20% to 40% of patients with CCD have concomitant mental health conditions such as depression and anxiety.<sup>10,11</sup> Meta-analyses have shown that negative psychological states (eg, general distress) are associated with MACE in men and women with CCD.<sup>12</sup> Despite being a modifiable prognostic risk factor for CCD outcomes, screening for mental health disorders is seldom addressed in the clinical setting.<sup>4,13</sup> Potentially underpinning the bidirectional relationship between mental health and CCD is the resulting influence on health behaviors (eg,

insufficient evidence is available that shows vitamin D supplementation reduces CVD events.<sup>14,15,51</sup> In a meta-analysis of 21 RCTs (vitamin D [n=41,669] versus placebo [n=41,662]), vitamin D supplementation did not lower the risk of MACE.<sup>15</sup> Additionally, antioxidant therapy is not associated with a decreased risk of CVD events.<sup>17,19,22,31</sup> Vitamin C, beta-carotene, multivitamins, or all of them do not decrease CVD event risk<sup>19</sup> or CVD mortality rate.<sup>52</sup> Insufficient data are available to support calcium supplementation (elemental calcium supplement ≥500 mg/d; carbonate, citrate, or gluconate formulation) in patients with CCD for CVD event reduction.<sup>21</sup> A meta-analysis of double-blind RCTs (n=14,692 [calcium supplement intervention] versus n=14,243 [placebo-controlled]) showed an increased risk of CVD and CHD events with calcium supplementation.<sup>21</sup> Mixed results on dietary calcium supplementation and CVD events suggests a U-shaped dose-response pattern.<sup>20,21</sup>

#### 4.2.2. Mental Health Conditions

medication and CR adherence, diet, physical activity, sleep, smoking) and risk factors (eg, BP, lipids, body mass index [BMI], inflammation, thrombosis).<sup>4,7</sup> Pharmacologic and psychotherapeutic treatments may reduce recurrent cardiovascular events and mortality rate in patients with CCD.<sup>5,14-17</sup> See [Section 4.1.4](#) for discussion of the interplay between mental health and SDOH.

#### Recommendation-Specific Supportive Text

1. Mental health factors, including depression, anxiety, anger or hostility, general distress and type D personality (where D stands for “distressed”), are common in diverse populations with CCD.<sup>12</sup> Psychological stress from environmental sources (eg, financial hardships, social isolation, discrimination) can have deleterious effects.<sup>7,18-22</sup> Studies consistently show that comorbid depression, anxiety, or emotional distress in patients with CCD is associated with diminished QOL,<sup>23</sup> atherosclerotic disease progression,<sup>24</sup> and negative effects on

**TABLE 6 Suggested Screening Tool to Assess Psychological Distress: Patient Health Questionnaire-2 Depression Screen**

Over the past 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
<b>Total score of <math>\geq 3</math> warrants further assessment for depression.</b>				

Data derived from Kroenke et al.<sup>31</sup> and Levine et al.<sup>7,46</sup> Reprinted with permission from Levine GN et al. Copyright 2021 American Heart Association, Inc.

**TABLE 7 Suggested Screening Questions to Assess Psychological Health**

Well-being parameter	Question
Health-related optimism	How do you think things will go with your health moving forward?
Positive affect	How often do you experience pleasure or happiness in your life?
Gratitude	Do you ever feel grateful about your health? Do you ever feel grateful about other things in your life?

Data derived from Levine GN et al.<sup>7,46</sup> Reprinted with permission from Levine GN et al. Copyright 2021 American Heart Association, Inc.

cardiovascular risk factors, leading to poorer cardiovascular outcomes.<sup>6,7,25-30</sup> An assessment of the use of depression screening found that among patients with recent ACS, screening positive for depression was associated with a 2-fold increase in MACE (adjusted hazard ratio, 2.15 [95% CI, 1.63-2.83]).<sup>2</sup> Patients randomized to antidepressants had significantly lower all-cause death than those not receiving treatment.<sup>2</sup> However, the CODIACS-QoL (Comparison of Depression Interventions After Acute Coronary Syndrome: Quality of Life) trial of patients after ACS showed no benefit of systematic depression screening (with or without subsequent treatment) on QOL or mortality.<sup>2,3</sup> Short, well-validated screening tools for depression or anxiety (eg, Patient Health Questionnaire-2, Generalized Anxiety Disorder Questionnaire-2) or brief questions on psychological health (eg, positive affect) are available for use in clinical settings (**Tables 7 and 8**).<sup>7,31,32</sup> It is reasonable to refer patients with positive screening for in-depth assessment by qualified mental health professionals or to accessible resources to promote mental health care.<sup>33</sup>

2. Despite the preponderance of data showing the association of depression with adverse cardiovascular outcomes, treatment with antidepressants (14%) and psychotherapies (<10%) is low in patients after MI.<sup>34</sup> Studies including patients after ACS with depression

found no definitive benefit of antidepressants on long-term cardiovascular outcomes.<sup>15,17,35-37</sup> However, the EsDEPACS (Escitalopram in Depressive Patients with Acute Coronary Artery Syndrome) study showed lower MACE after a median 8.1 years follow-up in patients with recent ACS treated with escitalopram compared with placebo (40.9% versus 53.6%; hazard ratio, 0.69 [95% CI, 0.49-0.96]).<sup>5</sup> The TRIUMPH (Lifestyle Interventions in Treatment-Resistant Hypertension) trial found a higher 1-year mortality rate among patients with untreated depression compared with patients with treated depression (rates similar to those without depression).<sup>6</sup> In a recent systematic review and meta-analysis, combination pharmacologic and psychotherapy, exercise, and antidepressants improved depressive symptoms among patients with CCD but had no mortality benefit.<sup>38</sup> CR (**Section 4.2.10**) improves depression, cardiovascular outcomes, and mortality in patients with CCD.<sup>39,40</sup> Mindfulness-based and psychotherapy interventions (eg, meditation, yoga, cognitive-behavioral therapy) improve depression, anxiety, stress, social support, and cardiovascular risk factors in patients with CCD but not all-cause or cardiovascular mortality, QOL, recurrent MI, or revascularization.<sup>41-44</sup> Pharmacological treatment of depression in patients with CCD is reasonable with consideration of adverse effects.<sup>4,45</sup>

### 4.2.3. Tobacco Products

#### Recommendations for Tobacco Products

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with CCD, tobacco use should be assessed at every health care visit to facilitate identification of those who may benefit from behavioral or pharmacologic interventions.* <sup>1-3</sup>
1	A	2. Patients with CCD who regularly smoke tobacco should be advised to quit at every visit.* <sup>4</sup>
1	A	3. In patients with CCD who regularly smoke tobacco, behavioral interventions are recommended to maximize cessation rates in combination with pharmacotherapy, including bupropion, varenicline, or combination long- and short-acting nicotine replacement therapy (NRT).* <sup>5-7</sup>
2b	B-R	4. In patients with CCD who regularly smoke tobacco, varenicline may be considered versus bupropion or NRT to increase cessation rates. <sup>6</sup>
2b	B-R	5. In patients with CCD who regularly smoke tobacco, the short-term use of nicotine-containing e-cigarettes may be considered to aid smoking cessation, although the risk of sustained use and unknown long-term safety may outweigh the benefits. <sup>8-10</sup>
3: Harm	B-NR	6. Patients with CCD should avoid secondhand smoke exposure to reduce risk of cardiovascular events.* <sup>11,12</sup>

\*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.<sup>13</sup>

#### Synopsis

Tobacco smoke exposure, in particular cigarette smoking, is a leading cause of CVD and cardiovascular events in persons with CCD.<sup>14-18</sup> Cigarette smoke adversely affects endothelial function, promotes atherosclerosis, and is prothrombotic.<sup>19</sup> Beneficial short-term effects of smoking cessation include a decrease in heart rate and BP and improved endothelial function.<sup>20,21</sup> Prospective cohort studies of patients with CCD show that smoking cessation is associated with a 36% reduction in death and a 32% reduction in MI.<sup>22</sup> Pharmacotherapy and behavioral therapy in combination can increase the success of smoking cessation. Observational studies on smokeless tobacco (including snuff, snus, and chewing tobacco) and cardiovascular risk have found mixed results, but an increased risk of coronary heart disease events may be observed, albeit to a lesser degree than cigarette smoking.<sup>23-26</sup>

#### Recommendation-Specific Supportive Text

1. Most persons who smoke report they want to quit smoking, although annual quit rates among those who smoke are <10%.<sup>2</sup> Systematic assessment of tobacco and e-cigarette use is the first step to facilitating smoking cessation, but clinicians often do not screen for tobacco use.<sup>3</sup> Routine screening for smoking status

by clinicians has been shown to increase the rate of clinician intervention to promote smoking cessation. Screening for smoking can also allow clinicians to reinforce continued abstinence among those who have successfully quit and identify patients who may have relapsed. Electronic health record-based interventions that include a means to document smoking status and other tools such as clinician prompts or decision support, can improve process outcomes, such as referral to smoking cessation programs or documentation of smoking cessation counseling, although electronic health record-based documentation of smoking status alone has not improved quit rates.<sup>27,28</sup> Data are unavailable on the effect of screening and most other tobacco cessation interventions on quit rates for persons who use smokeless tobacco and e-cigarettes. Nicotine-containing e-cigarette use is increasing, including among never-smokers, and many cigarette smokers have become “dual users,” using both e-cigarettes and cigarettes.<sup>29</sup> Meta-analyses suggest that smokeless tobacco use is associated with increased risk of CHD events, albeit to a lesser degree than cigarette smoking.<sup>23-25</sup> E-cigarettes may increase the risk of CHD and cardiovascular events, and long-term risks of e-cigarettes are unknown.<sup>8,30-37</sup> Given these risks, screening for use as part of comprehensive risk assessment may be reasonable.

**TABLE 8 Behavioral Resources for Smoking Cessation**

Resource	Description
Telephone-based: Quitline English: 1-800-QUIT-NOW (1-800-784-8669) Spanish: 1-855-DÉJEO-YA (1-855-335-3569) Mandarin and Cantonese: 1-800-838-8917 Korean: 1-800-556-5564 Vietnamese: 1-800-778-8440	Counseling by telephone from a trained tobacco coach who offers support via a series of scheduled telephone calls before and after a smoker's quit date. Patients can self-refer to the Quitline, or clinicians can refer patients, with their consent, proactively. Quitline services vary by state, can include text messaging and web coaching support, and may provide free samples of nicotine replacement therapy. State-by-state information about Quitline services is available at <a href="https://www.cdc.gov/tobacco/patient-care/quitting-other/index.html">https://www.cdc.gov/tobacco/patient-care/quitting-other/index.html</a>
Web-based: American Lung Association Freedom From Smoking <a href="https://www.lung.org/quit-smoking/join-freedom-from-smoking">https://www.lung.org/quit-smoking/join-freedom-from-smoking</a>	Created by the American Lung Association to support smoking cessation in persons who want to quit. The program also provides information about nicotine replacement therapy and pharmacotherapy. Multiple modes of support available to patients, including group clinics, a telephone-based "Lung HelpLine," a self-help guide, and a web-based interactive customized program. Interactive program available for computer, tablet, or smartphone interface.
Web-based: National Cancer Institute English: <a href="https://smokefree.gov">Smokefree.gov</a> Spanish: <a href="https://espanol.smokefree.gov/Spanish">https://espanol.smokefree.gov/Spanish</a>	Supported by the US Department of Health and Human Services and National Institutes of Health, created by the National Cancer Institute. Website contains information about quitting and resources for quitting and allows users to create a personalized quit plan. Specific websites are also available for women, teens, Veterans, and those >60 y of age. Programs available through the website include: SmokefreeTXT (text messaging program), QuitGuide, and quitSTART (mobile phone apps).
Web-based: Asian Smokers' Quitline Mandarin, Cantonese, Korean, and Vietnamese Speakers <a href="https://www.asiansmokersquitline.org/">https://www.asiansmokersquitline.org/</a>	Operated by the Moores Cancer Center at the University of California, San Diego, funded by a grant from the US Centers for Disease Control and Prevention. Created to support tobacco cessation for persons who speak Mandarin, Cantonese, Korean, and Vietnamese across the United States. Some participants may be eligible for a 2-wk starter kit of nicotine patches. Telephone counseling developed to deliver a quit plan and support quitting, and printed self-help materials sent to participants.
Web-based: BecomeAnEX Available in English and Spanish <a href="https://www.becomeanex.org">https://www.becomeanex.org</a>	Created by the Truth Initiative, a nonprofit public education in partnership with the Mayo Clinic Nicotine Dependence Center. Website with information about cessation of smoking, vaping, or use of smokeless tobacco, with resources to build an individualized quit plan. Includes support from experts and an online community, and a text message-based program for quitting vaping focused on teens and young adults, "This is Quitting." An employer-based program, the EX Program, is also available through the Truth Initiative.

2. Even brief advice to quit tobacco smoking provided by a clinician increases the rate of quitting in persons who smoke (relative risk, 1.66 [95% CI, 1.42-1.94]).<sup>4</sup> Other members of the care team, including nurses, community pharmacists, and oral health professionals, can also effectively provide behavioral support for smoking cessation.<sup>7</sup> Messages to patients should be clear, personalized, nonjudgmental, and focus on the benefits of smoking cessation, such as: "Quitting smoking is the most important thing you can do for your heart health."<sup>38</sup>
3. Behavioral therapy is also effective for smoking cessation including group and individual in-person counseling, telephone-based support, interactive internet-based interventions, and text message-based interventions.<sup>7</sup> A meta-analysis of 37 RCTs of behavioral interventions for smoking cessation in persons with CCD found a 22% increase in abstinence rates at 6 to 12 months.<sup>7,39</sup> Table 8 describes behavioral support programs available throughout the United States. NRT and varenicline have been shown to increase the success of smoking cessation in the overall population who smoke daily, including persons with CCD.<sup>6,40-46</sup> The effectiveness of NRT is highest when used as a

combination of long- and short-acting NRT.<sup>45</sup> Adding behavioral therapy to pharmacotherapy increases quit rates.<sup>47</sup> In 2011, the FDA issued a warning for possible increased risk of cardiovascular events in persons with CVD who use varenicline. One meta-analysis of trials through 2016 found no increased cardiovascular risk in persons receiving varenicline.<sup>48</sup> Subsequently, a trial randomized 8,058 persons to bupropion, varenicline, or NRT and found no difference in cardiovascular events among the 3 groups.<sup>44</sup> Trials of pharmacotherapy and behavioral therapy for smoking cessation typically enroll persons who smoke cigarettes daily; more research is needed on the efficacy and optimal strategy for smoking cessation among those who smoke intermittently, those who use smokeless tobacco, and those who use e-cigarettes.

4. Varenicline is more effective than bupropion or NRT in achieving abstinence from cigarette smoking in meta-analyses of randomized trials, with a pooled estimate from 5 trials (n=5,877 persons) showing a relative risk versus bupropion of 1.39 (95% CI, 1.25-1.54), and a pooled estimate of 8 trials (N=6,264 persons) showing a relative risk versus NRT of 1.25 (95% CI, 1.14-1.37) for abstinence favoring varenicline.<sup>49</sup> One network meta-

analysis evaluated the efficacy of RCTs of smoking cessation specifically among those with CVD and concluded that varenicline was more effective than bupropion or NRT, although no trials have compared various agents with each other in patients with CCD.<sup>6</sup> The ultimate choice of pharmacotherapy for smoking cessation should incorporate patients' previous experiences, preferences, and comorbidities (see "2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment" for dosing information and information about pharmacotherapy for smoking cessation).<sup>38</sup> No data are available on the efficacy of pharmacologic therapy to support cessation of either e-cigarettes or smokeless tobacco. More research is needed on how to optimize both pharmacologic and behavioral therapy to support cessation of smokeless tobacco and e-cigarettes.

5. Twenty-nine RCTs evaluated the efficacy of e-cigarettes on smoking cessation, including 5 at low risk of bias.<sup>9</sup> In meta-analyses, nicotine e-cigarettes appeared to be more effective than NRT for smoking cessation (relative risk, 1.69 [95% CI, 1.25-2.27]), corresponding to a 4% absolute increase in the success rates of smoking cessation compared with NRT.<sup>9</sup> Persons using e-cigarettes for smoking cessation are at risk of long-term dependence. In 1 trial, 80% of those assigned to the e-cigarette group who successfully quit smoking were still using the device at 1 year (versus only 9% still using NRT in the NRT arm).<sup>10</sup> Nicotine e-cigarettes appear to affect endothelial function, vascular stiffness, and BP less than combustible cigarettes.<sup>33,34,36</sup> No data are available

on the long-term risks of e-cigarettes on overall health and cardiovascular risk, but physiologic and toxicology studies suggest that e-cigarettes may increase cardiovascular risk.<sup>8,30-37</sup> Substantial variability exists in e-cigarette additives, flavorings, and nicotine dose in e-cigarette liquid; the effect on cardiovascular risk is unknown. Because of the lack of long-term safety data and high rates of ongoing use, nicotine e-cigarettes should not be recommended as first-line therapy for smoking cessation. Patients with CCD who use e-cigarettes to support smoking cessation should be warned about the risks of developing long-term dependence and encouraged to quit use of e-cigarettes promptly to avoid potential long-term risks.

6. Secondhand smoke exposure has similar deleterious physiologic effects as active cigarette smoking.<sup>50,51</sup> Even low doses of exposure to secondhand smoke exposure are associated with a marked increase in the risk of ischemic heart disease events, including recurrent events in patients with previous MI.<sup>11,12,50-52</sup> Many persons are exposed to secondhand smoke exposure via their workplaces and may not individually be able to avoid exposure. For this reason, policy-level interventions are necessary to decrease occupational secondhand smoke exposure. Policies designed to reduce secondhand smoke exposure, such as smoke-free workplaces and restaurant policies, are associated with lower population-level risk of CVD.

#### 4.2.4. Alcohol and Substance Use

##### Recommendations for Alcohol and Substance Use

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	C-LD	1. Patients with CCD should be routinely asked and counseled about substance use to reduce ASCVD events. <sup>1-5</sup>
2a	B-NR	2. In patients with CCD who consume alcohol, it is reasonable to limit alcohol intake ( $\leq 1$ drink/d for women, $\leq 2$ drinks/d for men) to reduce cardiovascular and all-cause death. <sup>6-8</sup>
3: No Benefit	B-NR	3. Patients with CCD should not be advised to consume alcohol for the purpose of cardiovascular protection. <sup>9,10</sup>

#### Synopsis

Various substances can have adverse effects on the cardiovascular system, including cocaine, amphetamines, opioids, alcohol, and marijuana (Table 9). These substances also have the potential for abuse and drug-drug interactions with

cardiovascular therapies. Because some of these substances are illicit (eg, cocaine, heroin), studies examining the link between substances and patients with CCD are limited, observational, and with imprecise measures of exposure risk. Although observational data show a J-shaped

relationship between alcohol consumption and cardiovascular risk, no RCTs support moderate alcohol consumption to reduce cardiovascular risk.<sup>6,11</sup> In fact, recent studies suggest that no safe level of alcohol use is acceptable and that previously observed cardioprotective effects of light-to-moderate alcohol use are likely confounded by other lifestyle and sociodemographic factors.<sup>8</sup> With the recent legalization of marijuana and its derivatives in some states, its use in patients with CCD is expected to grow.<sup>1</sup> A scientific statement from the AHA highlights the cardiac-specific effects of cannabis, including stimulation of the sympathetic nervous system, platelet activation, endothelial dysfunction, and carbon monoxide toxicity from smoking and inhalation.<sup>12</sup> Observational studies of the association between marijuana and cardiovascular events are limited by selection bias with rigorous data about the long-term effect of marijuana and cardiovascular risk lacking.<sup>12,13</sup> The AHA released a scientific statement discussing the importance of distinguishing and managing out-of-hospital cardiac arrests from opioids and in engaging patients with opioid use disorders in secondary prevention programs.<sup>14</sup> Because of potential cardiac toxicity, drug-drug interactions, and high risk for misuse, long-term opioid use for patients with CCD and chronic pain should be avoided. For recommendations regarding tobacco products, please see [Section 4.2.3](#).

#### Recommendation-Specific Supportive Text

1. Substance use is underrecognized and can be a significant contributor to CVD risk and outcomes.<sup>1,3,5</sup> Alcohol and other substances, such as cocaine, amphetamines, opioids, and marijuana can have particular adverse

cardiovascular effects among patients with CCD ([Table 9](#)) and lead to premature or recurrent CVD events. A study across 2 large tertiary care centers found that drug use was observed in 10% of patients <50 years of age presenting with an MI from 2000 to 2016.<sup>2</sup> Similarly, recreational substance use of alcohol, cannabis, and amphetamines was independently associated with premature CVD in the nationwide Veterans Affairs Health-care database and the VITAL (Veterans with Premature Atherosclerosis) registry.<sup>15</sup> Single-question screening for unhealthy alcohol and drug use has been validated in primary care settings.<sup>4</sup> These simple screening questions can also be self-administered.

2. There is a J-shaped relationship between alcohol consumption and death, although data on alcohol consumption is of variable quality. Proposed mechanisms supporting beneficial effects of moderate alcohol consumption include favorable effects on lipids, platelet aggregation, insulin resistance, and endothelial function.<sup>16</sup> In the United States, 1 “standard” drink contains about 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).<sup>17</sup> Observational studies have consistently found an inverse association between light-to-moderate alcohol consumption and vascular risk.<sup>18</sup> In patients with CVD, a similar observation has been documented with light-to-moderate alcohol consumption (5–25 g/d) associated with lower incidence of cardiovascular and all-cause death.<sup>6,8,7</sup> Conversely, heavy, episodic drinking (binge drinking)

**TABLE 9 Substances With Abuse Potential and Adverse Cardiovascular Effects for Patients With CCD\***

Substance	Potential Adverse Cardiovascular Effects
Alcohol	<ul style="list-style-type: none"> <li>■ J-shaped relationship between alcohol intake and cardiovascular risk in observational studies but limited by confounding.<sup>18</sup></li> <li>■ Heavy alcohol use and binge drinking associated with increased morbidity and mortality rates.<sup>9,10,19</sup></li> <li>■ May increase serum triglycerides.</li> <li>■ Potential drug-drug interactions with cardiovascular therapies.</li> </ul>
Cocaine, methamphetamine	<ul style="list-style-type: none"> <li>■ Stimulation of the sympathetic nervous system.<sup>5,20</sup></li> <li>■ Platelet activation and aggregation.<sup>20</sup></li> <li>■ Increased myocardial oxygen demand.<sup>5</sup></li> <li>■ Can present with cocaine-associated chest pain.</li> <li>■ MI risk independent of route of administration.<sup>21</sup></li> </ul>
Opioids	<ul style="list-style-type: none"> <li>■ Possible association with risk of MI in chronic use.<sup>22</sup></li> <li>■ High potential for dependence and abuse with chronic use.</li> <li>■ Potential for drug-drug interactions with cardiovascular therapies.</li> </ul>
Marijuana	<ul style="list-style-type: none"> <li>■ Stimulation of the sympathetic nervous system.</li> <li>■ Platelet activation.</li> <li>■ Endothelial dysfunction.</li> <li>■ Carbon monoxide toxicity from smoking and inhalation.<sup>12</sup></li> <li>■ Route of administration may impact toxicity, with edible products associated with fewer acute cardiovascular symptoms.<sup>23</sup></li> </ul>

\*List is not all inclusive.

CCD indicates chronic coronary disease; and MI, myocardial infarction.

is consistently associated with higher cardiovascular risk including acute myocardial infarction.

3. All available data on the benefit of alcohol on cardiovascular risk are observational and subject to confounding. In the absence of a randomized clinical trial, data are insufficient to recommend alcohol for cardioprotection.<sup>11</sup> In fact, a recent genetic analysis found that the causal association between light-to-moderate levels of alcohol intake and lower CVD risk are likely mediated by confounding lifestyle factors.<sup>8</sup> In patients with CCD, excessive alcohol is linked to hypertension, increased mortality rate, and recurrent cardiovascular events. PRIME (Prospective Epidemiological Study of Myocardial Infarction) found that binge drinking (>50 g at least once a week) was associated with a higher risk of coronary events (hazard ratio, 2.03 [95% CI, 1.41-2.94]) compared with regular drinking.<sup>10</sup> In the

Determinants of Myocardial Infarction Onset Study across 45 community and tertiary-care medical centers, binge drinking was associated with a 2-fold higher mortality rate after an acute MI.<sup>9</sup> The Global Burden of Disease 2016 analysis confirmed a J-shaped relationship with alcohol and outcomes, but the benefit appeared to be offset by increasing cancer risks, concluding that the level of alcohol consumption that minimized harm was zero.<sup>19</sup> Therefore, patients who do not drink alcohol or who have a medical reason to avoid alcohol (eg, liver dysfunction, drug-drug interactions) should not be encouraged to drink alcohol for the purposes of cardiovascular protection. Clinicians should further counsel their patients against binge drinking.

#### 4.2.5. Sexual Health and Activity

##### Recommendations for Sexual Health and Activity

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
2a	B-NR	1. In patients with CCD, it is reasonable to individualize resumption of sexual activity based on type of sexual activity, exercise capacity, and postprocedural healing.* <sup>1,2</sup>
2a	B-NR	2. In patients with CCD, cardiac rehabilitation and regular exercise can be useful to reduce the risk of cardiovascular complications with sexual activity.* <sup>3</sup>
3: Harm	B-NR	3. In patients with CCD, phosphodiesterase type 5 inhibitors should not be used concomitantly with nitrate medications because of risk for severe hypotension.* <sup>4</sup>

\*Modified from the 2012 AHA Scientific Statement on Sexual Activity and Cardiovascular Disease.<sup>5</sup>

#### Synopsis

Sexual health is important to QOL. Sexual activity represents moderate physical activity at around 3 to 5 metabolic equivalents.<sup>5</sup> If a patient with CCD can reach this level during exercise testing without ischemia or symptoms, then the risk for ischemia during sexual activity is low, especially considering the short exposure period.<sup>2</sup> It is rare for a patient to die from cardiac disease during sexual intercourse; in this regard, men appear more at risk than women,<sup>6</sup> with the absolute rate being very small. Sexual activity is associated with 1% of all MIs.<sup>3</sup> Men and women with CCD and its risk factors have a high prevalence of sexual dysfunction.<sup>7</sup> Recent MI and coronary artery bypass surgery may additionally compromise sexual function<sup>5</sup>; in this regard, sexual counseling may be helpful, and resuming sexual activity does not appear to be associated with an increased risk of death. Of particular relevance to patients with CCD is the need to avoid the combined use of nitrates with phosphodiesterase type 5 inhibitors.<sup>4</sup>

#### Recommendation-Specific Supportive Text

1. Recommendations after PCI and CABG may depend on whether femoral or radial access was performed, and

whether surgery was performed in a sternal-sparing manner.<sup>5,8</sup> The patient should be well compensated, euvoemic, and without significant angina. Patients with CCD who are functionally well compensated or patients with no or mild angina, given the low risk of MI or sudden death, should be considered safe for sexual activity. Sexual activity represents an exercise level of approximately 3 to 5 metabolic equivalents, compared with a typical exercise treadmill test that involves approximately 4 metabolic equivalents. The risk of MI or sudden death resulting from sexual activity is very low.<sup>3</sup> Patients with CCD who want to engage in sexual activity should undergo a medical evaluation, similar to other forms of exercise in the presence of CCD.<sup>5</sup> Because sexual activity is associated with increased metabolic requirements, patients with unstable or decompensated CCD should refrain from sexual activity.<sup>5</sup>

2. In addition to a recommendation for CR incorporating sexual counseling, in men with CCD, conservative measures such as sexual rehabilitation, consisting of 12 weeks of sexual rehabilitation with physical exercise training, pelvic floor exercise and psychoeducation,

was associated with better sexual function by the International Index of Erectile Function.<sup>9,10</sup>

3. Phosphodiesterase type 5 inhibitors should not be used concomitantly with nitrate medications, often used to treat CCD, because of the potential for severe hypotension.<sup>4</sup> Sildenafil and vardenafil have half-lives of ~4 hours. Tadalafil is long-acting and has a half-life of 17.5 hours. Patients on sildenafil or vardenafil should avoid taking nitroglycerine for ≥24 hours (≥48 hours

for tadalafil).<sup>5</sup> In patients on long-acting nitrate therapy who want to use a phosphodiesterase type 5 inhibitor, decision on the use of phosphodiesterase type 5 inhibitor should be guided by the need for continued nitrate therapy versus other alternative options available to the treating clinician.

#### 4.2.6. Lipid Management

##### Recommendations for Lipid Management

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	<ol style="list-style-type: none"> <li>In patients with CCD, high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of MACE.*<sup>1-3</sup></li> </ol>
1	A	<ol style="list-style-type: none"> <li>In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE.*<sup>2,4-8</sup></li> </ol>
1	A	<ol style="list-style-type: none"> <li>In patients with CCD, adherence to changes in lifestyle and effects of lipid-lowering medication should be assessed by measurement of fasting lipids in 4 to 12 weeks after statin initiation or dose adjustment and then every 3 to 12 months thereafter based on need to assess response or adherence to therapy.*<sup>2,9-11</sup></li> </ol>
Cost Value Statement: High Value	B-NR	<ol style="list-style-type: none"> <li>In patients with CCD, the use of generic formulations of maximally tolerated statin therapy is projected to be cost saving.<sup>12,13</sup></li> </ol>
2a	B-R	<ol style="list-style-type: none"> <li>In patients with CCD who are judged to be at very high risk (Table 10) and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), ezetimibe can be beneficial to further reduce the risk of MACE.*<sup>14-19</sup></li> </ol>
Cost Value Statement: High Value	B-NR	<ol style="list-style-type: none"> <li>In patients with CCD, addition of generic ezetimibe to maximally tolerated statin therapy in appropriately selected patients is projected to be of high economic value at US prices.<sup>12,20,21</sup></li> </ol>
2a	A	<ol style="list-style-type: none"> <li>In patients with CCD who are judged to be at very high risk (Table 10) and who have an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), or a non-high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL (≥2.6 mmol/L), on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE.*<sup>22-29</sup></li> </ol>
Cost Value Statement: Uncertain	B-NR	<ol style="list-style-type: none"> <li>In patients with CCD who are very high risk, the use of PCSK9 monoclonal antibodies is projected to be of uncertain economic value at US prices.<sup>12,20,21,30,31</sup></li> </ol>
2b	B-R	<ol style="list-style-type: none"> <li>In patients with CCD on maximally tolerated statin therapy with an LDL-C level &lt;100 mg/dL (&lt;2.6 mmol/L) and a persistent fasting triglyceride level of 150 to 499 mg/dL (1.7-5.6 mmol/L) after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death.<sup>32</sup></li> </ol>
2b	B-R	<ol style="list-style-type: none"> <li>In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), it may be reasonable to add ezetimibe to further reduce the risk of MACE.*<sup>14,15,18,19</sup></li> </ol>
2b	B-R	<ol style="list-style-type: none"> <li>In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid<sup>33,34</sup> or inclisiran<sup>35</sup> (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels.</li> </ol>
3: No Benefit	B-R	<ol style="list-style-type: none"> <li>In patients with CCD receiving statin therapy, adding niacin,<sup>36,37</sup> or fenofibrate<sup>38</sup> or dietary supplements containing omega-3 fatty acids, are not beneficial in reducing cardiovascular risk.<sup>39-41</sup></li> </ol>

\*Modified from the 2018 AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol.<sup>42</sup>

## Synopsis

LDL-C is a primary cause of atherosclerotic disease and target of lipid management.<sup>38</sup> RCTs established the efficacy and safety of high-intensity statin therapy as the preferred initial approach to reduce LDL-C levels by  $\geq 50\%$  and reduce cardiovascular morbidity and mortality rates (Figure 8).<sup>1–3</sup> Despite maximally tolerated statin therapy, residual cardiovascular risk persists, especially among patients with CCD and additional high-risk clinical factors (Table 10).<sup>14–17</sup> Several nonstatins<sup>36–38</sup> did not provide benefit when added to background statin therapy; however, ezetimibe, PCSK9 monoclonal antibodies, and icosapent ethyl further reduce cardiovascular risk when added to background statin therapy.<sup>15,22,23,32</sup> Bempedoic acid and inclisiran have only recently become available and, although they effectively reduce LDL-C levels,<sup>34,35</sup> RCTs are ongoing to determine their effect on MACE. Clinicians should prioritize use of ezetimibe and PCSK9 monoclonal antibodies when additional LDL-C lowering is necessary in patients on maximally tolerated statin therapy unless not tolerated or effective in achieving desired LDL-C levels. Regardless of the lipid-lowering regimen, lipid monitoring is essential to assess individual response to lipid-lowering therapy and monitor adherence and persistence with therapy over time.<sup>9–11</sup>

## Recommendation-Specific Supportive Text

1. The CTT (Cholesterol Treatment Trialists) meta-analysis of 5 RCTs showed that LDL-C lowering with high-intensity statins compared with moderate-intensity statins reduces major vascular events by 15% (Table 11).<sup>2</sup> This benefit occurred irrespective of age, even among patients  $>75$  years of age with established ASCVD.<sup>2,3</sup> Greater absolute reductions in LDL-C were associated with a greater proportional reduction in MACE. The greatest absolute benefit from statin therapy is observed in those with the highest baseline LDL-C levels and at similar risk of events. Furthermore, percent reduction in LDL-C appears to provide additional prognostic value overachieved LDL-C levels.<sup>43</sup> The expected percent reduction in LDL-C levels with high-intensity statin therapy is  $\geq 50\%$  and should be used to assess clinical efficacy. However, baseline LDL-C levels in patients before statin initiation are not always available in clinical practice. The threshold of LDL-C  $\geq 70$  mg/dL is then useful to determine whether to intensify lipid management.
2. Although high-intensity statin therapy is preferred, high-intensity statin therapy may not be tolerated by some patients or may be contraindicated because of clinically significant drug-drug interactions.<sup>44</sup> Statin intolerance is defined as adverse effects associated with statin therapy that improve or resolve with dose modification or discontinuation of statin therapy; and requires a trial of at least 2 statins with one at the lowest approved daily dose.<sup>45</sup> Statin intolerance may also be complete or partial (tolerating less than the recommended statin intensity). Clinicians should also consider the possibility of a “nocebo effect”—patient expectation of harm resulting in perceived adverse effects.<sup>46</sup> Multiple RCTs showed that moderate-intensity statin therapy also reduces cardiovascular events and death among patients with established ASCVD, including those  $>75$  years of age; therefore, a moderate-intensity statin should be used in patients unable to tolerate a high-intensity statin.<sup>2,4–8</sup> Additional strategies may also be used to identify a tolerable statin regimen (eg, low-intensity statin, alternative daily dosing) to reduce LDL-C but it is unclear if these strategies also reduce the risk of ASCVD events.<sup>47</sup>
3. The goal for LDL-C lowering is defined as percentage responses in LDL-C relative to baseline levels. Although reductions in LDL-C are expected with moderate- and high-intensity statins (Table 11), individual response can vary substantially.<sup>11</sup> The maximum percentage change in LDL-C occurs within 4 to 12 weeks after initiation of or change in lipid-lowering therapy. The Friedewald equation is known to underestimate LDL-C in the setting of elevated TG levels, thus other approaches to LDL-C measurement (eg, Martin/Hopkins method) may be desirable.<sup>48,49</sup> Obtaining lipid profile measurements every 3 to 12 months is associated with increased adherence to therapy and identification of patients requiring further intensification of treatment.<sup>9,10</sup> See Sections 4.4.3 and 5 of the 2018 AHA/ACC multisociety cholesterol guideline<sup>50</sup> for additional information regarding efficacy and safety monitoring.
4. The economic value of a lipid-lowering therapy depends on the absolute benefit (in terms of the number of cardiovascular events averted or quality-adjusted life years [QALY] gained) that patients derive from receiving the treatment relative to the comparator as well as the cost of the therapy being evaluated.<sup>13</sup> Because of the very low annual cost of generic formulations of statins in the United States, the use of maximally tolerated statin therapy in patients with CCD is projected to be cost-saving (ie, the lifetime savings from averted cardiovascular events more than offset the lifetime cost of statin therapy and resulting adverse effects).<sup>12</sup> Note that this value statement should not be extrapolated to higher-cost branded formulations of statins.
5. In IMPROVE-IT (Improved Reduction of Outcomes; Vytorin Efficacy International Trial), the addition of ezetimibe to moderate-intensity statin therapy among

**TABLE 10 Very High-Risk\* of Future ASCVD Events**

**Definition of Very High-Risk\***

History of multiple major ASCVD events

**OR**

One major ASCVD event **AND** ≥2 high-risk conditions

**Major ASCVD Events**

Recent ACS (within the past 12 mo)

History of MI (other than recent ACS events listed above)

History of ischemic stroke

Symptomatic peripheral artery disease (history of claudication with ABI <0.85, or previous revascularization or amputation)<sup>51</sup>

**High-Risk Conditions**

Age ≥65 y

Familial hypercholesterolemia<sup>†</sup>

History of previous coronary artery bypass graft surgery or percutaneous coronary intervention outside of the major ASCVD event(s)

Diabetes

Hypertension

Chronic kidney disease (eGFR, 15–59 mL/min/1.73 m<sup>2</sup>)<sup>15,29</sup>

Current tobacco smoking

Persistently elevated LDL-C ≥100 mg/dL despite maximally tolerated statin therapy and ezetimibe

History of congestive heart failure

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\*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

<sup>†</sup>Management of patients with familial hypercholesterolemia often requires combination lipid lowering therapy and referral to a lipid specialist, and possibly lipoprotein apheresis.<sup>58,59</sup>

ABI indicates ankle brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; and MI, myocardial infarction.

patients with ACS resulted in a significant ASCVD risk reduction (7% relative risk reduction; 2% absolute risk reduction) at a median follow-up of 6 years.<sup>15</sup> An analysis using the TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2 P) found the addition of ezetimibe was associated with significantly greater risk reduction (19% relative risk reduction; 6.3% absolute risk reduction) among patients with ≥3 high-risk features, with more modest benefit among those with 2 high-risk features and no benefit among those with 0 or 1 additional features.<sup>14</sup> Ezetimibe was allowed at study entry in both PCSK9 monoclonal antibody trials,<sup>23,24</sup> but only 3% and 5%, respectively, were on ezetimibe. No RCT has evaluated whether an ezetimibe-first strategy is preferred before adding a PCSK9 monoclonal antibody; however, clinicians should generally add ezetimibe first, then a PCSK9 monoclonal antibody, if necessary, to achieve desired LDL-C levels, given the generic availability of ezetimibe, its once-daily oral administration, and proven long-term safety and

tolerability. This is supported by 2 well-designed simulation studies showing that a high proportion of patients will achieve an LDL-C level of <70 mg/dL with the addition of ezetimibe to high-intensity statin therapy.<sup>18,19</sup>

6. Generic ezetimibe is an inexpensive drug, with net price of <\$10 for a 1-month supply. To the extent that LDL-C lowering with ezetimibe translates to fewer lifetime MACE, the use of generic ezetimibe is likely to be improve health outcomes at modest increase in cost, especially in very high-risk patients, resulting in high value (<\$50,000 per QALY gained).<sup>12,20,21</sup> However, the cost-effectiveness of adding generic ezetimibe to maximally tolerated statin therapy is sensitive to the assumption regarding the effect of ezetimibe on cardiovascular and all-cause death.
7. Very high risk ASCVD is defined in Table 10. The efficacy of alirocumab and evolocumab was shown in 2 RCTs.<sup>22,23</sup> The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition Subjects with Elevated Risk) trial evaluated evolocumab among those with established ASCVD with an LDL-C level of ≥70 mg/dL or non-HDL-C level of ≥100 mg/dL on maximal statin with or without ezetimibe. Cardiovascular events were significantly reduced by 15% with evolocumab, with greater benefit observed among those with additional high-risk clinical factors. No increased risk of neurocognitive adverse effects was observed, even among those achieving the very low levels of LDL-C.<sup>29</sup> The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) trial evaluated alirocumab use in patients with an ACS event 1 to 12 months earlier on maximal statin with or without ezetimibe. Cardiovascular events were significantly reduced by 15% with alirocumab, especially in those with additional high-risk clinical factors.<sup>25–27</sup> The absolute risk reduction was relatively modest (1.5% and 0.6%, respectively) in both trials, given the ~60% reduction in LDL-C levels. However, analyses from both FOURIER and ODYSSEY Outcomes trials subsequently showed that among several groups of patients noted in the very high-risk ASCVD category (Table 10), the absolute risk of future ASCVD events was significantly higher; therefore, the absolute risk reduction from the use of a PCSK9 monoclonal antibody was also much higher than the overall absolute risk reductions seen in the original trials.<sup>23,26,28,51,52</sup> Although generally well tolerated, injection site reactions can occur, and long-term safety data are limited. Maximal LDL-C-lowering therapy should include maximally tolerated statin plus ezetimibe; however, ezetimibe may be insufficient when a ≥25% reduction in the LDL-C level is

**TABLE 11** High-, Moderate-, and Low-Intensity Statin Therapy\*

	High Intensity	Moderate Intensity	Low Intensity
LDL-C Lowering†	≥50%	30%–49%	<30%
Statins	<b>Atorvastatin (40 mg‡), 80 mg Rosuvastatin 20 mg (40 mg)</b>	<b>Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§</b>	Simvastatin 10 mg
		<b>Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg</b>	<b>Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg</b>

Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database.<sup>11</sup> Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.<sup>60</sup> **Boldface type** indicates specific statins and doses that were evaluated in RCTs and the Cholesterol Treatment Trialists' 2010 meta-analysis.<sup>23</sup> These RCTs demonstrated a reduction in major cardiovascular events. Reprinted with permission from Grundy SM, et al.<sup>42</sup> Copyright 2019 American Heart Association, Inc., and American College of Cardiology Foundation.

\*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.<sup>11</sup>

†LDL-C lowering that should occur with the dosage listed below each intensity.

‡Evidence from 1 RCT only; down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.<sup>61</sup>

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

FDA indicates US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; VOYAGER, an individual patient data meta-analysis Of statin therapy In At risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin; and XL, extended release.

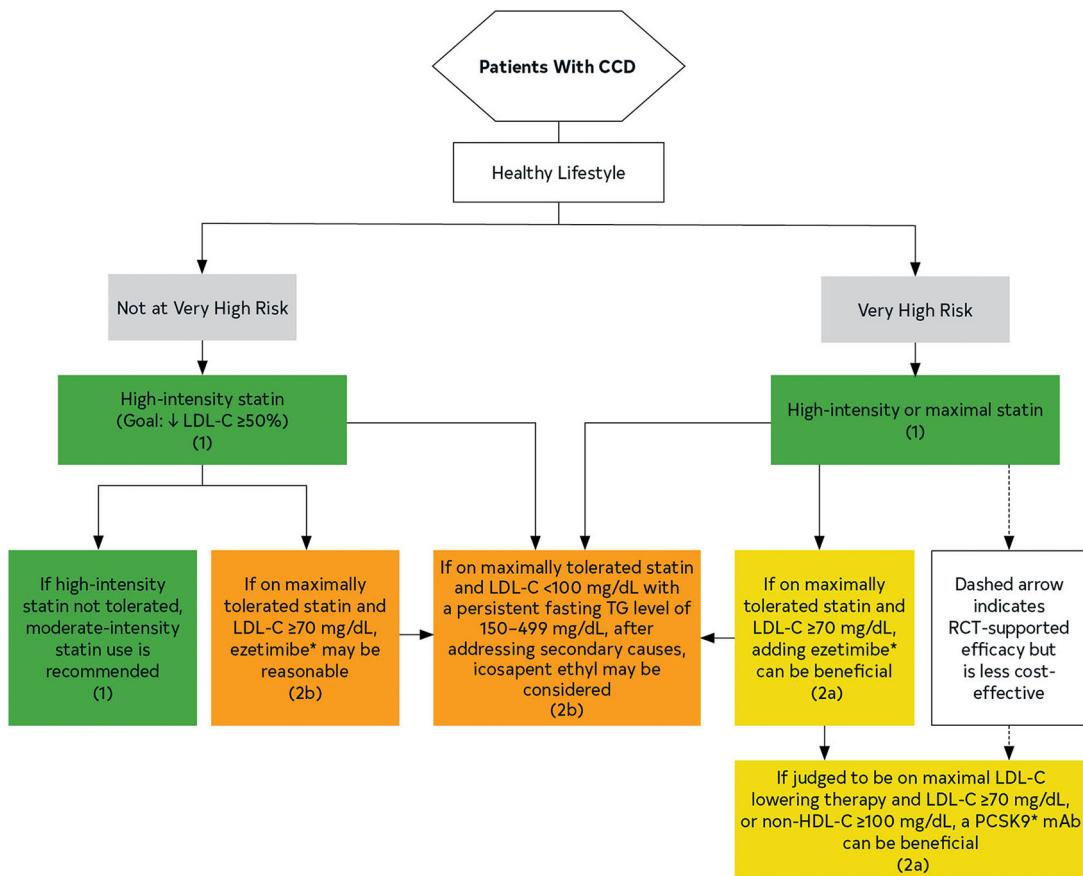
desired. Clinicians bypassing the addition of ezetimibe before adding a PCSK9 monoclonal antibody should recognize this may not be cost effective (**Figure 8**).

8. The US cost of PCSK9 monoclonal antibodies has declined by 60% since their initial market entry (from approximately \$14,000 per year to \$5,850 per year), which, all things being equal, has improved the cost-effectiveness of these drugs.<sup>12,20,21</sup> At this price point, the cost-effectiveness of the agents in very high risk patients with CCD is uncertain, with some studies projecting low economic value<sup>12,20</sup> and others suggesting intermediate to high economic value.<sup>30,31</sup> This value statement should not be extrapolated to patients with CCD who are at low to moderate risk of adverse cardiovascular events, in whom PCSK9 inhibitor monoclonal antibodies are of low economic value. The cost-effectiveness of a therapy is a function of the incremental cost of the therapy relative to the comparator, its effectiveness relative to the comparator, as well as baseline risk of cardiovascular events in the target population. Patients who have higher baseline risk are likely to derive a larger absolute health benefit from an effective drug. It follows that CVD prevention is more cost-effective in a population at higher risk of CVD events. Thus, PCSK9 inhibitors may be intermediate value in patients at higher-than-average risk of recurrent events, such as those with a recent ACS, symptomatic peripheral artery disease, or familial hypercholesterolemia (FH).<sup>12,20,21</sup> The cost-effectiveness of PCSK9 monoclonal antibody is also likely improved in patients who are unable to tolerate statins because of severe statin-associated side effects.<sup>12</sup>

9. REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) randomized

patients with established ASCVD or diabetes plus additional risk factors, triglyceride levels between 150 mg/dL and 499 mg/dL, and an LDL-C level of <100 mg/dL on background statin therapy, to either 4 g/day of icosapent ethyl (purified EPA only) or mineral oil placebo. Icosapent ethyl significantly reduced the relative risk of MACE by 25% and cardiovascular death by 20%.<sup>32</sup> The benefit appeared driven by the increase in EPA levels and not the modest 17% reduction in triglyceride levels. RESPECT-EPA (Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid) was another secondary prevention trial that showed a borderline significant reduction in MACE with icosapent ethyl 1800 mg/day (10.9% versus 14.9%;  $P=0.055$ ) in 2506 participants enrolled in Japan on background statin therapy. Limitations of this trial were the lack of placebo control, and it was under-powered. Contrarily, the STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial found no benefit with a 4 g/day carboxylic acid formulation of omega-3 fatty acids (EPA and DHA) compared with a corn oil placebo, and no association with harm or benefit in those at the highest achieved tertiles for EPA and DHA levels. Incident AF was more common with both icosapent ethyl and the carboxylic acid formulation of omega-3 fatty acids and has been observed in other studies of omega-3 fatty acid formulations. Several factors could explain the discrepant outcomes observed in these trials; however, the use of a mineral oil placebo in REDUCE-IT is of concern given its adverse effects on lipid and inflammatory biomarkers, suggesting mineral oil may not be an inert placebo.<sup>53</sup>

**FIGURE 8** Lipid Management in Patients With CCD



Colors correspond to Class of Recommendation in Table 3. Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 10). \*Only when ezetimibe and PCSK9 mAb are deemed insufficient or not tolerated should bempedoic acid or inclisiran (in place of PCSK9 mAb) be considered to further reduce LDL-C levels. The effect of bempedoic acid and inclisiran on MACE is being evaluated. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PCSK9 mAb, PCSK9 monoclonal antibody; RCT, randomized controlled trial; and TG, triglycerides. Adapted with permission from Grundy SM, et al.<sup>42</sup> Copyright 2019 American Heart Association, Inc., and American College of Cardiology Foundation.

For patients with LDL-C levels between 70 mg/dL and <100 mg/dL, it is unclear whether further LDL-C lowering or adding icosapent ethyl is more effective. Patient preference and shared decision-making are recommended, and secondary causes of elevated triglyceride levels (eg, medications, diabetes, lifestyle) should be addressed before considering icosapent ethyl. Dietary supplements containing omega-3 fatty acids are not acceptable substitutes for icosapent ethyl.

10. In patients not at very high risk, there may be instances where high-intensity statin therapy is insufficient to achieve desired LDL-C levels or not

tolerated. Although moderate-intensity statin therapy effectively reduces cardiovascular risk, it is inferior to high-intensity statin therapy.<sup>2</sup> Additional LDL-C lowering may also be necessary in patients on moderate-intensity statin therapy with LDL-C levels ≥70 mg/dL. Adding ezetimibe to moderate-intensity statin therapy may compensate for the reduced LDL-C lowering observed with moderate-intensity statin therapy alone. Although the net benefit of ezetimibe may be less robust among patients not at very high risk, it is preferred before a PCSK9 monoclonal antibody for reasons provided in Recommendation 5.

11. Bempedoic acid is a first-in class therapy adenosine triphosphate-citrate lyase<sup>54</sup> inhibitor that reduces LDL-C levels by 15% to 25% depending on the type and dose of background statin therapy and is associated with fewer muscle-related adverse effects.<sup>33,34</sup> It is also available in a combination product with ezetimibe that reduces LDL-C levels by ~35%. Although it can be combined with statins, bempedoic acid should be avoided when using doses of simvastatin >20 mg daily or pravastatin 40 mg daily because of an ~2-fold increase in serum levels of both statins. Elevation in uric acid levels may occur with bempedoic acid use, and rare cases of tendon rupture have been reported. Inclisiran is a first-in-class small interfering RNA directed to break down PCSK9 mRNA, resulting in reduced synthesis of PCSK9.<sup>35</sup> Inclisiran reduces LDL-C levels by approximately 50% and is administered as a single subcutaneous dose, with a second dose at 3 months, then every 6 months. Inclisiran administration must be performed by a health care professional, which may limit accessibility. It is generally well tolerated, but injection site reactions can occur. The effect of bempedoic acid and inclisiran on MACE is currently under investigation; therefore, nonstatin

therapies with proven efficacy (ie, ezetimibe, PCSK9 monoclonal antibody) should be prioritized over these 2 therapies. Preliminary modeling studies project that the use of bempedoic acid or inclisiran in patients unable to tolerate statin therapy because of severe statin-associated side effects is of intermediate value (\$50,000–\$150,000 per QALY gained), as is the use of inclisiran in patients with CCD and heterozygous FH.<sup>55</sup> However, the cost-effectiveness of these novel therapies is sensitive to assumptions regarding the effect of each drug on cardiovascular and all-cause death and should be updated when long-term outcomes data become available.

12. Dietary supplements containing omega-3 fatty acids (ie, fish oil) are widely used for presumed cardioprotective benefits. However, low-dose omega-3 fatty acid supplementation does not reduce MACE in patients with CCD.<sup>39–41</sup> The only omega-3 fatty acid formulation that can be recommended in patients with CCD is icosapent ethyl (EPA only) as described in Recommendation 9. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) trial found no benefit with the addition of extended-release

**TABLE 12 Nonpharmacologic Strategies for Blood Pressure Management\***

Nonpharmacologic Intervention		Dose	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	5
Healthy diet	DASH dietary pattern	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	2,3
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1,500 mg/d but aim for at least a 1,000-mg/d reduction in most adults.	–5/6 mm Hg	–2/3 mm Hg	29,30
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3,500–5,000 mg/d, preferably by consumption of a diet rich in potassium.	–4/5 mm Hg	–2 mm Hg	35
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	4,8
	Dynamic resistance	<ul style="list-style-type: none"> <li>■ 90–150 min/wk</li> <li>■ 50%–80% of 1 repetition maximum</li> <li>■ 6 exercises, 3 sets/exercise, 10 repetitions/set</li> </ul>	–4 mm Hg	–2 mm Hg	4
	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	36,37
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, limit alcohol to: <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	6

Resources: Your Guide to Lowering Your Blood Pressure With DASH—How Do I Make the DASH?<sup>38</sup> Available at: [https://www.nhlbi.nih.gov/files/docs/public/heart/new\\_dash.pdf](https://www.nhlbi.nih.gov/files/docs/public/heart/new_dash.pdf). Modified with permission from Whelton PK, et al.<sup>19</sup> Copyright 2018 American Heart Association, Inc., and American College of Cardiology Foundation.

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

†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).

DASH indicates Dietary Approaches to Stop Hypertension; and SBP, systolic blood pressure.

niacin to background statin therapy.<sup>36</sup> Another niacin trial in secondary prevention, HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events), also found no benefit with a combination product of niacin and laropiprant, a prostaglandin receptor antagonist; however, this product is no longer available.<sup>37</sup> ACCORD-LIPID (Action to Control Cardiovascular Risk in Diabetes-Lipid Trial)<sup>56</sup> found no benefit with the addition of fenofibrate to background statin therapy. Although this trial was conducted in patients with type 2 diabetes, more than half of the trial participants had established CVD at baseline, and no

benefit was observed in this subgroup of patients. A selective PPAR $\alpha$  modulator, pemetrexate, was investigated in the PROMINENT (Pemetrexate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients) trial in high-risk patients with diabetes, but this trial was stopped early for futility.<sup>57</sup> Fenofibrate should only be considered for severe hypertriglyceridemia (triglycerides,  $\geq 500$  mg/dL) to reduce the risk of acute pancreatitis.

#### 4.2.7. Blood Pressure Management

##### Recommendations for Blood Pressure Management

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	1. In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/ $<80$ mm Hg) (see Table 12). <sup>*1-9</sup>
1	B-R	2. In adults with CCD who have hypertension, a BP target of <130/<80 mm Hg is recommended to reduce CVD events and all-cause death. <sup>*10-14</sup>
1	B-R	3. In adults with CCD and hypertension (systolic BP $\geq 130$ and/or diastolic BP $\geq 80$ mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), or beta blockers <sup>15-17</sup> are recommended as first-line therapy for compelling indications (eg, recent MI or angina), with additional antihypertensive medications (eg, dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. <sup>*13,18</sup>

\*Modified from the 2017 ACC/AHA Multisociety Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.<sup>19</sup>

##### Synopsis

Hypertension is a well-established risk factor for CVD<sup>20</sup> and is a highly prevalent comorbid condition among individuals with CCD, affecting >60% of such individuals.<sup>21</sup> Individuals with CCD who also have hypertension are at increased risk of death and morbidity compared with individuals with CCD who are normotensive.<sup>22</sup> Treatment of hypertension with lifestyle<sup>1-6,22</sup> and medication therapies<sup>13,16,17,23-28</sup> helps control hypertension and reduce subsequent risk of MACE. The recommendations apply to individuals with CCD who have hypertension. See Section 4.2.1 for additional recommendations regarding nutritional therapies and Sections 4.2.10 to 4.2.11 for additional recommendations about physical activity and CR. For additional information, see the 2017 ACC/AHA multisociety guideline for the prevention, detection, evaluation, and management of high blood pressure in adults.<sup>19</sup>

##### Recommendation-Specific Supportive Text

1. Lifestyle-related factors influence BP levels, and lifestyle modifications are effective strategies to help lower elevated BP. These factors include weight loss,<sup>1,5</sup> a heart-healthy diet that is rich in fruits and vegetables,<sup>2,3</sup> reduced dietary sodium,<sup>29,30</sup> physical activity,<sup>4,8</sup> and reduction or elimination of alcohol intake.<sup>6</sup>

2. Among patients with increased cardiovascular risk, reduction of systolic BP to <130 mm Hg has been shown to reduce CVD complications by 25% and all-cause death by 27%.<sup>13</sup> Optimal diastolic BP for clinical outcomes appears to be in the range of 70 to 80 mm Hg.<sup>10,14</sup>
3. In the HOPE (Heart Outcomes Prevention Evaluation) trial, ramipril therapy in patients with CVD or at high risk for CVD reduced the risk of MI, stroke, or CVD by 22% compared with placebo.<sup>16</sup> In patients with CAD and hypertension who were randomized into the INVEST (International Verapamil SR/Trandolapril Study) trial, CCB and ACE inhibitor and beta-blocker/thiazide diuretic therapy had similar cardiovascular morbidity and death outcomes.<sup>31</sup> In the EUROPA (Exclusive Endocrine Therapy or Partial Breast Irradiation for Women  $\geq 70$  Years Early Stage Breast Cancer) study involving patients with CCD, ACE inhibitor therapy produced a 20% reduction in risk of CVD death, MI, or cardiac arrest compared with placebo.<sup>15</sup> Beta blockers are particularly effective in patients with CCD, especially those with recent MI and those with ongoing angina, given their ability to reduce angina, improve angina-free exercise tolerance, reduce exertion-related myocardial ischemia, and reduce risk of CVD events.<sup>17,23,27,32,33</sup> Because of the significant benefits

from beta blockers and ACE inhibitors and ARB agents in patients with CCD, these medications are recommended as a first-line therapy in the treatment of hypertension in such individuals. GDMT beta blockers for CCD and for lowering BP include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol.<sup>19</sup> Outcomes with atenolol appear to be inferior compared with other

antihypertensive drugs in the treatment of hypertension.<sup>34</sup> When beta blockers, ACE inhibitors, and ARB therapies do not sufficiently control BP, additional GDMT BP-lowering therapies can be added, including thiazide diuretics, CCB, and mineralocorticoid receptor antagonists.<sup>19</sup>

#### 4.2.8. SGLT2 Inhibitors and GLP-1 Receptor Agonists

##### Recommendations for Use of SGLT2 Inhibitors and GLP-1 Receptor Agonists

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	<ol style="list-style-type: none"> <li>In patients with CCD who have type 2 diabetes, the use of either an SGLT2 inhibitor<sup>1–8</sup> or a GLP-1 receptor agonist<sup>9–17</sup> with proven cardiovascular benefit is recommended to reduce the risk of MACE.</li> </ol>
Cost Value Statement: High Value	B-NR	<ol style="list-style-type: none"> <li>In patients with CCD and type 2 diabetes, addition of a GLP-1 receptor agonist at US prices is projected to be of high value compared with standard of care.<sup>18</sup></li> </ol>
Cost Value Statement: Intermediate Value	B-NR	<ol style="list-style-type: none"> <li>In patients with CCD and type 2 diabetes, addition of an SGLT2 inhibitor at US prices is projected to be of intermediate value compared with standard of care.<sup>18</sup></li> </ol>
1	A	<ol style="list-style-type: none"> <li>In patients with CCD and heart failure with LVEF ≤40%, use of an SGLT2 inhibitor is recommended to reduce the risk of cardiovascular death and heart failure hospitalization<sup>19–22</sup> and to improve QOL,<sup>23,24</sup> irrespective of diabetes status.*</li> </ol>
Cost Value Statement: Intermediate Value	B-NR	<ol style="list-style-type: none"> <li>In patients with CCD and heart failure with LVEF ≤40%, addition of an SGLT2 inhibitor to GDMT, irrespective of diabetes status, is projected to be of intermediate value at US prices.<sup>25,26</sup></li> </ol>
2a	B-R	<ol style="list-style-type: none"> <li>In patients with CCD and heart failure with LVEF &gt;40%, use of an SGLT2 inhibitor can be beneficial in decreasing heart failure hospitalizations<sup>27,28</sup> and to improve QOL,<sup>4,29</sup> irrespective of diabetes status.</li> </ol>
Cost Value Statement: Intermediate Value	B-NR	<ol style="list-style-type: none"> <li>In patients with CCD and heart failure with LVEF &gt;40%, addition of an SGLT2 inhibitor to GDMT, irrespective of diabetes status, is projected to be of uncertain value at US prices.<sup>30</sup></li> </ol>

\*Modified from the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.<sup>31</sup>

#### Synopsis

Comprehensive cardiovascular risk reduction strategies are effective in patients with CCD and type 2 diabetes.<sup>32</sup> Despite these efforts, cardiovascular event rates remain high among patients with type 2 diabetes, even among well-managed patients,<sup>1,10,33</sup> and CAD remains the leading cause of morbidity and death.<sup>34</sup> Two classes of glucose-lowering medications (SGLT2 inhibitors and GLP-1 receptor agonists) have potent cardiovascular benefits, independent of their effects on glycemic control.<sup>1,3,4,9,10,13</sup> Both medications improve glycemic control, facilitate weight loss, reduce progression of kidney disease, and reduce the risk of cardiovascular events through distinct pathways. Yet their adoption in clinical practice has been slow,<sup>35,36</sup> highlighting an opportunity for cardiovascular

specialists to have a greater collaborative role in the care of patients with CCD and type 2 diabetes.<sup>37</sup>

Comprehensive risk factor control should include lifestyle modifications<sup>38</sup> and GDMT to optimize dyslipidemia (Section 4.2.6, “Lipid Management”), hypertension (Section 4.2.7, “Blood Pressure Management”), weight management (Section 4.2.9), nutrition (Section 4.2.1), physical activity (Section 4.2.11), and hyperglycemia.<sup>39</sup> Regarding glucose control, the American Diabetes Association recommends a hemoglobin A1C goal of <7%<sup>40</sup> and a more conservative glycemic target (eg, hemoglobin A1c <8% or 8.5%) for those older (>65 years of age) with CCD and type 2 diabetes or comorbidities,<sup>41</sup> to limit the risk of hypoglycemia.<sup>40–48</sup> Among patients with CCD and type 2 diabetes, a patient-centered approach (Section 4.1.1,

“Team-Based Approach”) should guide shared decision-making (**Section 4.1.3**) about glycemic targets and the decision to initiate an SGLT-2 inhibitor, GLP-1 receptor agonist, or both.<sup>39</sup>

#### Recommendation-Specific Supportive Text

1. In patients with CCD and type 2 diabetes, both SGLT2 inhibitors and GLP-1 receptor agonists significantly reduce the risk of MACE, with additional benefits in terms of weight loss<sup>49</sup> and progression of kidney disease.<sup>7,16,17</sup> SGLT2 inhibitors do not appear to primarily reduce atherosclerosis as much as they reduce incident and worsening HF (for which patients with CCD and type 2 diabetes who are at risk).<sup>1-8</sup> In contrast, GLP-1 receptor agonists appear to primarily reduce the risk of atherosclerotic events, such as MI and stroke. Although there has been some inconsistency across the cardiovascular outcomes trials,<sup>9-15</sup> meta-analyses have shown no statistically significant heterogeneity in cardiovascular risk reduction across different GLP-1 receptor agonists.<sup>16,17</sup> Currently, no compelling evidence is available that either medication reduces cardiovascular risk in patients with CCD but without type 2 diabetes,<sup>50,51</sup> or in the case of SGLT2 inhibitors, without concomitant HF. Given their distinct mechanisms, the cardiovascular risk reduction may be greater using both classes of medications compared with either medication alone. Data on concurrent use are mostly limited to safety and metabolic endpoints,<sup>52</sup> but available studies showed benefit in BP and weight reduction with dual therapy.<sup>53,54</sup> Whether the effects on cardiovascular outcomes are additive, or even synergistic, is not yet known.
2. In a systematic review of cost-effectiveness analyses examining the addition of GLP-1 agonists compared with alternative therapies (including insulin or other classes of diabetes medications) among patients with diabetes, the use of a GLP-1 agonist is projected to be of high value (cost-saving or incremental cost-effectiveness ratio of <\$50,000 per QALY gained).<sup>18</sup> Although these analyses were performed in all patients with type 2 diabetes rather than specifically in patients with CCD, these results appear to be robust to a range of assumptions regarding underlying risk and are likely applicable to patients with CCD.
3. In a systematic review of cost-effectiveness analyses examining the addition of SGLT2 inhibitors to standard of care among patients with diabetes, the use of an SGLT2 inhibitor is projected to be of intermediate value (\$50,000 to <\$150,000 per QALY gained) compared with standard of care.<sup>18</sup> As noted previously, these analyses were performed in all patients with type 2 diabetes rather than specifically in patients with CCD, but these results appear to be robust to a range of

assumptions regarding underlying risk and are likely applicable to patients with CCD.

4. Among patients with HF with reduced ejection fraction (with or without type 2 diabetes), SGLT2 inhibitors reduce the risk of cardiovascular death and HF hospitalization<sup>19-22</sup> and improve functional capacity and QOL.<sup>23,24</sup> These effects were independent of cause of cardiomyopathy, because approximately half of enrolled patients across the trials had CCD. SGLT2 inhibitors should be avoided or used with caution in patients with type 1 diabetes or with advanced CKD (eg, eGFR <30 mL/min/1.73 m<sup>2</sup>).
5. Among patients with HF with reduced ejection fraction (with or without type 2 diabetes), the use of SGLT2 inhibitors is projected to be of intermediate value (\$50,000 to <\$150,000 per QALY gained) from a US health care sector perspective and a lifetime horizon. One modeling-based study compared dapagliflozin and GDMT with GDMT alone in a hypothetical cohort of adults in the United States with similar clinical characteristics as participants of the DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) trial.<sup>25</sup> Assuming the cost of dapagliflozin to be \$4,192 annually, dapagliflozin was projected to add 0.63 (95% uncertainty interval, 0.25-1.15) QALYs at an incremental lifetime cost of \$42,800 (95% uncertainty interval, \$37,100-\$50,300), for an incremental cost-effectiveness ratio of \$68,300 per QALY gained (95% uncertainty interval, \$54,600-\$117,600 per QALY gained; cost-effective in 94% of probabilistic simulations at a threshold of \$100,000 per QALY gained).<sup>25</sup> Findings were similar among individuals with or without diabetes but were sensitive to drug cost. Similar findings were independently reported by another group of investigators.<sup>26</sup>
6. Among patients with HF with preserved ejection fraction (with or without type 2 diabetes), SGLT2 inhibitors reduced the risk of HF hospitalization or cardiovascular death in the EMPEROR-PRESERVED (Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction) trial<sup>27</sup> and the risk of worsening HF or cardiovascular death in the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure), with the primary endpoints driven by significant reductions in HF hospitalization in both trials. SGLT2 inhibitors also improved functional capacity and QOL in the PRESERVED-HF and DELIVER trials.<sup>28,29</sup> CCD was diagnosed in 35% of enrolled patients in EMPEROR-PRESERVED and 20% of enrolled patients in PRESERVED-HF (Effects of Dapagliflozin on Symptoms and Functional Status in Patients with Heart Failure

and Preserved Ejection Fraction), with no significant difference in risk of HF hospitalization (subgroup was not tested in the QOL study); the CCD rate was not reported in DELIVER.

7. Among patients with HF with preserved ejection fraction (with or without type 2 diabetes), the economic value of SGLT2 inhibitors is sensitive to the effect of SGLT2 inhibitors on cardiovascular mortality. The reduction in cardiovascular mortality was not statistically significant in the EMPEROR-PRESERVED or DELIVER trials, or in a pooled analysis of the 2 trials. If one were to assume no reduction in cardiovascular mortality and minimal improvement in QOL among patients with HF with preserved ejection fraction, the use of empagliflozin is of low value (incremental cost-effectiveness ratio \$437,000).<sup>30</sup> However, if one were to assume a 9% reduction in cardiovascular mortality (as consistent with the point-estimate of EMPEROR-

PRESERVED), the incremental cost-effectiveness ratio is lowered to \$ 174,000 (which the authors defined as intermediate value after adjusting the ACC/AHA thresholds for interval change in per capita GDP). Although the trials included patients with and without CCD, it is likely that patients with CCD have a higher risk of events (including cardiovascular mortality) and therefore derive a larger-than-average benefit from SGLT2 inhibitors. Additional clinical studies that examine the effect of SGLT2 inhibitors on cardiovascular and noncardiovascular mortality, and additional economic evaluations that synthesize the available clinical evidence and consider a range of costs and risks, are needed to ascertain the value of SGLT2 inhibitors in patients with CCD and HF with preserved ejection fraction.

#### 4.2.9. Weight Management

##### Recommendations for Weight Management

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	C-EO	1. In patients with CCD, assessment of BMI with or without waist circumference is recommended during routine clinical follow-up. <sup>1–6</sup>
1	B-NR	2. Patients with CCD and overweight or obesity should receive counseling on diet, lifestyle, and goals for weight loss. <sup>7–10</sup>
2a	B-R	3. For patients with CCD and overweight or obesity in whom pharmacologic therapy is warranted for further weight reduction, a GLP-1 receptor agonist can be beneficial in addition to counseling for diet and physical activity, <sup>11,12</sup> and it is reasonable to choose semaglutide over liraglutide. <sup>13,14</sup>
2a	B-NR	4. In patients with CCD and severe obesity who have not met weight loss goals with lifestyle and pharmacologic intervention, and who have acceptable surgical risk, referral for consideration of a bariatric procedure is reasonable for weight loss and cardiovascular risk factor reduction. <sup>15–18</sup>
3: Harm	B-R	5. In patients with CCD, use of sympathomimetic weight loss drugs is potentially harmful. <sup>19</sup>

##### Synopsis

Compared with individuals with normal weight, patients with obesity experience CCD events at an earlier age, live with CCD for a greater proportion of their lifetime, and have a shorter average life span.<sup>6,20</sup> Excess adiposity accelerates atherosclerosis and promotes adverse changes in cardiac function through deleterious effects on the myocardium as well as the vasculature and through obesity-related comorbidities, including hypertension, dyslipidemia and type 2 diabetes.<sup>21–23</sup> Although BMI can be a heterogeneous marker of individual risk, increasing BMI is associated with increasing risk of morbidity and death across populations, and BMI thresholds continue to guide clinical diagnosis and management

of overweight and obesity (“2013 AHA/ACC Guideline for the Management of Overweight and Obesity in Adults”).<sup>24</sup> The general goals of weight loss and management are to: (1) prevent further weight gain, (2) reduce body weight, and (3) maintain a lower body weight over the long term. Weight loss in association with lifestyle modification (see Section 4.2.1, “Nutrition,” Section 4.2.11, “Physical Activity,” and Section 4.1.4 “Social Determinants of Health”) and select pharmacologic interventions (see Section 4.2.8, “SGLT2 Inhibitors and GLP-1 Receptor Agonists”) and surgical interventions for eligible patients with CCD improves metabolic and hemodynamic risk profiles, with potential for improved cardiovascular outcomes.

**TABLE 13 Core Components of CR<sup>18</sup>**

■ Patient assessment
■ Nutritional counseling
■ Weight management
■ Blood pressure management
■ Lipid management
■ Diabetes management
■ Tobacco cessation
■ Psychosocial management
■ Physical activity counseling
■ Exercise training

CR indicates cardiac rehabilitation.

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#### Recommendation-Specific Supportive Text

1. Patients with CCD should undergo routine measurement of BMI with or without waist circumference for initial evaluation and as a guide to efficacy of weight loss intervention.<sup>1-6</sup> Although not a measure of body composition, BMI remains the most practical way to evaluate for overweight and obesity, defined as a BMI 25 to 29.9 kg/m<sup>2</sup> and ≥30 kg/m<sup>2</sup>, respectively.<sup>24</sup> Waist circumference, a surrogate estimate of visceral adiposity, may be a better indicator of risk than BMI in some patients and populations,<sup>25,26</sup> with central obesity defined as a waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women.<sup>24</sup> As with BMI, racial and ethnic differences in waist circumference thresholds associated with cardiometabolic risk have been reported.<sup>27</sup> Recognizing that weight assessment in some individuals may represent a deterrent to seeking care, gender- and culturally sensitive approaches to assessing weight are recommended in all patients, with an option for patients to self-report values where appropriate.
2. Lifestyle modification (see [Section 4.2.1](#), “Nutrition” and [Section 4.2.11](#), “Physical Activity”) with associated weight loss improves obesity-related CCD comorbidities. With lifestyle measures alone, a weight loss of 5% to 7% of body weight is typical but often difficult to sustain. Multicomponent interventions including dietary modification, exercise, and behavioral counseling are more effective than interventions targeting single components.<sup>7,8</sup> A meta-analysis of 122 RCTs and 2 observational studies compared an intensive, multi-component behavior-based weight loss intervention with a comparison group receiving usual care. At 12 to 18 months, patients receiving multicomponent behavior-based interventions were more likely to achieve a ≥5% weight loss (relative risk, 1.94 [95% CI, 1.70-

2.22]).<sup>7</sup> In patients with CCD, regular physical activity with increased lean mass may be more important for improving survival than achieving a normal BMI.<sup>10</sup> Patients with CCD and overweight or obesity should be counseled to lose weight, especially if accomplished with increases in physical activity and improvements in cardiorespiratory fitness.<sup>9</sup>

3. Candidates for weight-loss drug therapy include individuals with a BMI ≥30 kg/m<sup>2</sup> or a BMI of 27 to 29.9 kg/m<sup>2</sup> with weight-related comorbidities who have not met weight-loss goals (eg, loss of ≥5% of total body weight at 3-6 months) with a comprehensive lifestyle intervention alone. The decision to initiate drug therapy in patients with CCD should be individualized, considering associated risks and benefits. The cardiovascular safety of certain weight-loss drugs, such as naltrexone/bupropion, has not been established and remains controversial.<sup>28</sup> Use of a GLP-1 receptor agonist ([Section 4.2.8](#)) is beneficial when pharmacologic therapy is warranted for further weight reduction.<sup>11,12,14</sup> Among eligible adults without diabetes, the STEP 8 (Semaglutide Treatment Effect in Patients with Obesity) randomized controlled trial (N=338, 3.3% with known CCD) found that once-weekly subcutaneous semaglutide 2.4 mg added to counseling for diet and physical activity resulted in significantly greater weight loss at week 68 compared with once-daily subcutaneous liraglutide 3.0 mg or placebo (mean weight change, -15.8% [95% CI, -17.6 to -13.9] versus -6.4% [95% CI, -8.2 to -4.6] versus -1.9% [95% CI, -4.0 to 0.2] for semaglutide versus liraglutide versus placebo, respectively).<sup>13</sup> Both semaglutide (0.5-1.0 mg weekly) and liraglutide (1.2-1.8 mg daily) were associated with reduced MACE in patients with type 2 diabetes and CCD.<sup>29,30</sup> Recently, the double-blind randomized controlled trial SURMOUNT-1 (A Study of Tirzepatide [LY3298176] in Participants with Obesity or Overweight) also showed a dose-dependent weight loss benefit (mean weight change up to -20.9% [95% CI, -21.8 to -19.9]) with once-weekly subcutaneous tirzepatide (at 5 mg, 10 mg, or 15 mg) relative to placebo in eligible obese adults without diabetes (N=2539, 3.1% with ASCVD) over 72 weeks.<sup>31</sup>
4. Patients with CCD and severe obesity (BMI ≥40 kg/m<sup>2</sup> or BMI 35-39.9 kg/m<sup>2</sup> with a weight-related comorbidity) who have not met weight loss goals with lifestyle and pharmacologic intervention may benefit from a bariatric procedure such as gastric bypass surgery. Bariatric procedures appear to be relatively safe and effective among patients with CCD, at least in those <65 years of age.<sup>15,17,18</sup> In the non-randomized prospective SOS (Swedish Obese Subjects) study, bariatric surgery was associated with prevention of type 2 diabetes and fewer

cardiovascular deaths and lower incidence of MI or stroke compared with matched obese controls (hazard ratio, 0.47 [95% CI, 0.29-0.76] for death, and hazard ratio, 0.67 [95% CI, 0.54-0.83] for MI or stroke).<sup>16,32</sup> These benefits do not appear to occur with liposuction, suggesting that the negative energy balance associated with bariatric intervention may be necessary for achieving the metabolic benefits of weight loss.<sup>33</sup> Specifically among patients with obesity and type 2 diabetes, bariatric surgery is an effective strategy for achieving weight loss, glycemic control, and reducing cardiovascular risk factors.<sup>34</sup> More recently, 2 retrospective observational studies of patients with CCD showed significant reductions in MACE among those undergoing bariatric surgery compared with matched controls.<sup>17,18</sup>

5. Sympathomimetic drugs (eg, phentermine, diethylpropion, benzphetamine, phendimetrazine) can increase heart rate and BP and are not recommended in patients with CCD. In a trial of sibutramine versus placebo in >10,000 patients with or at high risk for CCD, sibutramine was associated with a higher risk of nonfatal MI (4.1% versus 3.2%; hazard ratio, 1.28 [95% CI, 1.04-1.57]) and nonfatal stroke (2.6% versus 1.9%; hazard ratio, 1.36 [95% CI, 1.04-1.77]).<sup>19</sup> As a result, the FDA removed sibutramine from the US market in 2010, but it can still be found illicitly in dietary supplements marketed for weight loss and in other parts of the world.<sup>35</sup> Clinicians are encouraged to ask patients about potential use of dietary supplements for weight management.

#### 4.2.10. Cardiac Rehabilitation

##### Recommendation for Cardiac Rehabilitation

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
1	A*	1. All patients with CCD and appropriate indications*†‡ should be referred to a cardiac rehabilitation program to improve outcomes. <sup>1-3</sup>

\*After recent MI, PCI, or CABG.<sup>1-5</sup> †With stable angina<sup>2,3,6,7</sup> or after heart transplant.<sup>8-13</sup> ‡After recent spontaneous coronary artery dissection event.<sup>14-17</sup>

#### Synopsis

CR is a comprehensive, team-based, and evidence-based approach to delivering lifestyle, behavioral, and medical therapies of known benefit to individuals with CVD.<sup>18-23</sup> Because of underutilization of CR,<sup>24</sup> novel delivery models have been and continue to be developed, tested, and implemented, including home-based, remote CR services.<sup>25</sup> Home-based CR have similar shorter-term safety and clinical outcomes as facility-based CR and can be considered as an alternative option for patients who cannot attend facility-based CR.<sup>26-29</sup> This is of particular importance for patients with limited option for center-based CR, such as those living in rural settings and other areas with limited number of CR centers. In whatever delivery model CR is provided, the multidisciplinary CR team develops and applies patient-centered care based on specific core components (**Table 13**), including recovery and recuperation strategies, quality improvement, and adherence to lifestyle and medication therapies.<sup>18,30,31</sup> Key benefits from CR have been noted to be dose-related.<sup>32,33</sup> Published evidence suggests favorable cost-effectiveness of CR.<sup>34-36</sup> One multicenter, randomized trial of longer-term “maintenance” CR of up to 3 years was associated with moderate but significant improvements in cardiovascular outcomes compared with those who participated in the traditional

12-week course of CR.<sup>37</sup> For related information, refer to these Sections: 3.2, “Risk Stratification and Relationship to Treatment Selection”; 4.1.1, “Team-Based Approach”; 4.1.2, “Patient Education,” 4.1.3, “Shared Decision-Making”; 4.2.1, “Nutrition, Including Supplements”; 4.2.2, “Mental Health”; 4.2.6, “Lipid Management”; 4.2.7, “Blood Pressure Management”; 4.2.8, “Sodium Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists”; 4.2.9, “Weight Management”; 6.1, “Existing Heart Diseases and Conditions”; 6.9, “Post-Heart Transplant Cardiac Allograft Vasculopathy”; and 2022 ACC/AHA/HFSA heart failure guideline.<sup>38</sup>

#### Recommendation-Specific Supportive Text

1. Patients with CCD with a recent MI, PCI, or CABG procedure who participate in CR have significantly better outcomes compared with those who do not participate,<sup>39-41</sup> including lower all-cause and cardiovascular mortality rates,<sup>27,41,42</sup> lower rehospitalization rates (total, cardiovascular, and noncardiovascular),<sup>43-45</sup> and superior QOL.<sup>27,41,42,44,45</sup> Participation in CR appears to improve symptom control, functional capacity, and QOL in patients with stable angina.<sup>2,40</sup>

CR is also associated with improved outcomes in special populations with CCD. CR improves exercise capacity in

heart transplant recipients,<sup>8</sup> including those in maintenance (1–8 years after heart transplant) as well as de novo (7–16 weeks after heart transplant).<sup>9,10</sup> In maintenance of patients with heart transplant with or without cardiac allograft vasculopathy, high-intensity interval training versus usual care resulted in significantly lower rates of cardiac allograft vasculopathy progression at 1 year,<sup>11</sup> but these effects were no longer present on long-term (3–5 years) follow-up, suggesting that continued intermittent periods of high-intensity interval training may be necessary to maintain the initial benefits.<sup>12,46,47</sup> One observational study showed an association between the dose of

CR sessions and survival in patients with heart transplant.<sup>48</sup>

Similarly, patients with spontaneous coronary artery dissection (SCAD) who participated in CR, compared with those who did not, had lower MACE and lower rates of recurrent MI with favorable trends in physical, emotional, and mental domains.<sup>14–17</sup> For patients with CCD and concomitant HF, CR is also recommended as a Class 2a recommendation, LOE B-NR (see 2022 ACC/AHA/HFSA heart failure guideline).<sup>38</sup>

#### 4.2.11. Physical Activity

##### Recommendations for Physical Activity

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	<p>1. For patients with CCD who do not have contraindications, an exercise regimen is recommended, including ≥150 minutes/wk of moderate-intensity aerobic activities or ≥75 minutes/wk of higher-intensity aerobic activities to improve functional capacity and QOL, and to reduce hospital admission and mortality rates.<sup>1–3</sup></p>
1	B-R	<p>2. For patients with CCD who do not have contraindications, resistance (strength) training exercises are recommended on ≥2 days/wk to improve muscle strength, functional capacity, and cardiovascular risk factor control.<sup>4–6</sup></p>
2a	B-NR	<p>3. For patients with CCD who do not have contraindications, lower-intensity lifestyle activities (eg, walking breaks at work) to reduce sedentary behavior (ie, sitting time) are reasonable to improve functional capacity and reduce cardiovascular risk, especially in individuals with low levels of habitual leisure time physical activity.<sup>7–9</sup></p>

##### Synopsis

Habitual physical activities—including nonexercise lifestyle activities, aerobic (cardiovascular) exercise training, and resistance (strength) training—are associated with improved outcomes in individuals with CVD, including functional capacity, QOL, and mortality and morbidity rates.<sup>1–9</sup> Moving individuals from sedentary lifestyle habits to at least lower-intensity physical activities can improve metabolic and cardiovascular health.<sup>9–11</sup> Health benefits occur even with lower doses (eg, frequency, duration, and intensity) of physical activity and increase with increasing doses of physical activity.<sup>7</sup> Mechanisms of the benefits from physical activity and exercise training include anti-atherosclerotic, antiarrhythmic, antithrombotic, anti-ischemic, and antidepressant effects.<sup>12</sup>

Exercise is contraindicated in patients with severe, life-threatening, and unstable conditions. Contraindications include unstable angina, other high risk cardiovascular conditions (eg, high-grade arrhythmias, decompensated heart failure, active thromboembolic disease), or other unstable or life-threatening noncardiovascular conditions such as active infection, uncontrolled diabetes, end-stage cancer, or unstable psychological issues.

##### Recommendation-Specific Supportive Text

1. Moderate-to-higher intensity exercise training in individuals with CCD, which is done in CR programs, improves functional capacity, health-related QOL, cardiovascular risk factor control, and mortality rates.<sup>2,3,13,14</sup> In addition to continuous, moderate-intensity exercise training, high-intensity interval training also appears to be an effective and safe approach to aerobic exercise training in individuals with CCD.<sup>15,16</sup> US guidelines recommend that adults who do not have contraindications to exercise should do at least 150 to 300 minutes per week of moderate-intensity aerobic physical activity, or at least 75 to 150 minutes per week of vigorous (higher)-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.
2. Muscle-strengthening (resistance training) activities are recommended on ≥2 days a week.<sup>17</sup> Resistance training to safely improve muscular strength improves functional capacity and QOL.<sup>5,6,18</sup> Resistance training may also reduce mortality rates in individuals with CCD.<sup>19</sup>

3. Compared with a sedentary lifestyle, lower-intensity lifestyle activities (eg, gardening), office-based physical activities, and climbing stairs improve energy expenditure, functional capacity, and cardiometabolic risk, especially in previously sedentary individuals who are not exercising on a regular basis.<sup>20–25</sup> Interventions, such as the use of step counters and

walking prompts, may be helpful in decreasing sedentary time and increasing lifestyle activities in individuals with CCD.<sup>9–11,20–23,26</sup>

#### 4.2.12. Environmental Exposures

##### Recommendations for Environmental Exposures

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
2a	B-NR	1. In patients with CCD, minimization of exposure to ambient air pollution is reasonable to reduce the risk of cardiovascular events. <sup>1–7</sup>
2b	B-NR	2. In patients with CCD, minimization of climate-related exposures (eg, extreme temperatures, wildfire smoke) may be reasonable to reduce the risk of cardiovascular events. <sup>8–10</sup>

#### Synopsis

Adverse environmental exposures such as air pollution, extremes of ambient temperature, and excess noise should be systematically assessed in patients with CCD. Numerous ecological studies have examined the adverse effect on cardiovascular health of ambient air pollution such as that produced by transportation exhaust or wildfire smoke.<sup>1–7,11,12</sup> Exposure to extreme heat or extreme cold ambient temperatures has been associated with increased cardiovascular events among patients with CCD.<sup>8–10,13,14</sup> As extreme temperatures have become increasingly frequent, clinicians should identify at-risk individuals, provide guidance regarding medication titration (eg, loop diuretics) during extreme temperature events, and encourage the use of publicly available controlled-temperature environments during extreme weather events. Numerous observational studies document a connection between excess environmental noise and the progression of CCD,<sup>15,16</sup> but data are limited regarding the benefit of noise reduction devices. Adverse environmental exposures disproportionately affect racial and ethnic minority populations and individuals of low socioeconomic status; therefore, they contribute to inequitable health outcomes.<sup>17,18</sup> Policy interventions that reduce the burden of these exposures or provide resources to mitigate their adverse effects may reduce health disparities.<sup>18</sup>

#### Recommendation-Specific Supportive Text

- Ambient air pollution, especially small particulate matter with an aerodynamic diameter  $\leq 2.5$  microns (also referred to as “PM2.5”), is associated with worse cardiovascular outcomes.<sup>1–7</sup> Most outdoor and indoor PM2.5 pollutants are produced by combustion (eg, car engines, coal- or natural gas-fired power plants,

woodstoves, or wildfires). Proximity to automobile traffic or fossil fuel-dependent industries and use of poorly ventilated stoves are key predictors of exposure to increased PM2.5 levels. Long-term exposure to PM2.5 levels  $>10$  micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) is associated with a  $>10\%$  increase in the odds of having CCD, progression of CCD, and suffering an acute MI or cardiovascular mortality.<sup>1–5</sup> Even short-term exposure ( $<7$  days) to elevated levels is associated with increased hospitalization and cardiovascular death.<sup>6,7</sup> There are insufficient data to support regular use of in-home high-efficiency air purifiers or N95 filters to improve cardiovascular outcomes.<sup>19</sup> Other pollutants, such as ground-level ozone, are associated with a small increase in risk of cardiovascular death, but additional studies are needed to quantify the magnitude of risk.<sup>20</sup> Information regarding air pollutants and their relation to air quality in a specific geography can be found via the US Environmental Protection Agency at [AirNow.gov](http://AirNow.gov).<sup>21</sup>

- Exposure to extreme ambient heat or several consecutive days of extreme heat (“heat wave”) is associated with increased death from ischemic heart disease.<sup>8</sup> Older adults, individuals with outdoor jobs, and patients receiving certain medications such as loop diuretics are at increased risk.<sup>8,9</sup> The effects of extreme heat are exacerbated in urban areas because of the “urban heat island effect,” wherein dense concentrations of pavement and buildings absorb and retain heat.<sup>13</sup> Individualized assessment should include risk of exposure (ie, regional temperature and occupational exposure), clinical susceptibility (ie, age, comorbidities, and medications used), and capacity for adaptation (ie, cognitive skills, housing quality, and community resources).<sup>14</sup> Similarly, exposure to wildfire smoke has

been associated with increased hospitalizations for acute MI, ischemic heart disease, and cardiac arrest.<sup>12</sup> Wildfire smoke can be carried long distances, exposing individuals thousands of miles from the source.<sup>11</sup> The population health impact of wildfires is projected to increase in the coming years because of climate change-related increases in temperature and changes in precipitation patterns, as well as increased human habitation in wildland-urban interfaces.<sup>22</sup>

Minimizing exposure to these environmental extremes may improve outcomes for individuals with CCD.

#### **4.3. Medical Therapy to Prevent Cardiovascular Events and Manage Symptoms**

##### **4.3.1. Antiplatelet Therapy and Oral Anticoagulants**

##### **Recommendations for Antiplatelet Therapy and Oral Anticoagulants**

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATIONS
<b>Antiplatelet Therapy Without Oral Anticoagulants</b>		
1	A	1. In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75–100 mg) is recommended to reduce atherosclerotic events.* <sup>1-3</sup>
1	A	2. In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* <sup>4-7</sup>
2a	A	3. In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. <sup>8-12</sup>
2b	A	4. In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to 3 years may be reasonable to reduce MACE.* <sup>13,14</sup>
2b	B-R	5. In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. <sup>15-17</sup>
2b	B-R	6. In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. <sup>18</sup>
3: No benefit	A	7. In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE.* <sup>19</sup>
3: Harm	A	8. In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. <sup>15,20</sup>
3: Harm	B-R	9. In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. <sup>21</sup>
3: Harm	B-R	10. In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications.* <sup>22</sup>
<b>Antiplatelet Therapy With Direct Oral Anticoagulant (DOAC)</b>		
1	B-R	11. In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for 1 to 4 weeks followed by clopidogrel alone for 6 months should be administered in addition to DOAC.† <sup>23</sup>
2a	B-R	12. In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk.* <sup>23-25</sup>

## (continued)

2b

B-R

- 13.** In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered 1 year after PCI to reduce bleeding risk.\*<sup>26</sup>

2b

C-LD

- 14.** In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy.<sup>27–29</sup>

**Antiplatelet Therapy and Low-Dose DOAC**

2a

B-R

- 15.** In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE.<sup>30–32</sup>

**DAPT and Proton Pump Inhibitor (PPI)**

2a

B-R

- 16.** In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk.\*<sup>33</sup>

\*Modified from the 2016 ACC/AHA Guideline Focused Update on DAPT.<sup>34</sup> †Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.<sup>35</sup>

**Synopsis**

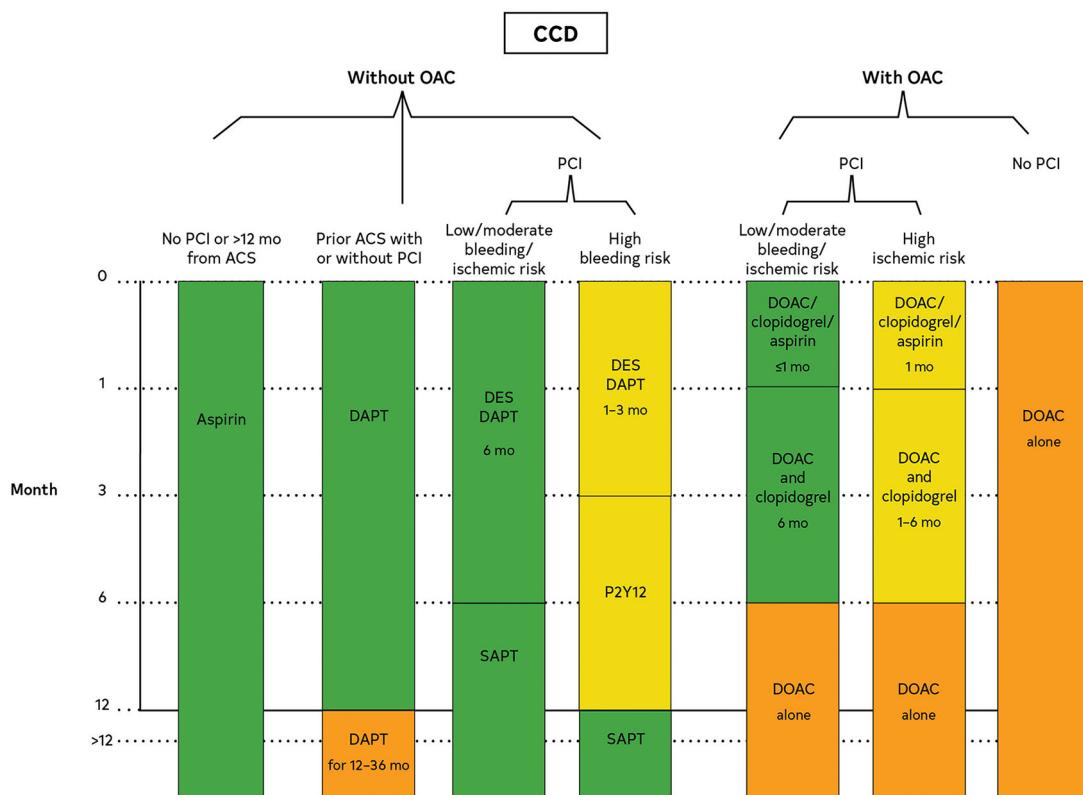
These recommendations on the use of antiplatelet therapy in patients with CCD update and supplement the 2016 AHA/ACC guideline for DAPT.<sup>34</sup> Significant benefits remain for aspirin use in secondary prevention.<sup>2,36,37</sup> The use of DAPT can be considered in those who have high thrombotic risk and low bleeding risk. Figure 9 summarizes recommendations for antiplatelet therapy in CCD. The use of validated risk scores to address bleeding risk can be useful in choice and duration of antiplatelet therapy. The more frequently used risk calculators are PRECISE DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy), DAPT, and PARIS (Patterns of Non-Adherence to Antiplatelet Regimen in Stented Patients) risk scores.<sup>18–20</sup> Several clinical trials have evaluated strategies for concurrent use of antiplatelet agents and DOACs in patients with atherosclerotic disease. The breadth and consistency of trials evaluating the efficacy and safety of DOAC use with or without antiplatelet therapy among patients with CCD and with or without AF is modest.<sup>27,28,30–32,38–44</sup> The combination of antiplatelet therapy and standard dose DOACs for reducing stroke risk among patients with atrial fibrillation (dabigatran 150 mg twice daily, apixaban 5 mg twice daily, rivaroxaban 20 mg daily, edoxaban 60 mg daily) is not without added bleeding risk. The variability in treatment duration, as well as various platelet adenosine diphosphate receptor (P2Y12) agents and DOAC regimens tested in these trials highlights the need for an individualized approach to achieve the optimal balance between ischemic and

bleeding risks. Although DES are the predominant stent used in the United States, bare metal stents are still used in a small proportion of patients. The reader is referred to the 2016 AHA/ACC guideline for DAPT<sup>34</sup> for specific treatment details for bare metal stents.

**Recommendation-Specific Supportive Text**

- The use of aspirin for secondary ASCVD prevention is well established for reduction in MACE.<sup>2,45</sup> More recently, the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term) trial used a large (N=15,076), open-label design to assign patients with established ASCVD to either 81 mg or 325 mg of aspirin.<sup>3</sup> No significant differences were observed in the primary composite of death from any cause, hospitalization for MI, or hospitalization for stroke by aspirin dose. No differences in major bleeding were observed. However, substantial dose switching was observed (41.6% of patients assigned to take 325 mg daily switched to 81 mg daily and 7.1% assigned to take 81 mg daily switched to 325 mg daily). As an alternative to low-dose aspirin, clopidogrel may be used in individuals who cannot tolerate aspirin therapy, and many of the contemporary trials have used clopidogrel monotherapy after a short course of DAPT.<sup>46,47</sup>
- To assess optimal duration of antiplatelet therapy, a meta-analysis of RCTs (n=31,666 patients) comparing shorter DAPT with longer DAPT showed that shorter DAPT was associated with lower all-cause mortality.<sup>4</sup>

**FIGURE 9 Recommended Duration of Antiplatelet Therapy\*†**



ACS indicates acute coronary syndrome; ASA, aspirin; CCD, chronic coronary disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DOAC, direct oral anticoagulant; MI, myocardial infarction; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy. \*Colors correspond to Class of Recommendation in Table 3. †This figure does not encompass all recommendations within this section.

Patients treated with DAPT for  $\leq 6$  months had similar mortality rates, MI, and stent thrombosis, but lower rates of major bleeding than patients treated with 1-year DAPT.<sup>4</sup> Data supporting the use of DAPT for 6 months with continued use of aspirin after 6 months come from several trials. The largest trial was ISAR-SAFE (Randomized, Double Blind Trial of 6 Versus 12 Months of DAPT After DES-Implantation; N=4,005 patients, of which 60% had stable CAD).<sup>7</sup> In these trials, aspirin use continued for the duration of the 12-month trial design.<sup>5,12</sup> Data are limited on which antiplatelet agent—aspirin or clopidogrel—is best for indefinite therapy after a 12-month period after PCI. The HOST-Exam (Harmonizing Optimal Strategy for Treatment of coronary artery diseases—Extended Antiplatelet Monotherapy) trial enrolled 5,530 East Asian participants if they tolerated DAPT for 6 to 18 months without any ischemic or major bleeding complication and randomized them to receive clopidogrel 75 mg

daily or aspirin 100 mg daily for 24 months.<sup>46</sup> The benefit of clopidogrel over aspirin was observed in both thrombotic and bleeding complications. This study used an open-label design in a homogenous East Asian population known to have lower rates of thrombotic complications, and the observed event rate was lower than expected. Therefore, further clinical trials would be useful to guide recommendations regarding the long-term use of clopidogrel versus aspirin as SAPT in CCD.<sup>46,48,49</sup>

3. Multiple clinical trials (SMART CHOICE [Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy after DES], STOP-DAPT2 [Short and Optimal Duration of Dual Antiplatelet Therapy after Everolimus-Eluting Cobalt-Chromium Stent-2 Acute Coronary Syndrome], TWILIGHT [Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention], and GLOBAL LEADERS [A Clinical Study Comparing Two Forms of Antiplatelet

Therapy After Stent Implantation]) found reduced bleeding complications without increased ischemic complications when DAPT was used for 1 to 3 months followed by P2Y12 monotherapy.<sup>8,9,47,50–52</sup> These trial populations comprised 35% to 62% in stable patients with stable CAD. In a network meta-analysis that included 29,089 patients randomized to short-term DAPT followed by P2Y12 inhibitor monotherapy versus standard duration DAPT, a net clinical benefit was seen that favored short-term DAPT followed by P2Y12 inhibitor monotherapy with less MI and bleeding.<sup>8</sup> A meta-analysis showed discontinuation of aspirin after 1 to 3 months with continuation of a P2Y12 agent (mostly prasugrel or ticagrelor) reduced the risk of major bleeding by 40% without an increased risk of MACE.<sup>10</sup> These trials were not powered to assess ischemic events, particularly stent thrombosis. Therefore, longer duration DAPT may be needed for patients with higher thrombotic risk (eg, several lesions, long stent length, bifurcation location, atherectomy use, lesion location [left main], bypass graft, or chronic occlusion).

4. A systematic review and meta-analysis of prospective RCTs of secondary prevention examined data from 33,435 participants. Of these, 20,203 were treated with DAPT and 13,232 were given only aspirin. Patients were considered high risk and almost half had previous MI. Comorbidities also included diabetes, previous PCI, and CKD. Extended DAPT for >1 year reduced MACE (relative risk, 0.78 [95% CI, 0.67–0.90];  $P=0.001$ ) and absolute risk difference of 1.09%, or a number needed to treat for benefit of 91 to prevent 1 MACE over 31-month follow up. This came with an increased absolute 0.8% risk of major bleeding without significant intracranial or fatal bleeding.<sup>13</sup> Similarly, a systematic review conducted for the 2016 ACC/AHA guidelines on DAPT<sup>34</sup> examined the incidence of death, major hemorrhage, MI, stent thrombosis, and major adverse cardiac events in 33,051 patients in 11 RCTs of prolonged versus short-course DAPT after stenting with DES and in secondary prevention after MI. Among those treated with DES, prolonged DAPT reduced stent thrombosis and MI but increased major hemorrhage. Patients with previous MI had evidence of reduced cardiovascular events at the expense of increased bleeding.<sup>53–55</sup> The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) trial enrolled 21,162 patients who had MI 1 to 3 years before being given ticagrelor 90 mg or 60 mg twice

daily compared with placebo on a background of low-dose aspirin.<sup>56</sup> Treatment with ticagrelor 60 mg reduced the risk of cardiovascular death, MI, or stroke by 16% and increased the risk of major bleeding at 33-month follow up.<sup>14</sup>

5. Given multiple pathways of platelet activation, options for additional suppression of platelet activity have been studied. PAR-1 is a key receptor for thrombin activation. Vorapaxar selectively inhibits PAR-1 on platelets, thereby potently inhibiting thrombin-induced platelet aggregation. The TRAP 2P TIMI 50 (Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis) trial randomized 26,449 patients with history of MI, ischemic stroke, or peripheral artery disease to either 2.5 mg of vorapaxar daily or placebo on a background of aspirin therapy. At a mean follow up of 3 years, patients who received vorapaxar experienced an ischemic event less often or died from cardiovascular causes; however, they had more major and intracranial bleeding.<sup>15</sup> In a prespecified subgroup analysis of 17,779 patients who had previous MI, there was a reduced incidence of cardiovascular death, MI, or stroke in the vorapaxar group compared with placebo; however, moderate or severe bleeding was increased.<sup>16</sup> In a prespecified analysis of 16,897 patients with previous MI without a history of stroke or TIA and on thienopyridine therapy, vorapaxar reduced the composite of cardiovascular death, MI, or stroke compared with thienopyridine use; however, GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) moderate or severe bleeding was increased. Three-year rates of fatal bleeding were 0.2% versus 0.1% in patients receiving vorapaxar versus thienopyridine. Intracranial hemorrhage rates were 0.5% versus 0.4% in that cohort. Vorapaxar had net clinical benefit with a combined risk of all-cause death, MI, stroke, or GUSTO severe bleeding decreased by 13% compared with placebo. Of note, thienopyridine use was not randomized in this study; therefore, formal comparison is limited. The thienopyridine used was clopidogrel therefore extrapolation to more potent P2Y12 agents is not possible.<sup>17</sup>
6. In a systematic review and meta-analysis of observational and RCTs (N=20,315 patients) comparing DAPT with SAPT after urgent or elective CABG,<sup>18</sup> investigators performed a pooled sensitivity analysis of studies with stable ischemic heart disease-predominant patients (>50% of study population), and found no difference between SAPT and DAPT after CABG in overall mortality (odds ratio, 0.83 [95% CI,

- 0.63-1.10];  $P=0.20$ ), cardiovascular mortality (odds ratio, 0.66 [95% CI, 0.34-1.29];  $P=0.23$ ), MI (odds ratio, 1.15 [95% CI, 0.66-1.99];  $P=0.63$ ), stroke (odds ratio, 0.58 [95% CI, 0.32-1.06];  $P=0.08$ ), combined incidence of cardiovascular death, MI, and stroke (odds ratio, 0.81 [95% CI, 0.57-1.16];  $P=0.25$ ), and arterial graft occlusions (odds ratio, 1.13 [95% CI, 0.73-1.73];  $P=0.59$ ). In the studies that had predominantly stable patients with CAD, the rate of saphenous vein graft occlusion was lower among those receiving DAPT (odds ratio, 0.74 [95% CI, 0.60-0.90];  $P<0.01$ ).
7. Clopidogrel plus aspirin is not more effective than aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes in patients at high risk for atherothrombotic events.<sup>19</sup>
  8. In the TRAP 2P-TIMI 50 trial, after 2 years the data and safety monitoring board recommended discontinuation of study treatment in patients with a history of stroke because of the risk of intracranial hemorrhage. Significant reduction in cardiovascular death, MI, stroke, or recurrent ischemia leading to revascularization was observed; however, the primary driver of benefit was in lower risk of MI, at a cost of increased moderate to severe bleeding along with increased intracranial bleeding.<sup>15,57</sup> Vorapaxar is FDA approved for use in patients with previous MI for the reduction in cardiovascular death, MI, stroke, or recurrent ischemia leading to revascularization; however, it carries a 55% increase in moderate or severe bleeding and is contraindicated with a history of stroke, TIA, or intracranial hemorrhage.
  9. In the TRITON-TIMI 38 (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) trial, patients with previous TIA or stroke had increased risk of intracranial hemorrhage leading to an FDA warning: Prasugrel can cause significant, sometimes fatal, bleeding and should not be used in patients with active pathological bleeding or with a history of TIA or stroke. Patients  $\geq 75$  years of age and weighing  $<60$  kg had less clinical efficacy with prasugrel use.<sup>21,58</sup>
  10. Investigators have assessed the vascular and gastrointestinal side effects in patients with vascular disease and have found major vascular events were increased by about a third by a coxib (relative risk, 1.37 [95% CI, 1.14-1.66];  $P=0.0009$ ) or diclofenac (relative risk, 1.41 [95% CI, 1.12-1.78];  $P=0.0036$ ), because of an increase in major coronary events (coxibs relative risk, 1.76 [95% CI, 1.31-2.37];  $P=0.0001$ ; diclofenac relative risk, 1.70 [95% CI, 1.19-2.41];  $P=0.0032$ ). Ibuprofen also significantly increased major coronary events (relative risk, 2.22 [95% CI, 1.10-4.48];  $P=0.0253$ ). Vascular death was increased significantly by coxibs (relative risk, 1.58 [99% CI, 1.00-2.49];  $P=0.0103$ ) and

diclofenac (relative risk, 1.65 [95% CI, 0.95-2.85],  $P=0.0187$ ). HF risk was doubled by all nonsteroidal anti-inflammatory drugs.<sup>22</sup> However, at moderate doses, celecoxib was found to be noninferior to naproxen or ibuprofen regarding increased cardiovascular risk in patients with arthritis who were considered high cardiovascular risk (stable angina, history of MI, unstable angina, status post CABG or PCI, TIA, or cerebrovascular accident within 3 months,  $>50\%$  stenosis, carotid disease, peripheral artery disease, diabetes, age  $>55$  years in men, age  $>65$  years in women, hyperlipidemia, hypertension, early family history of CAD, smoking). These trials involved celecoxib, rofecoxib, etoricoxib, and lumiracoxib and 3 high-dose nonsteroidal anti-inflammatory regimens: diclofenac 150 mg, ibuprofen 2,400 mg, and naproxen 1,000 mg daily.

11. A systematic review and network meta-analysis of 4 RCTs, including 10,026 patients (39%-72% with stable CAD)<sup>23,59</sup> showed that the combination of a DOAC with a P2Y12 inhibitor was associated with less bleeding compared with vitamin K agonists and DAPT. The omission of aspirin led to less bleeding, including intracranial bleeding, without differences in MACE, compared with strategies including aspirin.<sup>59</sup> In an updated network meta-analysis including these trials and a fifth trial (ENTRUST-AF PCI [Edoxaban Treatment Versus Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention]; N=11,542), fewer bleeding complications were observed with preserved antithrombotic efficacy when aspirin was discontinued within a few days (3-14 days) after PCI. The authors concluded that an antithrombotic regimen of vitamin K agonists plus DAPT should generally be avoided. The use of a DOAC (apixaban 5 mg twice daily or 2.5 mg twice daily in those with 2 of 3 criteria for high bleeding risk; rivaroxaban 15 mg daily; edoxaban 60 mg daily or 30 mg if creatinine clearance 15-50 mL/min, weight  $<60$  kg, or concurrent use of specific potent P-glycoprotein inhibitors; and dabigatran 110 mg or 150 mg twice daily) plus a P2Y12 inhibitor without aspirin may be the most favorable treatment option and the preferred antithrombotic regimen for most patients with AF undergoing PCI. The AUGUSTUS trial (A Study of Apixaban in Patients with AF, not Caused by a Heart Valve Problem, who are at Risk for Thrombosis due to having had a Recent Coronary Event, such as a Heart Attack or a Procedure to Open the Vessels of the Heart) examined randomized treatment effects of low-dose aspirin (compared with placebo) and apixaban (compared with vitamin K antagonist [VKA]) on the risk of stent thrombosis and found a 2-fold increase in bleeding with aspirin while the incidence of

- stent thrombosis was low, occurring in <1% over 6 months. However, the study had limited power to detect a difference in stent thrombosis. Rates of stent thrombosis were lower with aspirin compared with placebo and with apixaban compared with VKA. Among patients with a high risk of stent thrombosis and an acceptable bleeding risk, the use of aspirin up to 30 days after PCI should be considered.<sup>25</sup>
12. Triple therapy after PCI in patients with AF increases bleeding risk without significant reduction in ischemic risk.<sup>59</sup> A recent expert consensus document recommends triple therapy with aspirin, a P2Y12 inhibitor, and an oral anticoagulant for up to 30 days after PCI for patients at particularly high risk for coronary thrombosis such as previous MI, complex lesions, presence of select traditional cardiovascular risk factors, or extensive CVD but with bleeding risk that is judged to be low.<sup>29</sup> A subgroup analysis of the REDUAL PCI trial (Dual Therapy with Dabigatran/Ticagrelor Versus Dual Therapy with Dabigatran/Clopidogrel in ACS Patients with Indication for NOAC Undergoing PCI) examined effect of lesion complexity and clinical risk factors. This trial found that dabigatran dual therapy after PCI was associated with reduced bleeding risk compared with warfarin triple therapy, independent of the presence of procedural or clinical complexity factors. However, patients in the highest lesion complexity and clinical risk factor group had the highest hazard ratio (1.43 [95% CI, 0.74-2.77]) for death, thromboembolic event, or unplanned revascularization in the dabigatran 110 mg dual therapy compared with dabigatran 150 mg dual therapy (hazard ratio, 0.88 [95% CI, 0.33-2.36]) both compared with warfarin triple therapy.<sup>60-63</sup>
13. The AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban) trial was a multicenter, open-label trial that randomized 2,236 patients with AF who had previous PCI or CABG >1 year earlier or who had CCD to rivaroxaban versus rivaroxaban plus a single antiplatelet agent (70.2% received aspirin, and 26.8% received a P2Y12 inhibitor). The primary endpoint was a composite of stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause, with a safety endpoint of major bleeding. Rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety among patients with AF and stable CAD. In patients with stable CCD and AF, the addition of antiplatelet therapy to a VKA does not reduce the risk of recurrent coronary events or thrombosis; furthermore, this combination leads to significantly increased bleeding risk.<sup>26,64,65</sup>
14. Several studies have evaluated triple therapy with a DOAC and DAPT as well as a DOAC and SAPT in patients with AF and recent ACS.<sup>27,28,38-44</sup> Although these trials showed a lower risk of bleeding with a DOAC combined with a single antiplatelet agent compared with triple therapy, none of the studies were powered to clearly show differences in reducing ischemic events. Additionally, data are limited comparing either of these therapies for secondary prevention in patients with AF. This recommendation is based on historical data with warfarin as well as data extrapolated from more recent studies evaluating various combination therapies versus monotherapy in patients with a recent ACS.<sup>38-44,66-70</sup>
15. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial evaluated the efficacy and safety of low-dose rivaroxaban 2.5 mg twice daily, with or without low-dose aspirin therapy, in reducing CVD events in patients with stable ASCVD.<sup>30</sup> The primary outcome of cardiovascular death, stroke, or MI occurred in 4.1% of the aspirin plus rivaroxaban group, 4.9% of the rivaroxaban alone group, and 5.4% for aspirin monotherapy. The study was terminated early because of the observed benefit of rivaroxaban plus aspirin compared with aspirin alone. Evaluation of high-risk patients (multivessel CAD and at least one of the following: diabetes requiring medication, recurrent MI, peripheral artery disease, HF, or CKD with an eGFR of 15-59 mL/min/m<sup>2</sup><sup>69</sup>) showed an absolute net clinical benefit with combination therapy, with substantial reductions in ischemic events and all-cause death.<sup>31</sup> The high-risk population also derived a larger absolute risk reduction, resulting in an even lower number needed to treat.<sup>30-32</sup> The combination of rivaroxaban plus aspirin resulted in a higher risk of major bleeding compared with aspirin monotherapy (3.1% versus 1.9%; hazard ratio, 1.70 [95% CI, 1.40-2.05];  $P<0.001$ ). The use of DAPT was an exclusion criteria.
16. Increased bleeding including gastrointestinal bleeding is a common side effect of DAPT; the mitigation of this risk has been an area of clinical investigation. SAPT (aspirin or clopidogrel) compared with DAPT leads to lower gastric or small intestinal mucosal injury.<sup>71</sup> Aspirin increases gastroduodenal ulcer formation. When combined with aspirin therapy, P2Y12 inhibitors can promote gastric ulcer bleeding. Clopidogrel is a prodrug that requires cytochrome CYP P450 2C19 for metabolism to its active form. PPIs are also metabolized by the P450 system, thereby leading to concern for inadequate clopidogrel therapy in those on both PPIs and DAPT. The FDA has added a boxed warning to avoid use of omeprazole with clopidogrel as well as other potent CYP 2C19 inhibitors, including esomeprazole. Several studies assessed the safety and efficacy of PPI in the context

of DAPT. A meta-analysis of 6 RCTs (6,930 patients) showed that the use of PPIs is associated with a reduced risk of gastrointestinal bleeding in patients treated with DAPT after PCI. No significant differences were observed in the incidence of MACE, MI,

and all-cause death in patients with CAD on DAPT and PPIs.<sup>33</sup>

#### 4.3.2. Beta Blockers

##### Recommendations for Beta Blockers

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. <sup>1-3</sup>
1	A	2. In patients with CCD and LVEF <50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. <sup>*1,3-8</sup>
2b	B-NR	3. In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. <sup>9-15</sup>
3: No Benefit	B-NR	4. In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. <sup>†16-19</sup>

\*Modified from the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.<sup>20</sup> †Adapted from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.<sup>21</sup>

##### Synopsis

Beta blockers exhibit their clinical effects by decreasing myocardial oxygen demand, improving ischemic threshold, and impeding maladaptive LV remodeling.<sup>1,22-24</sup> Patients with CCD comprise patients with or without previous MI, LV systolic dysfunction, or both. These distinctions should be considered in determining the indications for use of beta-blocker therapy in patients with CCD. The strongest data for the benefit of beta-blocker therapy in CCD is for patients with LV systolic dysfunction but is less clear for patients without LV dysfunction.<sup>1,3-8,13-15,25-27</sup> Several ongoing RCTs hope to better elucidate the need for and duration of beta-blocker therapy for MACE reduction among post-MI patients with preserved LV systolic function in the contemporary era. Other primary indications for beta blockers may include their use for angina, uncontrolled hypertension, or arrhythmias. A comprehensive screening as well as assessment of their symptoms and comorbid conditions is recommended given that beta-blocker therapy may still be indicated for its antianginal properties (see Section 4.3.6), antihypertensive properties (see Section 4.2.7, “Blood Pressure Management”), or for its negative chronotropic effects among patients with rhythm disturbance disorders.<sup>28,29</sup>

##### Recommendation-Specific Supportive Text

- Multiple well-conducted RCTs from the precontemporary as well as modern era showed the efficacy of

beta-blocker therapy in reducing cardiovascular death and MACE among patients with LV systolic dysfunction.<sup>1-4,7,25</sup> This benefit was found among patients with previous MI and those without history of MI.<sup>1,2,4,5,25</sup> Furthermore, data from the KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institute of Health) registry suggest that the clinical benefits of beta-blocker therapy may extend beyond patients with reduced LVEF (≤40%) and even toward patients with mid-range LVEF (40%-49%).<sup>2</sup> Given unequivocal benefit of beta-blocker therapy, widespread use of these agents in this subset of patients has been recommended. For detailed discussion of beta-blocker use in heart failure patients, see the “2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.”<sup>20</sup>

- Different beta blockers have been at the center of multiple clinical investigations evaluating their effectiveness among patients with HF with LV systolic dysfunction.<sup>3,4,8,30-32</sup> CIBIS-II (Cardiac Insufficiency Bisoprolol Trial II), COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study), and MERIT-HF (Metoprolol Randomized Intervention Trial in Congestive Heart Failure) RCTs have shown clinical efficacy of bisoprolol, carvedilol, and metoprolol succinate among patients with LV systolic dysfunction in reducing cardiovascular death and MACE.<sup>3,4,30</sup> Continued dose titration was performed within these trials to target doses of 10 mg per day for bisoprolol, 200

mg per day for metoprolol succinate, and 25 mg twice daily for carvedilol (or 50 mg twice daily for patients weighing >84 kg).

3. Although previous iterations of the ACC/AHA guidelines on patients with stable ischemic heart disease recommended the use of beta-blocker therapy in patients with previous MI and preserved LV systolic function, this recommendation was based on data gathered from the noncontemporary era.<sup>33</sup> In the contemporary era of timely reperfusion/revascularization and progressive pharmacotherapy (including antithrombotic and lipid-lowering therapy) among patients with MI, the recommendation for long-term use (>1 year) of beta-blocker therapy in the absence of LV systolic dysfunction has been challenged.<sup>13,14</sup> Observational studies from the current era evaluating post-MI patients with preserved LV systolic function showed discrepant results with some studies suggesting clinical benefit while others showed lack of clinical benefit with long-term use of beta-blocker therapy.<sup>9-15,34</sup> Long-term use of beta-blocker therapy may also confer potential clinical risks including fatigue, depression, and drug-drug interactions, thereby necessitating future high-quality data to ascertain the need for and duration of beta-blocker use among this population. Several ongoing large randomized controlled clinical trials including REBOOT-CNIC (Treatment with Beta-blockers after MI without Reduced Ejection Fraction), REDUCE-SWEDEHEART (Evaluation of Decreased Usage of Beta-blockers After MI in the Swedeheart Registry), BETAMI (Beta-blocker Treatment after Acute MI in Revascularized Patients without Reduced LVEF), and DANBLOCK (Danish Trial of Beta-blocker Treatment

after MI Without Reduced LVEF) aim to provide more clarity on the efficacy, safety, and QOL associated with beta-blocker therapy in patients with CCD, including post-MI patients with preserved LV systolic function.

4. Protective clinical benefits of beta-blocker therapy in reducing cardiovascular death have not been shown among CCD patients without previous MI or LV systolic dysfunction. The REACH (Reduction of Atherothrombosis for Continued Health) registry evaluated patients with CAD without history of MI and studied the effect of beta-blocker therapy on the primary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke.<sup>18</sup> Among patients with CAD without a history of MI, the use of beta-blocker therapy was not associated with a significant reduction in event rates for the primary endpoint. Similarly, a recent analysis from the National Cardiovascular Data Registry Cath-PCI registry evaluated the clinical benefit of beta blockers among patients with stable angina without a history of MI, LV systolic dysfunction, or systolic HF who were undergoing PCI.<sup>19</sup> The authors showed that the use of beta blockers was not associated with improvement in cardiovascular morbidity or mortality rates at 30 days or at 3-year follow-up. Similar results were seen in a post-hoc analysis from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial in which no reduction in cardiovascular events was observed with the use of beta blockers among patients without previous MI or HF.<sup>17</sup>

#### 4.3.3. Renin-Angiotensin-Aldosterone Inhibitors

##### Recommendations for Renin-Angiotensin-Aldosterone Inhibitors

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor-intolerant, is recommended to reduce cardiovascular events. <sup>1-5</sup>
2b	B-R	2. In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. <sup>6-10</sup>

#### Synopsis

Patients at high risk for CCD who have structural abnormalities (LVEF ≤40%), comorbid conditions (eg, diabetes, CKD, hypertension), or both are at significantly elevated risk of developing symptomatic HF and recurrent cardiovascular events. In addition to lowering BP (see Section 4.2.6, “Lipid Management”), renin-angiotensin-aldosterone system inhibitors (RAASi) decrease MACE in high-risk patients with CCD.<sup>1,3,5,8</sup> In contrast, the efficacy

of RAASi is less certain among populations with CCD with LVEF >40% and without comorbid hypertension, diabetes, or CKD.<sup>6,8,9,11,12</sup> RAASi trials (PEACE [Prevention of Events with Angiotensin Converting Enzyme Inhibition], QUIET [Quinapril Ischemic Event Trial], CAMELOT [Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis], and IMAGINE [Clazakizumab for the Treatment of Chronic Active Antibody Mediated Rejection in Kidney Transplant Recipients]) in lower-risk

populations with CCD showed no consistent CVD event reduction.<sup>8,11,13</sup> Patients on RAASi therapy require close follow-up after medication initiation and titration, including assessment of adherence, BP control, laboratory testing, evaluation for potential adverse effects (eg, orthostatic hypotension), intolerance (eg, cough, angioedema), or both. ARBs should be used as an alternative for patients who are ACE intolerant.<sup>14,15</sup>

#### Recommendation-Specific Supportive Text

1. In RCTs,<sup>1–5</sup> RAASi improved symptoms, reduced hospitalizations, prolonged survival, or all 3 among high-risk patients with CCD. In patients with hypertension and diabetes, RAASi reduce the incidence of moderate albuminuria and end-stage renal disease.<sup>16–18</sup> For patients with CCD and LVEF ≤40% who are clinically symptomatic beyond stage B, refer to the 2022 AHA/ACC/HFSA heart failure guideline.<sup>19</sup>
2. In the HOPE trial,<sup>10</sup> high-risk patients with CCD and preserved LVEF assigned to ramipril 10 mg daily had significant reductions in the composite of death,

#### Recommendation for Colchicine

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
2b	B-R	1. In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. <sup>1,2</sup>

#### Synopsis

Inflammation is a key component in the development of atherosclerosis.<sup>3</sup> As a result, using select anti-inflammatory agents may have a role in improving cardiovascular outcomes. However, studies evaluating agents thus far have showed mixed results.<sup>4,5</sup> Colchicine exhibits anti-inflammatory properties by altering inflammatory cell-mediated chemotaxis and phagocytosis by inhibiting microtubule polymerization.<sup>6</sup> Colchicine also reduces the expression of adhesion molecules and has an effect on cytokine production.<sup>7</sup> Given its broad cellular effects and its established role in the management of pericarditis, there has been renewed interest in its potential benefits in patients with CCD. Colchicine is considered a drug with narrow therapeutic index, meaning there is a small difference in the dose that is effective and what can lead to serious or toxic adverse effects. Additionally, colchicine is metabolized by cytochrome P450 3A4 and p-glycoprotein, making it prone to drug-drug interactions. Therefore, monitoring for adverse effects is of paramount importance. Given this, there is a need for a highly individualized approach, limiting the use of colchicine to those patients who remain at very high risk despite maximum tolerated GDMT until further data

cardiovascular events, and stroke, although the concurrent use of other risk reduction medications was low compared with other trials.<sup>10</sup> The EUROPA trial compared perindopril 8 mg daily to placebo in a lower risk population.<sup>9</sup> In the PEACE trial,<sup>20</sup> which compared trandolapril versus placebo in populations with CCD and normal LVEF, RAASi were not associated with reduced total mortality rate; however, there was a benefit in a subset of patients with reduced renal function (eGFR, <60 mL/min/m<sup>2</sup>).<sup>11</sup> In QUIET,<sup>13</sup> quinapril had no effect on progression of atherosclerosis in patients with CCD and preserved LVEF, except in those with CKD. The CAMELOT study<sup>8</sup> found no reduction in MACE among patients with CCD and normal BP. The lack of overall benefit of RAASi in lower risk populations likely reflects both baseline comorbidities and levels of concurrent pharmacotherapies with other evidence-based therapies for CCD.<sup>20,21</sup>

#### 4.3.4. Colchicine

become available. A cost-effectiveness analysis of COLCOT (Colchicine Cardiovascular Outcomes Trial) showed a 47% reduction in the mean overall per patient costs and increased the QALYs from 1.30 to 1.34 for the trial period of 24 months with the addition of colchicine to standard of care for post MI treatment.<sup>8</sup> There was also a 69% reduction in lifetime per patient cost and an increase in QALYs from 8.82 to 11.68 with colchicine compared to placebo, respectively. Based on the dose tested in clinical trials, the recommended dose of colchicine for use in secondary prevention in patients with CCD is 0.5 mg daily.

#### Recommendation-Specific Supportive Text

1. The LoDoCo2 (Colchicine Reduces Risk of Major Cardiovascular Events in CCD) trial aimed to validate the LoDoCo (Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease) results among patients with clinically stable ASCVD who had shown a reduced risk of recurrent cardiovascular events in patients taking colchicine 0.5 mg daily compared with placebo.<sup>2,5</sup> The primary endpoint was a composite of cardiovascular death, spontaneous MI, ischemic stroke, or ischemic-driven revascularization, which occurred in 6.8% of

patients in the colchicine group compared with 9.6% in the placebo group ( $P<0.001$ ). Despite the positive results, the study showed a trend toward increased risk of death from noncardiovascular causes in the colchicine group. The first trial to evaluate the efficacy of colchicine in secondary prevention in patients with ACS was the COLCOT trial.<sup>8,9</sup> Of patients treated with colchicine, the primary endpoint of death from cardiovascular causes, MI, resuscitated cardiac arrest, stroke, or urgent hospitalization for angina leading to coronary revascularization occurred in 5.5% of patients compared with 7.1% in the placebo group ( $P=0.02$ ). These results were driven primarily by reductions in the incidence of strokes and urgent hospitalizations for angina leading

to coronary revascularization. Although studies evaluating colchicine in secondary prevention excluded patients with creatinine clearance of  $<50$  mL/min, these studies were also limited to a duration of just over 2 years.<sup>1,2</sup> Given its long half-life, narrow therapeutic window, and degree of dependence on renal function for clearance, use should be avoided in patients with advanced renal disease (eGFR,  $<30$  mL/min/m<sup>2</sup>). Additionally, colchicine is metabolized by CYP3A4 and is a substrate for P-glycoprotein, which necessitates careful evaluation for drug-drug interactions.<sup>10</sup>

#### 4.3.5. Immunizations

##### Recommendations for Immunizations

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. <sup>1–7</sup>
1	C-EO	2. In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. <sup>8–10</sup>
2a	B-NR	3. In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. <sup>11–13</sup>

#### Synopsis

Infections such as influenza, pneumococcal pneumonia, and COVID-19 are a contributing factor to MACE and all-cause death, especially in patients with CCD.<sup>1,2,8,12</sup> The mechanisms by which infections such as these increase cardiovascular events may be related to proinflammatory mediators, stimulation of the sympathetic system, and coagulation cascade activation, which may cause rupture of vulnerable atherosclerotic plaques.<sup>14</sup> Vaccination against these respiratory infections may not only improve clinical outcomes but also potentially reduce hospitalization and health care costs. RCTs and non-randomized clinical trials have concluded that vaccination for these infections offer the greatest benefit in the highest risk populations, which includes those with advanced age, CCD, or both. Vaccination promotion is the best defense in protecting those with CCD who may be exposed to these infections in the community and face potential adverse clinical outcomes as a result.

#### Recommendation-Specific Supportive Text

- Studies show a significant association between recent respiratory infection and acute MI.<sup>1</sup> Meta-analyses and systematic reviews showed that influenza vaccination

was associated with a lower risk of acute MI, cardiovascular death, MACE, and all-cause death in patients with CAD or HF.<sup>1–5,7</sup> However, 1 study found no significant reduction in MI among those who received the influenza vaccine compared with control.<sup>7</sup> In patients with previous stroke, there was a nonsignificant trend for reduction of recurrent stroke risk.<sup>3</sup> No reduction was seen in all-cause death or cardiopulmonary hospitalization in high-risk patients with CCD who received high-dose trivalent influenza vaccine versus standard-dose quadrivalent influenza vaccine, although more vaccine-related adverse reactions occurred in the high-dose trivalent influenza vaccine group.<sup>6</sup>

- Although outcome data about the benefit of the COVID-19 vaccination in patients with CCD are unavailable at the time of writing this guideline, the targeted population for whom this guideline is intended is among the highest risk for developing COVID-19-related complications and death.<sup>8</sup> Therefore, the writing committee supports COVID-19 vaccination for patients with CCD and that the benefits of the COVID-19 vaccination outweigh the potential adverse events related to the vaccine itself.<sup>8–10</sup> For reference, US Centers for Disease Control and Prevention (CDC) guidance

may be accessed at <https://www.cdc.gov/coronavirus/2019-ncov/communication/guidance.html>.<sup>15</sup>

3. Limited data are available that evaluate pneumococcal polysaccharide vaccination in patients with CCD and its effect on cardiovascular outcomes and all-cause death. A population-based cohort study of 6,171 patients (18% with ischemic heart disease) who were hospitalized for pneumonia within 90 days and received previous pneumococcal polysaccharide vaccination found a 58% reduction in ACS events (12 versus 16 events per 100 patient-years [adjusted hazard ratio, 0.42 (95% CI, 0.27-0.66)]).<sup>11</sup> A systematic review and meta-analysis of observational studies with >163,000 participants found that the PPSV23, PCV13, or both was associated with a 22% decrease in all-cause death in patients with CCD or those with very high cardiovascular risk, although the study

design of some included studies led to a decreased level of design confidence.<sup>12</sup> A retrospective observational study using the 2012-2015 US National Inpatient Sample database evaluated the combined use of pneumococcal polysaccharide vaccine (PPV) and influenza vaccine and found lower mortality rate (2.21% versus 1.03%;  $P=0.001$ ) and lower cardiac arrest (0.61% versus 0.51%;  $P<0.001$ ). The relative risk was 0.46 (95% CI, 0.43-0.49) in the adjusted analysis for this combined vaccination group. This group also had significantly reduced risk of mortality among those admitted with MI (relative risk, 0.46), TIAs (relative risk, 0.58), and stroke (relative risk, 0.42) compared with the nonvaccinated group.<sup>13</sup>

#### 4.3.6. Medical Therapy for Relief of Angina

##### Recommendations for Medical Therapy for Relief of Angina

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	B-R	1. In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms.* <sup>1-3</sup>
1	B-R	2. In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms.* <sup>3-6</sup>
1	B-R	3. In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies.* <sup>7,8</sup>
1	B-NR	4. In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms.* <sup>9,10</sup>
3: Harm	B-R	5. In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful.* <sup>11</sup>

\*Modified from the 2012 ACC/AHA Multisociety Guideline for the Diagnosis and Management of Patients With SIHD.<sup>12</sup>

#### Synopsis

Medical antianginal therapies for patients with CCD are understood to act via 2 general mechanisms: by decreasing myocardial oxygen demand or by increasing myocardial arterial blood supply.<sup>9</sup> Beta blockers, non-dihydropyridine CCBs, and ivabradine decrease myocardial oxygen demand (via decreasing contractility, heart rate, or both) while nitrates and dihydropyridine CCBs increase arterial oxygenated blood supply via vasodilatory actions. Ranolazine has a less well-defined mechanism of action, potentially by decreasing calcium overload through inhibition of the late sodium current. The overriding goal is to maximize relief of symptoms while choosing therapy that will not exacerbate comorbidities, will not have important interactions with concomitant medications and will be

well tolerated. In the context of CCD antianginal therapy, the justification for their use rests fully on their effectiveness in relieving symptoms. Specific circumstances may justify choosing 1 agent over another (eg, a beta blocker in a patient with concomitant LV dysfunction). Control of symptoms may be achieved by most patients, but full freedom from angina is only achieved in 40% to 50%, depending on anginal frequency at the onset of treatment.<sup>13</sup>

#### Recommendation-Specific Supportive Text

1. Beta blockers have been considered the first antianginal to use in patients with symptomatic CCD, although the evidence basis for this prioritization is not strong. Early randomized, placebo-controlled studies found that beta

blockers increased the percentage of patients free of exertional angina, reduced anginal attacks and reduced nitroglycerin consumption.<sup>1,2</sup> A meta-analysis of 72 studies comparing beta blockers with CCBs found fewer episodes of angina per week with beta blockers and lower rates of drug discontinuation.<sup>3</sup> No difference was observed in the rate of death or MI between the 2 drug classes. A more recent meta-analysis including only larger studies comparing beta blockers with calcium channel blockers found no difference in the primary endpoint of exercise duration.<sup>4</sup> In randomized, placebo-controlled trials, CCBs effectively relieve angina, decrease nitroglycerin consumption, and increase exercise duration.<sup>14,15</sup> Long-acting nitrates decrease angina and improve exercise duration.<sup>16</sup> Non-dihydropyridine CCBs (verapamil and diltiazem) can further depress LV function and should not be used in patients with CCD and significant LV dysfunction.<sup>17</sup>

2. In patients with CCD and angina refractory to 1 agent, a combination with another antianginal agent improves symptom control.<sup>5</sup> Non-dihydropyridine CCBs should be used with caution in patients on beta blockers because of the potential for synergistic induction or exacerbation of bradycardia and LV dysfunction. The addition of a long-acting nitrate to a beta blocker or a CCB improves exercise tolerance, reduces angina frequency and short-acting nitrate use.<sup>5</sup>
3. Two randomized, placebo-controlled studies showed that the addition of ranolazine on the background of standard anti-anginal therapy improved anginal outcomes.<sup>7,8</sup> In the CARISA (Combination Assessment of Ranolazine in Stable Angina) trial, 823 patients with CCD were randomized to placebo or 1 of 2 doses of ranolazine.<sup>7</sup> After 12 weeks of therapy, ranolazine improved exercise capacity and more effectively relieved angina compared with placebo. In the ERICA (Efficacy of Ranolazine in Chronic Angina) trial, 565 patients with CCD and persistent symptoms despite a

maximally tolerated dose of amlodipine were randomized to ranolazine or placebo.<sup>8</sup> After 6 weeks, patients randomized to ranolazine had significantly fewer anginal episodes and less nitroglycerin consumption.

4. Short-acting nitrates help to relieve acute episodes of angina.<sup>9</sup> One can decrease symptoms by administering a short-acting nitrate prior to activity that typically triggers symptoms. In randomized studies, nitroglycerin spray in comparison with a sublingual formulation is more effective and efficient at relieving angina, but with less headache.<sup>10</sup>
5. The role of ivabradine in patients with CCD has not been studied as extensively as other antianginal therapies. One study comparing ivabradine with atenolol and another comparing it with amlodipine in a double-blind, randomized manner both found similar improvements in exercise time and angina relief with ivabradine.<sup>18,19</sup> Another study found that the addition of ivabradine to atenolol in patients with CCD resulted in improved exercise capacity compared with placebo.<sup>18</sup> However, a more recent study randomized 19,102 patients with CCD, no evidence of HF, and a resting heart rate of at least 70 beats per minute to ivabradine or placebo in addition to GDMT, including standard anti-anginal treatment.<sup>11</sup> At approximately 28-month follow-up, the rate of the primary endpoint of cardiovascular death or MI was similar between both groups. In patients with activity-limiting angina, although ivabradine led to improvement in angina class in 24% compared with 18.8% receiving placebo ( $P=0.01$ ), the primary endpoint of death or MI was significantly higher in the patients randomized to ivabradine (7.6% versus 6.5%;  $P=0.02$ ), suggesting possible harm when ivabradine is used in this setting.

#### 4.3.7. Management of Refractory Angina

##### Recommendation for Management of Refractory Angina

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
2b	B-R	1. In patients with CCD, refractory angina, and no other treatment options, enhanced external counter-pulsation may be considered for relief of symptoms.* <sup>1</sup>

\*Modified from the 2012 ACC/AHA Multisociety Guideline for the Diagnosis and Management of Patients With SIHD.<sup>2</sup>

## Synopsis

Refractory angina represents a small but important segment of the CCD population.<sup>3</sup> Patients are identified by 3 major features: (1) anginal chest pain (or equivalent symptoms) that is uncontrolled despite intensive medical therapy; (2) objective evidence the anginal symptoms have an ischemic cause; and (3) no further options for coronary revascularization.<sup>4</sup> Typically, symptoms produce major lifestyle limitations, functional status limitations, and disabilities. Some definitions also specify Canadian Cardiovascular Society Class III/IV symptoms. Some sources include patients with microvascular angina in this category. No AHA/ACC class 1 recommendations are possible given the limited evidence currently available in this area. Enhanced external counterpulsation has the weak support of a single randomized trial reported in 2005, is FDA approved, but is very infrequently used.<sup>1,5</sup> Direct transmyocardial laser revascularization was studied in several RCTs and is FDA approved, but the largest trial of percutaneous transmyocardial laser revascularization with a placebo/sham control did not show any benefit and a possible signal of harm.<sup>6</sup> Earlier unblinded trials examining surgical transmyocardial laser revascularization reported a benefit in angina relief, but the operative mortality rate was in the range of 3% to 9%. The 2012 ACC/AHA stable ischemic heart disease guideline assigned a Class 2b recommendation to transmyocardial laser revascularization. Based on a thorough review of this evidence, the writing committee feels a recommendation is no longer warranted.<sup>7</sup>

## Recommendation-Specific Supportive Text

1. MUST-EECP (Multicenter Study of Enhanced External Counterpulsation) did not study refractory angina.<sup>1</sup> This therapy has evolved for use in patients with no other options, but the evidence base supporting this shift is inadequate, consisting of observational studies and small RCTs. Enhanced external counterpulsation was a Class 2b recommendation in the 2012 ACC/AHA stable ischemic heart disease guideline, and this was reaffirmed in the 2014 focused update.<sup>2,8</sup> No interval data are available that warrant a change in this recommendation. Enhanced external counterpulsation has limited availability and appears to be used primarily in patients who remain symptomatic and without other therapeutic options.

## 4.3.8. Chelation Therapy

### Synopsis

Chelation therapy refers to the therapeutic use of intravenous infusions of disodium EDTA.<sup>1</sup> Chelation has been used since the 1950s as a treatment for CCD, based until recently on anecdotal reports of benefit. EDTA avidly combines with biologically active heavy metal polyvalent cations, such as lead and cadmium, to form soluble complexes that can then be excreted.<sup>1</sup> Very small trials conducted in patients with intermittent claudication and with CCD failed to show clinically relevant benefits.<sup>2–5</sup> The first adequately powered trial of this intervention, TACT (Trial to Assess Chelation Therapy), randomized 1,708 patients with previous MI to 40 infusions of chelation or placebo.<sup>6</sup> The primary composite endpoint of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina occurred in 222 (26%) patients in the chelation group and 261 (30%) patients in the placebo group (hazard ratio, 0.82 [95% CI, 0.69–0.99];  $P=0.035$ ). Among the 633 TACT patients with diabetes, chelation reduced the primary composite endpoint by 41% reduction (hazard ratio, 0.59 [95% CI, 0.44–0.79];  $P=0.02$  for interaction).<sup>6,7</sup> EDTA is currently not approved by the FDA for preventing or treating cardiovascular disease. TACT2 (Trial to Assess Chelation Therapy 2) has randomized 1,000 patients with diabetes and previous MI using the same treatment regimen as TACT and will report results in 2024.<sup>8</sup>

## 5. REVASCULARIZATION

The topic of revascularization is evolving. We highlight certain management decisions in the next section. Recommendations are typically based on results of the major trials, meta-analyses, or both, covering varying amounts of the same material. We acknowledge that the trials do not cover the area consistently or address all questions comprehensively. Some trials begin with angiographically proven CAD (and a decision already made to proceed with revascularization), while others begin earlier in the clinical presentation. With this in mind, we have made a concerted effort to stay within the strongest evidence in shaping these recommendations for revascularization in patients with CCD.

## 5.1. Revascularization

### Recommendations for Revascularization

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
<b>Goals of Revascularization</b>		
1	A	1. In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms.* <sup>1-7</sup>
1	B-R	2. In patients with CCD who have significant left main disease or multivessel disease with severe LV dysfunction (LVEF ≤ 35%), CABG in addition to medical therapy is recommended over medical therapy alone to improve survival.* <sup>8-11</sup>
Cost Value Statement: Intermediate Value	B-NR	3. In patients with CCD and multivessel disease with severe LV dysfunction, CABG added to optimal medical therapy is of intermediate economic value compared with medical therapy alone. <sup>12</sup>
2a	B-R	4. In patients with CCD and multivessel CAD appropriate for either CABG or PCI, revascularization in addition to GDMT is reasonable to lower the risk of cardiovascular events such as spontaneous MI, unplanned urgent revascularizations, or cardiac death.* <sup>13-20</sup>
2a	B-NR	5. In selected patients with CCD and significant left main stenosis for whom PCI can provide equivalent revascularization to that possible with CABG, PCI is reasonable to improve survival.* <sup>21</sup>
<b>Decision-Making for Revascularization</b>		
1	A	6. In patients with CCD who have angina or an anginal equivalent, no previous evaluation for ischemia, and angiographically intermediate stenoses, the use of FFR or other proven nonhyperemic pressure ratios (eg, iFR) is recommended before proceeding with PCI.* <sup>22,23</sup>
Cost Value Statement: High Value	B-NR	7. In patients with CCD undergoing coronary angiography without previous stress testing, the use of invasive FFR to evaluate angiographically intermediate coronary stenoses before proceeding with PCI is a high economic value intervention.* <sup>24,25</sup>
1	B-NR	8. In patients with CCD with complex 3-vessel disease or for whom the optimal treatment strategy is unclear, a Heart Team approach that includes representatives from interventional cardiology and cardiac surgery is recommended to improve patient outcomes.* <sup>26-29</sup>

\*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.<sup>30</sup>

### Synopsis

The management of patients with CCD and stable angina is 3-fold: relief of symptoms, prevention of nonfatal events such as MI, and improving long-term survival. Medical therapy is often an effective option for these patients. However, revascularization results in a greater improvement in angina and QOL than does medical therapy alone. Similarly, revascularization among appropriate patients with CCD lowers the risk of cardiovascular death, MI and urgent revascularization, particularly among patients with multivessel disease.<sup>2,13,15,31</sup> However, the effect of revascularization on improving survival in patients with CCD is more nuanced.<sup>32</sup> Overall, multiple studies and subsequent meta-analyses have

confirmed an overall null effect of revascularization on all-cause death for CCD, with few exceptions.<sup>15,19,33</sup> Of note, patients in those studies tended to have a low atherosclerotic burden. Predictors of survival include anatomic and functional severity of the disease, LV function, and comorbidities such as diabetes and renal dysfunction.<sup>33</sup> For patients with CCD and LV dysfunction (particularly when LVEF is ≤35%) and for patients with left main disease, CABG has been shown to be superior to medical therapy alone for improving survival.<sup>8,10,11</sup>

### Recommendation-Specific Supportive Text

- In the COURAGE trial, patients initially randomized to GDMT who crossed over to early revascularization had

worse baseline Seattle Angina Questionnaire scores. When compared with patients who were randomized to PCI, these patients experienced worse health status over the initial year of treatment and more unstable angina admissions.<sup>6</sup> In the ISCHEMIA trial, the Seattle Angina Questionnaire summary scores were higher with an invasive strategy compared with a conservative strategy and sustained over 36 months of follow-up. Seattle Angina Questionnaire improvements were more pronounced among patients with greater frequency of baseline angina (daily/weekly > monthly > none). Similarly, the probability of being angina-free was greater among participants who had angina at baseline but was minimal among those who were asymptomatic before randomization.<sup>1</sup> In the ORBITA trial, PCI objectively reduced ischemia (assessed by dobutamine stress echocardiography), and although Seattle Angina Questionnaire scores did not differ among participants, PCI resulted in more patient-reported freedom from angina than placebo. Patients with greater ischemia burdens were more likely to have lower angina frequency score and freedom from angina with PCI than with the sham procedure.<sup>7</sup> In a pooled analysis of FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME-2 (Fractional Flow Reserve Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment [OMT] Versus OMT), patients with lower FFR, greater improvement in FFR post-PCI and higher angina class at baseline were associated with the greatest magnitude of QOL improvement at 1 month and 1 year.<sup>34</sup>

2. Although older studies suggested a mortality benefit with surgical revascularization, many recent studies and meta-analyses point to an overall null effect of revascularization on all-cause death for CCD.<sup>15,19,33,35</sup> Important reasons include advances in medical management and a lower mortality rate with CCD in the contemporary era. For example, the annualized mortality rate in the medical therapy arm of ACME-2 (Angioplasty Compared to Medicine: Two-Vessel Disease) was 4.0%, but 1.0% in FAME-2 and 1.6% in ISCHEMIA.<sup>33</sup> However, many of these trials also had high rates of crossover, and many patients had low angiographic complexity. Numerous technical advances in the field of revascularization also have occurred for CABG and PCI since some of these earlier trials were conducted.<sup>8,36,37</sup> Two subgroups with mortality benefit of CABG over GDMT alone are patients with multivessel disease and moderate to severe LV dysfunction (ejection fraction  $\leq 35\%$ ), and those with

left main disease, both of which may occur concurrently.<sup>38</sup> In the STICH trial, patients with ischemic cardiomyopathy and reduced LVEF ( $\leq 35\%$ ) who received CABG in addition to optimal medical therapy had improved survival at 10 years compared with patients who received medical therapy alone.<sup>11</sup> In the REVIVED-BCIS 2 trial (Revascularization for Ischemic Ventricular Dysfunction: a Randomized Comparison of PCI [with Optimal Medical Therapy] Versus Optimal Medical Therapy Alone for Treatment of HF Secondary to Coronary Disease), PCI among patients with ejection fraction  $\leq 35\%$  did not improve MACE including survival at a median follow-up of 3.4 years.<sup>39</sup> For patients with left main disease, the focus has been on comparing CABG and PCI in recent years; no recent trials are available that compare revascularization to GDMT alone for this indication. Further, most of the contemporary CCD trials have excluded patients with left main disease. Accordingly, the evidence to support revascularization is derived mainly from older RCTs, and no new data refute this evidence.<sup>8</sup>

3. Using data from the STICH trial, a decision-analytic patient-level simulation model was developed to estimate the lifetime costs (in 2019 US dollars) and benefits (in QALYs) of CABG for ischemic cardiomyopathy from the US healthcare sector perspective and the lifetime analytic horizon. In this analysis, patients receiving CABG arm accrued 6.53 lifetime QALYs (95% CI, 5.70-7.53) and a lifetime cost of \$140,059 (95% CI, \$106,401-\$180,992). In comparison, patients receiving medical therapy alone accrued 5.52 lifetime QALYs (95% CI, 5.06-6.09) and \$74,894 lifetime cost (95% CI, \$58,372-\$93,541). Thus, the incremental cost-effectiveness ratio for CABG compared with medical therapy alone was \$63,989 per QALY gained, with 87% of the simulations producing incremental cost-effectiveness ratios  $\leq \$100\,000$  per QALY gained. Thus, in patients with ischemic cardiomyopathy and reduced LV function, CABG has intermediate economic value (\$50,000-\$150,000/QALY gained) compared with medical therapy alone from the US healthcare sector perspective.<sup>12</sup>
4. Clinical events such as nonfatal MI, unstable angina, and urgent revascularization are important for patients from a prognostic and a QOL perspective. Nonfatal MI rates appear to correlate with ischemia severity.<sup>40</sup> Some ambiguity has been observed about the impact of revascularization on these clinical events. In MASS II (Medicine, Angioplasty, or Surgery Study), the 10-year rates of cardiac death were lower after CABG or PCI than after medical therapy alone.<sup>14</sup> In ISCHEMIA,

revascularization had a null effect on cardiovascular death and MI at 4 years overall, with a benefit noted among patients with most severe CAD (3-vessel severe stenosis [ $\geq 70\%$ ] or 2-vessel severe stenosis with proximal left anterior descending artery).<sup>40,41</sup> At 7-year follow-up, a reduction in cardiovascular mortality with revascularization was observed.<sup>35</sup> Moreover, in the ISCHEMIA trial, the incidence of procedural type 4a or type 5 MIs was increased with revascularization (20.1% of all MIs in the trial), but the incidence of late MI (spontaneous MI [type 1]), demand-induced MI (type 2), or MIs associated with stent thrombosis (type 4b) or with restenosis (4c) was reduced. A spontaneous MI was associated with a 2.4-fold increased hazard for all-cause death and a 3.4-fold increased hazard for cardiovascular mortality compared with no MI, whereas a procedural MI was not associated with all-cause or cardiovascular death.<sup>16</sup> A contemporary meta-analysis of patients with CCD noted a reduction in cardiac death and spontaneous MI with revascularization compared with medical therapy alone. On meta-regression, cardiac death risk reduction was linearly associated with reductions in spontaneous MI and percentage of multivessel disease at baseline.<sup>15</sup> Another contemporary meta-analysis confirmed a reduction in spontaneous MI with revascularization, but also noted an increase in procedural MI, with no improvement for MI overall with revascularization.<sup>33</sup> However, revascularization reduced unstable angina (particularly among contemporary stent era trials) and unplanned revascularization in this and other meta-analyses.<sup>19</sup>

5. There are no RCTs directly comparing PCI to medical therapy for the treatment of left main disease. Most of the recent trials have focused on CABG versus PCI.<sup>42–45</sup> Data from these trials and from subsequent meta-analyses suggest that patients with low-to-medium anatomic complexity left main disease that is equally suitable for surgical or percutaneous revascularization and predominantly with normal ejection fraction have similar survival with PCI and CABG.<sup>42,46–51</sup> In addition, several registry studies have reported a survival advantage of PCI over medical therapy in patients with left main CAD,<sup>52</sup> particularly using contemporary DES and PCI techniques.<sup>53–55</sup> A network meta-analysis of 19 studies found that the survival advantage for PCI over medical therapy in patients with left main CAD was similar to the survival advantage for CABG over medical therapy.<sup>21</sup>
6. In FAME-2, among patients with CCD, FFR-guided PCI (FFR,  $\leq 0.8$ ) of lesions  $\geq 50\%$  angiographic severity was superior to medical therapy alone in reducing the

primary MACE endpoint, primarily driven by a reduction in the need for urgent revascularization.<sup>31</sup> This benefit appeared to be sustained over 5 years of follow-up.<sup>2</sup> FFR-guided PCI is also superior to angiography-guided PCI for reducing MACE rates among patients with multivessel CAD.<sup>23</sup> More recently, iFR-guided PCI has been shown to be noninferior to FFR-guided PCI.<sup>22,56</sup> iFR can be accomplished with shorter procedure times compared with FFR. Patients with FFR  $>0.8$  or iFR  $>0.89$  appear to have low event rates with medical therapy alone.<sup>57,58</sup> Several other nonhyperemic pressure ratios, both wire-and angiography-based, have been developed and are undergoing further evaluation.<sup>59</sup>

7. In an economic evaluation of the FAME-2 trial (888 patients with stable single-vessel or multivessel coronary artery disease with reduced fractional flow reserve, randomly assigned to PCI plus medical therapy or medical therapy alone), mean initial costs were higher in the PCI group (\$9944 versus \$4440;  $P < 0.001$ ) but by 3 years were similar between the 2 groups (\$16,792 versus \$16,737;  $P = 0.94$ ).<sup>60</sup> The incremental cost-effectiveness ratio for PCI plus medical therapy compared with medical therapy alone was \$17,300 per QALY gained at 2 years and \$1,600 per QALY gained at 3 years. Thus, the use of FFR in this context is a high economic value intervention (incremental cost-effectiveness ratio  $< \$50,000$  per QALY gained). These findings were robust in sensitivity analyses. This suggested that FFR-guided PCI of lesions is economically attractive compared with medical therapy alone in patients with stable coronary artery disease. Further, iFR has been shown to be noninferior to FFR, with economic evaluations suggesting that it has lower procedural costs.<sup>61</sup> Thus, the use of iFR-guided PCI is also likely to be a high value intervention ( $< \$50,000$ /QALY gained) in this context.
8. A multidisciplinary Heart Team, involving an interventional cardiologist, cardiac surgeon, and other cardiovascular specialists, has become a critical component of the revascularization decision. Ideal situations for Heart Team consideration include patients with complex coronary disease/multivessel disease, comorbid conditions that could impact the success of the revascularization strategy, and other clinical or social situations that may impact outcomes. Treatment decisions should be patient-centered, incorporate patient preferences and goals, and include shared decision-making between the clinicians and the patients. For example, there may be patients who may prefer revascularization even if not on GDMT.

## 5.2. Revascularization: PCI Versus CABG

### Recommendations for Revascularization: PCI Versus CABG

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
<b>Patients With CCD</b>		
1	B-R	1. In patients with CCD who require revascularization for significant left main involvement associated with high-complexity CAD, CABG is recommended in preference to PCI to improve survival.* <sup>1,2</sup>
2a	B-R	2. In patients with CCD who require revascularization for multivessel CAD with complex and diffuse CAD (eg, SYNTAX score >33), it is reasonable to choose CABG over PCI to improve survival.* <sup>1,3-6</sup>
<b>Patients With CCD at High Surgical Risk</b>		
2a	B-NR	3. In patients with CCD who are appropriate for revascularization but poor candidates for surgery, it is reasonable to choose PCI over CABG to improve symptoms and reduce MACE. <sup>7-9</sup>
<b>Patients With CCD and Diabetes</b>		
1	A	4. In patients with CCD, diabetes, and multivessel CAD with involvement of the left anterior descending artery who are appropriate candidates for CABG, CABG (with a left internal mammary artery to the left anterior descending artery) is recommended in preference to PCI to reduce mortality and repeat revascularizations.* <sup>5,10-17</sup>
2b	B-R	5. In patients with CCD and diabetes who have left main stenosis and low- or intermediate-complexity CAD (eg, SYNTAX score ≤33), PCI may be considered as an alternative to CABG to reduce MACE.* <sup>10,18</sup>

\*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.<sup>19</sup>

### Synopsis

There are fundamental differences between how CABG and PCI restore blood flow to ischemic myocardium.<sup>20</sup> In CABG, bypass grafts deliver blood beyond the proximal coronary segments that are usually diseased and are at risk for development of de novo lesions. Thus, in addition to the immediate benefit of CABG in treating existing lesions, CABG could offer future protection against ischemic insults by furnishing an alternative route for blood that is unhindered by upstream native CAD. The field protection is unique to CABG because PCI only treats the coronary segment where the stent is implanted with no prophylactic potential. Improved outcomes associated with CABG are largely driven by a reduction in spontaneous MI and repeat revascularization compared with PCI.<sup>3,15,21-24</sup> However, certain subgroups of patients derive a survival benefit from CABG compared with PCI,<sup>1,2,4,25</sup> including patients with complex or diffuse coronary disease and those with diabetes. Although the evidence for the recommendations is based on studies that included predominantly patients with CCD, some studies incorporated patients with unstable or acute coronary ischemia. The choice of revascularization therapy

should be guided by Heart Team deliberations and shared decision-making (Section 4.1.3) in the context of available evidence and the patient's specific risk profile and life expectancy.

### Recommendation-Specific Supportive Text

1. The SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trial showed a significantly higher MACE and cardiac mortality rate at 5 years for the subgroup of patients with left main and high-complexity disease (defined as a SYNTAX score >33) who were treated with PCI.<sup>1</sup> Other RCTs that compared revascularization strategies in patients with left main disease excluded patients with complex disease.<sup>20-22,26</sup>
2. The 10-year follow-up of the SYNTAX trial found a 40% higher mortality rate with PCI compared with CABG in the group of patients with triple-vessel disease.<sup>4</sup> In a pooled analysis of individual data of 11,518 patients from 11 RCTs, Head et al showed a mortality benefit with CABG over PCI in patients with multivessel disease.<sup>5</sup> The SYNTAX score was a significant modifier of treatment effect, with higher scores ( $\geq 33$ ) favoring CABG.<sup>5</sup>

3. In a subgroup analysis of the 10-year follow-up of the SYNTAX trial comparing PCI with CABG in patients with left main CAD, triple-vessel disease, or both, preprocedural physical and mental health status was an important modifier of the relative treatment effects of the 2 different revascularization approaches. Among patients with low Physical Component Summary (PCS) scores, low Mental Component Summary (MCS) scores, or both, no significant difference was seen in the 10-year mortality rate between PCI and CABG.<sup>7</sup> Of the 3,075 patients who were treated in the SYNTAX trial, 198 (6.4%) and 1,077 (35.0%) patients were included in PCI and CABG registries, respectively. The main reason for inclusion in the CABG registry was too complex coronary anatomy, while the main reason for inclusion in the PCI registry was too high risk for surgery (70.7%).<sup>8</sup> In the OPTIMUM (Outcomes of Percutaneous Revascularization for Management of SUrgically Ineligible Patients with Multivessel or Left Main Coronary Artery Disease) registry, patients undergoing PCI (n=726) had complex clinical profiles that were incompletely represented by surgical prediction models. Poor distal targets or conduits (18.9%), severe LV dysfunction and nonviable myocardium (16.8%), severe lung disease (10.1%), and frailty or immobility (9.7%) were among the top reasons for surgical ineligibility. PCI was associated with significant improvements in patients' symptom burden, physical function, and QOL.<sup>9</sup>
4. The FREEDOM (Revascularization in Diabetics with Multivessel Disease) trial (n=1,900) compared CABG with PCI in patients with diabetes and multivessel CAD.<sup>10,11</sup> The trial excluded patients with significant left main stenosis. Of the enrolled patients, 82% in the PCI group and 85% in the CABG group had triple-vessel disease, and 91% of patients had left anterior descending artery involvement. At 5-year follow-up, all-cause death rate was higher in the PCI group than in the CABG group. In the FREEDOM follow-up study, all-cause death rate up to 8 years continued to be significantly higher with PCI (hazard ratio, 1.36 [95%

CI, 1.07-1.74]).<sup>11</sup> The Head et al meta-analysis showed consistent results, with a nearly 50% increase in 5-year mortality risk among patients with diabetes who were treated with PCI than among those treated with CABG.<sup>5</sup> A patient-level pooled analysis of 3 trials associated CABG with a reduction in the composite primary endpoint of death, MI, or stroke and the individual components of the endpoint except for stroke.<sup>17</sup>

5. To date, no RCTs have compared revascularization strategies that focus exclusively on patients with diabetes with stable left main CAD. In a prespecified subgroup analysis of the EXCEL (Evaluation of XIENCE versus CABG Surgery for Effectiveness of Left Main Revascularization) trial, which included patients with left main CAD, predominantly normal ejection fraction, and low- or intermediate-complexity CAD,<sup>27</sup> no difference was observed in the primary endpoint composite of death, stroke, or MI for PCI and CABG among patients with or without diabetes.<sup>18</sup> However, all-cause death at 3 years occurred in 13.6% of patients with diabetes treated with PCI and 8.0% of patients treated with CABG ( $P=0.046$ ). No difference in the mortality rate was seen among patients without diabetes (5.5% versus 5.0% among patients treated with PCI and CABG, respectively;  $P=0.71$ ).

## 6. SPECIAL POPULATIONS

In these sections, recommendations are highlighted for populations that are unique, either based on comorbidities, life stage, or mechanism of coronary pathology or pathophysiology. Unless modified or otherwise specified, the preceding recommendations for patients with CCD generally apply to these “special” populations. In some sections, additional recommendations that are unique to the populations being discussed are provided.

### 6.1. Existing Heart Diseases and Conditions

#### 6.1.1. Chronic Management After SCAD

#### Recommendations for Chronic Management After SCAD

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	C-LD	1. In patients with CCD who have experienced SCAD, counseling should be provided regarding potential triggers and risk of SCAD recurrence. <sup>1-12</sup>
2a	C-LD	2. In patients with CCD who have experienced SCAD, evaluation for underlying vasculopathies is reasonable to identify abnormalities in other vascular beds. <sup>1-4,7,10,13-15</sup>
2b	C-LD	3. In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. <sup>1</sup>

## Synopsis

SCAD is an underrecognized cause of MI.<sup>16,17</sup> SCAD is more common among women than men and occurs predominantly in younger women with low burden of classic risk factors for ASCVD. Triggers include pregnancy, vigorous physical exertion, and severe emotional distress.<sup>16,17</sup> SCAD may be a manifestation of an underlying arteriopathy.<sup>1,13,16,17</sup> Pregnancy-associated SCAD has a worse prognosis than SCAD in the absence of pregnancy.<sup>1,12,16,17</sup> Conservative medical management of the acute event is favored, but selected unstable patients may require percutaneous or surgical revascularization.<sup>16,17</sup> Medical care after SCAD is focused on managing sequelae of the acute event, evaluation and treatment of recurrent symptoms, and prevention of recurrent SCAD. In the absence of specific data among patients with SCAD, DAPT among those who have undergone stenting should follow current guidelines for DAPT (Section 4.3.1, “Anti-platelet Therapy and Oral Anticoagulants”), while being aware that excess uterine bleeding in premenopausal women may require treatment.<sup>1,2</sup> Management of LV dysfunction after the ischemic insult is addressed in Section 4.3.2, “Beta Blockers,” Section 4.3.3, “Renin-Angiotensin-Aldosterone Inhibitors,” and Section 6.1.2 “INOCA.” Observational data suggest benefits of CR<sup>18-21</sup> and beta blockade.<sup>1</sup> CR is addressed in Section 4.2.10.

## Recommendation-Specific Supportive Text

1. SCAD recurrence can be attributable to extension of the initial dissection or attributable to a new dissection. Recurrence rates are highest early after the initial dissection but can occur years later.<sup>2,22</sup> Reported recurrence rates of SCAD vary widely depending on participant characteristics, definition of recurrent SCAD, and length of follow-up, ranging from 0% to 26.9% at 1 year and estimated 5-year Kaplan-Meier rates up to 27%.<sup>1-3,5-9</sup> Similar to incident SCAD, recurrent SCAD may be triggered by intense physical exertion or psychosocial distress. Recurrent SCAD may be more common among patients with highly tortuous coronary arteries, underlying fibromuscular dysplasia, history of migraine headaches, and hypertension.<sup>1,4,10,11</sup> Pregnancy in women with previous SCAD was not associated with recurrent SCAD in multivariable modeling that controlled for age at first SCAD, year of first SCAD, and history of fibromuscular dysplasia.<sup>12</sup>
2. Multiple studies have reported a high prevalence of extracoronary vascular abnormalities (eg, cerebral aneurysms, pseudoaneurysms) and concomitant fibromuscular dysplasia among patients with SCAD. The true prevalence of these disorders is unclear because reports are based on screening rates between 30% and 80%.<sup>1-4,7,10,13-15</sup> Table 14 lists screening questions that may point toward an underlying vasculopathy and,

**TABLE 14** Screening Questions for SCAD-Associated Arteriopathies and Connective Tissue Disorders

Personal history (Have you ever been diagnosed with or experienced any of the following?)
Early-onset hypertension
Stroke or transient ischemic attack
Pulsatile tinnitus
Migraine headaches
Renal infarction
Subarachnoid hemorrhage
Aneurysm (aortic, peripheral, brain)
Dissection (aortic, peripheral)
Rupture of hollow organs (intestinal, bladder, uterine)
Pneumothorax
Tendon or muscle rupture
Joint dislocation
Talipes equinovarus (clubfoot)
Umbilical or inguinal hernia
Scoliosis or pectus deformity
Pregnancy complications (cervical incompetence, hemorrhage, uterine prolapse, hypertension)
Poor wound healing
Ectopia lentis
Myopia
Detached retina, early glaucoma, or early cataracts
Tall stature
Abnormality of cardiac valve
Systemic inflammatory disease
Family history (Does anyone in your family have the following?)
Dissection (coronary, aortic, peripheral)
Inherited arteriopathy or connective tissue disorder (eg, vascular Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome)
Early stroke, early myocardial infarction, sudden cardiac death
Review of systems (Are you currently experiencing any of the following?)
Headaches
Pulsatile tinnitus
Postprandial abdominal pain
Flank pain
Claudication
Easy bruising
Joint hypermobility or laxity

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SCAD indicates spontaneous coronary artery dissection.

together with a detailed vascular physical examination, may facilitate a patient-clinician discussion about benefits and risks of imaging extracoronary vascular beds.<sup>16</sup> Although some cerebral aneurysms detected by screening have been large enough to warrant intervention, no studies to date show that screening for underlying arteriopathies changes patient treatment or patient outcomes.

3. No randomized trials exist of pharmacological management after SCAD. Using multivariable modeling, a Canadian prospective follow-up study of 327 patients with SCAD found that use of beta blockade was associated with a 64% reduction in recurrent SCAD.<sup>1</sup> Given the pathophysiology of SCAD, statin therapy is not indicated for SCAD but should be continued for patients who qualify for statin therapy based on global cardiovascular risk or inherited disorders like FH.<sup>17</sup> Patients who received a stent during their acute

hospitalization for SCAD should continue DAPT (see **Section 4.3.1**, “Antiplatelet Therapy and Oral Anticoagulants”) in the outpatient setting.<sup>17</sup> Several prospective registries and a randomized trial are underway to improve understanding of the natural history of SCAD and potential treatments.<sup>23,24</sup>

### 6.1.2. Ischemia With Nonobstructive Coronary Arteries

#### Recommendation for INOCA

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
2a	B-R	1. In symptomatic patients with nonobstructive CAD, a strategy of stratified medical therapy* guided by invasive coronary physiologic testing can be useful for improving angina severity and QOL. <sup>1,2</sup>

\*See recommendation-specific supportive text for details.

#### Synopsis

Nonobstructive CAD is present in >50% of patients undergoing elective coronary angiography and is associated with an increased risk of all-cause death and MI.<sup>3–5</sup> INOCA refers to myocardial ischemia caused by coronary vasomotor dysfunction without obstructive CAD.<sup>6</sup> In INOCA, the myocardial oxygen supply-demand mismatch may be caused by coronary microvascular dysfunction, coronary vasospasm, or both. Microvascular angina is the clinical manifestation of coronary microvascular dysfunction, and vasospastic angina is the clinical manifestation of myocardial ischemia caused by dynamic epicardial coronary obstruction

caused by a vasomotor disorder. **Table 15** outlines the diagnostic criteria for microvascular angina proposed by COVADIS (Coronary Vasomotion Disorders International Study Group).<sup>7</sup> The criteria used to diagnose vasospastic angina are outlined in **Table 16**.<sup>8</sup> For nonobstructive CAD imaging recommendations, see **Section 3.1** (“Diagnostic Evaluation”) of this guideline and the 2021 AHA/ACC chest pain guideline.<sup>9</sup> The CorMicA (Coronary Microvascular Angina) trial showed that in patients with persistent stable chest pain and nonobstructive CAD, invasive coronary physiology testing is feasible and safe, with clear diagnostic use in identifying specific INOCA endotypes.<sup>1</sup>

**TABLE 15** Clinical Criteria for Suspecting Microvascular Angina\*

Criteria	Evidence	Diagnostic Parameters
1	Symptoms of myocardial ischemia	Effort or rest angina; exertional dyspnea
2	Absence of obstructive CAD (<50% diameter reduction or FFR >0.80)	Coronary CTA; invasive coronary angiography
3	Objective evidence of myocardial ischemia	Ischemic changes on ECG during an episode of chest pain; stress-induced chest pain and/or ischemic changes on ECG in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4	Evidence of impaired coronary microvascular function	Impaired coronary flow reserve (cut-off value depending on methodology between ≤0.20 and ≤0.25); coronary microvascular spasm, defined as reproduction of symptoms, ischemic shifts on ECG but no epicardial spasm during acetylcholine testing; abnormal coronary microvascular resistance indices (eg, IMR >25); coronary slow flow phenomenon, defined as TIMI frame count >25

Suspected microvascular angina is diagnosed if symptoms of ischemia are present (criteria 1) with no obstructive CAD (criteria 2) but only (a) objective evidence of myocardial ischemia (criteria 3) or (b) evidence of impaired coronary microvascular function (criteria 4) alone. Adapted with permission from Ong P, et al.<sup>7</sup> Copyright 2018, with permission from Elsevier.

\*Definitive microvascular angina is only diagnosed if all 4 criteria are present for a diagnosis of microvascular angina.

CAD indicates coronary artery disease; CFR, coronary flow reserve; CTA, computed tomographic angiography; ECG, electrocardiogram; FFR, fractional flow reserve; and IMR, index of microcirculatory resistance.

**TABLE 16 Diagnostic Criteria for Vasospastic Angina**

**Nitrate-responsive angina:** during spontaneous episode, *with at least 1* of the following:

- Rest angina, especially between night and early morning
- Marked diurnal variation in exercise tolerance, reduced in morning
- Hyperventilation can precipitate an episode
- Calcium channel blockers (not beta blockers) suppress episodes

**Transient ischemic electrocardiographic changes:** during spontaneous episode, including any of the following *in at least 2 contiguous leads:*

- ST segment elevation  $\geq 0.1$  mV
- ST segment depression  $\geq 0.1$  mV
- New negative U waves

**Coronary artery spasm:** defined as transient total or subtotal coronary artery occlusion ( $>90\%$  constriction) with angina and ischemic electrocardiographic changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)

"Definitive" vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischemic ECG changed during the spontaneous episodes or coronary artery spasm criteria are fulfilled. "Suspected" vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes but transient ischemic electrocardiographic changes are equivocal or unavailable and coronary artery spasm criteria are equivocal. Modified from Beltrame JF, et al.<sup>8</sup> by permission of Oxford University Press, copyright 2017; and by permission of The Author, copyright 2015.

ECG indicates electrocardiogram.

**TABLE 17 Invasive Coronary Function Testing Definition and Linked Pharmacotherapy for INOCA Endotypes**

Endotype	Disorder of Coronary Artery Function	Linked Pharmacotherapy
Microvascular angina (nonobstructive CAD and proven CMD)	↑ Microvascular resistance	IMR $\geq 25$ . IMR is a quantitative method for specifically assessing microvascular function independent resting hemodynamics. IMR is distal coronary pressure* transmit time (average time for 3 saline bolus runs at hyperemia).
	↓ Coronary vasorelaxation	CFR by thermodilution $< 2.0$ . This reflects the inability to increase coronary flow above 2 times the resting flow.
	↓ Microvasodilator capacity	Resistive reserve ratio $< 2.0$ . This reflects the vasodilator capacity of the microcirculation to change from baseline to hyperemia (resistance at rest divided by resistance at hyperemia).
	Microvascular spasm	Angina during acetylcholine infusion or bolus with typical ischemic ST-segment changes and epicardial coronary constriction $<90\%$ reduction in epicardial coronary artery diameter. Represents inappropriate susceptibility microvascular constriction.
Vasospastic angina	Epicardial spasm	Epicardial coronary artery spasm is defined as reduction in coronary diameter $>90\%$ after intracoronary acetylcholine in comparison with baseline resting condition after intracoronary glyceryl trinitrate (nitroglycerin) administration in any epicardial coronary artery segment together with symptoms and ST-segment deviation on the ECG.
Mixed MVA/VSA	CMD and epicardial vasospasm	Epicardial spasm plus any abnormality of: <ul style="list-style-type: none"> <li>■ Microvascular resistance</li> <li>■ Coronary vasorelaxation</li> <li>■ Microvasodilator capacity</li> </ul>
Obstructive CAD		$>50\%$ lesion by diameter stenosis in epicardial artery $>2.5$ mm or a FFR $\leq 0.80$
Noncardiac	None	Exclusion of diffuse or obstructive epicardial coronary disease (FFR $>0.8$ ) without any of the after abnormalities of coronary function: CFR $<2.0$ , IMR $\geq 25$ or functional angina/spasm during acetylcholine.

Modified with permission from Ford TJ, et al.<sup>1</sup> Copyright 2018 American College of Cardiology Foundation.

\*Currently unavailable in the United States.

ACEI indicates angiotensin converting enzyme inhibitor; CAD, coronary artery disease; CCB, calcium channel blocker; CFR, coronary flow reserve; CMD, coronary microvascular disease; DHP, dihydropyridine; ECG, electrocardiogram; FFR, fractional flow reserve; IMR, index of microvascular resistance; MVA, microvascular angina; and VSA, vasospastic angina.

### Recommendation-Specific Supportive Text

1. In the CorMicA trial, a stratified medical therapy approach guided by invasive coronary physiology testing (guidewire-based assessment of coronary flow reserve index of microvascular resistance [IMR], and FFR), followed by vasoreactivity testing with acetylcholine improved angina severity and QOL in patients with INOCA (<50% diameter reduction or FFR >0.80).<sup>1,2</sup> Based on the results of testing in the intervention arm (vasospastic angina versus microvascular angina), patients were stratified to medical therapy, as shown in Table 17.<sup>1</sup> Patients with noncardiac chest pain were discharged from the cardiology clinic and anti-anginal medications were discontinued. At 6 months, the intervention resulted in improvement of 11.7 units in the Seattle Angina Questionnaire summary score, as well as improvement in QOL, as assessed by the Euro-QoL (EQ-5D-5L).<sup>1</sup> No differences were observed in MACE between the intervention and control arms at 6-month follow-up. The improvements in angina severity and QOL were sustained at 1-year follow-up.<sup>2</sup>

#### 6.1.3. HF With Preserved or Reduced Ejection Fraction

##### Synopsis

CAD is the most common cause of HF in the United States and has a pivotal role in the development and

progression of both HF with preserved ejection fraction and HF with reduced ejection fraction.<sup>1,2</sup> Management of patients with CCD and HF with preserved ejection fraction and HF with reduced ejection fraction should follow associated guideline recommendations for revascularization<sup>3</sup> and HF,<sup>4,5</sup> as well as sections in this guideline: Section 4.2, “Guideline-Directed Management and Therapy,” Section 4.3, “Medical Therapy to Prevent Cardiovascular Events and Manage Symptoms,” and Section 5, “Revascularization.”

### 6.2. CCD With Valvular Heart Disease

##### Synopsis

Concurrent CCD is common in patients with valvular heart disease.<sup>1,2</sup> The evaluation and management of CCD at the time of valve intervention is discussed in the “2021 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease.”<sup>3</sup> After valve intervention, patients with valvular heart disease and concomitant CCD should be managed according to current recommendations for secondary prevention as outlined in this guideline. Patients with severe aortic stenosis and concomitant CCD who undergo PCI and transcatheter aortic valve implantation should be treated with DAPT according to the 2021 ACC/AHA/SCAI revascularization guidelines.<sup>4</sup>

### 6.3. Young Adults

#### Recommendation for Young Adults

Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATION
2a	C-LD	1. In young adults with CCD, after optimization of traditional cardiovascular risk factors, a comprehensive evaluation and treatment of nontraditional cardiovascular risk factors can be beneficial in reducing the risk of cardiovascular events. <sup>1–3</sup>

##### Synopsis

Young adults with CAD represent a unique subset of patients who remain at risk for prolonged cardiovascular morbidity, recurrent MACE, and loss of QALYs.<sup>1,4</sup> Most have ≥1 traditional cardiovascular risk factors (Table 18).<sup>5,6</sup> Suboptimal control of traditional risk factors has been associated with a higher incidence of recurrent MACE among young adults, thereby warranting optimization similar to older adults, including similar secondary prevention strategies.<sup>1,4,7,8</sup> Given a substantial prevalence of FH,<sup>3</sup> screening for FH can be beneficial (with genotypic screening performing less well than phenotypic screening in non-White population). Safety and efficacy of statin therapy in reduction of cardiovascular events was shown in a 20-year follow-up analysis of young patients with FH.<sup>9</sup> Among those diagnosed with FH or with increased

lipoprotein(a) levels, appropriate lipid screening of family members can be considered. Evaluation and treatment of nontraditional risk factors should be considered to decrease risk of future cardiovascular events. Furthermore, implementing strategies such as optimizing health care access, educating patients, motivational interviewing, using health information technology tools, and reducing barriers in obtaining medications may be beneficial in optimizing medication adherence<sup>10,11</sup> (see Section 4.1.2, “Patient Education” and Section 4.1.4, “Social Determinants of Health”). Evaluation and management of nonatherosclerotic causes such as coronary anomalies, Kawasaki disease, or myocardial bridging may be beneficial (Table 19).<sup>12–14</sup> Longitudinal follow-up of these patients with CVD specialists should be encouraged (see Section 7.1, “Follow-Up Plan and Testing”).

**TABLE 18 Traditional and Nontraditional Risk Factors Associated With CCD in Young Adults**

Traditional Risk Factors	Nontraditional Risk Factors
Hypertension (Section 4.2.7, "Blood Pressure Management")	HIV and ART (Section 6.8, "HIV/Autoimmune Disorders")
Obesity and metabolic syndrome (Section 4.2.9, "Weight Management")	Recreational substance use (cocaine and marijuana) (Section 4.2.4, "Alcohol and Substance Use")
Diabetes (Section 4.2.8, "Sodium Glucose Cotransporter 2 Inhibitors and Glucagon Peptide-1 Receptor Agonists")	Systemic inflammatory disorders (IBD, SLE, RA, gout, PsA, AS) and vasculitides
Unhealthy diet and physical inactivity (Section 4.2.1, "Nutrition, including Supplements," and Section 4.2.11, physical activity)	Pregnancy-related complications (IUGR, HDP, gestational diabetes) (Section 6.5, "Women, Including Pregnancy and Hormone Therapy")
Hyperlipidemia (LDL-C, Lp(a)) (Section 4.2.6, "Lipid Management")	Familial hypercholesterolemia
Tobacco use (Section 4.2.3, "Tobacco Products")	Miscellaneous (psychological well-being, sleep quality, social determinants of health (Section 4.1.4, "Social Determinants of Health," and Section 4.2.2, "Mental Health"))
Family history of premature CAD	History of chest radiation

Adapted from Mahtta D, et al.<sup>18</sup> by permission from Springer Nature, Copyright 2020.

ART indicates antiretroviral therapy; AS, ankylosing spondylitis; CCD, chronic coronary disease; Ch9p21, chromosome 9p21 locus; HDP, hypertensive disorders of pregnancy; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IUGR, intrauterine growth retardation; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); PsA, psoriatic arthritis; RA, rheumatoid arthritis; and SLE, systemic lupus erythematosus.

### Recommendation-Specific Supportive Text

1. AFIJI (Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention) was a prospective multicenter cohort study evaluating young patients diagnosed with CAD at age  $\leq 45$  years.<sup>1</sup> During their long-term follow-up, the investigators observed diabetes and current smoking to be associated with higher risk of recurrent MACE. Additionally, chronic inflammatory disease state (eg, HIV, viral hepatitis, systemic autoimmune disease) was associated with overall poor outcomes. More recently, similar observations were made by investigators from the YOUNG-MI (The Conundrum of Sex Differences in Outcomes of Young Patients with Acute MI)<sup>15</sup> and VITAL<sup>2</sup> registries that have highlighted the importance of traditional cardiometabolic risk factors along with nontraditional risk enhancers among young adults with CAD. Although the attributable risk of traditional risk

factors such as tobacco use, vaping, hypertension, and diabetes may supersede that of nontraditional risk factors among young adults with CCD, the role of these unique risk factors such as chronic inflammation, genetics (Ch9p21 locus, lipoprotein(a)), and recreational drug use remains at the center of clinical optimization. Assessing for and aggressive treatment of nontraditional cardiovascular risk factors (Table 18) such as inflammatory conditions or recreational drug use are important to reduce cardiovascular risk among young adults with CCD.<sup>1-3,16,17</sup> Evaluation for non-atherosclerotic causes of CCD among young adults (coronary anomalies, vasospasm, or spontaneous dissection) should also be prioritized (see Section 6.1, "Existing Heart Diseases and Conditions" and Section 6.5, "Women, Including Pregnancy and Hormone Therapy").

**TABLE 19 Nonatherosclerotic Causes of CCD in Young Adults: Evaluation and Management**

Cause	Presentation	Management
Kawasaki disease	■ Late sequelae: coronary artery aneurysm, stenosis, thrombosis, or fistula	■ Lifelong follow-up with quantitative assessment of luminal dimensions. ■ Low-dose aspirin therapy for small- or medium-sized coronary artery aneurysms. ■ Low-dose aspirin plus anticoagulant therapy for large coronary artery aneurysms.
Coronary artery anomalies	■ Anomalous left coronary artery from the pulmonary artery ■ Anomalous origin of the coronary artery from the opposite sinus of Valsalva with an interarterial course	■ Surgical repair – translocation of left coronary artery to aortic root for anomalous left coronary artery from the pulmonary artery. ■ Surgical correction among young adults with interarterial course of coronary artery originating from opposite sinus of Valsalva and symptoms during exercise suggestive of myocardial ischemia.
Myocardial bridging	■ Exercise-induced ischemia ■ Coronary artery vasospasm ■ Sudden cardiac death	■ Beta-adrenergic blocking agents in symptomatic patients. ■ Restriction to low-intensity sports. ■ Surgical correction if symptoms refractory to medical therapy.

CCD indicates chronic coronary disease.

## 6.4. Cancer

### Recommendation for Cancer

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
1	C-LD	<p>1. In patients with CCD and cancer, a multidisciplinary team including cardiology and oncology expertise is recommended to improve long-term CVD outcomes.<sup>1,2</sup></p>

### Synopsis

Cancer and CCD share mechanistic pathophysiology<sup>3–5</sup> and are the 2 leading causes of death worldwide,<sup>6</sup> sharing multiple risk factors such as sedentary lifestyle, obesity, smoking, diabetes, and age.<sup>4,7</sup> Cancer and CVD increasingly coexist, yet patients with CCD and cancer are often undertreated<sup>4</sup> and are high risk for cardiovascular adverse events. Commonly used chemotherapy and radiation therapy may have cardiac toxicity,<sup>8,9</sup> and some classes of cytotoxic chemotherapy increase CVD risk factors.<sup>10</sup> In 2022, AHA published a scientific statement on cardio-oncology drug interactions, noting communication between oncology and cardiology specialists is warranted.<sup>11</sup> If CCD medications are stopped because of cancer treatment, they should be resumed as soon as possible. In 2019, the AHA provided a scientific statement in favor of the development of cardio-oncology rehabilitation for patients at high risk of developing cardiovascular dysfunction.<sup>2</sup>

### Recommendation-Specific Supportive Text

1. A multidisciplinary cardio-oncology team should evaluate the patient before cancer treatment and monitor the patient throughout the course of treatment.<sup>10</sup> Longitudinal registries suggest that cardiovascular outcomes have improved with the introduction of multidisciplinary care teams in cancer treatment. In settings where

multidisciplinary teams are unavailable, clinicians should consider referral to relevant subspecialties as appropriate.<sup>1,12</sup> Cardio-oncology is a growing subspecialty that promotes the need for effective cancer treatment while minimizing negative cardiovascular adverse events.<sup>13</sup> The cardio-oncology team is involved in all aspects of the care of cancer patients, from informing pretreatment risk and regimen selection, addressing the complex cardiovascular adverse effects of cancer therapy, and mitigating the heightened long-term risks of CVD in survivorship. This team manages common conditions between subspecialties, such as antiplatelet therapy for venous thromboembolism prophylaxis. Patients with CCD and locally advanced or metastatic cancer can be at increased risk for arterial thrombosis and cardiovascular adverse events. If the patient is not already on an antithrombotic regimen, clinicians may offer thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin to selected high-risk outpatients with cancer.<sup>14</sup> Refer to [Section 4.1.1](#) (“Team-Based Approach”), [Section 4.1.2](#) (“Patient Education”), and [Section 4.1.4](#) (“Social Determinants of Health”) for management of the patient with CCD and comorbidities.

## 6.5. Women, Including Pregnancy and Postmenopausal Hormone Therapy

### Recommendations for Women, Including Pregnancy and Postmenopausal Hormone Therapy

Referenced studies that support the recommendations are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATIONS
<b>Pregnancy</b>		
1	C-LD	<p>1. Women with CCD who are contemplating pregnancy or who are pregnant should be risk-stratified and counseled regarding risks of adverse maternal, obstetric, and fetal outcomes.<sup>1–4</sup></p>
1	C-LD	<p>2. Women with CCD who are contemplating pregnancy or who are pregnant should receive care from a multidisciplinary cardio-obstetric care team beginning before conception and continuing throughout pregnancy, delivery, and postpartum to improve maternal and fetal outcomes.<sup>1,2,5</sup></p>
2b	C-LD	<p>3. In women with CCD, continuation of statin use during pregnancy may be considered.<sup>6</sup></p>

(continued)

3: Harm	C-LD	4. Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. <sup>2,7,8</sup>
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#### Postmenopausal Hormone Therapy

3: Harm	A	5. Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism. <sup>9-11</sup>
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#### Synopsis

CCD remains uncommon among pregnant women ranging from <2% to 3.6% in published registries.<sup>12-14</sup> Physiologic changes in pregnancy that could influence myocardial workload and myocardial perfusion and thus precipitate acute cardiovascular events that include increases in circulating blood volume, stroke volume, heart rate, and cardiac output, decreases in systemic vascular resistance, diastolic BP and LV end-diastolic pressure, physiologic anemia, and a hypercoagulable state.<sup>2,15</sup> Women with CCD who become pregnant are at high risk of adverse maternal and fetal outcomes<sup>1,3</sup> and are best managed by a multidisciplinary cardio-obstetrics team.<sup>16</sup> Pharmacologic therapy should balance maternal benefit and fetal risk.<sup>7</sup> Postmenopausal hormone therapy has been assessed among women with CCD in trials with angiographic endpoints<sup>17-20</sup> and in trials designed to evaluate angina or morbidity and mortality rates.<sup>9,10,21-23</sup> Trials tested either estrogen-only regimens (in women without a uterus) or combined estrogen and progestin regimens (in women with a uterus). None of these trials showed benefits on recurrent cardiovascular events. Venous thromboembolism was significantly increased in these trials. No RCTs exist that have tested transdermal hormone regimens to assess their effect on MACE and mortality.

#### Recommendation-Specific Supportive Text

1. A systematic review of 37 studies including 124 pregnancies in 116 women with CCD<sup>1</sup> reported cardiovascular complications in 32% of pregnancies, including ischemic cardiovascular events in 9%, and obstetric and fetal/neonatal complications in 58% and 42%, respectively. Only 21% of pregnancies were uncomplicated. In a study of 79 women with CCD (92 pregnancies of at least 24 weeks' gestation), 66% had adverse cardiac events and 14% developed preeclampsia; 25% of infants were delivered preterm, and 25% were born small for gestational age.<sup>13</sup> In the CARPREG II (Pregnancy Outcomes in Women with Heart Disease) prospective registry, a history of CCD was independently associated with adverse cardiac events (odds ratio, 3.0

[95% CI, 1.1-7.6]).<sup>3</sup> Women with CCD, including women with previous SCAD (Section 6.1.1), who are contemplating pregnancy should undergo thorough evaluation and risk stratification using a validated instrument such as the CARPREG II (Table 20) and be counseled regarding potential risks to mother and fetus.<sup>2,15</sup> Pharmacokinetics of medications may be altered in pregnancy because of changes in absorption, volume of distribution, serum protein binding, extraction ratio, hepatic and renal clearance, uteroplacental flow, and fetal metabolism.<sup>7</sup> Medication regimens should be

**TABLE 20 CARPREG II Risk Prediction Model**

CARPREG II Predictors	Points
Previous cardiac event or arrhythmia	3
Baseline NYHA functional class III to IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction	2
High-risk left-sided valve disease and LVOT obstruction	2
Pulmonary hypertension	2
CAD	2
High-risk aortopathy	2
No previous cardiac intervention	1
Late pregnancy assessment	1
CARPREG II Score	Predicted Risk, %
0 to 1	5
2	10
3	15
4	22
>4	41

The CARPREG (Cardiac Disease in Pregnancy Study) II risk score is based on 10 predictors, shown in the table. Each predictor is assigned a weighted point score. The sum of points represents the risk score. Risk scores are categorized into 5 groups. The predicted and observed frequency of primary cardiac events\* in the derivation and validation groups is available at the CARPREG II Study <https://doi.org/10.1016/j.jacc.2018.02.076>. Modified with permission from Silversides CK, et al.<sup>3</sup> Copyright 2018 American College of Cardiology Foundation.

\*Primary cardiac events were defined as any of these: maternal cardiac death; cardiac arrest; sustained arrhythmia requiring treatment; left-sided HF defined as pulmonary edema; right-sided HF; stroke or TIA; cardiac thromboembolism; MI; and vascular dissection.

CAD indicates coronary artery disease; HF, heart failure; LVOT, left ventricular outflow tract; MI, myocardial infarction; NYHA, New York Heart Association; and TIA, transient ischemic attack.

**TABLE 21****Safety of Cardiovascular Medications During Pregnancy and Lactation**

Medication	Safety in Pregnancy	Safety in Lactation
<b>Arrhythmias</b>		
Adenosine	S	LD
Metoprolol/propranolol	S	LD
Digoxin	S	S
Lidocaine	S	S
Verapamil	LD	LD
Diltiazem	LD	U
Procainamide	LD	LD
Sotalol	LD	U
Flecainide	LD	LD
Propafenone	LD	LD
Amiodarone*	C	C
<b>Heart Failure</b>		
Metoprolol	S	LD
Carvedilol	S	U
Furosemide	S	LD
Bumetanide	S	U
Dopamine	S	U
Dobutamine	S	U
Norepinephrine	S	U
Hydralazine	LD	S
Nitroglycerine	LD	U
Isosorbide dinitrate	LD	U
Torsemide	LD	U
Metolazone	LD	U
<b>Anticoagulants</b>		
Warfarin	LD	S
Unfractionated heparin	S	S
Enoxaparin	S	S
Fondaparinux	LD	U
Argatroban	LD	U
Bivalirudin	LD	U
<b>Antiplatelets</b>		
Aspirin (low dose)	LD	LD
Clopidogrel	LD	LD
Prasugrel	LD	U
Ticagrelor	LD	U
<b>Thrombolytics</b>		
Alteplase	LD	U
Streptokinase	LD	U
<b>Hypertension</b>		
Labetalol	S	LD
Nifedipine	S	S
Alpha-methyldopa (oral)	S	S
Hydralazine	LD	S

Continued in the next column

**TABLE 21** **Continued**

Medication	Safety in Pregnancy	Safety in Lactation
Nitroglycerin	LD	U
Nitroprusside	LD	LD
Isosorbide dinitrate	LD	U
Amlodipine	LD	LD
Furosemide	S	LD
Hydrochlorothiazide	LD	S
Clonidine	LD	U
<b>Cautionary Use and Contraindicated in Pregnancy</b>		
Atenolol	C	LD
ACE inhibitor class†	C	LD
ARB class	C	U
Aldosterone antagonists	C	C
Statins class	LD	C
DOAC	C	C
ERAs (eg, bosentan)	C	C

Color key: C, contraindicated; LD, limited data, use with caution; S, considered safe; and U, conflicting data, unknown. Adapted with permission from Halpern DG, et al.<sup>7</sup> Copyright 2019 American College of Cardiology Foundation.

\*May be used if other therapies fail.

†Captopril, benazepril, and enalapril are considered safe during lactation.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DOAC, direct oral anticoagulants; and ERA, endothelin-receptor antagonists.

optimized during family planning to ensure safety throughout pregnancy and lactation.<sup>2,7</sup> Recommendations for selected cardiovascular medications during pregnancy and lactation are summarized in **Table 21**.

2. A multidisciplinary cardio-obstetrics team (**Figure 10**) should evaluate the patient before conception and monitor the patient throughout her pregnancy, carefully plan for labor and delivery, and provide close follow-up during the postpartum period to address medication management during lactation, monitor for cardiovascular complications, manage cardiovascular risk factors, and advise on contraception.<sup>5,16</sup> Longitudinal registries suggest that pregnancy outcomes have improved with the introduction of multidisciplinary care teams.<sup>1</sup> In health care settings where multidisciplinary teams are unavailable, clinicians should consider referral to relevant subspecialties as appropriate.

3. Statins have been contraindicated in pregnancy since their approval in 1987. FDA guidance published in July 2021 requested removal of this contraindication from all statin labels.<sup>6</sup> A 2015 US propensity-based analysis among 886,996 completed pregnancies linked to live-born infants showed a 1.79-fold increase in risk of fetal malformations among the 1,152 pregnancies with first-trimester exposure to statins, but this increase in risk was accounted for by confounders such as preexisting diabetes, lowering the relative risk to 1.07 (95% CI,



0.85-1.37) in adjusted analyses.<sup>24</sup> A 2014 meta-analysis similarly found no increase in birth defects after statin exposure during pregnancy but found an increased risk of miscarriage that the authors attributed to underlying maternal comorbidities.<sup>25</sup> A 2017 analysis of the UK General Practice Research Database showed a 1.64-fold increased risk of fetal loss in statin-exposed pregnancies but could not fully account for differences in baseline characteristics in exposed and unexposed pregnancies.<sup>26</sup> The FDA concluded that data are insufficient at this time to determine whether there is statin-associated increased risk of miscarriage. Statins remain contraindicated during lactation (Table 21). Lipoprotein apheresis can be considered for women with heterozygous or homozygous familial hypercholesterolemia and CCD.<sup>27</sup>

4. ACE inhibitors, ARBs, direct renin inhibitors, and angiotensin receptor-neprilysin inhibitors can cause renal dysgenesis, oligohydramnios because of fetal oliguria, neonatal anuric renal failure, intrauterine growth retardation, pulmonary hypoplasia, and fetal death, especially when used in the second and third trimester of pregnancy.<sup>8</sup> Benazepril, captopril, and enalapril are safe during lactation.<sup>7</sup> Aldosterone antagonists are contraindicated in pregnancy because of their anti-androgen effects and potential teratogenesis. Aldosterone antagonists are also contraindicated during lactation.<sup>7</sup>
5. Data from secondary prevention trials of hormone therapy<sup>11</sup> concluded that there was no effect on cardiovascular death, nonfatal MI, stroke, angina, or coronary revascularization. A statistically significant increased risk of venous thromboembolism was observed (relative risk, 2.02 [95% CI, 1.13-3.62]). In the angiographic trials,<sup>17-20</sup> no benefit of hormone therapy was seen on progression of disease in native CAD with estrogen only or with estrogen-progestin therapy. The EAGAR (Effects of Aspirin in Gestation and Reproduction) study<sup>20</sup> showed enhanced progression in native coronary arteries yet slowing of disease progression in saphenous vein grafts; the reason for this differential response is unknown. Increased risk of thromboembolism also was documented in a trial of hormone therapy among women with previous venous thromboembolism.<sup>28</sup> Less is known about the risk of oral contraceptives among women with CCD. A recent review on estrogen and thrombosis<sup>29</sup> concluded that combined hormonal contraceptives and injectable depot medroxyprogesterone acetate should be avoided among women with CCD or previous stroke as both forms of contraceptive therapy increase thrombosis risk.<sup>30,31</sup>

Increased cardiovascular risk has been documented among transwomen with increased rates of venous

thromboembolism, acute MI, and stroke compared with ciswomen but not always when compared with cis-men.<sup>29,32</sup> This increase in cardiovascular risk is at least in part related to hormone therapy. Whether prevalent CCD further increases risk in hormone-treated transgender women is unknown with future research needed.

## 6.6. Older Adults

### Synopsis

Older patients, defined as  $\geq 75$  years of age in accordance with a recent statement published by the AHA, ACC, and American Geriatrics Society,<sup>1</sup> have a high prevalence of CCD and, when present, is more likely to be associated with high-risk anatomical features.<sup>2</sup> Although several retrospective studies, observational studies, and subgroup analyses have suggested that medical therapy<sup>3-6</sup> and revascularization,<sup>7-17</sup> when needed, may be effective in older patients, they are less likely to be treated.<sup>18</sup> A paucity of RCTs with a focus on older patients leaves clinicians with inadequate data to guide their decision-making. The available data are limited by a variable definition of the term older; in fact, some studies have included individuals as young as 60 years of age. Furthermore, many studies comprise patients with both acute and CCD, making it difficult to determine in which clinical scenario a treatment is efficacious. The treatment of CCD in older patients is further complicated by the presence of multiple comorbidities and polypharmacy, both of which can heighten the risk of treatment-related complications. Based on a patient's comorbidities and extent of polypharmacy, scenarios may exist where alternate treatment or procedural approaches (beta blockers,<sup>19</sup> antithrombotic and antiplatelet agents,<sup>9,20-23</sup> coronary angiography,<sup>24</sup> CABG,<sup>25-29</sup> CR<sup>30,31</sup>) may be preferable. For example, a meta-analysis of 6 RCTs comparing short-term versus long-term DAPT in elderly patients.<sup>21</sup> The use of short-term DAPT was not associated with an

**TABLE 22 The Geriatric 5 Ms**

MIND	Mentation, dementia, delirium, depression
MOBILITY	Impaired gait and balance, fall injury prevention
MEDICATIONS	Polypharmacy, deprescribing, optimal prescribing Adverse medication effects and medication burden
MULTICOMPLEXITY	Multimorbidity Complex biopsychosocial situations
MATTERS MOST	Each individual's own meaningful health outcome goals and care preferences

Adapted with permission from Molnar F, et al.<sup>42</sup> Copyright 2017 Canadian Geriatrics Society and from Molnar F, et al. Copyright 2019 The College of Family Physicians of Canada. The GERIATRIC 5Ms, Copyright © 2017 Frank Molnar, Allen Huang, Mary Tinetti. 2017. The Geriatric 5Ms may be used for educational purposes with full attribution and no alterations. This work is bound by the Creative Commons license CC-BY-NC-ND 4.0 (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

increase in cardiovascular events but was associated with a significant reduction in major bleeding. Additionally, traditional risk scoring systems in patients with CCD may need to be modified to most accurately assess an older patient's risk.<sup>32,33</sup> Older patients also have an increased prevalence of frailty,<sup>34-37</sup> malnourishment,<sup>38-41</sup> and cognitive decline, all of which may be associated with poor outcomes and treatment response. Equally important, older patients are more likely to prioritize the ability to remain independent, with a focus on maintaining their

mobility and functional status rather than reducing their mortality rate.<sup>3</sup> When considering treatment options, team-based care (Section 4.1.1) and shared decision-making (Section 4.1.3) are particularly important when caring for older patients. A framework that considers the 5 Ms of geriatric care<sup>42</sup> (Table 22) may be a useful approach to guide these discussions.

## 6.7. Chronic Kidney Disease

### Recommendation for CKD

Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATION
1	C-LD	1. In patients with CCD and CKD, measures should be taken to minimize the risk of treatment-related acute kidney injury.* <sup>1-3</sup>

\*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.<sup>4</sup>

### Synopsis

CKD increases the risk of CAD progression and is associated with poor outcomes after interventions.<sup>5-8</sup> The mortality rate for patients on hemodialysis is ~20% per year, with approximately 50% attributable to a cardiovascular cause.<sup>9-12</sup> Postmortem studies have revealed that patients with CKD not only have a higher burden of atherosclerosis but, also, the plaque features are more advanced, with evidence of increased inflammation.<sup>13-15</sup> Despite the higher prevalence of disease, noninvasive diagnostic testing is often less accurate.<sup>20-24</sup>

Guidance related to the use of pharmacological and interventional therapy is limited by underrepresentation of patients with CKD in clinical trials<sup>16</sup> and attributable to inconsistent definitions of CKD. It is unclear whether medical therapy is as efficacious in patients with CKD because of differences in the risk and benefit balance in the setting of underlying kidney disease.<sup>17,18-21</sup> In the absence of data from dedicated RCTs, patients with CKD should receive similar medical therapy as patients without CKD.<sup>22</sup>

Given the complex interactions, a team-based approach (Section 4.1.1) that includes individuals from the cardiac and renal teams, to include shared decision-making (Section 4.1.3), would be beneficial, especially when considering decisions such as revascularization for which decreased short-term risk must be balanced with long-

term benefit.<sup>23,24</sup> For additional reference, please see patient education and SDOH (Sections 4.1.2 and 4.1.4) within this guideline.

### Recommendation-Specific Supportive Text

1. In the ISCHEMIA-CKD (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, patients with a moderate to severe burden of ischemia and estimated glomerular filtration rate [eGFR] of <30 mL/min/1.73 m<sup>2</sup> of body-surface area or the receipt of dialysis did not have improved outcomes with the addition of revascularization to GDMT, suggesting that revascularization can be reserved for patients who remain symptomatic despite medical therapy,<sup>25</sup> clarifying conflicting data from previous studies.<sup>8,26</sup> When PCI is clinically needed, the risk of contrast-induced acute kidney injury (AKI) should not be a reason to withhold it in most patients with CKD.<sup>4</sup> When possible, attempts to minimize the risk of contrast nephropathy should be made through the avoidance of nephrotoxic agents, use of adequate hydration before the administration of iodinated contrast-agent,<sup>27-29</sup> and minimization of the volume of contrast media.<sup>30,31</sup> Additionally, high-dose statins may reduce the occurrence of contrast-induced

AKI.<sup>32</sup> The use of radial access may minimize the role of atheroembolism on the development of AKI<sup>33–35</sup>; however, conflicting data exist.<sup>36,37</sup> Delay of CABG in stable patients after angiography beyond 24 hours, when clinically feasible, can also help reduce the risk of AKI.<sup>38</sup>

There is no benefit of bicarbonate or N-acetyl-L-cysteine over normal saline for prevention of AKI.<sup>39</sup>

## 6.8. HIV and Autoimmune Disorders

### Recommendations for HIV and Autoimmune Disorders

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
<b>HIV</b>		
1	B-R	1. In adults with CCD and HIV, antiretroviral therapy is beneficial to decrease the risk of cardiovascular events. <sup>1,2</sup>
2a	B-R	2. In adults with CCD and HIV, it is reasonable to choose antiretroviral therapy regimens associated with more favorable lipid and cardiovascular risk profiles with consideration of drug-drug interactions. <sup>3–5</sup>
3: Harm	C-LD	3. In adults with CCD and HIV, lovastatin or simvastatin should not be administered with protease inhibitors as this may cause harm. <sup>5,7</sup>
<b>Autoimmune Disorders in CCD</b>		
2a	C-LD	4. In adults with CCD and rheumatoid arthritis, initiation and maintenance of disease-modifying anti-rheumatoid drugs is beneficial to decrease the risk of cardiovascular events. <sup>8–11</sup>
2b	C-LD	5. In adults with CCD and autoimmune diseases, treatment with biologics and other immune modulating therapies that reduce disease activity may be considered to decrease the risk of cardiovascular events. <sup>10,11</sup>
3: Harm	C-LD	6. In patients with CCD and rheumatoid arthritis, high-dose glucocorticoids should not be used long term if alternative therapies are available because of increased cardiovascular risk. <sup>11,12</sup>

### Synopsis

HIV and other chronic inflammatory conditions are associated with accelerated atherosclerosis and premature CVD. The 2018 ACC/AHA blood cholesterol guideline recommends that chronic inflammatory conditions be considered risk-enhancing factors that should guide clinician-patient risk discussion for cholesterol management.<sup>13</sup> Patients with HIV have a higher risk of CAD and MI compared with age- and sex-matched controls.<sup>14</sup> The increased risk may be attributable to HIV itself, the antiretroviral therapy,<sup>15</sup> and to a higher prevalence of traditional, modifiable risk factors.<sup>6</sup> Newer generation antiretroviral therapy regimens have more favorable lipid effects and are associated with improvements in subclinical markers of atherosclerosis. Similarly, although new treatments for autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, and inflammatory bowel diseases, can negatively affect lipid profiles, adequate control of disease activity

with steroid-sparing agents should be prioritized and may help lower cardiovascular risk.<sup>10</sup> Because of the rapidly changing and complex pharmacological landscape in treating HIV and other chronic inflammatory conditions, patients should receive care from a multidisciplinary care team that includes infectious disease, rheumatology expertise, or both.

### Recommendation-Specific Supportive Text

- The SMART (Strategies for Management of Antiretroviral Therapy) trial showed that, compared with continuous use of antiretroviral therapy, episodic use of antiretroviral therapy increased risk of opportunistic disease and death from any cause, including CVD.<sup>1</sup> The MI event rate was 1.3 per 100 person-years in the interruption arm versus 0.8 per 100 person-years in the continuous use of antiretroviral therapy arm. Higher CD4 cell count and lower HIV RNA levels are associated with a lower risk of ASCVD.<sup>6,16,17</sup>

**TABLE 23** Common Antiretroviral Therapy Drugs and Effects on Lipid Levels

Class	Drug	Effect on Blood Lipids
Protease inhibitors	Atazanavir	Increases HDL-C and decreases LDL-C levels
	Darunavir	Increases HDL-C levels
	Fosamprenavir	Hypertriglyceridemia
	Ritonavir*	Increases HDL-C levels
	Saquinavir	Neutral
	Tipranavir	Dyslipidemia
NRTIs	Abacavir	Increases total cholesterol, LDL-C, and HDL-C levels
	Lamivudine	Increases total cholesterol, LDL-C, and HDL-C levels
	Tenofovir fumarate disoproxil	Lowers LDL levels
	Zidovudine	Hypertriglyceridemia
NNRTIs	Efavirenz	Increases total cholesterol, LDL-C, HDL-C, and triglyceride levels
	Nevirapine	Neutral or decreases lipid levels
	Rilpivirine	Neutral
Integrase inhibitors	Dolutegravir	Neutral
	Raltegravir	Increases HDL levels

Adapted from Hsue PY et al.<sup>6</sup> by permission from Springer Nature, Copyright 2019.

\*Although ritonavir is a protease inhibitor, this drug is generally used as a pharmacokinetic enhancer.

HDL indicates high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NNRTI, nonnucleoside reverse-transcriptase inhibitor; and NRTI, nucleoside reverse-transcriptase inhibitor.

2. Excess cardiovascular risk in patients with HIV may be partly attributable to side effects from antiretroviral therapy, including adverse effects on lipid levels. In adults with CCD and HIV, it is reasonable to choose newer generation antiretroviral treatment regimens associated with more favorable lipid and cardiovascular risk profiles.<sup>3–5</sup> These include protease inhibitor regimens with lower doses of ritonavir for boosting and using atazanavir-ritonavir-containing regimens (see Table 23 for commonly used antiretroviral therapy drugs and the effect on lipid levels). In 1 randomized study, switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen was non-inferior in maintaining a viral suppression with improvement in lipid levels (7.7% LDL-C reduction).<sup>3</sup> Contemporary US guidelines recommend that individuals with HIV and CVD should switch from an abacavir-containing regimen because of its possible association with increased cardiovascular events.<sup>4,18</sup> Drug interactions are common among patients with HIV on antiretroviral therapy, which should be considered when starting or intensifying statin therapy for management of CCD.<sup>6,7,19,20</sup> Although pravastatin and pitavastatin are least likely to interact with antiretroviral therapy, rosuvastatin and atorvastatin may be preferred for more intense LDL-C reduction in patients with HIV and CCD.<sup>20,21</sup> Management of hypertriglyceridemia in patients with CCD and HIV should

follow standard treatment pathways.<sup>22</sup> Triglyceride levels  $\geq 500$  mg/dL should be treated pharmacologically to reduce the risk of pancreatitis. Drug-drug interactions with protease inhibitors can also occur with antiplatelet drugs like ticagrelor because of its CYP3A metabolism,<sup>23</sup> which may increase the risk of bleeding. 3. Because lovastatin and simvastatin are metabolized by intestinal and liver CYP3A4, the concomitant use of protease inhibitors can increase levels of these statins and may increase the risk of rhabdomyolysis.<sup>6,7,24</sup> 4. Patients with rheumatoid arthritis and other autoimmune disease have residual inflammatory risk, beyond that conferred by traditional CVD risk factors. For patients with rheumatoid arthritis, disease-modifying antirheumatoid drugs such as methotrexate are associated with lower risk of cardiovascular events in observational studies.<sup>10</sup> A single-center observational study found that use of biologic disease-modifying antirheumatoid drugs in patients with rheumatoid arthritis stabilized and decreased plaque as measured by CCTA.<sup>25</sup> 5. Janus kinase inhibitors, tumor necrosis factor inhibitors, and other immunomodulators for the treatment of autoimmune diseases (eg, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis) may reduce cardiovascular events by reducing disease activity and inflammation.<sup>11,26,27</sup> These treatments should be used in

combination with intensive management of traditional risk factors (see [Section 4.2.6](#), “Lipid Management,” [Section 4.2.7](#), “Blood Pressure Management,” and [Section 4.2.8](#), “Sodium Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists”).

6. Observational studies suggest that long-term use of higher doses of glucocorticoids ( $\geq 5$  mg of prednisone) in patients with rheumatoid arthritis are associated with a higher risk of cardiovascular events.<sup>12</sup> This

association has not been described with the use of steroid-sparing agents<sup>11</sup> or shorter duration use of steroids (<81 days in 6 months or cumulative doses of <751 mg in 6 months).<sup>12</sup> Using short courses of glucocorticoids for autoimmune disease flares is unlikely to increase cardiovascular risk.

## **6.9. Cardiac Allograft Vasculopathy in Heart Transplant Recipients**

### **Recommendations for Management of Cardiac Allograft Vasculopathy in Heart Transplant Recipients**

Referenced studies that support the recommendations are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATIONS
1	C-LD	1. In patients with cardiac allograft vasculopathy, statins are recommended for secondary prevention to reduce MACE. <sup>1</sup>
2a	C-LD	2. In patients with cardiac allograft vasculopathy, aspirin can be beneficial for secondary prevention to reduce MACE. <sup>2</sup>
2a	C-LD	3. In patients with severe cardiac allograft vasculopathy, revascularization is reasonable in those with suitable anatomy to potentially mitigate the adverse long-term consequences of cardiac allograft vasculopathy.* <sup>3-6</sup>

\*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.<sup>7</sup>

### **Synopsis**

Post-heart transplant cardiac allograft vasculopathy is the leading cause of long-term mortality and retransplantation among heart transplant recipients.<sup>8</sup> The incidence of cardiac allograft vasculopathy increases over time after heart transplant, developing in ~30% of patients at 5 years and ~50% of patients at 10 years.<sup>8</sup> Coronary angiography is the accepted clinical standard for screening and diagnosis of cardiac allograft vasculopathy.<sup>3,9</sup> Intravascular ultrasound is a useful adjunct to angiography and can improve detection of angiographically occult cardiac allograft vasculopathy.<sup>10</sup> Lifestyle modifications and optimal control of cardiovascular risk factors are important for the primary and secondary prevention of cardiac allograft vasculopathy.<sup>3,11</sup> In patients after heart transplant with or without established cardiac allograft vasculopathy, statins, aspirin, and high-intensity interval training delay cardiac allograft vasculopathy progression.<sup>1,2,12</sup> In patients with cardiac allograft vasculopathy, PCI can be beneficial in those with severe, proximal, discrete lesions, and the use of second-generation DES is associated with decreased rates of in-stent restenosis.<sup>4-7</sup> CABG is rarely used in highly selected patients with suitable anatomy, and retransplantation is reserved for patients with severe cardiac allograft vasculopathy not

amenable to revascularization.<sup>3</sup> In heart transplant recipients with established cardiac allograft vasculopathy, early substitution of mycophenolate mofetil, azathioprine, or calcineurin inhibitor with a proliferation signal inhibitor can slow cardiac allograft vasculopathy progression but is associated with an increased risk of grade  $\geq 2R$  rejection.<sup>13-17</sup> CR is addressed in [Section 4.2.10](#).

### **Recommendation-Specific Supportive Text**

1. Multiple RCTs have shown decreased incidence of cardiac allograft vasculopathy with simvastatin or pravastatin initiated early after heart transplant.<sup>18,19</sup> However, in patients with cardiac allograft vasculopathy, RCTs evaluating the safety and efficacy of statins for secondary prevention are lacking. In a retrospective observational study of 409 heart transplant recipients with or without established cardiac allograft vasculopathy, early (<2 years) versus late (>2 years) initiation of statin was associated with significantly lower rates of cardiac allograft vasculopathy progression as measured by change in plaque volume and plaque index by intravascular ultrasound, as well as decreased risk of cardiac allograft vasculopathy-related events (allograft failure associated with cardiac allograft vasculopathy, MI, or PCI) and the composite of all-cause death and

**TABLE 24 Drug-Drug Interactions With Statins and Immunosuppressants and Recommendations for Management**

Immunosuppressant	Statin	Effect	Magnitude	Recommendation
Cyclosporine/tacrolimus/ everolimus/sirolimus*	Atorvastatin	Increased statin exposure through multiple mechanisms.	Severe 6- to 15-fold increase in AUC of atorvastatin	Limit dose of atorvastatin to 10 mg daily
	Rosuvastatin	Increased risk for muscle-related toxicity.	Severe 7-fold increase in AUC of rosuvastatin	Limit dose of rosuvastatin to 5 mg daily
	Pravastatin		Severe 5- to 10-fold increase in AUC of pravastatin	Limit dose of pravastatin to 40 mg daily
	Fluvastatin		Moderate 2- to 4-fold increase in AUC of fluvastatin	Limit dose of fluvastatin 40 mg daily
	Simvastatin		Severe 6- to 8-fold increase in AUC of simvastatin	Avoid combination
	Lovastatin		Severe 5- to 20-fold increase in AUC of lovastatin	Avoid combination
	Pitavastatin		Severe 5-fold increase in AUC of pitavastatin	Avoid combination

Magnitude of drug-drug interactions based on AUC increase: minor, >1.25 to <2; moderate, ≥2 to 4.9; and severe, ≥5. Adapted with permission from Wiggins BS, et al.<sup>30</sup> Copyright 2016 American Heart Association, Inc.

\*Changes in magnitude of statin AUC are reported with cyclosporine. Limited data exist with tacrolimus, everolimus, and sirolimus.

AUC indicates area under the curve.

cardiac allograft vasculopathy-related events, over a median follow-up of 8.2 years.<sup>1</sup> The choice and dose of statin in heart transplant recipients is not well established and will often depend on the other medications (particularly immunosuppressants) that the patient is concomitantly taking (Table 24).<sup>20</sup> A recent retrospective analysis of 346 adult patients who underwent heart transplant between 2006 and 2018 found that moderate/high- versus low-intensity statin therapy was associated with a significant reduction in the primary composite of time to HF hospitalization, MI, revascularization, and all-cause death.<sup>21</sup>

2. Aspirin is frequently initiated early after heart transplant for prevention of cardiac allograft vasculopathy. Although the proposed benefits of aspirin use have not been validated in RCTs, evidence from small retrospective single-center studies support early initiation of aspirin after heart transplant.<sup>2,22-24</sup> In a retrospective observational study of 529 heart transplant recipients with or without established cardiac allograft vasculopathy, early (<1 year) versus late (>1 year) initiation of aspirin was associated with significantly lower rates of cardiac allograft vasculopathy progression as measured by change in plaque volume and plaque index by intravascular ultrasound, as well as decreased risk of all-cause death and cardiac allograft vasculopathy-related graft dysfunction, over a median follow-up of 6.7 years.<sup>2</sup>

3. Data showing improved outcomes with revascularization versus medical therapy alone for cardiac allograft vasculopathy are lacking. However, because increasing severity of cardiac allograft vasculopathy is associated with worse outcomes, revascularization is reasonable in patients with suitable anatomy.<sup>3</sup> PCI can be beneficial in patients with cardiac allograft vasculopathy who present with severe, proximal, discrete lesions.<sup>7</sup> Observational studies showed PCI for cardiac allograft vasculopathy is not only feasible with high procedural success rates but also associated with reliable mid- to long-term angiographic outcomes, especially with the use of second-generation DES.<sup>4-6</sup> PCI with everolimus-eluting stents for cardiac allograft vasculopathy was associated with in-stent restenosis rates of 3% to 5% at 6 to 12 months and 10% at 3 years, which are comparable to the use of everolimus-eluting stents in non-heart transplant CAD.<sup>4-6,25,26</sup> Coronary physiology assessment measuring FFR and the index of microcirculatory resistance early after heart transplant has prognostic significance.<sup>27,28</sup> However, the use of FFR to guide revascularization in patients with cardiac allograft vasculopathy (as opposed to those with non-heart transplant CAD) remains unknown. The use of CABG for severe cardiac allograft vasculopathy is limited by high early mortality rate (36% at 30 days) associated with surgical revascularization in this patient population.<sup>29</sup>

## 7. PATIENT FOLLOW-UP: MONITORING AND MANAGING SYMPTOMS

### 7.1. Follow-Up Plan and Testing in Stable Patients

#### Recommendations for Follow-Up Plan and Testing in Stable Patients

Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
2b	B-R	1. In stable patients with CCD and with previous ACS or coronary revascularization, referral to telehealth programs, community-based programs, or both for lifestyle interventions may be reasonable as an adjunct to usual care to improve management of cardiovascular risk factors. <sup>1–7</sup>
3: No benefit	B-R	2. In patients with CCD without a change in clinical or functional status on optimized GDMT, routine periodic testing with coronary CTA or stress testing with or without imaging is not recommended to guide therapeutic decision-making. <sup>8–10</sup>
3: No benefit	B-R	3. In patients with CCD without a change in clinical or functional status, routine periodic reassessment of LV function is not recommended to guide therapeutic decision-making. <sup>11,12</sup>
3: Harm	B-NR	4. In patients with CCD without a change in clinical or functional status, routine periodic invasive coronary angiography should not be performed to guide therapeutic decision-making. <sup>13–17</sup>

#### Synopsis

Patients with CCD are at elevated risk for future MACE and should be observed periodically in the outpatient setting.<sup>18,19</sup> Central components of the management of patients with CCD include long-term risk factor modification and active management of GDMT to achieve maximally tolerated doses,<sup>20</sup> with shared decision-making involving effective communication between cardiologists, primary, and specialty care teams (see Section 4.1, “General Approach to Treatment Decisions,” Section 4.1.1, “Team-Based Approach,” Section 4.1.2, “Patient Education,” and Section 4.1.4, “Social Determinants of Health”).<sup>21–23</sup> Over the past 2 decades, rates of MACE in patients with CCD have declined, and contemporary studies suggest overall low event rates in patients with CCD on GDMT, especially in the absence of anginal symptoms.<sup>19,24</sup> After index diagnostic evaluation, treatment, and optimization of lifestyle and medical interventions, follow-up testing should be reserved for instances when there has been a significant change in symptom and/or clinical status. Periodic recording of the standard resting 12-lead ECG in patients with CCD may provide a baseline waveform against which future tracings taken during symptoms may be reasonably compared to avoid overdiagnosis of a change in clinical status.<sup>14,15</sup> Patients with CCD who have accelerating symptoms or decreasing functional capacity despite optimized GDMT

should undergo assessment as per Section 3 (“Evaluation, Diagnosis, and Risk Stratification”). Recommendations regarding CR can be found in Section 4.2.10.

#### Recommendation-Specific Supportive Text

1. A Dutch multicenter trial randomized 374 adults <8 weeks after hospitalization for ACS to usual care plus telehealth coaching with the lifestyle intervention “Hartcoach” every 4 weeks versus usual care alone.<sup>1</sup> After 6 months of follow-up, patients randomized to Hartcoach had modest improvement in BMI, waist circumference, physical activity, intake of vegetables, self-management, and anxiety. An Australian trial randomized 430 adults with previous MI to a telephone-delivered 6-month secondary prevention program (“Proactive Heart”) versus usual care.<sup>2</sup> Patients in the intervention group had significantly improved health outcomes as assessed by health-related QOL and physical activity surveys, including anxiety outcomes.<sup>3</sup> A subsequent randomized trial of 121 adults found that a 6-month telehealth program (MoodCare) improved depression scores in patients post-ACS compared with usual care,<sup>4</sup> and effects persisted at 1-year follow-up in those with major depressive disorder.<sup>5</sup> In the RESPONSE-2 (Ruxolitinib Efficacy and Safety in Patients with HU Resistant or Intolerant Polycythemia Vera versus Best Available Therapy)

trial, nurse-coordinated referral of 711 patients with previous ACS, coronary revascularization, or both and their partners to 3 widely available community-based lifestyle programs in 15 hospitals in the Netherlands led to significant improvements in lifestyle-related factors.<sup>6</sup> Text messaging interventions may<sup>7</sup> or may not<sup>25,26</sup> be beneficial. The cost-effectiveness of such approaches remains uncertain.<sup>27</sup>

2. The evidence base surrounding the long-term prognosis and appropriate management of the spectrum of contemporary patients with CCD is evolving. Routine periodic anatomic or ischemic testing in asymptomatic, nonsedentary patients is not recommended. Limited data are available to guide management of asymptomatic patients with CCD on GDMT who receive functional or anatomic testing and have a positive result. In the ISCHEMIA trial, 5,179 patients with stable CAD and site-determined moderate-severe ischemia on stress testing were randomized to invasive versus conservative care strategies, with no difference in the composite primary MACE endpoint at 3.3 years of follow-up.<sup>8</sup> Only patients presenting with daily, weekly, or monthly angina experienced prompt and durable improvement in symptoms when randomized to invasive compared with conservative management.<sup>28</sup> In the CLARIFY (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease) registry of 32,105 outpatients with CCD across 45 countries, anginal symptoms during noninvasive testing, but not silent ischemia, were associated with increased risk of MACE, including cardiovascular death or nonfatal MI.<sup>9</sup> Recently, the multicenter, POST-PCI (Pragmatic Trial Comparing Symptom-Oriented versus Routine Stress Testing in High-Risk Patients Undergoing Percutaneous Coronary Intervention) RCT compared a strategy of routine functional stress testing (using exercise ECG with or without nuclear myocardial perfusion imaging or stress echocardiography) versus standard care alone 12 months after successful PCI in 1,706 high-risk patients. At 2 years of

follow-up, no differences were observed between groups in the primary endpoint of composite death, MI or hospitalization for unstable angina.<sup>10</sup>

3. Routine, periodic reassessment of LV function in asymptomatic patients without a change in functional status or clinical intervention is not recommended.<sup>11</sup> In a post-hoc analysis of the RCT MASS II in which patients with multivessel CCD treated by CABG, PCI, or medical therapy underwent evaluation of LVEF before randomization and after 10 years of follow-up (n=350), LVEF was stable over long-term follow-up in the absence of MACE.<sup>12</sup>
4. Asymptomatic patients in the ISCHEMIA trial did not derive a benefit when randomized to invasive compared with conservative management.<sup>8,28</sup> Routine follow-up invasive coronary angiography has been associated with increased revascularization of non-ischemic intermediate lesions without an improvement in rates of subsequent cardiac death or MI.<sup>16,17</sup> The ReACT (Randomized Evaluation of Routine Follow-up Coronary Angiography after PCI) trial was a prospective multicenter open-label trial in Japan in which 700 patients were randomized to receive routine follow-up coronary angiography 8 to 12 months after PCI versus clinical follow-up alone.<sup>14</sup> During median follow-up of 4.6 years, no clinical benefit was seen for routine follow-up coronary angiography despite increased early coronary revascularization rates. Routine angiographic follow-up after PCI in patients with diabetes was associated with an increased incidence of revascularization and MACE without a change in death or reinfarction rates.<sup>29</sup> In a contemporary Danish registry of patients with CCD, revascularization in those without ischemia conferred a higher risk of death and MI versus medical therapy alone.<sup>15</sup>

## 8. OTHER IMPORTANT CONSIDERATIONS

### 8.1. Cost and Value Considerations

#### Recommendation for Cost and Value Considerations

Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	RECOMMENDATION
1	B-NR	<p>1. When discussing treatment and prevention with patients who have CCD, it is recommended that the health care team discuss out-of-pocket costs for medications at the time of initiating a new medication and at least annually thereafter to preempt cost-related nonadherence.<sup>1-6</sup></p>

## Synopsis

Some new CCD therapies are only available as branded formulations, and their high out-of-pocket costs can impede adoption or increase the risk of cost-related nonadherence.<sup>1,2</sup> High out-of-pocket costs is a frequently cited reason for patients foregoing medications, delaying a prescription refill, or skipping or reducing medication doses.<sup>3</sup> The use of high-cost therapies in a large number of eligible patients increases pharmaceutical spending, which, in the long term, gets passed to the patient in the form of higher insurance premiums (in the case of private insurance) and to the taxpayer in the form of higher taxes (in the case of public insurance). Therefore, clinicians have a key role in ensuring access and adherence to effective therapies by regularly discussing out-of-pocket costs with their patients with CCD as a part of shared decision-making, using lower-cost alternatives when available, and guiding health systems to adopt cost-effective therapies when >1 alternative is appropriate (ie, choosing therapies that require lower incremental spending to generate 1 additional unit of health and meet conventional cost-effectiveness thresholds). For Level of Value Considerations, refer to **Table 1**. Refer also to the lipid management, SGLT2, and revascularization sections (**4.2.6**, **4.2.8**, and **5.1**) for applicable cost-value considerations.

## Recommendation-Specific Supportive Text

1. One in 8 persons with CVD in the United States reports cost-related medication nonadherence.<sup>3</sup> Patients may be responsible for hundreds of dollars in out-of-pocket costs for their prescriptions, which can be a barrier to initiating or continuing an effective therapy.<sup>1,2</sup> Most patients report a desire to discuss out-of-pockets with their clinicians, particularly when considering a new therapy.<sup>4–6</sup> Clinicians and their support team should familiarize themselves with out-of-pocket costs for commonly prescribed drugs but recognize that these may vary among patients by benefit design, time of year (eg, whether the annual deductible has been met), and concurrent medications. Clinicians or their care support team should identify the best source of out-of-pocket costs in their health systems; in some cases, information may be readily available in the electronic health record at the point of order entry, but in others, clinicians may have to order “test prescriptions” to ascertain coverage. Clinicians or their care support team should review each patient’s out-of-pocket costs when starting a new medication and periodically thereafter. Shared decision-making (**Section 4.1.3**) with patients is paramount because affordability may vary substantially based on the patient’s socioeconomic status (**Section 4.1.4**, “Social Determinants of Health”). Clinicians or their care support team should inform

patients of cost-saving approaches such as the use of mail order pharmacies or patient assistance programs or consider lower-cost alternatives when appropriate.

## 8.2. Evidence Gaps and Areas of Future Research Needs

Although the past decade has seen numerous advancements in the diagnosis and treatment of patients with CCD, several gaps still exist in our understanding. These gaps should serve as areas of future research and are described below.

- With an evolving definition of patients who have CCD, research is needed to determine how advances in noninvasive imaging technology (ie, allowing sensitive detection and quantification of calcified and non-calcified atherosclerotic plaque burden) may affect identification of patients with CCD, their prognostication, and their eligibility for preventive therapies.
- Comprehensive risk scores need to be developed and validated for MACE in patients with CCD in the contemporary era that include patient demographics, medical information, social determinants, and data from noninvasive test results, or invasive test results, or both.
- Although studies have shown deficiencies with clinician-estimation of patient’s symptoms, research is needed to understand whether routine use of patient-reported measures in clinical care improve patient-centered outcomes.
- Decision aids that are tested and validated in diverse populations are needed to support shared decision-making in patients with CCD.
- High-quality studies are needed to assess the effect of various substances, including marijuana, on cardiovascular outcomes in patients with CCD.
- With several therapies available to treat symptoms or improve outcomes in patients with CCD, research is needed on how to sequence GDMT in patients with CCD (ie, how to judge relative importance of different components of GDMT in specific patients).
- Randomized trials with longer-term cardiovascular outcomes are needed to determine the effectiveness of interventions that limit sedentary time.
- Research is needed to understand whether the efficacy of therapies used in patients with CCD is uniform across men and women with CCD and across various racial and ethnic groups of patients with CCD that have traditionally been underrepresented in clinical trials.
- Further research is needed to assess the use of personalized medicine approaches, including the assessment of the use of artificial intelligence, text messaging, wearable technology, genomics, and proteomics to improve risk assessment and treatment

approaches in diverse populations of patients with CCD.

- Additional research is needed to assess the effect of hybrid CR, as well as home-based CR, on longer-term clinical outcomes and on outcomes for various population subgroups, including women, older adults, and those from underrepresented racial and ethnic groups.
- Future research is needed on patients with CCD on the long-term effect of treatment of mental health conditions (namely depression): (1) patients with a previous (known) diagnosis of mental health condition and concomitant CCD, or (2) patients with a new diagnosis of a mental health condition after MI.
- Future research is needed on the long-term risk of e-cigarette use on cardiovascular health in patients with CCD.
- Further research is needed on whether there is utility for the use of GLP-1 receptor agonists in patients with CCD but not type 2 diabetes for cardiovascular risk reduction. Research is also needed to determine whether there is utility for the combined use of SGLT2 inhibitors and GLP-1 receptor agonists in patients with CCD.
- Further research is needed on the optimal antiplatelet regimen choices for patients with CCD who are 1 year post-MI or PCI.
- Further research is needed on what is the optimal antithrombotic strategy in patients with CCD and atrial fibrillation.
- In patients with CCD and refractory angina, research is needed to assess the utility of neuromodulation and thoracic spinal cord stimulation, therapeutic angiogenesis with cell/gene therapies, coronary sinus occlusion, and shockwave therapy.
- Additional research is needed in populations with SCAD to determine optimal pharmacological management strategy after SCAD and the potential impact of vasculopathy screening on future cardiovascular outcomes.
- As climate change-related extreme environmental events become more severe and more intense, high-quality research is needed to examine whether preventative strategies—such as indoor air purifiers and N95 masks during periods of substantial wildfire smoke exposure or public spaces with air-conditioning during extreme heat—are protective in patients with CCD who are at increased risk of cardiovascular events.
- Research is needed to explore how to best integrate SDOH into electronic health records to enable

practitioners to coordinate care for patients with CCD challenged with health inequities.

- Although some electronic health records allow estimation of patient out-of-pocket costs for medications, testing, and treatments, more work is needed in development and dissemination of tools to allow clinicians to determine patient costs accurately at the point of care.
- Research is needed to determine whether GDMT is associated with improved outcomes in older adults with CCD or patients with CCD on hemodialysis.
- Studies are needed to assess which interventions lead to effective guideline implementation in clinical practice. Similarly, research is needed to assess the effect of a new guideline release at the patient, clinic, hospital, health care systems, and the community levels.

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### 8.1. Cost and Value Considerations

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**KEY WORDS** ACC/AHA Clinical Practice Guidelines, acute coronary syndrome, air pollution, angina, antiplatelet therapy, aspirin, atherosclerosis, autoimmune diseases, cardiac events, cardiac rehabilitation, cardiovascular diseases, colchicine, coronary artery disease, coronary disease, cost-benefit analysis, depression, diabetes, type 2 diabetes, diet, diet therapy, dietary supplements, drug therapy, dual antiplatelet therapy, environmental exposure, exercise tolerance, factor Xa inhibitors, fibrinolytic agents, glucagon-like peptide-1 receptor agonists, guideline-directed management and therapy, health equity, heart disease risk factors, heart failure, health care outcome assessments, hormone replacement therapy, hypercholesterolemia, hypertension, immunization, ischemic heart disease, mental health, multidisciplinary, myocardial ischemia, outcomes, outpatient, patient care team, pharmacology, pregnancy, proton pump inhibitors, quality of life, safety, secondary prevention, sexual behavior, sexual health, smoking cessation, shared decision-making, social determinants of health, sodium-glucose cotransporter 2 inhibitors, spontaneous coronary artery dissection, stress, therapeutic use, therapy, vaccination

**APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—2023 AHA/ACC/ACCP/ASPC/NLA/PCNA GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC CORONARY DISEASE**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Salim S. Virani (Chair)	(Effective February 2023) Aga Khan University—Vice Provost, Research; Texas Heart Institute—Professional Staff (Until February 2023) Baylor College of Medicine—Professor, Cardiovascular Fellowship Program Director; Michael E. DeBakey VA Medical Center for Cardiovascular Disease Prevention (Clinic)—Staff Cardiologist/Co-Director, VA Advanced Fellowship Program in Health Services Research & Development	None	None	None	NOT RELEVANT ■ NIH/FIC (DSMB) ■ Tahir and Jooma Family* ■ U.S. Department of VA*	NOT RELEVANT ■ ACC* ■ ACC.org, Associate Editor for Innovations and Editorial lead, and Editorial lead for Prevention topic collection ■ ASPC ■ <i>Circulation</i> , Guest Editor ■ Current Atherosclerosis Reports, Current Cardiology Reports, Section Editor ■ <i>Journal of Clinical Lipidology</i> , Associate Editor ■ NIH* ■ NAACME ■ NLA ■ Tabba Heart Institute, Steering Committee Member, PAK-SEHAT ■ WHF†	None
L. Kristin Newby (Vice-Chair)	Duke University—Professor of Medicine, Division of Cardiology and Duke Clinical Research Institute	RELEVANT ■ CSL Behring ■ Medtronic* NOT RELEVANT ■ Beckman Coulter ■ NHLBI ■ NC DHHS	None	None	RELEVANT ■ Boehringer-Ingelheim NOT RELEVANT ■ David H. Murdoch Institute for Business and Culture ■ NIH* ■ NIH (DSMB)† ■ North Carolina DHHS* ■ Roche Diagnostics*	NOT RELEVANT ■ ACC† ■ AHA† ■ <i>American Heart Journal</i> , Editorial Board† ■ AstraZeneca Healthcare Foundation† ■ David H. Murdoch Research Institute† ■ <i>European Heart Journal- Acute Cardiovascular Care</i> , Editorial Board† ■ <i>JACC: Basic to Translational Science</i> * ■ WHF†	None
Suzanne V. Arnold	St. Luke's Mid America Heart Institute University of Missouri-Kansas City—Professor of Medicine	None	None	None	None	NOT RELEVANT ■ <i>Heart</i> , Associate Editor	None
Vera Bittner	University of Alabama at Birmingham, Division of Cardiovascular Disease—Professor of Medicine; Endowed Scholar in Cardiovascular Disease Prevention; Section Head General Cardiology, Prevention, and Imaging	RELEVANT ■ Pfizer NOT RELEVANT ■ ACC*	None	None	RELEVANT ■ Amgen ■ Novartis* NOT RELEVANT ■ Verve Therapeutics (DSMB)	RELEVANT ■ AstraZeneca* ■ Dalcor* ■ Esperion* ■ Sanofi-Aventis* NOT RELEVANT ■ AHA* ■ ACC* ■ Medscape ■ NLA	None

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## APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
LaPrincess C. Brewer	Mayo Clinic—Assistant Professor of Medicine, Preventive Cardiology	None	None	None	NOT RELEVANT ■ AHA, AHA EPI, Presidential Advisory, SDOH† ■ NIH ■ CDC	NOT RELEVANT ■ ABC† ■ ACC† ■ <i>American Journal of Preventive Cardiology</i> , Editorial Board ■ JAMA, Editorial Board ■ Current CV Risk Reports, Section Editor	None
Susan Halli Demeter	Mayo Clinic Arizona—Assistant Professor of Medicine Heart Health & Performance Program Lipid Clinic	None	NOT RELEVANT ■ Integrity ■ National Lipid Association/ Paradigm Medical Communication	None	None	NOT RELEVANT ■ Amgen‡ ■ Ionis Pharmaceuticals/Medpace‡ ■ NLA ■ PCNA†	None
Dave L. Dixon	Virginia Commonwealth University School of Pharmacy—Associate Professor and Department Chair, Department of Pharmacotherapy & Outcome Science	NOT RELEVANT ■ APhA	None	None	RELEVANT ■ Boehringer Ingelheim* NOT RELEVANT ■ Board of Pharmacy Specialties ■ CDC* ■ NIH ■ Mercatus*	NOT RELEVANT ■ ACC ■ ACCP, Cardiology Practice Research Network† ■ Accreditation Council for Clinical Lipidology† ■ AHA ■ Diabetes/Metabolism: Research and Reviews, Editorial Board ■ <i>Journal of Cardiovascular Pharmacology</i> ■ <i>Journal of Clinical Lipidology</i> , Associate Editor† ■ Medscape ■ NLA† ■ PCORI	None
William F. Fearon	Stanford University/VA Palo Alto Healthcare System—Professor of Medicine	RELEVANT ■ CathWorks ■ Siemens NOT RELEVANT ■ ACC ■ Genuity, LLC*	None	None	RELEVANT ■ Abbott† ■ Boston Scientific† ■ Edwards Lifesciences† ■ Medtronic† NOT RELEVANT ■ NIH	NOT RELEVANT ■ <i>Circulation</i> , Editorial Board ■ <i>Circulation: Cardiovascular Interventions</i> , Editorial Board ■ HeartFlow ■ <i>International Journal of Cardiology</i> , Editorial Board ■ JACC, Editorial Board ■ McGraw Hill ■ Neovasc Medical Inc. ■ Stanford University, Abbott† ■ Stanford University, Medtronic‡ ■ Zoll	None
Beverly Hess	Microsoft—Senior Director (Retired)	None	None	None	None	NOT RELEVANT ■ AHA Women of Impact, Nominee ■ AHA, Established Investigators Award Peer Review Panel	None

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## APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Heather M. Johnson	Christine E. Lynn Women's Health & Wellness Institute, Department of Preventive Cardiology Boca Regional Hospital; Baptist Health South Florida—Clinical Affiliate; Florida Atlantic University—Associate Professor; University of Wisconsin-Madison—Adjunct Associate Professor	NOT RELEVANT  ■ Best Doctors Advisory Panel ■ M3 Global Research	NOT RELEVANT  ■ ASPC ■ Medelligence† ■ WomenHeart	None	NOT RELEVANT  ■ NIH*	NOT RELEVANT  ■ AHA ■ <i>American Journal of Preventive Cardiology</i> , Editorial Board† ■ Applied Radiology† ■ ASPC† ■ CureMetrix† ■ Esperion ■ NIH	None
Dhruv S. Kazi	Harvard Medical School—Associate Professor; Beth Israel Deaconess Medical Center—Director, Cardiac Critical Care; Smith Center for Outcomes Research—Associate Director	None	None	None	NOT RELEVANT  ■ Harvard Medical School—Institutional Grant, Boston Scientific*	NOT RELEVANT  ■ AHA† ■ Bayer ■ <i>Circulation: Cardiovascular Quality and Outcomes</i> ■ Harvard Global Health Institute ■ Institute for Clinical Economic Review ■ Lahey Medical Center, Grand Rounds ■ NIH/NHLBI ■ Stanford University, Grand Rounds	None
Dhaval Kolte	Massachusetts General Hospital and Harvard Medical School—Instructor in Medicine Department of Medicine, Cardiology Division	None	None	None	None	NOT RELEVANT  ■ AHJ, Editorial Board ■ ACC† ■ AHA† ■ Biotronik ■ Medtronic ■ NIH ■ SCAI†	None
Dharam J. Kumbhani	UT Southwestern Medical Center—Associate Professor of Medicine and Section Chief, Interventional Cardiology William Clements University Hospital—Cath Lab Director	NOT RELEVANT  ■ ACC*	None	None	NOT RELEVANT  ■ PCORI	NOT RELEVANT  ■ <i>Circulation</i> , Associate Editor*	None
Jim LoFaso	Engineer (retired)	None	None	None	None	NOT RELEVANT  ■ AHA†	None
Dhruv Mahtta	Baylor College of Medicine—Cardiology Fellow, Department of Medicine, Division of Cardiovascular Disease	None	None	None	None	NOT RELEVANT  ■ AHJ, Editor ■ AstraZeneca ■ JAHA, Editor ■ Chiesi ■ <i>Current Cardiology</i> , Section Editor ■ <i>Current Atherosclerosis</i> , Section Editor	None

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## APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Daniel B. Mark	Duke University Medical Center—Professor of Medicine; Vice Chief for Academic Affairs Division of Cardiology, Department of Medicine	RELEVANT ■ Novartis	None	None	RELEVANT ■ Merck*	RELEVANT ■ Merck* NOT RELEVANT ■ AHJ, Editor ■ Elsevier* ■ Heartflow* ■ NIH*	NOT RELEVANT ■ Defendant, Arrhythmia issues, 2020 ■ Defendant, Acute SOP/CP, 2020 ■ Defendant, Respiratory Arrest, 2020 ■ Workers' Compensation Issues, 2020
Margo Minissian	Cedars-Sinai—Executive Director, Geri and Richard Brawerman Nursing Institute; Simms/ Mann Family Foundation Endowed Chair in Nurse Education, Innovation and Research and Assistant Professor, Department of Cardiology	NOT RELEVANT ■ Medtelligence* ■ MJH Lifesciences ■ North American Center for CME, LLC* ■ Vox Media	None	None	NOT RELEVANT ■ NIH* ■ NIHF*	NOT RELEVANT ■ Brawerman Nursing Institute, Endowed Chair† ■ NLA ■ Novo Nordisk ■ NAMS ■ MJH Life Sciences, LLC	None
Ann Marie Navar	UT Southwestern Medical Center—Associate Professor of Medicine Department of Medicine, Division of Cardiology	RELEVANT ■ AstraZeneca* ■ Amgen* ■ Bayer* ■ Boehringer Ingelheim* ■ Bristol Myers Squibb* ■ CSL Behring* ■ Eli Lilly and Company ■ Novartis* ■ NovoNordisk* ■ Pfizer* ■ Janssen Pharmaceutical ■ New Amsterdam Pharmaceutical NOT RELEVANT ■ Cerner Corporation	RELEVANT ■ Vindico	None	RELEVANT ■ Bristol Myers Squibb* ■ Esperion* ■ Janssen Pharmaceuticals ■ Novartis* ■ Amgen*	NOT RELEVANT ■ ACC ■ AHA ■ AHJ ■ <i>American Journal of Preventive Cardiology</i> ■ American Society for Preventive Cardiology ■ Asia Pacific Society of Cardiology ■ CardioNerds† ■ <i>JAMA Cardiology</i> ■ NHLBI ■ NIH ■ National Forum for Heart Disease & Stroke Prevention	None

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## APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Amit R. Patel	(effective January 2022) University of Virginia Health System—Professor of Medicine; Director, Noninvasive Cardiac Imaging Cardiovascular Division (through 12/2021) University of Chicago—Associate Professor; Director Cardiac MRI and CT, Department of Medicine and Radiology	None	NOT RELEVANT ■ General Electric	None	NOT RELEVANT ■ Arterys† ■ ASE* ■ Circle CVIT† ■ General Electric* ■ <i>Journal of Cardiovascular Magnetic Resonance</i> † ■ Neosoft† ■ NIH† ■ Philips* ■ Society of Cardiovascular Magnetic Resonance† ■ Society of Cardiovascular Computed Tomography	NOT RELEVANT ■ ACC ■ Amgen ■ APCAT† ■ Apple* ■ AstraZeneca ■ General Electric* ■ Novartis ■ Pfizer ■ Smith & Nephew ■ The Very Good Food Company, Inc.*	None
Mariann R. Piano	Vanderbilt University School of Nursing—Nancy and Hilliard Travis Professor of Nursing Senior Associate Dean for Research	None	None	None	None	None	None
Fatima Rodriguez	Stanford University School of Medicine—Associate Professor, Section Chief of Preventive Cardiology	RELEVANT ■ Amgen ■ Novartis NOT RELEVANT ■ HealthPals* ■ Medscape	None	NOT RELEVANT ■ Carta†	NOT RELEVANT ■ AHA ■ NIH	RELEVANT ■ AstraZeneca NOT RELEVANT ■ ACC ■ AHA ■ <i>Cardiology and Therapy</i> , Associate Editor ■ Medscape ■ <i>NEJM Journal Watch Cardiology</i> , Associate Editor ■ Novo Nordisk, CEAC*	None
Amy W. Talbot§	American Heart Association/American College of Cardiology Science and Health Advisor, Guidelines	None	None	None	None	None	None
Viviany R. Taqueti	Brigham and Women's Hospital; Harvard Medical School—Director, Cardiac Stress Laboratory	None	None	None	NOT RELEVANT ■ DOD, Warrior Trial (DSMB)	RELEVANT ■ Abbott ■ Broadview Ventures* NOT RELEVANT ■ ACC ■ Genetesis ■ NIH ■ ASNC, Board Member ■ NASEM, Committee Member, Identifying New/ Improved Diagnostic & Evaluative Techniques	None

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## APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Randal J. Thomas	Mayo Clinic—Professor, Department of Cardiovascular Medicine, Division of Preventive Cardiology	None	None	None	NOT RELEVANT ■ NHLBI† ■ NINR†	NOT RELEVANT ■ AACVPR ■ AHA ■ JRCP†	None
Sean van Diepen	University of Alberta, Edmonton, Alberta, Canada—Associate Professor, Department of Critical Care Medicine and Division of Cardiology, Department of Medicine	None	None	None	None	NOT RELEVANT ■ AHJ ■ Canadian Journal of Cardiology ■ European Heart Journal of Cardiovascular Care ■ JACC: Advances, Sr. Consulting Editor	None
Barbara Wiggins	South Carolina College of Pharmacy—Affiliate Professor Medical University of South Carolina—Clinical Pharmacy Specialist—Cardiology	NOT RELEVANT ■ LexiComp	None	None	None	NOT RELEVANT ■ ACC† ■ American Journal of Cardiovascular Drugs, Editorial Board† ■ PERT Consortium Clinical Protocols Committee† ■ scPharmaceuticals, (Salaried Employee)	None
Marlene S. Williams	Johns Hopkins Medical Institution Bayview Medical Center—Associate Professor of Medicine, Clinical Director of Cardiology Division of Cardiology, Department of Medicine	NOT RELEVANT ■ Haemonetics	NOT RELEVANT ■ National Association for Continuing Education	None	None	NOT RELEVANT ■ ABC ■ ACC† ■ AHA ■ American Journal of Cardiovascular Drugs† ■ PERT Consortium†	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. 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 ≥5% of the voting stock or share of the business entity, or ownership of ≥\$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. Please refer to <https://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.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

§Amy Talbot is an AHA/ACC joint staff member and acts as the Science and Health Advisor for the "2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease." No relevant relationships to report.

Nonvoting author or measures not included/ counted in the RWI balance for this writing committee.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AATS, American Association for Thoracic Surgery; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Clinical Pharmacy; AHA, American Heart Association; AHJ, American Heart Journal; APCA, Alliance for Physician Certification and Advancement; APHA, American Pharmacists Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; ASPC, American Society of Preventive Cardiology; CDC, US Centers for Disease Control and Prevention; CEAC, Clinical Event Adjudication Committee; CME, continuing medical education; DHHS, US Department of Health and Human Services; DOD, US Department of Defense; DSMB, data and safety monitoring board; ESC, European Society of Cardiology; FIC, Fogarty International Center; JACC, Journal of the American College of Cardiology; JAMA, Journal of the American Medical Association; JCRP, Journal of Cardiopulmonary Rehabilitation; NACCME, North American Center for Continuing Medical Education; NAMS, North American Menopause Society; NASEM, National Academies of Sciences, Engineering and Medicine; NEJM, New England Journal of Medicine; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NLA, National Lipid Association; NINR, National Institute of Nursing Research; PAK-SEHAT, joint collaboration with Getz Pharma and Tabba Heart Institute; PCNA, Preventive Cardiovascular Nurses Association; PCORI, Patient-Centered Outcomes Research Institute; PERT, Pulmonary Embolism Response Team; SCAI, Society for Cardiovascular Angiography and Interventions; UT, University of Texas, VA, Veterans Affairs; WCC, World Congress of Cardiology; and WHF, World Heart Federation.

**APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—2023 AHA/ACC/ACCP/ASPC/NLA/PCNA GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC CORONARY DISEASE**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
H. Vernon Anderson	AHA/ACC Chronic Coronary Disease Guideline Peer Review Committee Chair	The University of Texas Health Science Center at Houston	■ ACE	None	None	None	None	None
Sunil V. Rao	AHA/ACC Chronic Coronary Disease Guideline Peer Review Committee Vice Chair	New York University	None	None	None	■ NHLBI	■ NHLBI†	■ Defendant, Cardiac catheterization, 2021
Columbus Batiste II	AHA/ACC Chronic Coronary Disease Peer Review Committee	Kaiser Permanente Riverside and Moreno Valley Medical Centers	None	None	None	None	None	None
Roger Blumenthal	AHA/ACC Chronic Coronary Disease Peer Review Committee	Johns Hopkins University	None	None	None	None	None	None
Matthew A. Cavender	AHA/ACC Chronic Coronary Disease Peer Review Committee	UNC School of Medicine	■ Amgen ■ Bayer* ■ Medtronic* ■ Novo Nordisk* ■ Zoll	None	None	■ Amgen† ■ Boehringer Ingelheim* ■ CSL Behring†	■ Boston Scientific† ■ Edwards† ■ Novo Nordisk†	■ Third party, medical necessity, 2022*
Anne Carol Goldberg	AHA/ACC Chronic Coronary Disease Peer Review Committee, representing NLA	Washington University School of Medicine	■ Akcea ■ Ionis* ■ Novartis ■ Regeneron	■ ACC ■ NLA*	■ Amgen* ■ Arrowhead Pharmaceuticals* ■ Esperion* ■ Ionis* ■ New Amsterdam* ■ Novartis* ■ Regeneron* ■ Sanofi-Aventis*	■ ABIM ■ AHA† ■ Esperion† ■ Ionis, TIMI, Lead coordinator, Triglyceride study* ■ New Amsterdam, National Coordinator for Brooklyn Study* ■ NLA Foundation† ■ NLA* ■ The FH Foundation	None	None
Cynthia Jackevicius	AHA/ACC Chronic Coronary Disease Peer Review Committee, representing ACCP	Western University of Health Sciences	None	None	None	■ CIHR ■ Circulation: Cardiovascular Quality and Outcomes	■ AHA ■ Western University of Health Sciences*	None
Friederike K. Keating	AHA/ACC Chronic Coronary Disease Peer Review Committee	University of Vermont Medical Center	None	None	None	None	■ ASNC† ■ NHLBI† ■ University of Vermont Health Center†	None

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## APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Thomas S. Metkus	AHA/ACC Chronic Coronary Disease Peer Review Committee	Johns Hopkins University School of Medicine	<ul style="list-style-type: none"> <li>■ BestDoctors-Telehealth*</li> <li>■ McGraw-Hill*</li> <li>■ Nova Biomedical</li> <li>■ Oakstone-Ebix*</li> </ul>	None	None	None	None	None
Leslee J. Shaw	AHA/ACC Chronic Coronary Disease Peer Review Committee	Mount Sinai	None	None	None	None	None	None
Chloe D. Villavaso	AHA/ACC Chronic Coronary Disease Peer Review Committee, representing PCNA	Tulane University School of Medicine	<ul style="list-style-type: none"> <li>■ Amgen</li> <li>■ Novartis</li> </ul>	None	None	None	None	None
Brittany A. Zwischenberger	AHA/ACC Chronic Coronary Disease Peer Review Committee	Duke University	None	None	None	<ul style="list-style-type: none"> <li>■ DCRI†</li> <li>■ STS†</li> </ul>	None	

This table represents all reviewers' relationships 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. 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.

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ABIM indicates American Board of Internal Medicine; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Clinical Pharmacy; ACE, Accreditation for Cardiovascular Excellence; AHA, American Heart Association; ASNC, American Society of Nuclear Cardiology; ASPC, American Society of Preventive Cardiology; CIHR, Canadian Institutes of Health Research; DCRI, Duke Clinical Research Institute; FH, Family Heart; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; PCNA, Preventive Cardiovascular Nurses Association ; STS, Society of Thoracic Surgery; TIMI, Thrombolysis in Myocardial Infarction; and UNC, University of North Carolina.