2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

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This document was approved by the American College of Cardiology Board of Trustees, American Heart Association Science Advisory and Coordinating Committee, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons in July 2014.

The online-only Comprehensive Relationships Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000095/-/DC1.

The online-only Data Supplement files are available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000095/-/DC2.

The American Heart Association requests that this document be cited at follows: Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749–1767.

This article is copublished in the *Journal of the American College of Cardiology* and *Catheterization and Cardiovascular Interventions*.

(*Circulation*. 2014;130:1749-1767.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0000000000000095**

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Preamble

Keeping pace with emerging evidence is an ongoing challenge to timely development of clinical practice guidelines. In an effort to respond promptly to new evidence, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines (Task Force) has created a "focused update" process to revise the existing guideline recommendations that are affected by evolving data or opinion. New evidence is reviewed in an ongoing manner to respond quickly to important scientific and treatment trends that could have a major impact on patient outcomes and quality of care. Evidence is reviewed at least twice a year, and updates are initiated on an as-needed basis and completed as quickly as possible while maintaining the rigorous methodology that the ACC and AHA have developed during their partnership of >20 years.

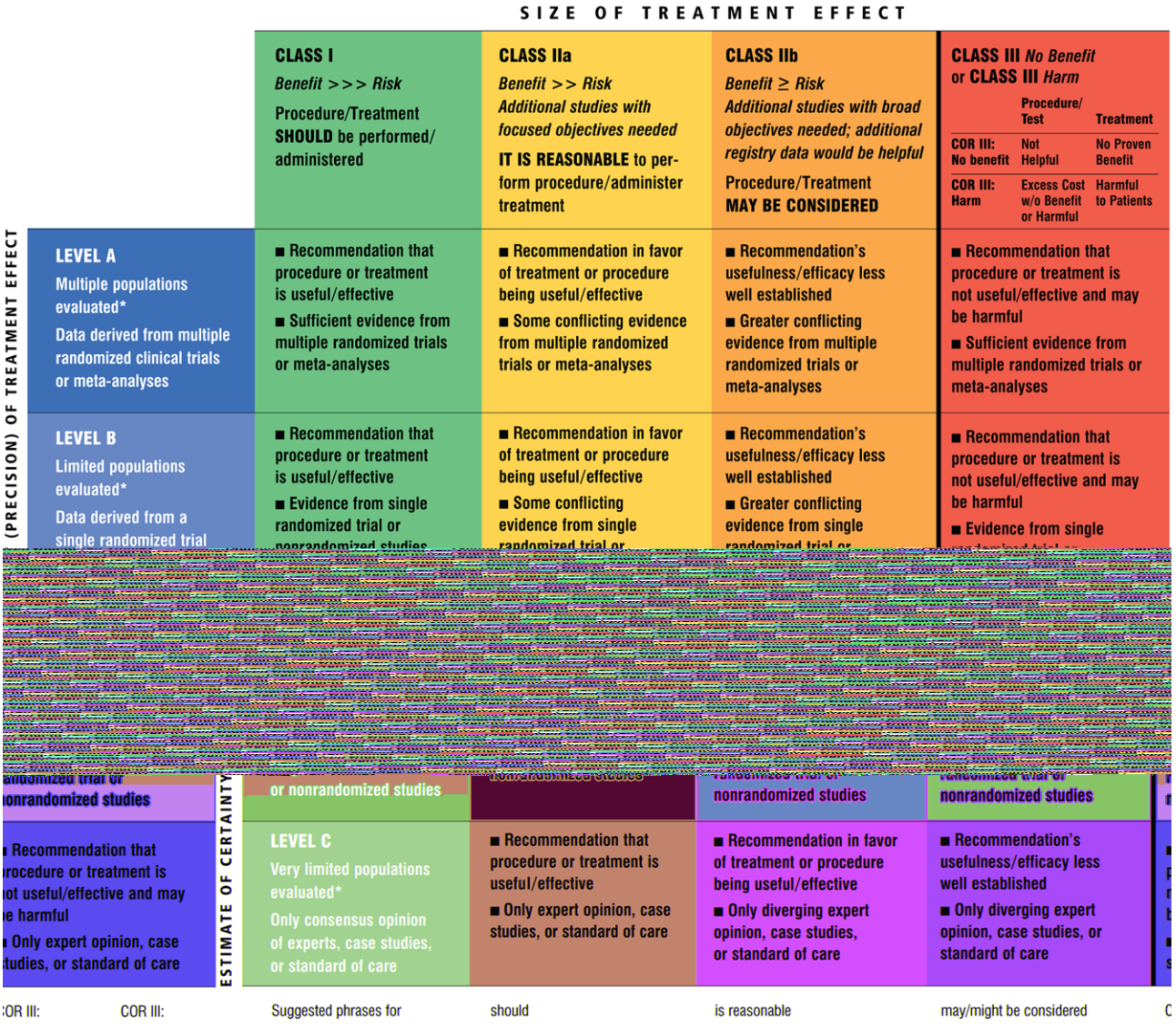
A focused update is initiated when new data that are deemed potentially important for patient care are published or presented at national and international meetings (Section 1.1, "Methodology and Evidence Review"). Through a broad-based vetting process, the studies included are identified as being important to the relevant patient population. The focused update is not intended to be based on a complete literature review from the date of the previous guideline publication but rather to include pivotal new evidence that may effect changes in current recommendations. Specific criteria or considerations for inclusion of new data include the following:

- Publication in a peer-reviewed journal;
- Large, randomized, placebo-controlled trial(s);
- Nonrandomized data deemed important on the basis of results affecting current safety and efficacy assumptions, including observational studies and meta-analyses;
- Strength/weakness of research methodology and findings;
- Likelihood of additional studies influencing current findings;
- Impact on current performance measures and/or likelihood of need to develop new performance measure(s);
- Request(s) and requirement(s) for review and update from the practice community, key stakeholders, and other sources free of industry relationships or other potential bias;
- Number of previous trials showing consistent results; and
- Need for consistency with a new guideline or guideline updates or revisions.

In analyzing the data and developing recommendations and supporting text, a writing committee uses evidence-based methodologies developed by the Task Force.[1] The Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits as well as evidence and/or agreement that a given treatment or procedure is or is not useful/effective and in some situations may cause harm. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation, with the weight of evidence ranked as LOE A, B, or C, according to specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized as appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues about which sparse data are available, a survey of current practice among the clinicians on the writing committee is the basis for LOE C recommendations, and no references are cited. The schema for COR and LOE is summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR. A new addition to this methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or is associated with "harm" to the patient. In addition, in view of the increasing number of comparative-effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another have been added for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term *guideline-directed medical therapy* (GDMT) to represent medical therapy that is strongly recommended by (primarily Class I and IIa) ACC/AHA guidelines. The term, GDMT, will be used herein. It is anticipated that what

Table 1. Applying Classification of Recommendations and Level of Evidence



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

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use. †For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

currently constitutes GDMT will evolve over time as new therapies and evidence emerge.

Because the ACC/AHA practice guidelines address patient populations (and healthcare providers) residing in North America, drugs that are currently unavailable in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, a writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and relevance to the ACC/AHA target population to determine whether the findings should inform a specific recommendation.

The ACC/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines are intended to define practices that meet the needs of most patients in most circumstances. The ultimate judgment about care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. As a result, situations may arise in which deviations from these guidelines are appropriate. In clinical decision making, consideration should be given to the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely

affect outcomes, physicians and other healthcare providers should engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks and benefits of and alternatives to a particular treatment and should be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships, professional biases, or personal interests among the members of the writing group. All writing committee members and peer reviewers of the guideline are required to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort. In December 2009, the ACC and AHA implemented a new policy for relationships with industry and other entities (RWI) that requires the writing committee chair plus a minimum of 50% of the writing committee to have no *relevant* RWI (Appendix 1 for the ACC/AHA definition of relevance). These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing committee and are updated as changes occur. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the voting members. Members are not permitted to draft or vote on any text or recommendations pertaining to their RWI. Members of this writing group, who recused themselves from voting, are indicated, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendices 1 and 2, respectively. Additionally, to ensure complete transparency, this writing group members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement. Comprehensive disclosure information for the Task Force is also available online. The work of this writing group is supported exclusively by the ACC, AHA, American Association for Thoracic Surgery (AATS), Preventive Cardiovascular Nurses Association (PCNA), Society for Cardiovascular Angiography and Interventions (SCAI), and Society of Thoracic Surgeons (STS) without commercial support. Writing group members volunteered their time for this activity.

To maintain relevance at the point of care for practicing physicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, several changes to these guidelines will be apparent, including limited narrative text and a focus on summary and evidence tables (with references linked to abstracts in PubMed).

In April 2011, the Institute of Medicine released 2 reports: *Finding What Works in Health Care: Standards for Systematic Reviews* and *Clinical Practice Guidelines We Can Trust*.[2,3] It is noteworthy that the ACC/AHA practice guidelines were cited as being compliant with many of the standards that were proposed. A thorough review of these reports and our current methodology is under way, with further enhancements anticipated.

The recommendations in this focused update are considered current until they are superseded in another focused update or the full-text guideline is revised. Guidelines are official policy of the ACC and AHA.

Jeffrey L. Anderson, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

1. Introduction

These guidelines are intended to apply to adult patients with stable known or suspected ischemic heart disease (IHD), including those with new-onset chest pain (ie, low-risk unstable angina) or stable pain syndromes. Patients who have "ischemic equivalents," such as dyspnea or arm pain with exertion, are included in the latter group. Many patients with IHD may become asymptomatic with appropriate therapy. Accordingly, the follow-up sections of this guideline pertain to patients who were previously symptomatic, including those who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). In this document, "coronary angiography" is understood to refer to invasive coronary angiography.

1.1. Methodology and Evidence Review

Late-breaking clinical trials presented at the 2012 scientific meetings of the ACC, AHA, and European Society of Cardiology, as well as other selected data reported through October, 2013, were reviewed by the 2012 stable ischemic heart disease (SIHD) guideline writing committee along with the Task Force and other experts to identify trials and other key data that might affect guideline recommendations. On the basis of the criteria and considerations noted previously (see Preamble), recently published trial data and other clinical information were considered important enough to prompt a focused update of the 2012 SIHD guideline.[4] Evidence considered for deliberation by the writing group was added to evidence tables in the Data Supplement available online, although it did not result in recommendation changes. Among the topics considered for inclusion in the focused update was the use of fractional flow reserve (FFR) for assessing intermediate coronary lesions, including newer data from the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) 2 study.[5] Although this was acknowledged to be an important new contribution to the literature, it did not alter the recommendations for FFR made in the 2012 full-text guideline.[4]

Consult the full-text version or the executive summary of the 2012 SIHD guideline for policy on clinical areas not covered by the focused update.[4,6] The individual recommendations in this focused update will be incorporated into future revisions or updates of the full-text guideline.

1.2. Organization of Committee and Relationships With Industry

For this focused update, representative members of the 2012 stable ischemic heart disease (SIHD) guideline writing committee were invited to participate, and they were joined by additional invited members to form a new writing group, referred to as the 2014 focused update writing group. Members were required to disclose all RWI relevant to the data under consideration. The writing group included representatives from the ACC, AHA, AATS, PCNA, SCAI, and STS.

1.3. Review and Approval

This document was reviewed by 5 official reviewers from the ACC and the AHA, as well as 1 reviewer each from the AATS, PCNA, SCAI, and STS; and 33 individual content

reviewers, including members of the American College of Physicians, ACC Imaging Section Leadership Council, ACC Interventional Section Leadership Council, ACC Prevention of Cardiovascular Disease Section Leadership Council, ACC Surgeons' Council, AHA Council on Clinical Cardiology, and the Association of International Governors. Reviewers' RWI information was collected and distributed to the writing group and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC, AHA, and by other partner organizations, the AATS, PCNA, SCAI, and STS.

2. Diagnosis of SIHD

2.3. Invasive Testing for Diagnosis of Coronary Artery Disease in Patients With Suspected SIHD: Recommendations (New Section)

See Online Data Supplement 1 for additional information.

Class I

1. **Coronary angiography is useful in patients with presumed SIHD who have unacceptable ischemic symptoms despite GDMT and who are amenable to, and candidates for, coronary revascularization.** ***(Level of Evidence: C)***

Class IIa

1. **Coronary angiography is reasonable to define the extent and severity of coronary artery disease (CAD) in patients with suspected SIHD whose clinical characteristics and results of noninvasive testing** ***(exclusive of stress testing)*** **indicate a high likelihood of severe IHD and who are amenable to, and candidates for, coronary revascularization.[7–12]** ***(Level of Evidence: C)***
2. **Coronary angiography is reasonable in patients with suspected symptomatic SIHD who cannot undergo diagnostic stress testing, or have indeterminate or nondiagnostic stress tests, when there is a high likelihood that the findings will result in important changes to therapy.** ***(Level of Evidence: C)***

Class IIb

1. **Coronary angiography might be considered in patients with stress test results of acceptable quality that do not suggest the presence of CAD when clinical suspicion of CAD remains high and there is a high likelihood that the findings will result in important changes to therapy.** ***(Level of Evidence: C)***

This section has been added to the 2014 SIHD focused update to fill a gap in the 2012 SIHD guideline.[4] It specifically addresses the role of coronary angiography for the diagnosis of CAD in patients with suspected SIHD.

Coronary angiography for *risk stratification* has been addressed in Section 3.3 of the 2012 SIHD full-text guideline.[4] Recommendations for use of coronary angiography in the following specific clinical circumstances have been addressed in other guidelines or statements and will not be discussed further here:

- Patients with heart failure and/or reduced ejection fraction[13]
- Patients who have experienced sudden cardiac death or sustained ventricular arrhythmia[14]
- Patients undergoing preoperative cardiovascular evaluation for noncardiac surgery (including solid organ transplantation)[15]
- Evaluation of cardiac disease among patients who are kidney or liver transplantation candidates[16,17]

Note that ACC/AHA guidelines for coronary angiography were published in 1999 but not updated, and they are now superseded by the above documents.

There are no high-quality data on which to base recommendations for performing diagnostic coronary angiography because no study has randomized patients with SIHD to either catheterization or no catheterization. Trials in patients with SIHD comparing revascularization and GDMT have, to date, all required angiography, most often after stress testing, as a prerequisite for subsequent revascularization. Additionally, the "incremental benefit" of detecting or excluding CAD by coronary angiography remains to be determined. The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial is currently randomizing patients with at least moderate ischemia on stress testing to a strategy of optimal medical therapy alone (with coronary angiography reserved for failure of medical therapy) or routine cardiac catheterization followed by revascularization (when appropriate) plus optimal medical therapy. Before randomization, however, patients with normal renal function will undergo "blinded" computed tomography (CT) angiography to exclude them if significant left main CAD or no significant CAD is present. The writing group strongly endorses the ISCHEMIA trial, which will provide contemporary, high-quality evidence about the optimal strategy for managing patients with nonleft main SIHD and moderate-to-severe ischemia.

In the majority of patients with suspected SIHD, noninvasive stress testing for diagnosis and risk stratification is the appropriate initial study. Importantly, coronary angiography is appropriate only when the information derived from the procedure will significantly influence patient management and if the risks and benefits of the procedure have been carefully considered and understood by the patient. Coronary angiography to assess coronary anatomy for revascularization is appropriate only when it is determined beforehand that the patient is amenable to, and a candidate for, percutaneous or surgical revascularization. In patients with abnormal, noninvasive stress testing for whom a diagnosis of CAD remains in doubt, many clinicians proceed to diagnostic coronary angiography. However, in some patients, multidetector CT angiography may be appropriate and safer than routine invasive angiography for this purpose. Indications and contraindications to CT angiography, including subsets of patients for whom it can be considered, are discussed in the 2010 expert consensus document on CT angiography[18] and the 2010 appropriate use criteria for cardiac CT.[19]

Although coronary angiography is considered the "gold standard" for the diagnosis of CAD, it has inherent limitations and shortcomings. Angiographic assessment of stenosis severity relies on comparison to an adjacent, nondiseased reference

segment. In diffusely diseased coronary arteries, lack of a normal reference segment may lead to underestimation of lesion severity by angiography. Multiple studies have documented significant interobserver variability in the grading of coronary artery stenosis,[20,21] with disease severity overestimated by visual assessment when coronary stenosis is ≥50%.[21,22] Although quantitative coronary angiography provides a more accurate assessment of lesion severity than does visual assessment, it is rarely used in clinical practice because it does not accurately assess the physiological significance of lesions.[23] Many stenoses considered to be severe by visual assessment of coronary angiograms (ie, ≥70% luminal narrowing) do not restrict coronary blood flow at rest or with maximal dilatation, whereas others considered to be "insignificant" (ie, <70% luminal narrowing) are hemodynamically significant.[24] Coronary angiography also cannot assess whether an atherosclerotic plaque is stable or "vulnerable" (ie, likely to rupture and cause an acute coronary syndrome).

Intravascular ultrasound and optical coherence tomography provide more precise information about the severity of stenosis and plaque morphology than does coronary angiography and, in certain cases, can be useful adjunctive tests.[9] These imaging procedures are discussed in the 2011 PCI guideline.[9] FFR can assess the hemodynamic significance of angiographically "intermediate" or "indeterminant" lesions and allows one to decide when PCI may be beneficial or safely deferred.[24,25] It has been suggested in several studies that a PCI strategy guided by FFR may be superior to a strategy guided by angiography alone.[5,24,26,27]

Invasive procedures may cause complications. Data from the ACC's National Cardiovascular Data Registry CathPCI Registry during the 2012 calendar year included a 1.5% incidence of procedural complications of diagnostic angiography. Complications in earlier reports included death, stroke, myocardial infarction (MI), bleeding, infection, contrast allergic or anaphylactoid reactions, vascular damage, contrast-induced nephropathy, arrhythmias, and need for emergency revascularization.[28–32] Complications are more likely to occur in certain patient groups, including those of advanced age (>70 years), and those with marked functional impairment (Canadian Cardiovascular Society class IV angina or New York Heart Association class IV heart failure), severe left ventricular dysfunction or CAD (particularly left main disease), severe valvular disease, severe comorbid medical conditions (eg, renal, hepatic, or pulmonary disease), bleeding disorders, or a history of an allergic reaction to radiographic contrast material.[28–32] The risk of contrast-induced nephropathy is increased in patients with renal insufficiency or diabetes mellitus.[9,33] In deciding whether angiography should be performed in these patients, these risks should be balanced against the increased likelihood of finding critical CAD. The concept of informed consent requires that risks and benefits of and alternatives to coronary angiography be explicitly discussed with the patient before the procedure is undertaken.

Despite these shortcomings and potential complications, coronary angiography is useful to a) ascertain the cause of chest pain or anginal equivalent symptoms, b) define coronary anatomy in patients with "high-risk" noninvasive stress test findings (Section 3.3 in the 2012 full-text guideline) as a requisite for revascularization, c) determine whether severe CAD may be the cause of depressed left ventricular ejection fraction, d) assess for possible ischemia-mediated ventricular arrhythmia, e) evaluate cardiovascular risk among certain recipient and donor candidates for solid-organ transplantation, and f) assess the suitability for revascularization of patients with unacceptable ischemic symptoms (ie, symptoms that are not controlled with medication and that limit activity or quality of life). Coronary angiography may also be helpful when initial stress testing is inconclusive or yields conflicting results and definitive determination of whether IHD is present will result in important changes to therapy. The exclusion of epicardial CAD in a patient with recurring chest pain or other potential ischemic symptoms is particularly useful when it leads to more appropriate treatment, including withdrawal of medications.

In a subset of patients, clinical characteristics, symptoms, and/or results of noninvasive testing alone indicating a high likelihood of multivessel or left main disease (eg, large ischemic burden) may prompt diagnostic angiography and revascularization, instead of initial stress testing. Patients with long-standing diabetes mellitus and end-organ damage, severe peripheral vascular disease (eg, abdominal aortic aneurysm), or previous chest (mantle) radiation therapy may have severe CAD—particularly when ischemic symptoms are present.[28–31] Patients with a combination of typical angina, transient heart failure, pulmonary edema, or exertional or unheralded syncope may have severe CAD. Noninvasive testing, such as rest echocardiography revealing multiple regional wall motion abnormalities or electrocardiography with diffuse ischemic changes in multiple territories, may reflect CAD with a large ischemic burden and justify diagnostic angiography without prior stress testing. The writing group has found that creating a recommendation governing the use of angiography for such high-risk patients remains controversial. The writing group recognizes, however, that many clinicians believe that prompt diagnostic angiography and revascularization, instead of initial stress testing, are appropriate for such high-risk patients who are likely to have underlying severe CAD for which revascularization would confer a survival advantage.

Coronary angiography is not routinely performed after adequate stress testing has been negative for ischemia. Still, stress tests can be falsely negative and, in a patient with high pretest likelihood of CAD, Bayes' theorem predicts that a high posttest likelihood of CAD will remain as well. Therefore, when clinicians strongly suspect that a stress test is falsely negative (eg, a patient with typical angina who also has multiple risk factors for CAD), diagnostic angiography may be warranted. When stress testing yields an ambiguous or indeterminate result in a patient with a high likelihood of CAD, coronary angiography may be preferable to another noninvasive test and may be the most effective means to reach a diagnosis.

The frequency with which coronary angiography is performed varies across geographic regions, and in some areas it may be underutilized or overutilized.[34] The optimal rate of "normal" coronary angiography in clinical practice remains undefined. In the ACC's National Cardiovascular Data Registry CathPCI Registry, approximately 45% of elective cardiac catheterizations performed at hospitals did not detect clinically significant (defined as >50% luminal diameter) stenoses,[29,35] although rates varied markedly between hospitals (ie, range, 0% to 77%).[35] Hospitals with lower rates of significant CAD at catheterization were more likely to have performed angiography on younger patients; those with no

symptoms or atypical symptoms; and those with negative, equivocal, or unperformed functional status assessment.[35] Even among those with a positive result on a noninvasive test, only 41% of patients were found to have significant CAD.[36] In a study performed within the Veterans Health Administration, 21% of patients undergoing elective catheterization had "normal" coronary arteries (defined as having no lesions ≥20%). The median proportion of normal coronary arteries was 10.8% among hospitals in the lowest quartile and 30.3% among hospitals in the highest quartile.[37] The authors concluded that factors causing variation in patient selection for coronary angiography exist in integrated non–fee-for-service health systems as well as in fee-for-service systems.

Angiographically normal or near-normal coronary arteries are more common among women, who are more likely than men to have myocardial ischemia due to microvascular disease. The relatively high proportion of patients with ischemia and no significant epicardial stenoses may indicate opportunities to improve patient selection for coronary angiography, or to consider the possibility of syndromes caused by abnormal coronary vasoreactivity. Nevertheless, the exclusion of significant epicardial CAD with a high level of confidence can be important for high-quality diagnosis and patient management, and therefore the reported frequencies of normal coronary findings should be understood within this context.[29,35–37]

4. Treatment

4.4. Guideline-Directed Medical Therapy

4.4.2. Additional Medical Therapy to Prevent MI and Death: Recommendation

4.4.2.5. Additional Therapy to Reduce Risk of MI and Death
*See Table 2 for the revised recommendation for chelation therapy and Online Data Supplement 2 for evidence supporting the recommend*ation.

4.4.2.5.4. Chelation Therapy. Chelation therapy, which consists of a series of intravenous infusions of disodium ethylene diamine tetraacetic acid (EDTA) in combination with other substances, has been touted as a putative noninvasive means of improving blood flow in atherosclerotic vessels, treating angina, and preventing cardiac events. EDTA combines with polyvalent cations, such as calcium and cadmium (a constituent of cigarette smoke that is associated with cardiovascular risk),[43,44] to form soluble complexes that can be excreted. Advocates maintain that this process can result in both regression of atherosclerotic plaques and relief of angina and that EDTA reduces oxidative stress in the vascular wall. Anecdotal reports have suggested that EDTA chelation therapy can result in relief of angina in patients with SIHD. Studies in patients with intermittent claudication and SIHD have failed to demonstrate improvements in exercise measures,[38,39] ankle-brachial index,[38,39] or digital subtraction angiograms with chelation.[40] A randomized controlled trial (RCT) examining the effect of chelation therapy on SIHD studied 84 patients with stable angina and a positive treadmill test for ischemia.[41] Those randomized to active therapy received weight-adjusted disodium EDTA chelation therapy for 3 hours per treatment, twice weekly for 15 weeks, and then once monthly for an additional 3 months. There were no differences between groups in changes in exercise time to ischemia, exercise capacity, or quality-of-life scores. The National Center of Complementary and Alternative Medicine and the National Heart, Lung, and Blood Institute conducted TACT (Trial to Assess Chelation Therapy),[42] an RCT comparing chelation with placebo in patients who had experienced MI. 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 to 0.99; P=0.035 [because of multiple comparisons, statistical significance was considered at P values ≤0.036]). No individual endpoint differed significantly between groups. Among patients with diabetes mellitus, there was a 39% reduction (hazard ratio: 0.61; 95% CI: 0.45 to 0.83) in the composite endpoint for the chelation-treated patients relative to the placebo-treated patients (P=0.02 for interaction). Despite these positive findings, the TACT investigators did not recommend the routine use of chelation therapy to reduce symptoms or cardiovascular complications for all patients with SIHD, given the modest overall benefit, high proportion of patient withdrawals (18% lost to follow-up), absence of adequate scientific basis for the therapy, and possibility of a false positive outcome. The large proportion of withdrawals was especially concerning given that 50% more patients withdrew from chelation therapy than from placebo, which raised important concerns about unmasking of treatment assignments that could have influenced key outcomes (eg, revascularization or hospitalization for angina). In addition, chelation therapy is not risk free. Disodium EDTA, particularly when infused too rapidly, may cause hypocalcemia, renal failure, and death.[45,46] Although disodium EDTA is approved by the US Food and Drug Administration for specific indications, such as iron overload and lead poisoning, it is not approved for use in preventing or treating cardiovascular disease. Accordingly, the writing group finds that the usefulness of chelation therapy in cardiac disease is highly questionable.

4.4.4. Alternative Therapies for Relief of Symptoms in Patients With Refractory Angina: Recommendation

See Table 3 for the recommendation on enhanced external counterpulsation (EECP) and Online Data Supplement 3 for evidence supporting the recommendation.

4.4.4.1. Enhanced External Counterpulsation

Although EECP was carefully reviewed in the 2012 SIHD guideline,[4] comments received after the guideline's publication prompted a re-examination of the existing literature, even though no truly new data have become available. EECP is a technique that uses inflatable cuffs wrapped around the lower extremities to increase venous return and augment diastolic blood pressure.[47] The cuffs are inflated sequentially from the calves to the thigh muscles during diastole and are deflated instantaneously during systole. The resultant diastolic augmentation increases coronary perfusion pressure, and the systolic cuff depression decreases peripheral resistance. Treatment is associated with improved left ventricular diastolic filling, peripheral flow-mediated dilation, and endothelial function. Other putative mechanisms for improvement in symptoms include recruitment of collaterals, attenuation of oxidative stress and proinflammatory cytokines,

Table 2. Recommendation for Chelation Therapy

2012 Recommendation	2014 Focused Update Recommendation	Comment
Class III: No Benefit	Class IIb	
1. Chelation therapy is not recommended with the intent of improving symptoms or reducing cardiovascular risk in patients with SIHD.[38–41] *(Level of Evidence: C)*	1. The usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with SIHD.[38–42] *(Level of Evidence: B)*	Modified recommendation (changed Class of Recommendation from III: No Benefit to IIb and Level of Evidence from C to B).

SIHD indicates stable ischemic heart disease.

promotion of angiogenesis and vasculogenesis, and a peripheral training effect.[48–51] EECP was approved by the US Food and Drug Administration in 1995 for the treatment of patients with CAD and refractory angina pectoris who fail to respond to standard revascularization procedures and aggressive pharmacotherapy. A treatment course typically consists of 35 sessions of 1 hour each, given 5 days a week. Contraindications include decompensated heart failure, severe peripheral artery disease, and severe aortic regurgitation.

The efficacy of EECP in treating stable angina pectoris has been evaluated in 2 RCTs and several observational registry studies. In MUST-EECP (Multicenter Study of Enhanced External Counterpulsation), 139 patients with angina, documented CAD, and evidence of ischemia on exercise testing were randomized to 35 hours of active counterpulsation or to inactive counterpulsation (with insufficient pressure to alter blood pressure).[47] Time to ≥1-mm ST-segment depression on stress testing increased significantly in patients treated with active counterpulsation (from 337±18 s to 379±18 s) compared with placebo (from 326±21 s to 330±20 s; P=0.01). The groups did not differ in terms of exercise duration, change in daily nitroglycerin use, or mean frequency of angina, although the percentage reduction in frequency of anginal episodes was somewhat greater among patients who received active counterpulsation. Of patients receiving EECP, 55% reported adverse events, including leg and back pain and skin abrasions, compared with 26% in the control group (relative risk: 2.13; 95% CI: 1.35 to 3.38), with approximately half of these events categorized as device related. An additional trial of EECP was conducted in 42 symptomatic patients with CAD who were randomized (2:1 ratio) to 35 hours of either EECP (n=28) or sham EECP (n=14).[51] Over the 7-week study period, average Canadian Cardiovascular Society angina class improved with EECP as compared with control (3.16±0.47 to 1.20±0.40 and 2.93±0.26 to 2.93±0.26 in EECP and sham control, respectively; P<0.001). Data from RCTs on long-term outcomes are lacking.

In a meta-analysis of 13 observational studies that tracked 949 patients, Canadian Cardiovascular Society anginal class was improved by ≥1 class in 86% of EECP-treated patients (95% CI: 82% to 90%). There was, however, a high degree of heterogeneity among the studies, which lessens confidence in the results of the meta-analysis (Q statistic P=0.008).[52] The EECP Consortium reported results from 2289 consecutive patients undergoing EECP therapy at 84 participating centers, including a subgroup of 175 patients from 7 centers who underwent radionuclide perfusion stress tests before and after therapy.[53] Treatment was associated with improved perfusion images and increased exercise duration. Similarly, the International EECP Registry reported improvement of ≥1 Canadian Cardiovascular Society angina class in 81% of patients immediately after the last EECP treatment.[54] Improvements in health-related quality of life have also been reported with EECP, but there is limited evidence with which to determine the duration of the health-related benefits of treatment.[55,56]

In general, existing data, largely from uncontrolled studies, suggest a benefit from EECP among patients with angina refractory to other therapy. Additional data from well-designed RCTs are needed to better define the role of this therapeutic strategy in patients with SIHD.[57] On the basis of this re-examination of the literature, the recommendation about EECP remains unchanged from the 2012 guideline.

5. CAD Revascularization

5.2. Revascularization to Improve Survival: Recommendations

See Table 4 for recommendations on CAD revascularization to improve survival and Online Data Supplement 4 for evidence supporting the recommendations.

5.6. CABG Versus PCI

5.6.2. CABG Versus Drug-Eluting Stents

See Online Data Supplement 5 for additional evidence table.

Although the results of 10 observational studies comparing CABG and drug-eluting stent (DES) implantation have been published,[70–79] most of these studies had short follow-up periods (12 to 24 months). In a meta-analysis of 24 268 patients with multivessel CAD treated with CABG or DES,[80] the incidences of death and MI were similar for the 2 procedures, but the frequency with which repeat revascularization was performed was roughly 4 times higher after DES implantation. Only 1 large RCT comparing CABG and DES implantation has been

Table 3. Recommendation for EECP

2012 Recommendation	2014 Focused Update Recommendation	Comment
Class IIb	Class IIb	
1. EECP may be considered for relief of refractory angina in patients with SIHD.[47] *(Level of Evidence: B)*	1. EECP may be considered for relief of refractory angina in patients with SIHD.[47] *(Level of Evidence: B)*	2012 recommendation remains current.

EECP indicates enhanced external counterpulsation and SIHD, stable ischemic heart disease.

Table 4. Recommendations for CAD Revascularization to Improve Survival

2012 Recommendation	2014 Focused Update Recommendations	Comments
Class IIa	Class I	
1. CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery.[58–65] *(Level of Evidence: B)*	1. A Heart Team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD.[66] *(Level of Evidence: C)*	New recommendation
	2. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD), particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery.[58–69] *(Level of Evidence: B)*	Modified recommendation (Class of Recommendation changed from IIa to I, wording modified, additional RCT added).

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; LAD, left anterior descending; LIMA, left internal mammary artery; PCI, percutaneous coronary intervention; and RCT, randomized controlled trial.

published. The SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial randomly assigned 1800 patients (of a total of 4337 who were screened) to receive DES or CABG.[66,81,82] Major adverse cardiac and cerebrovascular events (MACCE)—a composite of death, stroke, MI, or repeat revascularization during the 3 years after randomization—occurred in 20.2% of patients who had received CABG and 28.0% of those who had undergone DES implantation ($P<0.001$). The rates of death and stroke were not significantly different; however, MI (3.6% for CABG, 7.1% for DES) and repeat revascularization (10.7% for CABG, 19.7% for DES) were more likely to occur with DES implantation.[82] At 5 years of follow-up,[83] MACCE occurred in 26.9% of patients who had received CABG and 37.3% of those who had undergone DES implantation ($P<0.0001$). The combined endpoint of death, stroke, or MI was also lower in CABG-treated patients than in DES-treated patients (16.7% versus 20.8%; $P=0.03$).[83]

In SYNTAX, the extent of CAD was assessed using the SYNTAX score, which is based on the location, severity, and extent of coronary stenoses, with a low score indicating less complicated anatomic CAD. In post hoc analyses, a low score was defined as ≤22; intermediate, 23 to 32; and high, ≥33. The occurrence of MACCE correlated with the SYNTAX score for DES patients but not for those who had undergone CABG. At 12-month follow-up, the primary endpoint was similar for CABG and DES in those with a low SYNTAX score. In contrast, MACCE occurred more often after DES implantation than after CABG in those with an intermediate or high SYNTAX score.[66] At 3 years of follow-up, the mortality rate was greater in subjects with 3-vessel CAD treated with DES than in those treated with CABG (6.2% versus 2.9%). The differences in MACCE at 5-year follow-up between those treated with DES or CABG increased with an increasing SYNTAX score.[83]

Although the utility of the SYNTAX score in everyday clinical practice remains uncertain, it seems reasonable to conclude from SYNTAX and other data that survival rates of patients undergoing PCI or CABG with relatively uncomplicated and lesser degrees of CAD are comparable, whereas for those with complex and diffuse CAD, CABG appears to be preferable.[81–83]

5.7.2. Studies Comparing PCI and CABG for Left Main CAD

See 2012 SIHD Guideline Data Supplement (Table 8–13) for informational evidence tables.[4]

Of all patients undergoing coronary angiography, approximately 4% are found to have left main CAD,[84] >80% of whom also have significant (≥70% diameter) stenoses in other epicardial coronary arteries. In published cohort studies, it has been found that major clinical outcomes 1 year after revascularization are similar with PCI or CABG and that mortality rates are similar at 1, 2, and 5 years of follow-up; however, the risk of undergoing target-vessel revascularization is significantly higher with stenting than with CABG.

In the SYNTAX trial, 45% of screened patients with unprotected left main CAD had complex disease that prevented randomization; 89% of those underwent CABG.[66,81] In addition, 705 of the 1800 patients with unprotected left main CAD were randomized to either DES or CABG. The majority of patients with left main CAD and a low SYNTAX score had isolated left main CAD or left main CAD plus 1-vessel CAD. The majority of those with an intermediate score had left main CAD plus 2-vessel CAD, and most of those with a high SYNTAX score had left main CAD plus 3-vessel CAD. At 1 year, rates of all-cause death and MACCE were similar among patients who had undergone DES and those who had undergone CABG.[81] Repeat revascularization was performed more often in the DES group than in the CABG group (11.8% versus 6.5%), but stroke occurred more often in the CABG group (2.7% versus 0.3%). At 3 years of follow-up, the incidence of death in those undergoing left main CAD revascularization with low or intermediate SYNTAX scores (<33) was 3.7% after DES and 9.1% after CABG ($P=0.03$), whereas in those with a high SYNTAX score (≥33), the incidence of death after 3 years was 13.4% after DES and 7.6% after CABG ($P=0.10$).[81] Because the primary endpoint of the overall SYNTAX trial was not met (ie, noninferiority comparison of CABG and DES), the results of these subgroup analyses need to be applied with caution. At 5 years of follow-up, MACCE rates did not differ significantly between groups of patients with low or intermediate SYNTAX scores, but significantly more patients in the DES group with high

SYNTAX scores had MACCE than in the CABG group (46.5% versus 29.7%; *P*=0.003).[86]

In the LE MANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery) trial,[87] 105 patients with left main CAD were randomized to receive PCI or CABG. Although a low proportion of patients treated with PCI received DES (35%) and a low proportion of patients treated with CABG received internal mammary grafts (72%), the outcomes at 30 days and 1 year were similar between the groups. In the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial of 600 patients with left main disease, the composite endpoint of death, MI, or stroke at 2 years occurred in 4.4% of patients treated with DES and 4.7% of patients treated with CABG, but ischemia-driven target-vessel revascularization was required more often in the patients treated with PCI (9.0% versus 4.2%).[88]

The results from these 3 RCTs suggest (but do not definitively prove) that major clinical outcomes in *selected* patients with left main CAD are similar with CABG and PCI at 1- to 2-year follow-up but that repeat revascularization rates are higher after PCI than after CABG. RCTs with extended follow-up of ≥5 years are required to provide definitive conclusions about the optimal treatment of left main CAD; 2 such studies are under way. In a meta-analysis of 8 cohort studies and 2 RCTs,[89] death, MI, and stroke occurred with similar frequency in the PCI- and CABG-treated patients at 1, 2, and 3 years of follow-up. Target-vessel revascularization was performed more often in the PCI group at 1 year (OR: 4.36), 2 years (OR: 4.20), and 3 years (OR: 3.30).

Additional analyses using Bayesian methods, initiated by the Task Force, have affirmed the equivalence of PCI and CABG for improving survival in patients with unprotected left main CAD who are candidates for either strategy.[12] A Bayesian cross-design and network meta-analysis was applied to 12 studies (4 RCTs and 8 observational studies) comparing CABG with PCI (n=4574 patients) and to 7 studies (2 RCTs and 5 observational studies) comparing CABG with medical therapy (n=3224 patients). The ORs of death at 1 year after PCI compared with CABG did not differ among RCTs (OR: 0.99; 95% Bayesian credible interval 0.67 to 1.43), matched cohort studies (OR: 1.10; 95% Bayesian credible interval 0.76 to 1.73), and other types of cohort studies (OR: 0.93; 95% Bayesian credible interval 0.58 to 1.35). A network meta-analysis suggested that medical therapy is associated with higher risk of death at 1 year than is the use of PCI for patients with unprotected left main CAD (OR: 3.22; 95% Bayesian credible interval 1.96 to 5.30).[12] In that study, the Bayesian method generated a credible interval that has a high probability of containing the true OR. In other words, the true value for the OR has a 95% probability of lying within the interval of 0.68 to 1.45. Because the value 1 is included in the credible interval, which is also symmetrical, the results show no evidence of a difference between PCI and CABG for 1-year mortality rate. The possibility that PCI is associated with increased or decreased 1-year mortality over CABG is small (<2.5% for a possible 45% increase or for a 32% decrease, according to the definition of the 95% Bayesian credible interval).

5.12. Special Considerations

In addition to patients' coronary anatomy, left ventricular function, and history of prior revascularization, clinical features such as the existence of coexisting chronic conditions might influence decision making. However, the paucity of information about special subgroups is one of the greatest challenges in developing evidence-based guidelines applicable to large populations. As is the case for many chronic conditions, studies specifically geared toward answering clinical questions about the management of SIHD in women, older adults, and persons with chronic kidney disease are lacking. The "ACCF/AHA guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction"[90,91] address special subgroups. The present section echoes those management recommendations. Although this section will briefly review some special considerations for diagnosis and therapy in certain groups of patients, the general approach should be to apply the recommendations in this guideline consistently among groups.

5.12.3. Diabetes Mellitus

See Online Data Supplement 6 for additional evidence table.

In the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, 1900 patients with multivessel CAD were randomized to either PCI with DES or CABG.[68] The primary outcome—a composite of death, nonfatal MI, or nonfatal stroke—occurred less frequently in the CABG group (*P*=0.005), with 5-year rates of 18.7% in the CABG group and 26.6% in the DES group. The benefit of CABG was related to differences in rates of both MI (*P*<0.001) and death from any cause (*P*=0.049). Stroke was more frequent in the CABG group, with 5-year rates of 5.2% in the CABG group and 2.4% in the DES group (*P*=0.03).

Other studies have provided mixed evidence, but none has suggested a survival advantage of PCI. The 5-year update from the SYNTAX trial did not show a significant advantage in survival after CABG compared with survival after DES in patients with diabetes mellitus and multivessel CAD (12.9% versus 19.5%; *P*=0.065).[83] A meta-analysis of 4 trials showed no significant advantage in survival after CABG compared with survival after PCI for patients with diabetes mellitus (7.9% versus 12.4%; *P*=0.09).[92] In a pooled analysis, it was found that patients with diabetes mellitus assigned to CABG had improved survival (23% versus 29%; *P*=0.008 for the interaction between presence of diabetes mellitus and type of revascularization procedure after adjustment).[93]

The strongest evidence supporting the use of CABG over PCI for patients with diabetes mellitus and multivessel CAD comes from a published meta-analysis of 8 trials (including FREEDOM).[68] The study of 3131 patients showed that at 5-year or longest follow-up, patients with diabetes mellitus randomized to CABG had a lower all-cause mortality rate than did those randomized to PCI with either DES or bare metal stent (relative risk 0.67; 95% CI: 0.52 to 0.86; *P*=0.002).[94]

In summary, patients with SIHD and diabetes mellitus should receive GDMT. For patients whose symptoms compromise their quality of life, revascularization should be considered. CABG appears to be associated with lower risk of mortality than is PCI in most patients with diabetes mellitus and complex

multivessel disease, although the Heart Team may identify exceptions. To address the important issue of deciding between PCI and CABG in patients with diabetes mellitus and complex multivessel CAD, a Heart Team approach would be beneficial. This was an integral component of the FREEDOM, SYNTAX, and BARI trials[59,68,69] and is therefore emphasized in this setting. The Heart Team is a multidisciplinary team composed of an interventional cardiologist and a cardiac surgeon who jointly 1) review the patient's medical condition and coronary anatomy, 2) determine that PCI and/or CABG are technically feasible and reasonable, and, 3) discusses revascularization options with the patient before a treatment strategy is selected.

Future research may be facilitated by including a field in the National Cardiovascular Data PCI Registry and the STS database to identify cases "turned down" for the alternative revascularization strategy.

Presidents and Staff

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KEY WORDS: AHA Scientific Statements ■ cardiac catheterization ■ cardiovascular ■ chelation therapy ■ coronary angiography ■ coronary artery bypass ■ counterpulsation ■ diagnostic techniques ■ focused update ■ myocardial ischemia ■ percutaneous coronary intervention.

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Stephan D. Fihn (Chair)	Department of Veterans Affairs—Director, Office of Analytics and Business Intelligence	None	None	None	None	None	None	None
James C. Blankenship (Vice Chair)	Geisinger Medical Center—Staff Physician; Director, Cardiac Catheterization Laboratory	None	None	None	• AstraZeneca‡ • Boston Scientific‡ • Kai Pharmaceutical‡ • The Medicines Company‡ • Schering-Plough‡ • Volcano‡	None	None	2.2.5 4.4.2 4.4.4 5.2
Karen P. Alexander	Duke University Medical Center—Associate Professor of Medicine/ Cardiology	None	None	None	• Gilead	• Sanofi-aventis	None	2.2.5 4.4.2 4.4.4 5.2
John A. Bittl	Munroe Regional Medical Center—Invasive Cardiologist	None	None	None	None	None	None	None
John G. Byrne	Brigham and Women's Hospital—Chief, Division of Cardiac Surgery	None	None	None	None	None	None	None
Barbara J. Fletcher	University of North Florida—Clinical Associate Professor, School of Nursing	None	None	None	None	None	None	None
Gregg C. Fonarow	UCLA Cardiomyopathy Center—Professor of Medicine	• Boston Scientific • Johnson & Johnson • The Medicines Company • Medtronic	None	None	None	None	None	2.2.5 5.2
Richard A. Lange	University of Texas Health Science Center, San Antonio—Professor of Medicine	None	None	None	None	None	None	None
Glenn N. Levine	Baylor College of Medicine—Professor of Medicine; Director, Cardiac Care Unit	None	None	None	None	None	None	None
Thomas M. Maddox	VA Eastern Colorado Health Care System—Cardiologist	None	None	None	None	None	None	None
Srihari S. Naidu	Winthrop University Hospital—Director, Cardiac Catheterization Laboratory	None	None	None	None	None	None	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
E. Magnus Ohman	Duke Medicine—Professor of Medicine	• AstraZeneca • Bristol-Myers Squibb • Gilead Sciences† • The Medicines Company† • Merck • Sanofi-aventis	• Gilead Sciences†	None	• Daiichi-Sankyo† • Gilead Sciences†	None	None	2.2.5 4.4.2 4.4.4 5.2
Peter K. Smith	Duke University Medical Center—Professor of Surgery; Chief, Thoracic Surgery	None	None	None	None	None	None	None

This table represents the relationships of writing group members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing group during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

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

*Writing group members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply. Section numbers pertain to those in the full-text guideline.

†Significant relationship.

‡No financial benefit.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; AHA, American Heart Association; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and VA, Veterans Affairs.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Personal Research	Institutional, Organizational, or Other Financial Benefit
Judith S. Hochman	Official Reviewer—ACC/AHA Task Force on Practice Guidelines	New York University School of Medicine—Clinical Chief of Cardiology	None	None	• NIH (PI– ISCHEMIA trial)*	None
Bruce W. Lytle	Official Reviewer—AHA	Cleveland Clinic Foundation—Chairman, Thoracic and Cardiovascular Surgery	None	None	None	None
Margo B. Minissian	Official Reviewer—ACC Board of Governors	Cedar-Sinai's Heart Institute—Cardiology Nurse Practitioner; University of California Los Angeles—Assistant Clinical Professor	None	None	None	• Gilead Sciences*
C. Michael Valentine	Official Reviewer—ACC Board of Trustees	Centra Lynchburg General Hospital—Director, Cardiac Progressive Care Unit; Centra Stroobants Heart Center—Director of Clinical Quality	None	None	None	None
Lani M. Zimmerman	Official Reviewer—AHA	University of Nebraska Medical Center— Professor, College of Nursing	None	None	None	None
Robert S.D. Higgins	Organizational Reviewer—STS	Ohio State University—Director, Division of Cardiac Surgery	None	None	None	None
Ajay J. Kirtane	Organizational Reviewer—SCAI	Columbia University Medical Center—Chief Academic Officer; Director, Interventional Cardiology Fellowship Program; and Assistant Professor of Clinical Medicine	None	• Boston Scientific*	• Medtronic*	None
Joseph D. Schmoker	Organizational Reviewer—AATS	University of Vermont—Associate Professor of Surgery and Medicine; Fletcher Allen Health Care—Director of the Center for Thoracic Aortic Disease	None	None	None	None
Joanna D. Sikkema	Organizational Reviewer—PCNA	University of Miami—Adult Nurse Practitioner, School of Nursing and Health Studies	None	None	None	None
Nancy M. Albert	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Cleveland Clinic Foundation—Senior Director of Nursing and Research	None	None	None	None
Mohamed A. Sobhy Aly	Content Reviewer—AIG	Alexandria University—Professor of Cardiology, Head of Cardiology Department	None	None	None	None
Jeffrey L. Anderson	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Intermountain Medical Center—Associate Chief of Cardiology	• Sanofi-aventis	None	None	None

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Appendix 2. Continued

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Personal Research	Institutional, Organizational, or Other Financial Benefit
Eric R. Bates	Content Reviewer	University of Michigan Health System— Professor, Department of Internal Medicine	• AstraZeneca • Bristol-Myers Squibb • Daiichi-Sankyo • Merck • Sanofi-aventis	None	None	None
Ralph G. Brindis	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	University of California San Francisco—Clinical Professor of Medicine, Department of Medicine and Philip R. Lee Institute for Health Policy Studies	None	None	None	None
Biykem Bozkurt	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Michael E. DeBakey VA Medical Center—Chief, Cardiology Section; The Mary and Gordon Cain Chair and Professor of Medicine; Director, Winters Center for Heart Failure Research	None	None	None	None
Steven M. Bradley	Content Reviewer	VA Eastern Colorado Health Care System—Physician	None	None	None	None
James A. Burke	Content Reviewer—ACC Interventional Scientific Council	Lehigh Valley Heart Specialists—Cardiovascular Disease Doctor	None	None	None	None
John H. Calhoon	Content Reviewer	University of Texas Health Science Center—Professor; Chair, CT Surgery Department	None	None	None	None
Lesley Curtis	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Duke University School of Medicine—Associate Professor of Medicine	None	None	• GE Healthcare* • Johnson & Johnson*	None
Prakash C. Deedwania	Content Reviewer	University of California San Francisco—Chief of Cardiology	• Gilead Sciences†	None	None	None
Gregory J. Dehmer	Content Reviewer	Scott & White Healthcare—Director, Division of Cardiology; Texas A&M Health Science Center College of Medicine—Professor of Medicine	None	None	None	None
Linda D. Gillam	Content Reviewer—ACC Imaging Council	Morristown Medical Center—Professor of Cardiology; Vice Chair, Cardiovascular Medicine	None	None	• Edwards Lifesciences†	• Edwards Lifesciences†
Christopher B. Granger	Content Reviewer—AHA	Duke Clinical Research Institute—Associate Professor of Medicine; Director, Cardiac Care Unit	• AstraZeneca • Bristol-Myers Squibb •Daiichi-Sankyo • Eli Lilly • The Medicines Company	None	• Bristol-Myers Squibb* • Medtronic* • Merck* • Sanofi- aventis* • The Medicines Company*	• GE Healthcare* • Medtronic* • Philips Medical*

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Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Personal Research	Institutional, Organizational, or Other Financial Benefit
Robert A. Guyton	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Emory University School of Medicine—Professor of Surgery and Chief, Division of Cardiothoracic Surgery	• Medtronic	None	None	None
Jonathan L. Halperin	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Mt. Sinai Medical Center—Professor of Medicine	• AstraZeneca • Boston Scientific • Bristol-Myers Squibb • Daiichi-Sankyo • Johnson & Johnson • Medtronic • Sanofi-aventis*	None	None	None
Mark A. Hlatky	Content Reviewer	Stanford University School of Medicine—Professor of Health Research and Policy	• Blue Cross/Blue Shield • Gilead Sciences • HeartFlow*	None	None	None
Lloyd W. Klein	Content Reviewer	Rush University Medical Center—Professor, Internal Medicine	None	None	None	None
Richard J. Kovacs	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Krannert Institute of Cardiology—Professor of Clinical Medicine	None	None	None	• Cook Medical* • Eli Lilly
Stephen J. Lahey	Content Reviewer	University of Connecticut Health Center—Professor; Chief of Cardiothoracic Surgery	None	None	None	None
Michael J. Mack	Content Reviewer	Baylor Health Care System—Director	None	None	• Edwards Lifesciences†	None
Daniel B. Mark	Content Reviewer	Duke Clinical Research Institute—Professor of Medicine	None	None	• AstraZeneca† • Eli Lilly* • Gilead Sciences • Medtronic*	• Eli Lilly* • Medtronic*
David J. Maron	Content Reviewer	Vanderbilt University Medical Center—Director, Vanderbilt Chest Pain Center	None	None	• AstraZeneca* • Gilead Sciences* • Merck*	None
Hani K. Najm	Content Reviewer—ACC Surgeons' Scientific Council	National Guard Health Affairs—President, Saudi Heart Association	None	None	None	None
L. Kristin Newby	Content Reviewer	Duke University Medical Center—Associate Professor, Clinical Medicine	• AstraZeneca • Daiichi-Sankyo • Johnson & Johnson • Philips Medical • WebMD	None	• Amylin • Eli Lilly	• Bristol-Myers Squibb* • Merck*
Patrick T. O'Gara	Content Reviewer	Brigham and Women's Hospital—Director, Clinical Cardiology; Harvard Medical School—Professor of Medicine	None	None	None	• Lantheus Medical

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Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Personal Research	Institutional, Organizational, or Other Financial Benefit
Joseph F. Sabik	Content Reviewer—ACC Surgeons' Scientific Council	Cleveland Clinic—Department Chair, Thoracic and Cardiovascular Surgery	• Edwards Lifesciences • Medtronic	None	• Abbott Laboratories† • Edwards Lifesciences†	None
Vikas Saini	Content Reviewer	The Lown Institute—President	None	None	None	None
Frank W. Sellke	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Brown Medical School and Lifespan—Chief of Cardiothoracic Surgery	None	None	• The Medicines Company	None
William S. Weintraub	Content Reviewer	Christiana Care Health System—Section Chief, Cardiology	• Bristol-Myers Squibb • Daiichi-Sankyo • Eli Lilly	None	None	None
Christopher J. White	Content Reviewer	Ochsner Health System—Director, John Ochsner Heart and Vascular Institute	None	None	None	• St. Jude Medical (DSMB)
Sankey V. Williams	Content Reviewer—ACP	University of Pennsylvania Health System—Professor of General Medicine	None	None	None	None
Poh Shuan Daniel Yeo	Content Reviewer—AIG	Tan Tock Seng Hospital, Department of Cardiology—Cardiologist	None	None	None	• Boston Scientific† • Merck† • Schering-Plough†

No reviewer had a relevant ownership, partnership, or principal position to report. No reviewer reported acting as an expert witness in a relevant matter.

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*Significant relationship.

†No financial benefit.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ACP, American College of Physicians; AHA, American Heart Association; AIG, Association of International Governors; DSMB, Data Safety Monitoring Board; ISCHEMIA trial, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches trial; PCNA, Preventive Cardiovascular Nurses Association; PI, principle investigator; SCAI, Society for Cardiovascular Angiography and Interventions; and STS, Society of Thoracic Surgeons.