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

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**WRITING GROUP MEMBERS***

Stephan D. Fihn, MD, MPH, *Chair*†
James C. Blankenship, MD, MACC, *Vice Chair**†
Karen P. Alexander, MD, FACC*†
John A. Bittl, MD, FACC†
John G. Byrne, MD, FACC‡
Barbara J. Fletcher, RN, MN, FAAN§
Gregg C. Fonarow, MD, FACC, FAHA*‖
Richard A. Lange, MD, FACC†
Glenn N. Levine, MD, FACC†
Thomas M. Maddox, MD, MSc, FACC†
Srihari S. Naidu, MD, FACC, FAHA¶
E. Magnus Ohman, MD, FACC*#
Peter K. Smith, MD, FACC**

**ACC/AHA TASK FORCE MEMBERS**

Jeffrey L. Anderson, MD, FACC, FAHA, *Chair*
Jonathan L. Halperin, MD, FACC, FAHA, *Chair-Elect*
Nancy M. Albert, PhD, CCNS, CCRN, FAHA
Biykem Bozkurt, MD, PhD, FACC, FAHA
Ralph G. Brindis, MD, MPH, MACC
Lesley H. Curtis, PhD, FAHA
David DeMets, PhD††
Robert A. Guyton, MD, FACC††
Judith S. Hochman, MD, FACC, FAHA††
Richard J. Kovacs, MD, FACC, FAHA
E. Magnus Ohman, MD, FACC
Susan J. Pressler, PhD, RN, FAHA
Frank W. Sellke, MD, FACC, FAHA
Win-Kuang Shen, MD, FACC, FAHA

*Writing group members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information.
†ACC/AHA Representative.
‡American Association for Thoracic Surgery Representative.
§Preventive Cardiovascular Nurses Association Representative.
‖ACC/AHA Task Force on Performance Measures Liaison.
¶Society for Cardiovascular Angiography and Interventions Representative.
#ACC/AHA Task Force on Practice Guidelines Liaison.
**Society of Thoracic Surgeons Representative.
††Former Task Force member; current member during the writing effort.

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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 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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000095/-/DC1). Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. 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*

**Table 1. Applying Classification of Recommendations and Level of Evidence**

SIZE OF TREATMENT EFFECT

| ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT | CLASS I<br>*Benefit >>> Risk*<br>Procedure/Treatment **SHOULD** be performed/ administered | CLASS IIa<br>*Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br>**IT IS REASONABLE** to perform procedure/administer treatment | CLASS IIb<br>*Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; additional registry data would be helpful*<br>Procedure/Treatment **MAY BE CONSIDERED** | CLASS III *No Benefit* or CLASS III *Harm*<br>Procedure/ Test / Treatment<br>COR III: No benefit — Not Helpful — No Proven Benefit<br>COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients |
|---|---|---|---|---|
| **LEVEL A**<br>Multiple populations evaluated*<br>Data derived from multiple randomized clinical trials or meta-analyses | ■ Recommendation that procedure or treatment is useful/effective<br>■ Sufficient evidence from multiple randomized trials or meta-analyses | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Sufficient evidence from multiple randomized trials or meta-analyses |
| **LEVEL B**<br>Limited populations evaluated*<br>Data derived from a single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is useful/effective<br>■ Evidence from single randomized trial or nonrandomized studies | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Evidence from single randomized trial or nonrandomized studies |
| **LEVEL C**<br>Very limited populations evaluated*<br>Only consensus opinion of experts, case studies, or standard of care | ■ Recommendation that procedure or treatment is useful/effective<br>■ Only expert opinion, case studies, or standard of care | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation's usefulness/efficacy less well established<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Only expert opinion, case studies, or standard of care |
| Suggested phrases for writing recommendations | should<br>is recommended<br>is indicated<br>is useful/effective/beneficial | is reasonable<br>can be useful/effective/beneficial<br>is probably recommended or indicated | may/might be considered<br>may/might be reasonable<br>usefulness/effectiveness is unknown/unclear/uncertain or not well established | COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective<br>COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other |
| Comparative effectiveness phrases† | treatment/strategy A is recommended/indicated in preference to treatment B<br>treatment A should be chosen over treatment B | treatment/strategy A is probably recommended/indicated in preference to treatment B<br>it is reasonable to choose treatment A over treatment B | | |

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.

## 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 (i.e., 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 at (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000095/-/DC2), 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 (i.e., ≥70% luminal narrowing) do not restrict coronary blood flow at rest or with maximal dilatation, whereas others considered to be "insignificant" (i.e., <70% luminal narrowing) are hemodynamically significant (24). Coronary angiography also cannot assess whether an atherosclerotic plaque is stable or "vulnerable" (i.e., 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 (e.g., 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 (i.e., 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 (e.g., 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 (e.g., 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 post-test likelihood of CAD will remain as well. Therefore, when clinicians strongly suspect that a stress test is falsely negative (e.g., 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 (i.e., 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 recommendation.*

**Table 2. Recommendation for Chelation Therapy**

| 2012 Recommendation | 2014 Focused Update Recommendation | Comment |
|---|---|---|
| Class III: No Benefit<br><br>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)* | Class IIb<br><br>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.

#### 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 effectiveness 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 (e.g., 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 U.S. 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.*

**Table 3. Recommendation for EECP**

| 2012 Recommendation | 2014 Focused Update Recommendation | Comment |
|---|---|---|
| Class IIb<br><br>1. EECP may be considered for relief of refractory angina in patients with SIHD (47). (*Level of Evidence: B*) | Class IIb<br><br>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.

#### *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, promotion of angiogenesis and vasculogenesis, and a peripheral training effect (48-51). EECP was approved by the U.S. 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 2,289 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.*

**Table 4. Recommendations for CAD Revascularization to Improve Survival**

| 2012 Recommendation | 2014 Focused Update Recommendations | Comments |
|---|---|---|
| | Class I | |
| | 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 |
| Class IIa | | |
| 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)* | 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 (58,61-65,67-69). *(Level of Evidence: B)* | Modified recommendation (changed Class of Recommendation 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.

## 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 published. The SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial randomly assigned 1,800 patients (of a total of 4,337 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 by 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 (81,85). In addition, 705 of the 1,800 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 (i.e., 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 significantly differ 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=4,574 patients) and to 7 studies (2 RCTs and 5 observational studies) comparing CABG with medical therapy (n=3,224 patients). The ORs of death at 1year 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, 1,900 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 3,131 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 (67,68,83) 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



**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‡<br>• Boston Scientific‡<br>• Kai Pharmaceutical‡<br>• The Medicines Company‡<br>• Schering-Plough‡<br>• Volcano‡ | None | None | 2.2.5<br>4.4.2<br>4.4.4<br>5.2 |
| Karen P. Alexander | Duke University Medical Center—Associate Professor of Medicine/Cardiology | None | None | None | • Gilead | • Sanofi-aventis | None | 2.2.5<br>4.4.2<br>4.4.4<br>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 |

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|---|---|---|---|---|---|---|---|---|
| Gregg C. Fonarow | UCLA Cardiomyopathy Center—Professor of Medicine | • Boston Scientific<br>• Johnson & Johnson<br>• The Medicines Company<br>• Medtronic | None | None | None | None | None | 2.2.5<br>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 |
| E. Magnus Ohman | Duke Medicine—Professor of Medicine | • AstraZeneca<br>• Bristol-Myers Squibb<br>• Gilead Sciences†<br>• The Medicines Company†<br>• Merck<br>• Sanofi-aventis | • Gilead Sciences† | None | • Daiichi-Sankyo†<br>• Gilead Sciences† | None | None | 2.2.5<br>4.4.2<br>4.4.4<br>5.2 |
| Peter K. Smith | Duke University Medical Center—Professor of Surgery; Chief, Thoracic Surgery | None | None | None | None | None | None | None |

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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 | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|---|
| Judith S. Hochman | Official Reviewer—ACC/AHA Task Force on Practice Guidelines | New York University School of Medicine—Clinical Chief of Cardiology | None | None | None | • NIH (PI–ISCHEMIA trial)* | None | None |
| Bruce W. Lytle | Official Reviewer—AHA | Cleveland Clinic Foundation—Chairman, Thoracic and Cardiovascular Surgery | None | None | 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 | None | • Gilead Sciences* | None |
| 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 | None | None |
| Lani M. Zimmerman | Official Reviewer—AHA | University of Nebraska Medical Center—Professor, College of Nursing | None | None | None | None | None | None |
| Robert S.D. Higgins | Organizational Reviewer—STS | Ohio State University—Director, Division of Cardiac Surgery | None | None | None | None | None | None |

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|---|---|---|---|---|---|---|---|---|
| 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* | None | • Medtronic* | None | 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 | None | None |
| Joanna D. Sikkema | Organizational Reviewer—PCNA | University of Miami—Adult Nurse Practitioner, School of Nursing and Health Studies | None | None | 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 | None | None |
| Mohamed A. Sobhy Aly | Content Reviewer—AIG | Alexandria University—Professor of Cardiology, Head of Cardiology Department | None | None | 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 | None | None |
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|---|---|---|---|---|---|---|---|---|
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| 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 | None | None |
| Steven M. Bradley | Content Reviewer | VA Eastern Colorado Health Care System—Physician | None | None | None | None | None | None |
| James A. Burke | Content Reviewer—ACC Interventional Scientific Council | Lehigh Valley Heart Specialists—Cardiovascular Disease Doctor | None | None | None | None | None | None |
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| Lesley Curtis | Content Reviewer—ACC/AHA Task Force on Practice Guidelines | Duke University School of Medicine—Associate Professor of Medicine | None | None | None | • GE Healthcare*<br>• Johnson & Johnson* | None | None |
| Prakash C. Deedwania | Content Reviewer | University of California San Francisco—Chief of Cardiology | • Gilead Sciences† | None | None | 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 | None | None |

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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.

## References

1. American College of Cardiology/American Heart Association: Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf. Accessed April 29, 2014.
2. Institute of Medicine (U.S.). Finding What Works in Health Care: Standards for Systematic Reviews. Washington, D.C.: National Academies Press, 2011.
3. Institute of Medicine (U.S.). Committee on Standards for Developing Trustworthy Clinical Practice Guidelines: *Clinical Practice Guidelines We Can Trust*. Washington, D.C.: National Academies Press, 2011.
4. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-471.
5. de Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve--guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991-1001.
6. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:3097-137.
7. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease. Selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. Circulation. 1979;59:421-30.
8. Mark DB, Hlatky MA, Harrell Jr. FE, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med. 1987;106:793-800.
9. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:e574-651.
10. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e652-735.
11. Patel MR, Bailey SR, Bonow RO, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;59:1995-2027.
12. Bittl JA, He Y, Jacobs AK, et al. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. Circulation. 2013;127:2177-85.
13. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240–327.
14. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). Circulation. 2006;114:1088-132.

15. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society for Vascular Medicine. Circulation. 2014; in press
16. Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2012;126:617–63.
17. Raval Z, Harinstein ME, Skaro AI, et al. Cardiovascular risk assessment of the liver transplant candidate. J Am Coll Cardiol. 2011;58:223-31.
18. Mark DB, Berman DS, Budoff MJ, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Circulation. 2010;121:2509–43.
19. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. Circulation. 2010;122:e525-55.
20. Leape LL, Park RE, Bashore TM, et al. Effect of variability in the interpretation of coronary angiograms on the appropriateness of use of coronary revascularization procedures. Am Heart J. 2000;139:106-13.
21. Fleming RM, Kirkeeide RL, Smalling RW, et al. Patterns in visual interpretation of coronary arteriograms as detected by quantitative coronary arteriography. J Am Coll Cardiol. 1991;18:945-51.
22. Nallamothu BK, Spertus JA, Lansky AJ, et al. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. Circulation. 2013;127:1793-800.
23. Anderson RD, Pepine CJ. Coronary angiography: is it time to reassess? Circulation. 2013;127:1760-2.
24. Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. J Am Coll Cardiol. 2010;55:173-85.
25. Bech GJ, de Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation. 2001;103:2928-34.
26. Tonino PAL, de Bruyne B., Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360:213-24.
27. Pijls NHJ, Fearon WF, Tonino PAL, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol. 2010;56:177-84.
28. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Circulation. 1999;99:2345-57.
29. Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. J Am Coll Cardiol. 2012;60:2017-31.
30. Batyraliev T, Ayalp MR, Sercelik A, et al. Complications of cardiac catheterization: a single-center study. Angiology. 2005;56:75-80.
31. Chandrasekar B, Doucet S, Bilodeau L, et al. Complications of cardiac catheterization in the current era: a single-center experience. Catheter Cardiovasc Interv. 2001;52:289-95.
32. West R, Ellis G, Brooks N, et al. Complications of diagnostic cardiac catheterisation: results from a confidential inquiry into cardiac catheter complications. Heart. 2006;92:810-4.
33. Levine GN, Kern MJ, Berger PB, et al. Management of patients undergoing percutaneous coronary revascularization. Ann Intern Med. 2003;139:123-36.
34. Ko DT, Wang Y, Alter DA, et al. Regional variation in cardiac catheterization appropriateness and baseline risk after acute myocardial infarction. J Am Coll Cardiol. 2008;51:716-23.
35. Douglas PS, Patel MR, Bailey SR, et al. Hospital variability in the rate of finding obstructive coronary artery disease at elective, diagnostic coronary angiography. J Am Coll Cardiol. 2011;58:801-9.
36. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010;362:886-95.

37. Bradley SM, Maddox TM, Stanislawski MA, et al. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insights from the VA CART Program (Veterans Affairs Clinical Assessment Reporting and Tracking). J Am Coll Cardiol. 2014;63:417-26.
38. Guldager B, Jelnes R, Jørgensen SJ, et al. EDTA treatment of intermittent claudication–a double-blind, placebo-controlled study. J Intern Med. 1992;231:261-7.
39. van Rij AM, Solomon C, Packer SG, et al. Chelation therapy for intermittent claudication. A double-blind, randomized, controlled trial. Circulation. 1994;90:1194-9.
40. Sloth-Nielsen J, Guldager B, Mouritzen C, et al. Arteriographic findings in EDTA chelation therapy on peripheral arteriosclerosis. Am J Surg. 1991;162:122-5.
41. Knudtson ML, Wyse DG, Galbraith PD, et al. Chelation therapy for ischemic heart disease: a randomized controlled trial. JAMA. 2002;287:481-6.
42. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. JAMA. 2013;309:1241-50.
43. Tellez-Plaza M, Guallar E, Howard BV, et al. Cadmium exposure and incident cardiovascular disease. Epidemiology. 2013;24:421-9.
44. Xun P, Liu K, Morris S, et al. Association of toenail cadmium levels with measures of sub-clinical atherosclerosis: The Coronary Artery Risk Development in Young Adults (CARDIA) Trace Element Study. In: Abstracts From the Epidemiology and Prevention/Physical Activity, Nutrition and Metabolism 2012 Scientific Sessions. Circulation. 2012;125 (10 suppl): Abstract P301.
45. Centers for Disease Control and Prevention (CDC). Deaths associated with hypocalcemia from chelation therapy–Texas, Pennsylvania, and Oregon, 2003-2005. MMWR Morb Mortal Wkly Rep. 2006;55:204-7.
46. Howland MA. Edetate calcium disodium ($CaNa_2EDTA$). In Nelson, L, Goldfrank, LR, eds. Goldfrank's Toxicologic Emergencies. New York: McGraw-Hill Medical; 2011:1290-3.
47. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol. 1999;33:1833-40.
48. Akhtar M, Wu GF, Du ZM, et al. Effect of external counterpulsation on plasma nitric oxide and endothelin-1 levels. Am J Cardiol. 2006;98:28-30.
49. Shechter M, Matetzky S, Feinberg MS, et al. External counterpulsation therapy improves endothelial function in patients with refractory angina pectoris. J Am Coll Cardiol. 2003;42:2090-5.
50. Urano H, Ikeda H, Ueno T, et al. Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. J Am Coll Cardiol. 2001;37:93-9.
51. Braith RW, Conti CR, Nichols WW, et al. Enhanced external counterpulsation improves peripheral artery flow-mediated dilation in patients with chronic angina: a randomized sham-controlled study. Circulation. 2010;122:1612-20.
52. Shah SA, Shapiro RJ, Mehta R, et al. Impact of enhanced external counterpulsation on Canadian Cardiovascular Society angina class in patients with chronic stable angina: a meta-analysis. Pharmacotherapy. 2010;30:639-45.
53. Stys TP, Lawson WE, Hui JCK, et al. Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. Am J Cardiol. 2002;89:822-4.
54. Barsness G, Feldman AM, Holmes DRJ, et al. The International EECP Patient Registry (IEPR): design, methods, baseline characteristics, and acute results. Clin Cardiol. 2001;24:435-42.
55. Wu E, Mårtensson J, Broström A. Enhanced external counterpulsation in patients with refractory angina pectoris: a pilot study with six months follow-up regarding physical capacity and health-related quality of life. Eur J Cardiovasc Nurs. 2013;12:437-45.
56. McKenna C, McDaid C, Suekarran S, et al. Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis. Health Technol Assess. 2009;13:iii-iv, ix-xi, 1-90.
57. Amin F, Al Hajeri A., Civelek B, et al. Enhanced external counterpulsation for chronic angina pectoris. Cochrane Database Syst Rev. 2010;CD007219.
58. Sorajja P, Chareonthaitawee P, Rajagopalan N, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. Circulation. 2005;112:I311-6.
59. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 1997;96:1761-9.
60. Banning AP, Westaby S, Morice MC, et al. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. J Am Coll Cardiol. 2010;55:1067-75.
61. Hoffman SN, TenBrook JA, Wolf MP, et al. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. J Am Coll Cardiol. 2003;41:1293-304.

62. Hueb W, Lopes NH, Gersh BJ, et al. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation. 2007;115:1082-9.
63. Malenka DJ, Leavitt BJ, Hearne MJ, et al. Comparing long-term survival of patients with multivessel coronary disease after CABG or PCI: analysis of BARI-like patients in northern New England. Circulation. 2005;112:I371-6.
64. Niles NW, McGrath PD, Malenka D, et al. Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary revascularization: results of a large regional prospective study. Northern New England Cardiovascular Disease Study Group. J Am Coll Cardiol. 2001;37:1008-15.
65. Weintraub WS, Stein B, Kosinski A, et al. Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. J Am Coll Cardiol. 1998;31:10-9.
66. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360:961-72.
67. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 1997;96:1761-9.
68. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med. 2012;367:2375-84.
69. Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med. 2005;352:2174-83.
70. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med. 2008;358:331-41.
71. Briguori C, Condorelli G, Airoldi F, et al. Comparison of coronary drug-eluting stents versus coronary artery bypass grafting in patients with diabetes mellitus. Am J Cardiol. 2007;99:779-84.
72. Javaid A, Steinberg DH, Buch AN, et al. Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with drug-eluting stents for patients with multivessel coronary artery disease. Circulation. 2007;116:I200-6.
73. Lee MS, Jamal F, Kedia G, et al. Comparison of bypass surgery with drug-eluting stents for diabetic patients with multivessel disease. Int J Cardiol. 2007;123:34-42.
74. Park DW, Yun SC, Lee SW, et al. Long-term mortality after percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass surgery for the treatment of multivessel coronary artery disease. Circulation. 2008;117:2079-86.
75. Tarantini G, Ramondo A, Napodano M, et al. PCI versus CABG for multivessel coronary disease in diabetics. Catheter Cardiovasc Interv. 2009;73:50-8.
76. Varani E, Balducelli M, Vecchi G, et al. Comparison of multiple drug-eluting stent percutaneous coronary intervention and surgical revascularization in patients with multivessel coronary artery disease: one-year clinical results and total treatment costs. J Invasive Cardiol. 2007;19:469-75.
77. Yang JH, Gwon HC, Cho SJ, et al. Comparison of coronary artery bypass grafting with drug-eluting stent implantation for the treatment of multivessel coronary artery disease. Ann Thorac Surg. 2008;85:65-70.
78. Yang ZK, Shen WF, Zhang RY, et al. Coronary artery bypass surgery versus percutaneous coronary intervention with drug-eluting stent implantation in patients with multivessel coronary disease. J Interv Cardiol. 2007;20:10-6.
79. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al. Comparative effectiveness of revascularization strategies. N Engl J Med. 2012;366:1467-76.
80. Benedetto U, Melina G, Angeloni E, et al. Coronary artery bypass grafting versus drug-eluting stents in multivessel coronary disease. A meta-analysis on 24,268 patients. Eur J Cardiothorac Surg. 2009;36:611-5.
81. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2010;121:2645-53.
82. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J. 2011;32:2125-34.
83. Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg. 2013;43:1006-13.
84. Ragosta M, Dee S, Sarembock IJ, et al. Prevalence of unfavorable angiographic characteristics for percutaneous intervention in patients with unprotected left main coronary artery disease. Catheter Cardiovasc Interv. 2006;68:357-62.
85. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360:961-72.

86. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet. 2013;381:629-38.
87. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol. 2008;51:538-45.
88. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med. 2011;364:1718-27.
89. Naik H, White AJ, Chakravarty T, et al. A meta-analysis of 3,773 patients treated with percutaneous coronary intervention or surgery for unprotected left main coronary artery stenosis. JACC Cardiovasc Interv. 2009;2:739-47.
90. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2012;126:875–910.
91. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e663–828.
92. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation. 2008;118:1146-54.
93. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet. 2009;373:1190-7.
94. Verma S, Farkouh ME, Yanagawa B. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. The Lancet Diabetes & Endocrinology. 2013;1:317-28.

**2014 ACC/AHA/AATS/PCNA/SCAI/STS FOCUSED UPDATE OF THE GUIDELINE FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH STABLE ISCHEMIC HEART DISEASE—ONLINE AUTHOR LISTING OF RELATIONSHIPS WITH INDUSTRY AND OTHERS (COMPREHENSIVE; APRIL 2013)**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership / Principal | Personal Research | Institutional, Organizational or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Stephan D. Fihn, *Chair* | VA Puget Sound—Director, Office of Analytics and Business Intelligence | None | None | None | None | None | None |
| James C. Blankenship, *Vice Chair* | Geisinger Medical Center—Staff Physician; Director, Cardiac Catheterization Laboratory | None | None | None | • The Medicines Company<br>• Volcano<br>• Boston Scientific<br>• Schering-Plough<br>• AstraZeneca<br>• Kai Pharmaceutical<br>• Abiomed<br>• Novartis | None | None |
| E. Magnus Ohman | Duke Medicine—Professor of Medicine | • Janssen Pharmaceuticals*<br>• Sanofi Aventis<br>• Bristol-Myers Squibb<br>• Liposcience<br>• Pozen<br>• Roche<br>• Merck<br>• Boehringer Ingelheim<br>• AstraZeneca<br>• Gilead Sciences*<br>• WebMD*<br>• The Medicines Company* | • Janssen Pharmaceuticals<br>• Liposcience<br>• Gilead Sciences*<br>• Boehringer Ingelheim | None | • Gilead Sciences*<br>• Daiichi-Sankyo*<br>• Eli Lilly and Company* | None | None |
| Gregg C. Fonarow | UCLA Cardiomyopathy Center—Professor of Medicine | • The Medicines Company<br>• NCDR | None | None | • NIH/NIAID*<br>• Novartis*<br>• NHLBI* | None | None |

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|---|---|---|---|---|---|---|---|
| | | • Boston Scientific<br>• Johnson & Johnson<br>• Medtronic<br>• Gambro*<br>• Novartis* | | | | | |
| Glenn N. Levine | Baylor College of Medicine—Professor of Medicine; Director, Cardiac Care Unit | None | None | None | None | None | None |
| John Bittl | Munroe Regional Medical Center—Invasive Cardiologist | None | None | None | None | None | None |
| Richard A. Lange | University of Texas Health Science Center—Professor of Medicine | None | None | None | None | None | None |
| Thomas M. Maddox | VA Eastern Colorado Health Care System—Cardiologist | 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 |
| Barbara J. Fletcher | University of North Florida—Clinical Associate Professor, School of Nursing | None | None | None | None | None | None |
| Srihari Naidu | Winthrop University Hospital—Director, Cardiac Catheterization Laboratory | None | None | None | None | None | None |
| Peter K. Smith | Duke University Medical Center—Professor of Surgery; Chief, Thoracic Surgery | None | None | None | None | • CLS Behring (DSMB) | None |
| Karen P. Alexander | Duke University Medical Center—Associate Professor of Medicine/Cardiology | • Gilead* | None | None | • Gilead*<br>• Sanofi Aventis* | None | None |

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|---|---|---|---|---|---|---|---|
| Susan Croushore | The Christ Hospital—President and CEO | None | None | None | None | None | None |

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*Significant relationship.

†No financial benefit.

DSMB indicates Data and Safety Monitoring Board; NCDR, National Cardiovascular Data Registry; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Disease; NIH, National Institute of Health; and VA, Veterans Affairs.

# 2014 SIHD Focused Update Data Supplements

**(Section numbers correspond to the full-text guideline.)**



## Data Supplement 1. Studies of Flow Reserve Assessment for Intermediate Coronary Lesions

| Study Name | Study Type | Study Size | Inclusion/Exclusion Criteria | Primary Endpoint | Results/CABG P Values | Summary/Conclusions |
|---|---|---|---|---|---|---|
| DEFER (1) 11413082 | RCT | 325 pts | Elective PCI 3 groups based on </≥0.75 FFR (deferral, performance, and reference groups) | Absence of death, MI, PCI, CABG by 24 mo | Same event in pts with FFR ≥0.75 with PCI or deferred | In pts with SVCAD and no documented ischemia, FFR identifies those who benefit from PTCA. |
| DEFER (2) 17531660 | RCT | 325 pts | Elective PCI SVD with 3 groups (deferral, performance, and reference groups) based on </≥0.75 FFR | Absence of death, MI, PCI, CABG by 60 mo | Similar to 2-y follow-up<br>No benefit with PCI if FFR ≥0.75 | In pts with SVCAD and no documented ischemia, FFR identifies those who benefit from PTCA. |
| FAME (3) 19144937 | RCT | 1,005 pts (DES) | MVD PCI with angiography PCI only vs. angiography and FFR ≤0.80 | 1-y death, MI, or repeat revasc | 18.3% in angiography group;<br>13.2% in FFR group (p=0.02) | FFR-guided PCI in pts with MVD improves 1-y composite endpoints: death, MI, or revasc. |
| FAME (4) 20537493 | RCT | 1,005 pts (DES) | Pts with MVD with angiography PCI only or angiography and FFR ≤0.80 | 1-y death, MI, or repeat revasc | 22.4% in angiography group;<br>17.9% in FFR group (p=0.08) | FFR-guided PCI in pts with MVD improves 2-y composite endpoints: death, MI, or and revasc. |
| (FFR vs. IVUS) (5) 20723852 | NR | 167 pts | 40% to 70% PCI of stenosis with IVUS MLA ≤4.0 $cm^2$ or FFR ≤0.8 | 1-y death, MI, or repeat revasc | No difference: 3.6% FFR vs. 3.2% IVUS | No difference in events; more PCIs in IVUS group (91.5%) vs. FFR (33.7%) (p<0.001). |
| (LM) (6) 19327420 | NR | 142 consecutive pts | LM 30% to 60% or indeterminate. FFR <0.75 revasc recommended, >0.80 medical therapy recommended, or 0.75-0.80 either recommended | 14-mo follow-up death, MI, CABG, PCI | 13% medical vs. 7% revasc; Death or MI 6% vs. 7%, respectively | FFR may be helpful, but DM and dose of adenosine may influence decision. |
| (LM) (7) 19786633 | NR | 213 pts (209 with follow-up) | Equivalent LM FFR <0.80 surgery; 0.80 medical therapy | Event-free survival 3-y follow-up; 5 y estimated | 74.2% medical therapy vs. 82.8% surgery (p=0.48) | FFR is beneficial for equivocal LM lesions in deciding need for revasc. |
| FAME 2 (8) 22924638 | RCT | 888 randomized pts | FFR ≤0.80 randomized to PCI vs. GDMT | Death, MI, or urgent revasc | 12.7% medical therapy vs. 4.3% PCI (p<0.001) | Upfront stenting may prevent future urgent stenting; no decrease in death or MI with FFR-guided PCI. |

CABG indicates coronary artery bypass graft; DEFER, Deferral Versus Performance of Balloon Angioplasty in Patients Without Documented Ischemia; DES, drug-eluting stent; DM, diabetes mellitus; FAME, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; IVUS, intravascular ultrasound; LM, left main; MI, myocardial infarction; MLA, minimal luminal area; mo, month(s); MVD, multivessel

disease; NR, nonrandomized; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; pt(s), patient(s); RCT, randomized controlled trial; revasc, revascularization; SVCAD, single-vessel coronary artery disease; SVD, saphenous vein disease; and y, year(s).

## Data Supplement 2. Chelation Therapy

| Study Name, Author, Year | Aim of Study | Study Type | Study Size (N) | Study Intervent-ion Group (n) | Study Comparat-or Group (n) | Patient Population | | Study Intervention | Study Comparat or | Endpoints | | | P Values, OR: HR: RR and 95% CI | Study Limitations and Adverse Events |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Inclusion Criteria* | *Exclusion Criteria* | | | *Primary Endpoint (Efficacy) and Results* | *Safety Endpoint and Results* | *Secondary Endpoint and Results* | | |
| Guldager 1992 (9) 1556523 | To assess the effect of chelation therapy on severe IC | RCT | 153 | 75 | 78 | All pts included in study >40 y and suffered from stable IC for at least 12 mo | Vascular surgery within the last 12 mo; ischemic rest pain or gangrene; moderate or severe venous insufficiency; renal insufficiency; DM; thyroid and parathyroid disorders; hepatic dysfunction; significant cardiopulmonary failure (e.g., MI in prior year); coexistent carcinomas; tuberculosis within last year; pregnancy; other conditions that | 20 IV infusions of 3 g disodium EDTA | PC | 3-mo pain-free walking distances, measured on a treadmill (chelation 95±48 m; PC 102±42 m); 6-mo pain-free walking distances, measured on a treadmill (chelation 95±47 m; PC 119±93 m); 3-mo maximal walking distance (chelation 162±101 m; PC 204±248 m); 6-mo maximal walking distance (chelation 180±150 m; PC 194±127 m) | Before treatment, a physical examination was performed together with the following serum and urine analyses: hemoglobin, thrombocytes, hematocrit APTT, prothrombin (Factors 11, VII, and X), fasting glucose, fibrinogen, creatinine, albumin, calcium, phosphate, alkaline phosphatase, LDH, and urinary stick-test for protein, blood, and | ABI, BP, subjective evaluation, and lab tests (no differences between groups in any) | 3-mo pain-free walking distance (RR: 0.98; 95% CI: 0.85, 1.13); 6-mo pain-free walking distance (RR: 1.04; 95% CI: 0.91, 1.19); 3-mo max walking distance (RR: 0.94; 95% CI: 0.82, 1.08); 6-mo max walking distance (RR: 0.96; 95% CI: 0.79, 1.16) | Lab tests on entry to study were in the normal range, and only alkaline phosphatase activity changed significantly during the study period. Alkaline phosphatase in EDTA-treated group decreased from mean value + SD of 175±55 U 1-' to 148 +/-+42 U I-' (p<0.001). Because of symptoms of hypocalcemia, 8 pts received IV calcium gluconate (EDTA 5 pts; PC 3 pts). 1 pt (EDTA group) showed subnormal calcium levels. In 3 pts (EDTA, 1 pt: PC 2 pts), creatinine levels increased after the 10th infusion, but normalized 8 d after cessation of treatment. In 11 pts (EDTA, 4 pts: PC, 7 pts), creatinine levels increased after the 20th infusion.<br>Side effects were observed but were generally nonspecific and showed no |

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| | | | | | | | could limit the pt walking distance or reliable interpretation of study; pts receiving anticoagulants, nitroglycerine, or lithium; EDTA chelation therapy within last 24 mo | | | | glucose | | | preponderance in any groups. Incidence of phlebitis and pain at the infusion site, as well as GI side effects, were similar in the 2 groups. One pt developed Raynaud's phenomenon of 2 fingers after the 3rd EDTA treatment; symptoms persisted for 4 d then gradually disappeared spontaneously. EDTA pt developed localized dermatitis on nasal cheek fold after 6th infusion; this disappeared spontaneously after the treatment period. |
| van Rij 1994 (10) 8087928 | To assess the effect of chelation therapy in pts with IC | RCT | 32 | 15 | 17 | Pts with angiographically confirmed PAD who did not have indications for invasive procedures; variation of <20% in measured walking distance over 3 separate assessments | Other debilitating disease affecting walking; younger than 45 y; DM; renal disease | 20 IV infusions of 3 g disodium EDTA + IV vitamin supplements | PC + IV vitamin supplements | Measured walking distance (end of treatment chelation 208±135 m vs. PC 223±149 m; 3-mo chelation 233±135 m vs. PC 230±130 m); subjective walking distance (end of treatment chelation 413±775 m vs. PC 327±461 m; 3-mo chelation 448±556 m vs. PC 381 m ±473 m); ABI at rest (end of treatment chelation 0.7±0.36 vs. PC 0.6±0.15; 3-mo chelation 0.62±0.15 vs. PC 0.58±0.13) and | Lab monitoring of UA, hematology parameters, renal function, and serum Ca, Zn, Mg, and Fe; BP and heart rate monitoring during infusion therapy | Effect of chelation therapy on behavior and attitudes, as assessed by pt questionnaires (no significant difference noted between chelation and PC groups) | All p values for each primary outcome were >0.05, except for 3 mo resting ABI measure | No complications were noted in either the chelation or placebo groups. |

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| | | | | | | | | | | after ambulation (end of treatment chelation 0.32±0.18 vs. PC 0.34±0.17; 3-mo chelation 0.34±0.18 vs. PC 0.32±0.17) | | | | |
| Knudtson 2002 (11) 11798370 | To determine if current EDTA protocols have a favorable impact on exercise ischemia threshold and quality-of-life measures in pts with SIHD | RCT | 84 | 41 | 43 | Participants ≥21 y and have CAD proven by coronary angiography or documented MI and stable angina while receiving optimal MT. To qualify for randomization, pts were required to have a treadmill test, using a gradual ramping protocol, demonstrating at least 1 mm of horizontal or downsloping ST-segment depression from the isoelectric line 80 ms after | Exclusion criteria included planned revascularization, previous chelation therapy, evidence of HF, inability to walk on the treadmill, resting ECG changes that would interfere with ischemic assessment, abnormal renal or liver function, or untreated lipid abnormality at the time of randomization. | 33 IV infusions of 3 g disodium EDTA + IV vitamin supplements | Placebo + IV vitamin supplements | The primary endpoint was the change in time to reach ≥1 mm of ST-segment depression at the 27-wk evaluation (chelation 572±172 s vs. PC 589±176 s). | Laboratory monitoring (renal function, Ca levels) | Peak $VO_2$ (chelation change between baseline and 27 wk 84 mL/min (95% CI: 10, 159) vs. PC 40 mL/min (95% CI: 53, 134), time to reach anaerobic threshold (chelation change between baseline and 27 wk 31 s [95% CI: -11, 72] vs. PC 16 s [95% CI -27, 59]) | All between-group comparisons were nonsignificant (p>0.05) | 1 chelation pt was withdrawn from therapy because of elevation in serum creatinine. During first 10 treatments, pt serum creatinine level increased from 1.5 to 2.1 mg/dL (129 to 186 μmol/L respectively). Treatment was stopped, and serum creatinine level decreased to 1.6 mg/dL (138 μmol/L) after 10 wk. No other cause for the elevation in creatinine was found. In addition to the nonischemic events leading to discontinuation of therapy, 3 additional PC pts were hospitalized for nonischemic events: gout, lumbar back pain from a herniated disk, and GI bleeding. These events did not interfere with completion of the treatment phase. There were no electrolyte results out of normal range during the study. |

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| | | | | | | the J point. The study protocol required detection of ST-segment depression between 2-14 min from the onset of exercise. | | | | | | | | |
| TACT Lamas 2013 (12) 23532240 | To determine if an EDTA-based chelation regimen reduces CV events | RCT | 1,708 | 839 | 869 | Eligible pts were ≥50 y and experienced MI ≥6 wk before enrollment. | Pts ineligible if they were women of childbearing potential, had a serum creatinine level >2.0 mg/dL, platelet count <100,000/L, abnormal liver function studies, BP >160/100 mm Hg, past intolerance to the chelation or vitamin components, chelation therapy within 5 y, coronary or carotid revascularization planned or having taken place within 6 mo, cigarette smoking within | 40 IV infusions of 3 g disodium EDTA + IV vitamin supplements + oral vitamin supplements | IV and PO placebos | Primary endpoint was a composite of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina over a 5-y period, chelation (32.8% [95% CI: 29.1-36.5%]) vs. PC (38.5% [95% CI: 34.6-42.3%]) | Safety monitoring included periodic physical examinations and laboratory assessments: glucose, calcium, renal function, hepatic function, and hematologic parameters. Pts had body weight assessed before infusions to determine whether there was fluid retention. | The composite of CV death, reinfarction, or stroke was a prespecified secondary endpoint (96 chelation pts [11%] and 113 PC pts [13%]) | Primary outcome (HR: 0.82; 95% CI: 0.69-0.99; p=0.035). Secondary outcome (HR: 0.84; 95% CI: 0.64-1.11; p=0.22) | 4 unexpected severe adverse events occurred that were possibly or definitely attributed to study therapy, 2 in the chelation group (1 death) and 2 in PC group (1 death). HF was reported in 57 chelation pts (7%) and 71 PC pts (8%) (p=0.28). 330 (0.60%) of 55,222 infusions administered at least 30 min too rapidly. Hypocalcemia, defined as calcium level <8.5 mg/dL before an infusion, was reported in 52 chelation pts (6.2%) and 30 PC pts (3.5%) (p=0.008). 1 pt had hypocalcemia associated with muscle cramping that led to ED visit. |

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| | | | | | | | 3 mo, active HF or HF hospitalization within 6 mo, or inability to tolerate 500-mL infusions/wk | | | | | | | |

ABI indicates ankle/brachial indices; APTT, activated partial thromboplastin time; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; ECG, electrocardiographic; ED, emergency department; EDTA, ethylenediaminetetraacetic acid; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; IC, intermittent claudication; IV, intravenous; LDH, lactic dehydrogenase; m, meter(s); MI, myocardial infarction; mo, month(s); MT, medical therapy; OR, odds ratio; PAD, peripheral artery disease; PC, placebo; PO, per oral; pt(s), patient(s); RCT, randomized controlled trial; RR, relative risk; s, seconds; SIHD, stable ischemic heart disease; UA, unstable angina; wk, week(s); and y, year(s).

## Data Supplement 3. External Enhanced Counterpulsation

| Study Name, Author, Year | Aim of Study | Study Type | Study Size (N) | Study Intervention Group (n) | Study Comparator Group (n) | Patient Population | | Study Intervention | Study Comparator | Endpoints | | | P Values, OR: HR: RR and 95% CI | Study Limitations and Adverse Events |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Inclusion Criteria* | *Exclusion Criteria* | | | *Primary Endpoint (Efficacy) and Results* | *Safety Endpoint and Results* | *Secondary Endpoint and Results* | | |
| Arora 1999 (13) 10362181 | Evaluate ECCP in pts with angina | RCT | N=139 | EECP (n=72) | Sham Control (n=67) | Age 21-81 y Canadian CV Class I, II, or III angina Documented CAD Positive ETT | MI or CABG in preceding 3 mo, cardiac catheterization in the preceding 2 wk, UA, CHF, or LVEF <30%, significant valvular disease, BP >180/100 mm Hg, permanent pacemaker or ICD, left main stenosis >50%, severe symptomatic PVD, history of varicosities, DVT, AF | Evaluate ECCP in pts with angina | RCT | N=139 | EECP (n=72) | Sham Control (n=67) | Age 21-81 y Canadian CV Class I, II, or III angina Documented CAD Positive ETT | MI or CABG in preceding 3 mo, cardiac catheterization in the preceding 2 wk, UA, CHF, or LVEF <30%, significant valvular disease, BP >180/100 mm Hg, permanent pacemaker or ICD, left main stenosis >50%, severe symptomatic PVD, history of varicosities, DVT, AF were excluded |
| Braith 2010 (14) 20921442 | To investigate the | RCT | N=42 | EECP n=28 | Sham Control n=14 | Refractory chronic angina with | Absence of ST-segment depression during exercise testing; >75 y, | To investigate the | RCT | N=42 | EECP n=28 | Sham Control n=14 | Refractory chronic angina with | Absence of ST-segment depression during exercise testing; >75 y, |

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| | extracardiac effects of EECP on peripheral artery flow-mediated dilation | | | | | multivessel CAD | recent catheterization, CABG or PCI,; arrhythmia; CHF; LVEF <30%; valvular disease, ICD discharge within past 6 mo, history of DVT, uncontrolled HTN, pregnancy, pulmonary congestion, hypotension | extracardiac effects of EECP on peripheral artery flow-mediated dilation | | | | | multivessel CAD | recent catheterization, CABG, or PCI, arrhythmia; CHF; LVEF <30%; valvular disease, ICD discharge within past 6 mo, history of DVT, uncontrolled HTN, pregnancy, pulmonary congestion, hypotension were excluded |

AF indicates atrial fibrillation; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; DVT, deep vein thrombosis; EECP, external enhanced counterpulsation; ETT, exercise treadmill testing; HR, hazard ratio; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mo, month(s); OR, odds ratio; PCI, percutaneous coronary intervention; pts, patients; PVD, peripheral vascular disease; RCT, randomized controlled trial; RR, relative risk; UA, unstable angina; wk, week(s); and y, year(s).

## Data Supplement 4. Evidence for Survival Benefit After PCI or CABG (With LIMA Grafting to the LAD) in Patients With SIHD Who Are Receiving Medical Therapy and Are Suitable Candidates for Revascularization

| Anatomic Subgroups | Evidence Supporting CABG for Survival | Evidence Supporting PCI for Survival | Evidence Supporting Superiority of Either CABG or PCI for Survival | Evidence Supporting Equivalence of CABG and PCI for Survival |
|---|---|---|---|---|
| Unprotected left main CAD | CASS Registry* (15,16) 7729018 2785870<br>CASS† (17) 7025604<br>VA Cooperative† (18,19) 791537 6979435<br>Yusuf et al.† (20) 7914958<br>Dzavik et al.* (21) 11431667 | Bittl et al. (22) 23674397 | *CABG better:*<br>Wu* (23)<br>18805151<br><br>*PCI better: None found*<br><br>*CABG better:*<br><br>SYNTAX†(24) 21697170 | SYNTAX† (25) 20530001<br>LE MANS† (26) 18237682<br>Boudriot et al.† (27) 21272743<br>Chieffo et al.* (28,29) 16717151<br>20630452<br>Lee et al.* (30) 16487857<br>Lee et al.§ (31) 20723848<br>Naik et al.§ (32) 19695542<br>White et al.* (33) 19463306<br>Palmerini et al.* (34) 16784920<br>Park et al.* (35) 20451344<br>Sanmartín et al.* (36) 17826380<br>Brener et al.* (37) 18178401<br>Mäkikallio et al.* (38) 18608116 |

# 2014 SIHD Focused Update Data Supplements

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| 3-vessel disease with or without proximal LAD disease | *For:*<br>Dzavik et al.* (21) 11431667<br>ECSS† (39) 3260659<br>Jones et al.* (40) 8622299<br>MASS II* (41) 20733102<br>Myers et al.† (42) 2648078<br>Smith et al.* (43) 16996946<br>SYNTAX†(24) 21697170<br>Weintraub (44) 22452338<br>Yusuf et al.† (20) 7914958 | *For:*<br>Dzavik et al.* (21) 11431667<br>Smith et al.* (43) 16996946<br><br>*Against:*<br>Boden et al.† (45) 17387127 | *CABG better:*<br>Bair et al.* (46) 17846308<br>Booth et al.† (47) 18606919<br>Hannan et al.* (48) 9935010<br>Hannan et al.* (49) 18216353<br>Jones et al.* (40) 8622299<br>MASS II* (41) 20733102<br>Malenka et al.* (50) 16159849 | Bravata et al.† (51) 17938385<br>Daemen et al.† (52) 18725490<br>Dzavik et al.* (21) 11431667<br>ERACI II† (53) 12527674<br>Mercado et al.† (54) 12643887<br>RITA I† (55) 8094826<br>Van Domburg et al.* (56) 11922644 |
| 2-vessel disease with proximal LAD disease | *For:*<br>ECSS† (39) 3260659<br>Jones et al.* (40) 8622299<br>Smith et al.* (43) 16996946<br>Yusuf et al.† (20) 7914958 | *For:*<br>Dzavik et al.* (21) 11431667<br>Jones et al.* (40) 8622299<br>Smith et al.* (43) 16996946<br><br>*Against:*<br>Boden et al.† (45) 17387127 | *CABG better:*<br>Hannan et al.* (48) 9935010<br>Hannan et al.* (49) 18216353<br>Hannan et al.* (57) 15917382<br>Jones et al.* (40) 8622299 | Berger et al.† (58) 11691521<br>ERACI II† (53) 12527674<br>Malenka et al.* (50) 16159849 |
| 2-vessel disease without proximal LAD disease | *For:*<br>Smith et al.* (43) 16996946 | *For:*<br>Jones et al.* (40) 8622299<br>Smith et al.* (43) 16996946<br><br>*Against:*<br>Boden et al.† (45) 17387127<br>Cecil et al.† (59) 18690768<br>Pitt et al.† (60) 10395630 | *CABG better:*<br>Bair et al.* (46) 17846308<br>Booth et al.† (47) 18606919<br>Dzavik et al.* (21) 11431667<br>Hannan et al.* (57) 15917382<br>Hannan et al.* (49) 18216353<br>Jones et al.* (40) 8622299 | Bravata et al.† (51) 17938385<br>Daemen et al.† (52) 18725490<br>Dzavik et al.* (21) 11431667<br>Jones et al.* (40) 8622299<br>Mercado et al.† (54) 12643887<br>Van Domburg et al.* (56) 11922644 |
| 1-vessel proximal LAD disease | *For:*<br>Smith et al.* (43) 16996946<br><br>*Against:*<br>Greenbaum et al.* (61) 11113406 | *For:*<br>Jones et al.* (40) 8622299<br>Smith et al.* (43) 16996946<br><br>*Against:*<br>Greenbaum et al.* (61) 11113406 | *CABG better:*<br>Hannan et al.* (48) 9935010 | Aziz et al.† (62) 17337458<br>Ben-Gal et al.* (63) 17126111<br>Bravata et al.† (51) 17938385<br>Cisowski et al.§ (64) 15531937<br>Diegeler et al.† (65) 12192015<br>Drenth et al.† (66) 15566914<br>Fraund et al.* (67) 15797053<br>Goy et al.† (68,69) 7911175 18755343<br>Greenbaum et al.* (61) 11113406<br>Hong et al.† (70) 15619278<br>Jaffery et al.† (71) 17300948<br>Jones et al.* (40) 8622299<br>Kapoor et al.† (72) 19463349<br>MASS I† (73) 7594092 |

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|---|---|---|---|---|
| 1-vessel disease without proximal LAD involvement | *Against:*<br>Jones et al.* (40) 8622299<br>Smith et al.* (43) 16996946<br>Yusuf et al.† (20) 7914958 | *Against:*<br>Jones et al.* (40) 8622299 | *PCI better:*<br>Hannan et al.* (48) 9935010<br>Jones et al.* (40) 8622299 | Jones et al.* (40) 8622299 |
| Multivessel CAD, DM present | *For:*<br>MASSII† (74) 17184637<br>Sorajja et al.* (75) 16159837<br><br>*No benefit:*<br>BARI 2D† (76) 19502645 | *For:*<br>MASSII† (74) 17184637<br><br>*No effect:*<br>BARI 2D† (76) 19502645<br>Sorajja et al.* (75) 16159837 | *CABG better:*<br>BARI I† (77,78) 9323059 17433949<br>Brener et al.* (79) 15117846<br>Hlatky et al.† (80) 19303634<br>Javaid et al.* (81) 17846304<br>Malenka et al.* (50) 16159849<br>Niles et al.* (82) 11263600<br>Pell et al.* for 3-V CAD (83) 15209776<br>Weintraub et al.† (84) 9426011 | ARTS I* (85) 11479249<br>Bair et al.* (46) 17846308<br>Barsness et al.* (86) 9355893<br>Bravata et al.† (51) 17938385<br>CARDia† (87) 20117456<br>Dzavik et al.* (21) 11431667<br>MASS II† (74) 17184637<br>Pell et al.* for 3-V CAD (83) 15209776 |

*Observational study, including articles on long-term follow-up, clinical trials not specified as randomized, comparative registry studies, comparative studies, prospective cohort studies, prospective observational studies, prospective registries, and prospective studies.
†Randomized controlled trials, including meta-analyses.
‡Reviews (systematic or not).
§Unknown study design.

ARTS indicates Arterial Revascularization Therapies Study Part; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; BARI I, Bypass Angioplasty Revascularization Investigation I; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CAD, coronary artery disease; CARDia, Coronary Artery Revascularization in Diabetes; DM, diabetes mellitus; ECSS, European Coronary Surgery Study; ERACI II, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease II; LAD, left anterior descending; Le Mans, Study of Unprotected Left Main Stenting Versus Bypass Surgery; LIMA, left internal mammary artery; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomised Intervention Treatment of Angina; SIHD, stable ischemic heart disease; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; V, vessel; and VA, Veterans Administration.

## Data Supplement 5. RCTs Comparing CABG and DES

| | | | | | | Death % | MI % | Repeat Revascularization % | Primary Endpoint % | | RR and 95% CI | Follow-Up in Months |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trial | No. | Age (y) | Female | CAD | Enrollment Period | CABG/PCI | CABG/PCI | CABG/PCI | | CABG/PCI | | |
| Hong et al. (70) 15619278 | 189 | 61 | 36% | SV | 2003 | 2.9/0 | 2.9/1.7 | 5.9/1.7 | D, MI, Rep Revasc | 11.7/4.3 | N/A | 6 |
| Leipzig (88) 19539141 | 130 | 66 | 30% | SV | 2003-2007 | 0/0 | 7.7/1.5* | 0/6.2 | D+MI+Rep Revasc | 7.7/7.7 | N/A | 12 |
| SYNTAX (89,90) 19228612 | 1800 | 65 | 22% | MV | 2005-2007 | 6.7/8.6 | 3.6/7.1 | 10.7/19.7 | D+MI+CVA+Rep Revasc | 20.2/28.0 | Primary endpoint 12-mo follow-up; RR: 1.44; 95% CI: 1.15–1.81 | 36 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FREEDOM (91) 18215589 | 1900 | 63 | 29% | MV | 2005-2010 | 10.9/16.3 | 6.0/13.9 | 4.8/12.6 | D+MI+CVA | 18.7/26.6 | RR: 0.74; 95% CI: 0.61–0.89 | 60 |

*Statistically significant.

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CVA, cerebrovascular accident; D, death; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; DES, drug-eluting stent; MI, myocardial infarction; mo, month(s); MV, multivessel; N/A, not applicable; No., number of patients; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; Rep Revasc, repeat revascularization; SV, single vessel; and SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

## Data Supplement 6. Trials of PCI With CABG in Patients With Multivessel CAD and Diabetes Mellitus

| Author | Type of Study and Years of Recruitment | Number of Patients PCI/CABG | Primary Endpoint for PCI and CABG | Comments |
|---|---|---|---|---|
| SYNTAX (92,93) 20079596 23413014 | Randomized 2005-2007 | Overall 903/897<br>DM 231/221 | DM: 12-mo death, stroke, MI, or revasc: 26.0% vs. 14.2% (HR: 1.83; 95% CI: 1.22-1.73; p=0.003)<br>DM; 5-y death, stroke, MI, or revasc: 46.5% vs. 29.0% (HR: 1.81; 95% CI 1.31-2.48; p<0.001)<br>DM: 5-y death, stroke, MI: 23.9% vs. 19.1% (HR: 1.27; 95% CI 0.84-1.92; p=0.065) | Criterion for noninferiority of PCI to CABG was not met in overall study.<br>Criterion for noninferiority of PCI to CABG was not met in overall study. |
| CARDIa (87) 20117456 | Randomized 2002-2007 | DM 256/254 | DM: 1-y death, stroke, or MI: 13.0% vs. 10.5% (OR: 1.25; 95% CI: 0.75-2.09; p=0.39) | Criterion for noninferiority of PCI to CABG was not met. |
| BARI 2D (76) 19502645 | Prestratified/randomized to revasc-medical therapy, 2001-2005 | DM 798/807 | Death from any cause:<br>• Medical: 87.8%<br>• Revasc: 88.3%<br>• p=0.97 | 5-y freedom from death, MI, repeat revasc:<br>PCI vs. medical (77.0% vs. 78.9; p=0.15)<br>CABG vs. medical (77.6% vs. 69.5%; p=0.01)<br>Interaction p=0.002 |
| ARTS I (85,94,95) 11479249 11297702 16098418 | Randomized 1997-1998 | Overall 600/605<br>DM 112/96 | Overall: 5-y composite endpoint of death, stroke, or MI 18.2% vs. 14.9% (RR: 1.22; 95% CI: 0.95-1.58; p=0.14)<br>DM: 1-y freedom from death, stroke, MI, or revasc (63.4% vs. 84.4%; p< 0.001) | N/A |
| MASS II (74) 17184637 | Randomized 1995-2000 | Overall 205/203<br>DM 56/59 | DM: 1-y death 5.3% vs. 6.8% (p=0.5) | N/A |
| FREEDOM (91) 18215589 | Randomized 2005-2010 | DM 953/947 | DM: 5-y death: 16.3% vs. 10.9%; p=0.049<br>DM: 5-y primary composite endpoint of death, nonfatal MI, or nonfatal stroke (26.6% vs. 18.7%; p=0.005) | N/A |

ARTS indicates Arterial Revascularization Therapies Study; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass graft; CAD, coronary artery disease; CARDia, Coronary Artery Revascularization in Diabetes; CI, confidence interval; DM, diabetes mellitus; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; HR; hazard ratio; MASS II, Medicine, Angioplasty, or Surgery Study II; MI, myocardial infarction; mo, month(s); OR, odds ratio; PCI, percutaneous coronary intervention; revasc, revascularization; RR, relative risk; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and y, year(s).

## References


1. Bech GJ, de Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation. 2001;103:2928-34.
2. Pijls NHJ, van Schaardenburgh P., Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49:2105-11.
3. Tonino PAL, de Bruyne B., Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360:213-24.
4. Pijls NHJ, Fearon WF, Tonino PAL, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol. 2010;56:177-84.
5. Nam CW, Yoon HJ, Cho YK, et al. Outcomes of percutaneous coronary intervention in intermediate coronary artery disease: fractional flow reserve–guided versus intravascular ultrasound–guided. JACC Cardiovasc Interv. 2010;3:812-7.
6. Courtis J, Rodes-Cabau J, Larose E, et al. Usefulness of coronary fractional flow reserve measurements in guiding clinical decisions in intermediate or equivocal left main coronary stenoses. Am J Cardiol. 2009;103:943-9.
7. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve–guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation. 2009;120:1505-12.
8. de Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve--guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991-1001.
9. Guldager B, Jelnes R, Jørgensen SJ, et al. EDTA treatment of intermittent claudication–a double-blind, placebo-controlled study. J Intern Med. 1992;231:261-7.
10. van Rij AM, Solomon C, Packer SG, et al. Chelation therapy for intermittent claudication. A double-blind, randomized, controlled trial. Circulation. 1994;90:1194-9.
11. Knudtson ML, Wyse DG, Galbraith PD, et al. Chelation therapy for ischemic heart disease: a randomized controlled trial. JAMA. 2002;287:481-6.
12. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. JAMA. 2013;309:1241-50.
13. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol. 1999;33:1833-40.
14. Braith RW, Conti CR, Nichols WW, et al. Enhanced external counterpulsation improves peripheral artery flow-mediated dilation in patients with chronic angina: a randomized sham-controlled study. Circulation. 2010;122:1612-20.
15. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. Circulation. 1995;91:2325-34.
16. Taylor HA, Deumite NJ, Chaitman BR, et al. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry. Circulation. 1989;79:1171-9.
17. Chaitman BR, Fisher LD, Bourassa MG, et al. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). Am J Cardiol. 1981;48:765-77.
18. Takaro T, Hultgren HN, Lipton MJ, et al. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. Circulation. 1976;54:III107-7.
19. Takaro T, Peduzzi P, Detre KM, et al. Survival in subgroups of patients with left main coronary artery disease. Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. Circulation. 1982;66:14-22.
20. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet. 1994;344:563-70.
21. Dzavik V, Ghali WA, Norris C, et al. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Am Heart J. 2001;142:119-26.
22. Bittl JA, He Y, Jacobs AK, et al. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. Circulation. 2013;127:2177-85.
23. Wu C, Hannan EL, Walford G, et al. Utilization and outcomes of unprotected left main coronary artery stenting and coronary artery bypass graft surgery. Ann Thorac Surg. 2008;86:1153-9.
24. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J. 2011;32:2125-34.
25. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2010;121:2645-53.
26. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol. 2008;51:538-45.

27. Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol. 2011;57:538-45.
28. Chieffo A, Morici N, Maisano F, et al. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. Circulation. 2006;113:2542-7.
29. Chieffo A, Magni V, Latib A, et al. 5-year outcomes following percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass graft for unprotected left main coronary artery lesions: the Milan experience. JACC Cardiovasc Interv. 2010;3:595-601.
30. Lee MS, Kapoor N, Jamal F, et al. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol. 2006;47:864-70.
31. Lee MS, Bokhoor P, Park SJ, et al. Unprotected left main coronary disease and ST-segment elevation myocardial infarction: a contemporary review and argument for percutaneous coronary intervention. JACC Cardiovasc Interv. 2010;3:791-5.
32. Naik H, White AJ, Chakravarty T, et al. A meta-analysis of 3,773 patients treated with percutaneous coronary intervention or surgery for unprotected left main coronary artery stenosis. JACC Cardiovasc Interv. 2009;2:739-47.
33. White AJ, Kedia G, Mirocha JM, et al. Comparison of coronary artery bypass surgery and percutaneous drug-eluting stent implantation for treatment of left main coronary artery stenosis. JACC Cardiovasc Interv. 2008;1:236-45.
34. Palmerini T, Marzocchi A, Marrozzini C, et al. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). Am J Cardiol. 2006;98:54-9.
35. Park DW, Seung KB, Kim YH, et al. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. J Am Coll Cardiol. 2010;56:117-24.
36. Sanmartín M, Baz JA, Claro R, et al. Comparison of drug-eluting stents versus surgery for unprotected left main coronary artery disease. Am J Cardiol. 2007;100:970-3.
37. Brener SJ, Galla JM, Bryant R3eal. Comparison of percutaneous versus surgical revascularization of severe unprotected left main coronary stenosis in matched patients. Am J Cardiol. 2008;101:169-72.
38. Makikallio TH, Niemela M, Kervinen K, et al. Coronary angioplasty in drug eluting stent era for the treatment of unprotected left main stenosis compared to coronary artery bypass grafting. Ann Med. 2008;40:437-43.
39. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med. 1988;319:332-7.
40. Jones RH, Kesler K, Phillips HR, III, et al. Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. J Thorac Cardiovasc Surg. 1996;111:1013-25.
41. Hueb W, Lopes N, Gersh BJ, et al. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation. 2010;122:949-57.
42. Myers WO, Schaff HV, Gersh BJ, et al. Improved survival of surgically treated patients with triple vessel coronary artery disease and severe angina pectoris. A report from the Coronary Artery Surgery Study (CASS) registry. J Thorac Cardiovasc Surg. 1989;97:487-95.
43. Smith PK, Califf RM, Tuttle RH, et al. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. Ann Thorac Surg. 2006;82:1420-8.
44. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al. Comparative effectiveness of revascularization strategies. N Engl J Med. 2012;366:1467-76.
45. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503-16.
46. Bair TL, Muhlestein JB, May HT, et al. Surgical revascularization is associated with improved long-term outcomes compared with percutaneous stenting in most subgroups of patients with multivessel coronary artery disease: results from the Intermountain Heart Registry. Circulation. 2007;116:I226-31.
47. Booth J, Clayton T, Pepper J, et al. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). Circulation. 2008;118:381-8.
48. Hannan EL, Racz MJ, McCallister BD, et al. A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. J Am Coll Cardiol. 1999;33:63-72.
49. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med. 2008;358:331-41.
50. Malenka DJ, Leavitt BJ, Hearne MJ, et al. Comparing long-term survival of patients with multivessel coronary disease after CABG or PCI: analysis of BARI-like patients in northern New England. Circulation. 2005;112:I371-6.
51. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med. 2007;147:703-16.
52. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation. 2008;118:1146-54.

53. Rodriguez A, Rodriguez AM, Baldi J, et al. Coronary stenting versus coronary bypass surgery in patients with multiple vessel disease and significant proximal LAD stenosis: results from the ERACI II study. Heart. 2003;89:184-8.
54. Mercado N, Maier W, Boersma E, et al. Clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting. Implications for mechanical plaque sealing. Eur Heart J. 2003;24:541-51.
55. Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. Lancet. 1993;341:573-80.
56. van Domburg RT, Foley DP, Breeman A, et al. Coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. Twenty-year clinical outcome. Eur Heart J. 2002;23:543-9.
57. Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med. 2005;352:2174-83.
58. Berger PB, Velianou JL, Aslanidou VH, et al. Survival following coronary angioplasty versus coronary artery bypass surgery in anatomic subsets in which coronary artery bypass surgery improves survival compared with medical therapy. Results from the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol. 2001;38:1440-9.
59. Cecil WT, Kasteridis P, Barnes JW, Jr., et al. A meta-analysis update: percutaneous coronary interventions. Am J Manag Care. 2008;14:521-8.
60. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med. 1999;341:70-6.
61. Greenbaum AB, Califf RM, Jones RH, et al. Comparison of medicine alone, coronary angioplasty, and left internal mammary artery-coronary artery bypass for one-vessel proximal left anterior descending coronary artery disease. Am J Cardiol. 2000;86:1322-6.
62. Aziz O, Rao C, Panesar SS, et al. Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. BMJ. 2007;334:617.
63. Ben-Gal Y, Mohr R, Braunstein R, et al. Revascularization of left anterior descending artery with drug-eluting stents: comparison with minimally invasive direct coronary artery bypass surgery. Ann Thorac Surg. 2006;82:2067-71.
64. Cisowski M, Drzewiecka-Gerber A, Ulczok R, et al. Primary direct stenting versus endoscopic atraumatic coronary artery bypass surgery in patients with proximal stenosis of the left anterior descending coronary artery--a prospective, randomised study. Kardiol Pol. 2004;61:253-61.
65. Diegeler A, Thiele H, Falk V, et al. Comparison of stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery. N Engl J Med. 2002;347:561-6.
66. Drenth DJ, Veeger NJGM, Middel B, et al. Comparison of late (four years) functional health status between percutaneous transluminal angioplasty intervention and off-pump left internal mammary artery bypass grafting for isolated high-grade narrowing of the proximal left anterior descending coronary artery. Am J Cardiol. 2004;94:1414-7.
67. Fraund S, Herrmann G, Witzke A, et al. Midterm follow-up after minimally invasive direct coronary artery bypass grafting versus percutaneous coronary intervention techniques. Ann Thorac Surg. 2005;79:1225-31.
68. Goy JJ, Eeckhout E, Burnand B, et al. Coronary angioplasty versus left internal mammary artery grafting for isolated proximal left anterior descending artery stenosis. Lancet. 1994;343:1449-53.
69. Goy JJ, Kaufmann U, Hurni M, et al. 10-year follow-up of a prospective randomized trial comparing bare-metal stenting with internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis the SIMA (Stenting versus Internal Mammary Artery grafting) trial. J Am Coll Cardiol. 2008;52:815-7.
70. Hong SJ, Lim DS, Seo HS, et al. Percutaneous coronary intervention with drug-eluting stent implantation vs. minimally invasive direct coronary artery bypass (MIDCAB) in patients with left anterior descending coronary artery stenosis. Catheter Cardiovasc Interv. 2005;64:75-81.
71. Jaffery Z, Kowalski M, Weaver WD, et al. A meta-analysis of randomized control trials comparing minimally invasive direct coronary bypass grafting versus percutaneous coronary intervention for stenosis of the proximal left anterior descending artery. Eur J Cardiothorac Surg. 2007;31:691-7.
72. Kapoor JR, Gienger AL, Ardehali R, et al. Isolated disease of the proximal left anterior descending artery comparing the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. JACC Cardiovasc Interv. 2008;1:483-91.
73. Hueb WA, Bellotti G, de Oliveira SA, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol. 1995;26:1600-5.
74. Hueb W, Gersh BJ, Costa F, et al. Impact of diabetes on five-year outcomes of patients with multivessel coronary artery disease. Ann Thorac Surg. 2007;83:93-9.
75. Sorajja P, Chareonthaitawee P, Rajagopalan N, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. Circulation. 2005;112:I311-6.
76. BARI 2D Study Group FRL, August P, Hardison RM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009;360:2503-15.
77. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 1997;96:1761-9.
78. BARI Investigators. The final 10-year follow-up results from the BARI randomized trial. J Am Coll Cardiol. 2007;49:1600-6.
79. Brener SJ, Lytle BW, Casserly IP, et al. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. Circulation. 2004;109:2290-5.

80. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet. 2009;373:1190-7.
81. Javaid A, Steinberg DH, Buch AN, et al. Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with drug-eluting stents for patients with multivessel coronary artery disease. Circulation. 2007;116:I200-6.
82. Niles NW, McGrath PD, Malenka D, et al. Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary revascularization: results of a large regional prospective study. Northern New England Cardiovascular Disease Study Group. J Am Coll Cardiol. 2001;37:1008-15.
83. Pell JP, Pell ACH, Jeffrey RR, et al. Comparison of survival following coronary artery bypass grafting vs. percutaneous coronary intervention in diabetic and non-diabetic patients: retrospective cohort study of 6320 procedures. Diabet Med. 2004;21:790-2.
84. Weintraub WS, Stein B, Kosinski A, et al. Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. J Am Coll Cardiol. 1998;31:10-9.
85. Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. Circulation. 2001;104:533-8.
86. Barsness GW, Peterson ED, Ohman EM, et al. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. Circulation. 1997;96:2551-6.
87. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol. 2010;55:432-40.
88. Thiele H, Neumann-Schniedewind P, Jacobs S, et al. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. J Am Coll Cardiol. 2009;53:2324-31.
89. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360:961-72.
90. SYNTAX Score. Available at: http://www.syntaxscore.com. Accessed April 30, 2014.
91. Farkouh ME, Dangas G, Leon MB, et al. Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) Trial. Am Heart J. 2008;155:215-23.
92. Banning AP, Westaby S, Morice MC, et al. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. J Am Coll Cardiol. 2010;55:1067-75.
93. Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg. 2013;43:1006-13.
94. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med. 2001;344:1117-24.
95. Serruys PW, Ong ATL, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol. 2005;46:575-81.