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PRACTICE GUIDELINE

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

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The writing committee gratefully acknowledges the memory of James T. Dove, MD, who died during the development of this document but contributed immensely to our understanding of stable ischemic heart disease.

This document was approved by the American College of Cardiology Foundation Board of Trustees, American Heart Association Science Advisory and Coordinating Committee, American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons in July 2012.

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Preamble

The medical profession should play a central role in evaluating the evidence related to drugs, devices, and procedures for the detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist physicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force), charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, directs and oversees this effort. Writing committees are charged with regularly reviewing and evaluating all available evidence to develop balanced, patient-centric recommendations for clinical practice.

Experts in the subject under consideration are selected by the ACCF and AHA to examine subject-specific data and write guidelines in partnership with representatives from other medical organizations and specialty groups. Writing committees are asked to perform a literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected outcomes where such data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and outcomes constitute the primary basis for the recommendations contained herein.

In analyzing the data and developing recommendations and supporting text, the 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 or 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 for 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 optimal medical therapy as defined by ACCF/AHA guideline (primarily Class I)–recommended therapies. This new term, *GDMT*, will be used herein and throughout all future guidelines.

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Table 1. Applying Classification of Recommendations and Level of Evidence

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

Because the ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing committee reviews the potential influence of different practice patterns and patient populations on the treatment effect and relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/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 attempt 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 might be appropriate. Clinical decision making should involve consideration of 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. The Task Force recognizes that situations arise in which

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additional data are needed to inform patient care more effectively; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, 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 or personal interests among the members of the writing committee. All writing committee members and peer reviewers of this guideline were required to disclose all such current health care-related relationships, including those existing 24 months (from 2005) before initiation of the writing effort. The writing committee chair may not have any relevant relationships with industry or other entities (RWI); however, RWI are permitted for the vice chair position. In December 2009, the ACCF and AHA implemented a new policy that requires a minimum of 50% of the writing committee to have no *relevant* RWI; in addition, the disclosure term was changed to 12 months before writing committee initiation. The present guideline was developed during the transition in RWI policy and occurred over an extended period of time. In the interest of transparency, we provide full information on RWI existing over the entire period of guideline development, including delineation of relationships that expired more than 24 months before the guideline was finalized. This information is included in Appendix 1. These statements are reviewed by the Task Force and all members during each conference call and 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 who recused themselves from voting are indicated in the list of writing committee members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of the writing committee is supported exclusively by the ACCF, AHA, American College of Physicians (ACP), 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 committee members volunteered their time for this activity.

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

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

1. Introduction

1.1. Methodology and Evidence Overview

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted as the document was compiled through December 2008. Repeated literature searches were performed by the guideline development staff and writing committee members as new issues were considered. New clinical trials published in peer-reviewed journals and articles through December 2011 were also reviewed and incorporated when relevant. Furthermore, because of the extended development time period for this guideline, peer review comments indicated that the sections focused on imaging technologies required additional updating, which occurred during 2011. Therefore, the evidence review for the imaging sections includes published literature through December 2011.

Searches were limited to studies, reviews, and other evidence in human subjects and that were published in English. Key search words included but were not limited to the following: *accuracy, angina, asymptomatic patients, cardiac magnetic resonance (CMR), cardiac rehabilitation, chest pain, chronic angina, chronic coronary occlusions, chronic ischemic heart disease (IHD), chronic total occlusion, connective tissue disease, coronary artery bypass graft (CABG) versus medical therapy, coronary artery disease (CAD) and exercise, coronary calcium scanning, cardiac/coronary computed tomography angiography (CCTA), CMR angiography, CMR imaging, coronary stenosis, death, depression, detection of CAD in symptomatic patients, diabetes, diagnosis, dobutamine stress echocardiography, echocardiography, elderly, electrocardiogram (ECG) and chronic stable angina, emergency department, ethnic, exercise, exercise stress testing, follow-up testing, gender, glycemic control, hypertension, intravascular ultrasound, fractional flow reserve (FFR), invasive coronary angiography, kidney disease, low-density lipoprotein (LDL) lowering, magnetic resonance imaging (MRI), medication adherence, minority groups, mortality, myocardial infarction (MI), noninvasive testing and mortality, nuclear myocardial perfusion, nutrition, obesity, outcomes, patient follow-up, patient education, prognosis, proximal left anterior descending (LAD) disease, physical activity, reoperation, risk stratification, smoking, stable ischemic heart disease (SIHD), stable angina and reoperation, stable angina and revascularization, stress echocardiography, radionuclide stress testing, stenting versus CABG, unprotected left main, weight reduction, and women.* Appendix 3 contains an list of abbreviations used in this document.

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To provide clinicians with a comprehensive set of data, the absolute risk difference and number needed to treat or harm, if they were published and their inclusion was deemed appropriate, are provided in the guideline, along with confidence intervals (CIs) and data related to the relative treatment effects, such as odds ratio (OR), relative risk (RR), hazard ratio, or incidence rate ratio.

1.2. Organization of the Writing Committee

The writing committee was composed of physicians, cardiovascular interventionalists, surgeons, general internists, imagers, nurses, and pharmacists. The writing committee included representatives from the ACP, AATS, PCNA, SCAI, and STS.

1.3. Document Review and Approval

This document was reviewed by 2 external reviewers nominated by both the ACCF and the AHA; 2 reviewers nominated by the ACP, AATS, PCNA, SCAI, and STS; and 19 content reviewers, including members of the ACCF Imaging Council, ACCF Interventional Scientific Council, and the AHA Council on Clinical Cardiology. Reviewers' RWI information was collected and distributed to the writing committee and is published in this document (Appendix 2). Because extensive peer review comments resulted in substantial revision, the guideline was subjected to a second peer review by all official and organizational reviewers. Lastly, the imaging sections were peer reviewed separately, after an update to that evidence base.

This document was approved for publication by the governing bodies of the ACCF, AHA, ACP, AATS, PCNA, SCAI, and STS.

1.4. Scope of the Guideline

These guidelines are intended to apply to adult patients with stable known or suspected IHD, including new-onset chest pain (i.e., low-risk unstable angina [UA]), or to adult patients with stable pain syndromes (Figure 1). Patients who have "ischemic equivalents," such as dyspnea or arm pain with exertion, are included in the latter group. Many patients with IHD can 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 CABG.

This guideline also addresses the initial diagnostic approach to patients who present with symptoms that suggest IHD, such as anginal-type chest pain, but who are not known to have IHD. In this circumstance, it is essential that the practitioner ascertain whether such symptoms represent the initial clinical recognition of chronic stable angina, reflecting gradual progression of obstructive CAD or an increase in supply/demand mismatch precipitated by a change in activity or concurrent illness (e.g., anemia or infection), or whether they represent an acute coronary syndrome (ACS), most likely due to an unstable plaque causing acute thrombosis. For patients with newly diagnosed stable angina, this guideline should be used. Patients with ACS have either acute myocardial infarction (AMI) or UA. For patients with AMI, the reader is referred to the "ACCF/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction" (STEMI) (2,3). Similarly, for patients with UA that is believed to be due to an acute change in clinical status attributable to an unstable plaque or an abrupt change in supply (e.g., coronary occlusion with myocardial supply through collaterals), the reader is referred to the "ACCF/AHA Guidelines for the Management of Patients With Unstable Angina/non–ST-Elevation Myocardial Infarction" (UA/NSTEMI) (4,4a). There are, however, patients with UA who can be categorized as low risk and are addressed in this guideline (Table 2).

A key premise of this guideline is that once a diagnosis of IHD is established, it is necessary in most patients to assess their risk of subsequent complications, such as AMI or death. Because the approach to diagnosis of suspected IHD

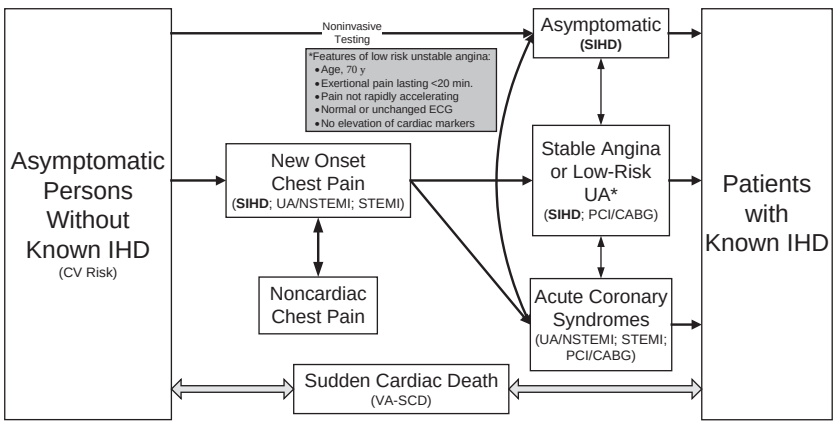

Figure 1. Spectrum of IHD

Guidelines relevant to the spectrum of IHD are in parentheses. CABG indicates coronary artery bypass graft; CV, cardiovascular; ECG, electrocardiogram; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; SCD, sudden cardiac death; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; UA, unstable angina; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; and VA, ventricular arrhythmia.

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Table 2. Short-Term Risk of Death or Nonfatal MI in Patients With UA/NSTEMI

Feature	High Risk	Intermediate Risk	Low Risk
	At least 1 of the following features must be present:	*No high-risk features are present, but patient must have 1 of the following:*	*No high- or intermediate-risk features are present, but patient may have any of the following:*
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG Prior aspirin use	N/A
Characteristics of pain	Prolonged ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (>20 min) or relieved with rest or sublingual NTG Nocturnal angina New-onset or progressive CCS Class III or IV angina in previous 2 wk without prolonged (>20 min) rest pain but with intermediate or high likelihood of CAD	Increased angina frequency, severity, or duration Angina provoked at a lower threshold New-onset angina with onset 2 wk to 2 mo before presentation
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening mitral regurgitation murmur S_3 or new/worsening rales Hypotension, bradycardia, or tachycardia Age >75 y	Age >70 y	N/A
ECG	Angina at rest with transient ST-segment changes >0.5 mm Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes Pathological Q waves or resting ST-depression <1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged ECG
Cardiac markers	Elevated cardiac TnT, TnI, or CK-MB (i.e., TnT or TnI >0.1 ng/mL)	Slightly elevated cardiac TnT, TnI, or CK-MB (i.e., TnT >0.01 but <0.1 ng/mL)	Normal

Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA or NSTEMI is a complex multivariable problem that cannot be fully specified in a table such as this. Therefore, the table is meant to offer general guidance and illustration rather than rigid algorithms.

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CK-MB, creatine kinase-MB fraction; ECG, electrocardiogram; MI, myocardial infarction; NTG, nitroglycerin; N/A, not available; TnI, troponin I; TnT, troponin T; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

Modified from Braunwald et al. (6).

and the assessment of risk in a patient with known IHD are conceptually different and are based on different literature, the writing committee constructed this guideline to address these issues separately. It is recognized, however, that a clinician might select a procedure for a patient with a moderate to high pretest likelihood of IHD to provide information for both diagnosis and risk assessment, whereas in a patient with a low likelihood of IHD, it could be sensible to select a test simply for diagnostic purposes without regard to risk assessment. By separating the conceptual approaches to ascertaining diagnosis and prognosis, the goal of the writing committee is to promote the sensible application of appropriate testing rather than routine use of the most expensive or complex tests whether warranted or not. It is not the intent of the writing committee to promote unnecessary or duplicate testing, although in some patients this could be unavoidable.

Additionally, this guideline addresses the approach to asymptomatic patients with SIHD that has been diagnosed solely on the basis of an abnormal screening study, rather than on the basis of clinical symptoms or events such as anginal symptoms or ACS. The inclusion of such asymptomatic patients does not constitute an endorsement of such tests for the purposes of screening but is simply an acknowledgment of the clinical reality that asymptomatic patients often present for evaluation after such tests have been performed. Multiple ACCF/AHA guidelines and scientific statements have discouraged the use of ambulatory monitoring, treadmill testing, stress echocardiography, stress myocardial perfusion imaging (MPI), and computed tomography (CT) scoring of coronary calcium or coronary angiography as routine screening tests in asymptomatic individuals. The reader is referred to these documents for a detailed discussion of screening, which is beyond the scope of this guideline (Table 3).

Patients with known IHD who were previously asymptomatic or whose symptoms were stable can develop new or recurrent chest pain or other symptoms suggesting ACS. Just as in the case of patients with new-onset chest pain, the clinician must determine whether such recurrent or worsening pain is consistent with ACS or simply represents symptoms more consistent with chronic stable angina that do not require emergent attention. As indicated previously, patients with AMI or moderate- to high-risk UA fall outside of the scope of

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Table 3. Associated Guidelines and Statements

Document	Reference(s)	Organization	Publication Year
Guidelines			
Chronic Stable Angina: 2007 Focused Update	(19)	ACCF/AHA	2007
Valvular Heart Disease	(20)	ACCF/AHA	2008
Heart Failure: 2009 Update	(21)	ACCF/AHA	2009
STEMI	(2,3,22)	ACCF/AHA	2009
Assessment of Cardiovascular Risk in Asymptomatic Adults	(5)	ACCF/AHA	2010
Coronary Artery Bypass Graft Surgery	(9)	ACCF/AHA	2011
Percutaneous Coronary Intervention	(10)	ACCF/AHA/SCAI	2011
Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease	(8)	AHA/ACCF	2011
UA/NSTEMI: 2007 and 2012 Updates	(4,4a)	ACCF/AHA	2012
Statements			
NCEP ATP III Implications of Recent Clinical Trials	(18,24)	NHLBI	2004
National Hypertension Education Program (JNC VII)	(17)	NHLBI	2004
Referral, Enrollment, and Delivery of Cardiac Rehabilitation/Secondary Prevention Programs at Clinical Centers and Beyond: A Presidential Advisory From the AHA	(25)	AHA	2011

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; ATP III, Adult Treatment Panel 3;JNC VII, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NHLBI, National Heart, Lung and Blood Institute; and SCAI, Society for Cardiovascular Angiography and Interventions.

this guideline, whereas those with chronic stable angina or low-risk UA are addressed in the present guideline.

When patients with documented IHD develop recurrent chest pain, the symptoms still could be attributable to another condition. Such patients are included in this guideline if there is sufficient suspicion that their heart disease is a likely source of symptoms to warrant cardiac evaluation. If the evaluation demonstrates that IHD is unlikely to cause the symptoms, the evaluation of noncardiac causes is beyond the scope of this guideline. If the evaluation demonstrates that IHD is the likely cause of their recurrent symptoms, subsequent management of such patients does fall within this guideline.

The approach to screening and management of asymptomatic patients who are at risk for IHD but who are not known to have IHD is also beyond the scope of this guideline, but it is addressed in the "ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults" (5). Similarly, the present guideline does not apply to patients with chest pain symptoms early after revascularization by either percutaneous techniques or CABG. Although the division between "early" and "late" symptoms is arbitrary, the writing committee believed that this guideline should not be applied to patients who develop recurrent symptoms within 6 months of revascularization. Pediatric patients are beyond the scope of this guideline, because IHD is very unusual in such patients and is related primarily to the presence of coronary artery anomalies. Patients with chest pain syndromes after cardiac transplantation also are not included in this guideline.

1.5. General Approach and Overlap With Other Guidelines or Statements

This guideline overlaps with numerous clinical practice guidelines published by the ACCF/AHA Task Force on Practice Guidelines; the National Heart, Lung, and Blood Institute; and the ACP (Table 3). To maintain consistency, the writing committee worked with members of other committees to harmonize recommendations and eliminate discrepancies. Some recommendations from earlier guidelines have been updated as warranted by new evidence or a better understanding of earlier evidence, whereas others that were no longer accurate or relevant or were overlapping were modified; recommendations from previous guidelines that were similar or redundant were eliminated or consolidated when possible.

Most of the topics mentioned in the present guideline were addressed in the "ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina—Summary Article" (7), and many of the recommendations in the present guideline are consistent with those in the 2002 document. Whereas the 2002 update dealt individually with specific drugs and interventions for reducing cardiovascular risk and medical therapy of angina pectoris, the present document recommends a combination of lifestyle modifications and medications that constitute GDMT. In addition, recommendations for risk reduction have been revised to reflect new evidence and are now consistent with the "AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update" (8). Also in the present guideline, recommendations and text related to revascularization are the result of extensive collaborative discussions between the PCI and CABG writing committees, as well as key members of the SIHD and UA/NSTEMI writing committees. In a major undertaking, the PCI and CABG guidelines were written concurrently with input from the STEMI guideline writing committee and additional collaboration with the SIHD guideline writing committee, allowing greater collaboration between these writing committees on revascularization

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strategies in patients with CAD (including unprotected left main PCI, multivessel disease revascularization, and hybrid procedures) (9,10). Section 5 is included as published in both the PCI and CABG guidelines in its entirety.

In addition to cosponsoring practice guidelines, the ACCF has sponsored appropriate use criteria (AUC) documents for imaging testing, diagnostic catheterization, and coronary revascularization since 2005 (11–16). Practice guideline recommendations are based on evidence from clinical and observational trials and expert consensus; AUCs are complementary to practice guidelines and make every effort to be concordant with their recommendations. In general, the recommendations in this guideline and current AUCs are consistent. Apparent discrepancies usually reflect differing frameworks or imaging methodologies. Moreover, where guidelines leave "gaps" (i.e., unaddressed applications), AUCs can provide additional clinical guidance based on the best available clinical evidence and use a prospective, expert consensus methodology (16). Specifically, AUCs provide detailed indications for testing and procedures to aid clinical decision making, categorizing each indication as appropriate, uncertain, or inappropriate. Thus, ACCF AUCs provide an additional means to identify candidates for testing or procedures as well as those for whom they would be inappropriate or for whom the optimal approach is uncertain. Inappropriate candidates are those for whom compelling evidence indicates that testing is not indicated or, in some cases, results in reduced accuracy. Uncertain indications are those with either published evidence or lack of expert consensus on testing use.

AUCs also include relevant clinical scenarios not addressed by these guidelines (11), such as the issue of testing during follow-up of patients with SIHD with stress echocardiography (15), single-photon emission computed tomography (SPECT) MPI (12), CMR, and CCTA (13,14). These AUC documents address the intervals between testing for various stress imaging indications. As with all standards documents, ongoing evaluation is required to update the recommendations on the value, limitations, timing, costs, and risks of imaging as an adjunct to clinical assessment during follow-up of patients with established SIHD. Review of these AUCs is beyond the scope of the present document, and the reader is referred to the most recent AUC documents to complement the guidelines provided here.

As the scientific basis of the approach to management of cardiovascular disease has rapidly expanded, the size and scope of clinical practice guidelines have grown commensurately to a point where they have become too unwieldy for routine use by practicing clinicians. The most current national guidelines for management of hypertension (Joint National Committee VII) (17) and hyperlipidemia (Adult Treatment Panel III) (18) combined comprise nearly 400 pages. Thus, the writing committee recognized that it would be unfeasible to produce a document that would be simultaneously practical and exhaustive and, therefore, has tried to create a resource that provides a comprehensive approach to management of SIHD for which the relevant evidence is succinctly summarized and referenced. The writing committee used current and credible meta-analyses, when available, instead of conducting a systematic review of all primary literature.

1.6. Magnitude of the Problem

IHD remains a major public health problem nationally and internationally. It is estimated that 1 in 3 adults in the United States (about 81 million) has some form of cardiovascular disease, including >17 million with coronary heart disease and nearly 10 million with angina pectoris (26,27). Among persons 60 to 79 years of age, approximately 25% of men and 16% of women have coronary heart disease, and these figures rise to 37% and 23% among men and women ≥80 years of age, respectively (27).

Although the survival rate of patients with IHD has been steadily improving (28), it was still responsible for nearly 380,000 deaths in the United States during 2010, with an age-adjusted mortality rate of 113 per 100,000 population (29). Although IHD is widely known to be the number 1 cause of death in men, this is also the case for women, among whom this condition accounts for 27% of deaths (compared with 22% due to cancer) (30). IHD also accounts for the vast majority of the mortality and morbidity of cardiac disease. Each year, >1.5 million patients have an MI. Many more are hospitalized for UA and for evaluation and treatment of stable chest pain syndromes. Beyond the need for hospitalization, many patients with chronic chest pain syndromes are temporarily unable to perform normal activities for hours or days and thus experience a reduced quality of life. Among patients enrolled in the BARI (Bypass Angioplasty Revascularization Investigation) study (31), about 30% never returned to work after coronary revascularization, and 15% to 20% of patients rated their own health as "fair" or "poor" despite revascularization. Similarly, observational studies of patients recovering from an AMI demonstrated that 1 in 5 patients, even after intensive treatment at the time of their AMI, still suffered angina 1 year later (32). These data confirm the widespread clinical impression that IHD continues to be associated with considerable patient morbidity despite the decline in cardiovascular mortality rate. Patients who have had ACS, such as AMI, remain at risk for recurrent events even if they have no, or limited, symptoms and should be considered to have SIHD.

In approximately 50% of patients, angina pectoris is the initial manifestation of IHD (27). The incidence of angina rises continuously with age in women, whereas the incidence of angina in men peaks between 55 and 65 years of age before declining (27). Despite angina's clinical importance and high frequency, modern, population-based data are quite limited, and these figures likely underestimate the true prevalence of angina (33).

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The annual rates per 1,000 population of new episodes of angina for nonblack men are 28.3 for ages 65 to 74 years, 36.3 for ages 75 to 84 years, and 33.0 for age ≥85 years. For nonblack women in the same age groups, the rates are 14.1, 20.0, and 22.9, respectively. For black men, the rates are 22.4, 33.8, and 39.5, and for black women, the rates are 15.3, 23.6, and 35.9, respectively (30). In a study conducted in Finland, the age-standardized, annual incidence of angina was 2.03 in men and 1.89 in women per 100 populations (33).

Further estimates of the prevalence of chronic, symptomatic IHD can be obtained by extrapolating from data on ACS and, more specifically, AMI. About one half of patients presenting to the hospital with ACS have preceding angina (27). One current estimate is that about 50% of patients who suffer an AMI each year in the United States survive until hospitalization (27). Two older population-based studies from Olmsted County, MN, and Framingham, MA, examined the annual rates of MI in patients with symptoms of angina and reported similar rates of 3% to 3.5% per year (34,35). On this basis, it can be estimated that there were 30 patients with stable angina for every patient with infarction who was hospitalized, which represents 16.5 million persons with angina in the United States. However, since the data reported in these studies were collected, it is likely that the much greater use of effective medical therapies, including antianginal medications and revascularization procedures, has reduced the proportion of patients with symptomatic angina—although there are still many patients whose symptoms are poorly controlled (36–38).

The costs of caring for patients with IHD are enormous, estimated at $156 billion in the United States for both direct and indirect costs in 2008. More than one half of direct costs are related to hospitalization. In 2003, the Medicare program alone paid $12.2 billion for hospitalizations for IHD, including $12,321 per discharge for AMI and $11,783 per discharge for admissions for coronary atherosclerosis (39).

Another major expense is for invasive procedures and related costs. In 2006 in the United States, there were 1,313,000 inpatient PCI procedures, 448,000 inpatient coronary artery bypass procedures, and 1,115,000 inpatient diagnostic cardiac catheterizations (27,40). In addition, ≥13 million outpatient visits for IHD occur in the United States annually (41). It was estimated that the costs of outpatient and emergency department visits in 2000 by patients with chronic angina were $922 million and $286 million, respectively, and prescriptions accounted for $291 million. Long-term care costs—including skilled nursing, home health, and hospice care—were $2.6 billion, which represented 30% of the total cost of care for chronic angina (42).

Although the direct costs associated with SIHD are substantial, they do not account for the significant indirect costs of lost workdays, reduced productivity, long-term medication, and associated effects. The indirect costs have been estimated to be almost as great as the direct costs (27,43) (Table 4). The magnitude of the problem can be summarized succinctly: SIHD affects many millions of Americans, with associated annual costs that are measured in tens of billions of dollars.

1.7. Organization of the Guideline

The overarching framework adopted in constructing this guideline reflects the complementary goals of treating patients with known SIHD, alleviating or improving symptoms, and prolonging life. This guideline is divided into 4 basic sections summarizing the approaches to diagnosis, risk assessment, treatment, and follow-up. Five algorithms summarize the management of stable angina: diagnosis (Figure 2), risk assessment (Figure 3), GDMT (Figure 4), and revascularization (Figures 5 and 6). We readily acknowledge, however, that in actual clinical practice, the elements comprising the 4 sections and the steps delineated in the algorithms often overlap and are not always separable. Some low-risk patients, for example, might require only clinical assessment to determine that they do not need any further evaluation or treatment. Other patients might require only clinical assessment and further adjustment of medical therapy if their preferences and comorbidities preclude revascularization, thus obviating the necessity for risk stratification. The stress testing/angiography algorithm might be applicable for diagnostic purposes in patients with symptoms that suggest SIHD or to perform risk assessment in patients with established SIHD.

Table 4. Estimated Direct and Indirect Costs (in Billions of Dollars) of Heart Disease and Coronary Heart Disease: United States: 2010

	Heart Disease ($ in billions)	Coronary Heart Disease ($ in billions)
Direct costs		
Hospital	110.2	56.6
Nursing home	24.7	13.0
Physicians/other professionals	24.7	13.9
Drugs/other		
Medical durables	22.5	10.0
Home health care	8.3	2.5
Total expenditures	189.4	96.0
Indirect costs		
Lost productivity/morbidity	25.6	11.3
Lost productivity/mortality*	101.4	69.8
Grand totals	316.4	177.1

All estimates prepared by Thomas Thom, National Heart, Lung, and Blood Institute.
*Lost future earnings of persons who will die in 2010, discounted at 3%.
Reproduced from Lloyd-Jones et al. (27).

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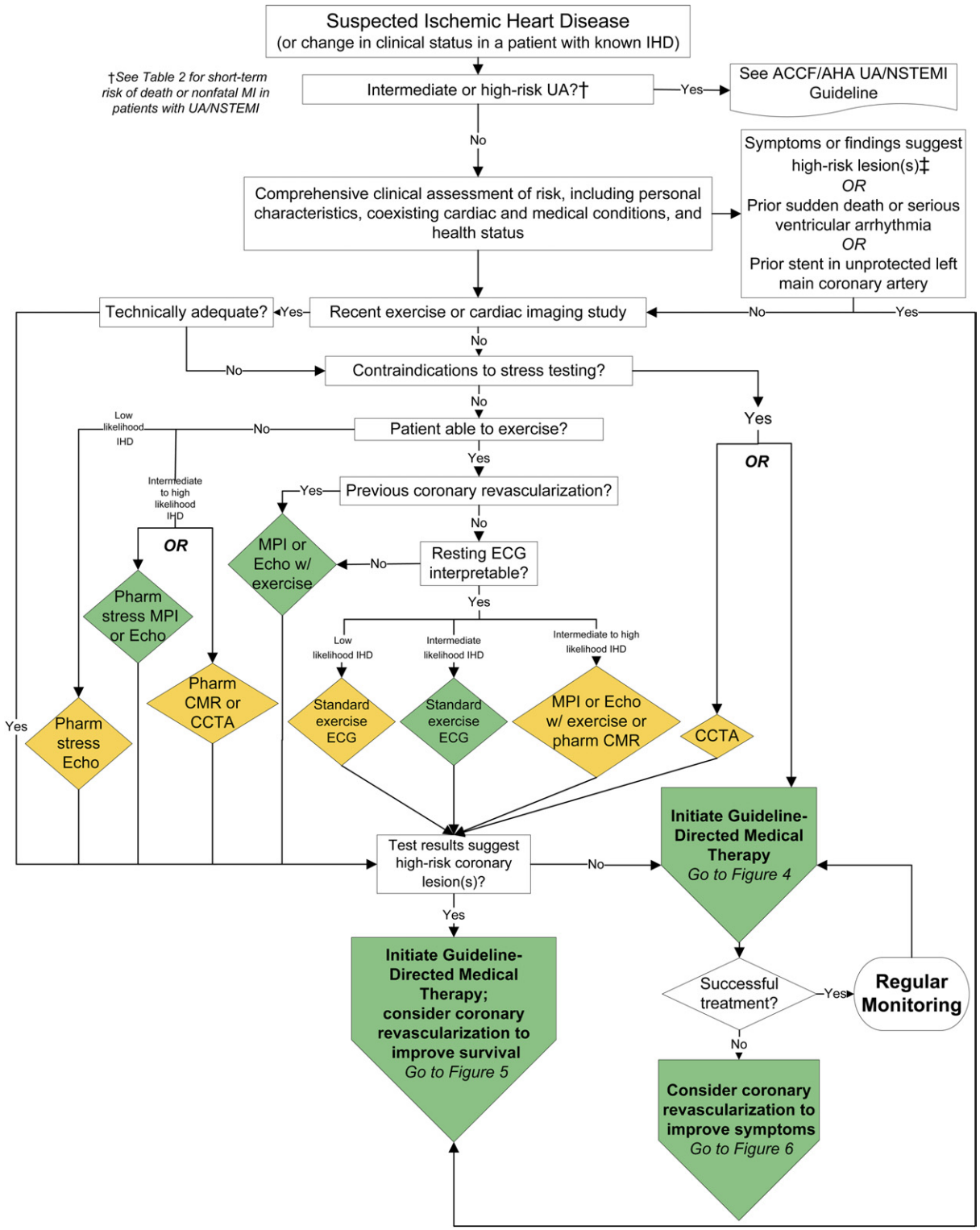

Figure 2. Diagnosis of Patients with Suspected Ischemic Heart Disease*

*Colors correspond to the class of recommendations in the ACCF/AHA Table 1. The algorithms do not represent a comprehensive list of recommendations (see text for all recommendations). †See Table 2 for short-term risk of death or nonfatal MI in patients with UA/NSTEMI. ‡CCTA is reasonable only for patients with intermediate probability of IHD. CCTA indicates computed coronary tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiogram; Echo, echocardiography; IHD, ischemic heart disease; MI, myocardial infarction; MPI, myocardial perfusion imaging; Pharm, pharmacological; UA, unstable angina; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

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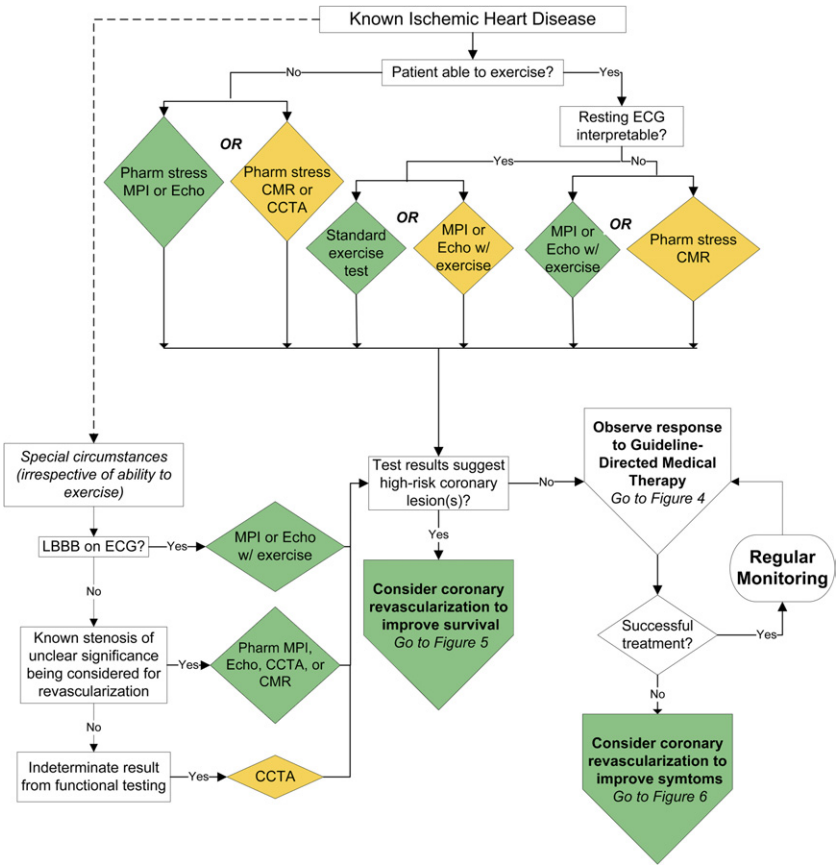

Figure 3. Algorithm for Risk Assessment of Patients With SIHD*

*Colors correspond to the class of recommendations in the ACCF/AHA Table 1. The algorithms do not represent a comprehensive list of recommendations (see text for all recommendations). CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiogram; Echo, echocardiography; LBBB, left bundle-branch block; MPI, myocardial perfusion imaging; and Pharm, pharmacological.

1.8. Vital Importance of Involvement by an Informed Patient: Recommendation

CLASS I

1. **Choices about diagnostic and therapeutic options should be made through a process of shared decision making involving the patient and provider, with the provider explaining information about risks, benefits, and costs to the patient. *(Level of Evidence: C)***

In accordance with the principle of autonomy, the healthcare provider is obliged to solicit and respect the patient's preferences about choice of therapy. Although this principle, in the setting of cardiovascular disease, has received only limited study, the concept of shared decision making increasingly is viewed as an approach that ensures that patients remain involved in key decisions. This approach leads to higher quality of care (44,45).

To ensure that the patient is able to make the most informed decisions possible, the provider must give sufficient information about the underlying disease process, along with all relevant diagnostic and therapeutic options—including anticipated outcomes, risks, and costs to the patient (46). This information should be provided in a manner that is readily comprehensible and permits the opportunity for dialog and questions.

Patients should be encouraged to seek additional information from other sources, including those on the Internet, such as those maintained by the National Institutes of Health, the Centers for Disease Control and Prevention, and the ACCF/AHA. Substantial research indicates that when informed about absolute or marginal benefit, patients often elect to postpone or forego invasive procedures. Two patients with similar pretest probabilities of IHD could prefer different approaches because of variations in personal beliefs, economic situation, or stage of life. Because of the variation in symptoms and clinical characteristics among patients, as well as their unique perceptions, expectations, and preferences, there is often no single correct approach to any given set of clinical circumstances. In assisting patients to reach an informed decision, it is essential to elicit the breadth of their knowledge, values, preferences, and concerns.

The healthcare provider has a responsibility to ensure that patients understand and consider both the upside and downside of available options, in both the near and long terms. All previous guidelines reviewed by the writing committee have recognized the crucial role that patient preferences play in the selection of a treatment strategy (9,10,47–49). It is essential that these discussions be con-

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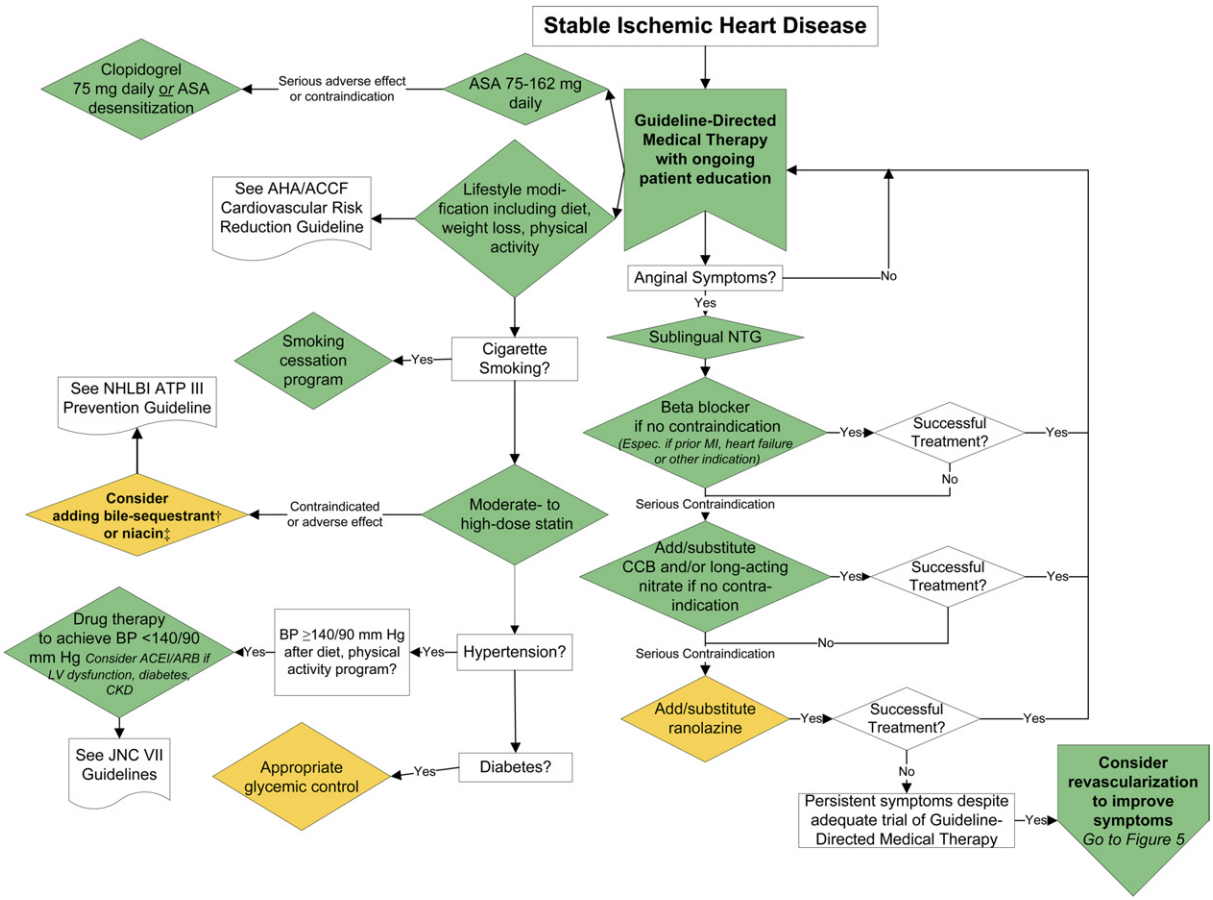

Figure 4. Algorithm for Guideline-Directed Medical Therapy for Patients With SIHD*

*Colors correspond to the class of recommendations in the ACCF/AHA Table 1. The algorithms do not represent a comprehensive list of recommendations (see text for all recommendations). †The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dL and is contraindicated when triglycerides are ≥500 mg/dL. ‡Dietary supplement niacin must not be used as a substitute for prescription niacin. ACCF indicates American College of Cardiology Foundation; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin-receptor blocker; ASA, aspirin, ATP III, Adult Treatment Panel 3; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol, JNC VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; MI, myocardial infarction; NHLBI, National Heart, Lung, and Blood Institute; and NTG, nitroglycerin.

ducted in a location and atmosphere that permits adequate time for discussion and contemplation. Initiating a discussion about the relative merits of PCI or CABG while a patient is in the midst of a procedure, for example, is not usually consistent with these principles.

In crafting a diagnostic strategy, the objective is to ascertain, as accurately as possible, whether the patient has IHD while minimizing the expense, discomfort, and potential harms of any tests or procedures. This includes avoiding procedures that are likely to yield false positive or false negative results or that are unnecessary or inappropriate. The objective for procedures intended to assess prognosis is similar.

Treatment options should be emphasized, especially in cases where there is no substantial advantage of one strategy over others. For most patients, the goal of treatment should be to simultaneously maximize survival and to achieve prompt and complete (or nearly complete) elimination of anginal chest pain with return to normal activities—in other words, a functional capacity of Canadian Cardiovascular Society (CCS) Class I angina (50). For example, for an otherwise healthy, active patient, the treatment goal is usually the complete elimination of chest pain and a return to vigorous physical activity. Conversely, an elderly patient with more severe angina and several serious coexisting medical problems might be satisfied with a reduction in symptoms that permits limited activities of daily living. Patients with anatomy that would ordinarily favor the choice of CABG could have comorbidities that make the risk of surgery unacceptable, in which case PCI or medical therapy is a more attractive option.

In counseling patients, the healthcare provider should be aware of, and help to rectify, common misperceptions. Many patients assume, for example, that opening a partially blocked artery will naturally prevent a heart attack and prolong life irrespective of other anatomic and clinical factors. When there is little expectation of an improvement in survival from revascularization, patients should be so informed. When evidence points to probable benefit from

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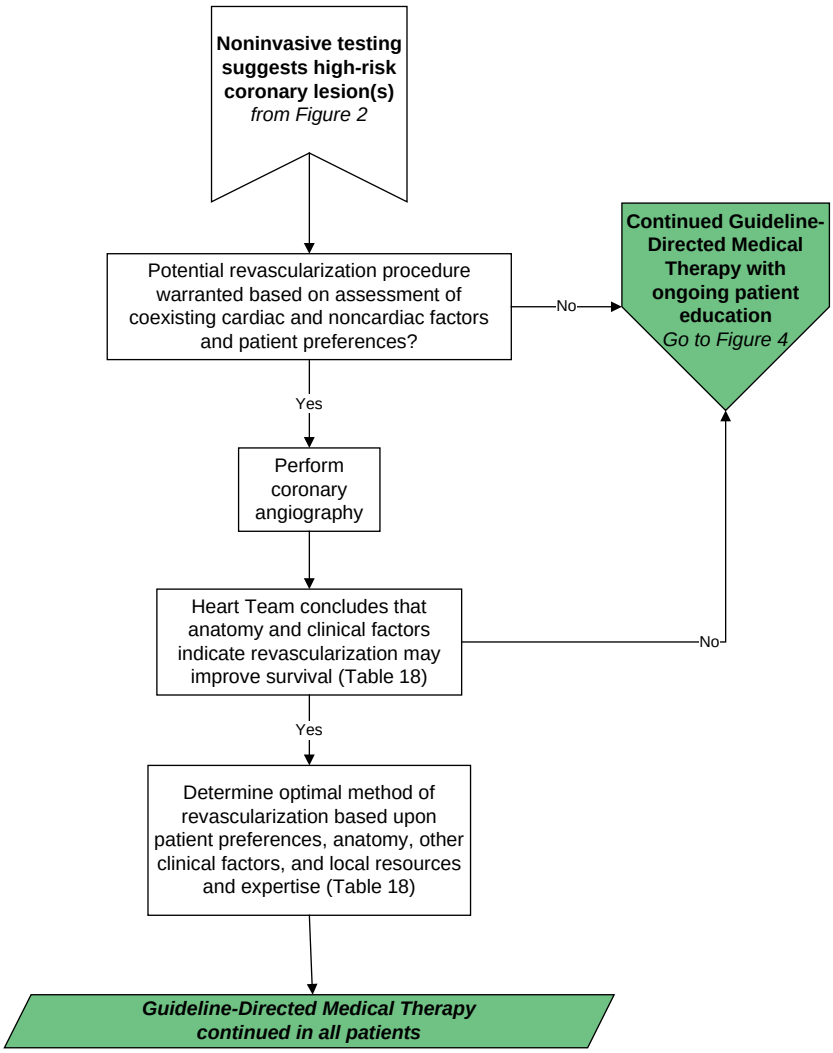

Figure 5. Algorithm for Revascularization to Improve Survival of Patients With SIHD*

*Colors correspond to the class of recommendations in the ACCF/AHA Table 1. The algorithms do not represent a comprehensive list of recommendations (see text for all recommendations).

either revascularization or medical therapy, it should be quantified to the extent possible, with explicit acknowledgment of uncertainties, and should be discussed in the context of what treatment option is best for that particular patient. When possible, the relative time course of response to therapy should be described for therapeutic choices. Some patients might, for example, initially opt for PCI over medical therapy because relief of symptoms is typically more rapid. However, when informed of the immediate risk of complications of PCI, some patients could prefer conservative therapy. Similarly, many patients choose PCI over CABG because it is less invasive and provides for quicker recovery, despite the fact that repeat revascularization procedures are performed more frequently after PCI. Patients' preferences in these circumstances often are influenced by their attitudes toward risk and by the tendency to let immediate smaller benefits outweigh larger future risks, a phenomenon termed "temporal discounting" (51).

2. Diagnosis of SIHD

2.1. Clinical Evaluation of Patients With Chest Pain

2.1.1. Clinical Evaluation in the Initial Diagnosis of SIHD in Patients With Chest Pain: Recommendations

CLASS I

1. Patients with chest pain should receive a thorough history and physical examination to assess the probability of IHD before additional testing (52). (*Level of Evidence: C*)
2. Patients who present with acute angina should be categorized as stable or unstable; patients with UA should be further categorized as being at high, moderate, or low risk (4,4a). (*Level of Evidence: C*)

2.1.2. History

The clinical examination is the key first step in evaluating a patient with chest pain and should include a detailed assessment of symptoms, including quality, location, sever-

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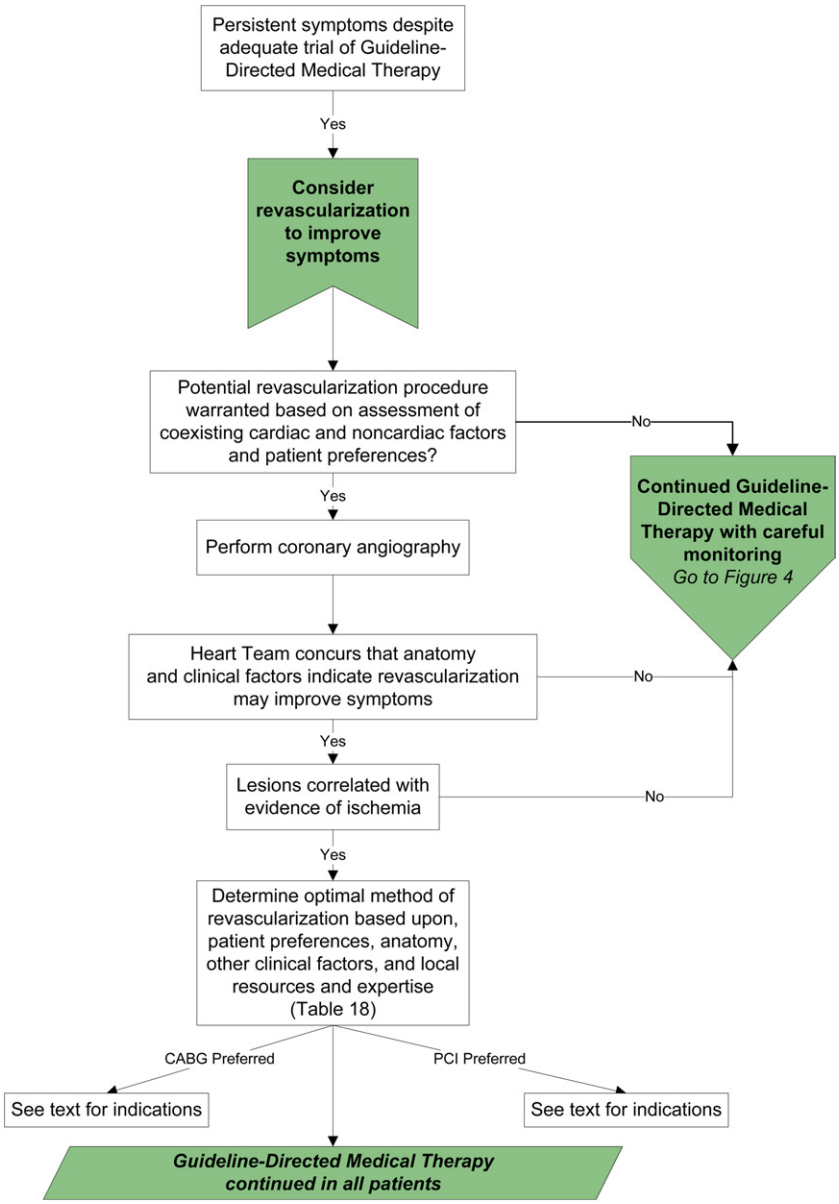

Figure 6. Algorithm for Revascularization to Improve Symptoms of Patients With SIHD*

*Colors correspond to the class of recommendations in the ACCF/AHA Table 1. The algorithms do not represent a comprehensive list of recommendations (see text for all recommendations). CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention.

ity, and duration of pain; radiation; associated symptoms; provocative factors; and alleviating factors. Adjectives often used to describe anginal pain include "squeezing," "grip-like," "suffocating," and "heavy," but it is rarely sharp or stabbing and typically does not vary with position or respiration. On occasion the patient might demonstrate the classic Levine's sign by placing a clenched fist over the precordium to describe the pain. Many patients do not, however, describe angina as frank pain but as tightness, pressure, or discomfort. Other patients, in particular women and the elderly, can present with atypical symptoms such as nausea, vomiting, midepigastric discomfort, or sharp (atypical) chest pain. In the WISE (Women's Ischemic Syndrome Evaluation) study, 65% of women with ischemia presented with atypical symptoms (54).

Anginal pain caused by cardiac ischemia typically lasts minutes. The location is usually substernal, and pain can radiate to the neck, jaw, epigastrium, or arms. Pain above the mandible, below the epigastrium, or localized to a small area over the left lateral chest wall is rarely angina. Angina is often precipitated by exertion or emotional stress and relieved by rest. Sublingual nitroglycerin also usually relieves angina, within 30 seconds to several minutes. The history can be used to classify symptoms as typical, atypical, or noncardiac chest pain (6) (Table 5). The patient presenting with angina must be categorized as having stable angina or

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Table 5. Clinical Classification of Chest Pain

Typical angina (definite)	1) Substernal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress and 3) relieved by rest or nitroglycerin
Atypical angina (probable)	Meets 2 of the above characteristics
Noncardiac chest pain	Meets 1 or none of the typical anginal characteristics

Adapted from Braunwald et al. (6).

UA (4,4a). UA is defined as new onset, increasing (in frequency, intensity, or duration), or occurring at rest (50) (Table 6). However, patients presenting with UA are subdivided by their short-term risk (Table 2). Patients at high or moderate risk often have experienced rupture of coronary artery plaque and have a risk of death higher than that of patients with stable angina but not as great as that of patients with AMI. These patients should be transferred promptly to an emergency department for evaluation and treatment. The short-term prognosis of patients with low-risk UA, however, is comparable to those with stable angina, and their evaluation can be conducted safely and expeditiously in an outpatient setting.

After thorough characterization of chest pain, the presence of risk factors for IHD (55) should be determined. These include smoking, hyperlipidemia, diabetes mellitus, hypertension, obesity or metabolic syndrome, physical inactivity, and a family history of premature IHD (i.e., onset in a father, brother, or son before age 55 years or a mother, sister, or daughter before age 65 years). A history of cerebrovascular or peripheral artery disease (PAD) also increases the likelihood of IHD.

2.1.3. Physical Examination

The examination is often normal or nonspecific in patients with stable angina (56) but could reveal related conditions such as heart failure, valvular heart disease, or hypertrophic cardiomyopathy. An audible rub suggests pericardial or pleural disease. Evidence of vascular disease includes carotid or renal artery bruits, a diminished pedal pulse, or a palpable abdominal aneurysm. Elevated blood pressure (BP), xanthomas, and retinal exudates point to the presence of IHD risk factors. Pain reproduced by pressure on the chest wall suggests a musculoskeletal etiology but does not eliminate the possibility of angina due to IHD.

2.1.4. Electrocardiography

2.1.4.1. RESTING ELECTROCARDIOGRAPHY TO ASSESS RISK: RECOMMENDATION

CLASS I

1. A resting ECG is recommended in patients without an obvious, noncardiac cause of chest pain (57–59). *(Level of Evidence: B)*

Patients with SIHD who have the following abnormalities on a resting ECG have a worse prognosis than those with normal ECGs (57–59): evidence of prior MI, especially Q waves in multiple leads or an R wave in V1 indicating a posterior infarction (60); persistent ST-T-wave inversions, particularly in leads V1 to V3 (61–64); left bundle-branch block (LBBB), bifascicular block, second- or third-degree atrioventricular (AV) block, or ventricular tachyarrhythmia (65); or left ventricular (LV) hypertrophy (62,66).

2.1.5. Differential Diagnosis

Although the symptoms of some patients might be consistent with a very high probability of IHD, in others, the etiology might be less certain, and alternative diagnoses should be considered (Table 7). However, even when angina seems likely to be related to IHD, other coexisting conditions can precipitate symptoms by inducing or exacerbating myocardial ischemia, by either increased myocardial oxygen demand or decreased myocardial oxygen supply (Table 8). When severe, these conditions can cause angina in the absence of significant anatomic coronary obstruction. Chest pain in women is less often due to IHD than in men, even when the pain is typical. Nevertheless, pain in women can be related to vascular dysfunction in the absence of epicardial CAD. Entities that cause increased oxygen demand include hyperthermia (particularly if accompanied by volume contraction) (67), hyperthyroidism, and cocaine or methamphetamine abuse. Sympathomimetic toxicity, due, for example, to cocaine intoxication, not only increases myocardial oxygen demand but also induces coronary vasospasm and can cause infarction in young patients. Long-term cocaine use can cause premature development of IHD (68,69). Severe uncontrolled hypertension increases LV wall tension, leading to increased myocardial oxygen demand and decreased subendocardial perfusion. Hypertrophic cardiomyopathy and aortic stenosis can induce even more severe LV hypertrophy and resultant wall tension. Ventricular or supraventricular tachycardias are another cause of increased myocardial oxygen demand, but when paroxysmal these are difficult to diagnose.

Anemia is the prototype for conditions that limit myocardial oxygen supply. Cardiac output rises when the hemoglobin drops to <9 g/dL, and ST-T-wave changes (depression or inversion) can occur at levels <7 g/dL.

Hypoxemia resulting from pulmonary disease (e.g., pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial fibrosis, or obstructive sleep apnea) can also precipitate angina. Polycythemia, leukemia, thrombocytosis, and hypergammaglobulinemia

Table 6. Three Principal Presentations of UA

Rest angina	Angina occurring at rest and usually prolonged >20 min, occurring within 1 wk of presentation
New-onset angina	Angina of at least CCS Class III severity with onset within 2 mo of initial presentation
Increasing angina	Previously diagnosed angina that is distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by ≥1 CCS class within 2 mo of initial presentation to at least CCS Class III severity)

CCS indicates Canadian Cardiovascular Society.
Reproduced from Braunwald (50).

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Table 7. Alternative Diagnoses to Angina for Patients With Chest Pain

Nonischemic Cardiovascular	Pulmonary	Gastrointestinal	Chest Wall	Psychiatric
Aortic dissection	Pulmonary embolism	Esophageal	Costochondritis	Anxiety disorders
		Esophagitis	Fibrositis	Hyperventilation
		Spasm	Rib fracture	Panic disorder
		Reflux	Sternoclavicular arthritis	Primary anxiety
			Herpes zoster (before the rash)	
Pericarditis	Pneumothorax	Biliary		Affective disorders (i.e., depression)
	Pneumonia	Colic		Somatiform disorders
	Pleuritis	Cholecystitis Choledocholithiasis		Thought disorders (i.e., fixed delusions)
		Cholangitis		
		Peptic ulcer		
		Pancreatitis		

Reproduced from Gibbons et al. (7).

are associated with increased blood viscosity that can decrease coronary artery blood flow and precipitate angina, even in patients without significant coronary stenoses.

2.1.6. Developing the Probability Estimate

When the clinical evaluation is complete, the practitioner must determine whether the probability of IHD is sufficient to recommend further testing, which is often a standard exercise test. When the probability of disease is <5%, further testing is usually not warranted because the likelihood of a false-positive test (i.e., positive test in the absence of obstructive CAD) is actually higher than that of a true positive. On the other hand, when the exercise test is negative in a patient who has a very high likelihood of IHD on the basis of the history, there is a substantial chance that in reality the result is falsely negative. Thus, further testing is most useful in patients in whom the cause of chest pain is truly uncertain (i.e., the probability of IHD is between 20% and 70%). It is necessary to note, however, that these probabilities relate solely to the presence of obstructive CAD and do not pertain to ischemia due to microvascular disease or other causes. They also do not reflect the likelihood that a nonobstructing plaque could become unstable and cause ischemia.

Table 8. Conditions Provoking or Exacerbating Ischemia

Increased Oxygen Demand	Decreased Oxygen Supply
Noncardiac	*Noncardiac*
Hyperthermia	Anemia
Hyperthyroidism	Hypoxemia
Sympathomimetic toxicity (i.e., cocaine use)	Pneumonia
Hypertension	Asthma
Anxiety	Chronic obstructive pulmonary disease
Arteriovenous fistulae	Pulmonary hypertension
	Interstitial pulmonary fibrosis
	Obstructive sleep apnea
	Sickle cell disease
	Sympathomimetic toxicity (i.e., cocaine use, pheochromocytoma)
	Hyperviscosity
	Polycythemia
	Leukemia
	Thrombocytosis
	Hypergammaglobulinemia
Cardiac	*Cardiac*
Hypertrophic cardiomyopathy	Aortic stenosis
Aortic stenosis	Hypertrophic cardiomyopathy
Dilated cardiomyopathy	Significant coronary obstruction
Tachycardia	Microvascular disease
Ventricular	
Supraventricular	

Modified from Gibbons et al. (7).

A landmark study (52) showed how information about the type of pain and age and sex of the patient can provide a reasonable estimate of the likelihood of IHD. For instance, a 64-year-old man with typical angina has a 94% likelihood of having significant coronary stenosis. A 32-year-old woman with nonanginal chest pain has a 1% chance of coronary stenosis (70–72). Other clinical characteristics that improved the accuracy of prediction include active or recent smoking, Q-wave or ST-T-wave changes on the ECG, hyperlipidemia (defined at the time of study as a total cholesterol level >250 mg/dL), and diabetes mellitus (defined at that time as a fasting glucose level >140 mg/dL). Of these characteristics, diabetes mellitus had the greatest influence on increasing the probability of IHD. The presence of hypertension or a family history of premature IHD did not provide additional predictive accuracy. The results of the aforementioned landmark study subsequently were replicated with data from CASS (Coronary Artery Surgery Study) (73) and were within 5% of the original estimates for 23 of 24 patient groupings. The single major exception was the category of adults who were ≤50 years of age with atypical angina, for whom the CASS estimate was 17% higher. On the basis of this high degree of concordance, the data from these studies were merged in the 2002 Chronic Stable Angina guideline (7,52,73) (Table 9).

Additional validation studies were conducted with data from the Duke Databank for Cardiovascular Disease, which also incorporated electrocardiographic findings (Q waves or ST-T changes) and information about risk factors (smoking, diabetes mellitus, hyperlipidemia) (71). Table 10 presents the Duke data for mid-decade patients (35, 45, 55, and 65 years of age). Two probabilities are given. The first is for a low-risk patient with no risk factors and a normal ECG.

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Table 9. Pretest Likelihood of CAD in Symptomatic Patients According to Age and Sex* (Combined Diamond/Forrester and CASS Data)

	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
Age, y	Men	Women	Men	Women	Men	Women
30–39	4	2	34	12	76	26
40–49	13	3	51	22	87	55
50–59	20	7	65	31	93	73
60–69	27	14	72	51	94	86

CAD indicates coronary artery disease; and CASS, Coronary Artery Surgery Study.
*Each value represents the percent with significant CAD on catheterization.
Adapted from Forrester and Diamond (52,73).

The second is for a high-risk patient who smokes and has diabetes mellitus and hyperlipidemia but has a normal ECG. A key contribution of the Duke Databank is the value of incorporating data about risk factors into the probability estimate.

A limitation of these predictive models, however, is that because they were developed with data from patients referred to university medical centers, they tended to overestimate the likelihood of IHD in patients at lower risk. It is possible to correct this referral (or ascertainment) bias by using the overall prevalence of IHD in the primary-care population (72), although these adjustments are themselves subject to error if the prevalence estimates are flawed.

An additional limitation of these models is that they were derived from populations of patients ≤70 years of age. Yet another drawback is that they perform less well in women, in part because the prevalence of obstructive CAD is lower in women than in men. As shown in Table 9, the Diamond-Forrester model substantially overestimates the likelihood of CAD compared with the prevalence observed in the WISE study (52,74).

After integrating data from the clinical evaluation, model predictions, and other relevant factors to develop a probability estimate, the clinician must then engage the patient in a process of shared decision making, as noted in Section 1.8, to determine whether further testing is warranted.

Table 10. Comparing Pretest Likelihood of CAD in Low-Risk Symptomatic Patients With High-Risk Symptomatic Patients (Duke Database)

	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
Age, y	Men	Women	Men	Women	Men	Women
35	3–35	1–19	8–59	2–39	30–88	10–78
45	9–47	2–22	21–70	5–43	51–92	20–79
55	23–59	4–21	45–79	10–47	80–95	38–82
65	49–69	9–29	71–86	20–51	93–97	56–84

Each value represents the percentage with significant CAD. The first is the percentage for a low-risk, mid-decade patient without diabetes mellitus, smoking, or hyperlipidemia. The second is that of a patient of the same age with diabetes mellitus, smoking, and hyperlipidemia. Both high- and low-risk patients have normal resting ECGs. If ST-T-wave changes or Q waves had been present, the likelihood of CAD would be higher in each entry of the table.
CAD indicates coronary artery disease; and ECG, electrocardiogram.
Reprinted from Pryor et al. (71).

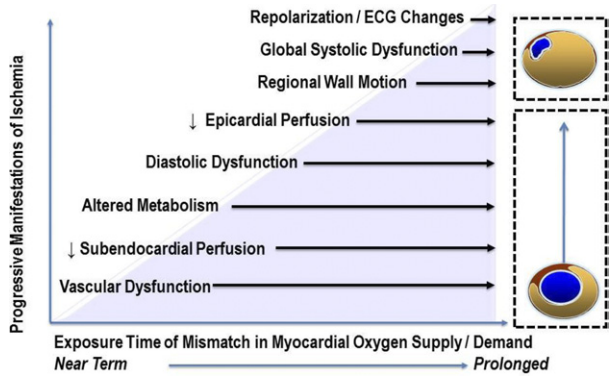

Figure 7. The Ischemic Cascade

Reproduced with permission from Shaw et al. (75).

2.2. Noninvasive Testing for Diagnosis of IHD

2.2.1. Approach to the Selection of Diagnostic Tests to Diagnose SIHD

Functional or stress testing to detect inducible ischemia has been the "gold standard" and is the most common noninvasive test used to diagnose SIHD. All functional tests are designed to provoke cardiac ischemia by using exercise or pharmacological stress agents either to increase myocardial work and oxygen demand or to induce vasodilation-elicited heterogeneity in induced coronary flow. These techniques rely on the principles embodied within the ischemic cascade (Figure 7), in which graded ischemia of increasing severity and duration produces sequential changes in perfusion, relaxation and contraction, wall motion, repolarization, and, ultimately, symptoms, all of which can be detected by an array of cardiovascular testing modalities (75). The production of ischemia, however, depends on the severity of stress imposed (i.e., submaximal exercise can fail to produce ischemia) and the severity of the flow disturbance. Coronary stenoses <70% are often undetected by functional testing.

Because abnormalities of regional or global ventricular function occur later in the ischemic cascade, they are more likely to indicate severe stenosis and, thus, demonstrate a higher diagnostic specificity for SIHD than do perfusion defects, such as those seen on nuclear MPI. Isolated perfusion defects, on the other hand, can result from stenoses of borderline significance, raising the sensitivity of nuclear MPI for underlying CAD but lowering the specificity for more severe stenosis.

The recent availability of multislice CCTA allows for the noninvasive visualization of anatomic CAD with high-resolution images similar to invasive coronary angiography. As would be expected, CCTA and invasive angiography exhibit a high degree of concordance, as they are both anatomic tests, and CCTA is more sensitive in detecting obstructive CAD, especially at diameter stenosis ≤70%, than is nuclear MPI (76).

The accuracy of a CCTA reader in estimating coronary stenosis within a vessel is hindered by the presence of dense

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coronary calcification and a tendency to overestimate the severity of lesions relative to invasive angiography (77). No direct comparisons of the effectiveness of a functional approach with inducible ischemia or an anatomic approach assessing coronary stenosis have been completed in the noninvasive setting, although several randomized controlled trials (RCTs) are under way, which will directly or indirectly compare test modalities: PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain; clinicaltrials.gov identifier NCT01174550), RESCUE (Randomized Evaluation of Patients With Stable Angina Comparing Diagnostic Examinations; clinicaltrials.gov identifier NCT01262625), and ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; clinicaltrials.gov identifier NCT01471522).

In 2010, the United Kingdom's National Institute for Clinical Excellence Guidance for "Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin" provide, for a healthcare system that allocates resources differently from that of the United States, recommendations for an initial assessment of CAD. This Guidance recommends beginning in people without confirmed CAD with a detailed clinical assessment and performing a 12-lead ECG in those in whom stable angina cannot be diagnosed or excluded on the basis of clinical assessment alone. The Guidance suggests that there is no need for further testing in those with an estimated likelihood <10%. In those with an estimated likelihood of CAD of 10% to 29%, the National Institute for Clinical Excellence document recommends beginning with CT coronary artery calcium (CAC) scoring as the first-line diagnostic investigation, whereas the present SIHD guideline provides a Class IIb recommendation for several reasons, as outlined in Section 2.2.4.2.

2.2.1.1. ASSESSING DIAGNOSTIC TEST CHARACTERISTICS

A hierarchy of diagnostic test evidence has been proposed by Fryback and Thornbury (78) and ranges from evidence on technical quality (level 1) through test accuracy (sensitivity and specificity associated with test interpretation), to changes in diagnostic thinking, effect on patient management, and patient outcomes, to societal costs and benefits (level 6). A similar framework has been proposed for biomarkers by Hlatky et al. (79). In practice, although knowledge of the effect of diagnostic testing on outcomes would be highly desirable, the vast majority of available evidence is on diagnostic or prognostic accuracy. Therefore, this information most commonly is used to compare test performance.

Diagnostic accuracy is commonly represented by the terms *sensitivity* and *specificity*, which are calculated by comparing test results to the "gold standard" of the results of invasive coronary angiography. The sensitivity of any noninvasive test to diagnose SIHD expresses the frequency that a patient with angiographic IHD will have a positive test result, whereas the specificity measures the frequency that a patient without IHD will have a negative result. In addition, predictive accuracy represents the frequency that a patient with a positive test does have IHD (positive predictive value) or that a patient with a negative test truly does not have IHD (negative predictive value). The predictive accuracy may be used for both diagnostic and prognostic accuracy analyses; in the latter case, the comparison is to subsequent cardiovascular events. It is important to note that apparent test performance can be altered substantially by the pretest probability of IHD (52,80,81), making the accurate assessment of pretest probability and proper patient selection essential for diagnostic interpretation statements on IHD prevalence by test results. The positive predictive value of a test declines as the disease prevalence decreases in the population under study, whereas the negative predictive accuracy increases (82). Finally, the performance of noninvasive tests also varies in certain patient populations, such as obese patients, the elderly, and women (Section 5.12), who often are underrepresented in clinical studies.

Estimates of all test characteristics are subject to workup bias, also known as verification or posttest referral bias (81,83,84). This bias occurs when the results of stress testing are used to decide which patients undergo the standard reference procedure (invasive coronary angiography) to establish a definitive diagnosis of IHD (i.e., patients with positive results on stress testing are referred for coronary angiography, whereas those with negative results are not). This bias has the effect of raising the measured sensitivity and lowering the measured specificity in relation to their true values. Mathematical corrections can be applied to estimate corrected values (84–86).

Diagnostic testing is most valuable when the pretest probability of IHD is intermediate—for example, when a 50-year-old man has atypical angina, and the probability of IHD is approximately 50% (Table 9). The precise definition of intermediate probability (i.e., between 10% and 90%, 20% and 80%, or 30% and 70%) is somewhat arbitrary. In addition to these boundaries, other factors are important in the decision to refer a patient to testing, including the degree of uncertainty acceptable to the physician and patient; the likelihood of an alternative diagnosis; the accuracy of the diagnostic test selected (i.e., sensitivity and specificity), test reliability, procedural cost, and the potential risks of further testing; and the benefits and risks of treatment in the absence of additional testing. A definition of 10% and 90%, first advocated in 1980 (87), has been applied in several studies (88,89). Although broad, this range still excludes several sizable patient groups (e.g., older men with typical angina and younger women with nonanginal pain). When the probability of IHD is high, a positive test result is merely confirmatory, whereas a negative test result might not diminish the probability of disease sufficiently to be clinically useful and could even be misleading because of the possibility that it is a false negative result. When the probability of IHD is very low, however, a

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negative test result is simply confirmatory, whereas a positive test result might not be clinically useful and could be misleading if falsely positive. The importance of relying on clinical judgment and refraining from testing in very low-risk populations is well illustrated by a thought experiment proposed by Diamond and Kaul in a letter to the editor of *The New England Journal of Medicine*:

> "As an example, suppose we have a test marker with 80% sensitivity and 80% specificity (typical of cardiac stress tests). Given 100 individuals with a10% disease prevalence, there will be 8 true positives (100 × 0.1 × 0.8) and 18 false positives (100 × 0.9 × 0.2). If we refer only these 26 positive responders for angiography, the observed "diagnostic yield" is only 31% (8/26). Moreover, the test's sensitivity will appear to be 100% (all diseased subjects having a positive test), and its specificity will appear to be 0% (all non-diseased subjects also having a positive test). Hence, the more we rely on a test, the less well it appears to perform." (90, p. 93)

The likelihood of CAD proposed above differs substantially from that in the populations from which the estimates of noninvasive test performance were derived; the overall prevalence of CAD from a meta-analysis was 60% (91). Instead, contemporary age-, sex-, and symptom-based IHD probability estimates can be gleaned from a multicenter cohort of 14,048 patients with suspected IHD undergoing CCTA (92).

2.2.1.2. SAFETY AND OTHER CONSIDERATIONS POTENTIALLY AFFECTING TEST SELECTION

All forms of noninvasive stress testing carry some risk. Maximal exercise testing is associated with a low but finite incidence of cardiac arrest, AMI, and even death. Pharmacological stress agents fall into 2 broad categories: beta-agonists such as dobutamine, which increase heart rate and inotropy, and vasodilators such as adenosine, dipyridamole, or regadenoson, which act to increase blood flow to normal arteries while decreasing perfusion to stenotic vessels. Each of these pharmacological stress agents also carries a very small risk of drug-specific adverse events (dobutamine: ventricular arrhythmias; dipyridamole/adenosine: bronchospasm in chronic obstructive pulmonary disease).

Nuclear perfusion imaging and CCTA use ionizing radiation techniques for visualizing myocardial perfusion and anatomic CAD, respectively. Risk projections are based largely on observations from atomic bomb survivors exposed to higher levels of ionizing radiation. The Linear-No-Threshold hypothesis states that any exposure could result in an increased projected cancer risk and that there is a dose–response relationship to elevated cancer risk with higher exposures. Considerable controversy exists surrounding the extrapolation of projected cancer risk to low-level exposure in medical testing, and no reported evidence links low-level exposure to observed cancer risk. Even when the Linear-No-Threshold hypothesis is used, the projected incident cancer is estimated to be very low for nuclear MPI and CCTA (93–95). Nevertheless, general agreement exists that the overriding principle of caution and safety should apply by projecting the Linear-No-Threshold hypothesis.

The principle of As Low as Reasonably Achievable (ALARA) should be applied in all patient populations. For CCTA performed with contemporary equipment in accordance with the Society of Cardiovascular Computed Tomography recommendations, average estimated radiation dose ranges from 5 to 10 mSv (96). For stress nuclear MPI, when the American Society of Nuclear Cardiology–recommended rest-stress Tc-99m SPECT or Rb-82 positron emission tomography (PET) protocol (97) is used, the estimated radiation dose is approximately 11 or 3 mSV, respectively (97,98). On the basis of American Society of Nuclear Cardiology guidelines, dual-isotope or rest-stress Tl-201 imaging is discouraged for diagnostic procedures because of its high radiation exposure. The use of new high-efficiency nuclear MPI cameras results in a similar or lower effective dose for both dual-isotope and rest-stress Tc-99m imaging (99–101). For both CT and nuclear imaging, the AHA, Society of Cardiovascular Computed Tomography, and American Society of Nuclear Cardiology recommend widespread application of dose-reduction techniques whenever possible (96–98). Clinicians should apply the concept of benefit-to-risk ratio when considering testing. When testing is used appropriately, the clinical benefit in terms of supportive diagnostic or prognostic accuracy exceeds the projected risk such that there is an advantage to testing (13,14). When it is used inappropriately or overused, the benefit of testing is low, and the risk of exposure is unacceptably high. Of note, care should be taken when exposing low-risk patients to ionizing radiation. This is particularly of concern in younger patients for whom the projected cancer risk is elevated (102).

Use of contrast agents with CCTA can cause allergic reactions. Contrast agents also can affect renal function and therefore should be avoided in patients with chronic kidney disease. CMR might be contraindicated in patients with claustrophobia or implanted devices, and use of gadolinium contrast agents is associated rarely with nephrogenic systemic fibrosis. For this reason, gadolinium is contraindicated in patients with severe renal dysfunction (estimated glomerular filtration rates <30 mL/min per 1.73 m^2), and the dose should be adjusted for patients with mild to moderate dysfunction (estimated glomerular filtration rates 30 to 60 mL/min per 1.73 m^2). As with all safety considerations, the potential risks need to be considered carefully in concert with the potential benefits from the added information obtained to guide care.

In addition to pretest likelihood, a variety of clinical factors influence noninvasive test selection (103–105). Chief among these are the patient's ability to exercise, body habitus, cardiac medication use, and ECG interpretability. The decision to add imaging in patients who have an interpretable ECG and are capable of vigorous exercise is important because imaging and nonimaging testing have

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different diagnostic accuracies, predictive values, and costs. Most, but not all, studies evaluating cohorts of patients undergoing both exercise ECG and stress imaging have shown that the addition of imaging information provides incremental benefit in terms of both diagnostic and prognostic information with an acceptable increase in cost (Section 2.2.1.5) (106–117).

Other factors affecting test choice include local availability of specific tests, local expertise in test performance and interpretation, the presence of multiple diagnostic or prognostic questions better addressed by one form of testing over another, and the existence of prior test results (especially when prior images are available for comparison). Finally, although echocardiographic, radionuclide, and CMR stress imaging can have complementary roles for estimating patient prognosis, there is rarely a reason to perform multiple tests in the same patient, unless the results of the initial imaging test are unsatisfactory for technical reasons or the findings are equivocal or require confirmation.

2.2.1.3. EXERCISE VERSUS PHARMACOLOGICAL TESTING

When a patient is able to perform routine activities of daily living without difficulty, exercise testing to provoke ischemia is preferred because it often can provide a higher physiological stress than would be achieved by pharmacological testing. This can translate into a superior ability to detect ischemia as well as providing a correlation to a patient's daily symptom burden and physical work capacity not offered by pharmacological stress testing. In addition, exercise capacity alone is a very strong prognostic indicator (118,119).

The goal of exercise testing for suspected SIHD patients is 1) to achieve high levels of exercise (i.e., maximal exertion), which in the setting of a negative ECG generally and reliably excludes obstructive CAD, or 2) to document the extent and severity of ECG changes and angina at a given workload (i.e., demand ischemia) so as to predict the likelihood of underlying significant or severe CAD. Thus, candidates for exercise testing must possess sufficient functional capacity to attain maximal, volitional stress levels. Because there is high variability in age-predicted maximal heart rate among subjects of identical age (120), achieving 85% of age-predicted maximal heart rate might not indicate sufficient effort during exercise testing and should not be used as a criterion to terminate a stress test (121). Failure to reach peak heart rate (if beta blockers have been held as recommended) or to achieve adequate levels of exercise in the setting of a negative ECG is consistent with functional disability and results in an indeterminate estimation of CAD. Female-specific age-predicted maximal heart rate and functional capacity measurements are available (118,122).

Standard treadmill protocols initiate exercise at 3.2 to 4.7 metabolic equivalents (METs) of work and increase by several METs every 2 to 3 minutes of exercise (e.g., modified or standard Bruce protocol). Most activities of daily living require approximately 4 to 5 METs of physical work to perform. Thus, reported limitations in activities of daily living identify a patient who might be unable to perform maximal exercise. Gentler treadmill protocols, with incremental stages of 1 MET, or bicycle stress can help some patients achieve maximal exercise capacity.

Optimal candidates with sufficient physical functioning may be identified as those capable of performing at least moderate physical functioning (i.e., performing at least moderate household, yard, or recreational work *and* most activities of daily living) and with no disabling comorbidity (including frailty, advanced age, marked obesity, PAD, chronic obstructive pulmonary disease, or orthopedic limitations). Patients incapable of at least moderate physical functioning or with disabling comorbidity should be referred for pharmacological stress imaging. In the setting of submaximal exercise and a negative stress ECG, consideration should be given to performing additional testing with pharmacological stress imaging to evaluate for inducible ischemia.

2.2.1.4. CONCOMITANT DIAGNOSIS OF SIHD AND ASSESSMENT OF RISK

Although the primary goal of testing among patients with new onset of symptoms suggesting SIHD is to diagnose or exclude obstructive CAD, the various modalities also can provide additional information about long-term risk (Section 3.3.2), and this prognostic ability may influence the selection of an initial test. Exercise capacity remains one of the strongest indicators of long-term risk (including death) for men and women with suspected and known CAD (118,123–125). In addition, information derived from treadmill exercise (e.g., Duke treadmill score (126,127) and heart rate recovery) provides incremental diagnostic and prognostic information. For this reason, it is preferable to perform exercise stress if the patient is able to achieve a maximal workload. For the exercise-capable patient with a normal baseline ECG, the decision to perform imaging with nuclear or echocardiographic techniques along with stress ECG should be based on many factors, including the likelihood of garnering substantial incremental prognostic information that is likely to alter clinical and therapeutic management.

2.2.1.5. COST-EFFECTIVENESS

Estimates of cost-effectiveness of various testing strategies in symptomatic patients have been used to inform responses to rising healthcare costs. However, to be of value, estimates of cost-effectiveness must use contemporary estimates of effectiveness that incorporate considerations of disease prevalence and test accuracy. Furthermore, costs must reflect not only the index test but also the episode of care and the longer-term induced costs and outcomes of diagnosed and undiagnosed SIHD. Ideally, these data would be derived from RCTs or registries designed to compare the effectiveness of testing strategies and observed associated costs. However, in the interim until such evidence is available, mixed methods and decision analytic models provide general estimates of the

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cost-effectiveness of various forms of testing. Mixed methods use observational evidence of index and downstream procedures, hospitalization, and drug costs and apply cost weights to estimate cumulative costs (128–130), whereas decision analytic models simulate clinical and financial data (131–137). Regardless of the approach, inherent assumptions and uncertainties with regard to the data and incomplete consideration of risks and benefits require that such calculations be considered as estimates only (138).

In most studies, stress imaging is estimated to provide a benefit over exercise ECG at a reasonable cost, commensurate with accepted values for cost effectiveness (i.e., at the threshold for economic efficiency of <$50,000 per added year of life), a result driven primarily by more frequent angiography and adverse cardiovascular events for those with a negative exercise ECG. Results of decision analytic and mixed modeling approaches comparing stress echocardiography with myocardial perfusion SPECT vary, with some favoring exercise echocardiography and others favoring exercise nuclear MPI (128,133).

The patient's pretest likelihood of CAD also influences cost-effectiveness such that exercise echocardiography is more cost-effective in lower-risk patients (with annual risk of death or MI <2%) than in higher-risk patients, in whom nuclear MPI is more cost-effective. Use of invasive coronary angiography as a first test is not cost-effective in patients with a pretest probability <75% (139,140). Finally, it is important to note that as the reimbursement for stress imaging decreases (it is now less than half the value used in older studies), the relative cost-effectiveness (dollars/quality-adjusted life-year saved) of stress imaging is more favorable than that of exercise ECG, and the comparative advantage of lower- to higher-cost imaging procedures is minimized.

The cost-efficiency of CCTA is less well studied but also depends on disease prevalence (139,140). Data conflict as to whether patients undergoing CCTA as initial imaging modality are less or more likely to undergo invasive coronary angiography or revascularization, although it appears that they have similar or lower rates of adverse cardiovascular events (128,130,141,142). As a result, CCTA performed alone or in combination with functional testing minimizes adverse cardiac events, maximizes quality-adjusted life-years (140,143), and is estimated to be cost-effective.

Although data on cost-effectiveness and patient satisfaction for CMR are limited, evidence suggests that CMR can improve patient management. The German Pilot/European Cardiovascular Magnetic Resonance (EuroCMR) registry of 11,040 consecutive patients evaluated for cardiomyopathy, ischemia, and myocardial viability found that CMR satisfied all requested imaging needs in 86% of patients so that no further imaging was required (144). In the 3,351 stress CMR cases, invasive angiography was avoided in 45%, compared with 18% in patients who underwent nuclear imaging.

2.2.2. Stress Testing and Advanced Imaging for Initial Diagnosis in Patients With Suspected SIHD Who Require Noninvasive Testing: Recommendations

See Table 11 for a summary of recommendations from this section.

2.2.2.1. ABLE TO EXERCISE

CLASS I

1. Standard exercise ECG testing is recommended for patients with an intermediate pretest probability of IHD who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity (114,145–147). *(Level of Evidence: A)*
2. Exercise stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who have an *un*interpretable ECG and at least moderate physical functioning or no disabling comorbidity (91,132,148–156). *(Level of Evidence: B)*

CLASS IIa

1. For patients with a low pretest probability of obstructive IHD who do require testing, standard exercise ECG testing can be useful, provided the patient has an interpretable ECG and at least moderate physical functioning or no disabling comorbidity. *(Level of Evidence: C)*
2. Exercise stress with nuclear MPI or echocardiography is reasonable for patients with an intermediate to high pretest probability of obstructive IHD who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity (91,132,148–156). *(Level of Evidence: B)*
3. Pharmacological stress with CMR can be useful for patients with an intermediate to high pretest probability of obstructive IHD who have an *un*interpretable ECG and at least moderate physical functioning or no disabling comorbidity (153,157,158). *(Level of Evidence: B)*

CLASS IIb

1. CCTA might be reasonable for patients with an intermediate pretest probability of IHD who have at least moderate physical functioning or no disabling comorbidity (158–166). *(Level of Evidence: B)*
2. For patients with a low pretest probability of obstructive IHD who do require testing, standard exercise stress echocardiography might be reasonable, provided the patient has an interpretable ECG and at least moderate physical functioning or no disabling comorbidity. *(Level of Evidence: C)*

CLASS III: No Benefit

1. Pharmacological stress with nuclear MPI, echocardiography, or CMR is not recommended for patients who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity (155,167,168). *(Level of Evidence: C)*
2. Exercise stress with nuclear MPI is not recommended as an initial test in low-risk patients who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity. *(Level of Evidence: C)*

2.2.2.2. UNABLE TO EXERCISE

CLASS I

1. Pharmacological stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical

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Table 11. Stress Testing and Advanced Imaging for Initial Diagnosis in Patients With Suspected SIHD Who Require Noninvasive Testing

Test	Exercise Status		ECG Interpretable		Pretest Probability of IHD			COR	LOE	References
	Able	Unable	Yes	No	Low	Intermediate	High			
Patients able to exercise*										
Exercise ECG	X		X			X		I	A	(114,145–147)
Exercise with nuclear MPI or Echo	X			X		X	X	I	B	(91,132,148–156)
Exercise ECG	X		X		X			IIa	C	N/A
Exercise with nuclear MPI or Echo	X		X			X	X	IIa	B	(91,132,148–156)
Pharmacological stress CMR	X			X		X	X	IIa	B	(153,157,158)
CCTA	X		Any			X		IIb	B	(158–166)
Exercise Echo	X		X			X		IIb	C	N/A
Pharmacological stress with nuclear MPI, Echo, or CMR	X		X		Any			III: No Benefit	C	(155,167,168)
Exercise stress with nuclear MPI	X		X		X			III: No Benefit	C	N/A
Patients unable to exercise										
Pharmacological stress with nuclear MPI or Echo		X	Any			X	X	I	B	(148–150,152–156)
Pharmacological stress Echo		X	Any		X			IIa	C	N/A
CCTA		X	Any		X	X		IIa	B	(158–166)
Pharmacological stress CMR		X	Any			X	X	IIa	B	(153,157,158,169–172)
Exercise ECG		X		X	Any			III: No Benefit	C	(91,132,148–156,161)
Other										
CCTA If patient has any of the following: a) Continued symptoms with prior normal test, or b) Inconclusive exercise or pharmacological stress, or c) Unable to undergo stress with MPI or Echo	Any		Any			X		IIa	C	(173)
CAC score	Any		Any		X			IIb	C	(174)

CAC indicates coronary artery calcium; CCTA, cardiac computed tomography angiography; CMR, cardiac magnetic resonance imaging; COR, class of recommendation; ECG, electrocardiogram; Echo, echocardiography; IHD, ischemic heart disease; LOE, level of evidence; MPI, myocardial perfusion imaging; N/A, not available; and SIHD, stable ischemic heart disease.

*Patients are candidates for exercise testing if they are capable of performing at least moderate physical functioning (i.e., moderate household, yard, or recreational work *and* most activities of daily living) and have no disabling comorbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.

functioning or have disabling comorbidity (148–150,152–156). *(Level of Evidence: B)*

CLASS IIa

1. Pharmacological stress echocardiography is reasonable for patients with a low pretest probability of IHD who require testing and are incapable of at least moderate physical functioning or have disabling comorbidity. *(Level of Evidence: C)*
2. CCTA is reasonable for patients with a low to intermediate pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity (158–166). *(Level of Evidence: B)*
3. Pharmacological stress CMR is reasonable for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity (153,157,158,169–172). *(Level of Evidence: B)*

CLASS III: No Benefit

1. Standard exercise ECG testing is not recommended for patients who have an *un*interpretable ECG or are incapable of at least moderate physical functioning or have disabling comorbidity (91,132,148–156,161). *(Level of Evidence: C)*

2.2.2.3. OTHER

CLASS IIa

1. CCTA is reasonable for patients with an intermediate pretest probability of IHD who a) have continued symptoms with prior normal test findings, or b) have inconclusive results from prior exercise or pharmacological stress testing, or c) are unable to undergo stress with nuclear MPI or echocardiography (173). (*Level of Evidence: C*)

CLASS IIb

1. For patients with a low to intermediate pretest probability of obstructive IHD, noncontrast cardiac CT to determine the CAC score may be considered (174). *(Level of Evidence: C)*

See Online Data Supplement 1 for additional data on diagnostic accuracy of stress testing and advanced imaging for the diagnosis of suspected SIHD.

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2.2.3. Diagnostic Accuracy of Nonimaging and Imaging Stress Testing for the Initial Diagnosis of Suspected SIHD

2.2.3.1. EXERCISE ECG

The exercise ECG has been the cornerstone of diagnostic testing of SIHD patients for several decades. The diagnostic endpoint for an ischemic ECG is ≥1 mm horizontal or down-sloping (at 80 ms after the J point) ST-segment depression at peak exercise. ST-segment elevation (in a non–Q-wave lead and excluding aortic valve replacement) during or after exercise occurs infrequently but represents a high-risk ECG finding consistent with an ACS. The diagnostic accuracy of exertional ST-segment depression has been studied extensively in several meta-analyses, systematic reviews, large observational registries, and RCTs (114,145–147,175). The composite diagnostic sensitivity and specificity, unadjusted for referral bias, is 61% and ranges from 70% to 77%, but it is lower in women (146,147,175) and lower than that for stress imaging modalities. A similar accuracy has been reported for correlation of ECG ischemia with anatomic CAD by CCTA (176). Diagnostic accuracy is improved when consideration is given to additional non-ECG factors, such as exercise duration, chronotropic incompetence, angina, ventricular arrhythmias, heart rate recovery, and hemodynamic response to exercise (i.e., drop in systolic BP), or when combination scores such as the Duke treadmill or Lauer scores are applied (118,177–180).

Multiple factors in addition to the patient's inability to achieve maximal exercise levels influence the accuracy of the ECG during exercise testing to diagnose obstructive CAD. Resting ECG abnormalities preclude accurate interpretation of exercise-induced changes and reduce test accuracy; these include abnormalities affecting the ST segment, such as LV hypertrophy, LBBB, ventricular-paced rhythm, or any resting ST-segment depression ≥0.5 mm. Although some have proposed calculating the difference from rest to exercise of changes ≥1 mm for patients with significant resting ST-segment changes, the accuracy of this approach has been less extensively studied and validated. The interpretation of ST-segment changes in patients with right bundle-branch block can be limited, especially in the precordial leads. Certain medications, including digitalis, also influence ST-segment changes and can produce ischemic ECG changes that are frequently false positive findings. In addition, anti-ischemic therapies can reduce heart rate and myocardial workload, and therefore, a lack of ischemic ECG changes can reflect false negative findings when the test is used to diagnose SIHD. It is routine practice to withhold beta-blocker therapy for 24 to 48 hours before testing. Patients who are candidates for an exercise ECG must be able to exercise and must have an interpretable ECG, which is defined as a normal 12-lead ECG or one with minimal resting ST-T-wave abnormalities (<0.5 mm).

2.2.3.2. EXERCISE AND PHARMACOLOGICAL STRESS ECHOCARDIOGRAPHY

The diagnostic endpoint of exercise and pharmacological stress echocardiography is new or worsening wall motion abnormalities and changes in global LV function during or immediately after stress. In addition to the detection of inducible wall motion abnormalities, most stress echocardiography includes screening images to evaluate resting ventricular function and valvular abnormalities. This information can be helpful in a symptomatic patient without a proven diagnosis.

Pharmacological stress echocardiography in the United States is performed largely by using dobutamine with an endpoint of inducible wall motion abnormalities (Table 11). Vasodilator agents such as adenosine are used rarely in the United States but are used more commonly in Europe. The diagnostic accuracy of exercise and pharmacological stress echocardiography has been studied extensively in multiple meta-analyses, systematic reviews, and large, multicenter, observational registries (91,148–152,154,175). In several contemporary meta-analyses, the diagnostic sensitivity (uncorrected for referral bias) ranged from 70% to 85% for exercise and 85% to 90% for pharmacological stress echocardiography (91,150,152,154). The uncorrected diagnostic specificity ranges from 77% to 89% and 79% to 90% for exercise and pharmacological stress echocardiography, respectively. The use of intravenous ultrasound contrast agents can improve endocardial border delineation and can result in improved diagnostic accuracy (181). Myocardial contrast echocardiography also has been examined for determination of rest and stress myocardial perfusion, with the results showing comparability to myocardial perfusion SPECT findings in small patient series (182). However, the technique is currently in limited use in the United States.

The diagnostic accuracy of all imaging modalities is influenced by technical factors that could be inherent in the technique (i.e., variable correlation between perfusion and wall motion abnormalities and CAD extent and severity) or that result from physical characteristics of the patient that reduce image quality. For echocardiography, reduced image quality, defined as reduced LV endocardial visualization, has been reported for obese individuals and those with chronic lung disease, although the use of intravenous contrast enhancement results in sizeable improvement in endocardial border delineation.

2.2.3.3. EXERCISE AND PHARMACOLOGICAL STRESS NUCLEAR MYOCARDIAL PERFUSION SPECT AND MYOCARDIAL PERFUSION PET

Myocardial perfusion SPECT generally is performed with rest and (for exercise or pharmacological stress) with stress Tc-99m agents, with Tl-201 having limited applications (e.g., viability) because of its higher radiation exposure (97). Pharmacological stress generally is used with vasodilator agents administered as a continuous infusion (adenosine, dipyridamole) or bolus (regadenoson) injection. The diagnostic endpoint of nuclear MPI is reduction in myocardial perfusion after stress. Nonperfusion high-risk markers in-

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clude a markedly abnormal ECG, extensive stress-induced wall motion abnormalities, reduced post-stress left ventricular ejection fraction (LVEF) ≥5% or global LVEF (rest or post-stress) <45%, transient ischemic LV dilation, increased lung or right ventricular uptake, or abnormal coronary flow reserve with myocardial perfusion PET (183–186).

The diagnostic accuracy for detection of obstructive CAD of exercise and pharmacological stress nuclear MPI has been studied extensively in multiple meta-analyses, systematic reviews, RCTs, and large, multicenter, observational registries (91,114,132,147,148,152,155,156,175). From these reports, the uncorrected diagnostic sensitivity ranged from 82% to 88% for exercise and 88% to 91% for pharmacological stress nuclear MPI. The uncorrected diagnostic specificity ranged from 70% to 88% and 75% to 90% for exercise and pharmacological stress nuclear MPI, respectively.

Diagnostic image quality is affected in obese patients, as well as in women and men with large breasts. Reductions in breast tissue artifact have been reported with the use of the Tc-99m agents as well as with attenuation-correction algorithms or prone imaging (187–190). For myocardial perfusion SPECT, global reductions in myocardial perfusion, such as in the setting of left main or 3-vessel CAD, can result in balanced reduction and an underestimation of ischemic burden.

Myocardial perfusion PET is characterized by high spatial resolution of the photon attenuation–corrected images with ^{82}Rubidium or ^{13}N-ammonia used as myocardial blood flow tracers. Although less well studied than myocardial perfusion SPECT, a meta-analysis of 19 studies suggests that PET has a slightly higher (uncorrected) sensitivity for detection of CAD (191,192), including in women and obese patients (193).

2.2.3.4. PHARMACOLOGICAL STRESS CMR WALL MOTION/PERFUSION

In recent years, more centers have used pharmacological stress CMR in the diagnostic evaluation of SIHD patients. The imaging endpoint depends on the stress agent: development of a new wall motion abnormality for cine CMR with dobutamine stress or a new perfusion abnormality with vasodilator stress. From a contemporary meta-analysis of 37 studies, the uncorrected diagnostic sensitivity and specificity of dobutamine-induced CMR wall motion imaging were 83% and 86%, whereas the uncorrected diagnostic sensitivity and specificity of vasodilator stress–induced CMR MPI were 91% and 81% (153). Several small comparative series have reported accuracy data in relation to stress echocardiography and nuclear imaging. Importantly, normal CMR perfusion has a high negative predictive value for obstructive CAD (194). One multicenter study that enrolled 234 patients demonstrated similar diagnostic accuracy between CMR perfusion and SPECT MPI in detecting obstructive CAD (172). More recently, a randomized study of 752 patients directly compared pharmacological stress CMR with SPECT MPI and reported higher sensitivity by pharmacological stress CMR than SPECT MPI in the detection of angiographically significant coronary stenosis (87% versus 67%; $p<0.0001$) (169). With dobutamine stress, CMR wall motion had high accuracy for detection of obstructive CAD in patients with suboptimal echocardiographic acoustic window (170). CMR dobutamine wall motion imaging demonstrated higher accuracy than dobutamine echocardiography wall motion (171). Although wall motion and perfusion imaging are used to assess the presence and extent of ischemia, most experienced centers also acquire late gadolinium enhancement (LGE) imaging in the same session to delineate the extent and severity of scarred myocardium.

2.2.3.5. HYBRID IMAGING

Current imaging is based largely on the use of a single modality, but combined or hybrid applications increasingly are available, which include both PET and CT or SPECT and CT, thus allowing for combined anatomic and functional testing. In addition, newer scanning techniques have allowed assessment of perfusion and FFR by CCTA alone, in addition to coronary anatomy (195–201). Notably, these combined assessments allow for a fused image in which the physiological assessment of flow is coupled with the anatomic extent and severity of CAD and also provides information on plaque composition and arterial remodeling. Limited evidence is available on hybrid imaging, although several reports have reported prognostic accuracy for cardiac events with both ischemic and anatomic markers (202–206). Other combinations of imaging modalities also are being developed, including PET/CMR, which is currently a research application. The strength of combined imaging is the added value of anatomy guiding interpretation of ischemic and scarred myocardium as well as providing information to guide therapeutic decision making. Hybrid imaging also can overcome technical limitations of myocardial perfusion SPECT or myocardial perfusion PET by providing anatomic correlates to guide interpretative accuracy (207) and can provide the functional information that an anatomic technique like CCTA or magnetic resonance angiography lacks; however, radiation dose is increased.

2.2.4. Diagnostic Accuracy of Anatomic Testing for the Initial Diagnosis of SIHD

2.2.4.1. CORONARY CT ANGIOGRAPHY

With improvements in temporal and spatial resolution as well as volume coverage, evaluation of coronary arteries with CCTA is now possible with a high degree of image quality (208). The extent and severity of angiographic CAD are 2 of the most important prognostic factors and remain essential for revascularization decision making (209). Five meta-analyses and 3 controlled clinical trials have reported the diagnostic accuracy of CCTA with 64-slice CT, yielding sensitivity values ranging from 93% to 97% and specificity values ranging from 80% to 90% (159–166) for detecting obstructive CAD on invasive coronary angiography, unad-

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justed for referral bias. In a small series of women, the diagnostic accuracy of CCTA was similarly high (210). Prior reports included subsets of patients who already had been referred for invasive angiography, and as such, test performance would be altered by the biases inherent in a preselected population. Factors related to diminished accuracy include image quality, the extent of coronary calcification, and body mass index (BMI) (208).

A potential advantage of CCTA over standard functional testing is its very high negative predictive value for obstructive CAD, which can reassure caregivers that providing GDMT and deferring consideration of revascularization constitute a sensible strategy. In addition to documentation of stenotic lesions, CCTA can qualitatively visualize arterial remodeling and nonobstructive plaque, including calcified, noncalcified, or mixed plaque (211–216). The presence of nonobstructive plaque has been shown to be helpful to guiding risk assessment and can aid in discerning the etiology of patient symptoms (211,215,216). CT information has been correlated with functional stress testing (203,204,215). Not every obstructive lesion produces ischemia, and ischemia can be present in the absence of a significant stenosis in epicardial vessels, which results in discordance between anatomic imaging with CCTA and functional stress testing. Several series have reported the positive predictive value of an anatomic lesion detected on CCTA to range from 29% to 44% when ischemia on a stress study is used as a reference standard (203,204). The evidence on concordance, however, remains incomplete, with current research showing the highest degree of concordance between ischemia and mixed plaque. Because the presence of significant calcification often can preclude the accurate assessment of lesion severity or cause a false positive study, CCTA should not be performed in patients who have known extensive calcification or a high risk of CAD.

2.2.4.2. CAC SCORING

CT also provides measurement of a CAC score, calculated as the product of the CAC area by maximal plaque density (in Hounsfield units) (217). The CAC score frequently has been applied for risk assessment in asymptomatic individuals (5), and it also has been used to predict the presence of high-grade coronary stenosis as the cause of chest pain in symptomatic patients. When the data from 2 large multicenter registries, including a total of 3,615 symptomatic patients, were combined, the estimated diagnostic sensitivity for the CAC score to predict obstructive CAD on invasive angiography was 85%, with a specificity of 75% (218). In a recent meta-analysis of 18 studies, which included 10,355 symptomatic patients, the presence of nonzero CAC score had a pooled sensitivity and specificity of 98% and 40%, respectively, for detection of significant CAD on invasive coronary angiography (174).

Although the diagnostic sensitivity of CAC to detect obstructive CAD is fairly high, the frequency of false negative exams (i.e., significant CAD in the absence of CAC) is not well established. In small single-center studies, perfusion defects on nuclear MPI or high-grade coronary stenosis on coronary angiography can be present in 0% to 39% of symptomatic patients with a calcium score of zero (219–223). In the recent large, multicenter, CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry) registry, CCTA showed mild, nonobstructive CAD in 13%, stenosis ≥50% in 3.5%, and stenosis ≥70% in 1.4% of the 10,037 symptomatic patients without known CAD who had a CAC score of zero (214). Documentation of obstructive CAD without CAC occurs more often in younger patients in whom atherosclerotic plaque has not advanced to the stage of calcification.

Previous official documents from the AHA and ACCF (218) concluded that "patients considered to be at low risk of coronary disease by virtue of atypical cardiac symptoms may benefit from CAC testing to help in ruling out the presence of obstructive coronary disease" (218) or that "coronary calcium assessment may be reasonable for the assessment of symptomatic patients, especially in the setting of equivocal treadmill or functional testing (Class IIb, LOE: B)." The present writing committee believed that additional evidence in sufficiently large cohorts of patients establishing the uncorrected diagnostic accuracy of CAC to rule in or rule out high-grade coronary artery stenosis in symptomatic patients was needed.

2.2.4.3. CMR ANGIOGRAPHY

Although not widely applied, CMR angiography has been performed for the detection of the extent and severity of obstructive CAD. As a result of small coronary artery size, tortuosity, and motion, the diagnostic accuracy of CMR angiography is reduced as compared with CCTA (224). A multicenter, controlled clinical trial of patients referred to invasive angiography revealed that magnetic resonance angiography had an 81% negative predictive value for excluding CAD (225). Several meta-analyses that included a total of 59 studies have reported diagnostic sensitivity and specificity ranging from 87% to 88% and 56% to 70%, respectively (158,226), with reports of a lower accuracy than that of CCTA (164). Variability in diagnostic accuracy with CMR angiography has been attributed to a lack of uniformity in pulse sequences and the application of varying analytic methods (227). Recent improvements applying 32-channel 3.0-T CMR have shown comparable abilities to detect CAD as compared with CCTA (228). No recommendations for the use of CMR angiography are included in this guideline.

3. Risk Assessment

3.1. Clinical Assessment

3.1.1. Prognosis of IHD for Death or Nonfatal MI: General Considerations

IHD is a chronic disorder with a natural history that spans multiple decades. The disease typically cycles through clin-

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ically defined phases: asymptomatic, stable angina, accelerating angina, and ACS (UA or AMI), although the progression from one state to another is not necessarily linear. The specific approach to assessing risk of subsequent adverse outcomes varies according to the patient's clinical phase, even though for those with SIHD, there is no universally accepted approach. This represents a key area for future research. The approach recommended in the present guideline is informed by the treatment goals of prolonging survival and optimizing health status and by the concept that the benefits of treatment are often proportional to the patient's underlying risk. From this perspective, it is essential to quantify the patient's prognosis as accurately as possible. Several approaches to estimating the risk of cardiovascular mortality or events are provided later in this guideline. In the absence of an established prognostic model, the following considerations are highlighted:

1. *Sociodemographic characteristics:* Age is the single strongest determinant of survival, whereas ethnicity and sex have conflicting and less important effects on risk. Lower socioeconomic status also is associated with worse outcomes (229).
2. *Cardiovascular risk factors:* Smoking, hypertension, dyslipidemia, family history of premature CAD, obesity, and sedentary lifestyle confer a greater risk of complications.
3. *Coexisting medical conditions:* Diabetes mellitus (230), chronic kidney disease (CKD) (231), chronic pulmonary disease, and malignancy are the most important noncardiac conditions to influence prognosis (232–234).
4. *Cardiovascular comorbidities:* Heart failure, PAD, and cerebrovascular diseases are strong prognostic risk factors for mortality.
5. *Psychosocial characteristics:* Depression repeatedly has been demonstrated to be strongly and independently associated with worse survival, and anxiety has also been implicated (235–242). Poor social support, poverty, and stress also are associated with adverse prognosis (236,243–245).
6. *Health status:* Patients' symptoms, functional capacity, and quality of life are associated significantly with survival and the incidence of subsequent ACS (246,247). In a large, prospective cohort of patients in the Veterans Affairs healthcare system, physical limitations due to angina were second only to age in predicting mortality (246).
7. *Anginal frequency:* Frequency of angina is a very strong predictor of subsequent ACS hospitalizations (246).
8. *Cardiac disease severity:* The degree and distribution of stenoses measured by coronary angiography, findings on exercise testing and stress imaging, and LV function measured with a variety of technologies all provide meaningful prognostic information that supplements more clinical information.

3.1.2. Risk Assessment Using Clinical Parameters

Although there are several models to predict the likelihood of complications and survival in asymptomatic, general populations and in patients with ACS, there is a relative paucity of information about models for assessing the risk of patients with known SIHD that incorporate a broad range of relevant data. Accurate risk assessment according to clinical variables is essential to determining optimal treatment strategies. Lauer and colleagues developed a risk index that incorporates variables from the history and exercise test on the basis of data from >32,000 individuals (248). They found that their index, which can be calculated by using a nomogram (Figure 8), was better able to predict individuals with a low (<3%) risk of death than was the Duke treadmill score. Daly and colleagues reported an index to estimate risk of death or nonfatal AMI derived from data on an international sample of approximately 3,000 patients who presented with angina and were followed up for 18 months (Figures 9 and 10). Obstructive CAD was documented in one third, whereas another third had negative evaluations. The *c* statistic for the model was 0.74, which indicates a relatively high level of accuracy (57).

Several risk-assessment schemes have been developed to assist in identifying patients with severe CAD, including left main disease, although several of these studies are up to 2 decades old. One study (70) identified 8 clinical characteristics that are important in estimating the likelihood of severe IHD: typical angina, previous MI, age, sex, duration of chest pain symptoms, risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking), carotid bruit, and chest pain frequency. A subsequent study (71) provided detailed equations to predict both severe IHD and survival on the basis of clinical parameters. One study (249) developed a simple risk score for predicting severe (left main or 3-vessel) CAD that was based on 5 clinical variables: age, sex, history of MI, presence of typical angina, and diabetes mellitus with or without insulin use. This same score was validated subsequently for prognostic purposes (250,251). This score can be easily memorized and calculated (Figure 11) and yields an integer ranging from 0 to 10 (57). The score can be applied to determine if a patient is more suitable for stress testing or possibly (in appropriate patients who are at highest risk) for proceeding directly to coronary angiography. Each curve shows the probability of severe IHD as a function of age for a given cardiac risk score. As shown on the Figure 11 graph, some patients have a high likelihood (>50%) of having severe disease for which revascularization might improve survival on the basis of clinical parameters alone. For example, a 50-year-old male patient who has diabetes mellitus, is taking insulin, and has typical angina and a history of previous MI has a likelihood of severe coronary stenosis >60% and thus might proceed directly to angiography if warranted by his preferences and other clinical factors, although in most circumstances stress testing will assist in planning further tests and treatments (87,252). Creation of valid, quantitative models on the basis of data from current registries and trials to accurately identify patients with anatomic distributions of CAD for

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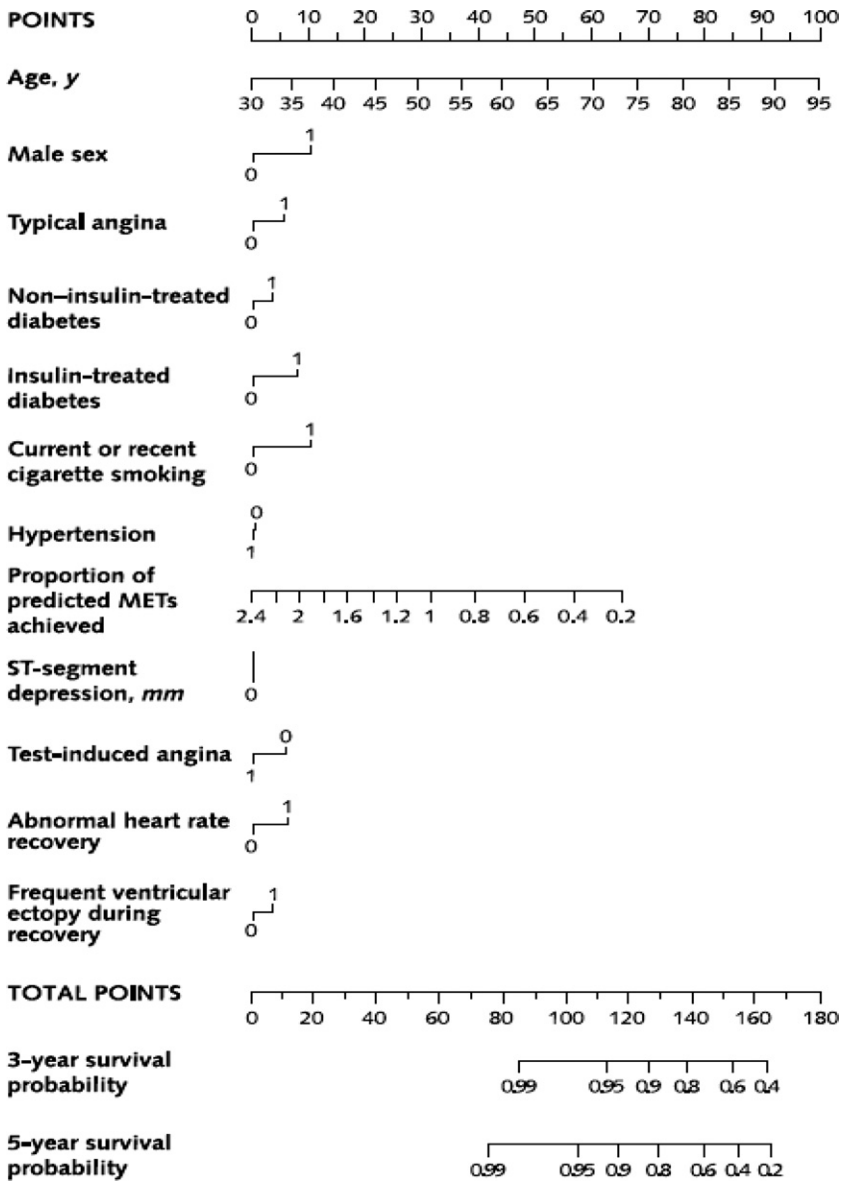

Figure 8. Nomogram to Predict Risk of Death Based on Clinical Data and Results of Exercise Testing

To determine risk, draw a vertical line from each risk marker to the top line, labeled "POINTS," to calculate points for each risk marker. The sum of all these points is then marked on the line labeled "TOTAL POINTS." Drop vertical lines from there to yield the 3- and 5-year survival probabilities. For binary variables, 1 means yes and 0 means no. MET indicates metabolic equivalent. Reproduced from Lauer et al. (248).

which revascularization has been shown to improve survival, such as left main disease, should be a research priority.

Studies have suggested that addition of levels of novel biomarkers such as C-reactive protein and brain natriuretic peptide can improve prediction of mortality and cardiovascular events (5,57). Considerable controversy remains; however, as to whether these tests truly provide incremental information beyond more well-accepted risk factors, and few of the studies have focused on patients with SIHD (253–255). Inflammatory biomarkers, such as myeloperoxidase (256), biochemical markers of lipid-related atherogenic processes [lipoprotein(a), apolipoprotein B, small dense LDL, and lipoprotein-associated phospholipase A2] (257,258), and low levels of circulating troponin detected by high-sensitivity assays (259) also are under investigation as indices of risk in patients with SIHD.

3.2. Advanced Testing: Resting and Stress Noninvasive Testing

3.2.1. Resting Imaging to Assess Cardiac Structure and Function: Recommendations

CLASS I

1. Assessment of resting LV systolic and diastolic ventricular function and evaluation for abnormalities of myocardium, heart valves, or pericardium are recommended with the use of Doppler echocardiography in patients with known or suspected IHD and a prior MI,

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Risk Factor	Score Contribution	Individual's Score
Comorbidity		
No	0	
Yes	86	
Diabetes		
No	0	
Yes	57	
Angina score		
Class I	0	
Class II	54	
Class III	91	
Duration of symptoms		
≥6 months	0	
<6 months	80	
Abnormal ventricular function		
No	0	
Yes	114	
ST depression or T wave inversion on resting electrocardiogram		
No	0	
Yes	34	
		Total =

Figure 9. Euro Heart Score Sheet to Calculate Risk Score for Patients Presenting With Stable Angina (Derived From 3,779 Patients With Newly Diagnosed SIHD)

*≥1 of previous cerebrovascular event; hepatic disease defined as chronic hepatitis or cirrhosis, or other hepatic disease causing elevation of transaminases ≥3 times upper limit of normal; PVD defined as claudication either at rest or on exertion, amputation for arterial vascular insufficiency, vascular surgery (reconstruction or bypass) or angioplasty to the extremities, documented aortic aneurysm, or noninvasive evidence of impaired arterial flow; chronic renal failure defined as chronic dialysis or renal transplantation or serum creatinine >200 mmol/L; chronic respiratory disease defined as a diagnosis previously made by physician or patient receiving bronchodilators or FEV_1 <75%, arterial pO_2 <60%, or arterial pCO_2 >50% predicted in previous studies; chronic inflammatory conditions defined as a diagnosis of rheumatoid arthritis, systemic lupus erythematosus or other connective tissue disease, polymyalgia rheumatica, and so on; malignancy defined as a diagnosis of malignancy within a year of active malignancy. FEV_1 indicates forced expiratory volume; pO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; and PVD, peripheral vascular disease. Reproduced from Daly et al. (57).

pathological Q waves, symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur (21,57,58,260,261). *(Level of Evidence: B)*

CLASS IIb

1. Assessment of cardiac structure and function with resting echocardiography may be considered in patients with hypertension or diabetes mellitus and an abnormal ECG. *(Level of Evidence: C)*
2. Measurement of LV function with radionuclide imaging may be considered in patients with a prior MI or pathological Q waves, provided there is no need to evaluate symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur. *(Level of Evidence: C)*

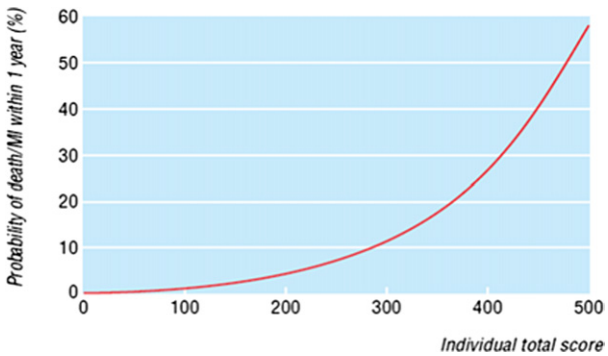

Figure 10. Risk of Death or MI Over 1-Year After Diagnosis of SIHD According to Euro Heart Score

Plot to assign estimated probability of death or nonfatal MI within 1 year of presentation according to combination of clinical and investigative features in patients with stable angina. MI indicates myocardial infarction. Reproduced from Daly et al. (57).

CLASS III: No Benefit

1. Echocardiography, radionuclide imaging, CMR, and cardiac CT are not recommended for routine assessment of LV function in patients with a normal ECG, no history of MI, no symptoms or signs suggestive of heart failure, and no complex ventricular arrhythmias. *(Level of Evidence: C)*
2. Routine reassessment (<1 year) of LV function with technologies such as echocardiography radionuclide imaging, CMR, or cardiac CT is not recommended in patients with no change in clinical status and for whom no change in therapy is contemplated. *(Level of Evidence: C)*

See Online Data Supplement 2 for additional data on using resting imaging to assess cardiac structure and function.

In the presence of signs or symptoms suggestive of heart failure, it is imperative to obtain an objective measure of LV function if a prognosis-altering change in therapy could be based on the findings. For example, a rest ejection fraction (EF) <35% is associated with an annual mortality rate >3% per year (260). Resting 2-dimensional echocardiography with Doppler echocardiography is the preferred approach because it provides a thorough assessment of all aspects of cardiac structure and function, including identifying the mechanism of heart failure and differentiating systolic LV from diastolic dysfunction.

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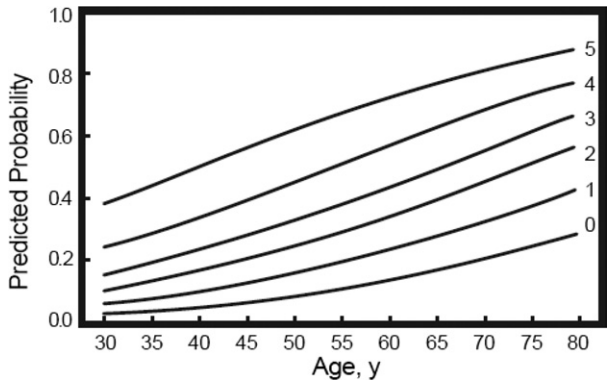

Figure 11. Nomogram Showing the Probability of Severe (3-Vessel or Left Main) Coronary Disease Based on a 5-Point Score

One point is awarded for each of the following variables: male sex, typical angina, history and electrocardiographic evidence of MI, and diabetes mellitus and use of insulin. Each curve shows the probability of severe coronary disease as a function of age. Reproduced from Hubbard et al. (249).

Rest imaging also can provide valuable therapeutic guidance and prognostic information in patients without symptoms or signs of ventricular dysfunction or changing clinical status, especially in those with evidence of other forms of heart disease (e.g., hypertensive, valvular). For example, echocardiography can identify LV or left atrial dilation; identify aortic stenosis (a potential non-CAD mechanism for angina-like chest pain); measure pulmonary artery pressure; quantify mitral regurgitation; identify a LV aneurysm; identify a LV thrombus, which increases the risk of death (262); and measure LV mass and the ratio of wall thickness to chamber radius—all of which predict cardiac events and mortality (20,117,263–267).

Although nuclear imaging accurately measures EF, it does not provide additional information on valvular or pericardial disease and requires exposure to ionizing radiation (21,268). Although CMR is applied less widely, it also accurately measures LV performance and provides insight into myocardial and valvular structures (269). Use of delayed hyperenhancement techniques can identify otherwise undetected scarred as well as viable myocardium. Cardiac CT also provides high-resolution detection of cardiac structures and EF. Nevertheless, all 3 tests generally are more expensive than a resting echocardiogram. Although the amount of ionizing radiation required in cardiac CT and nuclear MPI has been lowered over the years and will continue to reduce, the use of these tests for risk assessment is discouraged in patients with low pretest probability of CAD and in young patients.

3.2.2. Stress Testing and Advanced Imaging in Patients With Known SIHD Who Require Noninvasive Testing for Risk Assessment: Recommendations

See Table 12 for a summary of recommendations from this section.

3.2.2.1. RISK ASSESSMENT IN PATIENTS ABLE TO EXERCISE

CLASS I

1. Standard exercise ECG testing is recommended for risk assessment in patients with SIHD who are able to exercise to an adequate workload and have an interpretable ECG (106–110,112–114,132–134). (*Level of Evidence: B*)
2. The addition of either nuclear MPI or echocardiography to standard exercise ECG testing is recommended for risk assessment in patients with SIHD who are able to exercise to an adequate workload but have an *un*interpretable ECG not due to LBBB or ventricular pacing (7,111,264–266,270,299,300). *(Level of Evidence: B)*

CLASS IIa

1. The addition of either nuclear MPI or echocardiography to standard exercise ECG testing is reasonable for risk assessment in patients with SIHD who are able to exercise to an adequate workload and have an interpretable ECG (271–279). (*Level of Evidence: B*)
2. CMR with pharmacological stress is reasonable for risk assessment in patients with SIHD who are able to exercise to an adequate workload but have an *un*interpretable ECG (279–284). *(Level of Evidence: B*)

CLASS IIb

1. CCTA may be reasonable for risk assessment in patients with SIHD who are able to exercise to an adequate workload but have an *un*interpretable ECG (285,286). *(Level of Evidence: B)*

CLASS III: No Benefit

1. Pharmacological stress imaging (nuclear MPI, echocardiography, or CMR) or CCTA is not recommended for risk assessment in patients with SIHD who are able to exercise to an adequate workload and have an interpretable ECG. *(Level of Evidence: C)*

3.2.2.2. RISK ASSESSMENT IN PATIENTS UNABLE TO EXERCISE

CLASS I

1. Pharmacological stress with either nuclear MPI or echocardiography is recommended for risk assessment in patients with SIHD who are unable to exercise to an adequate workload regardless of interpretability of ECG (7,264–266,287–290). (*Level of Evidence: B)*

CLASS IIa

1. Pharmacological stress CMR is reasonable for risk assessment in patients with SIHD who are unable to exercise to an adequate workload regardless of interpretability of ECG (280–284,291). (*Level of Evidence: B)*
2. CCTA can be useful as a first-line test for risk assessment in patients with SIHD who are unable to exercise to an adequate workload regardless of interpretability of ECG (286). *(Level of Evidence: C)*

3.2.2.3. RISK ASSESSMENT REGARDLESS OF PATIENTS' ABILITY TO EXERCISE

CLASS I

1. Pharmacological stress with either nuclear MPI or echocardiography is recommended for risk assessment in patients with SIHD who have LBBB on ECG, regardless of ability to exercise to an adequate workload (287–290,292). *(Level of Evidence: B*)
2. Either exercise or pharmacological stress with imaging (nuclear MPI, echocardiography, or CMR) is recommended for risk assessment in patients with SIHD who are being considered for revascularization of known coronary stenosis of unclear physiological significance (266,278,293,294). *(Level of Evidence: B)*

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Table 12. Using Stress Testing and Advanced Imaging for Patients With Known SIHD Who Require Noninvasive Testing for Risk Assessment

Test	Exercise Status		ECG Interpretable		COR	LOE	References	Additional Considerations
	Able	Unable	Yes	No				
Patients able to exercise*								
Exercise ECG	X		X		I	B	(106–110,112–114,132–134)	
Exercise with nuclear MPI or Echo	X			X	I	B	(7,111,264–266,270,299,300)	Abnormalities other than LBBB or ventricular pacing
Exercise with nuclear MPI or Echo	X		X		IIa	B	(271–279)	
Pharmacological stress CMR	X			X	IIa	B	(279–284)	
CCTA	X			X	IIb	B	(285,286)	
Pharmacological stress imaging (nuclear MPI, Echo, CMR) or CCTA	X		X		III: No Benefit	C	N/A	
Patients unable to exercise								
Pharmacological stress with nuclear MPI or Echo		X	Any		I	B	(7,264–266,287–290)	
Pharmacological stress CMR		X	Any		IIa	B	(280–284,291)	
CCTA		X	Any		IIa	C	(286)	Without prior stress test
Regardless of patient's ability to exercise								
Pharmacological stress with nuclear MPI or Echo	Any			X	I	B	(287–290,292)	LBBB present
Exercise/pharmacological stress with nuclear MPI, Echo, or CMR	Any		Any		I	B	(266,278,293,294)	Known coronary stenosis of unclear physiological significance being considered for revascularization
CCTA	Any		Any		IIa	C	N/A	Indeterminate result from functional testing
CCTA	Any		Any		IIb	C	N/A	Unable to undergo stress imaging or as alternative to coronary catheterization when functional testing indicates moderate to high risk and angiographic coronary anatomy is unknown
Requests to perform multiple cardiac imaging or stress studies at the same time	Any		Any		III: No Benefit	C	N/A	

*Patients are candidates for exercise testing if they are capable of performing at least moderate physical functioning (i.e., moderate household, yard, or recreational work *and* most activities of daily living) and have no disabling comorbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.

CCTA indicates cardiac computed tomography angiography; CMR, cardiac magnetic resonance imaging; COR, class of recommendation; ECG, electrocardiogram; Echo, echocardiography; LBBB, left bundle-branch block; LOE, level of evidence; MPI, myocardial perfusion imaging; and N/A, not available.

CLASS IIa

1. CCTA can be useful for risk assessment in patients with SIHD who have an indeterminate result from functional testing (286). *(Level of Evidence: C)*

CLASS IIb

1. CCTA might be considered for risk assessment in patients with SIHD unable to undergo stress imaging or as an alternative to invasive coronary angiography when functional testing indicates a moderate- to high-risk result and knowledge of angiographic coronary anatomy is unknown. *(Level of Evidence: C)*

CLASS III: No Benefit

1. A request to perform either a) more than 1 stress imaging study or b) a stress imaging study and a CCTA at the same time is not recommended for risk assessment in patients with SIHD. *(Level of Evidence: C)*

See Online Data Supplement 2 for additional data on risk assessment.

3.2.2.4. EXERCISE ECG

To assess the risk of cardiovascular events in patients who are able to exercise to an adequate workload and have an interpretable resting ECG, exercise is the preferred stressor because it provides an objective assessment of functional capacity and correlative information with activities of daily living. The occurrence of ST-segment depression at a reduced workload or persisting into recovery coupled with exertional symptoms is associated with a high risk of cardiovascular mortality (302). Other risk markers for mortality include low exercise capacity (generally defined as less than stage II of the Bruce protocol or ≤20% age- and

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sex-predicted values) (118), failure to increase systolic BP to >120 mm Hg or a sustained >10–mm Hg decrease from resting values during exercise, complex ventricular ectopy or arrhythmias during stress or recovery, and delayed heart rate recovery (e.g., <10- or 12-beats-per-minute reduction in the first minute) (303). The Duke treadmill score and the Lauer nomogram score are validated predictive instruments that incorporate parameters from an exercise ECG test. The Duke treadmill score includes duration of exercise, severity of ST-depression or elevation, and angina (limiting and nonlimiting); has been demonstrated to be highly predictive across an array of patient populations, including women and men with suspected and known SIHD; and has been shown to provide independent risk information beyond clinical data, coronary anatomy, and LVEF (126,177). It stratifies patients into risk groups that could prove useful for patient management, as follows: no further testing for low-risk patients, consideration for invasive testing for high-risk patients, and stress imaging for the intermediate-risk patients. By comparison, the Lauer score incorporates clinical variables, which results in more effective classification of low-risk (<1% annual mortality rate) patients (248).

3.2.2.5. EXERCISE ECHOCARDIOGRAPHY AND EXERCISE NUCLEAR MPI

Evidence from thousands of patients evaluated in multiple large registries and clinical trials and meta-analyses confirm that a normal exercise echocardiogram or exercise nuclear MPI is associated with a very low risk of death due to cardiovascular causes or AMI (111,265,304). The extent and severity of inducible abnormalities in wall motion or perfusion are directly correlated with the degree of risk. For nuclear MPI, reversible perfusion defects encompassing 10% of the myocardium (determined either semiquantitatively with summed scores or quantitatively) to assess defect extent and severity are considered moderately abnormal, and reversible perfusion defects encompassing ≥15% of the myocardium are considered severely abnormal (277, 305,306). Other findings also indicative of elevated risk include a reduction in reduced post-stress LVEF ≥5% or a global LVEF <45%, transient ischemic LV dilation, increased lung or right ventricular uptake, or abnormal coronary reserve (detected on myocardial perfusion PET). For echocardiography, a wall motion abnormality extending beyond 2 to 3 segments as well as the presence of change in >1 coronary territory are suggestive of higher risk. For both tests, multiple defects in different coronary territories with either moderately reduced perfusion (or ≥10% of the myocardium) or inducible wall motion abnormalities with transient ischemic dilatation are suggestive of severe CAD. Currently, the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored ISCHEMIA trial is under way and is comparing the effectiveness of a conservative versus catheterization-based initial management strategy for patients with moderate–severe ischemia.

Several large single-center and multicenter registries have demonstrated consistently that both stress nuclear MPI and stress echocardiography provide incremental prognostic value beyond that provided by a standard ECG (115,272,299,305,307–315). The addition of imaging is mandatory for patients who have an uninterpretable baseline ECG (including the presence of LBBB or ventricular pacing, LV hypertrophy, use of digitalis or electrolyte abnormalities, coexisting resting ST-segment abnormality, or preexcitation syndromes) and might be of value in patients with equivocal stress-induced (316) ECG ST changes (317) or an intermediate Duke treadmill score (316). Poornima et al., demonstrated that nuclear MPI has independent prognostic value even in patients with low-risk Duke treadmill scores, but only if there is increased clinical risk, such as a history of typical angina, MI, diabetes mellitus, and advanced age (318,319). Similarly, information from exercise echocardiography appears to provide improved prediction of mortality among patients with low-risk Duke treadmill scores (311,318). From a large registry, the extent of ischemic myocardium as quantified by summed difference score by nuclear MPI has been shown to form an effective prognostic score for the prediction of cardiac mortality (320). Results from exercise nuclear MPI and exercise stress echocardiography appear to provide accurate estimates of the likelihood of death among men and women with suspected and known SIHD and for patients from different ethnic groups (314,321,322).

From a review of large single- and multicenter registries and meta-analyses (111,115,272), the following conclusions can be made:

1. A normal exercise nuclear MPI study or a normal exercise stress echocardiogram during which the age-predicted target heart rate is achieved is associated with a very low annual risk of cardiac death and AMI (generally <1%) in both men and women.
2. Normal and mildly abnormal nuclear MPI or exercise stress echocardiography is associated with a low frequency of referral for coronary revascularization or worsening clinical status and UA admission (1.3% and 1% annually, respectively) (141).
3. Rates of cardiac ischemic events increase in proportion to the degree of abnormalities on stress nuclear MPI or echocardiography, with moderate to severe abnormalities associated with an annual risk of cardiovascular death or MI ≥5% (115,278,279,284,305,306,310,313,314,323–330).
4. For patients with mild abnormalities, coronary angiography might be considered if the patient exhibits other features that might indicate the likelihood of "high-risk" CAD, including low EF on gated nuclear MPI or echocardiographic imaging (331) or transient ischemic dilatation of the left ventricle (332).
5. Moderate to severe abnormalities, such as abnormal wall motion in ≥4 segments or multivessel abnormalities, indicate an increased risk (range: 6- to 10-fold) over that of patients with a normal stress imaging study (271).

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Nonetheless, the current literature with regard to exercise nuclear MPI or exercise echocardiography should be clarified in several ways. Although a normal exercise nuclear MPI or exercise echocardiogram usually is associated with a low annual risk of cardiac death or AMI, the negative predictive value is reduced among patients with a higher pretest likelihood of CAD (111,115,279,284,305,306,310,313,314,323–328,330). Furthermore, although trials have shown that imaging is useful to detect ischemia and guide intervention in patients with SIHD and that a reduction in ischemia by stress nuclear MPI is associated with an observed (unadjusted) event-free survival (306,333), there is no trial evidence comparing the effectiveness of a strategy of imaging testing for risk stratification versus a strategy of nontesting in patients with SIHD.

3.2.2.6. DOBUTAMINE STRESS ECHOCARDIOGRAPHY AND PHARMACOLOGICAL STRESS NUCLEAR MPI

In one third to one half of patients who undergo risk assessment, exercise stress is not recommended because of an inability to exercise or an abnormal ECG. Similar to exercise echocardiography, multiple large single-center reports have shown that dobutamine stress echocardiography accurately classifies patients into high-risk and very-low-risk groups. A normal dobutamine echocardiogram is associated with a risk of an adverse cardiac event of 1% to 2% (312,334). Classification as high risk by dobutamine stress echocardiography is most reliable when ischemia is detected in the territory of the LAD and is somewhat less reliable in patients with diabetes mellitus (335). In specialized centers, either quantification of strain rate or myocardial contrast enhancement on dobutamine echocardiography has been shown to provide information that supplements the wall motion score alone in predicting cardiac mortality (336). Dobutamine echocardiography also has been used extensively in risk-stratifying patients with SIHD undergoing noncardiac vascular surgery. Because the risk of a cardiac event in the perioperative period is quite low, the positive predictive value of dobutamine echocardiography is also low, although the negative predictive value of a normal result is very high and is associated with a very low likelihood of a perioperative event (337,338).

Similar to exercise SPECT, vasodilator stress nuclear MPI has been shown to effectively assess risk of subsequent events in patients with SIHD, with a low annualized event rate of 1.6% observed in patients with a normal adenosine SPECT versus 10.6% in patients with a severely abnormal study (summed stress score >13) (339). This event rate also was observed in elderly patients with normal pharmacological SPECT (340,341). Because of greater comorbidity in patients who cannot exercise, the annualized event rate of patients who had a normal pharmacological stress nuclear MPI increase the event rate nearly 2-fold higher than that of exercising patients who had a normal nuclear MPI, after adjustment for age and comorbidity (342). Additional nonperfusion risk markers can be derived from pharmacological stress, including an abnormal ECG, high resting heart rate, and low peak/rest heart rate ratio (276,332). To facilitate clinical risk assessment, a nomogram based on robust risk markers, including LV function and extent of myocardial ischemia by SPECT, has been developed and validated (Appendix 4) (276).

3.2.2.7. PHARMACOLOGICAL STRESS CMR IMAGING

Although clinical experience with using stress CMR for risk assessment is substantially less than with stress echocardiography and nuclear MPI, available evidence indicates that stress CMR can provide highly accurate prognostic information. On the basis of 16 single-site studies providing data from 7,200 patients (283) (8 of these studies used vasodilator stress perfusion imaging, 6 dobutamine stress CMR cine imaging, and 2 combined stress perfusion and cine imaging), the following general conclusions can be drawn:

1. A normal stress CMR study with either vasodilator myocardial perfusion or inotropic stress cine imaging is associated with a low annual rate of cardiac death or MI, ranging from 0.01% to 0.6% (280,283), and provides accurate risk assessment in patients of either sex (281,343).
2. Detection of myocardial ischemia (by either perfusion or cine imaging) and LGE imaging of infarction appear to provide complementary information.
3. An abnormal stress CMR with evidence of ischemia is associated with elevated likelihood of cardiac death or MI, with hazard ratios ranging from 2.2 to 12 (279,282).

The current evidence related to CMR for risk assessment of patients is limited by the predominance of data collection from tertiary care centers with high experience in CMR, heterogeneity of imaging techniques and equipment, and evolution of interpretative standards.

3.2.2.8. SPECIAL PATIENT GROUP: RISK ASSESSMENT IN PATIENTS WHO HAVE AN UNINTERPRETABLE ECG BECAUSE OF LBBB OR VENTRICULAR PACING

Isolated "false-positive" reversible perfusion defects of the septum on nuclear MPI due to abnormal septal motion causing a reduction in diastolic filling time have been reported in patients with LBBB without significant coronary stenosis. Compared to patients without LBBB, use of exercise stress in patients with LBBB or ventricular pacing substantially reduced diagnostic specificity (289,292). Although a normal nuclear perfusion scan in this clinical setting is highly accurate in indicating the absence of a significant coronary stenosis and a low risk of subsequent cardiac events (288), an abnormal study can be nondiagnostic (148,287). In patients with LBBB on a rest ECG, dobutamine stress echocardiography is less sensitive but more specific than nuclear MPI in detecting coronary stenosis and provides prognostic information that is incremental to clinical findings (344). One meta-analysis demonstrated that abnormal stress nuclear MPI and stress echocardiography each confer an up to 7-fold increased risk of adverse cardiovascular events (148).

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3.2.3. Prognostic Accuracy of Anatomic Testing to Assess Risk in Patients With Known CAD

3.2.3.1. CORONARY CT ANGIOGRAPHY

Given the high accuracy in detecting angiographically significant coronary stenosis, estimates of cardiovascular risk according to the Duke CAD index with data obtained via CCTA appear to be as accurate as those obtained from cardiac catheterization. However, the actual event rates in patients undergoing CCTA have been substantially lower because of differences in the underlying risk profiles of patient groups that have been referred for these 2 procedures (345). Furthermore, data from CONFIRM suggest that the finding of nonobstructive CAD on CCTA supplements clinical information in predicting risk of mortality (286). For example, 20% to 25% of patients with an intermediate pretest likelihood of risk (1% to 3% annual mortality rate) based on clinical information (without EF) were reassigned to a different risk category according to information from CCTA. Given that failed bypass grafts can result in unprotected CAD, which confers a higher risk, the assessment of the extent of graft patency by CCTA is also of prognostic value (346,347). Although exercise stress testing in general is preferred in risk assessment, for patients unlikely to achieve conclusive results, consensus opinion suggests that it is reasonable to proceed with a CCTA for risk-assessment purposes.

Several ongoing trials are comparing the prognostic values of CCTA and functional imaging modalities such as nuclear MPI and stress echocardiography (348). At present, there are no prospectively gathered trial data demonstrating that CCTA leads to better patient selection for medical or invasive intervention or to better clinical outcomes.

3.3. Coronary Angiography

3.3.1. Coronary Angiography as an Initial Testing Strategy to Assess Risk: Recommendations

CLASS I

1. Patients with SIHD who have survived sudden cardiac death or potentially life-threatening ventricular arrhythmia should undergo coronary angiography to assess cardiac risk (349–351). *(Level of Evidence: B)*
2. Patients with SIHD who develop symptoms and signs of heart failure should be evaluated to determine whether coronary angiography should be performed for risk assessment (352–355). *(Level of Evidence: B)*

3.3.2. Coronary Angiography to Assess Risk After Initial Workup With Noninvasive Testing: Recommendations

CLASS I

1. Coronary arteriography is recommended for patients with SIHD whose clinical characteristics and results of noninvasive testing indicate a high likelihood of severe IHD and when the benefits are deemed to exceed risk (59,126,260,310,356–362). *(Level of Evidence: C)*

CLASS IIa

1. Coronary angiography is reasonable to further assess risk in patients with SIHD who have depressed LV function (EF <50%) and moderate risk criteria on noninvasive testing with demonstrable ischemia (363–365). *(Level of Evidence: C)*
2. Coronary angiography is reasonable to further assess risk in patients with SIHD and inconclusive prognostic information after noninvasive testing or in patients for whom noninvasive testing is contraindicated or inadequate. *(Level of Evidence: C)*
3. Coronary angiography for risk assessment is reasonable for patients with SIHD who have unsatisfactory quality of life due to angina, have preserved LV function (EF >50%), and have intermediate risk criteria on noninvasive testing (306,366). *(Level of Evidence: C)*

CLASS III: No Benefit

1. Coronary angiography for risk assessment is not recommended in patients with SIHD who elect not to undergo revascularization or who are not candidates for revascularization because of comorbidities or individual preferences (306,366). *(Level of Evidence: B)*
2. Coronary angiography is not recommended to further assess risk in patients with SIHD who have preserved LV function (EF >50%) and low-risk criteria on noninvasive testing (306,366). *(Level of Evidence: B)*
3. Coronary angiography is not recommended to assess risk in patients who are at low risk according to clinical criteria and who have not undergone noninvasive risk testing. *(Level of Evidence: C)*
4. Coronary angiography is not recommended to assess risk in asymptomatic patients with no evidence of ischemia on noninvasive testing. *(Level of Evidence: C)*

Coronary angiography defines coronary anatomy, including the location, length, diameter, and contour of the epicardial coronary arteries; the presence and severity of coronary luminal obstruction(s); the nature of the obstruction; the presence and extent of angiographically visible collateral flow; and coronary blood flow. Despite the ability of newer noninvasive imaging modalities such as CT angiography to visualize and characterize the coronary tree, invasive coronary angiography currently remains the "gold standard." Coronary angiography has 2 clinical goals: 1) to assess a patient's risk of death and future cardiovascular events through characterization of the presence and extent of obstructive CAD and 2) to ascertain the feasibility of percutaneous or surgical revascularization. The likelihood that revascularization might decrease angina and improve a patient's quality of life should be considered when a patient deems his or her quality of life unsatisfactory despite a conscientious program of evidence-based medical therapy.

The most commonly used nomenclature for defining coronary anatomy is that which was developed for CASS (367) and further modified by the BARI study group (368). This scheme is based on the assumption that there are 3 major coronary arteries: the LAD, the circumflex, and the right coronary artery, with a right-dominant, left-dominant, or codominant circulation. The extent of disease is defined as 1-vessel, 2-vessel, 3-vessel, or left main disease, with a significant stenosis ≥70% diameter

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reduction. Left main disease, however, also has been defined as a stenosis ≥50%.

Despite being recognized as the traditional "gold standard" for clinical assessment of coronary atherosclerosis, coronary angiography is not without limitations. First, the technical quality of angiograms in many settings can make accurate interpretation difficult or impossible. In a random sample of >300 coronary angiograms performed in New York State during the 1990s, 4% were of unacceptable quality, and 48% exhibited technical deficiencies that could interfere with accurate interpretation (369). Although more modern techniques and equipment likely have eliminated some of these deficiencies, few studies have addressed this issue, particularly in patients who present technical challenges, such as those who are obese. Second, problems also exist with interobserver reliability. These investigators also found only 70% overall agreement among readers with regard to the severity of stenosis, and this was reduced to 51% when restricted to coronary vessels rated as having some stenosis by any reader. Third, angiography in isolation provides only anatomic data and is not a reliable indicator of the functional significance of a given coronary stenosis unless a technique such as FFR (discussed below) is used to provide information about the physiological significance of an anatomic stenosis. Lastly, coronary angiography does not distinguish between a vulnerable plaque, with a large lipid core, thin fibrous cap, and increased macrophages, and a stable plaque that does not exhibit these features. Serial angiographic studies performed before and after acute events and early after MI suggest that plaques resulting in UA and MI commonly were found to be <50% obstructive before the acute event and were therefore angiographically "silent" (370,371). Diagnostic testing to determine vulnerable plaque, and therefore the subsequent risk for MI, remains intensely studied, but no "gold standard" yet has emerged (372). Despite these limitations of coronary angiography, the extent and severity of CAD remain very significant predictors of long-term patient outcomes (Table 13) (55,70,71,373,374).

For patients who are found to be at high risk of coronary events or death on the basis of clinical data and noninvasive testing, coronary angiography is often warranted to provide a more complete risk assessment even though cardiac symptoms might not be severe. Certain clinical characteristics, though relatively infrequent in patients with IHD, have been associated with a high likelihood of severe disease, including the following: chest pain leading to pulmonary edema, chest pain associated with lightheadedness, syncope or hypotension, exertional syncope, and an exercise-induced gallop sound on cardiac auscultation. In addition to clinical signs and symptoms, findings on noninvasive studies could also suggest that certain patients are at high risk of serious cardiac events. These findings include abnormal physiological response to exercise or imaging studies that suggest extensive myocardial ischemia (Table 14). Some examples from Table 14 (high-risk category) which may suggest somewhat less extensive myocardial ischemia: CCTA 2-vessel disease, CAC score >400 Agatston units, severe resting LV dysfunction (LVEF <35%) not readily explained by noncoronary causes, stress defects at 10% level, 2 coronary beds wall motion abnormality on stress echocardiography but only 2 segments.

Table 13. CAD Prognostic Index

Extent of CAD	Prognostic Weight (0–100)	5-Year Survival Rate (%)*
1-vessel disease, 75%	23	93
1-vessel disease, 50% to 74%	23	93
1-vessel disease, ≥95%	32	91
2-vessel disease	37	88
2-vessel disease, both ≥95%	42	86
1-vessel disease, ≥95% proximal LAD artery	48	83
2-vessel disease, ≥95% LAD artery	48	83
2-vessel disease, ≥95% proximal LAD artery	56	79
3-vessel disease	56	79
3-vessel disease, ≥95% in ≥1 vessel	63	73
3-vessel disease, 75% proximal LAD artery	67	67
3-vessel disease, ≥95% proximal LAD artery	74	59

*Assuming medical treatment only. CAD indicates coronary artery disease; LAD, left anterior descending.

Reproduced from Califf et al. (55).

Coronary angiography helps to quantify risk on the basis of an anatomic prognostic index; the simplest and most widely used is the classification of disease into 1-, 2-, or 3-vessel or left main CAD (358,375–377). In the CASS registry (364) of medically treated patients, the 12-year survival rate of patients with normal coronary arteries was 91%, compared with 74% for those with 1-vessel disease, 59% for those with 2-vessel disease, and 40% for those with 3-vessel disease. The probability of survival declines progressively with the number of coronary arteries that are occluded. The presence of severe proximal LAD artery disease significantly reduces the survival rate. The 5-year survival rate with 3-vessel disease plus >95% proximal LAD stenosis was reported to be 59%, as compared with a rate of 79% for 3-vessel disease without LAD stenosis (Table 13).

With the use of data accumulated in the 1980s, a nomogram was developed to predict 5-year survival rate on the basis of clinical history, physical examination, coronary angiography, and LVEF (Figure 12). The importance of considering clinical factors and especially LV function in estimating the risk of a given coronary angiographic finding is illustrated by comparing the predicted 5-year survival rate of a 65-year-old man with stable angina, 3-vessel disease, and normal ventricular function with that of a 65-year-old man with stable angina, 3-vessel disease, heart failure, and an EF of 30%. The 5-year survival rate for the former was estimated to be 93%, whereas patients with the same characteristics but with heart failure and reduced EF had a predicted survival rate of only 58%. Because of advances in treatment, it is almost certain that the survival rate has

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Table 14. Noninvasive Risk Stratification

High risk (>3% annual death or MI)

1. Severe resting LV dysfunction (LVEF <35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities ≥10% of the myocardium in patients without prior history or evidence of MI
3. Stress ECG findings including ≥2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF <45% or drop in LVEF with stress ≥10%)
5. Stress-induced perfusion abnormalities encumbering ≥10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving >2 segments or 2 coronary beds)
8. Wall motion abnormality developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. CAC score >400 Agatston units
10. Multivessel obstructive CAD (≥70% stenosis) or left main stenosis (≥50% stenosis) on CCTA

Intermediate risk (1% to 3% annual death or MI)

1. Mild/moderate resting LV dysfunction (LVEF 35% to 49%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities in 5% to 9.9% of the myocardium in patients without a history or prior evidence of MI
3. ≥1 mm of ST-segment depression occurring with exertional symptoms
4. Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating 1 vascular territory with abnormalities but without LV dilation
5. Small wall motion abnormality involving 1 to 2 segments and only 1 coronary bed
6. CAC score 100 to 399 Agatston units
7. One vessel CAD with ≥70% stenosis or moderate CAD stenosis (50% to 69% stenosis) in ≥2 arteries on CCTA

Low risk (<1% annual death or MI)

1. Low-risk treadmill score (score ≥5) or no new ST segment changes or exercise-induced chest pain symptoms; when achieving maximal levels of exercise
2. Normal or small myocardial perfusion defect at rest or with stress encumbering <5% of the myocardium*
3. Normal stress or no change of limited resting wall motion abnormalities during stress
4. CAC score <100 Agaston units
5. No coronary stenosis >50% on CCTA

*Although the published data are limited; patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF <35%).

CAC indicates coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; LV, left ventricular; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

Adapted from Gibbons et al. (7).

improved since these studies were conducted, but the relative differences in survival likely persist.

The development of symptomatic LV failure in a patient with SIHD is often an indication of severe, obstructive CAD and demands expeditious evaluation for the presence of active ischemia. Depending on the acuity and severity of symptoms, angiography or evaluation for ischemia with noninvasive testing is warranted.

An additional, but less quantifiable, benefit of coronary angiography and LV function assessment derives from the ability of experienced angiographers to integrate the findings on coronary angiography and left ventriculography to estimate the potential benefit of revascularization strategies discussed below. The characteristics of coronary lesions (e.g., stenosis severity, length, complexity, and presence of thrombus), the number of lesions posing jeopardy to regions of contracting myocardium, the possible role of collaterals, and the mass of jeopardized viable myocardium also can afford some insight into the consequences of subsequent vessel occlusion. For example, a patient with a noncontracting inferior or lateral wall and severe proximal stenosis of a very large LAD artery is presumably at substantial risk of developing cardiogenic shock if the LAD artery were to become occluded.

In view of the importance of proximal versus distal coronary stenoses, a "jeopardy score" has been developed, which takes the prognostic significance of a lesion's location into consideration (378). Angiographic studies indicate that a direct correlation also exists between the angiographic severity of CAD and the amount of angiographically insignificant plaque buildup elsewhere in the coronary tree. These studies suggest that the higher mortality rate of patients with multivessel disease could occur because they have more mildly stenotic or nonstenotic plaques that are potential sites for acute coronary events than do patients with 1-vessel disease (379).

For many years, it has been known that patients with severe stenosis of the left main coronary artery have a poor prognosis when treated medically. A gradation of worsening risk also has been found with increasing degrees of stenosis of the left main in medically managed patients (380–382). Angiographic determination of the significance of left main disease can be difficult, with suboptimal intraobserver agreement with regard to the degree of severity of any given stenosis (381,383,384). However, multiple other modalities are available to the angiographer to assist in accurately determining the significance of a left main lesion (i.e., FFR and intravascular ultrasound). Despite the challenges posed by angiographic determination of left main disease, it remains the best option for the diagnosis and reevaluation of left main disease if concern exists about progression of previously diagnosed disease because of the inability to consistently detect and evaluate this condition with noninvasive testing or clinical assessment (385–390).

4. Treatment

4.1. Definition of Successful Treatment

The paramount goals of treating patients with SIHD are to minimize the likelihood of death while maximizing health and function. The more specific objectives are to:

- Reduce premature cardiovascular death;

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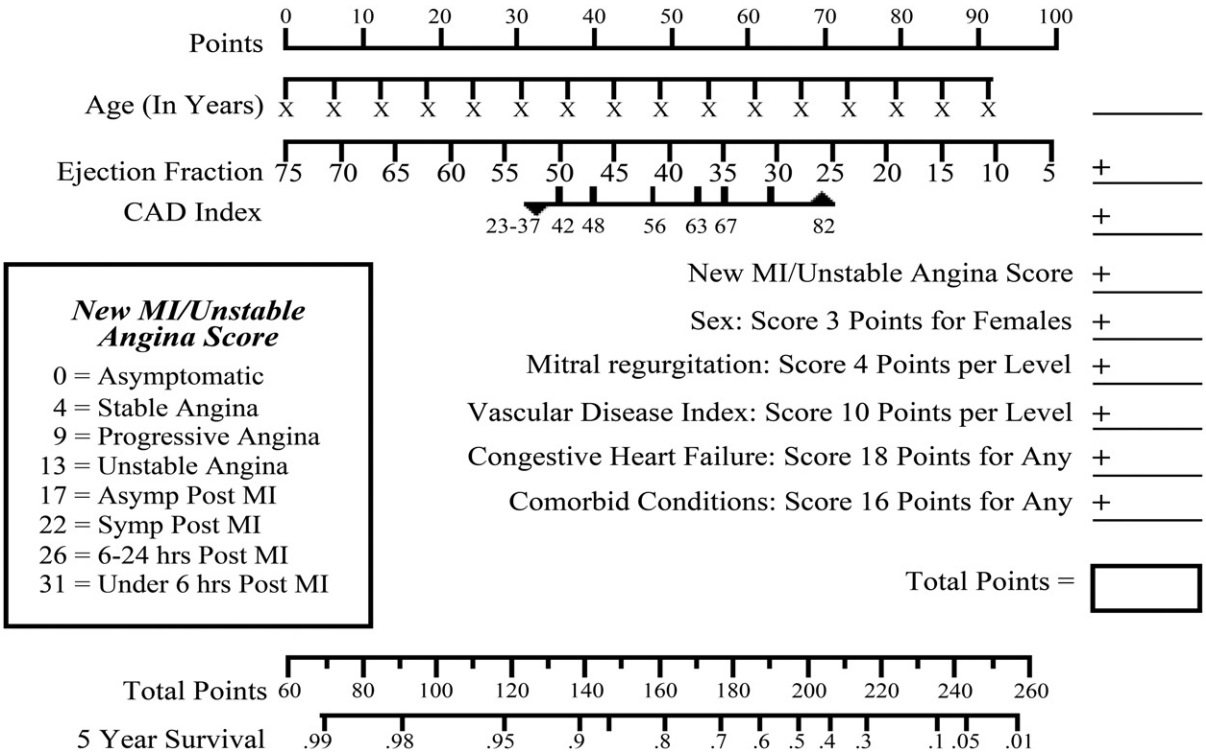

Figure 12. Nomogram for Prediction of 5-Year Survival From Clinical, Physical Examination, and Cardiac Catheterization Findings

Asymp indicates asymptomatic; CAD, coronary artery disease; MI, myocardial infarction; and Symp, symptomatic. Reproduced from Califf et al. (55).

- Prevent complications of SIHD that directly or indirectly impair patients' functional well-being, including nonfatal AMI and heart failure;
- Maintain or restore a level of activity, functional capacity, and quality of life that is satisfactory to the patient;
- Completely, or nearly completely, eliminate ischemic symptoms; and
- Minimize costs of health care, in particular by eliminating avoidable adverse effects of tests and treatments, by preventing hospital admissions, and by eliminating unnecessary tests and treatments.

These goals are pursued with 5 fundamental, complementary, and overlapping strategies:

1. Educate patients about the etiology, clinical manifestations, treatment options, and prognosis of IHD, to support active participation of patients in their treatment decisions.

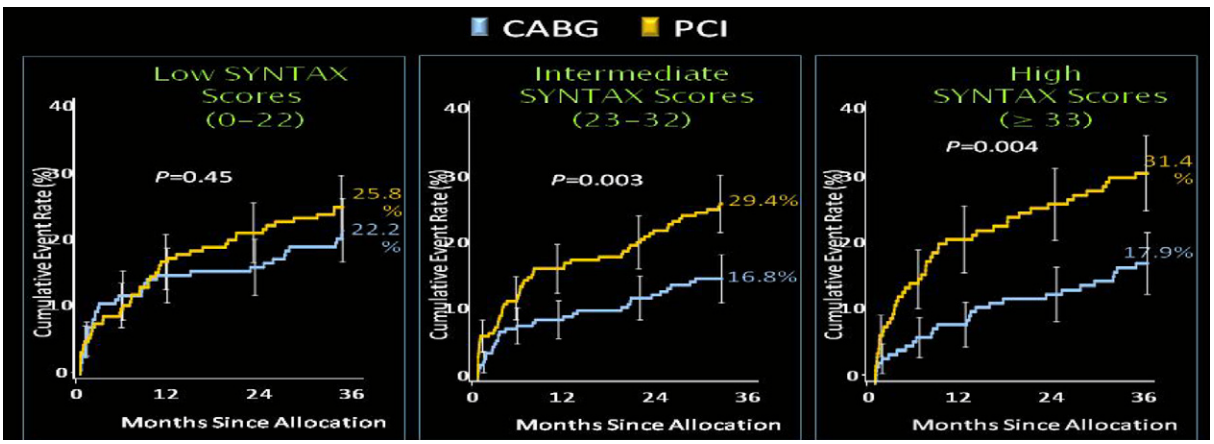

Figure 13. Cumulative Incidence of MACE in Patients With 3-Vessel CAD Based on SYNTAX Score at 3-Year Follow-Up in the SYNTAX Trial Treated With Either CABG (Blue) or PCI (Gold)

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention; and SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. Adapted from Kappetein (980).

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2. Identify and treat conditions that contribute to, worsen, or complicate IHD.
3. Effectively modify risk factors for IHD by both pharmacological and nonpharmacological methods.
4. Use evidence-based pharmacological treatments to improve patients' health status and survival, with attention to avoiding drug interactions and side effects.
5. Use revascularization by percutaneous catheter-based techniques or CABG when there is clear evidence of the potential to improve patients' health status and survival.

4.2. General Approach to Therapy

The writing committee has constructed these guidelines from the perspective that when making decisions about diagnostic tests and therapeutic interventions, their potential effects on improving survival and health status should be considered independently. Although treatment choices often are intended to achieve both goals simultaneously, circumstances exist in which a treatment is administered in pursuit of only one of these goals. For example, when pharmacotherapy such as aspirin or angiotensin-converting enzyme (ACE) inhibitors is prescribed, the goal is to improve survival but not necessarily quality of life. Similarly, revascularization can be performed to improve symptoms, even when there is no expectation of improved survival. Occasionally, treatment recommendations related to achieving these goals can be at odds, such as when a patient is encouraged to take a medication that significantly reduces the risk of death even though it causes mild or moderate adverse side effects.

It might also be the case that a patient expresses a preference for a treatment approach (e.g., PCI) when the practitioner believes another approach (e.g., GDMT) would be preferable. Although practitioners always should engage patients in a detailed discussion about their individual goals and values in order to tailor therapy, this is particularly important when therapeutic goals or the patient's or provider's preferences are not aligned. It is essential that these discussions be conducted in a location and atmosphere that permits adequate time for discussion and contemplation. Initiating a discussion about the relative merits of medical therapy versus revascularization while a patient is in the midst of procedure, for example, is not usually consistent with these principles.

Reducing the risk of mortality should be pursued as intensively as is sensible for all patients with SIHD. It has been estimated that nearly half of the dramatic decline in cardiovascular mortality observed during the past 40 years is attributable to interventions directed at modifying risk factors. Of this change, 47% can be attributed to treatments, including risk factor reduction after AMI, other guideline-based treatments for UA and heart failure, and revascularization for chronic angina (391). An additional 44% reduction in age-adjusted death is attributed to population-based changes in risk factors (391). Unfortunately, these changes have been offset somewhat by increases in BMI and type 2 diabetes mellitus, which result in an increased number of deaths (391).

The 2011 secondary prevention and risk reduction therapy statement (8) summarizes the key interventions known to improve survival and prevent subsequent cardiac events. Worldwide, it has been estimated that 90% of the risk of MI is attributable to 9 measureable risk factors, including smoking, diabetes mellitus, hypertension, obesity, impaired psychological well-being, poor diet, lack of exercise, alcohol consumption, and dyslipidemia (392). The initial approach to all patients should be focused on eliminating unhealthy behaviors such as smoking and effectively promoting lifestyle changes (e.g., maintaining a healthy weight, engaging in physical activity, adopting a healthy diet [Figure 4]). In addition, for most patients, an evidence-based set of pharmacological interventions is indicated to reduce the risk of future events. The presumed mechanism by which these interventions work is stabilization of the coronary plaque to prevent rupture and thrombosis (8). These include antiplatelet agents (393), statins (394–401), and beta blockers, along with other agents if indicated, to control hypertension (402,403). ACE inhibitors are indicated in many patients with SIHD, especially those with diabetes mellitus or LV dysfunction (296,301,404). Similarly, tight glycemic control not only has not been shown to reduce the risk of macrovascular complications in patients with type 2 diabetes mellitus, it also appears to increase the risk of cardiovascular death and complications. Nonetheless, weight loss, aerobic exercise, an AHA Step II diet, and ACE inhibitors in patients with diabetes mellitus with proteinuria all can improve patients' risks of microvascular complications and, potentially, cardiac events.

For the purposes of this guideline, the writing committee elected to retain the classification for risk of cardiovascular events that has been accepted by consensus over the past 2 decades. Patients with a predicted annual cardiac mortality rate of <1% per year are considered to be at low risk, those with a predicted rate of 1% to 3% per year are considered to be at intermediate risk, and those with a predicted average >3% per year are considered to be at high risk.

For patients at high risk of mortality, the prevalence of severe CAD (e.g., left main coronary occlusion) is higher, and coronary angiography can define the coronary anatomy and help to plan further therapy beyond standard GDMT (Figure 5). If the patient is at low or intermediate risk for mortality, therapeutic decisions should be directed toward improving symptoms and function, and catheterization may be deferred if symptoms can be controlled with medical therapy alone. For patients in whom angiography is performed and who are determined to be at low or intermediate risk, evidence reaffirms that it is safe to defer revascularization and institute a program of evidence-based medical

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therapy, because neither survival nor adverse cardiac events are averted by proceeding immediately to revascularization (366,397,405–409). If a patient in this category has symptoms that are completely or almost completely relieved with medical therapy, it is usually prudent to continue with medical therapy without proceeding to revascularization. If symptoms persist, however, then a discussion with the patient to elicit his or her preferences and goals is necessary, along with a frank discussion of the benefits and risks of PCI and CABG, to ascertain whether the symptoms have been ameliorated sufficiently to warrant simply continuing with medical therapy alone (Figures 4 and 5).

Coronary revascularization generally improves survival among certain subgroups of patients, particularly those with severe left main coronary stenosis. When revascularization is being considered on an elective basis solely for reducing the risk of death, the healthcare provider should engage the patient in an explicit consideration of the estimated improvement in survival relative to the potential risks and costs of the procedure and related interventions. Because reliable estimates of benefit, such as absolute risk reduction, are frequently unavailable for many specific subgroups, the risk for death can be estimated before treatment and the anticipated absolute risk reduction calculated (obtained by multiplying the RR reduction by the pretreatment risk). In the STICH (Surgical Treatment for Ischemic Heart Failure) trial, in which 1,212 patients with an LVEF ≤35% and CAD amenable to revascularization were randomized to CABG or medical therapy, there was no significant difference in overall mortality rate, but during a median follow-up of 56 months, 28% of those assigned to CABG died of a cardiovascular cause, compared with 33% of those receiving medical therapy (410). This information can be converted to a more interpretable framework, such as the average reduction in risk of events or number needed to treat. In this example, the average reduction in cardiovascular events was 19%, and it would be necessary to perform bypass surgery on about 5 patients with LV dysfunction to prevent 1 cardiovascular death at 5 years (i.e., number needed to treat = 5, calculated as 1 ÷ absolute risk reduction, or 1/0.19 [although there would be no effect on overall mortality rate]). This process complies with the Institute of Medicine's goals for transparently sharing evidence with patients so that they can control (or more actively participate in) their own decisions (411). In general, a beneficial effect of revascularization on survival has been demonstrated most clearly among patients with the highest cardiovascular risk (412). Although traditional methods of risk stratification have relied on coronary anatomy and LV function, other strategies described in this guideline can be used (Figure 5).

The specific anatomic features of the patient and the likelihood of procedural success often influence the approach to a patient for whom revascularization is being considered. For example, a given patient with 1-vessel disease might have coronary anatomic features that would make the risk of PCI high enough and the likelihood of success low enough that CABG or medical therapy would be preferred. In general, complete revascularization leads to better outcomes than incomplete revascularization (413–418). In patients with chronic total occlusion, CABG could be preferable to PCI (419), but this is still controversial. Although the technology and techniques for PCI of chronic total occlusions are improving, there remains no current evidence that survival is improved after successful PCI of a chronic total occlusion. Some patients with diabetes mellitus can have such diffuse disease that neither CABG nor PCI is likely to produce sustained benefits. Other patients can have small-caliber arteries or diffuse disease that is likely to lead to early graft failure. Still others can have long, complex lesions that are very likely to undergo restenosis after PCI, although use of drug-eluting stents (DES) can reduce this risk.

The majority of patients with SIHD have clinical features indicating that revascularization is unlikely to improve life expectancy or the risk of subsequent MI. For such patients, antianginal therapy and intensive treatment for risk factors are recommended before consideration of PCI or CABG to relieve symptoms. A broad range of highly effective drugs is available, including beta blockers, calcium channel blockers, long-acting nitrates, and newer agents such as ranolazine. Comparative trials among these medications are relatively few and for the most part small (420). On the basis of the available data, however, all of the classes of agents appear to be relatively similar in antianginal efficacy, and all have very acceptable profiles of safety and tolerability. Beta blockers have been shown to improve survival in patients after AMI and in patients with hypertension; they provide 24-hour coverage and have a long history of clinical use. For these reasons, the writing committee recommends these agents as first-line drugs for treating angina. In patients who do not tolerate or adequately respond to beta blockers, calcium channel blockers and/or long-acting nitrates may be substituted or added. Ranolazine has been shown to inhibit the late sodium current in humans and has demonstrated lusitropic properties (421). Clinical trials have shown that this agent is comparable to other agents in alleviating angina. Although this agent has been approved by the U.S. Food and Drug Administration (FDA) for first-line use in patients with chronic angina, the writing committee recommends that ranolazine be considered in circumstances in which beta blockers, calcium channel blockers, and nitrates are not adequately effective or are not tolerated.

4.2.1. Factors That Should Not Influence Treatment Decisions

The 2 medical indications for revascularization are to prevent death and cardiovascular complications and to improve symptoms and quality of life. Nonetheless, the use of revascularization has risen dramatically in the past 3 decades. Much of this increase appears to be for indications

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for which benefits in survival or symptoms in comparison with noninvasive therapies are unlikely (422). National data suggest that about 12% of PCIs could be inappropriate because they lack evident potential to improve either survival or symptoms (423). Several reasons influence patients and physicians to prefer revascularization when the likelihood of benefit is less than the potential risk of the procedure. An ingrained preference for action (i.e., revascularization) over perceived inaction (i.e., medical therapy alone) likely often influences the decision making of both patients and physicians (252). Moreover, some healthcare professionals are unduly pessimistic about survival with conservative medical therapy and inaccurately optimistic about the survival benefits of revascularization procedures (424). As indicated earlier, patients often believe mistakenly that PCI has the potential to prevent AMI and prolong survival (423,425). In addition, the attendant expense and risk of combined antiplatelet therapy for an uncertain period of time might not be fully considered. Physicians are professionally obligated to provide accurate estimates of the risks, benefits, and costs of various therapeutic options that are based on the best available scientific data. Other factors can induce physicians to recommend revascularization. These include medicolegal concerns (often exaggerated) and feeling compelled to satisfy the expectations of patients and referring physicians (which are sometimes misinformed or unrealistic) (426). Additionally, there are well-documented regional variations in the use and appropriateness of cardiac procedures that appear to reflect local practice styles (427). This might partly reflect a mistaken belief by some physicians that "more care is better care" (428). Although successful procedures can be psychologically satisfying to the physician and the patient, this does not justify the attendant economic costs and risk of complications of procedures that offer minimal, if any, genuine benefit (429–431).

Although rarely discussed explicitly, financial incentives seem to affect the willingness of a minority of physicians and institutions to recommend certain procedures or drug therapies. Strong incentives created by the payment system encourage overutilization. Also, a small number of physicians might have financial relationships with the manufacturers of devices or drugs that might represent apparent conflicts that ought to be disclosed to patients. At a higher level, those responsible for the payment system, the manufacturers of devices and drugs, and physicians making clinical decisions must commit to supporting guideline-based interventions. Any and all conflicts of interest must be revealed to patients in the process of informed consent before any invasive or noninvasive procedure.

4.2.2. Assessing Patients' Quality of Life

In addition to interventions undertaken to improve survival and prevent cardiovascular complications, therapy also is prescribed to improve patients' *health status,* a general term that incorporates many facets, including severity of symptoms, functional limitations, and quality of life. Assessment of health status is often unstructured and exclusively qualitative, but efforts to standardize this assessment are recommended, beginning with a structured inventory of activity, symptoms, and quality of life, supplemented by the use of simple, semiquantitative scales such as the CCS and New York Heart Association classifications (432,433).

The CCS and New York Heart Association classifications are limited, however, because they quantify health status from the physicians' perspective, rather than directly reporting patients' experiences, and they are known to have limited reproducibility and sensitivity to important clinical changes. Furthermore, even these simple classifications of health status are recorded infrequently in health records (432,434). One approach to directly eliciting perceptions of health status from patients with IHD is to use the self-administered Seattle Angina Questionnaire (SAQ), a valid, sensitive, and prognostically important questionnaire, to quantify the symptoms, functional limitations, and quality of life of patients with SIHD (246,247,435). Although such instruments typically are used in research trials, they are readily applicable to clinical practice and can be used serially to assess and monitor the effectiveness of therapy, including antianginal medications and revascularization (434). The formal assessment of a patient's disease-specific health status, through either the CCS or the SAQ, has been endorsed as a performance measure of healthcare quality (436).

4.3. Patient Education: Recommendations

CLASS I

1. Patients with SIHD should have an individualized education plan to optimize care and promote wellness, including:
   a. education on the importance of medication adherence for managing symptoms and retarding disease progression (437–439) *(Level of Evidence: C);*
   b. an explanation of medication management and cardiovascular risk reduction strategies in a manner that respects the patient's level of understanding, reading comprehension, and ethnicity (8,440–444) *(Level of Evidence: B);*
   c. a comprehensive review of all therapeutic options (8,441–444) *(Level of Evidence: B)*;
   d. a description of appropriate levels of exercise, with encouragement to maintain recommended levels of daily physical activity (8,445–448) *(Level of Evidence: C);*
   e. introduction to self-monitoring skills (445,447,448) *(Level of Evidence: C);* and
   f. information on how to recognize worsening cardiovascular symptoms and take appropriate action. *(Level of Evidence: C)*

2. Patients with SIHD should be educated about the following lifestyle elements that could influence prognosis: weight control, maintenance of a BMI of 18.5 to 24.9 kg/m^2, and maintenance of a waist circumference less than 102 cm (40 inches) in men and less than 88 cm (35 inches) in women (less for certain racial groups) (8,440,449–452); lipid management (18); BP control (17,453); smoking cessation and avoidance of exposure to secondhand smoke (8,454,455); and individualized medical, nutrition, and life-

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style changes for patients with diabetes mellitus to supplement diabetes treatment goals and education (456). *(Level of Evidence: C)*

CLASS IIa

1. It is reasonable to educate patients with SIHD about:
   a. adherence to a diet that is low in saturated fat, cholesterol, and *trans* fat; high in fresh fruits, whole grains, and vegetables; and reduced in sodium intake, with cultural and ethnic preferences incorporated (8,17,18,457,458) *(Level of Evidence: B);*
   b. common symptoms of stress and depression to minimize stress-related angina symptoms (459) *(Level of Evidence: C)*;
   c. comprehensive behavioral approaches for the management of stress and depression (237,460–462) *(Level of Evidence: C)*; and
   d. evaluation and treatment of major depressive disorder when indicated (237,238,437,461,463,464,467,468). *(Level of Evidence: B)*

Multiple risk factors for heart disease, vascular disease, and stroke are typically present in persons with SIHD, including hypertension, smoking, dyslipidemia, diabetes mellitus, overweight, and physical inactivity (27,392). At a national level, in 2000, only 5% of individuals without IHD and 7% of those with IHD were fully adherent to recommendations for physical activity, fruit and vegetable consumption, and nonsmoking.

The approach to managing risk factors usually requires partnerships among the healthcare team, the patient, their family, and their community. The goal of this partnership is to assure an effective exchange of information, sharing of concerns, and an improved understanding of treatments, with the aim of improving quality of life and health outcomes. The American Academy of Family Physicians defines patient education as "the process of influencing patient behavior through the provision of information and counseling that is designed to produce changes in knowledge, attitudes, and skills necessary to maintain or improve health" (469). The Joint Commission mandates patient education as a principal guiding policy to improve health outcomes. Effective patient education and counseling are based on a collaborative approach that acknowledges individual patient needs through an understanding of cognitive, behavioral, and sociodemographic factors. Patients actively involved in care decisions are more likely to follow a treatment plan and engage in behaviors that can improve their health.

When educating patients, it is important to communicate an understanding of a specific disease process, the need for laboratory testing, medication management and adherence, reporting of efficacy and side effects, and behavioral lifestyle change (8). Unfortunately, the type, intensity, frequency, and duration of educational programs are not well established for individual risk factors. For example, the Ask, Advise, Assess, Assist, and Arrange algorithm for smoking cessation often is used, although supporting data from RCTs are lacking (470). In addition, who should deliver education programs and how to evaluate efficacy are not well studied. In smoking cessation, the most effective intervention continues to be a physician's recommendation for the patient "to quit." However, quit rates for smoking are also dependent on the appropriate use of medical therapies and group support programs (442,471). In diabetes care, patient education has the potential to be as effective as or more effective than medical therapies (472). The management of hypertension, heart failure, dyslipidemia, type 2 diabetes mellitus, weight loss, and physical activity is enhanced by ongoing health education and support in addition to physician office visits.

Factors that complicate effective patient education include low literacy, adverse sociodemographic factors (e.g., poverty, social isolation, and emotional disorders such as depression), cultural beliefs and language barriers, environmental factors, advanced age, and the presence of complex comorbidities. These factors and others play an important role in the adoption of healthy lifestyles and adherence to recommended medical therapies. In addition, how to best provide cost-effective educational strategies remains a challenge in today's healthcare environment (473). The lack of payment for these activities remains an important barrier. Clinic-based education generally consists of the following:

1. *Individual counseling.* This educational format commonly is used in the context of a routine clinic visit. It tends to be directive and didactic, generally not interactive or behaviorally oriented, relatively brief, and sometimes supported with written materials. Follow-up to ascertain effectiveness is not commonly practiced.
2. *Group education.* Group care or shared office visits have been tested in multispecialty group practices. They offer the benefit of providing education to larger numbers of patients with similar diagnoses (e.g., type 2 diabetes mellitus), combined with an individualized physician visit. They tend to be behaviorally oriented with planned follow-up for effectiveness and outcomes.
3. *Self-monitoring.* Self-monitoring skills enhance patient education and behavior change. Examples such as home BP and blood glucose monitoring and tracking daily calories and physical activity minutes can support important lifestyle change. Review of self-monitoring logs by patient and provider at subsequent clinic visits supports the continued importance of and attention to behavior change. In some healthcare plans, these data can be entered via web portals for patients (474).
4. *Internet- and computer-based education.* A growing number of health plans provide health information via websites and special programs. This approach is often low in cost to the patient but requires adequate computer access and skills, higher reading levels, and self-motivation to change behavior (e.g., AHA Choose to Move) (475).
5. *Hand-held computer devices, smartphones, and other portable devices.* Portable devices have the potential to provide motivational reminders and prompts for lifestyle change but have not yet been thoroughly tested.

Present efforts to improve the effectiveness of patient education and lifestyle interventions integrate key constructs

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related to behavior change theory. A summary of the most common models is provided below:

1. *Motivational interviewing,* a social learning theory, promotes behavioral change through empathetic and reflective listening, encouraging patients to determine their reasons for change, helping healthcare professionals deal with resistance, and supporting self-efficacy (476).
2. *Self-efficacy theory* posits that the ability to change behavior depends upon one's self-confidence to perform a specific action (such as walking 30 minutes daily) and the belief that one can persist with this action. Low self-efficacy predicts poor ability to achieve a specified lifestyle change. Improving one's self-efficacy will improve the ability to change a particular lifestyle (477).
3. The *Transtheoretical Model* of behavior change is based on "stages of change." The theory relies on the observation that many individuals traverse 5 distinct temporal processes in achieving permanent change. These include precontemplation, contemplation, preparation, action, and maintenance. Application of this model of change entails categorizing an individual's progress in the process of change and recognizing that cycling through phases is common in the process of achieving permanent change (478).

The interventions described above should be provided within a medical environment that provides coordinated, team-based care. Data accumulating from interventions that incorporate principles of the chronic care model (479), such as the patient-centered medical home, have demonstrated beneficial effects not only on intermediate outcomes such as glycemic and BP but also on cost, utilization, and mortality rate (480,481). This approach depends on the active participation of an engaged, informed patient, which in turn relies on the patient's understanding of his or her condition, ability to adhere safely to complex medical therapies, and willingness to communicate on a regular basis with the healthcare team. In addition to counseling about the approach to management of SIHD and risk reduction, patients often seek information about other aspects of their health, particularly issues that are often not directly addressed by healthcare providers.

One such topic that commonly arises is possible restrictions on sexual activity. Regrettably, there are relatively limited scientific data on the cardiovascular demands and potential risks of sexual activity in patients with heart disease, some of it dating back 3 or 4 decades and nearly all of it dealing with men. In general, sexual activity is equivalent to mild to moderate physical activity requiring 3 to 5 METs (i.e., the equivalent of climbing 2 flights of stairs or walking briskly) (482). The few available studies suggest that AMI within 1 to 2 hours of sexual activity is associated with an average RR of 2.7 among middle-aged men, with the greatest risk among those who are sedentary (483–486). Because the overall incidence of AMI is low in the population and periods of exposure relatively infrequent, it has been postulated that the absolute risk is exceedingly low for any individual (487). However, ECG monitoring during sexual activity in 1 study of men with IHD revealed that nearly a third developed ST depression and nearly half developed arrhythmias. It appeared, however, that these findings also were found during similarly stressful activities that did not involve sex, and the arrhythmias were largely benign. Moreover, these patients were not initially on anti-ischemic medications, and it was reported that the ischemic changes on ECG resolved when subjects took beta blockers. Thus, it seems that sexual activity should not necessarily be regarded as appreciably different from other types of physical activity that impose equivalent metabolic demands. Needless to say, patients should be treated to maximize their capacity for physical activity, as described subsequently in this guideline.

Patients often express concerns that medications given to treat symptoms or reduce cardiovascular risk could cause erectile dysfunction. Although these perceptions are often firmly and widely held, studies and reviews have not delineated a clear association between these drugs, including beta blockers, and sexual dysfunction (488–492).

A related issue that could arise is use of phosphodiesterase 5 inhibitors, such as sildenafil, vardenafil, or tadalafil, to improve erectile function. Although, as discussed in the section on treatment of SIHD, current evidence has shown that these drugs do not raise the risk of adverse cardiovascular events in men with SIHD (493,494), there is a clear risk of serious hypotension when they are taken in conjunction with nitrates, and the combination is absolutely contraindicated. There are also potential drug–drug interactions with alpha-blockers that are sometimes used to treat hypertension (495).

4.4. Guideline-Directed Medical Therapy

4.4.1. Risk Factor Modification: Recommendations

4.4.1.1. LIPID MANAGEMENT

CLASS I

1. **Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with SIHD (18,496). *(Level of Evidence: B)***
2. **Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), *trans* fatty acids (to <1% of total calories), and cholesterol (to <200 mg/d) (18,497–500). *(Level of Evidence: B)***
3. **In addition to therapeutic lifestyle changes, a moderate or high dose of a statin therapy should be prescribed, in the absence of contraindications or documented adverse effects. (18,398,400,458,501). *(Level of Evidence: A)***

CLASS IIa

1. **For patients who do not tolerate statins, LDL cholesterol–lowering therapy with bile acid sequestrants,* niacin,† or both is reasonable (502,504,505). *(Level of Evidence: B)***

*The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dL and is contraindicated when triglycerides are ≥500 mg/dL.
†Dietary supplement niacin must not be used as a substitute for prescription niacin.

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Epidemiological studies have established serum cholesterol as an important coronary heart disease risk factor. The Framingham Heart Study, Multiple Risk Factor Intervention trial, and the Lipid Research Clinics trials all found a continuous, graded increase in coronary events with increasing LDL cholesterol in men and women who were initially free of IHD (502,506–508). A similar relationship has been observed among patients with SIHD (509–511). The association between LDL cholesterol and cardiovascular risk is curvilinear, or log-linear, meaning that the decrease in RR for a given 1-mg/dL decrease in LDL cholesterol seems to be the same at any level of baseline LDL cholesterol. The principal lipid modification strategy recommended by the NCEP ATP-III (National Cholesterol Education Program Adult Treatment Panel III) in patients with SIHD is the reduction of LDL cholesterol (18,24). This should start with therapeutic lifestyle changes, including dietary therapy, daily physical activity, and weight management. Most patients also will benefit from cholesterol-lowering drug therapy, preferably with a statin.

Effective dietary approaches to lowering LDL cholesterol include replacing saturated and *trans* fatty acids with dietary carbohydrates or unsaturated fatty acids and reducing dietary cholesterol. Although the response to dietary interventions is variable, a diet low in saturated fat and cholesterol typically lowers LDL cholesterol by 10% to 15% (497–500). Other beneficial dietary interventions can include addition of plant stanols/sterols (2 g/d), which trials suggest lower LDL cholesterol by 5% to 15%, and addition of viscous fiber (>10 g/d), which reduces LDL cholesterol by 3% to 5% (512–515). A 10-lb weight loss reduces LDL cholesterol by 5% to 8% (496). Regular physical activity is also a key component of therapeutic lifestyle modification. Although exercise does not reliably lower LDL cholesterol, it facilitates weight loss and has other beneficial effects on the lipid profile (516–518).

Controlled clinical trials of lipid-lowering drug therapy have demonstrated that lowering of LDL cholesterol is associated with a reduced risk of adverse cardiovascular events. Earlier trials used bile acid sequestrants (cholestyramine), fibric acid derivatives (gemfibrozil and clofibrate), or niacin. More contemporary studies have convincingly established the efficacy of statins in the primary and secondary prevention of coronary events (394–396,398,400, 501,519–522). In a prospective meta-analysis published by the Cholesterol Treatment Trialist Collaborators in 2010 that examined data from 26 randomized trials of statin therapy (comparing higher- to lower-dose statin therapy or statin therapy to a control regimen), the mean difference in LDL cholesterol was 31 mg/dL, ranging from 12 to 68 mg/dL. Each 40-mg/dL reduction in LDL cholesterol was associated with a 10% reduction in all-cause mortality and a 20% reduction in coronary mortality, with corresponding reductions in nonfatal MI, need for coronary revascularization, and first nonfatal ischemic stroke (458). The absolute benefit of therapy was a function of an individual's absolute risk of fatal MI (458). In trials comparing higher- to lower-dose statin therapy, the average, weighted reduction in LDL cholesterol at 1 year was 20 mg/dL among those receiving higher-dose regimens. Among patients assigned to more intensive regimens, there was a 15% lower incidence of major vascular events (95% CI: 11 to 18; $p<0.0001$), which reflected a 13% lower risk of coronary death or nonfatal MI (95% CI: 7 to 19; $p<0.0001$), a 19% lower risk of undergoing coronary revascularization (95% CI: 15 to 24; $p<0.0001$), and a 16% lower risk of ischemic stroke (95% CI: 5 to 26; $p=0.005$). The reductions in serum LDL cholesterol and in cardiovascular risk were similar in magnitude to those observed in trials comparing statin therapy to a control regimen. The absolute benefit of therapy was defined chiefly by an individual's absolute risk of death due to coronary occlusion (458). Appropriate treatment goals for patients with SIHD have been informed by several trials of intensive lipid-lowering therapy. The HPS (Heart Protection Study) compared simvastatin 40 mg daily to placebo in patients with IHD, other occlusive vascular disease, or diabetes mellitus. On-treatment LDL cholesterol levels averaged 88 mg/dL in those allocated to simvastatin and 127 mg/dL in those randomized to placebo. A consistent and early benefit of therapy was demonstrated, with a 13% reduction in mortality rate and an 18% reduction in coronary death rate (398). Similar reductions in RR were observed regardless of baseline levels of LDL cholesterol, including in those with initial levels <116 mg/dL or <97 mg/dL. (Of note, LDL cholesterol levels in the HPS were not drawn with patients in the fasting state and were measured values rather than the calculated values used in clinical practice and in most trials; measured LDL cholesterol is generally about 15% higher than calculated LDL cholesterol) (398). In the TNT (Treating to New Targets) trial, patients with clinically apparent IHD and LDL cholesterol >130 mg/dL were randomly assigned to either 10 mg or 80 mg of atorvastatin per day. The mean LDL cholesterols were 77 mg/dL during treatment with 80 mg of atorvastatin and 101 mg/dL during treatment with 10 mg of atorvastatin. There was a 22% reduction in a composite cardiovascular endpoint and a 20% reduction in cardiac deaths with more intensive therapy but no reduction in all-cause mortality (400). In the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study patients with a past history of MI were randomly assigned to intensive lipid-lowering therapy with atorvastatin 80 mg daily or simvastatin 20 mg daily. During treatment, mean LDL cholesterol levels were 104 mg/dL in the simvastatin group and 80 mg/dL in the atorvastatin group. The results showed a nonsignificant trend toward reduction of the primary composite endpoint of coronary death, nonfatal MI, or cardiac arrest (hazard ratio: 0.89; 95% CI: 0.78 to 1.01); significant reductions in some secondary endpoints such as nonfatal MI and coronary revascularization; and no effect on all-cause mortality (501). It should be noted that both these trials compared 2 drug

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regimens and did not directly test the benefit of achieving a given level of LDL cholesterol and that, to date, there is no clear evidence that treating to a specific target, as opposed to treating with a higher dose of a higher-potency statin, is beneficial. The mean achieved LDL cholesterol levels among patients treated in the high-dose atorvastatin arms of the TNT and IDEAL studies were 77 and 81 mg/dL, respectively.

These data support intensive LDL cholesterol lowering with statins in patients with SIHD. An update of the ATP-III report (18,24) recommends treatment to an LDL cholesterol level <100 mg/dL in patients with established CAD or other high-risk features, with an LDL cholesterol goal of <70 mg/dL as a therapeutic option in patients at very high risk. However, as discussed above, although the presence of data confirming the use of a specific, numeric target LDL cholesterol level for all patients with SIHD has been challenged, the benefit of therapy with moderate- to high-dose statin therapy is well established (458). For this reason, the recommendations in this guideline stress the importance of prescribing a statin in at least a moderate dose. The ATP-IV report is anticipated later in 2012 and is expected to provide guidance for the treatment of LDL cholesterol levels on the basis of the results of an extensive systematic review. Factors that identify patients at very high risk in the ATP-III update include the presence of established coronary vascular disease, plus 1) multiple major risk factors, especially diabetes mellitus; 2) severe and poorly controlled risk factors, especially continued tobacco use; and 3) multiple risk factors for the metabolic syndrome. Again, it should be acknowledged that no studies have assessed the benefits of titrating lipid-lowering drugs to achieve a specific LDL cholesterol target. In addition, trials of intensive lipid lowering for secondary prevention have used statins alone. Although the addition of other agents could lower LDL cholesterol in patients in whom a target level cannot be achieved with a statin, the utility of this approach in reducing risk of cardiovascular morbidity and mortality has not been firmly established.

A secondary target of therapy introduced by ATP-III is non–HDL cholesterol in patients with elevated triglycerides (18,24). Non–HDL cholesterol is defined as the difference between total cholesterol and HDL cholesterol. It includes all cholesterol and lipoprotein particles that are considered atherogenic, including LDL cholesterol, lipoprotein, intermediate-density lipoprotein, and very-low-density lipoprotein, and is a predictor of cardiovascular death (523). Because statins lower LDL cholesterol and non–HDL cholesterol to a similar extent, the relative benefits of lowering these 2 lipid measures cannot be distinguished from recent clinical trials. Fibrates could reduce the risk of coronary events in patients with high triglycerides and low HDL cholesterol levels and could have an adjunctive role in these patients in combination with statins (503,524). Nicotinic acid raises HDL cholesterol, and several trials support the efficacy of niacin when used alone or in combination with statins (504,505,525).

Observational studies and treatment trials suggest that consumption of omega-3 fatty acids reduces cardiovascular risk. Cohort and case–control studies have found an RR reduction of about 15% for fish consumption versus little or no fish consumption (526). In the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) Prevention study in patients with prior MI, 1 g daily of fish oil supplement resulted in a 20% reduction in mortality at 42 months (527). Pharmacological treatment with fish oil at higher doses (2 to 4 g daily) is effective in reducing triglyceride levels (528).

4.4.1.2. BLOOD PRESSURE MANAGEMENT

CLASS I

1. **All patients should be counseled about the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products (17,529–537). *(Level of Evidence: B)***
2. **In patients with SIHD with BP 140/90 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications (538–543). *(Level of Evidence: A)***
3. **The specific medications used for treatment of high BP should be based on specific patient characteristics and may include ACE inhibitors and/or beta blockers, with addition of other drugs, such as thiazide diuretics or calcium channel blockers, if needed to achieve a goal BP of less than 140/90 mm Hg (544,545). *(Level of Evidence: B)***

Hypertension is an important independent risk factor for ischemic cardiovascular events. Observational studies have demonstrated a continuous and graded relationship between BP and cardiovascular risk. In a collaborative meta-analysis of prospective studies of nearly 1 million adults without preexisting vascular disease, the risk of a vascular death increased linearly over the BP range of 115/75 mm Hg to 185/115 mm Hg, without a threshold effect. Each increment of 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP was associated with a doubling of risk (546). RCTs indicate that treatment results in a reduction of cardiovascular risk consistent with predictions from epidemiological studies (538–543,547).

Treatment of high BP should begin with lifestyle measures. Maintenance of an appropriate body weight (BMI <25 kg/m^2) is a key element of the nonpharmacological strategies recommended to improve BP control; weight loss of 10 kg typically results in a decrease in BP of 5 to 20 mm Hg (529–531,548,549). Consumption of a diet rich in fruits, vegetables, and low-fat dairy products (532,533); reduction of dietary sodium intake (529,531,533,534,550); regular physical activity (535); and moderation of alcohol consumption (536) also result in significant lowering of BP.

In many patients with SIHD, therapy with medications will be required to lower BP to the desired level. Treatment trials have definitively demonstrated a beneficial effect of

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antihypertensive drug therapy on cardiovascular disease risk. An overview of 17 placebo-controlled trials, most of which focused on lowering diastolic BP, showed that reducing diastolic BP 5 to 6 mm Hg (or an estimated 10 to 20 mm Hg in systolic BP) within a population was associated with a significant reduction in vascular mortality, with approximately 40% reduction in stroke and 20% reduction in coronary events (547). This benefit of treatment also has been observed in studies of older adult patients with isolated systolic hypertension (539,551,552).

Despite the plethora of clinical studies, the appropriate BP threshold for initiating medical therapy and specific treatment goals for patients with chronic IHD remain controversial. RCTs have demonstrated a benefit from antihypertensive therapy in patients with a diastolic BP >90 mm Hg (547) and also in patients with isolated systolic hypertension and a systolic BP >160 mm Hg (539,551,552). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target BP of <140/90 mm Hg in patients with uncomplicated hypertension and of <130/80 mm Hg in patients with diabetes mellitus or CKD (17). Observations from epidemiological studies and the relatively high absolute risk of cardiovascular events in patients with vascular disease have led some to suggest that a lower BP target might also be appropriate in individuals with SIHD (553).

On the other hand, excessive reduction in diastolic BP could compromise coronary perfusion in SIHD patients, and some studies have demonstrated a J-shaped relationship between diastolic BP and coronary events (554). The ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP trial (555), which enrolled patients with type 2 diabetes mellitus at high risk of cardiovascular events, found no benefit of targeting a systolic BP of 120 mm Hg compared with a systolic BP of 140 mm Hg in reducing a composite endpoint of MI, stroke, or death from cardiovascular causes. In a related vein, in AASK (African-American Study of Kidney Diseases and Hypertension) (556), 1,094 black patients with hypertensive kidney disease (diastolic pressure >95 mm Hg and glomerular filtration rate of 20 to 60 mL/min) and no diabetes mellitus were randomly assigned to achieve a mean arterial pressure target ≤92 mm Hg (corresponding to 130/80 mm Hg) or to a target of 102 to 107 mm Hg (corresponding to 140/90 mm Hg). Overall, there was no advantage to more intensive BP control with regard to progression to end-stage kidney disease or death (556).

Although in patients with uncomplicated hypertension there are a variety of considerations in selecting a medication, effective BP lowering is the most important factor in preventing stroke and MI. Clinical trials have failed to convincingly demonstrate superiority of any single antihypertensive drug class in preventing cardiovascular events (544,545). In many patients with SIHD, the choice of medications is guided by compelling indications for specific classes of drugs, as discussed elsewhere in this guideline (Table 15) (557). ACE inhibitors improve outcomes in most patients with CAD, especially those with a history of MI, LV dysfunction and heart failure, or CKD or diabetes mellitus (295,296,301,558–562). Angiotensin-receptor blockers (ARBs) are beneficial in the same spectrum of patients (563–566). Beta blockers are recommended in patients with angina pectoris, a history of MI, or LV dysfunction (567–571). Aldosterone antagonists improve prognosis in patients with LV dysfunction and heart failure (572,573). Calcium antagonists are useful in the treatment of angina. Many patients with SIHD will require a combination of drugs, including a diuretic, to achieve optimal BP control.

The role of emotional stress in relationship to hypertension has yet to be fully elucidated. It might be important to acknowledge the potential relationship of stress to many of the cardiovascular risk factors, particularly hypertension, when counseling patients.

4.4.1.3. DIABETES MANAGEMENT

CLASS IIa

1. **For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal hemoglobin A1c (HbA1c) of 7% or less is reasonable (574–576). *(Level of Evidence: B)***
2. **A goal HbA1c between 7% and 9% is reasonable for certain patients according to age, history of hypoglycemia, presence of microvascu-**

Table 15. Indications for Individual Drug Classes in the Treatment of Hypertension in Patients With SIHD*

	Recommended Drugs					
Indication	Diuretic	Beta Blocker	ACE Inhibitor	ARB	Calcium-Channel Blocker	Aldosterone Antagonist
Heart failure	•	•	•	•		•
LV dysfunction			•	•		
After myocardial infarction		•	•	•		•
Angina		•			•	
Diabetes mellitus		•	•	•		
Chronic kidney disease			•	•		

*Table indicates drugs that should be considered and does not indicate that all drugs should necessarily be prescribed in an individual patient (e.g., ACE inhibitors and ARB typically are not prescribed together).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and LV, left ventricular.

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lar or macrovascular complications, or presence of coexisting medical conditions (577,578). *(Level of Evidence: C)*

CLASS IIb

1. Initiation of pharmacotherapy interventions to achieve target HbA1c might be reasonable (456,579–588). *(Level of Evidence: A)*

CLASS III: Harm

1. Therapy with rosiglitazone should not be initiated in patients with SIHD (589,590). *(Level of Evidence: C)*

Diabetes mellitus is an important independent risk factor for cardiovascular disease. Type 1 diabetes mellitus is associated with at least a 10-fold increase in cardiovascular events (591,592), and patients with type 2 diabetes mellitus have a risk of death from cardiovascular causes that is 2 to 6 times that of persons without diabetes mellitus (593–595). The complications of atherosclerosis account for 80% of deaths among patients with diabetes mellitus, and IHD is responsible for the majority of deaths (574,596). Diabetes mellitus is associated with a poor outcome in patients with SIHD, even after the extent of disease and other clinical characteristics are taken into account. In the CASS registry, for example, patients with diabetes mellitus had a 57% greater risk of death after adjustment for other risk factors (597).

Clinical trials have demonstrated a salutary effect of intensive glycemic control on the development of microvascular complications of diabetes mellitus, such as retinopathy, nephropathy, and peripheral and autonomic neuropathy (574,575,598), with secondary analyses suggesting a benefit extending into the normal range of HbA1c. However, the efficacy of intensive diabetes therapy in reducing cardiovascular disease is less well established. In the DCCT (Diabetes Control and Complications Trial), patients with type 1 diabetes mellitus were randomized to intensive (mean achieved HbA1c 7.4%) or conventional (mean achieved HbA1c 9.1%) therapy. During the mean 6.5 years of observation, fewer cardiovascular events occurred in the intensive-treatment group, but the number of events was small, and the difference between groups did not reach statistical significance (574). In a long-term follow-up study of this population, however, intensive therapy reduced the risk of cardiovascular events by 42% (579). Intensive glycemic controlled to a reduction in microvascular complications (primarily the need for retinal laser photocoagulation) but not cardiovascular events in the patients with type 2 diabetes mellitus who participated in the UKPDS (UK Prospective Diabetes Study) (575). In a secondary analysis, treatment with metformin seemed to confer most of the benefit, whereas treatment with a sulfonylurea was not associated with a significant improvement in any endpoint (599). Patients in UKPDS treated with metformin had a lower median HbA1c (7.4% versus 8.0%) and a 37% reduction in ≥1 diabetes endpoints compared with those in the conventional therapy (diet alone) group (580). In the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study, patients with type 2 diabetes mellitus and evidence of vascular disease were randomized to pioglitazone or placebo. HbA1c averaged 7.8% at baseline and decreased by 0.3% in the placebo group and by 0.8% in those on active therapy. There was no significant difference between treatment groups in the primary study endpoint, although pioglitazone resulted in a statistically significant 16% relative reduction in a secondary endpoint of mortality, nonfatal MI, and stroke (581).

Three studies in patients with type 2 diabetes mellitus suggest that even more intensive glucose lowering fails to reduce the incidence of cardiovascular events and could cause harm (576,578,600). The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial tested a strategy of intensive glucose control with a target HbA1c of 6.5%, with the sulfonylurea gliclazide (modified release) and other drugs used as required (576). After a median 5 years of follow-up, HbA1c averaged 6.5% in the intensive-control group and 7.3% in the standard-control group. Intensive control reduced the incidence of microvascular events but had no effect on a composite of macrovascular events that included nonfatal MI, nonfatal stroke, or death from cardiovascular causes (576). In the ACCORD study, patients were assigned to receive intensive therapy with a goal of normalizing the HbA1c (to <6%) or standard therapy targeting a level of 7.0% to 7.9% (600). Median achieved HbA1c levels at 1 year were 6.4% and 7.5% in the 2 groups, respectively. Over 3.5 years, the use of intensive therapy did not significantly reduce major cardiovascular events (nonfatal MI, nonfatal stroke, and death from cardiovascular causes) but was associated with a 22% greater all-cause mortality (578,600). The VADT (Veterans Affairs Diabetes Trial) examined macrovascular complications in patients randomized to standard glycemic control or to intensive therapy (goal HbA1c of <6%), with a planned HbA1c separation of ≥1.5% (578). Median HbA1c levels were 8.4% and 6.9% in the standard- and intensive-therapy groups, respectively. There were no differences in the primary endpoint of time to occurrence of a cardiovascular event or all-cause mortality in the 2 groups over a median follow-up of 5.6 years.

In summary, the most appropriate goal level for HbA1c in patients with diabetes mellitus has not been established definitively by clinical trials. A goal HbA1c <7%—a level approximating that achieved in the intensive-therapy arms of the DCCT, UKPDS, and PROactive studies—is reasonable for many younger patients, depending on their duration of diabetes mellitus, comorbidities, adherence, and personal preferences. Secondary analyses of the DCCT and UKPDS and microvascular data from the ADVANCE trial suggest that even lower HbA1c levels could be beneficial in selected individuals. On the other hand, treatment to achieve a HbA1c <7% might not be safe or practical for some patients, and factors such as life expectancy, advanced microvascular or macrovascular complications, cognitive function, comorbidities, and risk of hypoglycemia should be

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considered in every patient before intensifying the therapeutic regimen.

Regardless of the degree of glycemic control, treatment of other modifiable risk factors that often accompany diabetes mellitus, such as hypertension and dyslipidemia, results in a substantial reduction in cardiovascular risk. The benefits of a target-driven, multifactorial intervention in patients with type 2 diabetes mellitus were demonstrated in the Steno-2 study (601). Behavioral modification and pharmacological therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria lowered the risk of cardiovascular disease by >50% (601).

When the patient and provider elect to use pharmacological therapy to improve glycemic control, several factors should be considered in selecting an agent, including acceptability and safety. Although head-to-head comparisons of different pharmacological regimens are largely lacking, limited evidence suggests that all agents are not equivalent. For example, long-term follow-up from the UKPDS indicates that patients receiving metformin, particularly those who were overweight, had a lower incidence of diabetic complications, MI, and death than those who received insulin plus a sulfonylurea (588). In addition, available information suggests that certain agents lack an acceptable safety profile. The FDA, for example, has imposed restrictions on use of rosiglitazone, a thiazolidinedione, because of data that suggest an increased risk of cardiovascular complications. Prescriptions for rosiglitazone should not be initiated for patients with SIHD. Patients who are already receiving this agent and whose blood glucose is well controlled should be counseled about the potential hazards, and switching to a different agent should be strongly considered. In this light, when deciding whether to prescribe newer hypoglycemic agents, providers should bear in mind the potential for safety concerns that could emerge when these drugs are adopted into wider use.

4.4.1.4. PHYSICAL ACTIVITY

CLASS I

1. **For all patients, the clinician should encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%) (602–604). *(Level of Evidence: B)***
2. **For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription (605–608). *(Level of Evidence: B)***
3. **Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at-risk patients at first diagnosis (602,609,610). *(Level of Evidence: A)***

CLASS IIa

1. **It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week (611,612). *(Level of Evidence: C)***

Physical activity counseling is an integral component of a comprehensive coronary risk factor modification strategy in patients with SIHD. Consistent with the American College of Sports Medicine and AHA recommendations for healthy adults (603), most patients with CAD should be encouraged to engage in 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, on most, and preferably all, days of the week. Similar recommendations (2 hours and 30 minutes of moderate-intensity aerobic activity and muscle-strengthening activities on ≥2 days a week) have been advanced by the Centers for Disease Control and Prevention (18,613). Many patients benefit from participation in a cardiac rehabilitation program that incorporates supervised exercise into a comprehensive secondary prevention program (614).

Multiple controlled clinical trials have examined the benefits of exercise training and cardiac rehabilitation in patients with IHD. Most of these studies have been relatively small, but in aggregate they demonstrate that regular exercise reduces mortality in patients with IHD. A systematic review and meta-analysis published in 2004 examined 48 RCTs of exercise interventions in a total of 8,940 patients with IHD (602). The median intervention duration was 3 months (range, 0.25 to 30 months), and the median duration of follow-up was 15 months (range, 6 to 72 months). Exercise training resulted in a 20% reduction in all-cause mortality and a 26% reduction in total cardiac mortality; favorable but nonsignificant trends were noted in nonfatal MI, CABG, and percutaneous coronary revascularization procedures. There was no difference between the mortality rate effects of exercise-only and more comprehensive cardiac rehabilitation interventions, and the benefits were independent of actual amount and intensity of exercise.

Many of the studies demonstrating the efficacy of exercise-based cardiac rehabilitation enrolled patients after an AMI or coronary revascularization procedure. Clear benefits of exercise training also have been shown in patients with stable angina. Controlled trials consistently have demonstrated an improvement in functional capacity and a delay in the onset of ischemia in anginal patients who complete an exercise training program (444,615–620). Exercise-based cardiac rehabilitation could also reduce subjective evidence of ischemia and could ameliorate symptoms (615,619,621,622).

The reduction in mortality rate associated with exercise interventions might be explained partially by modification of traditional cardiovascular risk factors. Controlled trials have demonstrated reductions in total cholesterol, triglycerides, and BP, although these findings have not been uniform. Exercise also can enhance smoking quit rates. Other potential mechanisms include decreased fibrinogen and coagulability (623), moderation of inflammation (624), improved endothelial function (625–627), and improved autonomic regulation (628,629).

Several studies have documented the safety of exercise-based cardiac rehabilitation in patients with documented SIHD (630–633). The 2007 AHA Scientific Statement on

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Exercise and Acute Cardiovascular Events estimates the risk of a major adverse cardiac event (MACE) at 1 in 80,000 patient-hours (447). This low event rate applies to medically supervised programs that evaluate patients before participation, provide serial surveillance, and are equipped to handle emergencies. Specific strategies for reducing exercise-related cardiovascular events have not been evaluated. It seems prudent, however, that patients at high risk of cardiac complications (i.e., those with a history of multiple MIs or cardiac arrest, New York Heart Association functional class III or IV or exercise capacity <6 METs, or significant exercise-induced ischemia on treadmill testing) participate in a medically supervised program for at least 8 to 12 weeks to establish the safety of the prescribed exercise regimen.

The value of resistance exercise increasingly is recognized for improving functional capacity, independence, and quality of life in patients with and without cardiovascular disease. Although the risks and benefits of resistance therapy have not been evaluated extensively in patients with SIHD, several small studies have indicated that resistance therapy is well tolerated and is associated with improvements in quality of life, strength, and endurance when added to a program of regular aerobic exercise (611,612).

Although previous guidelines have recommended that all patients undergo an exercise test before participating in a cardiac rehabilitation program, according to the World Health Organization (634), an exercise test is not considered necessary for medical and economic reasons if the patient enters a low- or moderate-intensity-level training program.

4.4.1.5. WEIGHT MANAGEMENT

CLASS I

1. **BMI and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance or reduction through an appropriate balance of lifestyle physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain or achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference less than 102 cm (40 inches) in men and less than 88 cm (35 inches) in women (less for certain racial groups) (257,449,635–642). *(Level of Evidence: B)***
2. **The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline. With success, further weight loss can be attempted if indicated. *(Level of Evidence: C)***

Population studies consistently have demonstrated an association of increased BMI with ischemic cardiac events. In a meta-analysis of 21 cohort studies including >300,000 persons, the risks for cardiovascular events in patients who were overweight (BMI 25.0 to 29.9 kg/m^2) and obese (BMI >30 kg/m^2) compared with those of normal weight were 32% and 81% higher, respectively, after adjustment for age, sex, physical activity, and smoking (635). Cardiovascular risk is increased particularly in patients with central obesity, which can be identified by a waist circumference >102 cm (40 inches) in men or >88 cm (35 inches) in women (643,644), and in those with extreme obesity, defined as a BMI >40 kg/m^2 (645).

Obesity likely contributes to increased cardiovascular risk through multiple pathophysiological pathways. Obesity is associated with traditional cardiovascular risk factors, such as diabetes mellitus, dyslipidemia, and hypertension, but in and of itself obesity increases sympathetic tone, induces a hypercoagulable state, and is associated with markers of inflammation (646). Curiously, despite the strong association of BMI with cardiovascular risk in population studies, a similar relationship between BMI and death is not observed consistently in cohorts with established IHD (647). This could be due to weaknesses of BMI as a measure of adiposity; confounding factors such as age, smoking, or medications; or weight loss in association with advanced chronic illness.

No clinical trials have examined specifically the effects of weight loss on cardiovascular event rates in patients with SIHD. In the SOS (Swedish Obese Subjects) study, however, weight losses of 20% to 32% at 1 year achieved with bariatric surgery were associated with a 24% reduction in mortality rate (648). The association of adiposity with other cardiovascular risk factors suggests that weight reduction is indicated in all overweight or obese patients. Reducing caloric intake is a cornerstone of weight management therapy. Referral to an experienced dietitian or to a reputable weight loss program for nutritional counseling and behavioral modification therapy can be helpful. The effects of caloric restriction are potentiated by regular aerobic physical activity. Therapy with medications or bariatric surgery may be considered in selected patients who are unable to achieve adequate weight loss by conventional lifestyle modifications (649).

4.4.1.6. SMOKING CESSATION COUNSELING

CLASS I

1. **Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD. Follow-up, referral to special programs, and pharmacotherapy are recommended, as is a stepwise strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, Avoid) (650–652). *(Level of Evidence: B)***

Observational studies over the past 4 decades have furnished incontrovertible evidence that smoking increases the risk of cardiovascular disease events (653,654). A dose–response relationship exists between cigarettes smoked and cardiovascular risk, with an RR approaching 5.5 for cardiovascular events among heavy smokers compared with nonsmokers (654). Potential mechanisms by which smoking predisposes to cardiovascular events include adverse effects on fibrinogen levels (655), platelet adhesion (656), and endothelial function (657); reduced HDL cholesterol levels (658); and coronary artery vasoconstriction (659).

Although RCTs have not been performed in patients with SIHD, results of observational studies strongly suggest that smoking cessation is an effective strategy for secondary

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prevention of coronary events. A meta-analysis of 20 prospective cohort studies found a 30% reduction in RR of mortality for those who quit compared with those who continued smoking, and a similar reduction was noted in nonfatal MIs (650). Some studies suggest that most of the reduction in risk occurs within 2 or 3 years of quitting (660,661).

The most effective smoking-cessation therapies include both nonpharmacological and medical interventions. Physician advice has a significant effect on quit rates (662). Self-help programs, telephone counseling, behavioral therapy, and perhaps exercise programs also have modest efficacy in increasing cessation rates (663–667). Nicotine-replacement therapy (gum, patch, tablet, lozenge, or nasal spray) approximately doubles the chances of success of a quit attempt (668). Similar efficacy has been demonstrated with bupropion sustained-release (669). Varenicline, a partial agonist of the $\alpha 4\beta 2$ nicotinic receptor, is the most recent FDA-approved agent for smoking cessation and compares favorably with placebo and with bupropion in clinical trials (670,671). There have, however, been concerns about possible worsening of preexisting depression and the risk of suicide due to varenicline, and the FDA has issued an alert warning that serious neuropsychiatric symptoms can occur in patients taking this drug (672,673).

Physicians should approach smoking cessation by using the 6 A's framework:

- *Ask* each patient about tobacco use at every visit;
- *Advise* each smoker to quit;
- *Assess* each smoker's willingness to make a quit attempt;
- *Assist* each smoker in making a quit attempt by offering medication and referral for counseling;
- *Arrange* for follow-up; and
- *Avoid* exposure to environmental tobacco smoke.

4.4.1.7. MANAGEMENT OF PSYCHOLOGICAL FACTORS

CLASS IIa

1. **It is reasonable to consider screening SIHD patients for depression and to refer or treat when indicated (237,239,323,457,463,674,675). *(Level of Evidence: B)***

CLASS IIb

1. **Treatment of depression has not been shown to improve cardiovascular disease outcomes but might be reasonable for its other clinical benefits (237,238,676). *(Level of Evidence: C)***

Depression is a major cause of disability in developed countries and often coexists with SIHD (677,678). About 20% of patients with angiographic evidence of CAD and a similar percentage of those recovering from AMI have comorbid depression (679–682).

Multiple observational studies have demonstrated an association between depression and cardiovascular events. In several studies involving ≥1,000 outpatients with SIHD, those with symptoms of depression had more physical limitation, more frequent angina, and lower perceived quality of life than patients without depressive symptoms (239,683). One meta-analysis examined 21 prospective studies in healthy populations and 34 studies in patients with existing IHD (684). The studies in healthy cohorts demonstrated an 81% greater incidence of ischemic events (MI or fatal IHD) among patients with symptoms of depression over an average follow-up period of 10.8 years. A similarly increased risk was observed in patients with established IHD who had symptoms of depression. Relatively few studies, however, have reported estimates of risk that have been adjusted for traditional risk factors or severity of CAD. Although in aggregate the observational cohort studies suggest that depression confers a significant risk for adverse cardiovascular outcomes, confounding by other risk factors or by disease severity is difficult to exclude. Moreover, most studies in patients with CAD have enrolled patients after recent MI or CABG, and the relevance to patients with SIHD is uncertain.

Putative mechanisms for a contribution of depression to atherogenesis and adverse cardiovascular events include both behavioral and biological effects. Depression is associated with poor compliance with risk factor–modification strategies and with poor adherence to prescribed medication regimens (460,462). Patients diagnosed with this disorder are 2- to 4-fold less likely to adhere to medications and lifestyle recommendations, engage in self-management practices, or comply with recommendations for testing and follow-up (462,675,685–691). Alternatively, some studies suggest the possibility of more direct pathophysiological links, including platelet activation (692–695), endothelial dysfunction (696), reduced heart rate variability (697–699), and inflammation (700).

Despite the association of depression with adverse cardiovascular outcomes, no clinical trials have established a reduction in cardiovascular risk with either counseling or antidepressant therapy. In the ENRICHD (Enhancing Recovery in Coronary Heart Disease) trial, 2,481 patients with depression or low social support after MI were randomized to usual care or cognitive behavioral therapy, supplemented by a selective serotonin reuptake inhibitor when indicated. Active therapy was associated with improvements in depression and low social support but with no improvement in event-free survival after a mean 24 months of follow-up (237). A secondary analysis, however, demonstrated a significantly lower risk of death or MI in patients treated with a selective serotonin reuptake inhibitor (676). The safety and efficacy of sertraline in patients with a recent ACS were demonstrated in SADHART (Sertraline Antidepressant Heart Attack Randomized Trial). Patients were randomized to sertraline or placebo for 24 weeks. Sertraline resulted in improved depressive symptoms and no change in LVEF, ventricular ectopy, or QT interval. The study was not powered to detect a difference in cardiovascular outcomes (238). Similarly, citalopram, a selective serotonin reuptake inhibitor, and mirtazapine, a dual-acting antidepressant, improved depression in postinfarction pa-

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Table 16. Patient Health Questionnaire-2

Over the past 2 weeks, how often have you been bothered by any of the following problems?
1) Little interest or pleasure in doing things
2) Feeling down, depressed, or hopeless

Reproduced from Kroenke et al. (702).

tients (463,674). Thus, treatment of depression in patients with SIHD by cognitive therapy or medication is safe and contributes to relief of depressive symptoms but does not have proven efficacy in reducing cardiovascular morbidity and mortality rates.

Either the 2-item Patient Health Questionnaire (PHQ)-2 or the 9-item PHQ-9 can be used as a screening tool for depression (701,702) (Tables 16 and 17). Patients who respond affirmatively to either item on the PHQ-2 or to item 9 on the PHQ-9 or who have a score ≥10 on the PHQ-9 should be referred for a more comprehensive clinical evaluation (701,702) (Table 17).

Patients with SIHD report high levels of psychosocial stress, and indices of stress are associated with an increased risk of cardiovascular events (245). Counseling to reduce psychological stress is recommended as a core component of comprehensive cardiac rehabilitation programs. Stress-management interventions use relaxation techniques and provide instruction in specific skills to reduce cognitive, behavioral, and psychological stress levels. Although stress-management programs are not of proven value in reducing the risk of cardiovascular events, they are effective in relieving anxiety and reducing depressive symptoms (461).

4.4.1.8. ALCOHOL CONSUMPTION

CLASS IIb

1. **In patients with SIHD who use alcohol, it might be reasonable for nonpregnant women to have 1 drink (4 ounces of wine, 12 ounces of beer, or 1 ounce of spirits) a day and for men to have 1 or 2 drinks a day, unless alcohol is contraindicated (such as in patients with a history of alcohol abuse or dependence or with liver disease) (703–705). *(Level of Evidence: C)***

Observational studies suggest that light to moderate alcohol consumption is associated with a lower risk of IHD and all-cause mortality. Most studies report a J-shaped relationship between alcohol consumed and cardiovascular event rate or mortality; light to moderate drinkers have less risk than abstainers, but heavy drinkers are at greatest risk. A meta-analysis of 34 prospective studies found mortality rate reductions of 17% in men and 18% in women with low levels of alcohol intake, with the lowest mortality rate at 6 g of alcohol (approximately one half drink) per day (703). Most of these studies were performed in healthy cohorts, and data in patients with IHD are limited. One study (704) examined survival rate among early survivors of MI and found that moderate alcohol consumption in the year before presentation was predictive of lower all-cause mortality. Similarly, among participants in the Physician's Health Study who experienced a self-reported MI, moderate drinkers had a 30% lower risk of death than abstainers (705).

Light to moderate alcohol consumption might confer protection against cardiovascular disease through beneficial effects on the lipid profile and on insulin sensitivity. Alcohol intake modestly increases HDL cholesterol in a dose-dependent fashion (706,707). Consumption of 2 drinks per day lowers fasting and postprandial insulin levels and increases insulin sensitivity in healthy subjects (708). Light to moderate alcohol consumption might also have antiinflammatory effects, as reflected by a reduction in C-reactive protein (709,710). Alternatively, the apparent cardioprotective effects of modest alcohol consumption reported in observational studies could represent uncontrolled confounding, as many coronary risk factors are more prevalent in nondrinkers than in light to moderate drinkers (711).

There are no RCTs in either healthy individuals or in patients with SIHD demonstrating improved clinical outcomes with alcohol consumption. Because of the many health and societal consequences of alcohol abuse, patients who do not already drink alcohol should not be encouraged to start. Patients who do consume alcoholic beverages should be counseled to do so in moderation: no more than 1 drink (4 ounces of wine or 1 ounce of spirits) per day for women and no more than 2 drinks per day for men.

4.4.1.9. AVOIDING EXPOSURE TO AIR POLLUTION

CLASS IIa

1. **It is reasonable for patients with SIHD to avoid exposure to increased air pollution to reduce the risk of cardiovascular events (712–715). *(Level of Evidence: C)***

Although they are seldom an explicit focus in provision of care to individual patients, environmental influences such as exposure to air pollution can increase the risk of cardiovascular events, possibly because of progression of atherosclerosis due to oxidative stress and inflammation (715). In particular, fine particulate matter, defined as particulate

Table 17. Patient Health Questionaire-9: Depression Screening Scales

Over the past 2 weeks, how often have you been bothered by any of the following problems?
1) Little interest or pleasure in doing things
2) Feeling down, depressed, or hopeless
3) Trouble falling asleep, staying asleep, or sleeping too much
4) Feeling tired or having little energy
5) Poor appetite or overeating
6) Feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down
7) Trouble concentrating on things such as reading the newspaper or watching television
8) Moving or speaking so slowly that other people could have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual
9) Thinking that you would be better off dead or that you want to hurt yourself in some way

Reproduced from Kroenke et al. (702).

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matter <2.5 microns in diameter (PM2.5), is associated with a heightened risk of death due to cardiovascular causes (714). In nonsmokers, the relative odds of AMI death rise 22% for each 10 mcg increase in PM2.5 (712). Short-term exposure to higher concentrations of pollution, for example after a forest fire, also is associated with the risk for ACS and death (713). Thus, patients with SIHD may be advised to avoid exposure to increased air pollution (i.e., by remaining indoors during transient elevations of air pollution). Public policy efforts to minimize small particulate matter (i.e., through tighter regulations on the emissions from coal-fired power plants) have the potential to reduce cardiac complications among patients with SIHD.

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

4.4.2.1. ANTIPLATELET THERAPY

CLASS I

1. **Treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with SIHD (716,717). (*Level of Evidence: A*)**
2. **Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD (718). (*Level of Evidence: B*)**

CLASS IIb

1. **Treatment with aspirin 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD (719). (*Level of Evidence: B*)**

CLASS III: No Benefit

1. **Dipyridamole is not recommended as antiplatelet therapy for patients with SIHD (720–722). (*Level of Evidence: B*)**

4.4.2.1.1. ANTIPLATELET AGENTS. Because platelet aggregation is a key element of the thrombotic response to plaque disruption, platelet inhibition is recommended in patients with SIHD unless contraindicated. Aspirin is a cyclooxygenase inhibitor that produces irreversible blockade of prostaglandin endoperoxide formation. Among 2,920 patients with SIHD, a comprehensive meta-analysis of source data revealed an association of aspirin use with a 37% reduction in the risk of serious vascular events, including a 46% decrease in the risk for UA and a 53% decrease in the risk of requiring coronary angioplasty (716). Almost two thirds of the patients included in this meta-analysis were participants in SAPAT (Swedish Angina Pectoris Aspirin Trial), in which patients with SIHD were assigned randomly to aspirin 75 mg per day or placebo for a median of 15 months (717). Aspirin in a dose of 75 to 162 mg daily is equally as effective as 325 mg in secondary prevention and is associated with a lower risk of bleeding. Doses <75 mg have less proven benefit (716,723). Aspirin is relatively contraindicated in patients with known allergies to nonsteroidal antiinflammatory drugs and in patients with the syndrome of asthma, rhinitis, and nasal polyps.

Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation via selective and irreversible inhibition of the adenosine diphosphate P2Y12 receptor. Clopidogrel 75 mg has been compared with aspirin 325 mg in patients with previous MI, stroke, or symptomatic PAD in the prospective, randomized CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study (718). Although clopidogrel demonstrated superiority over aspirin in the secondary prevention of MI and death in this group of patients, the magnitude of difference was small. Because no additional trials comparing aspirin and clopidogrel in patients with SIHD have been conducted, clopidogrel remains an acceptable alternative agent to aspirin.

In certain high-risk patients, combined treatment with aspirin and clopidogrel has been shown to be beneficial. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study, patients with a recent NSTEMI were randomized to clopidogrel plus aspirin (300 mg/d and 75 mg/d) for an average of 9 months. These patients experienced fewer deaths from cardiovascular causes, nonfatal MIs, and strokes than did patients receiving placebo plus aspirin (75 to 325 mg/d) (724). Similar results were found in the CREDO (Clopidogrel for Reduction of Events During Observation) study. Combined therapy for an average of 1 year significantly reduced the risk of death, MI, or stroke (725). In contradistinction to these positive results among high-risk patients, a comparison of aspirin alone versus aspirin combined with clopidogrel in 15,603 patients with multiple cardiovascular risk factors (most of whom were without a prior cardiovascular event) in the CHARISMA (Clopidogrel for High Atherothrombotic Risk Ischemic Stabilization, Management, and Avoidance) trial demonstrated no differences in the rates of MI, stroke, or death (393). A post hoc analysis of this study suggested that a subgroup of patients with documented prior MI, ischemic stroke, or symptomatic PAD might have had better outcomes from dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin (719). In a meta-analysis of 5 RCTs comparing clopidogrel plus aspirin to aspirin alone in patients with IHD, the incidence of all-cause mortality, MI, and stroke was found to be reduced in the clopidogrel-plus-aspirin group, whereas the risk of major bleeding increased significantly (726). Overall, it appears that the addition of clopidogrel to aspirin could be beneficial in certain high-risk groups of patients with SIHD, but data on specific subgroups are lacking (727), and further research will be required to identify the ideal target population.

The effectiveness of clopidogrel depends on generation of the active metabolite in 2 steps that are catalyzed by enzymes of the cytochrome P450 system, principally *CYP2C19*. Variants of the *CYP2C19* gene have been identified that are associated with impaired antiplatelet effects, as measured by ex vivo platelet aggregation assays, and with higher cardiovascular event rates after ACS and percutaneous revascularization procedures (728–731). Poor metabolizers of clopidogrel can be identified by clinically available tests, but optimal dosing strategies for these individuals have not been established in clinical outcome trials (732,733). Other drugs that are metabolized by *CYP2C19* could

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competitively inhibit the enzyme and impair metabolism of clopidogrel. Several studies have demonstrated a pharmacodynamic interaction between proton pump inhibitors and clopidogrel (734,735). Observational studies have suggested that use of a proton pump inhibitor in combination with clopidogrel is associated with an approximately 25% increased RR of adverse cardiovascular events (736,737), although post hoc analyses of several clinical trials and a recent observational study have failed to demonstrate a clinically significant interaction (738,739). Pantoprazole is less likely than other proton pump inhibitors to inhibit *CYP2C19* and does not impair the pharmacodynamic response to clopidogrel (740–742); alternatively, treatment with an H2 antagonist or antacid could be sufficient in some patients. The combination of clopidogrel with a statin can be prescribed safely on the basis of a secondary analysis of the CHARISMA trial in 10,078 patients with cardiovascular disease or multiple high-risk coronary risk factors (743). There was no difference in the composite endpoint of MI, stroke, or cardiovascular death between the agents, independent of the metabolism pathway of the statin. Clopidogrel requires a loading dose to accelerate the onset, intensity, and consistency of inhibition (744,745).

Prasugrel is a third-generation thienopyridine that has more potent antiplatelet effects and is associated with less interpatient variability in response than clopidogrel. In TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) 38, there was a 19% reduction in RR of the primary efficacy endpoint (cardiovascular death, nonfatal MI, or nonfatal stroke) but an increased risk of bleeding with prasugrel compared with clopidogrel in ACS patients scheduled for percutaneous revascularization (746). Clinical trials evaluating prasugrel in patients with SIHD have not been conducted. It has not been tested or approved for use in patients with SIHD. Ticagrelor is a newly approved agent that has been shown to be beneficial in patients with ACS but has not been tested in patients with SIHD (747).

Ticlopidine is a thienopyridine derivative that also inhibits platelet aggregation but compares less favorably to clopidogrel as an alternative to aspirin, because it has limited evidence for cardiovascular event reduction among patients with SIHD and an associated risk of blood dyscrasias (720,721). For these reasons, its use is quite limited for secondary prevention among patients with SIHD.

The pyrimido-pyrimidine derivative, dipyridamole, possesses antiplatelet effects but does not have a proven role in patients with SIHD. The combination of aspirin and dipyridamole was not clearly superior to aspirin alone in preventing reinfarction in the PARIS (Persantine-Aspirin Reinfarction Study) (722). Because dipyridamole vasodilates coronary resistance vessels and can provoke exercise-induced myocardial ischemia, it is not recommended for secondary prevention in patients with SIHD (748,749).

4.4.2.1.2. ORAL ANTICOAGULANT THERAPY. Fibrinolytic function can be disturbed in patients with IHD, particularly related to activation of the extrinsic coagulation pathway leading to formation of thrombin. Thrombin, in turn, generates fibrin and promotes platelet activation and aggregation, thereby amplifying the activity of both the coagulation and platelet pathways (750–752). These observations have provided a potential rationale for antithrombotic therapy in patients with SIHD. A systematic review of randomized trials of oral anticoagulants with and without antiplatelet therapy among 20,000 patients with IHD, however, failed to provide evidence of benefit from anticoagulation, and it is not recommended (753). Similarly, there is no evidence that individuals with defects in the coagulation system, such as G1691A factor V Leiden, G20201A prothrombin, G455A fibrinogen chain, G10976A factor VII, or the plasminogen activator inhibitor-1 4G/5G polymorphisms, are at higher risk of cardiac events, and they should not receive anticoagulation therapy solely to prevent such events (754–756).

4.4.2.2. BETA-BLOCKER THERAPY

CLASS I

1. **Beta-blocker therapy should be started and continued for 3 years in all patients with normal LV function after MI or ACS (757–759). *(Level of Evidence: B)***
2. **Beta-blocker therapy should be used in all patients with LV systolic dysfunction (EF ≤40%) with heart failure or prior MI, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce risk of death.) (571,760–763) *(Level of Evidence: A)***

CLASS IIb

1. **Beta blockers may be considered as chronic therapy for all other patients with coronary or other vascular disease. *(Level of Evidence: C)***

Beta-receptor activation is associated with increases in heart rate, accelerated AV nodal conduction, and increased contractility, which contribute to increased myocardial oxygen demand. Decreases in the rate–BP product, AV nodal conduction, and myocardial contractility from beta blockers reduce myocardial oxygen demand, counteracting beta-receptor activity and contributing to a reduction in angina onset, with improvement in the ischemic threshold during exercise and in symptoms (764–769). These agents significantly reduce deaths and recurrent MIs in patients who have suffered a MI and are especially effective when a STEMI is complicated by persistent or recurrent ischemia or tachyarrhythmias early after the onset of infarction (757). However, no large trials have assessed effects of beta blockers on survival or coronary event rates in patients with SIHD.

Many clinically important differences exist between beta blockers. These differences relate to cardioselectivity, presence of intrinsic sympathomimetic activity or vasodilating properties, and relative lipid solubility in the presence of renal or hepatic impairment. Despite these differences, all

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beta blockers seem to be equally efficacious in SIHD (765–767,770,771).

Two large long-term follow-up studies investigating the prognostic importance of heart rate showed that all-cause mortality rate progressively increases with higher resting heart rate after adjustment for exercise capacity, age, diabetes mellitus, systolic arterial pressure, BMI, and level of physical activity (772,773). Therefore, it is recommended that beta-blocker dosing be adjusted to limit the heart rate to 55 to 60 beats per minute at rest.

In large prospective studies, bisoprolol, carvedilol, and metoprolol, when administered on a background of ACE inhibitors and diuretics with or without digoxin, have been shown to reduce the risk of death and to improve symptoms, clinical status, and quality of life in patients with chronic systolic heart failure. Importantly, these benefits were seen in patients with and without IHD (571,760,761).

Studies on multiple polymorphisms in the gene encoding for the beta-adrenergic receptor have variously shown associations with physiological responses to exercise (774–781). Clinical studies with a variety of beta blockers in different patient populations with hypertension have, however, yielded divergent results in terms of associations with BP and heart rate (782–785), but it remains to be studied whether this variation is mainly a function of beta-adrenergic receptor genotype and whether genotype influences the clinical outcome of beta-blocker use in patients with SIHD.

Beta blockers have been compared with and combined with dihydropyridine calcium channel blockers in controlled clinical trials. The results of the APSIS (Angina Prognosis Study in Stockholm), TIBBS (Total Ischemic Burden Bisoprolol Study), and IMAGE (International Multicenter Angina Exercise) studies showed that a beta blocker was more effective than a calcium channel blocker in control of angina, reduction of cardiovascular events, and need for revascularization (786–788). A rationale for combining these agents is a reduction of dihydropyridine-induced tachycardia by beta-blockade. When combined, beta blockers and dihydropyridine calcium channel blockers have increased exercise time and shown a trend toward a lower rate of cardiovascular outcomes (788,789). Caution is warranted when a beta blocker is combined with verapamil or diltiazem because of the potential for development of bradycardia, AV block, or excessive fatigue.

The combination of a beta blocker with a nitrate could be an additive combination in patients with SIHD. Nitrates increase sympathetic tone, which can lead to reflex tachycardia, which is attenuated by the beta blocker. Beta blockers can increase LV wall tension associated with decreased heart rate, which is counteracted by the concomitant use of nitroglycerin. Clinical trials have validated this rationale, showing that the combination is more effective in controlling angina than is either monotherapy alone (790,791).

Absolute contraindications to beta blockers are severe bradycardia, preexisting high-degree AV block, sick sinus syndrome (without a pacemaker in place), and refractory heart failure. Relative contraindications include bronchospastic disease or active PAD (beta blockers without vasodilating properties or selective agents at low doses may be used). Because they can mask symptoms of hypoglycemia, beta blockers should be used with caution in patients with insulin-dependent diabetes mellitus. Abrupt beta-blocker withdrawal should be avoided because heightened beta-receptor density and sensitivity can result in a rebound phenomenon associated with an increased risk for AMI and sudden death. If withdrawal is necessary, beta blockers should be tapered over a 1- to 3-week period, with consideration given to use of sublingual nitroglycerin or substitution with a nondihydropyridine calcium channel blocker during the withdrawal period.

The principle adverse effects of beta blockers are fatigue, exercise intolerance, lethargy, insomnia, nightmares, and impotence.

4.4.2.3. RENIN-ANGIOTENSIN-ALDOSTERONE BLOCKER THERAPY

CLASS I

1. **ACE inhibitors should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LVEF 40% or less, or CKD, unless contraindicated (295–298,301). (*Level of Evidence: A*)**
2. **ARBs are recommended for patients with SIHD who have hypertension, diabetes mellitus, LV systolic dysfunction, or CKD and have indications for, but are intolerant of, ACE inhibitors (792–794). (*Level of Evidence: A*)**

CLASS IIa

1. **Treatment with an ACE inhibitor is reasonable in patients with both SIHD and other vascular disease (795,796). (*Level of Evidence: B*)**
2. **It is reasonable to use ARBs in other patients who are ACE inhibitor intolerant (797). (*Level of Evidence: C*) (Table 15)**

A substantial body of evidence supports the concept that ACE inhibitors have cardiovascular protective effects, reducing the risks of future ischemic events. ACE inhibitors result in a reduction in angiotensin II with an increase in bradykinin. These changes in the physiological balance between angiotensin II and bradykinin could contribute to the reductions in LV and vascular hypertrophy, atherosclerosis progression, plaque rupture, and thrombosis; the favorable changes in cardiac hemodynamics; and the improved myocardial oxygen supply/demand that result from treatment with ACE inhibitors and ARBs (798–801). Clinical studies have demonstrated significant reductions in the incidence of AMI, UA, and the need for coronary revascularization in patients after MI with LV dysfunction, independent of etiology (559,561,801).

The benefits of ACE inhibitors extend to patients with IHD in the absence of LV dysfunction. In patients with atherosclerotic vascular disease or diabetes mellitus and at least 1 other IHD risk factor, the HOPE (Heart Outcomes Prevention Evaluation) study (301) showed that compared with placebo, ramipril significantly decreased the primary composite endpoint of cardiovascular death, AMI, and stroke by 22% (301). MICRO-HOPE (Microalbuminuria,

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Cardiovascular, and Renal Outcomes), a substudy of HOPE, additionally showed, in middle-aged patients with diabetes mellitus who were at high risk for cardiovascular events, significant reductions in MI by 22%, stroke by 33%, cardiovascular death by 37%, and the combined primary event outcome by 25% (802). Furthermore, the need for revascularization and incidence of worsening angina also were significantly reduced. The EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) trial provided added support to the HOPE trial results in patients with SIHD without clinical evidence of heart failure (296). In 12,218 patients followed up for a mean of 4.2 years, there was a 20% relative increase in the time to the primary composite endpoint of cardiovascular death, nonfatal MI, or cardiac arrest with perindopril compared with placebo (296). Perindopril was further tested in the PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibitor) trial, which enrolled 4,158 patients with SIHD and normal or slightly reduced LV function (i.e., absence of LV wall-motion abnormalities) (295). The incidence of the primary endpoint of death from cardiovascular causes, MI, or coronary revascularization was equivalent between perindopril and placebo, but the overall rate of cardiovascular events was lower than in the HOPE and EUROPA trials. Equivalent results were seen in HOPE and EUROPA when examined by age, sex, known IHD, LV function, previous MI, hypertension, or diabetes mellitus. In QUIET (Quinapril Ischemic Event Trial), there was also no significant reduction with quinapril in ischemic events and progression of CAD in coronary angioplasty patients without systolic LV dysfunction (RR: 13%; p=0.49), although this finding has been attributed to study design limitations (797). Similarly, the IMAGINE (Ischemia Management With Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme) study demonstrated no reduction in clinical outcomes in low-risk patients (LVEF >40%) with quinapril after surgical revascularization (803). In a meta-analysis of ACE-inhibitor therapy versus placebo in 31,555 patients from HOPE, EUROPA, PEACE, and QUIET, ACE-inhibitor therapy produced 14% reductions in all-cause mortality and MI (both p=0.0004), a 23% reduction in stroke (p=0.0004), and a 7% reduction in revascularization procedures (p=0.025) compared with placebo (796).

Although the cited studies involved a variety of ACE inhibitors that differ with regard to structure, bioavailability, potency, receptor-binding characteristics, tissue distribution, metabolism, and excretion properties, there is little evidence that these differences are associated with therapeutic advantages. Because the benefits of ACE inhibitors seem to reflect a class effect, the selection of a particular agent can be based on such factors as availability in local formularies, cost, and tolerability.

ACE inhibitors are recommended for all patients with SIHD and hypertension, diabetes mellitus, LV dysfunction (EF ≤40%), or CKD. Also included in the HOPE (301) or EUROPA (296) trials were participants who did not have one of these conditions but did have multiple cardiac risk factors, and it seems that they also benefited from use of ACE inhibitors (797).

ARBs also play an important role in vascular protection. They bind in a competitive or insurmountable manner to the type 1 angiotensin II receptor, increasing plasma renin activity, plasma renin, and angiotensin I and II concentrations. In patients with hypertension or cardiovascular disease, ARBs produce reductions in BP equivalent to those achieved with ACE inhibitors (804). These agents significantly reduce LV mass and stroke incidences compared with beta blockers and improve outcomes in diabetic nephropathy and heart failure (563,565,792,805). A meta-regression analysis of 26 trials compared the effects of ACE inhibitors and ARBs on major vascular events by BP effects (804). Treatment with ACE inhibitor–based regimens was associated with a reduction in the risk for stroke (by 19%), IHD (by 16%), and heart failure (by 27%) for each 5–mm Hg reduction in BP; corresponding figures for the reduction in risk for ARBs were 26%, 17%, and 12%, respectively. There were no significant differences between ARB- and ACE inhibitor–based regimens in the risk of stroke, IHD, and heart failure for each 5–mm Hg reduction in BP. When these outcomes were assessed at zero BP reduction, the risk reduction for IHD was significantly greater for ACE inhibitors than for ARBs (p=0.002). Furthermore, unlike ARBs, ACE inhibitors were associated with a significant additional risk reduction for IHD of 9% (p=0.004), without differences seen for stroke or heart failure versus ARBs. It is therefore recommended that ARBs be substituted for ACE inhibitors in patients with SIHD and hypertension who are intolerant of ACE inhibitors (563,565,792,804,805).

4.4.2.4. INFLUENZA VACCINATION

CLASS I

1. An annual influenza vaccine is recommended for patients with SIHD (806–810). *(Level of Evidence: B)*

In patients with chronic medical conditions such as cardiovascular disease, influenza contributes to a higher risk for mortality and hospitalization and exacerbates underlying medical conditions. The World Health Organization and the AHA/ACCF recommend annual vaccination with inactivated vaccine (administered intramuscularly) against seasonal influenza to prevent all-cause mortality and morbidity in patients with underlying cardiovascular conditions (806,807). A cohort study in 1,340 elderly (i.e., ≥65 years of age) patients with heart failure or IHD showed that annual influenza vaccinations reduced the risk of mortality by 37% during the winter period (January through April), but not the summer period (June through September), resulting in a number needed to treat to prevent 1 death during 1 influenza period of 122 annual vaccinations (808). Further mechanistic and confirmatory studies in heart failure and other cardiovascular disease are needed to confirm these findings. Evidence from 2 prospective randomized clinical

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studies in patients ≥65 years of age who were medically stable supports increasing influenza vaccine doses to achieve higher serum antibody titers and potentially improved protection from influenza infection (809,810). This dosing scheme was associated with higher injection site reactions, including pain and myalgias. Currently, it is recommended that patients with SIHD receive an annual influenza vaccination in the standard dose.

4.4.2.5. ADDITIONAL THERAPY TO REDUCE RISK OF MI AND DEATH

CLASS III: No Benefit

1. **Estrogen therapy is not recommended in postmenopausal women with SIHD with the intent of reducing cardiovascular risk or improving clinical outcomes (811–814). *(Level of Evidence: A)***
2. **Vitamin C, vitamin E, and beta-carotene supplementation are not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD (398,527,815–818,818). *(Level of Evidence: A)***
3. **Treatment of elevated homocysteine with folate or vitamins B6 and B12 is not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD (819–822). *(Level of Evidence: A)***
4. **Chelation therapy is not recommended with the intent of improving symptoms or reducing cardiovascular risk in patients with SIHD (823–826). *(Level of Evidence: C)***
5. **Treatment with garlic, coenzyme Q10, selenium, or chromium is not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD. *(Level of Evidence: C)***

4.4.2.5.1. HORMONE REPLACEMENT THERAPY. Numerous observational studies have suggested that estrogen therapy might provide protection against the development of IHD in postmenopausal women (827–829). Beneficial effects of exogenous estrogen include an increase in HDL cholesterol, a decrease in LDL cholesterol, and enhanced endothelial function (830–833). In light of the epidemiological data and evidence of salutary physiological effects, postmenopausal estrogen replacement previously was advocated for the primary and secondary prevention of CAD in women. Clinical trials in women with and without established CAD, however, have failed to confirm a decrease in cardiovascular events with hormone therapy. In HERS (Heart and Estrogen/progesterone Replacement Study), 2,763 postmenopausal women with CAD were randomized to therapy with 0.625 mg of conjugated estrogen plus 2.5 mg of medroxy progesterone acetate or placebo and were followed up for an average of 4.4 years. Despite an 11% lower level of LDL cholesterol and a 10% higher level of HDL cholesterol in the hormone therapy group, there was no difference in the composite primary endpoint of MI or IHD death, and an early increase in cardiovascular events was observed (811). In HERS-II, an unblinded follow-up study of HERS, the lack of benefit with estrogen/progestin therapy persisted at an average of 6.8 years (834). A subsequent angiographic study demonstrated a nonsignificant worsening of coronary stenoses in patients prescribed estrogen therapy (835). The Women's Health Initiative, a randomized controlled primary prevention trial, also found no evidence that estrogen protects against IHD (812–814). Thus, the weight of current scientific evidence suggests that estrogen/progestin therapy in postmenopausal women does not reduce the risk of vascular events or coronary deaths in secondary prevention. Women who are taking estrogen therapy and who have vascular disease can continue this therapy if it is prescribed for other well-established indications and if no better alternative therapies are appropriate, although the FDA recommends use in the lowest dose and shortest duration acceptable. There is, however, no basis for adding or continuing estrogens in postmenopausal women with clinically evident SIHD in an effort to prevent or retard progression of their atherosclerotic disease.

4.4.2.5.2. VITAMIN C, VITAMIN E, AND BETA-CAROTENE. Epidemiological and population studies have suggested that antioxidant vitamins, such as vitamin E, vitamin C, and beta-carotene, could lower cardiovascular risk (836,837). Controlled clinical trials, however, have failed to demonstrate a beneficial effect of antioxidant supplements on risk of cardiovascular morbidity and mortality (398,527,815–817). A meta-analysis of antioxidant vitamin studies examined 7 trials of vitamin E treatment and 8 trials of beta-carotene treatment with >1,000 subjects in each. Most of these studies were performed in patients with CAD or at risk of CAD. Vitamin E had no effect on all-cause mortality or cardiovascular death (838). Beta-carotene led to a small but statistically significant increase in all-cause mortality and cardiovascular death. Thus, existing scientific evidence does not justify routine use of antioxidant supplements for the prevention or treatment of cardiovascular disease.

4.4.2.5.3. FOLATE AND VITAMINS B6 AND B12. Prospective observational studies have demonstrated that the serum homocysteine level is a strong, independent risk factor for ischemic events (839–841). Homocysteine levels can be lowered with folic acid or B-vitamins. Trials of folate and vitamin B supplementation, however, consistently have failed to demonstrate a decrease in cardiovascular morbidity or mortality rates. The VISP (Vitamin Intervention for Stroke Prevention) trial randomized patients with prior nondisabling stroke to varying doses of folic acid, B6, and B12. Despite a reduction in homocysteine that was 2 mmol/L greater in the group allocated to the high dose of supplementation, there were no differences in the incidence of recurrent stroke, IHD, or death (822). Similarly, the HOPE 2 (Heart Outcome in Prevention) trial found no benefit of folate and vitamins B6 and B12 in patients with vascular disease or diabetes mellitus (821). The NORVIT (Norwegian Vitamin Trial) examined 3 combinations of folate and B vitamins in patients who had an AMI and observed no decrease in the risk of cardiovascular events (820). A meta-analysis of these and 9 other smaller trials also found no reduction in cardiovascular events or mortality with folate supplementation (819). These studies indicate that routine use of folate and B vitamins for the prevention

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or treatment of cardiovascular disease should not be recommended.

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 promoted as a noninvasive means of improving blood flow in atherosclerotic vessels. EDTA combines with polyvalent cations, such as calcium ions, to form soluble complexes that can be excreted. Advocates maintain that this process can result in 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. In general, however, the efficacy of chelation therapy in atherosclerotic disease is not supported by clinical trials. Studies in patients with intermittent claudication have failed to demonstrate improvements in exercise measures (823,824), ankle-brachial index (823,824), or digital subtraction angiograms with chelation (825). The only RCT examining the effectiveness of chelation therapy on SIHD (826) studied 84 patients with stable angina and a positive treadmill test for ischemia. 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 have sponsored TACT (Trial to Assess Chelation Therapy) (842), an RCT comparing chelation to placebo in patients who had experienced an MI. There is insufficient evidence to support chelation therapy for improving symptoms or preventing adverse outcomes in patients with SIHD. Moreover, this therapy is costly and time consuming, can result in harm, and could result in patients failing to pursue proven treatment strategies.

4.4.2.5.5. GARLIC, COENZYME Q10, SELENIUM, AND CHROMIUM. Nutritional supplements for the prevention and treatment of cardiovascular disease have grown increasingly popular in the United States. These alternative therapies often are promoted with anecdotal claims of efficacy but have not been studied rigorously. When data are available, they often conflict and consist of results of small, open-label trials. At present, there is no definitive evidence to recommend treatment with garlic, coenzyme Q10, selenium, or chromium for improving cardiovascular outcomes in patients with SIHD.

4.4.3. Medical Therapy for Relief of Symptoms

4.4.3.1. USE OF ANTI-ISCHEMIC MEDICATIONS: RECOMMENDATIONS

CLASS I

1. **Beta blockers should be prescribed as initial therapy for relief of symptoms in patients with SIHD (757,765,766). *(Level of Evidence: B)***
2. **Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when beta blockers are contraindicated or cause unacceptable side effects in patients with SIHD (420,768,769). *(Level of Evidence: B)***
3. **Calcium channel blockers or long-acting nitrates, in combination with beta blockers, should be prescribed for relief of symptoms when initial treatment with beta blockers is unsuccessful in patients with SIHD (420). *(Level of Evidence: B)***
4. **Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD (843–845). *(Level of Evidence: B)***

CLASS IIa

1. **Treatment with a long-acting nondihydropyridine calcium channel blocker (verapamil or diltiazem) instead of a beta blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD (420). *(Level of Evidence: B)***
2. **Ranolazine can be useful when prescribed as a substitute for beta blockers for relief of symptoms in patients with SIHD if initial treatment with beta blockers leads to unacceptable side effects or is ineffective or if initial treatment with beta blockers is contraindicated (846). *(Level of Evidence: B)***
3. **Ranolazine in combination with beta blockers can be useful when prescribed for relief of symptoms when initial treatment with beta blockers is not successful in patients with SIHD (847,848). *(Level of Evidence: A)***

4.4.3.1.1. BETA BLOCKERS. Beta blockers are recommended as the initial agents to relieve symptoms in most patients with SIHD. Beta blockers reduce myocardial oxygen consumption by reducing heart rate, myocardial contractility, and afterload, with attenuation of cardiovascular remodeling by decreasing LV wall tension with long-term use. The reduction in myocardial oxygen demand is directly proportional to the level of adrenergic tonic stimulation. Furthermore, the reduction in heart rate also shifts the cardiac cycle, permitting more diastolic time and greater coronary perfusion, thereby improving myocardial oxygen supply.

Long-term beta-blocker treatment is well tolerated, has proven benefit in SIHD by reducing ischemic burden and threshold, and improves survival in patients with LV dysfunction or history of MI (757,765,766). When prescribed in combination with agents that block the renin-angiotensin-aldosterone system, beta blockers are the preferred agents for the treatment of angina in patients with LV dysfunction after MI and in patients with heart failure, on the basis of documented improvements in survival and ventricular performance (402,571,760,792,801).

A meta-analysis of comparison trials between beta blockers and calcium channel blockers (dihydropyridine and nondihydropyridine agents) showed negligible differences in the rate of death or MI over relatively brief durations of administration (i.e., 6 wk to 6 mo), although patients with heart failure, heart block, or significant pulmonary disease were excluded from the meta-analysis (420). Beta blockers were found to exhibit an advantage with regard to control of angina and withdrawals from therapy due to adverse events, a problem that was most pronounced with nifedipine (420).

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Calcium channel blockers, however, have not been shown to improve survival after MI, as beta blockers have, but have been shown to offer protection against severe angina and to reduce the risk of reinfarction after MI (849–851).

Adherence to beta-blocker therapy can be influenced by the occurrence of adverse effects such as fatigue, lethargy, sexual dysfunction, or sleep disturbances. Although beta blockers have the potential to worsen symptoms in patients with significant depressive illness or PAD, these effects are observed rarely in clinical practice. For patients with severe PAD or those with vasospastic (Prinzmetal's) angina, worsening symptoms due to vasoconstriction from unopposed alpha-adrenergic activity can be avoided by using beta blockers with alpha-adrenergic blocking (e.g., labetalol or carvedilol) or direct vasodilator (e.g., nebivolol) properties.

4.4.3.1.2. CALCIUM CHANNEL BLOCKERS. If adverse effects or contraindications limit the use of beta blockers, calcium channel blockers are recommended for relief of anginal symptoms. These agents noncompetitively limit calcium ion influx through voltage-dependent L-type calcium channels, resulting in negative inotropic effects, cardiac pacemaker depression, slowing conduction, and smooth muscle relaxation. There are 3 classes of calcium channel blockers: the dihydropyridines (e.g., nifedipine) and 2 types of nondihydropyridines, the phenylalkylamines (e.g., verapamil) and the benzothiazepines (e.g., diltiazem). All classes improve myocardial oxygen supply by decreasing coronary vascular resistance and augmenting epicardial conduit vessel and systemic arterial blood flow. Myocardial demand is decreased by a reduction in myocardial contractility, systemic vascular resistance, and arterial pressure. However, the phenylalkylamines and, to a lesser extent, the benzothiazepines also depress cardiac pacemaker rate and slow conduction. This depressant effect can cause sinus bradycardia or can worsen preexisting conduction defects, leading to heart block. Myocardial contractile depression also is a common feature, although the degree is variable according to drug class. As a result of these pharmacological properties, the calcium channel blockers are effective anti-ischemic drugs, but their use must be individualized (852,853).

All classes of calcium channel blockers reduce anginal episodes, increase exercise duration, and reduce use of sublingual nitroglycerin in patients with effort-induced angina (854–856). Because all 3 classes also reduce the frequency of Prinzmetal's variant angina, they are the drugs of choice, along with nitrates, used alone or in combination (857–859).

Because the 3 classes seem to be equally efficacious in treating angina, the choice of a particular agent should be based on potential drug interactions and adverse events. The dihydropyridine class is preferred over other calcium channel blockers in patients with cardiac conduction defects such as sick sinus syndrome, sinus bradycardia, or significant AV conduction disturbances. Dihydropyridines should be used with caution in patients with severe aortic valve stenosis. Short-acting dihydropyridines in patients with fixed lesions can exacerbate angina, possibly by excessive lowering of arterial pressure with reflex tachycardia, and therefore should be avoided. Short-acting nifedipine seems to increase mortality in patients with hypertension (860), but there is currently no evidence that these concerns apply to extended-release preparations (861,862). Because of their effects on contractility, none of the calcium channel blockers are recommended for routine treatment of patients with current or prior symptoms of heart failure and a reduced LVEF (21).

Many drug interactions associated with calcium channel blockers occur because of rapid absorption or low bioavailability due to high first-pass metabolism by the cytochrome P450 (i.e., *CYP3A4*) system. These pharmacokinetic properties result in high intraindividual and interindividual variability, necessitating dosage adjustment. These drugs should be used with caution when combined with cyclosporine, carbamazepine, lithium carbonate, amiodarone, or digoxin (i.e., 50% to 70% increase in digoxin concentrations in first week of therapy). Combining verapamil or diltiazem with beta blockers generally should be avoided because of potentially profound adverse effects on AV nodal conduction, heart rate, or cardiac contractility.

Overall, calcium channel blockers, particularly diltiazem, are well tolerated. The major adverse effects of dihydropyridines are related to vasodilation and systemic hypotension, including headache, dizziness, palpitations, and flushing. Many patients experience peripheral edema because of excessive arterial vasodilation unmatched to venous dilation. Verapamil can cause constipation that can be severe, particularly in the elderly.

4.4.3.1.3. NITRATES. Nitrates are effective in the treatment of all forms of angina. They relax vascular smooth muscle in the systemic arteries, inclusive of the coronary arteries, and veins (predominant effect at lower doses) in patients with SIHD. Short-term continuous nitroglycerin delivery by the intravenous or transdermal route for only 2 to 4 hours protects the endothelium from experimental ischemia in healthy volunteers and reduces ischemia during coronary angioplasty and physical exercise in IHD patients (863–865). Oxygen free radical release seems to be associated with these protective outcomes. Nitroglycerin causes dilation of the artery wall not affected by plaque, but independent of an intact endothelium, leading to reduced resistance across the obstructed lumen (866). Furthermore, nitroglycerin contributes to coronary blood flow redistribution, by augmenting collateral flow and lowering ventricular diastolic pressure, from areas of normal perfusion to ischemic zones (867). Preload is reduced, leading to reductions in myocardial wall tension and myocardial oxygen demand, although this effect is offset by increased heart rate and myocardial contractile state due to reflex sympathetic activity. Nitroglycerin also has demonstrated antithrombotic and antiplatelet effects (868,869).

Long-term nitrate therapy, however, could offset the beneficial short-term ischemic preconditioning effects.

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Long-term nitroglycerin therapy is associated with endothelial dysfunction via accumulation of the same oxygen free radicals that seem to be beneficial in short-term administration (870,871). The oxygen free radical accumulation increases arterial sensitivity to vasoconstrictors such as angiotensin II, which can be counteracted by concomitant treatment with an ACE inhibitor or hydralazine (872–875). Importantly, these physiological changes are independent of dose or the presence or absence of a nitrate-free interval and can result in a decrease in the anginal threshold during the nitrate-free interval (876). Further research to better understand the balance between the long-term benefits and safety concerns of these compounds is warranted in patients with SIHD.

Despite these physiological observations, nitrates improve exercise tolerance, time to ST-segment depression, and time to onset of angina in patients with SIHD, albeit in small patient studies conducted for relatively short periods (876–878). Comparisons of nitrates to beta blockers or calcium channel blockers have not shown significant differences with regard to weekly anginal episodes, time to ST-segment depression, total exercise time, or sublingual nitroglycerin use (420). Withdrawal for adverse effects was also not statistically different between the drug classes.

All patients with SIHD should be prescribed sublingual nitroglycerin tablets or nitroglycerin spray for immediate relief of angina. Most patients respond within 5 minutes of taking 1 to 2 sublingual dose(s) of 0.3 to 0.6 mg. Nitroglycerin spray is available in a 0.4-mg metered-dose canister that dispenses 200 doses. The tablets should be placed under the tongue and not swallowed. If the spray is used, it should be applied to the tongue and not swallowed or inhaled. If additional doses are necessary, they should be taken at 5-minute intervals, for a maximum dose of ≤1.2 mg within 15 minutes. During this timeframe, if relief does not occur, the patient should seek immediate medical attention. These products are also effective for prevention of effort-induced angina when administered 5 to 10 minutes before activity, with relief lasting approximately 30 to 40 minutes. The tablets must be kept in the manufacturer's bottle (loss of potency can occur in a few hours if out of the bottle) and should be stored in a cool, dry place but should not be refrigerated. The tablets should not be used 6 to 12 months after opening the bottle. Patients usually are able to detect when tablets have lost potency by the absence of a burning sensation beneath the tongue. Nitroglycerin ointment also may be used for short-term relief of angina. Applied to the chest in doses of 0.5 to 2.0 inches, with a delay in relief of 30 minutes, this preparation can be effective for 4 to 6 hours. Absorption can be increased by rotating the application sites, covering the paste with plastic, or not applying the ointment continuously (i.e., maintenance of a nitrate-free interval) (879–881). All short-acting nitrate preparations can cause hypotension, sometimes severe, and headaches that limit adherence to these agents. Patients should be counseled about these adverse effects and advised to seek medical treatment if syncope or resistant chest pain occurs. The ointment can cause permanent discoloration of clothing.

Long-acting nitrate preparations (e.g., nitroglycerin, isosorbide dinitrate, isosorbide-5-mononitrate) are recommended for treatment of angina when initial therapy with a beta blocker or nondihydropyridine calcium channel blocker is contraindicated or poorly tolerated or when additional therapy to control angina is necessary. Isosorbide dinitrate undergoes rapid high first-pass metabolism, resulting in low bioavailability. However, substantial interpatient variability exists in the metabolic enzyme systems responsible for isosorbide dinitrate conversion. Isosorbide mononitrate, the active metabolite of the dinitrate formulation, is 100% bioavailable. Nitroglycerin also can be delivered through silicone gel or polymer matrix release patch systems. The rate of release varies between these systems, necessitating individualization of dosing. With all formulations, titration of dose is important to gain adequate anginal control with the lowest possible dose to limit the occurrence of headaches, avoid nitrate tolerance, and facilitate long-term adherence. The effectiveness of all of these formulations seems to be roughly equivalent despite differences in the preparation and dosing schedules (843,882). With all of them, it is necessary to maintain a daily nitrate-free interval of 10 to 14 hours to avoid development of nitrate tolerance (843). Nitrate tolerance does not develop with the sublingual route of administration. Use of long-acting nitrates also does not result in tolerance to the use of sublingual products.

Nitrates are relatively well tolerated if a titration schedule is used at initiation and with discontinuation. The most common side effects are headache, flushing, and hypotension. Patients should be instructed to remain seated when taking rapid-acting nitrate products as a safety precaution to avoid syncope from vasodilation. Tolerance to the headaches could develop after a few weeks of continuing the medication. Prophylactic analgesics can be helpful until headache tolerance develops. Methemoglobinemia is a rare adverse effect, usually seen only with large doses. Nitrates are relatively contraindicated in hypertrophic obstructive cardiomyopathy because of the potential to increase the outflow tract obstruction and mitral regurgitant flow. They should be avoided in patients with severe aortic valvular stenosis. Coadministration of the phosphodiesterase inhibitors sildenafil, tadalafil, or vardenafil with long-acting nitrates should be strictly avoided within 24 hours of nitrate administration because of the risk of profound hypotension (e.g., 25–mm Hg drop in systolic BP). Patients should be advised not to take phosphodiesterase inhibitors within 24 hours of long-acting nitrates, and nitrates should not be taken for 24 hours after use of sildenafil or 48 hours after tadalafil; a suitable time interval after vardenafil has not been determined. Patients should be made aware of the possibility of intensification of their angina if nitrates are discontinued abruptly. This effect could be reduced by concomitant administration of other antianginals or by tapering of the long-acting nitrate dosage.

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4.4.3.1.4. RANOLAZINE. Ranolazine inhibits the late inward sodium current, indirectly reducing the sodium-dependent calcium current during ischemic conditions and leading to improvement in ventricular diastolic tension and oxygen consumption. Minimal changes in mean heart rate (<2 beats per minute) and systolic BP (<3 mm Hg) occur in controlled studies. At maximal exercise, the rate–pressure product is not increased, independent of age, or in the presence of diabetes mellitus, reactive airway disease, or heart failure (883). Ranolazine is currently indicated for the treatment of chronic angina and may be used in combination with beta blockers, nitrates, dihydropyridine calcium channel blockers, ACE inhibitors, ARBs, and antiplatelet and lipid-lowering therapy. It should be prescribed only in low doses in combination with verapamil or diltiazem, as described later. The lack of an effect on BP and heart rate makes ranolazine an attractive alternative in patients with bradycardia or low BP. Although ranolazine has been well studied in SIHD, the agent was not administered in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study (366), and further clinical evaluation is needed, especially of ranolazine as an element of intensive interventions for multiple risk factors.

The ranolazine extended-release preparation reduces the frequency of angina, improves exercise performance, and delays the development of exercise-induced angina and ST-segment depression (847,884). In one study, ranolazine reduced weekly anginal frequency by 36% and nitroglycerin use by 43% in comparison with placebo (848). Other studies indicated that among patients with ACS, ranolazine did not reduce the incidence of MI or death (885) but did reduce recurrent ischemia in the postinfarction period (886). In patients with preexisting angina, it was superior to placebo in improving patients' angina and quality of life (887). Ranolazine could exert a beneficial effect on glycemic control and has demonstrated consistent reductions in HbA1c in patients with diabetes mellitus in 2 studies (883,888,889).

Ranolazine blocks the delayed rectifier potassium current and prolongs the QTc interval in a dose-related manner, resulting in a mean increase in QTc of approximately 6 msec at maximal recommended dosing. Currently, there is limited experience with concomitant administration of ranolazine and other drugs that prolong the QT interval, including Class IA and III antiarrhythmics and certain antipsychotics (thioridazine and ziprasidone). In 3,162 patients with ACS, there was no increased risk of proarrhythmia or sudden death. In this study, there was a significantly lower incidence of arrhythmias, including ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation, in patients treated with ranolazine (80%) versus placebo (87%) (883,885,890,891).

Ranolazine does not require dose adjustment for age, sex, New York Heart Association class I–IV heart failure, or diabetes mellitus. Plasma concentrations of ranolazine are increased by up to 50% in patients with Stage 4 CKD (creatinine clearance <30 mL/min) (892). The drug is contraindicated in patients with clinically significant hepatic impairment because of increased plasma concentrations and QT prolongation. In general, dosing in the elderly should start at the low end of the dosing range (883).

Ranolazine is contraindicated in combination with potent inhibitors of the *CYP3A4* pathway, including ketoconazole (3.2-fold increase in ranolazine plasma levels) and other azole antifungals, macrolide antibiotics, HIV (human immunodeficiency virus) protease inhibitors, grapefruit products or juice, diltiazem (1.8- to 2.3-fold increase in ranolazine plasma levels), itraconazole, clarithromycin, and certain HIV protease inhibitors. When administered with moderate inhibitors of *CYP3A* such as diltiazem, verapamil, aprepitant, erythromycin, fluconazole, or grapefruit juice, the dose of ranolazine should be limited to 500 mg twice daily because of an approximately 2-fold increase in ranolazine plasma levels. No dose adjustment is required in patients treated with cimetidine or paroxetine. Coadministration of ranolazine (1,000 mg twice daily) with simvastatin increases the plasma concentration of simvastatin and its active metabolite 2-fold. Digoxin plasma concentrations are increased 1.5-fold, but this interaction might not be clinically relevant with lower digoxin dosing (0.125 mg daily). Coadministration of ranolazine with drugs that inhibit *CYP2D6*, with the exceptions of tricyclic antidepressants and some antipsychotics, does not require dosage adjustment.

Ranolazine is well tolerated; the major adverse effects are constipation, nausea, dizziness, and headache. The incidence of syncope is <1%.

4.4.3.1.5. ANTIANGINAL AGENTS NOT CURRENTLY AVAILABLE IN THE UNITED STATES

4.4.3.1.5.1. *Nicorandil.* Nicorandil is a nicotinamide ester with a dual mechanism of action. It activates adenosine triphosphate–sensitive potassium channels and promotes systemic venous and coronary vasodilation through a nitrate moiety (893). This dual action increases coronary blood flow, with reductions in afterload, preload, and oxidative injury (893). The agent does not exhibit effects on contractility or conduction (894,895). The antianginal efficacy and safety of nicorandil are similar to those of oral nitrates, beta blockers, and calcium channel blockers (893,896,897). In a prospective, randomized, study of 5,126 patients with chronic stable angina, the addition of nicorandil to standard therapy was found to produce a 17% RR reduction in the composite endpoint of IHD death, nonfatal MI, or unplanned hospital admission for cardiac chest pain (898). There was, however, no difference between nicorandil and placebo with regard to death from IHD or nonfatal MI (894). Tolerance can develop with long-term dosing (899). Common side effects include flushing; palpitation; weakness; headache; ulceration of the mouth, perianal, ileal, and peristomal areas; nausea; and vomiting. The agent is not currently available in the United States.

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4.4.3.1.5.2. Ivabradine. Ivabradine is a specific inhibitor of the *If* current of pacemaker cells in the sinoatrial node at concentrations that do not inhibit other cardiac currents (900). This action results in heart rate reduction, prolonging diastole and thereby improving myocardial oxygen balance. Ivabradine has no effect on BP, myocardial contractility, or intracardiac conduction parameters (901–903). Ivabradine improves exercise capacity and reduces anginal frequency in comparison to atenolol among patients with chronic stable angina (904,905). In 5,479 patients with IHD and LV systolic dysfunction, however, ivabradine added to standard treatment had no effect, when compared with placebo, on the composite endpoint of cardiovascular death, admission to the hospital for AMI, and admission to the hospital for new-onset or worsening heart failure (906). The most common adverse event, reported in 14.5% of patients, is phosphenes, described as a transient enhanced brightness in a limited area of the visual field that typically occurs within the first 2 months of treatment. Most of these luminous visual-field disturbances (77%) resolve without discontinuing treatment. The drug is approved in Europe (not currently available in the United States) for the symptomatic treatment of chronic stable angina in patients with normal sinus rhythm with a contraindication or intolerance to beta blockers.

4.4.3.1.5.3. Trimetazidine. Trimetazidine seems to improve cellular tolerance to ischemia by inhibiting fatty acid metabolism and secondarily by stimulating glucose metabolism, although the exact anti-ischemic mechanisms are unknown (907). In patients with chronic stable angina, this agent increases coronary flow reserve, delaying the onset of ischemia associated with exercise and reducing the number of weekly angina episodes and weekly nitroglycerin consumption (908,909). The anti-ischemic effects are not associated with changes in heart rate or systolic BP. Few data exist on the effect of trimetazidine on cardiovascular endpoints, mortality, or quality of life. The most frequently reported adverse events are gastrointestinal disorders, but the incidence is low. The agent is not available in the United States but is available in Europe and reportedly in >80 countries worldwide.

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

CLASS IIb

1. Enhanced external counterpulsation (EECP) may be considered for relief of refractory angina in patients with SIHD (910). *(Level of Evidence: B)*
2. Spinal cord stimulation may be considered for relief of refractory angina in patients with SIHD (911,912). *(Level of Evidence: C)*
3. Transmyocardial revascularization (TMR) may be considered for relief of refractory angina in patients with SIHD (913–915). *(Level of Evidence: B)*

CLASS III: No Benefit

1. Acupuncture should not be used for the purpose of improving symptoms or reducing cardiovascular risk in patients with SIHD (916,917). *(Level of Evidence: C)*

TMR has been used as either a percutaneous or a surgical procedure concomitant with CABG or as sole therapy in patients with angina refractory to medical therapy (913–915,918), although the mechanism by which it might be efficacious is unknown (919,920). Early studies of the percutaneous approach demonstrated no therapeutic benefit, and it was promptly abandoned (921). When used as sole therapy by a surgical approach, TMR is reserved for the patient with incapacitating, medically refractory angina and no other feasible therapeutic options. Proposed mechanisms of action include stimulation of microcirculation, creation of myocardial scarring, and denervation of ischemic myocardium (922). Various energy sources have been used, including carbon dioxide XeCl excimer and holmium:YAG lasers (923–925). There is no convincing evidence that one energy source is superior to the others. TMR also has been combined with cardiac denervation by thoracic sympathectomy (926).

Numerous single-center and a few multicenter randomized trials have been published that compare TMR with medical therapy for relief of refractory angina (927–930). Most have shown better angina relief with TMR but no survival benefit. The exception is a single multicenter trial that shows a survival benefit as well as better relief of angina at 5 years (931). A 5-year follow-up of a multicenter, prospectively randomized trial reported not only sustained angina relief but also improved survival in CCS Class IV angina, and patients with no additional options for therapy who were randomized to sole-therapy TMR (931). A meta-analysis of 7 RCTs involving 1,053 patients evaluated the effect of TMR on survival and angina relief (932). The conclusion was that at 1 year, TMR improved angina class but not survival when used as the sole procedural intervention compared with medical therapy alone. A number of other series also have reported sustained angina relief and improved quality of life in randomized patients receiving TMR at 3 to 5 years after treatment (Section 5.10 for additional information on TMR in revascularization).

A growing number of patients with SIHD have refractory angina, defined as multivessel CAD with ischemia and symptoms that cannot be controlled with medical therapy or surgical or percutaneous revascularization. The prevalence of this syndrome is not well established, but data from registries suggest that about 10% of patients referred for angiography for symptomatic SIHD have coronary anatomy that is not amenable to revascularization (933–935). Other nonpharmacological therapies may be considered in these patients in an effort to improve quality of life.

4.4.4.1. ENHANCED EXTERNAL COUNTERPULSATION

EECP is a technique that uses inflatable cuffs wrapped around the lower extremities to increase venous return and

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augment diastolic BP. 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 LV diastolic filling and improved endothelial function (936–938); other putative mechanisms for improvement in symptoms include recruitment of collaterals, release of proangiogenic cytokines, and a peripheral training effect. A treatment course typically consists of 35 hour-long treatment sessions, given 5 days a week. Contraindications include decompensated heart failure, severe PAD, and severe aortic regurgitation.

The efficacy of EECP in treating stable angina pectoris has been evaluated in a single RCT 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 (910). Time to ≥1-mm ST-segment depression 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), although there was no difference between the groups in exercise duration. More active counterpulsation patients experienced a decrease in anginal episodes. Of patients receiving EECP, 55% reported adverse events, including leg and back pain and skin abrasions, compared with 26% in the control group, with approximately half of these events categorized as device related.

In a meta-analysis of 13 observational studies that tracked 949 patients, anginal class as categorized by the CCS classification was improved by ≥1 class in 86% (95% CI: 82% to 90%) (939). The EECP Consortium reported results in 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 (940). Treatment was associated with improved perfusion images and increased exercise duration. Similarly, the International EECP Registry reported improvement of ≥1 angina class in 81% of patients immediately after the last treatment (941).

In general, existing data, largely from uncontrolled studies, suggest a benefit from EECP in 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 (942).

4.4.4.2. SPINAL CORD STIMULATION

Spinal cord stimulation at the T1 to T2 level has been advocated as a therapeutic option for patients with angina pectoris that is refractory to medical therapy and coronary revascularization. The stimulation lead is inserted into the epidural space and is connected to a pulse generator implanted subcutaneously. A paresthetic stimulus is delivered in a continuous, cyclic, or intermittent manner. The mechanisms by which spinal cord stimulation leads to reduced angina are not well established. Although inhibition of pain transmission plays a role, some studies suggest that spinal cord stimulation also might reduce myocardial ischemia (943–945).

The efficacy of spinal cord stimulation has been evaluated in several observational and cohort studies. The Prospective Italian Registry described outcomes in 104 patients with severe angina refractory to medical therapy over an average of 13 months after initiation of spinal cord stimulation (946). A >50% reduction in anginal symptoms was observed in 73% of patients. CCS class improved by ≥1 class in 80% and by ≥2 classes in 42% of patients. Similarly, in a cohort of 51 patients with refractory CCS Class III or IV angina, spinal cord stimulation was associated with a significant reduction in anginal episodes in 88% of subjects at 24 months of follow-up (947). There were no significant complications of therapy in either series.

The published RCTs of spinal cord stimulation were small. One study tested the efficacy of spinal cord stimulation in 13 patients with chronic, intractable angina compared with 12 controls over 6 weeks (912). Patients with spinal cord stimulation demonstrated greater exercise duration and time to angina during treadmill testing and fewer bouts of angina and fewer episodes of ST depression on ambulatory echocardiographic monitoring. A subsequent trial compared spinal cord stimulation to CABG (911). Subjects included 104 patients with severe angina who would not be expected to derive survival benefit from revascularization, were at increased risk of surgical complications, and were unsuitable for PCI. Patients in both groups had significant symptom relief. Those assigned to bypass surgery had greater increases in exercise capacity and less ST depression on treadmill testing than did those treated with spinal cord stimulation. Mortality and cardiovascular morbidity rates were lower in the spinal cord stimulation group.

In summary, studies of spinal cord stimulation suggest that this technique might have some use as a method to relieve angina in patients with symptoms that are refractory to standard medical therapy and revascularization. There is a paucity of data on the mechanisms and long-term risks and benefits of this therapeutic approach, however.

4.4.4.3. ACUPUNCTURE

Acupuncture is used by some practitioners for the relief of acute and chronic pain. The efficacy of acupuncture in the treatment of angina pectoris has not been studied rigorously, however. In part this is due to the difficulty of blinding both patients and healthcare providers. Twenty-six patients with severe angina resistant to standard medical therapy were studied in one of the first randomized trials comparing acupuncture and sham acupuncture (917). There was no difference between groups in the frequency of angina or use of nitroglycerin, although patients treated with acupuncture

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achieved a higher pressure–rate product on exercise testing. A subsequent study by the same investigators in patients with less severe ischemia failed to show a difference in either exercise variables or subjective measures between acupuncture and placebo patients (916). In contrast, a decrease in anginal episodes and an increase in the workload required to induce ischemia were observed with acupuncture in a crossover study of 21 patients with stable angina. The control condition in this trial was a pill placebo, however, so neither subjects nor investigators were blinded (948).

In summary, acupuncture has not been studied sufficiently to warrant recommendation as a treatment option for relief of symptoms in patients with SIHD.

5. CAD Revascularization

Recommendations and text in this section are the result of extensive collaborative discussions between the PCI and CABG writing committees, as well as key members of the SIHD and UA/NSTEMI writing committees. Certain issues, such as older versus more contemporary studies, primary analyses versus subgroup analyses, and prospective versus post hoc analyses, have been carefully weighed in designating COR and LOE; they are addressed in the appropriate corresponding text. The goals of revascularization for patients with CAD are to 1) improve survival and 2) relieve symptoms.

Revascularization recommendations in this section are based predominantly on studies of patients with symptomatic SIHD and should be interpreted in this context. As discussed later in this section, recommendations on the type of revascularization are, in general, applicable to patients with UA/NSTEMI. In some cases (e.g., unprotected left main CAD), specific recommendations are made for patients with UA/NSTEMI or STEMI.

Historically, most studies of revascularization have been based on and reported according to angiographic criteria. Most studies have defined a "significant" stenosis as ≥70% diameter narrowing; therefore, for revascularization decisions and recommendations in this section, a "significant" stenosis has been defined as ≥70% diameter narrowing (≥50% for left main CAD). Physiological criteria, such as an assessment of FFR, have been used in deciding when revascularization is indicated. Thus, for recommendations about revascularization in this section, coronary stenoses with FFR ≤0.80 can also be considered to be "significant."

As noted, the revascularization recommendations have been formulated to address issues related to 1) improved survival and/or 2) improved symptoms. When one method of revascularization is preferred over the other for improved survival, this consideration, in general, takes precedence over improved symptoms. When options for revascularization are discussed with the patient, he or she should understand when the procedure is being performed in an attempt to improve symptoms, survival, or both.

Although some results from the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) study are best characterized as subgroup analyses and "hypothesis generating," SYNTAX nonetheless represents the latest and most comprehensive comparison of PCI and CABG (949,950). Therefore, the results of SYNTAX have been considered appropriately when formulating our revascularization recommendations. Although the limitations of using the SYNTAX score for certain revascularization recommendations are recognized, the SYNTAX score is a reasonable surrogate for the extent of CAD and its complexity and serves as important information that should be considered when making revascularization decisions. Recommendations that refer to SYNTAX scores use them as surrogates for the extent and complexity of CAD.

Revascularization recommendations to improve survival and symptoms are provided in the following text and are summarized in Tables 18 and 19. References to studies comparing revascularization with medical therapy are presented when available for each anatomic subgroup. When such studies have been completed only for CABG, RCTs or cohort studies comparing CABG with PCI are presented, but the LOE for PCI is downgraded.

See Online Data Supplements 3 and 4 for additional data regarding the survival and symptomatic benefits with CABG or PCI for different anatomic subsets.

5.1. Heart Team Approach to Revascularization Decisions: Recommendations

CLASS I

1. **A Heart Team approach to revascularization is recommended in patients with unprotected left main or complex CAD (950–952). *(Level of Evidence: C)***

CLASS IIa

1. **Calculation of the STS and SYNTAX scores is reasonable in patients with unprotected left main and complex CAD (949,950,953–957). *(Level of Evidence: B)***

One protocol used in RCTs (950–952,958) often involves a multidisciplinary approach referred to as the Heart Team. Composed of an interventional cardiologist and a cardiac surgeon, the Heart Team 1) reviews the patient's medical condition and coronary anatomy, 2) determines that PCI and/or CABG are technically feasible and reasonable, and 3) discusses revascularization options with the patient before a treatment strategy is selected. Support for using a Heart Team approach comes from reports that patients with complex CAD referred specifically for PCI or CABG in concurrent trial registries have lower mortality rates than those randomly assigned to PCI or CABG in controlled trials (951,952).

The SIHD, PCI, and CABG guideline writing committees endorse a Heart Team approach in patients with unprotected left main CAD and/or complex CAD in whom the optimal revascularization strategy is not straightforward.

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Table 18. Revascularization to Improve Survival Compared With Medical Therapy

Anatomic Setting	COR	LOE	References
UPLM or complex CAD			
CABG and PCI	I—Heart Team approach recommended	C	(950–952)
CABG and PCI	IIa—Calculation of STS and SYNTAX scores	B	(949,950,953–957)
UPLM*			
CABG	I	B	(73,381,412,959–962)
PCI	IIa—For SIHD when *both* of the following are present: • Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score of ≤22, ostial or trunk left main CAD) • Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%)	B	(949,953,955,958,963–980)
	IIa—For UA/NSTEMI if not a CABG candidate	B	(949,968–971,976–979,981)
	IIa—For STEMI when distal coronary flow is TIMI flow grade <3 and PCI can be performed more rapidly and safely than CABG	C	(965,982,983)
	IIb—For SIHD when *both* of the following are present: • Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low-intermediate SYNTAX score of <33, bifurcation left main CAD) • Clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate—severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted operative mortality >2%)	B	(949,953,955,958,963–980,984)
	III: Harm—For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B	(73,381,412,949,953,955,959–964)
3-vessel disease with or without proximal LAD artery disease*			
CABG	I	B	(353,412,959,985–987)
	IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score >22) who are good candidates for CABG.	B	(964,980,987–989)
PCI	IIb—Of uncertain benefit	B	(366,959,980,985,987)
2-vessel disease with proximal LAD artery disease*			
CABG	I	B	(353,412,959,985–987)
PCI	IIb—Of uncertain benefit	B	(366,959,985,987)
2-vessel disease without proximal LAD artery disease*			
CABG	IIa—With extensive ischemia	B	(327,990–992)
	IIb—Of uncertain benefit without extensive ischemia	C	(987)
PCI	IIb—Of uncertain benefit	B	(366,959,985,987)
1-vessel proximal LAD artery disease			
CABG	IIa—With LIMA for long-term benefit	B	(412 987,993,994)
PCI	IIb—Of uncertain benefit	B	(366,959,985,987)
1-vessel disease without proximal LAD artery involvement			
CABG	III: Harm	B	(306,327,412,985,990,995–998)
PCI	III: Harm	B	(306,327,412,985,990,995–998)
LV dysfunction			
CABG	IIa—EF 35% to 50%	B	(365,412,999–1002)
CABG	IIb—EF <35% without significant left main CAD	B	(355,365,410,412,999–1002)
PCI	Insufficient data		N/A
Survivors of sudden cardiac death with presumed ischemia-mediated VT			
CABG	I	B	(350,1003,1004)
PCI	I	C	(1003)
No anatomic or physiological criteria for revascularization			
CABG	III: Harm	B	(306,327,412,985,990,995–998)
PCI	III: Harm	B	(306,327,412,985,990,995–998)

***In patients with multivessel disease who also have diabetes mellitus, it is reasonable to choose CABG (with LIMA) over PCI** (30,991,1005–1011) (*Class IIa; LOE: B*).

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; COR, class of recommendation; EF, ejection fraction; LAD, left anterior descending; LIMA, left internal mammary artery; LOE, level of evidence; LV, left ventricular; N/A, not available; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; STS, Society of Thoracic Surgeons; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIMI, Thrombolysis In Myocardial Infarction; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; UPLM, unprotected left main disease; and VT, ventricular tachycardia.

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Table 19. Revascularization to Improve Symptoms With Significant Anatomic (≥50% Left Main or ≥70% Non–Left Main CAD) or Physiological (FFR ≤0.80) Coronary Artery Stenoses

Clinical Setting	COR	LOE	References
≥1 significant stenoses amenable to revascularization and unacceptable angina despite GDMT	1—CABG	A	(366,407,1012–1020)
	1—PCI		
≥1 significant stenoses and unacceptable angina in whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences	IIa—CABG	C	N/A
	IIa—PCI	C	N/A
Previous CABG with ≥1 significant stenoses associated with ischemia and unacceptable angina despite GDMT	IIa—PCI	C	(1021–1024)
	IIb—CABG	C	(1025)
Complex 3-vessel CAD (e.g., SYNTAX score >22) with or without involvement of the proximal LAD artery and a good candidate for CABG	IIa—CABG preferred over PCI	B	(980,987–989)
Viable ischemic myocardium that is perfused by coronary arteries that are not amenable to grafting	IIb—TMR as an adjunct to CABG	B	(923,927,929,1026,1027)
No anatomic or physiological criteria for revascularization	III: Harm—CABG	C	N/A
	III: Harm—PCI	C	N/A

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COR, class of recommendation; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; LOE, level of evidence; N/A, not available; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and TMR, transmyocardial revascularization.

A collaborative assessment of revascularization options, or the decision to treat with GDMT without revascularization, involving an interventional cardiologist, a cardiac surgeon, and (often) the patient's general cardiologist, followed by discussion with the patient about treatment options, is optimal. Particularly in patients with SIHD and unprotected left main and/or complex CAD for whom a revascularization strategy is not straightforward, an approach has been endorsed that involves terminating the procedure after diagnostic coronary angiography is completed; this allows a thorough discussion and affords both the interventional cardiologist and cardiac surgeon the opportunity to discuss revascularization options with the patient. Because the STS score and the SYNTAX score have been shown to predict adverse outcomes in patients undergoing CABG and PCI, respectively, calculation of these scores is often useful in making revascularization decisions (949,950,953–957).

5.2. Revascularization to Improve Survival: Recommendations

Left Main CAD Revascularization

CLASS I

1. CABG to improve survival is recommended for patients with significant (≥50% diameter stenosis) left main coronary artery stenosis (73,381,412,959–962). *(Level of Evidence: B)*

CLASS IIa

1. PCI to improve survival is reasonable as an alternative to CABG in selected stable patients with significant (≥50% diameter stenosis) unprotected left main CAD with: 1) anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score [≤22], ostial or trunk left main CAD); *and* 2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%) (949,953,955,958, 963–979). *(Level of Evidence: B)*
2. PCI to improve survival is reasonable in patients with UA/NSTEMI when an unprotected left main coronary artery is the culprit lesion and the patient is not a candidate for CABG (949,968–971,976–979,981). *(Level of Evidence: B)*
3. PCI to improve survival is reasonable in patients with acute STEMI when an unprotected left main coronary artery is the culprit lesion, distal coronary flow is less than TIMI (Thrombolysis In Myocardial Infarction) grade 3, and PCI can be performed more rapidly and safely than CABG (965,982,983). *(Level of Evidence: C)*

CLASS IIb

1. PCI to improve survival may be reasonable as an alternative to CABG in selected stable patients with significant (≥50% diameter stenosis) unprotected left main CAD with: a) anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low–intermediate SYNTAX score of <33, bifurcation left main CAD); *and* b) clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate–severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery; STS-predicted risk of operative mortality >2%) (949,953,955,958,963–979,984). *(Level of Evidence: B)*

CLASS III: Harm

1. PCI to improve survival should not be performed in stable patients with significant (≥50% diameter stenosis) unprotected left main CAD who have unfavorable anatomy for PCI and who are good candidates for CABG (73,381,412,949,953,955,959–964). *(Level of Evidence: B)*

Non–Left Main CAD Revascularization

CLASS I

1. CABG to improve survival is beneficial in patients with significant (≥70% diameter) stenoses in 3 major coronary arteries (with or without involvement of the proximal LAD artery) or in the proximal LAD artery plus 1 other major coronary artery (353,412,959,985–987). *(Level of Evidence: B)*
2. CABG or PCI to improve survival is beneficial in survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (≥70% diameter) stenosis in a major coronary artery. *(CABG Level of Evidence: B* [350,1003,1004]; *PCI Level of Evidence: C* [1003]*)*

CLASS IIa

1. CABG to improve survival is reasonable in patients with significant (≥70% diameter) stenoses in 2 major coronary arteries with severe

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or extensive myocardial ischemia (e.g., high-risk criteria on stress testing, abnormal intracoronary hemodynamic evaluation, or >20% perfusion defect by myocardial perfusion stress imaging) or target vessels supplying a large area of viable myocardium (327,990–992). *(Level of Evidence: B)*

2. CABG to improve survival is reasonable in patients with mild–moderate LV systolic dysfunction (EF 35% to 50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal LAD coronary artery stenosis, when viable myocardium is present in the region of intended revascularization (365,412,999–1002). *(Level of Evidence: B)*
3. CABG with a left internal mammary artery (LIMA) graft to improve survival is reasonable in patients with significant (≥70% diameter) stenosis in the proximal LAD artery and evidence of extensive ischemia (412,987,993,994). *(Level of Evidence: B)*
4. It is reasonable to choose CABG over PCI to improve survival in patients with complex 3-vessel CAD (e.g., SYNTAX score >22), with or without involvement of the proximal LAD artery who are good candidates for CABG (964,980,987–989). *(Level of Evidence: B)*
5. 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 (991,1005–1008,1008–1011). *(Level of Evidence: B)*

CLASS IIb

1. The usefulness of CABG to improve survival is uncertain in patients with significant (70%) diameter stenoses in 2 major coronary arteries not involving the proximal LAD artery and without extensive ischemia (987). *(Level of Evidence: C)*
2. The usefulness of PCI to improve survival is uncertain in patients with 2- or 3-vessel CAD (with or without involvement of the proximal LAD artery) or 1-vessel proximal LAD disease (366,959,985,987). *(Level of Evidence: B)*
3. CABG might be considered with the primary or sole intent of improving survival in patients with SIHD with severe LV systolic dysfunction (EF <35%) whether or not viable myocardium is present (355,365,410,412,999–1002). *(Level of Evidence: B)*
4. The usefulness of CABG or PCI to improve survival is uncertain in patients with previous CABG and extensive anterior wall ischemia on noninvasive testing (1021–1025,1029–1032). *(Level of Evidence: B)*

CLASS III: Harm

1. CABG or PCI should not be performed with the primary or sole intent to improve survival in patients with SIHD with 1 or more coronary stenoses that are not anatomically or functionally significant (e.g., <70% diameter non–left main coronary artery stenosis, FFR >0.80, no or only mild ischemia on noninvasive testing), involve only the left circumflex or right coronary artery, or subtend only a small area of viable myocardium (306,327,412,985,990,995–998). *(Level of Evidence: B)*

5.3. Revascularization to Improve Symptoms: Recommendations

CLASS I

1. CABG or PCI to improve symptoms is beneficial in patients with 1 or more significant (≥70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite GDMT (366,407,1012–1018,1020,1033). *(Level of Evidence: A)*

CLASS IIa

1. CABG or PCI to improve symptoms is reasonable in patients with 1 or more significant (≥70% diameter) coronary artery stenoses and unacceptable angina for whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences. *(Level of Evidence: C)*
2. PCI to improve symptoms is reasonable in patients with previous CABG, 1 or more significant (≥70% diameter) coronary artery stenoses associated with ischemia, and unacceptable angina despite GDMT (1021,1023,1024). *(Level of Evidence: C)*
3. It is reasonable to choose CABG over PCI to improve symptoms in patients with complex 3-vessel CAD (e.g., SYNTAX score >22), with or without involvement of the proximal LAD artery, who are good candidates for CABG (964,980,987–989). *(Level of Evidence: B)*

CLASS IIb

1. CABG to improve symptoms might be reasonable for patients with previous CABG, 1 or more significant (≥70% diameter) coronary artery stenoses not amenable to PCI, and unacceptable angina despite GDMT (1025). *(Level of Evidence: C)*
2. TMR performed as an adjunct to CABG to improve symptoms may be reasonable in patients with viable ischemic myocardium that is perfused by arteries that are not amenable to grafting (923, 927,929,1026,1027). *(Level of Evidence: B)*

CLASS III: Harm

1. CABG or PCI to improve symptoms should not be performed in patients who do not meet anatomic (≥50% diameter left main or ≥70% non–left main stenosis diameter) or physiological (e.g., abnormal FFR) criteria for revascularization. *(Level of Evidence: C)*

5.4. CABG Versus Contemporaneous Medical Therapy

In the 1970s and 1980s, 3 RCTs established the survival benefit of CABG compared with contemporaneous (although minimal by current standards) medical therapy without revascularization in certain subjects with stable angina: the Veterans Affairs Cooperative Study (1035), European Coronary Surgery Study (986), and CASS (1036). Subsequently, a 1994 meta-analysis of 7 studies that randomized a total of 2,649 patients to medical therapy or CABG (412) showed that CABG offered a survival advantage over medical therapy for patients with left main or 3-vessel CAD. The studies also established that CABG is more effective than medical therapy for relieving anginal symptoms. These studies have been replicated only once during the past decade. In MASS II (Medicine, Angioplasty, or Surgery Study II), patients with multivessel CAD who were treated with CABG were less likely than those treated with medical therapy to have a subsequent MI, need additional revascularization, or experience cardiac death in the 10 years after randomization (1016).

Surgical techniques and medical therapy have improved substantially during the intervening years. As a result, if CABG were to be compared with GDMT in RCTs today, the relative benefits for survival and angina relief observed several decades ago might no longer be observed. Conversely, the concurrent administration of GDMT may substantially improve long-term outcomes in patients

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treated with CABG in comparison with those receiving medical therapy alone. In the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial of patients with diabetes mellitus, no significant difference in risk of mortality in the cohort of patients randomized to GDMT plus CABG or GDMT alone was observed, although the study was not powered for this endpoint, excluded patients with significant left main CAD, and included only a small percentage of patients with proximal LAD artery disease or LVEF <0.50 (408). The PCI and CABG guideline writing committees endorse the performance of the ISCHEMIA trial, which will provide contemporary data on the optimal management strategy (medical therapy or revascularization with CABG or PCI) of patients with SIHD, including multivessel CAD, and moderate to severe ischemia.

5.5. PCI Versus Medical Therapy

Although contemporary interventional treatments have lowered the risk of restenosis compared with earlier techniques, meta-analyses have not shown that the introduction of bare metal stents (BMS) confers a survival advantage over balloon angioplasty (1037–1039) or that the use of DES confers a survival advantage over BMS (138,1040).

No study to date has demonstrated that PCI in patients with SIHD improves survival rates (138,366,408,959,985,987,1041–1044). Neither COURAGE (366) nor BARI 2D (408), which treated all patients with contemporary optimal medical therapy, demonstrated any survival advantage with PCI, although these trials were not specifically powered for this endpoint. Although 1 large analysis evaluating 17 RCTs of PCI versus medical therapy (including 5 trials of subjects with ACS) found a 20% reduction in death with PCI compared with medical therapy (1043), 2 other large analyses did not (138,1042). An evaluation of 13 studies reporting the data from 5,442 patients with nonacute CAD showed no advantage of PCI over medical therapy for the individual endpoints of all-cause death, cardiac death or MI, or nonfatal MI (1044). Evaluation of 61 trials of PCI conducted over several decades shows that despite improvements in PCI technology and pharmacotherapy, PCI has not been demonstrated to reduce the risk of death or MI in patients without recent ACS (138).

The findings from individual studies and systematic reviews of PCI versus medical therapy can be summarized as follows:

- PCI reduces the incidence of angina (366,407,1016,1020,1033,1045).
- PCI has not been demonstrated to improve survival in stable patients (138,1041,1042).
- PCI may increase the short-term risk of MI (366,397,1041,1045).
- PCI does not lower the long-term risk of MI (138,366,397,408,1041,1042).

5.6. CABG Versus PCI

The results of 26 RCTs comparing CABG and PCI have been published: Of these, 9 compared CABG with balloon angioplasty (30,368,1017,1046–1059), 14 compared CABG with BMS implantation (1022,1054,1060–1076), and 3 compared CABG with DES implantation (950,1077,1078).

5.6.1. CABG Versus Balloon Angioplasty or BMS

A systematic review of the 22 RCTs comparing CABG with balloon angioplasty or BMS implantation concluded the following (1079):

1. Survival was similar for CABG and PCI (with balloon angioplasty or BMS) at 1 year and 5 years. Survival was similar for CABG and PCI in subjects with 1-vessel CAD (including those with disease of the proximal portion of the LAD artery) or multivessel CAD.
2. Incidence of MI was similar at 5 years after randomization.
3. Procedural stroke occurred more commonly with CABG than with PCI (1.2% versus 0.6%).
4. Relief of angina was accomplished more effectively with CABG than with PCI 1 year after randomization and 5 years after randomization.
5. During the first year after randomization, repeat coronary revascularization was performed less often after CABG than after PCI (3.8% versus 26.5%). This was also demonstrated after 5 years of follow-up (9.8% versus 46.1%). This difference was more pronounced with balloon angioplasty than with BMS.

A collaborative analysis of data from 10 RCTs comparing CABG with balloon angioplasty (6 trials) or with BMS implantation (4 trials) (1080) permitted subgroup analyses of the data from the 7,812 patients. No difference was noted with regard to mortality rate 5.9 years after randomization or the composite endpoint of death or MI. Repeat revascularization and angina were noted more frequently in those treated with balloon angioplasty or BMS implantation (1080). The major new observation of this analysis was that CABG was associated with better outcomes in patients with diabetes mellitus and in those >65 years of age. Of interest, the relative outcomes of CABG and PCI were not influenced by other patient characteristics, including the number of diseased coronary arteries.

The aforementioned meta-analysis and systematic review (1079,1080) comparing CABG and balloon angioplasty or BMS implantation were limited in several ways:

1. Many trials did not report outcomes for other important patient subsets. For example, the available data are insufficient to determine if race, obesity, renal dysfunction, PAD, or previous coronary revascularization affected the comparative outcomes of CABG and PCI.
2. Most of the patients enrolled in these trials were male, and most had 1- or 2-vessel CAD and normal LV

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systolic function (EF >50%)—subjects known to be unlikely to derive a survival benefit and less likely to experience complications after CABG (412).

3. The patients enrolled in these trials represented only a small fraction (generally <5% to 10%) of those who were screened. For example, most screened patients with 1-vessel CAD and many with 3-vessel CAD were not considered for randomization.

See Online Data Supplements 5 and 6 for additional data on CABG versus PCI.

5.6.2. CABG Versus DES

Although the results of 9 observational studies comparing CABG and DES implantation have been published (964,1081–1088), most of them had short (12 to 24 months) follow-up periods. In a meta-analysis of 24,268 patients with multivessel CAD treated with CABG or DES (1089), 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 trial randomly assigned 1,800 patients (of a total of 4,337 who were screened) to receive DES or CABG (949,950,980). MACE, a composite of death, stroke, MI, or repeat revascularization during the 3 years after randomization, occurred in 20.2% of CABG patients and 28.0% of those undergoing DES implantation ($p<0.001$). The rates of death and stroke were similar; 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 (980).

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 MACE correlated with the SYNTAX score for DES patients but not for those undergoing CABG. At 12-month follow-up, the primary endpoint was similar for CABG and DES in those with a low SYNTAX score. In contrast, MACE occurred more often after DES implantation than after CABG in those with an intermediate or high SYNTAX score (950). At 3 years of follow-up, the mortality rate was greater in subjects with 3-vessel CAD treated with PCI than in those treated with CABG (6.2% versus 2.9%). The differences in MACE between those treated with PCI or CABG increased with an increasing SYNTAX score (Figure 12) (980).

Although the utility of using a SYNTAX score in everyday clinical practice remains uncertain, it seems reasonable to conclude from SYNTAX and other data that outcomes of patients undergoing PCI or CABG in those with relatively uncomplicated and lesser degrees of CAD are comparable, whereas in those with complex and diffuse CAD, CABG appears to be preferable (949,980).

See Online Data Supplements 6 and 7 for additional data comparing CABG with DES.

5.7. Left Main CAD

5.7.1. CABG or PCI Versus Medical Therapy for Left Main CAD

CABG confers a survival benefit over medical therapy in patients with left main CAD. Subgroup analyses from RCTs performed 3 decades ago included 91 patients with left main CAD in the Veterans Administration Cooperative Study (961). A meta-analysis of these trials demonstrated a 66% reduction in RR of death with CABG, with the benefit extending to 10 years (412). The CASS Registry (381) contained data from 1,484 patients with ≥50% diameter stenosis left main CAD initially treated surgically or nonsurgically. Median survival duration was 13.3 years in the surgical group and 6.6 years in the medical group. The survival benefit of CABG over medical therapy appeared to extend to 53 asymptomatic patients with left main CAD in the CASS Registry (962). Other therapies that subsequently have been shown to be associated with improved long-term outcome, such as the use of aspirin, statins, and internal mammary artery grafting, were not widely used in that era.

RCTs and subgroup analyses that compare PCI with medical therapy in patients with "unprotected" left main CAD do not exist.

5.7.2. Studies Comparing PCI Versus CABG for Left Main CAD

Of all subjects undergoing coronary angiography, approximately 4% are found to have left main CAD (1090), >80% of whom have significant (≥70% diameter) stenoses in other epicardial coronary arteries.

Published cohort studies have found that major clinical outcomes are similar with PCI or CABG 1 year after revascularization and that mortality rates are similar at 1, 2, and 5 years of follow-up; however, the risk of needing 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 these underwent CABG (949,950). In addition, 705 of the 1,800 patients who were randomized had revascularization for unprotected left main CAD. 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 MACE were similar for the 2 groups (949). Repeat revascularization rates were higher in the PCI group than the CABG group (11.8% versus 6.5%), but

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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 (≤32) was 3.7% after PCI 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 PCI and 7.6% after CABG (p=0.10) (949). Because the primary endpoint of SYNTAX was not met (i.e., noninferiority comparison of CABG and PCI), these subgroup analyses need to be considered in that context.

In the LE MANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery) trial (958), 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 PCI and 4.7% of patients treated with CABG, but ischemia-driven target-vessel revascularization was more often required in the patients treated with PCI (9.0% versus 4.2%) (984).

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 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. In a meta-analysis of 8 cohort studies and 2 RCTs (973), 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).

See Online Data Supplements 8 to 13 for additional data comparing PCI with CABG for left main CAD.

5.7.3. Revascularization Considerations for Left Main CAD

Although CABG has been considered the "gold standard" for unprotected left main CAD revascularization, more recently PCI has emerged as a possible alternative mode of revascularization in carefully selected patients. Lesion location is an important determinant when PCI is considered for unprotected left main CAD. Stenting of the left main ostium or trunk is more straightforward than treating distal bifurcation or trifurcation stenoses, which generally requires a greater degree of operator experience and expertise (1091). In addition, PCI of bifurcation disease is associated with higher restenosis rates than when disease is confined to the ostium or trunk (971,1092). Although lesion location influences technical success and long-term outcomes after PCI, location exerts a negligible influence on the success of CABG. In subgroup analyses, patients with left main CAD and a SYNTAX score ≥33 with more complex or extensive CAD had a higher mortality rate with PCI than with CABG (949). Physicians can estimate operative risk for all CABG candidates by using a standard instrument, such as the risk calculator from the STS database. The above considerations are important factors when choosing among revascularization strategies for unprotected left main CAD and have been factored into revascularization recommendations. Use of a Heart Team approach has been recommended in cases in which the choice of revascularization is not straightforward. As discussed in Section 5.9.5, the ability of the patient to tolerate and comply with DAPT is also an important consideration in revascularization decisions.

The 2005 PCI guideline (987) recommended routine angiographic follow-up 2 to 6 months after stenting for unprotected left main CAD. However, because angiography has limited ability to predict stent thrombosis and the results of SYNTAX suggest good intermediate-term results for PCI in subjects with left main CAD, this recommendation was removed in the 2009 STEMI/PCI focused update (3).

Experts have recommended immediate PCI for unprotected left main CAD in the setting of STEMI (983). The impetus for such a strategy is greatest when left main CAD is the site of the culprit lesion, antegrade coronary flow is diminished (e.g., TIMI flow grade 0, 1, or 2), the patient is hemodynamically unstable, and it is believed that PCI can be performed more quickly than CABG. When possible, the interventional cardiologist and cardiac surgeon should decide together on the optimal form of revascularization for these subjects, although it is recognized that these patients are usually critically ill and therefore not amenable to a prolonged deliberation or discussion of treatment options.

5.8. Proximal LAD Artery Disease

A cohort study (985) and a meta-analysis (412) from the 1990s suggested that CABG confers a survival advantage over contemporaneous medical therapy for patients with disease in the proximal segment of the LAD artery. Cohort studies and RCTs (412,1050,1062,1063,1065,1077,1093–1095) as well as collaborative analyses and meta-analyses (1080,1096–1098) showed that PCI and CABG result in similar survival rates in these patients.

See Online Data Supplements 6 and 14 for additional data on proximal LAD artery disease.

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5.9. Clinical Factors That May Influence the Choice of Revascularization

5.9.1. Completeness of Revascularization

Most patients undergoing CABG receive complete or nearly complete revascularization, which seems to influence long-term prognosis positively (1099). In contrast, complete revascularization is accomplished less often in subjects receiving PCI (e.g., in <70% of patients), and the extent to which the absence of complete initial revascularization influences outcome is less clear. Rates of late survival and survival free of MI appear to be similar in patients with and without complete revascularization after PCI. Nevertheless, the need for subsequent CABG is usually higher in those whose initial revascularization procedure was incomplete (compared with those with complete revascularization) after PCI (1100–1102).

5.9.2. LV Systolic Dysfunction

Several older studies and a meta-analysis of the data from these studies reported that patients with LV systolic dysfunction (predominantly mild to moderate in severity) had better survival with CABG than with medical therapy alone (365,412,999–1002). For patients with more severe LV systolic dysfunction, however, the evidence that CABG results in better survival compared with medical therapy is lacking. In the STICH trial of subjects with LVEF <35% with or without viability testing, CABG and GDMT resulted in similar rates of survival (death from any cause, the study's primary outcome) after 5 years of follow-up. For several secondary outcomes at this time point, including 1) death from any cause or hospitalization for heart failure, 2) death from any cause or hospitalization for cardiovascular causes, 3) death from any cause or hospitalization for any cause, or 4) death from any cause or revascularization with PCI or CABG, CABG was superior to GDMT. Although the primary outcome (death from any cause) was similar in the 2 treatment groups after an average of 5 years of follow-up, the data suggest the possibility that outcomes would differ if the follow-up were longer in duration; as a result, the study is being continued to provide follow-up for up to 10 years (355,410).

Only very limited data comparing PCI with medical therapy in patients with LV systolic dysfunction are available (1002). In several ways, these data are suboptimal, in that many studies compared CABG with balloon angioplasty, many were retrospective, and many were based on cohort or registry data. Some of the studies demonstrated a similar survival rate in patients having CABG and PCI (988,1080,1103–1105), whereas others showed that those undergoing CABG had better outcomes (964). The data that exist at present on revascularization in patients with CAD and LV systolic dysfunction are more robust for CABG than for PCI, although data from contemporary RCTs in this patient population are lacking. Therefore, the choice of revascularization in patients with CAD and LV systolic dysfunction is best based on clinical variables (e.g., coronary anatomy, presence of diabetes mellitus, presence of CKD), magnitude of LV systolic dysfunction, patient preferences, clinical judgment, and consultation between the interventional cardiologist and the cardiac surgeon.

5.9.3. Previous CABG

In patients with recurrent angina after CABG, repeat revascularization is most likely to improve survival in subjects at highest risk, such as those with obstruction of the proximal LAD artery and extensive anterior ischemia (1021–1025,1029–1032). Patients with ischemia in other locations and those with a patent LIMA to the LAD artery are unlikely to experience a survival benefit from repeat revascularization (1023).

Cohort studies comparing PCI and CABG among post-CABG patients report similar rates of mid- and long-term survival after the 2 procedures (1022,1024,1025,1029,1031,1032,1106). In the patient with previous CABG who is referred for revascularization for medically refractory ischemia, factors that may support the choice of repeat CABG include vessels unsuitable for PCI, number of diseased bypass grafts, availability of the internal mammary artery for grafting chronically occluded coronary arteries, and good distal targets for bypass graft placement. Factors favoring PCI over CABG include limited areas of ischemia causing symptoms, suitable PCI targets, a patent graft to the LAD artery, poor CABG targets, and comorbid conditions.

5.9.4. Unstable Angina/Non–ST-Elevation Myocardial Infarction

The main difference between management of the patient with SIHD and the patient with UA/NSTEMI is that the impetus for revascularization is stronger in the setting of UA/NSTEMI, because myocardial ischemia occurring as part of an ACS is potentially life threatening, and associated anginal symptoms are more likely to be reduced with a revascularization procedure than with GDMT (1107–1109). Thus, the indications for revascularization are strengthened by the acuity of presentation, the extent of ischemia, and the ability to achieve full revascularization. The choice of revascularization method is generally dictated by the same considerations used to decide on PCI or CABG for patients with SIHD.

5.9.5. DAPT Compliance and Stent Thrombosis: Recommendation

CLASS III: Harm

1. **PCI with coronary stenting (BMS or DES) should not be performed if the patient is not likely to be able to tolerate and comply with DAPT for the appropriate duration of treatment based on the type of stent implanted (1110–1113). *(Level of Evidence: B)***

The risk of stent thrombosis is increased dramatically in patients who prematurely discontinue DAPT, and stent thrombosis is associated with a mortality rate of 20% to 45% (1110). Because the risk of stent thrombosis with BMS is

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greatest in the first 14 to 30 days, this is the generally recommended minimum duration of DAPT therapy for these individuals. Consensus in clinical practice is to treat DES patients for ≥12 months with DAPT to avoid late (after 30 days) stent thrombosis (1110,1114). Therefore, the ability of the patient to tolerate and comply with ≥30 days of DAPT with BMS treatment and ≥12 months of DAPT with DES treatment is an important consideration in deciding whether to use PCI to treat patients with CAD.

5.10. Transmyocardial Revascularization

A single randomized multicenter comparison of TMR (with a holmium:YAG laser) plus CABG and CABG alone in patients in whom some myocardial segments were perfused by arteries considered not amenable to grafting (1026) showed a significant reduction in perioperative mortality rate (1.5% versus 7.6%, respectively), and the survival benefit of the TMR–CABG combination was present after 1 year of follow-up (1026). At the same time, a large retrospective analysis of data from the STS National Cardiac Database, as well as a study of 169 patients from the Washington Hospital Center who underwent combined TMR–CABG, showed no difference in adjusted mortality rate compared with CABG alone (1027,1115). In short, a TMR–CABG combination does not appear to improve survival compared with CABG alone. In selected patients, however, such a combination may be superior to CABG alone in relieving angina.

5.11. Hybrid Coronary Revascularization: Recommendations

CLASS IIa

1. **Hybrid coronary revascularization (defined as the planned combination of LIMA-to-LAD artery grafting and PCI of ≥1 non-LAD coronary arteries) is reasonable in patients with 1 or more of the following (1116–1122) *(Level of Evidence: B):***
   a. **Limitations to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI);**
   b. **Lack of suitable graft conduits;**
   c. **Unfavorable LAD artery for PCI (i.e., excessive vessel tortuosity or chronic total occlusion).**

CLASS IIb

1. **Hybrid coronary revascularization (defined as the planned combination of LIMA-to-LAD artery grafting and PCI of ≥1 non-LAD coronary arteries) may be reasonable as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk–benefit ratio of the procedures. *(Level of Evidence: C)***

Hybrid coronary revascularization, defined as the planned combination of LIMA-to-LAD artery grafting and PCI of ≥1 non-LAD coronary arteries (1123), is intended to combine the advantages of CABG (i.e., durability of the LIMA graft) and PCI (1124). Patients with multivessel CAD (e.g., LAD and ≥1 non-LAD stenoses) and an indication for revascularization are potentially eligible for this approach. Hybrid revascularization is ideal in subjects in whom technical or anatomic limitations to CABG or PCI alone may be present and for whom minimizing the invasiveness (and therefore the risk of morbidity and mortality) of surgical intervention is preferred (1118) (e.g., patients with severe preexisting comorbidities, recent MI, a lack of suitable graft conduits, a heavily calcified ascending aorta, or a non-LAD coronary artery unsuitable for bypass but amenable to PCI, and situations in which PCI of the LAD artery is not feasible because of excessive tortuosity or chronic total occlusions).

Hybrid coronary revascularization may be performed in a hybrid suite in one operative setting or as a staged procedure (i.e., PCI and CABG performed in 2 different operative suites, separated by hours to 2 days, but typically during the same hospital stay). Because most hospitals lack a hybrid operating room, staged procedures are usually performed. With the staged procedure, CABG before PCI is preferred, because this approach allows the interventional cardiologist to 1) verify the patency of the LIMA-to-LAD artery graft before attempting PCI of other vessels and 2) minimize the risk of perioperative bleeding that would occur if CABG were performed after PCI (i.e., while the patient is receiving DAPT). Because minimally invasive CABG may be associated with lower graft patency rates compared with CABG performed through a midline sternotomy, it seems prudent to angiographically image all grafts performed through a minimally invasive approach to confirm graft patency (1118).

To date, no RCTs involving hybrid coronary revascularization have been published. Over the past 10 years, several small, retrospective series of hybrid revascularization using minimally invasive CABG and PCI have reported low mortality rates (0% to 2%) and event-free survival rates of 83% to 92% at 6 to 12 months of follow-up. The few series that have compared the outcomes of hybrid coronary revascularization with standard CABG report similar outcomes at 30 days and 6 months (1116–1122).

5.12. Special Considerations

In addition to patients' coronary anatomy and LV function and whether they have undergone prior revascularization, clinical features such as the existence of coexisting chronic conditions might influence decision making. However, the paucity of information about special subgroups represents 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 individuals with diabetes mellitus or CKD are lacking. Moreover, clinicians are often guided by misconceptions and biases that serve to deprive patients of potentially beneficial therapies. ACCF/AHA guidelines for the management of patients with UA/NSTEMI (4,4a) address special subgroups by recommending that diagnostic, pharmacological and revascularization strategies be congruent with those in men, the young, and those without diabetes mellitus. This section echoes those management recommendations. Although this section will briefly review some special considerations in diagnosis and

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therapy in certain groups of patients, the general approach should be to apply the recommendations in this guideline consistently among groups.

5.12.1. Women

Women generally have a lower incidence of SIHD than men until older age, but their outcomes after MI are worse (1125). Microvascular disease, typically with preserved LV function, is more common among women, particularly those who are younger, whereas obstructive epicardial CAD is less prevalent. Up to 50% of women with typical or atypical anginal symptoms undergoing cardiac catheterization are found not to have obstructive CAD (1126,1127). Contrary to earlier perceptions, the prognosis of women with chest pain and nonobstructive disease is not necessarily better (1128,1129). As women age, the prevalence of obstructive CAD increases.

Stable angina is the most frequent initial manifestation of SIHD in women, as opposed to AMI and sudden death in men (35,1130). Atypical chest pain and angina-equivalent symptoms such as dyspnea are more common in women, although women still present with similar patterns, duration, and frequency of symptoms. The lower prevalence of obstructive disease in conjunction with technical challenges makes the interpretation of ischemia on imaging studies somewhat more difficult. Accumulating evidence suggests that vascular reactivity related to abnormalities in microvascular and endothelial function and possibly plaque erosion or distal microembolization contribute to ischemia to a greater extent in women than in men (75).

On exercise testing, ST-segment changes are less accurate for the detection of CAD in women than in men (175), although marked ST-segment changes (a visual interpretation ≥1 mm of horizontal or downsloping ST-segment depression or elevation for ≥60 to 80 ms after the end of the QRS complex) remain diagnostic for all patients. Challenges with exercise testing in women include their generally lower physical work capacity and the high prevalence of obesity, diabetes mellitus, frailty, and other comorbid conditions. Numerous reports (14,315,1131,1132) and an expert consensus statement (175) have examined the diagnostic accuracy of the exercise ECG and various imaging modalities in large cohorts of women. Overall, most reports document an improvement in diagnostic accuracy with imaging when compared to a standard exercise ECG (175), although that improvement does not necessarily translate into improved clinical outcomes (147). From a meta-analysis, the diagnostic sensitivity and specificity were 72% and 88% for women undergoing dobutamine stress echocardiography (149). From a small controlled clinical trial, diagnostic specificity was improved considerably when using gated Tc-99m myocardial perfusion SPECT over Tl-201 myocardial perfusion SPECT (92% versus 67%) because of improved image quality (1133). Overall, sensitivity and specificity of myocardial perfusion SPECT were reported as 88% and 96% for women (86,175,1134). For CMR, one study reported a diagnostic sensitivity and specificity of 92% and 80% with vasodilator stress magnetic resonance myocardial perfusion (281).

In part related to differing pathophysiology and clinical presentation, substantial differences in provision of clinical care have been observed between men and women with CAD (1135). Despite increasing recognition of the risks of worsening IHD and attendant complications in women, the frequency with which they are prescribed important risk-modifying therapies such as statins, aspirin, and beta blockers after episodes of ACS remains significantly lower than among men (1136,1137). Among patients with documented SIHD, however, the differences between men and women appear to be much smaller with regard to prescription of these therapies (1138).

Data from COURAGE suggest that the benefits of GDMT alone in comparison with GDMT plus PCI were similar for men and women (366,1138). Moreover, the outcomes of revascularization appear to be less favorable among women than men (1139–1142), although very few women were enrolled in COURAGE. In various risk models, the odds of in-hospital death after PCI have ranged from 25% to 80% higher for women than for men (1143–1147), although this trend might have improved in recent years after the higher incidence of diabetes mellitus and hypertension in women is taken into account (1148). The risk of procedural complications also appears to be significantly higher in women (1149). Although fewer data on the experience of women after CABG are available, in the New York State registry, the odds of in-hospital death for women were 2-fold higher than for men (1149,1150). On the basis of these observations, the initial approach to therapy for women with SIHD should be to prescribe a full regimen of GDMT and to reserve consideration of revascularization for patients who do not obtain a satisfactory response or who experience unacceptable adverse effects. On the basis of the higher risk associated with PCI in women, it might be reasonable to adopt a more conservative approach in undertaking this procedure than in men, although the general principle of using revascularization in patients whose symptoms are refractory to medical therapy and who are not satisfied with their current level of angina persists.

5.12.2. Older Adults

In older adults, often defined as >75 years of age, coronary stenoses are likely to be more diffuse and more severe, with a higher prevalence of 3-vessel and left main disease. Several factors complicate the diagnosis and treatment of SIHD in this age group. Common coexisting conditions of the pulmonary, gastrointestinal, and musculoskeletal systems can cause chest pain, making diagnosis more difficult, even in patients with documented IHD. Physiological changes in older adults, including alterations in cardiac output through various mechanisms, muscle loss and deconditioning, neuropathies, lung disease, and degenerative joint disease, make stress testing more difficult. Thus, many elderly patients are

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incapable of responding to graded increases in workload as required by standard exercise ECG protocols (118,1151). For patients who are unable to exercise, pharmacological stress imaging is indicated. Although the majority of investigations have focused on prognosis by markers of ischemia in the elderly, the results generally reveal a similar accuracy of testing when compared with younger individuals presenting with SIHD (1152–1155).

Baseline ECG changes, arrhythmias, and LV hypertrophy, which are more common in older adults who have accumulated cardiac comorbidities, also limit the value of stress testing (1156,1157). The higher prevalence of SIHD in older adults results in more tests that are falsely negative, and the prognostic value of the Duke treadmill score in older adults might be limited (1158).

Data based on RCTs to guide therapy in older adults are relatively sparse because of the common exclusion of older patients from early clinical trials. Several studies have shown less frequent use of evidence-based therapies in older adults, such as early invasive procedures, anticoagulants, beta blockers, and glycoprotein IIb/IIIa inhibitors (1156, 1159,1160). The findings are likely related to several factors. Pharmacotherapy is more difficult in older adults because of changes in drug bioavailability and elimination. Drug–drug interactions are more common because of polypharmacy. A more conservative approach to coronary angiography is often appropriate given the higher risk of contrast-induced nephropathy in older adults (1161). Moreover, the risks of morbidity and mortality associated with CABG are increased in older adults.

Despite the complexities and concerns related to evaluating and treating elderly patients with SIHD, findings from the COURAGE trial indicated that initial medical therapy was not significantly less effective than medical therapy plus PCI in relieving angina (73% in the GDMT group at 60 months, versus 80% in the medical therapy–plus–PCI group) (1162). Although the mortality rate was 50% higher among patients >65 years of age than among younger patients, there were no significant differences between the 2 treatment groups in either patients younger or older than 65 years. Furthermore, although the incidence of MI and stroke was also higher in older patients, there were no significant differences between treatment groups. In the TIME (Trial of Invasive versus Medical Therapy in the Elderly) trial, 301 patients ≥75 years of age with chronic angina with CCS Class II or higher despite treatment with ≥2 antianginal drugs were randomized to GDMT or to an invasive strategy of coronary angiography followed by revascularization with PCI or CABG, if feasible (1163). Patients who were assigned to the early revascularization group experienced greater improvement in symptoms at 6 months. This difference disappeared by 12 months, at which time both groups had shown a 2-class improvement in their CCS scores and similar results on other quality-of-life measures. It should be noted that 45% of the group assigned to medical therapy ultimately underwent revascularization because of refractory symptoms.

Considerable evidence indicates that elderly patients have higher mortality following PCI and CABG than do younger patients, and the risk appears to rise monotonically when >65 years of age (1144–1147,1164–1166). Compared with patients ≤65 years of age, adjusted odds of short-term mortality after PCI among patients between the ages of 60 and 80 have ranged from 2.2 to 7.6 in various registries, and the odds of death among those ≥80 years have ranged from 2.7 to >13. Unfortunately, far fewer data are available on the outcomes of elderly patients undergoing CABG, and much of it could be outdated. On the basis of data from 16,120 patients entered into the New York State registry, the odds of in-hospital mortality rose 8% per year of age >60 years (OR: 1.08; 95% CI: 1.06 to 1.09) (1150). On the other hand, in an analysis of 505,645 records from the registry maintained by the STS, age was not found to be a predictor of mortality (1167). In older studies, elderly patients were reported to have favorable results after CABG (1168,1169), and long-term survival rates for elderly patients with SIHD treated medically versus surgically were similar (406).

Older adults constitute a growing proportion of patients with SIHD. On the basis of the available data, it is recommended that management by GDMT be the initial approach in most patients. Given concerns about higher mortality rate, particularly in patients >75 or 80 years of age, decisions to recommend revascularization should be undertaken only after careful consideration of patient preferences, functional capacity, quality-of-life and end-of-life issues, as well as therapeutic alternatives (4,4a).

5.12.3. Diabetes Mellitus

Type 1 and type 2 diabetes mellitus are associated with a greater risk of SIHD, and the effects of other risk factors such as hypercholesterolemia are magnified (1170). Cardiovascular mortality rate is 3-fold higher in men with diabetes mellitus and between 2- and 5-fold higher in women with diabetes than in patients without diabetes mellitus (1171,1172). Sudden cardiac death occurs more frequently in patients with diabetes mellitus. Although direct evidence is lacking, asymptomatic ischemia could be more prevalent in patients with diabetes mellitus, possibly because of autonomic neuropathy (1173).

The risk of death in a patient with SIHD and diabetes mellitus has been equated to the risk of death in a patient with SIHD and a previous MI (1171,1174). Aggressive management of cardiovascular risk factors, including hypercholesterolemia, hypertension, smoking, low physical activity, and obesity, is essential, along with appropriate glycemic control.

Among patients with IHD, the presence of concomitant diabetes mellitus increases the risk of adverse events, irrespective of whether the patient is treated medically or with revascularization. Two studies have suggested that survival

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among patients with diabetes mellitus is more favorable after bypass surgery than with medical therapy, although these results are based on subgroup analyses from observational data (991,1175). Of 2 studies comparing PCI and medical therapy in patients with diabetes mellitus, one reported longer survival (1175), but the other did not (991).

A subgroup analysis of data from the BARI trial suggested that patients with diabetes mellitus who underwent CABG with 1 arterial conduit had improved survival compared with those who underwent PCI (368). Several retrospective cohort studies have compared outcomes among patients with diabetes mellitus undergoing PCI versus CABG. Three observational studies have reported a survival advantage for CABG over PCI, whereas a fourth found no significant difference, and no studies located reported better outcomes after PCI.

In the BARI 2D study, 2,368 patients with type 2 diabetes mellitus and SIHD were initially selected as candidates for either PCI or CABG on the basis of clinical and angiographic assessment and then were randomly assigned to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy (408). The study was not designed to compare PCI with CABG. At 5 years, overall survival was similar between the revascularization and medical-therapy groups (88.3% versus 87.8%), as was the incidence of MACE (77.2% versus 75.9%) (409). Patients with the most severe CAD were assigned to the CABG stratum and those with the least severe CAD to the PCI stratum. In the PCI stratum, there was no significant difference in primary endpoints between the revascularization group and the medical-therapy group. In the 763 patients randomized to the CABG stratum, survival was similar but AMI less frequent among those assigned to revascularization plus intensive medical therapy compared with intensive medical therapy (10.0% versus 17.6%; $p=0.003$), and the composite endpoints of all-cause death or MI (21.1% versus 29.2%; $p=0.010$) and cardiac death or MI ($p=0.03$) were also less frequent. Compared with those selected for PCI, patients in the CABG stratum had more 3-vessel disease (20% versus 52%), more total occlusions (32% versus 61%), more proximal LAD stenoses >50% (10% versus 19%), and a significantly higher myocardial jeopardy score (409).

One-year follow-up data from the SYNTAX study demonstrated a higher rate of repeat revascularization in patients with diabetes mellitus treated with PCI than in those treated with CABG, driven by a tendency for higher repeat revascularization rates in those with higher SYNTAX scores undergoing PCI (1006).

A large meta-analysis that included the BARI trial but not BARI 2D failed to identify any significant difference in mortality rate after CABG versus PCI for patients with diabetes mellitus (1079). In a more recent, collaborative analysis that pooled patient-level data from 10 randomized trials (again, not including BARI 2D), Hlatky and colleagues found that of the 1,233 patients with diabetes mellitus, 23% of those assigned to CABG died, compared with 29% of those assigned to PCI (1080). By contrast, of the 6,561 patients without diabetes mellitus, 13% and 14% died, respectively ($p=0.014$ for interaction). The interaction between diabetes mellitus and treatment remained highly significant after adjustment for multiple patient characteristics and after exclusion of patients enrolled in the BARI 2D trial.

Some evidence indicates that the presence of diabetes mellitus adversely affects the outcomes of revascularization. An analysis of the 2009 data on 7,812 patients (1,233 with diabetes mellitus) in 10 RCTs demonstrated a worse long-term survival rate in patients with diabetes mellitus after balloon angioplasty or BMS implantation than after CABG (1080). Analyses from 3 registries found significantly elevated adjusted ORs for short-term mortality after PCI that ranged from 1.25 to 1.54 in relation to patients without diabetes mellitus (1144,1146,1165). Data from the STS registry indicated that patients with diabetes mellitus on oral therapy had an adjusted OR of 1.15 for death within 30 days (95% CI: 1.09 to 1.21), as well as significantly higher odds of stroke, renal failure, or sternal wound infection than those of patients without diabetes mellitus (1167). For patients on insulin, the adjusted OR for death within 30 days was 1.50 (95% CI: 1.42 to 1.58), and the risks for other complications were also correspondingly higher.

In summary, in subjects requiring revascularization for multivessel CAD, current evidence supports diabetes mellitus as an important factor to consider when deciding on a revascularization strategy, particularly when complex or extensive CAD is present (Figure 14).

The basis of the currently available data, an intensive approach to reducing cardiovascular risk and symptoms in patients with diabetes mellitus by using GDMT should be the initial approach. For patients whose symptoms are inadequately managed or who experience intolerable adverse effects, revascularization should be considered. CABG might be associated with lower risk of mortality in patients with diabetes mellitus and multivessel disease than PCI, but this remains uncertain. The ongoing FREEDOM (Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial could help resolve this question (1177).

5.12.4. Obesity

Obese individuals frequently have reduced physical work capacity and exaggerated dyspnea on exertion. Furthermore, weight limits of exercise and imaging equipment preclude testing the very obese (1178,1179). Because of limitations in exercise testing and challenges with imaging through increased breast tissue or chest girth, reduced diagnostic accuracy has been reported for obese patients (1180). Because of breast tissue artifact, myocardial perfusion PET is more accurate than myocardial perfusion SPECT for the obese patient (191,193,323), although attenuation-correction algo-

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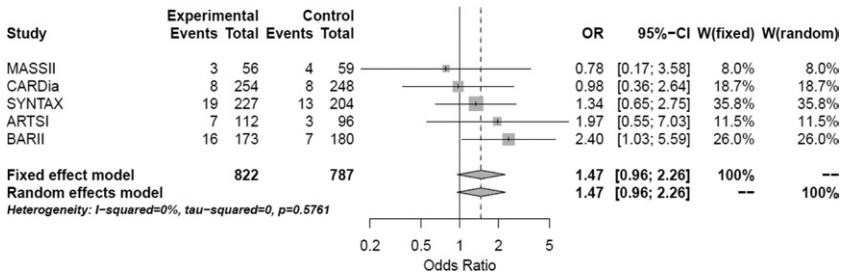

Figure 14. One-Year Mortality Rates in Randomized Trials of Patients With Diabetes and Multivessel CAD, Comparing PCI (Experimental) With CABG (Control)

An OR >1 suggests an advantage of CABG over PCI. ARTS1 indicates Arterial Revascularization Therapy Study I (1033); BARI I, Bypass Angioplasty Revascularization Investigation I (1005); CARDia, Coronary Artery Revascularization in Diabetes (1176); CI, confidence interval; DM, diabetes mellitus; MASS II, Medicine, Angioplasty, or Surgery Study II (1008); OR, odds ratio; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and W, weighted (1006).

rithms or prone imaging can help improve myocardial perfusion SPECT accuracy (187,188). Intravenous contrast enhancement improves image quality in obese patients and results in improved diagnostic certainty for stress echocardiography (181).

5.12.5. Chronic Kidney Disease

CKD confers greater risk for developing SIHD, for its progression, and for poor outcomes after interventions for AMI (1181–1183). The mortality rate for patients on hemodialysis is >20% per year, and approximately 50% of deaths among these patients are due to a cardiovascular cause (27,1184). To avoid worsening underlying kidney disease, physicians should consider creatinine clearance in pharmacotherapy and should apply risk scores for predicting the likelihood of contrast-induced nephropathy (1161,1185) in conjunction with the use of renal protective strategies such as isosmolar contrast agents during angiography (3,4,4a).

Unfortunately, studies evaluating the outcomes of revascularization in patients with renal disease have not applied a consistent definition of renal disease. Only one study identified by the writing committee used the Kidney Disease Outcome Quality Definition of renal disease grades: Stage 1, creatinine clearance of 90 to 120 mL/min; Stage 2, 60 to 89 mL/min; Stage 3, 30 to 59 mL/min; Stage 4, 15 to 29 mL/min; and Stage 5, <15 mL/min or ongoing dialysis (1186). Others studies simply described patients as receiving dialysis (1187,1188) or defined renal disease as any creatinine clearance <60 mL/min (1189,1190) or any serum creatinine above approximately 2.3 mg/dL (1191,1192). Ongoing studies are beginning to use the AKIN (Acute Kidney Injury Network) or RIFLE (Risk, Injury, Failure, Loss, and End-stage) criteria and should ensure more consistency in the study of periprocedural complications of percutaneous revascularization.

Among patients who were enrolled in the COURAGE trial, the presence of CKD was associated with odds of 1.48 for death, MI, or new heart failure relative to patients without kidney disease (1193). Medical therapy, however, was effective and associated with the same BP and lipid levels as in patients without CKD. Patients with CKD also experience significant and sustained improvement in angina with both PCI and GDMT, and there was no significant interaction between the presence of CKD and treatment assignment in survival rate, incidence of AMI, or improvement in symptoms.

To date, randomized comparisons of coronary revascularization (with CABG or PCI) and medical therapy in patients with CKD have not been reported. Some, but not all, observational studies or subgroup analyses have demonstrated an improved survival rate with revascularization compared with medical therapy in patients with CKD and multivessel CAD (1191,1193,1194), despite the fact that the incidence of periprocedural complications (e.g., death, MI, stroke, infection, renal failure) is higher in patients with CKD than in those without renal dysfunction. In 2 cohort studies involving patients with a spectrum of kidney disease ranging from mild to severe, adjusted survival was superior for those who underwent bypass surgery compared with those who received only medical therapy (1191,1194). In 1 study, survival after PCI was improved (compared with medical therapy) in patients with mild, moderate, or severe kidney disease but not in those with end-stage kidney disease. The other study yielded opposite results, with longer survival after PCI in patients with end-stage renal disease but *not* in those with mild, moderate, or severe kidney disease.

Some studies have shown that CABG is associated with a greater survival benefit than PCI among patients with severe renal dysfunction (1187–1192,1194). Five studies have suggested that survival is prolonged among patients with CKD after CABG compared with after PCI (1187,1188,1191,1192,1194), whereas 3 other studies indicated that survival is similar after either of the 2 revascularization strategies, regardless of the severity of underlying renal disease (1189,1190,1192).

5.12.6. HIV Infection and SIHD

HIV infection appears to be associated with an increased risk of premature coronary and cerebrovascular atherosclerosis, which is often accelerated, diffuse, and circumferen-

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tial, involving whole arteries (1195,1196). AMI is often the initial manifestation (1197). The etiology is likely multifactorial and related to both the underlying infection and antiretroviral therapy. The former appears to promote proliferation of smooth muscle cells and elastin leading to luminal obstruction, although there is poor correlation between CD4 cell counts and severity of CAD. Of the therapeutic agents used to treat HIV infection, protease inhibitors in particular have been epidemiologically linked to dyslipidemia and insulin resistance (1198–1200). The protease inhibitors amprenavir/fosamprenavir with or without ritonavir and lopinavir with ritonavir have the strongest association with risk of AMI, although saquinavir and nelfinavir do not appear to be associated with MI (1201,1202). The nucleoside reverse-transcriptase inhibitors didanosine and abacavir also are associated with risk of AMI (1202). Other agents, such as nonnucleoside reverse-transcriptase inhibitors (nevirapine and efavirenz), entry inhibitors, and integrase inhibitors, do not appear to be associated with an increased risk of IHD.

Despite the increase in prevalence of IHD among patients with HIV, the absolute increase in incidence of AMI is relatively low, and overall mortality does not appear to be increased (1198,1203). It is likely that this reflects the otherwise enormous benefit conferred by treatment with highly active antiretroviral therapy in the course of HIV infection. Nonetheless, patients receiving highly active antiretroviral therapy should be assessed for cardiovascular risk factors and monitored for signs and symptoms of IHD. It is prudent to recommend a healthy diet, regular physical activity, and avoidance of smoking. Patients with hypercholesterolemia should be managed in a fashion similar to other patients at risk for IHD (1204).

5.12.7. Autoimmune Disorders

Connective tissue disease represents a less well-studied issue in SIHD. In rheumatoid arthritis, findings from at least one study show increased inflammation in the coronary artery walls, with increased frequency of vulnerable plaques (1205). Accelerated atherosclerosis in systemic lupus erythematosis, due to impaired endothelial function and novel atherogenic and thrombotic risk factors, requires special attention inasmuch as the adjusted rate of SIHD in systemic lupus erythematosis is ≥50-fold higher than in patients without it (1206,1207). A younger population is more frequently affected in systemic lupus erythematosis (1208), and coronary artery spasm is a frequent complication in connective tissue disease (1209).

5.12.8. Socioeconomic Factors

Low socioeconomic status is highly associated with the risk of cardiovascular disease (1210). Men 30 to 59 years of age with low socioeconomic status are at 55% higher risk of death due to IHD than are those of higher status (RR: 1.55; 95% CI: 1.51 to 1.60), and the risk is >2-fold higher among women (RR: 2.13; 95% CI: 1.98 to 2.29) (1211).

In addition to lower socioeconomic status being associated with a higher prevalence of IHD, it has been amply demonstrated that patients of lower socioeconomic status and those who are members of an ethnic or racial minority (in particular African Americans and Hispanics) are less likely to receive a wide variety of diagnostic and therapeutic interventions. These disparities have been observed with regard to cardiac procedures as well as access to cardiologists (1212). Moreover, African Americans and Hispanics are 10% to 40% less likely to receive outpatient secondary prevention therapies for cardiovascular disease (1213). Although lower rates of diagnostic and interventional services have not been adequately explained (1214,1215), it is clear that individuals of lower socioeconomic status and ethnic minorities typically have fewer healthcare resources, have worse general health and cardiac risk profiles, and are less knowledgeable about SIHD symptoms. Healthcare providers and systems should strive to eliminate or ameliorate barriers to care for patients who have SIHD and are of low socioeconomic class or ethnic minorities.

5.12.9. Special Occupations

Although not recommended for the general population, routine surveillance with functional testing is recommended in a few occupations in which the presence of even asymptomatic cardiac disease could endanger others, such as commercial pilots, police, firefighters, and bus drivers. The general parameters of test performance noted above apply in these circumstances, with the caveat that most of these individuals are at low risk and therefore could be more likely to have false positive results.

6. Patient Follow-Up: Monitoring of Symptoms and Antianginal Therapy

The goals of clinical follow-up of patients with SIHD are to maximize function and to minimize long-term mortality and morbidity. In this context, the primary goal of follow-up testing should be to reassess residual or new ischemic burden in the setting of persistent or worsening (but not unstable) symptoms. Thus, follow-up assessment and testing will vary according to the clinical status of the patient and with the evolution of evidence-based practice. Unnecessary testing should be avoided. For patients with SIHD who show no change in symptoms or functional capacity, periodic follow-up serves multiple purposes:

- Ongoing reassessment of adherence to and effectiveness of the therapeutic regimen, including clinical response, occurrence of adverse effects, and treatment goals, on the basis of evolving scientific evidence and preferences of the patient.
- Evaluation of the effectiveness of interventions to modify risk factors such as exertional hypertension.

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- Assessment of the status of coexisting chronic medical conditions that could directly or indirectly affect the management of stable cardiac ischemia.

Patients with SIHD who have accelerating symptoms or decreasing functional capacity require prompt reassessment. Patients with SIHD who develop new ACS should be evaluated and treated according to established guidelines (3,4,4a,9,10). Patients who have been treated for an ACS (i.e., AMI or UA) within the previous 6 months and who develop chest pain within 30 days of the AMI should be evaluated according to the STEMI or UA/NSTEMI guidelines as warranted (2–4,4a). Patients who have undergone revascularization with either PCI or CABG within 6 months should be monitored according to the PCI and CABG guidelines (9,10). Patients with SIHD should be evaluated before elective or emergent surgery according to established perioperative guidelines (4,4a,9,10).

6.1. Clinical Evaluation, Echocardiography During Routine, Periodic Follow-Up: Recommendations

CLASS I

1. Patients with SIHD should receive periodic follow-up, at least annually, that includes all of the following *(Level of Evidence: C)*:
   a. Assessment of symptoms and clinical function;
   b. Surveillance for complications of SIHD, including heart failure and arrhythmias;
   c. Monitoring of cardiac risk factors; and
   d. Assessment of the adequacy of and adherence to recommended lifestyle changes and medical therapy.
2. Assessment of LVEF and segmental wall motion by echocardiography or radionuclide imaging is recommended in patients with new or worsening heart failure or evidence of intervening MI by history or ECG. *(Level of Evidence: C)*

CLASS IIb

1. Periodic screening for important comorbidities that are prevalent in patients with SIHD, including diabetes mellitus, depression, and CKD, might be reasonable. *(Level of Evidence: C)*
2. A resting 12-lead ECG at 1-year or longer intervals between studies in patients with stable symptoms might be reasonable. *(Level of Evidence: C)*

CLASS III: No Benefit

1. Measurement of LV function with a technology such as echocardiography or radionuclide imaging is not recommended for routine periodic reassessment of patients who have not had a change in clinical status or who are at low risk of adverse cardiovascular events (117). *(Level of Evidence: C)*

Standard risk-assessment tools that have been developed from clinical and laboratory evaluation of ambulatory populations with suspected CAD, as discussed in detail in Section 2 of this guideline, include patients who have noncardiac causes of presenting symptoms. However, the performance of these same tools in predicting short-term and long-term risk for coronary mortality and coronary events might vary in patients with known SIHD as compared with patients without known disease who present with chest pain syndromes that might or might not represent angina. Although mortality and morbidity rates intuitively might be considered to be higher in patients with documented as opposed to suspected CAD, evidence-based medical management, including adherence to appropriate lifestyle changes, and possibly appropriate revascularization in patients with ACS or patients identified as high risk with worsening clinical status or persistent symptoms despite GDMT, might explain the generally low mortality risk that has been found in several studies of patients with established SIHD (57,58,366,1216,1217). The incidence of adverse events during longitudinal follow-up of SIHD has declined and can be expected to vary with evolving medical management and with accruing information about the outcomes of revascularization (295,898,1163,1217–1219).

Although data on serial testing are limited, one approach to identifying candidates for follow-up testing is to apply prognostic scores for detection of patients with SIHD who are at high risk of MACE. The findings of studies that have examined the prognostic value of testing among patients with known stable CAD who are receiving contemporary GDMT (306,1220–1223) could provide clues for identifying candidates and appropriate intervals for follow-up testing. In the TIBET (Total Ischemic Burden European Trial) study group, which comprised 682 patients with stable angina and positive exercise ECG tests, adverse outcome was predicted by time to ischemia during exercise, prior infarction or prior CABG, ECG evidence for LV hypertrophy, and LV enlargement by echocardiography (58). Easily available clinical characteristics have been the strongest predictors of risk during follow-up of patients with SIHD in other studies. The Euro Heart Survey found that a score based on the cumulative presence of comorbidity, diabetes mellitus, severity of angina, onset of recurrent symptoms <6 months previously, abnormal ventricular function, and resting ECG repolarization abnormalities was associated with an increase in the 1-year risk of death or nonfatal infarction that ranged nearly 100-fold (from 0.5% to 47%) among >3,000 outpatients (57). The ACTION (A Coronary Disease Trial Investigating Outcome with Nifedipine Gastrointestinal Therapeutic System) trial derived a clinical risk score that separated 5-year risk of death, MI, or stroke from 4% to 35% in >7,300 patients with stable angina on the basis of commonly available clinical variables. In order of decreasing importance, the variables included age, LVEF, smoking, white blood cell count, presence of diabetes mellitus, casual (any time of day without regard to time since the last meal) blood glucose concentration, creatinine, prior stroke, frequent angina, findings at coronary angiography, lipid-lowering treatment, QT interval on the resting ECG, systolic hypertension, number of drugs used for angina, prior infarction, and sex (1216). Because the populations enrolled in these studies varied and the results have not been independently validated, additional prospective studies of patients with established SIHD are required to establish appropriate follow-up evaluation strat-

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egies and to establish efficient time intervals for evaluation in stable patients (307,320,1223,1224).

6.2. Follow-Up of Patients With SIHD

Standard risk assessment tools that have been developed from clinical and laboratory evaluation of ambulatory populations with suspected CAD, as discussed in detail in Section 2 of this guideline, include patients who have noncardiac causes of presenting symptoms. Estimates of the likelihood of future cardiac events using the Framingham score (508,1225), which was derived from populations that included large numbers of low-risk individuals without disease in their low-risk subsets, are not generally useful when applied to patients with known SIHD. In fact, prediction of risk for coronary mortality and coronary events during short-term and long-term follow-up of patients with SIHD differs from risk stratification in less-ascertained populations with chest pain syndromes. Although mortality and morbidity rates intuitively might be considered to be higher in patients with documented as opposed to suspected IHD, several circumstances serve to confound this assumption. Patients at highest risk, for example, are often identified and aggressively treated during the course of ACS or during initial risk assessment of chest pain. After being treated, asymptomatic patients are typically at low risk for adverse events. Moreover, patients with recognized SIHD could be more likely to receive and adhere to effective therapies than are those whose disease has not been documented. Finally, patients who have been stable for long periods of time could be less prone to development of ACS than are newly ascertained patients with SIHD. Thus, evidence-based medical management, including adherence to appropriate lifestyle changes and possibly appropriate revascularization in patients with ACS or patients identified as high risk with worsening clinical status or persistent symptoms despite GDMT, could explain the generally low mortality risk that has been found in several studies of patients with established but stable SIHD (57,58,366,1216,1217). Moreover, large trials conducted during the past decade have shown a declining mortality rate among patients with established SIHD (295,898,1163,1217,1218). Accordingly, risk could change with advances in therapy and patient management, and these advances could alter risk-prediction models.

A key component in following up patients with SIHD is to systematically and reproducibly monitor their symptoms and functional status. This should be done, at a minimum, yearly and ideally at each visit. Even though the CCS classification system is the most common metric with which to quantify patients' symptoms and function, as noted previously, it is limited by being from the physician's perspective rather than the patient's. Moreover, it has limitations in its reproducibility and interrater reliability. To obtain a valid, reliable, reproducible, and sensitive assessment of patients' symptoms, function, and quality of life from patients' perspectives, the SAQ can be used (435,1226). The SAQ is a 19-item, self-reported questionnaire that takes approximately 5 minutes for most patients to complete and explicitly quantifies patients' angina frequency, recent changes in their angina, their physical limitations due to angina, their satisfaction with treatment, and their perceptions of how their angina limits their quality of life. Scores on the SAQ have been shown to be associated with subsequent survival. ACS admissions and costs (246,247,1227) can be integrated into prognostic models to identify patients warranting more aggressive treatment because of an adverse prognosis. In the CADENCE (Coronary Artery Disease in General Practice) study, conducted in 207 primary care clinics throughout Australia (1228), Beltrame and colleagues found wide variation in anginal symptoms according to the SAQ. Routine use of the SAQ has been endorsed as a performance measure of quality in SIHD (407,436).

6.2.1. Focused Follow-Up Visit: Frequency

Patients with SIHD should receive regular follow-up to monitor symptoms and progression or complications of disease. Regular visits with a healthcare provider are also necessary to evaluate patients' adherence to and effectiveness of therapy as well as occurrence of any adverse effects. Although there are scant data on which to base a definitive recommendation, the writing committee recommends a clinical follow-up evaluation every 4 to 12 months. A more precise interval cannot be recommended because many factors influence the length of the follow-up period, including sharing of care by family physicians, internists, and cardiologists, which will vary with regional practice patterns, patient preference, and physician availability. During the first year of therapy, evaluations every 4 to 6 months are recommended. After the first year of therapy, evaluations every 6 to 12 months are recommended if the patient is stable and reliable enough to call or make an appointment when symptoms or functional capacity become worse. Limited data from observational studies indicate that outcomes might be better for patients who receive follow-up from a cardiologist (1229,1230). When patients are managed jointly by their primary care physician and cardiologist, effective communication between physicians is essential. This ultimately will be facilitated by effective implementation of accessible electronic medical records. Periodic office visits can be supplemented by telephone, e-mail, or other types of contact between the patient and the healthcare team.

6.2.2. Focused Follow-Up Visit: Interval History and Coexisting Conditions

Although follow-up of patients with SIHD often is focused on periodic testing, the most crucial element is a careful interval history. Key elements of the history are:

- Changes in physical activity or symptoms;
- Response to therapy, adverse effects, and adherence to recommendations; and
- Development of relevant, new chronic conditions or changes in existing conditions.

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Symptomatic change and decreasing functional capacity are important markers for increased risk in patients with SIHD, particularly with increasing age and additional comorbidities. The evaluation of symptoms should be detailed and directed, as many patients are reluctant to volunteer such information. It should be noted whether patients have reduced their activity, perhaps in an effort to ameliorate anginal symptoms or as a symptom of ventricular dysfunction. The adverse prognostic importance of frequent, typical angina in patients with SIHD is evident in both older and newer studies of risk (57,126,127,1231,1232). Motivation and compliance with risk-reduction measures should be carefully assessed. In particular, assistance with smoking cessation by means of a structured program might be necessary for some patients. Careful attention must be paid to concomitant conditions, such as hypertension, diabetes mellitus, dyslipidemia, heart failure, and depression.

6.2.3. Focused Follow-Up Visit: Physical Examination

The physical examination should be directed according to the patient's history. Every patient should have weight, BP, and heart rate measured. BMI and waist circumference can provide signs of additional risk. Signs of heart failure, such as elevated jugular venous pressure, hepatojugular reflux, pulmonary crackles, new murmurs or gallops, or edema, should be sought. The vascular examination should identify any change in peripheral pulses or new bruits. Coexistence of SIHD with extracranial carotid disease makes palpation and auscultation of the carotid arteries particularly important, and examination of the abdomen should include special attention to bruits or abnormally prominent pulsations of the abdominal aorta.

6.2.4. Focused Follow-Up Visit: Resting 12-Lead ECG

An ECG is necessary when there is a change in anginal pattern, symptoms or findings suggestive of a dysrhythmia or conduction abnormality, and near or frank syncope. It is important to recognize that periodic recording of the standard 12-lead ECG has clinical value that is independent of diagnostic and prognostic content: It provides a baseline waveform against which tracings taken during symptoms reasonably can be compared. Because many patients with SIHD have resting repolarization abnormalities, absence of a timely tracing for comparison with a tracing taken during atypical symptoms can lead to overdiagnosis of acute ischemia (1233,1234). Conversely, repolarization abnormalities during symptoms that might be new or significantly more marked can also be consistent with old disease and lead to underdiagnosis or undertreatment of unstable disease (1235). New repolarization abnormalities during serial study have been shown to predict cardiovascular events during the longitudinal study of hypertensive patients in the Framingham Heart Study (318). A study of hypertensive patients that included a subgroup with established SIHD also demonstrated an increased risk of cardiovascular endpoints after the development of new repolarization changes during serial evaluation (318,1236). Although there are no prospective randomized data demonstrating that intervention based on routine, periodic evaluation of the ECG alone will alter outcomes in patients with SIHD, pending such evidence, the clinical value of a change in the resting ECG is widely accepted. In patients with established SIHD, a change in a periodically obtained ECG can be the only evidence of intercurrent silent infarction, inadequately treated hypertension, or complex arrhythmia that would modify treatment. The timing between routine recordings of the 12-lead ECG that would be required and adequate to accomplish these purposes has not been established, but a consensus recommendation based on expert opinion and common practice would be not greater than once yearly for stable patients with SIHD, as well as at the time of any clinical change.

6.2.5. Focused Follow-Up Visit: Laboratory Examination

Patients not known to have diabetes mellitus should have a fasting blood glucose measurement every 3 years to detect new-onset diabetes mellitus, and those with established diabetes mellitus should have glycosylated hemoglobin measured at least annually to assess glycemic control. A lipid profile should be obtained as clinically warranted. Long-term studies (up to 7 years) demonstrate sustained benefit from continued therapy (18,318). Measurement of creatinine kinase also could be appropriate at these times. In circumstances in which the patient is not concurrently followed up by a primary care physician, measurements of hemoglobin, thyroid function, serum electrolytes, and renal function should be obtained annually, or sooner when prompted by a change in symptoms or signs.

6.3. Noninvasive Testing in Known SIHD

For any patients with known SIHD who have recurrent but stable symptoms after having been symptom free for a period of time on GDMT or after revascularization and who do not fall into any of the categories listed in the previous paragraph, the concepts underlying the recommendations for "Noninvasive Testing for Diagnosis of SIHD" from Section 2.2 generally apply, with the modifications and special consideration discussed below.

6.3.1. Follow-Up Noninvasive Testing in Patients With Known SIHD: New, Recurrent, or Worsening Symptoms Not Consistent With Unstable Angina: Recommendations

See Table 20 for a summary of recommendations from this section.

6.3.1.1. PATIENTS ABLE TO EXERCISE

CLASS I

1. Standard exercise ECG testing is recommended in patients with known SIHD who have new or worsening symptoms not consistent with UA and who have a) at least moderate physical functioning and no disabling comorbidity and b) an interpretable ECG (114,145–147). *(Level of Evidence: B)*

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Table 20. Follow-Up Noninvasive Testing in Patients With Known SIHD: New, Recurrent, or Worsening Symptoms Not Consistent With UA

Test	Exercise Status		ECG Interpretable		COR	LOE	References	Additional Considerations
	Able	Unable	Yes	No				
Patients able to exercise*								
Exercise ECG	X		X		I	B	(114,145–147)	
Exercise with nuclear MPI or Echo	X			X	I	B	(172,276,278,284,306,313,314,320,324,327–329,1237–1240)	
Exercise with nuclear MPI or Echo	X		Any		IIa	B	(1241,1242)	• Prior requirement for imaging with exercise • Known or at high risk for multivessel disease
Pharmacological stress nuclear MPI/Echo/CMR	X		X		III: No Benefit	C	(333)	
Patients unable to exercise								
Pharmacological stress nuclear MPI or Echo		X	Any		I	B	(148–150,152–156)	
Pharmacological stress CMR		X	Any		IIa	B	(280,281,283)	
Exercise ECG		X		X	III: No Benefit	C	N/A	
Irrespective of ability to exercise								
CCTA	Any		Any		IIb	B	(1244–1248)	Patency of CABG or coronary stent ≥3 mm diameter
CCTA	Any		Any		IIb	B	(158,161,1244)	In the absence of known moderate or severe calcification and intent to assess coronary stent <3 mm in diameter
CCTA	Any		Any		III: No Benefit	B	(1244–1248)	Known moderate or severe native coronary calcification or assessment of coronary stent <3 mm in diameter in patients who have new or worsening symptoms not consistent with UA

*Patients are candidates for exercise testing if they are capable of performing at least moderate physical functioning (i.e., moderate household, yard, or recreational work *and* most activities of daily living) and have no disabling comorbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.

CABG indicates coronary artery bypass graft surgery; CCTA, cardiac computed tomography angiography; CMR, cardiac magnetic resonance; COR, class of recommendation; ECG, electrocardiogram; Echo, echocardiography; LOE, level of evidence; MPI, myocardial perfusion imaging; N/A, not available; SIHD, stable ischemic heart disease; and UA, unstable angina.

2. Exercise with nuclear MPI or echocardiography is recommended in patients with known SIHD who have new or worsening symptoms not consistent with UA and who have a) at least moderate physical functioning or no disabling comorbidity but b) an *un*interpretable ECG (172,276,278,284,306,313,314,320,324,327–329,1237–1240). *(Level of Evidence: B)*

CLASS IIa

1. Exercise with nuclear MPI or echocardiography is reasonable in patients with known SIHD who have new or worsening symptoms not consistent with UA and who have a) at least moderate physical functioning and no disabling comorbidity, b) previously required imaging with exercise stress, or c) known multivessel disease or high risk for multivessel disease (1241,1242). *(Level of Evidence: B)*

CLASS III: No Benefit

1. Pharmacological stress imaging with nuclear MPI, echocardiography, or CMR is not recommended in patients with known SIHD who have new or worsening symptoms not consistent with UA and who are capable of at least moderate physical functioning or have no disabling comorbidity (333). *(Level of Evidence: C)*

6.3.1.2. PATIENTS UNABLE TO EXERCISE

CLASS I

1. Pharmacological stress imaging with nuclear MPI or echocardiography is recommended in patients with known SIHD who have new or worsening symptoms not consistent with UA and who are incapable of at least moderate physical functioning or have disabling comorbidity (148–150,152–156). *(Level of Evidence: B)*

CLASS IIa

1. Pharmacological stress imaging with CMR is reasonable in patients with known SIHD who have new or worsening symptoms not consistent with UA and who are incapable of at least moderate physical functioning or have disabling comorbidity (280,281,283). *(Level of Evidence: B)*

CLASS III: No Benefit

1. Standard exercise ECG testing should not be performed in patients with known SIHD who have new or worsening symptoms not consistent with UA and who a) are incapable of at least

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moderate physical functioning or have disabling comorbidity or b) have an *un*interpretable ECG. *(Level of Evidence: C)*

6.3.1.3. IRRESPECTIVE OF ABILITY TO EXERCISE

CLASS IIb

1. CCTA for assessment of patency of CABG or of coronary stents 3 mm or larger in diameter might be reasonable in patients with known SIHD who have new or worsening symptoms not consistent with UA, irrespective of ability to exercise (1244–1248). *(Level of Evidence: B)*
2. CCTA might be reasonable in patients with known SIHD who have new or worsening symptoms not consistent with UA, irrespective of ability to exercise, in the absence of known moderate or severe calcification or if the CCTA is intended to assess coronary stents less than 3 mm in diameter (158,161,1244). *(Level of Evidence: B)*

CLASS III: No Benefit

1. CCTA should not be performed for assessment of native coronary arteries with known moderate or severe calcification or with coronary stents less than 3 mm in diameter in patients with known SIHD who have new or worsening symptoms not consistent with UA, irrespective of ability to exercise (1244–1248). *(Level of Evidence: B)*

See Online Data Supplement 1 for additional data on noninvasive testing in known SIHD: recurrent or worsening symptoms.

Strategies for the selection and use of noninvasive testing in the evaluation of new or worsening symptoms in patients with documented SIHD are similar to those in suspected SIHD. As always, in patients with interpretable rest ECGs who are capable of exercise, treadmill exercise ECG testing remains the first choice. Whenever possible, initial and follow-up testing should be performed with the same stress and imaging techniques so that any interval change can be attributed more reliably to alterations in clinical status rather than mere differences in technique. Loss of the ability to exercise on follow-up testing, in and of itself, suggests deterioration in functional and clinical status. In general, the diagnostic accuracy of stress testing is similar in patients with and without known SIHD (Section 2.2.3). A few meta-analyses examining the effect of prior MI on diagnostic accuracy have found that the specificity of exercise ECG was higher in mixed populations (145), whereas the diagnostic performance of exercise echocardiography was reduced. In contrast, the specificity of exercise SPECT was increased because of the predictive value of total stress perfusion abnormalities, which includes both the risk of ischemia plus infarcted myocardium (91). Although CMR LGE imaging detects MI, current evidence indicates that assessment of myocardial ischemia provides incremental diagnostic (1249) and prognostic value above LGE detection of infarction (284) in patients with or without known SIHD.

In contrast to stress testing, the diagnostic value of CCTA differs in patients with and without known CAD. Limitations of image quality relating to coronary calcification, coronary stents, or vascular clips can reduce diagnostic accuracy, and revascularization also affects results. The large caliber of venous conduits facilitates the assessment of patients who have undergone CABG with CCTA and has sensitivities of 89% to 98% and specificities of 89% to 97% for the identification of >50% diameter stenoses in grafts on invasive coronary angiography (1244–1246). The accurate evaluation of coronary stents with CCTA depends on the material and diameter of the stent, with image artifacts related to the stents' metallic structure preventing assessment of 9% to 11% of stents (1247,1248). Typically, stents >3 mm in diameter can be assessed (1248), with sensitivities for detecting a >50% diameter in-stent restenosis on invasive coronary angiography of 86% to 94% and specificities of 91% to 93%.

6.3.2. Noninvasive Testing in Known SIHD—Asymptomatic (or Stable Symptoms): Recommendations

See Table 21 for a summary of recommendations from this section.

CLASS IIa

1. Nuclear MPI, echocardiography, or CMR with either exercise or pharmacological stress can be useful for follow-up assessment at 2-year or longer intervals in patients with SIHD with prior evidence of silent ischemia or who are at high risk for a recurrent cardiac event and a) are unable to exercise to an adequate workload, b) have an *un*interpretable ECG, or c) have a history of incomplete coronary revascularization (10,12,15). *(Level of Evidence: C)*

CLASS IIb

1. Standard exercise ECG testing performed at 1-year or longer intervals might be considered for follow-up assessment in patients with SIHD who have had prior evidence of silent ischemia or are at high risk for a recurrent cardiac event and are able to exercise to an adequate workload and have an interpretable ECG. *(Level of Evidence: C)*
2. In patients who have no new or worsening symptoms or no prior evidence of silent ischemia and are not at high risk for a recurrent cardiac event, the usefulness of annual surveillance exercise ECG testing is not well established. *(Level of Evidence: C)*

CLASS III: No Benefit

1. Nuclear MPI, echocardiography, or CMR, with either exercise or pharmacological stress or CCTA, is not recommended for follow-up assessment in patients with SIHD, if performed more frequently than at a) 5-year intervals after CABG or b) 2-year intervals after PCI (10,12,15). *(Level of Evidence: C)*

See Online Data Supplement 1 for additional data on noninvasive testing in known SIHD: asymptomatic (or stable symptoms).

6.3.3. Factors Influencing the Use of Follow-Up Testing

The appropriateness of performing noninvasive testing in patients who either are asymptomatic or have stable symptoms (i.e., routine surveillance testing) depends on factors related to the likelihood of significant findings, such as the patient's risk for rapidly advancing disease, propensity to have silent ischemia, and length of time since revasculariza-

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Table 21. Noninvasive Testing in Known SIHD: Asymptomatic (or Stable Symptoms)

Test	Exercise Status		ECG Interpretable		Pretest Probability of Ischemia	COR	LOE	References	Additional Considerations
	Able*	Unable	Yes	No					
Exercise or pharmacological stress with nuclear MPI, Echo, or CMR at ≥2-y intervals		X		X	Prior evidence of silent ischemia or high risk for recurrent cardiac event. Meets criteria listed in additional considerations.	IIa	C	(10,12,15)	a) Unable to exercise to adequate workload or b) *Un*interpretable ECG or c) History of incomplete coronary revascularization
Exercise ECG at ≥1-y intervals	X		X		Any	IIb	C	N/A	a) Prior evidence of silent ischemia OR b) At high risk for recurrent cardiac event
Exercise ECG	X		X		No prior evidence of silent ischemia and not at high risk of recurrent cardiac event.	IIb	C	N/A	For annual surveillance
Exercise or pharmacological stress with nuclear MPI, Echo, or CMR or CCTA	Any		Any		Any	III: No Benefit	C	(10,12,15)	a) <5-y intervals after CABG, or b) <2-y intervals after PCI

*Patients are candidates for exercise testing if they are capable of performing at least moderate physical functioning (i.e., moderate household, yard, or recreational work *and* most activities of daily living) and have no disabling comorbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.

CABG indicates coronary artery bypass graft surgery; CCTA, cardiac computed tomography angiography; CMR, coronary magnetic resonance; COR, class of recommendation; CCTA, computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiogram; Echo, echocardiography; LOE, level of evidence; MPI, myocardial perfusion imaging; N/A, not available; PCI, percutaneous coronary intervention; and SIHD, stable ischemic heart disease.

tion. The data supporting follow-up testing are sparse and insufficient to support routine, repeat testing in asymptomatic individuals. However, evidence exists that persistent ischemia on testing is a prognostically poor finding. Exploratory data from a small cohort of 314 patients with SIHD enrolled in the COURAGE trial nuclear substudy revealed that a reduction in the ischemic myocardium is associated with an (unadjusted) reduction in the incidence of death or MI combined (306). In the BARI 2D trial, at 1 year of follow-up, more extensive and severe stress myocardial perfusion SPECT abnormalities were associated with higher rates of death or MI (276).

There are, however, several circumstances in which a decision to perform follow-up testing is thought to be warranted in the absence of a change in clinical status, although data supporting this approach are limited. These circumstances include, but are not limited to, evaluation of incomplete revascularization, assessment of the adequacy of medical therapy by provocative exercise testing, a substantial change in risk profile, or the need to reevaluate coronary status in anticipation of major noncardiovascular surgery when the patient's exercise capacity is limited or unknown (although revascularization in this circumstance has not been shown to reduce the risk of perioperative cardiovascular complications), as detailed in the ACCF/AHA Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery Guideline (1250). Care should be taken when interpreting paired testing results to incorporate not only the change in the extent and severity of ischemia but also the workload at onset and total exercise capacity achieved, as these factors relate to the patient's symptom burden and functional correlates in daily life. Outside of such special circumstances, routine periodic testing is not recommended in patients who are at low risk for progression or had overt symptoms on initial presentation (i.e., those without known silent ischemia) or very early after revascularization. In addition to a lack of evidence for testing to detect ischemia, currently there is also little research to support exercise stress testing for risk assessment in asymptomatic patients with known CAD, except for cardiac rehabilitation and exercise prescription purposes (Section 4.4.1.4).

6.3.4. Patient Risk and Testing

By using clinical, noninvasive, and invasive data acquired during the initial evaluation and subsequently, recommendations about stress testing in patients with known SIHD can be formulated on the basis of the following considerations: In the absence of a change in clinical status, patients with a low projected annual mortality rate (<1%) are those with low-risk Duke treadmill scores, either without imaging or with negative imaging findings, whose 4-year cardiovascular survival rate approximates 99%. The low-risk category also includes patients with normal stress imaging who lack adverse prognostic characteristics, such as diabetes mellitus or prior MI. Younger women without diabetes mellitus or a prior MI who have normal stress nuclear MPI remain at very low risk for as long as 7 to 9 years (307), depending on specific clinical characteristics, and probably do not require repeat stress imaging during that period in the absence of changes in clinical status (307).

Data are more limited with regard to the value of serial testing strategies in patients at intermediate risk of cardiac mortality (1% to 3% per year). Follow-up testing probably should be performed only if decisions about a change in pharmacological management, level of exercise, or revascularization will be influenced directly by the test result or if the patient has persistent symptoms despite adequate GDMT. Thus, in the patient with known SIHD, the goal

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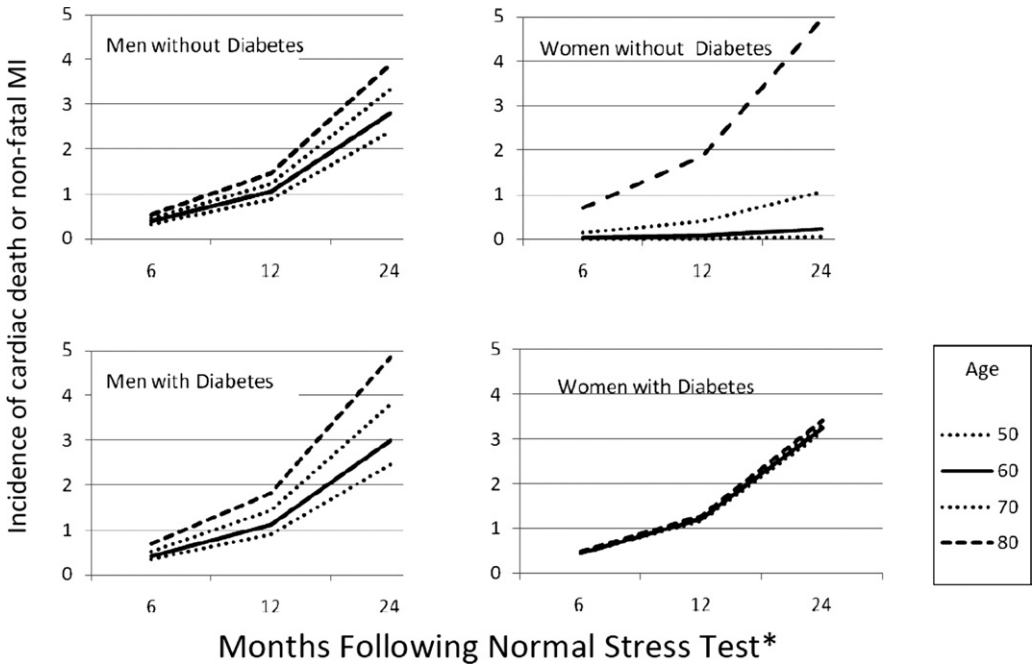

Figure 15. Incidence of Cardiac Death or Nonfatal MI During Follow-Up After a Normal Stress MPI

Adapted with permission from Hachamovitch et al. (327). MI indicates myocardial infarction; MPI, myocardial perfusion imaging.

of repeat testing is the assessment of residual ischemic burden after optimization of GDMT or the consideration of revascularization as a result of failed optimal medical management. Furthermore, to be considered significant, findings should be outside the expected range of variability of test results, which is approximately 5% for stress nuclear MPI (306,366), such that patients move into a higher or lower risk category.

Even for high-risk patients, the value of annual exercise testing (or serial exercise testing at alternative intervals) in the absence of a change in symptoms has not been studied adequately. Yearly exercise testing could be useful in patients with SIHD who have >3% risk of mortality per year, because a marked decrease in exercise capacity or a marked increase in ischemic burden can warrant reevaluation of the medical regimen or interventional plan. Examples of such patients are those with a high-risk Duke treadmill score, patients with an EF <50% and significant CAD in >1 major vessel, patients with diabetes mellitus, and those with multivessel disease who have not undergone CABG. Some data also suggest that ischemic burden might be useful in targeting ischemia-guided revascularization. In a substudy of the COURAGE trial, the overall event-free survival rate was 86.6% in patients with ≥5% reduction in ischemic myocardium versus 75.3% in those without significant reduction in ischemic burden after 6 to 18 months (unadjusted p=0.037; adjusted p=0.26) (306). Although this trial substudy was not powered to examine differences in clinical outcomes, the results are similar to the BARI 2D trial, in which patients with high myocardial jeopardy scores randomized to CABG had fewer cardiovascular events (AMI and composite endpoint of all-cause mortality or MI and cardiac death or MI) than those with high scores who received only medical therapy (276,409).

6.3.5. Stability of Results After Normal Stress Testing in Patients With Known SIHD

The durability of information gained from a stress test over time varies widely according to the characteristics of the patients and the type of test performed. Among patients with several clinical risk factors and negative stress imaging studies, the relative hazard for cardiac death or MI can increase after a 2-year follow-up time period, whereas among other groups, the risk remains low through 2 years and can be safely assumed to remain low for an extended period of time. In 1 large single-site study, the factors associated with an earlier increase in risk included diabetes mellitus, male sex, increased age (i.e., ≥70 years), a history of previous MI or revascularization, and having undergone a pharmacological stress test rather than an exercise test (327) (Figure 15). The relationships were, however, complex and covarying. Importantly, among patients who were younger and female and did not have diabetes mellitus or a history of MI or revascularization, the annual risk of adverse cardiovascular events was predicted to remain <1% for as long as 9 years, on the basis of hard events observed during the 2-year follow-up period. In contrast, in an 80-year-old man with a normal pharmacological stress study, the risk of an adverse event rose to >1% in <1 year after an index-negative perfusion evaluation.

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6.3.6. Utility of Repeat Stress Testing in Patients With Known CAD

The interpretation of repeat testing should be based on a threshold change value that exceeds the expected variability in test results, even in patients at high risk for recurrent events, and especially in those with no interval clinical change (1244). Although the variability of exercise and stress testing results is not well established (306,1251), factors such as differences in day-to-day operations in the same laboratory, interobserver variability, and differences between practices in different imaging laboratories are important contributory factors in observed differences in serial testing. A 5% change in the percent of ischemic myocardium (based on extent and severity) has been suggested by some investigators as a threshold that indicates clinically significant change for stress nuclear MPI (306,1251). The findings from different exercise or stress imaging modalities (echocardiography versus nuclear MPI) can be even more difficult to compare, such that clinicians should use the same imaging modality over time whenever possible. Despite these concerns, significant changes in risk category (such as shifting to a lower- or higher-risk patient subset) may be used to guide interpretability of interval change in repeat testing (306,333), and the presence of significant interval change can alter risk assessment. For example, in the ACME (Angioplasty Compared to Medicine) trial, patients whose exercise nuclear MPI normalized after 6 months of randomized treatment had an improved survival rate (92%) compared with those with persistent ischemia (82%, $p=0.02$) (333). The ongoing technical evolution within imaging modalities is, in part, aimed at minimizing intraobserver, interobserver, and intertest variability.

6.3.7. Future Developments

Numerous opportunities to improve the diagnosis and management of SIHD remain. Large registries have the potential to improve the diagnosis of IHD and to assess risk according to clinical information and results from noninvasive testing. Risk-assessment strategies from older databases should be updated with modern information and statistical techniques. Technical development across all cardiac imaging modalities continues to evolve rapidly, often outpacing the ability to perform rigorous clinical validation and application. Current and anticipated technical developments of CT scanners and software are intended to improve the spatial and temporal resolution of cardiac CT images while reducing the radiation dose received from a typical examination. They include wider detector arrays that allow higher numbers of simultaneously acquired image slices, faster x-ray tube rotation times, and the use of alternative image reconstruction techniques that target image noise, all of which could improve the diagnostic value of CCTA in currently challenging scenarios, such as calcified coronary arteries and coronary stents. The improvement also will foster the study and clinical use of newer applications of cardiac CT, such as coronary plaque characterization, late enhancement imaging for the detection of myocardial scar, and MPI to detect myocardial ischemia (1252). Efforts currently under way to obtain perfusion information from CCTA images are promising (196–201), with one report also calculating FFR with CCTA (195). Moreover, plaque quantification software is in development and could further guide accurate detection of atherosclerotic disease burden (1253).

Several new developments in stress nuclear MPI have occurred, including new radioisotopes: 1) an F18 PET perfusion agent (in Phase III trials), which will allow exercise PET testing; 2) ^{123}I-beta-methyl-iodophenylpentadecanoic acid SPECT, with the unique ability to document metabolic alterations representing prior ischemic episodes (i.e., ischemic memory); and 3) ^{123}I-labeled meta-iodobenzylguanidine SPECT, which could be helpful for assessment of arrhythmic risk in SIHD patients (1254). Several new SPECT cameras also have been introduced into the marketplace and offer the opportunity for improved image quality within a substantially shorter time period and with a lower radiation dose (1255,1256). Several studies have correlated atherosclerotic plaque characteristics with the extent of ischemic myocardium by stress nuclear MPI (202–206,215). Finally, the diagnostic and prognostic value of PET flow reserve data is currently under intense investigation (185,1257).

Echocardiography, being the most portable and widely available stress imaging technique, has developed novel methods that are promising in the assessment of SIHD patient. Speckle-tracking echocardiography provides a 2-dimensional, angle-independent, real-time evaluation of myocardial strain and has been shown to detect myocardial ischemia incremental to wall motion analysis (1258,1259). Recent reports of contrast echocardiography MPI during vasodilating stress indicate that it is a potentially robust and clinically viable tool in detection of CAD (1260). Finally, 3-dimensional techniques can provide an improved assessment of cardiac size and function in patients with SIHD.

Increasing recognition of the ability of CMR to accurately assess abnormal myocardial physiology of CAD by combined imaging of rest and stress ventricular function, perfusion, and myocardial viability is expected to increase its use in SIHD (172,1261,1262). With rapid data acquisition by parallel imaging, real-time cine, or sub-second single-shot imaging methods, a diagnostically adequate CMR can be obtained without the need for patient breath-holding or ECG gating (1263). A routine CMR assessment of CAD can be achieved in <30 minutes. These developments likely will improve diagnostic consistency and patient throughput of CMR. CMR myocardial perfusion and LGE imaging for ischemia and scar, respectively, have improved image quality at 3.0T field strength compared to 1.5T and have been shown to improve diagnostic accuracy in detecting CAD (1264). Whole-heart 3-dimensional coronary magnetic resonance angiography with navigator respiratory-gating has

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shown promising pilot results and is being evaluated in clinical trials (1265,1266).

Further studies on lipid management are warranted to ascertain the optimal drug regimens for patients with SIHD. Questions remain as to the optimal dose of statins and the effectiveness of combining lipid-lowering medications. In addition, studies that establish the effectiveness of CABG in comparison with contemporary GDMT are necessary, as are studies that better define the relative benefits of different revascularization techniques. (Figure 13).

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Key Words: cardiovascular diagnostic techniques ■ coronary artery disease ■ coronary stenosis ■ minimally invasive surgical procedures ■ myocardial ischemia ■ myocardial revascularization ■ prognosis ■ risk factors ■ stable angina.

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT): 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS GUIDELINES 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)*	Veterans Health Administration—Director, Office of Analytics and Business Intelligence; University of Washington—Professor of Medicine and of Health Services; Head, Division of General Internal Medicine	None	None	None	None	None	None	None
Julius M. Gardin *(Vice Chair)*	Hackensack University Medical Center—Professor and Chairman, Department of Internal Medicine	• Arena Pharmaceuticals (Expired Dec. 2008) • AstraZeneca (Expired Dec. 2009) • Bristol-Myers Squibb (Expired Dec. 2009) • CV Therapeutics (Expired Dec. 2007) • Pfizer (Expired Dec. 2009) • Sanofi-aventis (Expired 2009) • Takeda (Expired Dec. 2007)	• Bristol-Myers Squibb (Expired Dec. 2009) • CV Therapeutics (Expired Dec. 2007) • Pfizer (Expired Dec. 2009) • Takeda (Expired Dec. 2007)	None	• Merck (Expired Dec. 2009)	None	None	4.4.1.1 4.4.1.2 4.4.1.3 4.4.1.5 4.4.2.1 4.4.2.2 4.4.2.3 4.4.3.1 4.4.4
Jonathan Abrams	University of New Mexico, Office of CME—Professor of Medicine (Cardiology)	None	None	None	None	None	None	None
Kathleen Berra	Stanford Prevention Research Center—Clinical Trial Director	• Boehringer Ingelheim • CV Therapeutics • Gilead Sciences • Novartis‡ • Pfizer	• Sanofi-aventis	None	• Kai Pharmaceuticals	• PCNA—Board Member‡	None	4.4.1.1 4.4.1.2 4.4.2.1 4.4.2.2 4.4.2.3 4.4.3.1

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Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
James C. Blankenship	Geisinger Medical Center—Director Cardiology; Director Cardiac Catheterization Laboratory	None	• Sanofi-aventis	None	• Abiomed • AstraZeneca • Boston Scientific • Conor Medsystems • Kai Pharmaceutical • Novartis • Schering-Plough • The Medicines Company	None	None	4.4.2.1
Apostolos P. Dallas	Carilion Roanoke Memorial Hospital—Director of Continuing Medical Education	None	None	• GlaxoSmithKline† • Johnson & Johnson† • Novartis† • Sanofi-aventis†	None	None	None	4.4.1.1 4.4.1.2 4.4.1.3 4.4.1.6 4.4.2.1 4.4.2.2 4.4.2.3 4.4.3.1
Pamela S. Douglas	Duke University Medical Center—Ursula Geller Professor of Research in Cardiovascular Diseases	None	None	None	• Novartis‡	None	None	4.4.1.1 4.4.1.2 4.4.1.3 4.4.2.3
JoAnne M. Foody	Harvard Medical School—Associate Professor; Brigham and Women's/ Faulkner Hospitals	• Abbott • Amarin • Gilead • Merck • Novartis • Pfizer • Sanofi-aventis	None	None	None	None	None	2.2.2.2 2.2.3.3 3.2.2.6 4.4.1.1 4.4.1.2 4.4.1.3 4.4.3.1.4
Thomas C. Gerber	Mayo Clinic—Radiology, Professor of Medicine	None	None	None	None	None	None	None
Alan L. Hinderliter	University of North Carolina: Division of Cardiology—Associate Professor	None	None	None	None	None	None	None
Spencer B. King III	Saint Joseph's Heart and Vascular Institute—President; Saint Joseph's Health System—Executive Director Academic Affairs	• Medtronic (Expired June 2007)†	None	None	None	• Merck (DSMB) • Wyeth Pharmaceuticals (DSMB)	None	4.4.2.1 4.4.2.2 4.4.2.3 4.4.3.1
Paul D. Kligfield	Cornell Medical Center—Professor of Medicine	• Cardiac Science • GE Healthcare • MDS Pharma Services† • Mortara Instrument • Philips Medical Systems	None	None	None	None	None	2.2.1 2.2.4.2 2.2.4.3 3.2.2 6.1
Harlan M. Krumholz	Yale University School of Medicine—Harold H. Hines, Jr. Professor of Medicine and Epidemiology and Public Health	None	None	None	None	None	None	None
Raymond Y.K. Kwong	Brigham & Women's Hospital Medicine, Cardiovascular Division—Instructor of Medicine	None	None	None	None	None	None	None
Michael J. Lim	St. Louis University—Associate Professor of Medicine; Division of Cardiology, Interim Director; J. Gerard Mudd Cardiac Catheterization Laboratory, Director	• Bristol-Myers Squibb • Cordis • Sanofi-aventis • Schering-Plough	None	None	None	None	None	4.4.1.1 4.4.1.2 4.4.1.3 4.4.2.1.1 4.4.2.3
Jane A. Linderbaum	Mayo Clinic—Assistant Professor of Medicine	None	None	None	None	None	None	None
Michael J. Mack	The Heart Hospital Baylor Plano—Director	None	None	None	None	None	None	None
Mark A. Munger	University of Utah College of Pharmacy—Professor Pharmacotherapy and Internal Medicine; Associate Dean, Academic Affairs	None	• Gilead	None	• Novartis†	None	None	4.4.3.1
Richard L. Prager	University of Michigan Hospitals and Health Centers—Professor of Surgery, Section of Cardiac Surgery	None	None	None	None	None	None	None

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Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Joseph F. Sabik	Cleveland Clinic Foundation—Professor of Surgery	• Medtronic • Novo Nordisk	None	None	None	None	None	4.4.1.3
Leslee J. Shaw	Emory University School of Medicine—Professor of Medicine	None	None	None	• Bracco Diagnostics†	None	None	3.2.2.6.
Joanna D. Sikkema	University of Miami School of Nursing	None	• AstraZeneca	None	None	None	None	4.4.1.1 4.4.1.2
Craig R. Smith, Jr	Columbia University—Chairman, Department of Surgery	None	None	None	None	None	None	None
Sidney C. Smith, Jr	Center for Cardiovascular Science and Medicine—Professor of Medicine; Director	• Eli Lilly (Expired July 2007) • Sanofi-aventis (Expired Sept. 2009)	• AstraZeneca (Expired Nov. 2009) • Bayer (Expired Oct. 2009) • Fornier (Expired May 2009) • Sanofi-aventis (Expired Nov. 2009)	None	• GlaxoSmithKline (DSMB) (Expired March 2009)	None	None	4.4.2.1
John A. Spertus	MidAmerica Heart Institute of St. Luke's Hospital—Director, Outcomes Research; University of Missouri–Kansas City	• Gilead	None	None	• BMS/sanofi-aventis† • Cordis† • Eli Lilly† • Johnson & Johnson† • Roche Diagnostics‡	None	None	4.4.1.1 4.4.1.2 4.4.1.3 4.4.3.1 6.3.1
Sankey V. Williams	Hospital of the University of Pennsylvania—Solomon Katz Professor of General Medicine, Division of General Internal Medicine	None	None	• Johnson & Johnson • Merck	None	None	None	4.4.1.1 4.4.1.2 4.4.1.3 4.4.1.5 4.4.1.6 4.4.2.1 4.4.2.2 4.4.2.3

This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the–Solomon Katz Professor of General Medicine voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Writing committee members are required to recuse from voting on sections to which their specific relationships with industry and other entities could apply. Section numbers apply to the full-text guideline (2). †Significant relationship. ‡No financial benefit.

The current guideline was developed during the transition in RWI policy and occurred over an extended period of time. In the interest of transparency, we provide full information on RWI existing over the entire period of guideline development, including delineation of relationships that expired >24 months before the guideline was finalized.

CV indicates cardiovascular; DSMB, data safety and monitoring board; and SAQ, Seattle Angina Questionnaire.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT): 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH STABLE ISCHEMIC HEART DISEASE

Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ralph G. Brindis	Official Reviewer—ACCF Board of Trustees	None	None	None	None	None	None
Timothy D. Henry	Official Reviewer—AHA	• CV Therapeutics • Sanofi-aventis	None	None	• Baxter* • CV Therapeutics*	None	None
Judith S. Hochman	Official Reviewer—ACCF/AHA Task Force on Practice Guidelines	• Eli Lilly • GlaxoSmithKline	None	None	• Johnson & Johnson • Merck		
Robert H. Jones	Official Reviewer—STS	None	None	None	None	None	None
Janet B. Long	Official Reviewer—PCNA	None	• AstraZeneca	None	None	None	None
Bruce W. Lytle	Official Reviewer—AATS	None	None	None	None	None	None
Douglass A. Morrison	Official Reviewer—SCAI	None	None	None	None	None	None
E. Magnus Ohman	Official Reviewer—AHA	• Abiomed • Datascope • Inovise* • Liposcience • The Medicines Company • Response Biomedical	• CV Therapeutics* • The Medicines Company*	Inovise*	• Bristol-Myers Squibb* • Daiichi-Sankyo* • Eli Lilly* • The Medicines Company* • Millennium Pharmaceuticals* • Sanofi-aventis* • Schering-Plough*	None	None
Douglas K. Owens	Official Reviewer—ACP	• GE Healthcare*	None	None	None	None	None
Paul Poirier	Official Reviewer—ACCF Board of Governors	None	None	None	None	None	None

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Joyce L. Ross	Official Reviewer—PCNA	• Kaneka America	• Abbott • AstraZeneca* • Bristol-Myers Squibb • Oscient • Pfizer • Sanofi–aventis	None	None	None	None
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Kim A. Eagle	Content Reviewer	None	None	None	None	None	None
Gordon A. Ewy	Content Reviewer	None	None	None	None	None	None
Victor Ferrari	Content Reviewer—ACCF Imaging Council	None	None	None	None	None	None
Raymond J. Gibbons	Content Reviewer	• Cardiovascular Clinical Studies • Lantheus Medical Imaging • Medscape • Molecular Insight • TherOx	None	None	• Velomedix*	None	None
Linda Gillam	Content Reviewer—ACCF Imaging Council	• Abbott Vascular • Edwards Lifesciences	None	None	None	• Core Lab Services	None
Robert A. Guyton	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	• Edwards Lifesciences	None	None
L. David Hillis	Content Reviewer	None	None	None	None	None	None
David R. Holmes	Content Reviewer—ACCF Interventional Scientific Council	None	None	None	None	None	None
Hani Jneid	Content Reviewer—AHA Council on Clinical Cardiology	None	None	None	None	None	None
Sanjay Kaul	Content Reviewer	None	None	None	None	None	None
Howard C. Lewin	Content Reviewer—ACCF Imaging Council	None	None	• Positron Imaging Partners	None	None	None
Todd D. Miller	Content Reviewer—AHA Council on Clinical Cardiology	• The Medicines Company • TherOx	None	None	• Kai Pharmaceuticals • King Pharmaceuticals • Lantheus Medical Imaging • Molecular Insight Pharmaceuticals	None	None
L. Kristin Newby	Content Reviewer—AHA Council on Clinical Cardiology	• Adolor • Biovascular • CV Therapeutics • Inverness Medical • Johnson & Johnson • Novartis • Roche Diagnostics	• Daiichi-Sankyo	None	• AstraZeneca • BG Medicine • Carvio Dx* • GlaxoSmithKline* • Medicare* • Millennium Pharmaceuticals • Schering-Plough*	None	None
Elizabeth Ross	Content Reviewer	None	None	None	None	None	None
William S. Weintraub	Content Reviewer	• AstraZeneca* • Bayer* • Bristol-Myers Squibb • Cardionet • Eli Lilly • Pfizer* • Sanofi-aventis • Shionogi	None	None	• Abbott* • AstraZeneca* • Bristol-Myers Squibb* • Otsuka* • Sanofi-aventis*	None	• 2004; Defendant; Aprotinin • 2008; Defendant; Quetiapine • 2008; Defendant; Celebrex

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships noted in this table are modest unless otherwise noted.

*Significant relationship.

AATS indicates American Association for Thoracic Surgery; ACCF, American College of Cardiology Foundation; ACP, American College of Physicans; AHA, American Heart Association; NIH, National Institutes of Health; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Interventions and Angiography; and STS, Society of Thoracic Surgeons.

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APPENDIX 3. ABBREVIATIONS LIST

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
AMI = acute myocardial infarction
ARB = angiotensin-receptor blocker
AV = atrioventricular
BMI = body mass index
BMS = bare-metal stent
BP = blood pressure
CABG = coronary artery bypass graft
CAC = coronary artery calcium
CAD = coronary artery disease
CCS = Canadian Cardiovascular Society
CCTA = coronary/cardiac computed tomography angiography
CKD = chronic kidney disease
CMR = cardiac magnetic resonance
CT = computed tomography
DAPT = dual antiplatelet therapy
DES = drug-eluting stent
ECG = electrocardiogram
EDTA = ethylene diamine tetraacetic acid
EECP = enhanced external counterpulsation
EF = ejection fraction
FDA = U.S. Food and Drug Administration
FFR = fractional flow reserve
GDMT = guideline-directed medical therapy
HbA1c = hemoglobin A1c
HDL = high-density lipoprotein
HIV = human immunodeficiency virus
IHD = ischemic heart disease
LAD = left anterior descending
LBBB = left bundle-branch block
LDL = low-density lipoprotein
LGE = late gadolinium enhancement
LIMA = left internal mammary artery
LV = left ventricular
LVEF = left ventricular ejection fraction
MACE = major adverse cardiac event
MET = metabolic equivalent
MI = myocardial infarction
MPI = myocardial perfusion imaging
NSTEMI = non–ST-elevation myocardial infarction
PAD = peripheral artery disease
PCI = percutaneous coronary intervention
PET = positron emission tomography
PHQ = Patient Health Questionnaire
RCT = randomized controlled trial
SAQ = Seattle Angina Questionnaire
SIHD = stable ischemic heart disease
SPECT = single-photon emission computed tomography
STEMI = ST-elevation myocardial infarction
TMR = transmyocardial revascularization
UA = unstable angina
UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction

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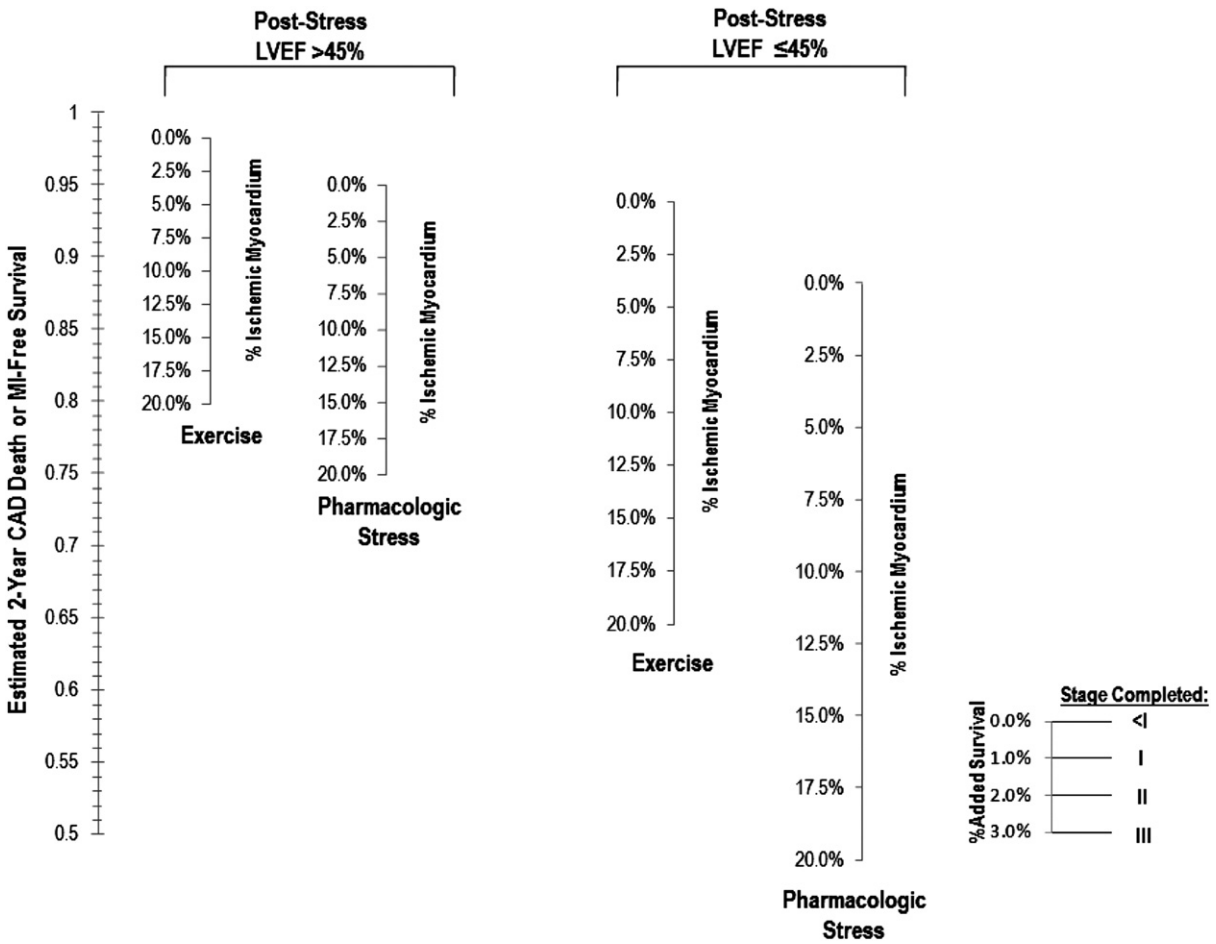

Appendix 4. Nomogram for Estimating 2-Year CAD Event-Free Survival (i.e., Freedom From CAD Death or Nonfatal MI) by Using Percent Ischemic Myocardium in Intermediate-Likelihood Patients by Post-Stress LV

CAD indicates coronary artery disease, LVEF, left ventricular ejection fraction; MI, myocardial infarction; and SPECT, single-photon emission computed tomography. Reproduced with permission from Shaw et al. (276).

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