JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 78, NO. 22, 2021

PUBLISHED BY ELSEVIER

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain

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

Writing Committee Members*

Martha Gulati, MD, MS, FACC, FAHA, *Chair*†
Phillip D. Levy, MD, MPH, FACC, FAHA, *Vice Chair*†
Debabrata Mukherjee, MD, MS, FACC, FAHA, *Vice Chair*†

Ezra Amsterdam, MD, FACC†
Deepak L. Bhatt, MD, MPH, FACC, FAHA†
Kim K. Birtcher, MS, PharmD, AACC‡
Ron Blankstein, MD, FACC, MSCCT§
Jack Boyd, MD†
Renee P. Bullock-Palmer, MD, FACC, FAHA, FASE, FSCCT†
Theresa Conejo, RN, BSN, FAHA‖
Deborah B. Diercks, MD, MSc, FACC¶
Federico Gentile, MD, FACC#
John P. Greenwood, MBChB, PhD, FSCMR, FACC**
Erik P. Hess, MD, MSc†
Steven M. Hollenberg, MD, FACC, FAHA, FCCP††
Wael A. Jaber, MD, FACC, FASE‡‡
Hani Jneid, MD, FACC, FAHA§§
José A. Joglar, MD, FAHA, FACC‡
David A. Morrow, MD, MPH, FACC, FAHA†
Robert E. O'Connor, MD, MPH, FAHA†
Michael A. Ross, MD, FACC†
Leslee J. Shaw, PhD, FACC, FAHA, MSCCT†

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information.
†ACC/AHA Representative.
‡ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison.
§Society of Cardiovascular Computed Tomography Representative.
‖Lay Patient Representative.
¶Society for Academic Emergency Medicine Representative.
#Former ACC/AHA Joint Committee member; current member during the writing effort.
**Society for Cardiovascular Magnetic Resonance Representative.
††American College of Chest Physicians Representative.
‡‡American Society of Echocardiography Representative.
§§Task Force on Performance Measures, Liaison.

This document was approved by the American College of Cardiology Clinical Policy Approval Committee in May 2021, the American Heart Association Science Advisory and Coordinating Committee in May 2021, the Society of Cardiovascular Computed Tomography in July 2021, the Society for Academic Emergency Medicine in June 2021, the Society for Cardiovascular Magnetic Resonance in June 2021, the American College of Chest Physicians in June 2021, the American Society of Echocardiography in June 2021, the American Heart Association Executive Committee in July 2021, and the American College of Cardiology Science and Quality Committee in July 2021.

The American College of Cardiology requests that this document be cited as follows: Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, Diercks DB, Gentile F, Greenwood JP, Hess EP, Hollenberg SM, Jaber WA, Jneid H, Joglar JA, Morrow DA, O'Connor RE, Ross MA, Shaw LJ. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 78(22):e187-e285.

This article has been copublished in *Circulation*.

Copies: This document is available on the websites of the American College of Cardiology (www.acc.org) and the American Heart Association (professional.heart.org). For copies of this document, please contact the Elsevier Inc. Reprint Department via fax (212-633-3820) or e-mail (reprints@elsevier.com).

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2021.07.053

JACC VOL. 78, NO. 22, 2021
NOVEMBER 30, 2021:e187–e285

ACC/AHA Joint Committee Members

Patrick T. O'Gara, MD, MACC, FAHA, *Chair*
Joshua A. Beckman, MD, MS, FAHA, FACC, *Chair-Elect*
Glenn N. Levine, MD, FACC, FAHA, *Immediate Past Chair*#

Sana M. Al-Khatib, MD, MHS, FACC, FAHA#
Anastasia L. Armbruster, PharmD, FACC
Kim K. Birtcher, MS, PharmD, AACC#
Ralph G. Brindis, MD, MPH, MACC#
Joaquin E. Cigarroa, MD, FACC#
Lisa de las Fuentes, MD, MS, FASE, FAHA
Anita Deswal, MD, MPH, FACC, FAHA
Dave L. Dixon, PharmD, FACC#
Lee A. Fleisher, MD, FACC, FAHA#
Federico Gentile, MD, FACC#
Zachary D. Goldberger, MD, MS, FACC, FAHA#
Bulent Gorenek, MD, FACC
Norrisa Haynes, MD
Adrian F. Hernandez, MD
Mark A. Hlatky, MD, FACC, FAHA#
John S. Ikonomidis, MD, PhD, FAHA#
José A. Joglar, MD, FAHA, FACC
W. Schuyler Jones, MD, FACC
Joseph E. Marine, MD, FACC#
Daniel B. Mark, MD, MPH, FACC
Debabrata Mukherjee, MD, MS, FACC, FAHA
Latha P. Palaniappan, MD, MS, FAHA, FACC
Mariann R. Piano, RN, PhD, FAHA
Tanveer Rab, MD, FACC
Barbara Riegel, PhD, RN, FAHA#
Erica S. Spatz, MD, MHS, FACC
Jacqueline E. Tamis-Holland, MD, FACC
Duminda N. Wijeysundera, MD, PhD#
Y. Joseph Woo, MD, FAHA, FACC

#Former ACC/AHA Joint Committee member; current member during the writing effort.

ABSTRACT

AIM This clinical practice guideline for the evaluation and diagnosis of chest pain provides recommendations and algorithms for clinicians to assess and diagnose chest pain in adult patients.

METHODS A comprehensive literature search was conducted from November 11, 2017, to May 1, 2020, encompassing randomized and nonrandomized trials, observational studies, registries, reviews, and other evidence conducted on human subjects that were published in English from PubMed, EMBASE, the Cochrane Collaboration, Agency for Healthcare Research and Quality reports, and other relevant databases. Additional relevant studies, published through April 2021, were also considered.

STRUCTURE Chest pain is a frequent cause for emergency department visits in the United States. The "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain" provides recommendations based on contemporary evidence on the assessment and evaluation of chest pain. This guideline presents an evidence-based approach to risk stratification and the diagnostic workup for the evaluation of chest pain. Cost-value considerations in diagnostic testing have been incorporated, and shared decision-making with patients is recommended.

CONTENTS

ABSTRACT e188

TOP 10 TAKE-HOME MESSAGES FOR THE EVALUATION AND DIAGNOSIS OF CHEST PAIN . . . e190

PREAMBLE e190

1. INTRODUCTION e192
- 1.1. Methodology and Evidence Review e192
- 1.2. Organization of the Writing Committee e192
- 1.3. Document Review and Approval e193
- 1.4. Scope of the Guideline e193
  - 1.4.1. Scope of the Problem e195
  - 1.4.2. Defining Chest Pain e195
- 1.5. Abbreviations e196

2. INITIAL EVALUATION e197
- 2.1. History e197
  - 2.1.1. A Focus on the Uniqueness of Chest Pain in Women e198
  - 2.1.2. Considerations for Older Patients With Chest Pain e199
  - 2.1.3. Considerations for Diverse Patient Populations With Chest Pain e200
  - 2.1.4. Patient-Centric Considerations e200

2.2. Physical Examination . . . e201
2.3. Diagnostic Testing . . . e202
2.3.1. Setting Considerations . . . e202
2.3.2. Electrocardiogram . . . e203
2.3.3. Chest Radiography . . . e204
2.3.4. Biomarkers . . . e205

3. CARDIAC TESTING GENERAL CONSIDERATIONS . . . e206
3.1. Anatomic Testing . . . e207
3.1.1. Coronary Computed Tomography Angiography . . . e207
3.1.2. Invasive Coronary Angiography . . . e207
3.2. Diagnostic Testing . . . e207
3.2.1. Exercise ECG . . . e207
3.2.2. Echocardiography/Stress Echocardiography . . . e208
3.2.3. Stress Nuclear (PET or SPECT) Myocardial Perfusion Imaging . . . e209
3.2.4. Cardiovascular Magnetic Resonance Imaging . . . e209
3.3. Cardiac Testing Considerations for Women Who Are Pregnant, Postpartum, or of Child-Bearing Age . . . e210

4. CHOOSING THE RIGHT PATHWAY WITH PATIENT-CENTRIC ALGORITHMS FOR ACUTE CHEST PAIN . . . e210
4.1. Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI) . . . e212
4.1.1. Low-Risk Patients With Acute Chest Pain . . . e215
4.1.1.1. Cost-Value Considerations in the Evaluation of Low-Risk Patients . . . e216
4.1.2. Intermediate-Risk Patients With Acute Chest Pain . . . e217
4.1.2.1. Intermediate-Risk Patients With Acute Chest Pain and No Known CAD . . . e217
4.1.2.1.1. Cost-Value Considerations e220
4.1.2.2. Intermediate-Risk Patients With Acute Chest Pain and Known CAD . . . e220
4.1.3. High-Risk Patients With Acute Chest Pain . . . e222
4.1.4. Acute Chest Pain in Patients With Prior Coronary Artery Bypass Graft (CABG) Surgery . . . e223
4.1.5. Evaluation of Patients With Acute Chest Pain Receiving Dialysis . . . e224
4.1.6. Evaluation of Acute Chest Pain in Patients With Cocaine and Methamphetamine Use . . . e224
4.1.7. Shared Decision-Making in Patients With Acute Chest Pain . . . e225
4.2. Evaluation of Acute Chest Pain With Nonischemic Cardiac Pathologies . . . e226
4.2.1. Acute Chest Pain With Suspected Acute Aortic Syndrome . . . e226
4.2.2. Acute Chest Pain With Suspected PE . . . e227
4.2.3. Acute Chest Pain With Suspected Myopericarditis . . . e227
4.2.4. Acute Chest Pain With Valvular Heart Disease (VHD) . . . e228
4.3. Evaluation of Acute Chest Pain With Suspected Noncardiac Causes . . . e229
4.3.1. Evaluation of Acute Chest Pain With Suspected Gastrointestinal Syndromes . . . e231
4.3.2. Evaluation of Acute Chest Pain With Suspected Anxiety and Other Psychosomatic Considerations . . . e231
4.3.3. Evaluation of Acute Chest Pain in Patients With Sickle Cell Disease . . . e232

5. EVALUATION OF PATIENTS WITH STABLE CHEST PAIN . . . e232
5.1. Patients With No Known CAD Presenting With Stable Chest Pain . . . e232
5.1.1. Pretest Risk Probability to Guide Need for Stress and Anatomic Tests . . . e233
5.1.2. Low-Risk Patients With Stable Chest Pain and No Known CAD . . . e233
5.1.3. Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD . . . e235
5.2. Patients With Known CAD Presenting With Stable Chest Pain . . . e239
5.2.1. Patients With Obstructive CAD Who Present With Stable Chest Pain . . . e239
5.2.1.1. Patients With Prior CABG Surgery With Stable Chest Pain . . . e242
5.2.2. Patients With Known Nonobstructive CAD Presenting With Stable Chest Pain . . . e243
5.2.3. Patients With Suspected Ischemia and No Obstructive CAD (INOCA) . . . e244
5.3. Cost-Value Considerations in Diagnostic Testing . . . e246
5.3.1. CCTA and CAC Scanning Cost-Value Considerations . . . e246
5.3.2. Exercise Electrocardiographic Cost-Value Considerations . . . e246
5.3.3. Stress Echocardiographic Cost-Value Considerations . . . e246
5.3.4. Stress Nuclear MPI Cost-Value Considerations . . . e246
5.3.5. Stress CMR Cost-Value Considerations . . . e247

6. EVIDENCE GAPS AND FUTURE RESEARCH . . . e247

REFERENCES . . . e249

APPENDIX 1

Author Relationships With Industry and Other Entities (Relevant) . . . e273

JACC VOL. 78, NO. 22, 2021
NOVEMBER 30, 2021:e187–e285

APPENDIX 2

Reviewer Relationships With Industry and Other Entities (Comprehensive) e276

TOP 10 TAKE-HOME MESSAGES FOR THE EVALUATION AND DIAGNOSIS OF CHEST PAIN

1. **Chest Pain Means More Than Pain in the Chest.** Pain, pressure, tightness, or discomfort in the chest, shoulders, arms, neck, back, upper abdomen, or jaw, as well as shortness of breath and fatigue should all be considered anginal equivalents.
2. **High-Sensitivity Troponins Preferred.** High-sensitivity cardiac troponins are the preferred standard for establishing a biomarker diagnosis of acute myocardial infarction, allowing for more accurate detection and exclusion of myocardial injury.
3. **Early Care for Acute Symptoms.** Patients with acute chest pain or chest pain equivalent symptoms should seek medical care immediately by calling 9-1-1. Although most patients will not have a cardiac cause, the evaluation of all patients should focus on the early identification or exclusion of life-threatening causes.
4. **Share the Decision-Making.** Clinically stable patients presenting with chest pain should be included in decision-making; information about risk of adverse events, radiation exposure, costs, and alternative options should be provided to facilitate the discussion.
5. **Testing Not Needed Routinely for Low-Risk Patients.** For patients with acute or stable chest pain determined to be low risk, urgent diagnostic testing for suspected coronary artery disease is not needed.
6. **Pathways.** Clinical decision pathways for chest pain in the emergency department and outpatient settings should be used routinely.
7. **Accompanying Symptoms.** Chest pain is the dominant and most frequent symptom for both men and women ultimately diagnosed with acute coronary syndrome. Women may be more likely to present with accompanying symptoms such as nausea and shortness of breath.
8. **Identify Patients Most Likely to Benefit From Further Testing.** Patients with acute or stable chest pain who are at intermediate risk or intermediate to high pretest risk of obstructive coronary artery disease, respectively, will benefit the most from cardiac imaging and testing.
9. **Noncardiac Is In. Atypical Is Out.** "Noncardiac" should be used if heart disease is not suspected. "Atypical" is a misleading descriptor of chest pain, and its use is discouraged.
10. **Structured Risk Assessment Should Be Used.** For patients presenting with acute or stable chest pain, risk for coronary artery disease and adverse events should be estimated using evidence-based diagnostic protocols.

Figure 1 illustrates the take-home messages.

PREAMBLE

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

Intended Use

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

Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

Methodology and Modernization

The ACC/AHA Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine (1,2), and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to healthcare professionals at the point of care.

FIGURE 1 **Take-Home Messages for the Evaluation and Diagnosis of Chest Pain**

Numerous modifications to the guidelines have been implemented to make them shorter and enhance "user friendliness." Guidelines are written and presented in a modular, "knowledge chunk" format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review.

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

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of "full revision" and "focused update" will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual (4) and other methodology articles (5-7). The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the

JACC VOL. 78, NO. 22, 2021
NOVEMBER 30, 2021:e187–e285

basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1) (8).

Selection of Writing Committee Members

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

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found online. Appendix 1 of the guideline lists writing committee members' relevant RWI; for the purposes of full transparency, their comprehensive disclosure information is available in the Supplemental Appendix. Comprehensive disclosure information for the Joint Committee is also available online.

Evidence Review and Evidence Review Committees

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

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

Guideline-Directed Management and Therapy

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

Patrick T. O'Gara, MD, MACC, FAHA
Chair, ACC/AHA Joint Committee on
Clinical Practice Guidelines

1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from November 11, 2017, to May 1, 2020. Key search words included but were not limited to the following: *acute coronary syndrome, angina, angina pectoris, aortic valve stenosis, biomarker, biomarkers, brain natriuretic peptide, cardiac-gated single photon emission computer-assisted tomography, cardiovascular magnetic resonance, chest pain, CKMB, coronary angiography, coronary arteriosclerosis, coronary artery disease, creatine kinase, creatine kinase MB, echocardiography, electrocardiography, heart valve disease, hypertrophic cardiomyopathy, magnetic resonance imaging, mitral valve stenosis, multidetector computed tomography, myocardial infarction, myocardial ischemia, myocardium, NT-proBNP, perfusion imaging, positron-emission tomography, pulmonary hypertension, stable angina, troponin I, troponin T, unstable angina, x-ray computed tomography*. Additional relevant studies, published through November 2020 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the Online Data Supplement and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

1.2. Organization of the Writing Committee

The writing committee consisted of cardiac intensivists, cardiac interventionalists, cardiac surgeons, cardiologists, emergency physicians, epidemiologists, and a lay/patient representative. The writing committee included representatives from the ACC, AHA, American Society of Echocardiography (ASE), American College of Chest Physicians (CHEST), Society for Academic Emergency

TABLE 1 **Applying ACC/AHA Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)***

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
CLASS 1 (STRONG) — **Benefit >>> Risk** **Suggested phrases for writing recommendations:** • Is recommended • Is indicated/useful/effective/beneficial • Should 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	**LEVEL A** • High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
CLASS 2a (MODERATE) — **Benefit >> Risk** **Suggested phrases for writing recommendations:** • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	**LEVEL B-R** (Randomized) • Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
CLASS 2b (WEAK) — **Benefit ≥ Risk** **Suggested phrases for writing recommendations:** • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	**LEVEL B-NR** (Nonrandomized) • Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only) — **Benefit = Risk** **Suggested phrases for writing recommendations:** • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	**LEVEL C-LD** (Limited Data) • Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Class 3: Harm (STRONG) — **Risk > Benefit** **Suggested phrases for writing recommendations:** • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	**LEVEL C-EO** (Expert Opinion) • Consensus of expert opinion based on clinical experience

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

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

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

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

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

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

Medicine (SAEM), Society of Cardiovascular Computed Tomography (SCCT), and Society for Cardiovascular Magnetic Resonance (SCMR). Appendix 1 lists writing committee members' relevant RWI. For the purposes of full transparency, the writing committee members' comprehensive disclosure information is available in the Supplemental Appendix.

1.3. Document Review and Approval

This document was reviewed by 16 official reviewers nominated by the ACC, the American College of Emergency Physicians, AHA, ASE, American Society of Nuclear Cardiology, CHEST, SAEM, SCCT, and SCMR, and 39 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the ASE, CHEST, SAEM, SCCT, and SCMR.

1.4. Scope of the Guideline

The charge of the writing committee was to develop a guideline for the evaluation of acute or stable chest pain or other anginal equivalents, in various clinical

settings, with an emphasis on the diagnosis on ischemic causes. This guideline will not provide recommendations on whether revascularization is appropriate or what modality is indicated. Such recommendations can be found in the forthcoming ACC/AHA coronary artery revascularization guideline. In developing the "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain," the writing committee first reviewed previous published guidelines and related statements. Table 2 contains a list of these publications deemed pertinent to this writing effort and is intended for use as a resource, thus obviating the need to repeat existing guideline recommendations.

TABLE 2 Associated Guidelines and Statements

Title	Organization	Publication Year (Reference)
Guidelines		
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/SCAI/STS	2014 (1)* 2012 (2)
Atrial fibrillation	AHA/ACC/HRS	2014 (3)* 2019 (4)
Non-ST elevation ACS	AHA/ACC	2014 (5)
Blood cholesterol	AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA	2018 (6)
Heart failure	ACC/AHA	2013 (7)* 2017 (8)
Primary prevention of cardiovascular disease	ACC/AHA	2019 (9)
Management of overweight and obesity in adults	AHA/ACC/TOS	2014 (10)
ST-elevation myocardial infarction	ACC/AHA	2013 (11)
Ventricular arrhythmias and the prevention of sudden cardiac death	AHA/ACC/HRS	2017 (12)
Coronary artery bypass graft surgery	ACC/AHA	2011 (13)
Hypertrophic cardiomyopathy	ACC/AHA	2020 (14)
Percutaneous coronary intervention	ACC/AHA/SCAI	2011 (15)* 2015 (16)
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011 (17)
Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care—part 9: postcardiac arrest care	AHA	2010 (18)* 2019 (19)
Prevention, detection, evaluation, and management of high blood pressure in adults	ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA	2017 (20)
Statements		
Testing of low-risk patients presenting to the emergency department with chest pain	AHA	2010 (21)
Prevention of cardiovascular disease in adults with type 2 diabetes mellitus	AHA/ADA	2015 (22)
Prevention and control of seasonal influenza with vaccines	CDC	2018 (23)

*The full-text guideline and focused update references are provided.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; AATS, American Association for Thoracic Surgery; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; CDC, Centers for Disease Control and Prevention; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; NMA, National Medical Association; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and TOS, The Obesity Society.

1.4.1. Scope of the Problem

Synopsis

After injuries, chest pain is the second most common reason for adults to present to the emergency department (ED) in the United States and accounts for >6.5 million visits, which is 4.7% of all ED visits (1). Chest pain also leads to nearly 4 million outpatient visits annually in the United States (2). Chest pain remains a diagnostic challenge in the ED and outpatient setting and requires thorough clinical evaluation. Although the cause of chest pain is often noncardiac, coronary artery disease (CAD) affects >18.2 million adults in the United States and remains the leading cause of death for men and women, accounting for >365,000 deaths annually (3). Distinguishing between serious and benign causes of chest pain is imperative. The lifetime prevalence of chest pain in the United States is 20% to 40% (4), and women experience this symptom more often than men (5). Of all ED patients with chest pain, only 5.1% will have an acute coronary syndrome (ACS), and more than half will ultimately be found to have a noncardiac cause (6). Nonetheless, chest pain is the most common symptom of CAD in both men and women.

1.4.2. Defining Chest Pain

Recommendations for Defining Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 1 and 2.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. An initial assessment of chest pain is recommended to triage patients effectively on the basis of the likelihood that symptoms may be attributable to myocardial ischemia (1-7).
1	C-LD	2. Chest pain should not be described as atypical, because it is not helpful in determining the cause and can be misinterpreted as benign in nature. Instead, chest pain should be described as cardiac, possibly cardiac, or noncardiac because these terms are more specific to the potential underlying diagnosis.

Synopsis

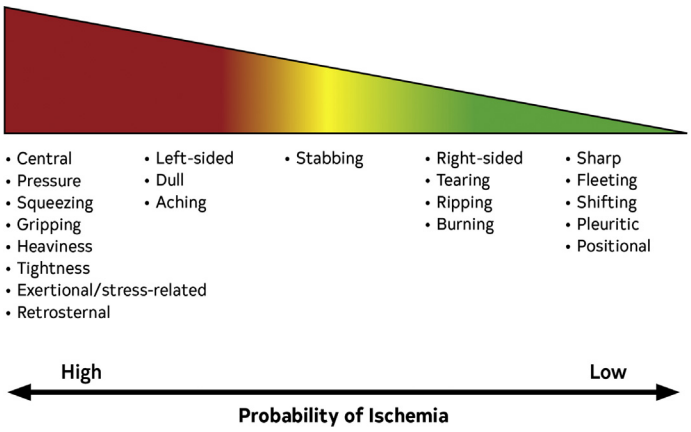
Chest pain is one of the most common reasons that people seek medical care. The term "chest pain" is used by patients and applied by clinicians to describe the many unpleasant or uncomfortable sensations in the anterior chest that prompt concern for a cardiac problem. Chest pain should be considered *acute* when it is new onset or involves a change in pattern, intensity, or duration compared with previous episodes in a patient with recurrent symptoms. Chest pain should be considered *stable* when symptoms are chronic and associated with consistent precipitants such as exertion or emotional stress.

Although the term chest pain is used in clinical practice, patients often report pressure, tightness, squeezing, heaviness, or burning. In this regard, a more appropriate term is "chest discomfort," because patients may not use the descriptor "pain." They may also report a location other than the chest, including the shoulder, arm, neck, back, upper abdomen, or jaw. Despite individual variability, the discomfort induced by myocardial ischemia is often characteristic and therefore central to the diagnosis. For this reason, features more likely to be associated with ischemia have been described as typical versus atypical; however, the latter can be confusing because it is frequently used to describe symptoms considered nonischemic as well as noncardiac. Although other nonclassic symptoms of ischemia, such as shortness of breath, nausea, radiating discomfort, or numbness, may be present, chest pain or chest discomfort remains the predominant symptom reported in men and women who are ultimately diagnosed with myocardial ischemia (3-7). Pain—described as sharp, fleeting, related to inspiration (pleuritic) or position, or shifting locations—suggests a lower likelihood of ischemia.

Recommendation-Specific Supportive Text

1. Like most visceral discomfort, the sensation produced by myocardial ischemia is characteristically deep, difficult to localize, and usually diffuse. Point tenderness renders ischemia less likely. Reported symptoms lie somewhere on a continuum of higher or lower probability of ischemia based on the presence or absence of specific characteristics (**Figure 2**). Other clinical elements (e.g., duration, provoking and relieving factors, patient age, cardiac risk factors) provide further focus toward or away from ischemia in the diagnostic process. It is essential to ascertain the characteristics of the chest pain directly from the patient for optimal interpretation (1-7). A patient's history is the most important basis for considering presence or absence of myocardial ischemia, but the source of cardiac symptoms is complex, and their expression is variable. The diagnosis of ischemia may require data

FIGURE 2 Index of Suspicion That Chest "Pain" Is Ischemic in Origin on the Basis of Commonly Used Descriptors



beyond history alone. In some patients, what appears to be noncardiac chest pain may be ischemic in origin.

2. Chest pain has been traditionally stratified into "typical" and "atypical" types. Chest pain that is more likely associated with ischemia consists of substernal chest discomfort provoked by exertion or emotional stress and relieved by rest or nitroglycerin. The more classic the chest discomfort is based on quality, location, radiation, and provoking and relieving factors, the more likely it is to be of cardiac ischemic origin. Atypical chest pain is a problematic term. Although it was intended to indicate angina without typical chest symptoms, it is more often used to state that the symptom is noncardiac in origin. As such, we discourage the use of atypical chest pain. Emphasis is more constructively placed on specific aspects of symptoms that suggest their origin in terms of probable ischemia. Of note, chest pain is broadly defined to also include referred pain in the shoulders, arms, jaw, neck, and upper abdomen. To diminish ambiguity, use "cardiac," "possible cardiac," and "noncardiac" to describe the suspected cause of chest pain is encouraged.

1.5. Abbreviations

Abbreviation	Meaning/Phrase
ACS	acute coronary syndrome
AMI	acute myocardial infarction
CABG	coronary artery bypass graft
CAC	coronary artery calcium
CAD	coronary artery disease
CCTA	coronary computed tomographic angiography

Continued in the next column

Abbreviation	Meaning/Phrase
CDP	clinical decision pathway
CMR	cardiovascular magnetic resonance
cTn	cardiac troponin
ECG	electrocardiogram
ED	emergency department
EMS	emergency medical services
FFR-CT	fractional flow reserve with computed tomography
GDMT	guideline-directed medical therapy
hs-cTn	high-sensitivity cardiac troponin
ICA	invasive coronary angiography
INOCA	ischemia and no obstructive coronary artery disease
MACE	major adverse cardiovascular events
MBFR	myocardial blood flow reserve
METs	metabolic equivalents
MINOCA	myocardial infarction and nonobstructive coronary arteries
MPI	myocardial perfusion imaging
NSTE-ACS	non-ST-segment-elevation acute coronary syndrome
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PET	positron emission tomography
SIHD	stable ischemic heart disease
SPECT	single-photon emission computed tomography
STEMI	ST-segment-elevation myocardial infarction
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
VF	ventricular fibrillation
VHD	valvular heart disease
VT	ventricular tachycardia

2. INITIAL EVALUATION

2.1. History

Recommendation for History

COR	LOE	RECOMMENDATION
1	C-LD	1. In patients with chest pain, a focused history that includes characteristics and duration of symptoms relative to presentation as well as associated features, and cardiovascular risk factor assessment should be obtained.

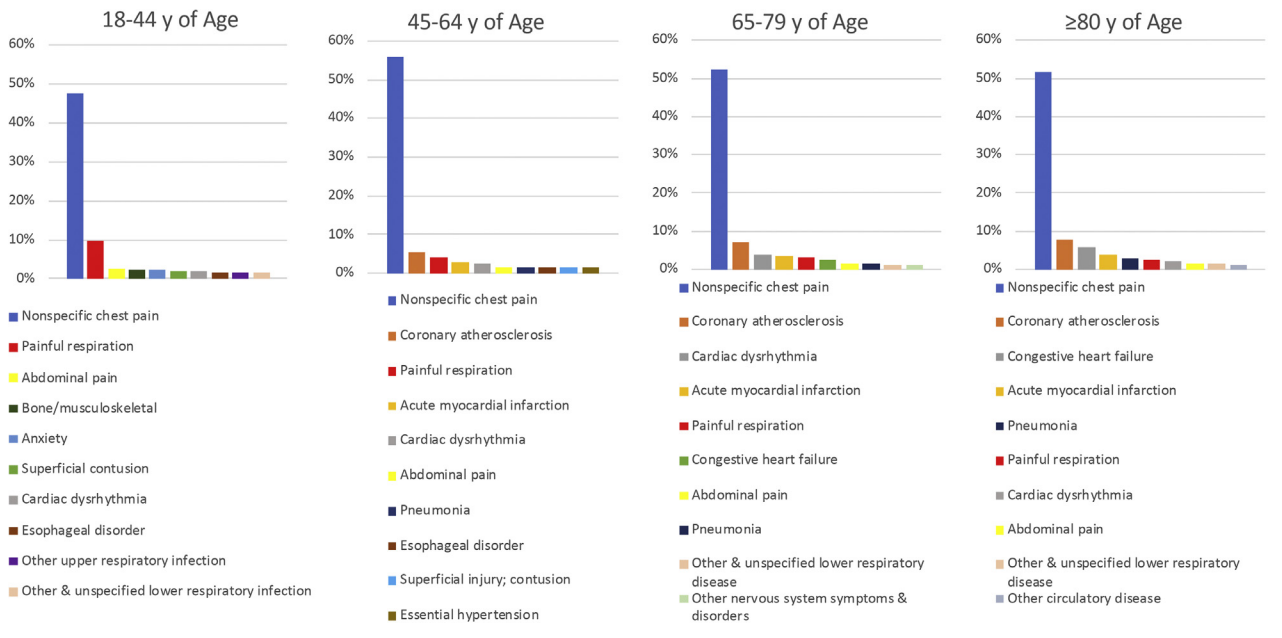
Synopsis

Chest pain or chest pain equivalent will be referred to in these guidelines as "chest pain." Patients presenting to the ED with nontraumatic chest pain are a frequent diagnostic challenge (1). The priorities are: 1) rapid initiation of optimal management in patients with life-threatening conditions such as ACS, aortic dissection, and pulmonary embolism (PE), as well as nonvascular syndromes (e.g., esophageal rupture, tension pneumothorax); and 2) deliberate therapy for those with less critical illness. Although there are several life-threatening causes, chest pain usually reflects a more benign condition (**Figure 3**) (2-4). The initial ECG is important to the evaluation, but history, examination, biomarkers, and other aids remain essential. There is frequently a lack of correlation between intensity of symptoms and seriousness of disease and general similarity of symptoms among different causes of chest pain. A comprehensive history that captures all the characteristics of chest pain (**Table 3**), including but not limited to its: 1) nature; 2) onset and duration; 3) location and radiation; 4) precipitating factors; 5) relieving factors; and 6) associated symptoms can help better identify potential cardiac causes and should be obtained from all patients.

Recommendation-Specific Supportive Text

1. Angina pectoris is perceived as a retrosternal chest discomfort that builds gradually in intensity (over several minutes), is usually precipitated by stress (physical or emotional) or occurring at rest (as in the case of an ACS) with characteristic radiation (e.g., left

FIGURE 3 Top 10 Causes of Chest Pain in the ED Based on Age (Weighted Percentage)



Created using data from Hsia RY, et al. (3). ED indicates emergency department.

TABLE 3 Chest Pain Characteristics and Corresponding Causes

Nature
Anginal symptoms are perceived as retrosternal chest discomfort (e.g., pain, discomfort, heaviness, tightness, pressure, constriction, squeezing) (Section 1.4.2, Defining Chest Pain).
Sharp chest pain that increases with inspiration and lying supine is unlikely related to ischemic heart disease (e.g., these symptoms usually occur with acute pericarditis).
Onset and duration
Anginal symptoms gradually build in intensity over a few minutes.
Sudden onset of ripping chest pain (with radiation to the upper or lower back) is unlikely to be anginal and is suspicious of an acute aortic syndrome.
Fleeting chest pain—of few seconds' duration—is unlikely to be related to ischemic heart disease.
Location and radiation
Pain that can be localized to a very limited area and pain radiating to below the umbilicus or hip are unlikely related to myocardial ischemia.
Severity
Ripping chest pain ("worse chest pain of my life"), especially when sudden in onset and occurring in a hypertensive patient, or with a known bicuspid aortic valve or aortic dilation, is suspicious of an acute aortic syndrome (e.g., aortic dissection).
Precipitating factors
Physical exercise or emotional stress are common triggers of anginal symptoms.
Occurrence at rest or with minimal exertion associated with anginal symptoms usually indicates ACS.
Positional chest pain is usually nonischemic (e.g., musculoskeletal).
Relieving factors
Relief with nitroglycerin is not necessarily diagnostic of myocardial ischemia and should not be used as a diagnostic criterion.
Associated symptoms
Common symptoms associated with myocardial ischemia include, but are not limited to, dyspnea, palpitations, diaphoresis, lightheadedness, presyncope or syncope, upper abdominal pain, or heartburn unrelated to meals and nausea or vomiting.
Symptoms on the left or right side of the chest, stabbing, sharp pain, or discomfort in the throat or abdomen may occur in patients with diabetes, women, and elderly patients.

ACS indicates acute coronary syndrome.

arm, neck, jaw) and its associated symptoms (e.g., dyspnea, nausea, lightheadedness). When actively treated or spontaneously resolving, it dissipates over a few minutes. Relief with nitroglycerin is not necessarily diagnostic of myocardial ischemia and should not be used as a diagnostic criterion, especially because other entities demonstrate comparable response (e.g., esophageal spasm) (1,5). Associated symptoms such as shortness of breath, nausea or vomiting, lightheadedness, confusion, presyncope or syncope, or vague abdominal symptoms are more frequent among patients with diabetes, women, and the elderly. A detailed assessment of cardiovascular risk factors, review of systems, past medical history, and family and social history should complement the assessment of presenting symptoms.

2.1.1. A Focus on the Uniqueness of Chest Pain in Women

Recommendations for a Focus on the Uniqueness of Chest Pain in Women
Referenced studies that support the recommendations are summarized in Online Data Supplements 3 and 4.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. Women who present with chest pain are at risk for underdiagnosis, and potential cardiac causes should always be considered (1-7).
1	B-NR	2. In women presenting with chest pain, it is recommended to obtain a history that emphasizes accompanying symptoms that are more common in women with ACS (1-7).

Synopsis

Most patients who present to the ED with chest pain are women, particularly among those ≥65 years of age (8). The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial demonstrated that women with moderate-to-severe ischemia are more symptomatic than men (9). Women are less likely to have timely and appropriate care (10). This could be explained by the fact that women are more likely to experience prodromal symptoms when they seek medical care (11). Women may also present with accompanying symptoms (e.g., nausea, fatigue, and shortness of breath) more often than men (12-14). However, chest pain remains the predominant symptom reported by women among those ultimately diagnosed with ACS, occurring with a frequency equal to men (3,5-7,15,16).

Recommendation-Specific Supportive Text

1. Traditional risk score tools and physician assessments often underestimate risk in women and misclassify them as having nonischemic chest pain (1,2). The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial looked at sex differences in the presentation, risk factors, demographics, noninvasive test referrals, and results of 10,003 stable outpatients with suspected CAD (1). Women commonly presented with chest pain symptoms similar to men but also had a greater prevalence of other symptoms such as palpitations, jaw and neck pain, as well as back pain. Women also had more cardiovascular risk factors, including hypertension (66.6% versus 63.2%; p<0.001), hyperlipidemia (68.9% versus 66.3%; p=0.004), older age (62.4±7.9 years of age versus 59.0±8.4 years of age, p<0.001), cerebral or peripheral artery disease (6.2% versus 4.7%; p<0.001), family history of premature CAD (34.6% versus 29.3%; p<0.001), and sedentary lifestyle (53.5% versus 43.4%; p<0.001). Physician assessments often misclassify chest pain as nonanginal. The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial reported that women with diabetes had a higher prevalence of angina than their male counterparts, with a lower functional capacity and a lower incidence of obstructive CAD (16).
2. In the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study, men and women ≤55 years of age were equally likely to present with chest pain (defined as pain, pressure, tightness, discomfort; 89.5% versus 87%, respectively). Women were more likely to report ≥3 associated symptoms than men (e.g., epigastric symptoms, palpitations, and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% of women versus 54.8% of men; p<0.001) (3). Similar results were found in the YOUNG-MI (Myocardial Infarction) registry where young men and women (≤50 years of age) were equally likely to present with chest pain, although women were more likely to also have other associated symptoms (7). The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke) study used cardiolinguistic machine learning to record patient-reported symptoms and, in those diagnosed with obstructive CAD, there was no sex difference in the occurrence of chest pain (6). In a prospective trial of 1941 patients (39% women) with suspected ACS examining the diagnostic value of high-sensitivity cardiac troponin (cTn), chest pain was reported in 92% of women and 91% of men (5). Additionally, women with acute myocardial infarction (AMI) were more likely to present with “typical” symptoms than men (77% versus 59%; p=0.007).

2.1.2. Considerations for Older Patients With Chest Pain

Recommendation for Considerations for Older Patients With Chest Pain

COR	LOE	RECOMMENDATION
1	C-LD	1. In patients with chest pain who are >75 years of age, ACS should be considered when accompanying symptoms such as shortness of breath, syncope, or acute delirium are present, or when an unexplained fall has occurred (1).

Synopsis

Increased age is a significant risk factor for ACS. However, it is also a risk factor for comorbidities that are associated with alternative diagnoses associated with chest pain. As a result, a more extensive diagnostic workup is required in older patients. Although patients >75 years of age account for 33% of all cases of ACS, alternative diagnoses are still more common than a cardiac cause of chest pain at presentation (2,3). A substudy of the PROMISE trial has shown that patients >75 years of age, with stable symptoms suggestive of CAD, are more likely to have a positive noninvasive test and more coronary artery calcification than younger people. For these older patients, when compared with anatomic noninvasive testing for obstructive CAD with cardiac CT, a positive stress test

result was associated with increased risk of cardiovascular death or MI (4).

Recommendation-Specific Supportive Text

1. Patients >75 years of age may have symptoms of shortness of breath, syncope, mental impairment, or abdominal pain, or experienced an unexplained fall. The physician should have a heightened awareness to understand that these symptoms may be associated with ACS, in addition to chest pain (1).

2.1.3. Considerations for Diverse Patient Populations With Chest Pain

Recommendations for Considerations for Diverse Patient Populations With Chest Pain

COR	LOE	RECOMMENDATIONS
1	C-LD	1. Cultural competency training is recommended to help achieve the best outcomes in patients of diverse racial and ethnic backgrounds who present with chest pain.
1	C-LD	2. Among patients of diverse race and ethnicity presenting with chest pain in whom English may not be their primary language, addressing language barriers with the use of formal translation services is recommended.

Synopsis

There are marked racial and ethnic disparities when triaging patients who present for the evaluation of chest pain. Despite a greater number of Black patients presenting with angina pectoris relative to other races, this population is less likely to be treated urgently and less likely to have an ECG performed, samples for cardiac biomarkers drawn, cardiac monitoring performed, or pulse oximetry measured (1-4). Similar treatment disparities are found with Hispanic patients and those who are covered by Medicaid or are uninsured. Derived from a nationally representative sample from the National Hospital Ambulatory Health Care Survey reflecting an estimated 78 million ED visits in the United States over a 10-year period, these findings have been unchanged over time (5). Such disparity in the management of chest pain among diverse population subgroups contributes to worse outcomes, including the greater incidence of AMI and fatal coronary events seen in these key population subgroups (6,7). There are also disparities in the management of patients of South Asian descent who present with ACS, with the diagnosis often missed or delayed, resulting in poor outcomes (8-11). Consideration of race and ethnicity in the evaluation of patients with suspected ACS and in the outpatient evaluation of symptomatic patients is paramount to improving outcomes. Cultural competency training of providers is recommended to address health disparities in the evaluation and management of diverse patient population subgroups with chest pain.

Recommendation-Specific Supportive Text

1. In patients of various diverse groups presenting with chest pain, cultural competency training of providers to address racial and ethnic disparities may help to improve diagnosis, treatment, and outcomes. Attention to race, ethnicity, and sociocultural differences should be considered in the evaluation and management of such patients. Cultural competency training can help address difficulties in the assessment of patients because there may be differences in the description and perception of chest pain among various diverse patient groups. Such training may also help to minimize potential unconscious biases on the part of providers. Disparities in the management of chest pain among diverse populations contribute to worse outcomes, including the greater incidence of MI and fatal coronary events (1).
2. In patients of various racial and ethnic subgroups presenting with suspected ACS in whom English may not be their primary language, adequately addressing language barriers with the use of language translation is vital to obtain an accurate and complete history. Formal translation services such as those provided through institutions and virtual translation are recommended.

2.1.4. Patient-Centric Considerations

Recommendation for Patient-Centric Considerations

COR	LOE	RECOMMENDATION
1	C-LD	1. In patients with acute chest pain, it is recommended that 9-1-1 be activated by patients or bystanders to initiate transport to the closest ED by emergency medical services (EMS) (1).

Synopsis

Although chest pain remains one of the most common reasons that patients seek evaluation, among both sexes, there is a tendency for some patients to minimize perceived risk for cardiac disease, resulting in potentially avoidable delays in care (1). To alleviate this problem, efforts should be made to educate all people regarding their risk for a cardiac event and educate patients about the need for timely care if a heart attack is suspected. Education is essential regarding the need to call 9-1-1, provide transportation by EMS to the nearest ED, initiate early assessment and management of suspected ACS, including transmittal of prehospital ECGs (2), and intervene if complications occur en route to the ED (3). The ACC's Early Heart Attack Care guide is a resource to help educate the public about early recognition of potential cardiac symptoms and the importance of activating 9-1-1 for transportation (4,5).

Recommendation-Specific Supportive Text

1. To ensure the timely delivery of appropriate care, especially reperfusion therapy, it is strongly recommended that patients with acute chest pain be transported to the ED by trained EMS personnel (2,3). EMS transportation is associated with substantial reductions in ischemic time and treatment delays. Moreover, 1 in 300 patients with chest pain transported to the ED by private vehicle suffers a cardiac arrest en route (3). Understanding the mode of transportation to the ED for patients with chest pain and educating those who arrive by private vehicle on the associated dangers is an important aspect of management.

2.2. Physical Examination

Recommendation for Physical Examination

COR	LOE	RECOMMENDATION
1	C-EO	1. In patients presenting with chest pain, a focused cardiovascular examination should be performed initially to aid in the diagnosis of ACS or other potentially serious causes of chest pain (e.g., aortic dissection, PE, or esophageal rupture) and to identify complications.

Synopsis

Life-threatening causes of chest pain include, but are not limited to, ACS, PE, aortic dissection, and esophageal rupture. Because ST-segment-elevation myocardial infarction (STEMI) can be recognized on the ECG, the major challenge is to distinguish between non-ST-segment-elevation (NSTE)-ACS and noncardiac chest pain (1). With an uncomplicated AMI, the examination may be negative. Sudden onset of severe chest pain or back pain associated with limb pulse differential suggest aortic dissection (2), but sensitivity of the latter finding alone was only 30% (3). PE may result in tachycardia, dyspnea, and accentuated P2. Noncoronary causes of chest pain include aortic stenosis, aortic regurgitation, and hypertrophic cardiomyopathy, which produces characteristic murmurs and pulse alterations. Chest pain of pericarditis increases in the supine position and may be associated with a friction rub. Stress cardiomyopathy presents in a similar manner as ACS. Chest pain accompanied by a painful, tympanic abdomen may indicate a potentially life-threatening gastrointestinal etiology such as esophageal rupture (4). Pneumonia may cause localized pleuritic chest pain accompanied by a friction rub. Pneumothorax may be accompanied by pleuritic chest pain and unilateral absence of breath sounds. Tenderness to palpation of the costochondral joints may indicate a musculoskeletal cause. Herpes zoster produces a painful rash in a dermatomal distribution.

Recommendation-Specific Supportive Text

1. Although the causes of chest pain are numerous, the initial evaluation should focus on those that are life-threatening, such as ACS, PE, aortic dissection, and esophageal rupture, to facilitate rapid implementation of appropriate treatment (1). Specific clues can be helpful (**Table 4**). Chest tenderness on palpation or pain with inspiration markedly reduce the probability of ACS (1,5,6). Integrating the examination with other elements of the evaluation is crucial to establishing the correct diagnosis.

TABLE 4 Physical Examination in Patients With Chest Pain

Clinical Syndrome	Findings
Emergency	
ACS	Diaphoresis, tachypnea, tachycardia, hypotension, crackles, S3, MR murmur (2); examination may be normal in uncomplicated cases
PE	Tachycardia + dyspnea—>90% of patients; pain with inspiration (7)
Aortic dissection	Connective tissue disorders (e.g., Marfan syndrome), extremity pulse differential (30% of patients, type A>B) (8) Severe pain, abrupt onset + pulse differential + widened mediastinum on CXR >80% probability of dissection (9) Frequency of syncope >10% (8), AR 40%–75% (type A) (10)
Esophageal rupture	Emesis, subcutaneous emphysema, pneumothorax (20% patients), unilateral decreased or absent breath sounds
Other	
Noncoronary cardiac: AS, AR, HCM	AS: Characteristic systolic murmur, tardus or parvus carotid pulse AR: Diastolic murmur at right of sternum, rapid carotid upstroke HCM: Increased or displaced left ventricular impulse, prominent *a* wave in jugular venous pressure, systolic murmur
Pericarditis	Fever, pleuritic chest pain, increased in supine position, friction rub
Myocarditis	Fever, chest pain, heart failure, S3
Esophagitis, peptic ulcer disease, gall bladder disease	Epigastric tenderness Right upper quadrant tenderness, Murphy sign
Pneumonia	Fever, localized chest pain, may be pleuritic, friction rub may be present, regional dullness to percussion, egophony
Pneumothorax	Dyspnea and pain on inspiration, unilateral absence of breath sounds
Costochondritis, Tietze syndrome	Tenderness of costochondral joints
Herpes zoster	Pain in dermatomal distribution, triggered by touch; characteristic rash (unilateral and dermatomal distribution)

ACS indicates acute coronary syndrome; AR, aortic regurgitation; AS, aortic stenosis; CXR, chest x-ray; LR, likelihood ratio; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; PE, pulmonary embolism; and PUD, peptic ulcer disease.

2.3. Diagnostic Testing

2.3.1. Setting Considerations

Recommendations for Setting Considerations
Referenced studies that support the recommendations are summarized in Online Data Supplement 5.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. Unless a noncardiac cause is evident, an ECG should be performed for patients seen in the office setting with stable chest pain; if an ECG is unavailable the patient should be referred to the ED so one can be obtained (1-5).
1	C-LD	2. Patients with clinical evidence of ACS or other life-threatening causes of acute chest pain seen in the office setting should be transported urgently to the ED, ideally by EMS (1-9).
1	C-LD	3. In all patients who present with acute chest pain regardless of the setting, an ECG should be acquired and reviewed for STEMI within 10 minutes of arrival (1-3,6,7,10).
1	C-LD	4. In all patients presenting to the ED with acute chest pain and suspected ACS, cTn should be measured as soon as possible after presentation (8,9).
3: Harm	C-LD	5. For patients with acute chest pain and suspected ACS initially evaluated in the office setting, delayed transfer to the ED for cTn or other diagnostic testing should be avoided.

Synopsis

The goals in patients presenting to the ED or office with acute chest pain are: 1) identify life-threatening causes; 2) determine clinical stability; and 3) assess need for hospitalization versus safety of outpatient evaluation and management. These concerns entail consideration of the full extent of clinical data. The ACC/AHA STEMI and NSTE-ACS guidelines categorize chest pain cause into 4 types: STEMI, NSTE-ACS, stable angina, and noncardiac (6,7). The 12-lead ECG, which should be acquired and interpreted within 10 minutes of arrival to a medical facility (1-7,11) (Section 2.3.2, ECG), is pivotal in the evaluation because of its capacity to identify and triage patients with STEMI to urgent coronary reperfusion. Other ST-T abnormalities consistent with possible ischemia also mandate prompt evaluation in a hospital setting. In both cases, transfer should be by EMS; personal automobile for this purpose is associated with increased risk and should be avoided (3-5). Patients with stable angina or noncardiac chest pain that is not life-threatening should be managed as outpatients.

Recommendation-Specific Supportive Text

1. The ECG is central to the evaluation of stable angina in the office setting to ensure that ACS is not missed (1,2,6,7). If an ECG cannot be obtained, transfer to the ED should be initiated.
2. Transfer by EMS from the office setting for acute chest pain with suspected ACS or other life-threating conditions is recommended because of the important advantages provided by EMS including: 1) acquisition of a prehospital ECG, which can facilitate reperfusion if ST elevation is present; 2) presence of trained personnel who can provide treatment for chest pain, arrhythmias, and implement defibrillation en route; and 3) shorter travel time to the ED (1-7,10).
3. Early recognition of STEMI improves outcomes (1-3,6,7). Therefore, regardless of the setting, an ECG should be obtained and interpreted within 10 minutes of arrival. If this cannot be achieved in the office setting, immediate transfer to the ED by EMS is recommended. A substantial proportion of patients with chest pain are transferred to the ED without a prehospital ECG (1-3,6,7). This results in an important and avoidable delay in readiness of the ED and reperfusion teams to implement optimally timed reperfusion therapy (1-7,10).
4. cTn is the most sensitive test for diagnosing acute myocardial injury and, in conjunction with other essential clinical data (e.g., history, examination, ECG), its measurement is necessary to implement appropriate therapy (8,9).
5. Delayed transfer to the hospital for determination of cTn or other diagnostic testing beyond the ECG in the office setting can be detrimental and should be avoided (1-7,10).

2.3.2. Electrocardiogram

Recommendations for Electrocardiogram
Referenced studies that support the recommendations are summarized in Online Data Supplement 6.

COR	LOE	RECOMMENDATIONS
1	C-EO	1. In patients with chest pain in which an initial ECG is nondiagnostic, serial ECGs to detect potential ischemic changes should be performed, especially when clinical suspicion of ACS is high, symptoms are persistent, or the clinical condition deteriorates (1).
1	C-EO	2. Patients with chest pain in whom the initial ECG is consistent with an ACS should be treated according to STEMI and NSTE-ACS guidelines (1,2).
2a	B-NR	3. In patients with chest pain and intermediate-to-high clinical suspicion for ACS in whom the initial ECG is nondiagnostic, supplemental electrocardiographic leads V7 to V9 are reasonable to rule out posterior MI (3-5).

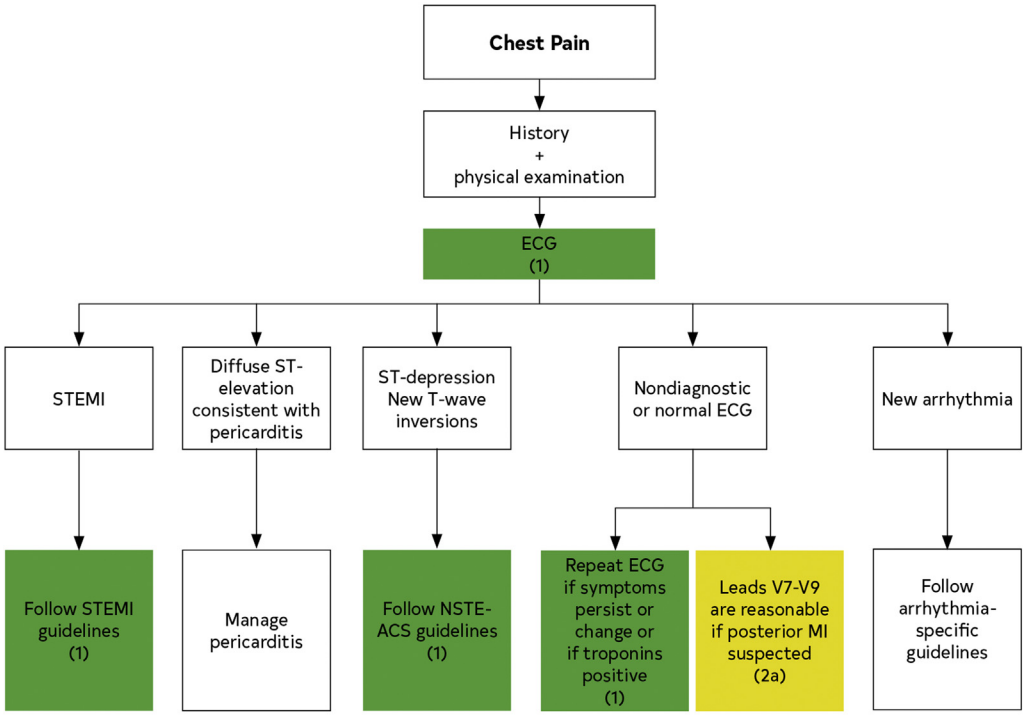
Synopsis

Patients with chest pain and new ST-elevation, ST depression, or new left bundle branch block on ECG should be treated according to STEMI and NSTE-ACS guidelines (1,2,6). An initial normal ECG does not exclude ACS. Patients with an initial normal ECG should have a repeat ECG, if symptoms are ongoing, until other diagnostic testing rules out ACS. An ECG may identify other nonischemic causes of chest pain (e.g., pericarditis, myocarditis, arrhythmia, electrolyte abnormalities, paced rhythm, hypertrophic cardiomyopathy, pulmonary hypertension, congenital long QT, or normal variant). Figure 4 depicts an algorithm for the role of the ECG to help direct care for individuals presenting with chest pain or chest pain equivalents.

Recommendation-Specific Supportive Text

1. When an ECG is nondiagnostic, it should be compared with previous ECGs, if available (7). A normal or unchanged ECG is reasonably useful but not sufficient at

FIGURE 4 Electrocardiographic-Directed Management of Chest Pain



ECG indicates electrocardiogram; NSTE-ACS, non-ST-segment–elevation acute coronary syndrome; MI, myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

ruling out ACS (8-10). Thus, decision-making should not be based solely on a single normal or nondiagnostic ECG. Left ventricular hypertrophy, bundle branch blocks, and ventricular pacing may mask signs of ischemia or injury (11). Up to 6% of patients with evolving ACS are discharged from the ED with a normal ECG (12-17). In patients where the initial ECG is normal or is without ST elevation, hyperacute T waves, left bundle branch block, or ST depression, serial ECGs should be performed and management should be guided by new electrocardiographic changes or other diagnostic testing (see Section 2.3.4 on Biomarkers, Section 3.1 on Anatomic Testing, or Section 3.2 on Stress Testing) (7,18-20). The timing for repeat ECG should also be guided by symptoms, especially if chest pain recurs or a change in clinical condition develops (21).

2. When ST-elevation is present on the initial ECG, management should follow the prescribed STEMI treatment algorithms in associated guidelines (2,22). Furthermore, if ST depression is identified on the initial ECG, management should follow the NSTE-ACS guidelines (1).
3. A normal ECG may be associated with left circumflex or right coronary artery occlusions and posterior wall ischemia, which is often "electrically silent"; therefore, right-sided ECG leads should be considered when such lesions are suspected (2-5).

2.3.3. Chest Radiography

Recommendation for Chest Radiography

COR	LOE	RECOMMENDATION
1	C-EO	1. In patients presenting with acute chest pain, a chest radiograph is useful to evaluate for other potential cardiac, pulmonary, and thoracic causes of symptoms.

Synopsis

Chest radiographs are rapid, noninvasive tests that can be used to screen for several disorders that may present with chest pain. The yield of chest radiography depends on the pretest probability and will thus be higher when history or physical examination point to a greater likelihood of a given diagnosis. However, chest radiographs often do not lead to a diagnosis that requires intervention (1), and their use should be guided by clinical suspicion.

Recommendation-Specific Supportive Text

1. The AHA/ACC guidelines for NSTE-ACS and heart failure all recommend chest radiographs on presentation, although this should not delay urgent revascularization if it is indicated (2,3). In patients with acute chest pain and heart failure, chest radiographs are useful to assess heart size and pulmonary congestion, as well as identifying potential pulmonary causes that may have contributed to symptoms. Chest radiographs may demonstrate a widened mediastinum in patients with aortic dissection, although they are not sensitive enough in this setting to rule out the diagnosis (4). Chest radiographs may be most useful in the evaluation of patients with acute chest pain to detect alternative cardiac, pulmonary, or other conditions that may cause symptoms, including pneumonia, pneumothorax, or rib fractures. Pleural effusions, pulmonary artery enlargement, and infiltrates may suggest PE, which would need to be confirmed by further testing.

2.3.4. Biomarkers

Recommendations for Biomarkers
Referenced studies that support the recommendations are summarized in Online Data Supplement 7.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients presenting with acute chest pain, serial cTn I or T levels are useful to identify abnormal values and a rising or falling pattern indicative of acute myocardial injury (1-21).
1	B-NR	2. In patients presenting with acute chest pain, high-sensitivity cTn is the preferred biomarker because it enables more rapid detection or exclusion of myocardial injury and increases diagnostic accuracy (17,21-25).
1	C-EO	3. Clinicians should be familiar with the analytical performance and the 99th percentile upper reference limit that defines myocardial injury for the cTn assay used at their institution (23,26).
3: No benefit	B-NR	4. With availability of cTn, creatine kinase myocardial (CK-MB) isoenzyme and myoglobin are not useful for diagnosis of acute myocardial injury (27-32).

Synopsis

Cardiovascular biomarkers can be useful for the diagnostic and prognostic assessment of patients with chest pain. Their most important application in clinical practice is for the rapid identification or exclusion of myocardial injury. The preferred biomarker to detect or exclude myocardial injury is cTn (I or T) because of its high sensitivity and specificity for myocardial tissue (1-21,33). hs-cTn is preferred and can detect circulating cTn in the blood of most “healthy” individuals, with different sex-specific thresholds (17,21,34). cTn is organ-specific but not disease-specific. Numerous ischemic, noncoronary cardiac, and noncardiac causes of cardiomyocyte injury can result in elevated cTn concentrations (17,21,24,25). Therefore, interpretation of cTn results requires integration with all clinical information (17,21).

Although multiple other cardiovascular biomarkers, including some in common clinical use such as natriuretic peptides, have been shown to be associated with the risk of adverse cardiovascular outcomes in patients with chest pain, none have sufficient diagnostic accuracy for myocardial injury to be recommended for that purpose. The use of D-dimer for diagnosis of PE is discussed in Section 4.2.2.

Recommendation-Specific Supportive Text

1. The preferred biomarker to detect or exclude cardiac injury is cTn (I or T) because of its high sensitivity and specificity for myocardial tissue (1-21). Detection of myocardial cell injury, possibly indicative of AMI, is predicated on a rise or fall of this biomarker in blood (1,3,4,10-21). A cTn concentration >99th percentile

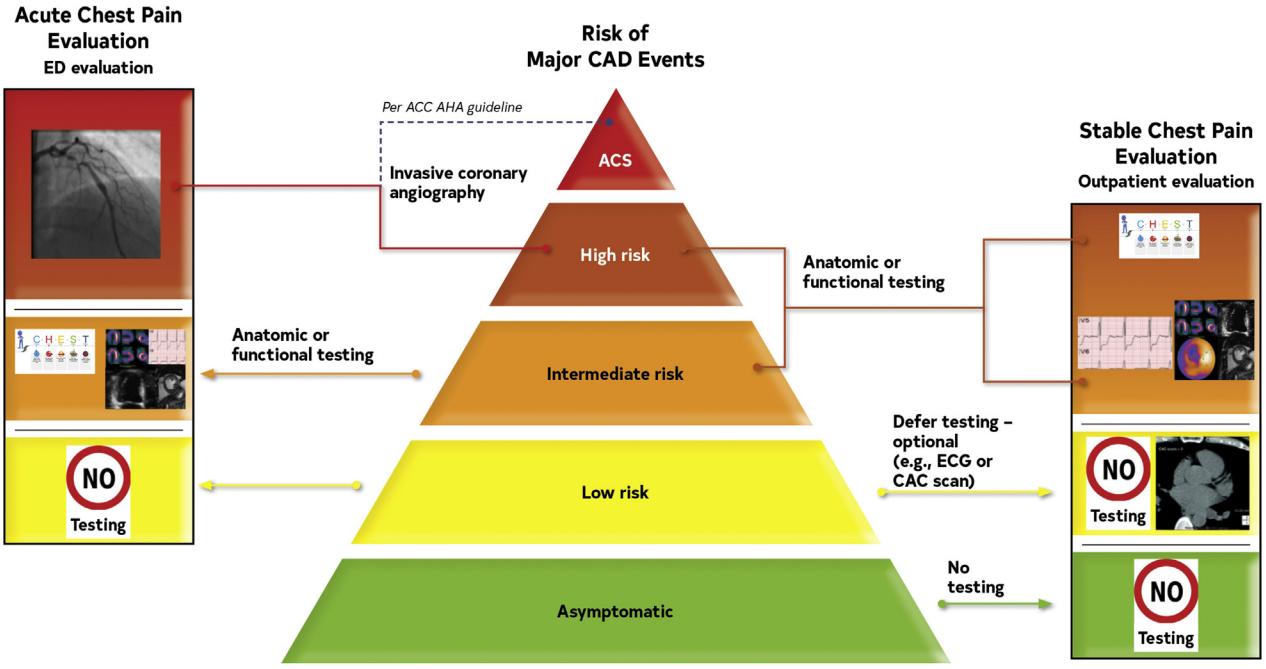
upper reference limit, which is assay-dependent, is an indicator of myocardial injury (1,9,21). The coefficient of variation at the 99th percentile upper reference limit for each assay should be ≤10% (8,21).

2. There is ample evidence for the superiority of hs-cTn assays over conventional cTn assays in multiple aspects of evaluation for patients presenting with chest pain with and without AMI (17,21,24,25,33). The sensitivity and negative predictive values are greater with hs-cTn compared with previous generation assays (17,21,24,25). In addition, the time interval from onset of chest pain to a detectable concentration at patient presentation is shorter with hs-cTn, affording more rapid rule-in and rule-out algorithms (22). Although it is sometimes challenging to diagnostically discriminate among these causes of myocardial injury, irrespective of the final diagnosis, the presence of myocardial injury is associated with a higher risk of adverse outcomes among patients with chest pain (35).
3. The level of detection, 99th percentile upper reference limit, analytical precision, and criteria for a significant delta are assay-specific, including among the many different manufacturers of the same analyte (e.g., hs-cTnI). To appropriately apply a cTn assay, clinicians must be familiar with these analytical performance properties for the assay(s) that they use in their practice (21).
4. Comparative studies have confirmed the superiority of cTn over CK-MB and myoglobin for diagnosis and prognosis of AMI (27-32). The addition of CK-MB or myoglobin to cTn for evaluation of patients presenting with chest pain is not beneficial.

3. CARDIAC TESTING GENERAL CONSIDERATIONS

For acute and stable chest pain, noninvasive and invasive diagnostic testing is a core component of the evaluation underpinning its importance. Over the past decade, the quality of evidence supporting clinical indications for noninvasive testing has grown dramatically. The approach outlined in this guideline focuses on selective use of testing, optimization of lower cost evaluations, reducing layered testing, and deferring or eliminating testing when the diagnostic yield is low (**Figure 5**).

FIGURE 5 Chest Pain and Cardiac Testing Considerations



The choice of imaging depends on the clinical question of importance, to either a) ascertain the diagnosis of CAD and define coronary anatomy or b) assess ischemia severity among patients with an expected higher likelihood of ischemia with an abnormal resting ECG or those incapable of performing maximal exercise. ACS indicates acute coronary syndrome; CAC, coronary artery calcium; CAD, coronary artery disease; and ECG, electrocardiogram. Please refer to Section 4.1. For risk assessment in acute chest pain, see **Figure 9**. For risk assessment in stable chest pain, see **Figure 11**.

Reducing unnecessary testing can provide a means to exert cost savings within the diagnostic evaluation of populations (1). In the same manner, elimination of testing where evidence is lacking and the reduction in testing among low-risk patients for whom deferred testing is appropriate are emphasized in this guideline.

Testing choice will be influenced by site expertise and availability, but knowledge regarding which test may be preferable is useful when selecting between different modalities. Cost should also be considered, when known by the ordering clinician and there is equipoise between available modalities (2). The exercise ECG is the lowest cost procedure used in the diagnostic evaluation when compared with stress imaging or anatomic procedures, with the exception of coronary artery calcium (CAC) scoring (**Figure 6**). For all imaging procedures, costs vary by payer and site of services.

The following sections provide a brief overview of the various noninvasive tests available for use in the evaluation of symptomatic patients. Previously, the term known as CAD had been used to define those with a significant obstructive stenosis (i.e., ≥50%). In this guideline, we revise the term *known CAD* to include patients with prior anatomic testing (invasive angiography or coronary computed tomographic angiography [CCTA]) with identified nonobstructive atherosclerotic plaque and obstructive CAD. We recognize this is a departure from convention, but our intent was to ensure that those with lesser degrees of stenosis who do not require coronary intervention but would benefit from optimized preventive therapy do not get overlooked. However, throughout the document, the term "obstructive", consistent with convention, will be used to indicate CAD with ≥50% stenosis and nonobstructive CAD will be used to indicate CAD <50% stenosis. In addition, the term "high risk CAD" is used to denote patients with obstructive stenosis who have left main stenosis ≥50% or anatomically significant 3-vessel disease (≥70% stenosis).

3.1. Anatomic Testing

3.1.1. Coronary Computed Tomography Angiography

CCTA can visualize and help to diagnose the extent and severity of nonobstructive and obstructive CAD, as well as atherosclerotic plaque composition and high-risk features (e.g., positive remodeling, low attenuation plaque) (1-8). Calculation of fractional flow reserve with CT (FFR-CT) provides an estimation of lesion-specific ischemia (9). Current radiation dosimetry is low for CCTA, with effective doses for most patients in the 3 to 5 mSv range (10). CCTA contraindications are reported in **Table 5** Although in select situations imaging protocols that evaluate the coronary arteries, aorta, and pulmonary arteries may be useful, the general approach should be to use imaging protocols tailored to the most likely diagnosis, rather than a "triple rule out" approach (**Figure 6**).

3.1.2. Invasive Coronary Angiography

Invasive coronary angiography (ICA) defines the presence and severity of a luminal obstruction of an epicardial coronary artery, including its location, length, and diameter, as well as coronary blood flow (1,2). For ICA, the primary goal is the characterization and detection of a high-grade obstructive stenosis to define feasibility and necessity of percutaneous or surgical revascularization. The use of physiologic indices (IFR and FFR) provides complementary functional information (1). Radiation exposure to the patient during an interventional procedure averages 4 to 10 mSv and is dependent on procedural duration and complexity (3,4).

ICA has a spatial resolution of 0.3 mm; as such, it is impossible to visualize arterioles (diameter of 0.1 mm) that regulate myocardial blood flow (5). Coronary vascular functional studies can be performed during coronary angiography. Normal angiography does not exclude abnormal coronary vascular function, and it is possible to assess coronary microcirculation and coronary vasomotion. Coronary function testing may assist in management of the underlying condition, in addition to providing prognostic information (6-8).

3.2. Diagnostic Testing

3.2.1. Exercise ECG

Symptom-limited exercise ECG involves graded exercise until physical fatigue, limiting chest pain (or discomfort), marked ischemia, or a drop in blood pressure occurs (1). Candidates for exercise ECG are those: a) without disabling comorbidity (e.g., frailty, marked obesity [body mass index >40 kg/m^2], peripheral artery disease, chronic obstructive pulmonary disease, or orthopedic limitations) and capable of performing activities of daily living or able to achieve ≥5 metabolic equivalents of exercise (METs) (2); and b) without rest ST-T abnormalities (e.g., >0.5-mm ST depression, left ventricular hypertrophy, paced rhythm, left bundle branch block, Wolff-Parkinson-White pattern, or digitalis use). Exercise electrocardiographic contraindications are reported in **Table 5**.

FIGURE 6 Choosing the Right Diagnostic Test

Pretest likelihood of CAD	Low →	No testing necessary →	Option for CAC for ASCVD risk stratification		
	Intermediate-high →	Younger patient (<65 y of age)	**OR**	Less obstructive CAD suspected →	CCTA favored
	Intermediate-high →	Older patient (≥65 y of age)	**OR**	More obstructive CAD suspected →	Stress testing favored

	Favors use of CCTA	Favors use of stress imaging
Goal	• Rule out obstructive CAD • Detect nonobstructive CAD	• Ischemia-guided management
Availability and expertise	• High-quality imaging and expert interpretation routinely available	• High-quality imaging and expert interpretation routinely available
Likelihood of obstructive CAD	• Age <65 y	• Age ≥65 y
Prior test results	• Prior functional study inconclusive	• Prior CCTA inconclusive
Other compelling indications	• Anomalous coronary arteries • Require evaluation of aorta or pulmonary arteries	• Suspect scar (especially if PET or stress CMR available) • Suspect coronary microvascular dysfunction (when PET or CMR available)

Stress testing information					
	ETT	**Stress echocardiography**	**SPECT MPI**	**PET MPI**	**Stress CMR MPI**
Patient capable of exercise	✓	✓	✓		
Pharmacologic stress indicated		✓	✓	✓	✓
Quantitative flow				✓	✓
LV dysfunction/scar		✓	✓	✓	✓

ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance; ETT, exercise tolerance test; LV, left ventricular; MPI, myocardial perfusion imaging; PET, positron emission tomography and SPECT, single-photon emission computed tomography.

3.2.2. Echocardiography/Stress Echocardiography

Transthoracic echocardiography (TTE) can visualize and aid in the differential diagnosis among the numerous causes of acute chest pain such as acute aortic dissection, pericardial effusion, stress cardiomyopathy, and hypertrophic cardiomyopathy (1,2). Although TTE does provide information, for patients with acute chest pain, visualization of left and right ventricular function and regional wall motion abnormalities allows for the assessment of CAD risk and may help to guide clinical decision-

making. Performance of TTE at the bedside is ideal for patients with acute chest pain and can be done using point-of-care or handheld devices in institutions where such capabilities are available.

After ACS has been ruled out, stress echocardiography can be used to define ischemia severity and for risk stratification purposes. For TTE and stress echocardiography, ultrasound-enhancing agents are helpful for left ventricular opacification when ≥2 contiguous segments or a coronary territory is poorly visualized (3). Coronary flow velocity reserve in the mid-distal left anterior descending coronary artery has been shown to improve risk stratification and may be helpful in the select patient with known CAD, including nonobstructive CAD (4-6). Contraindications to stress type (exercise versus pharmacologic) and stress echocardiography are reported in **Table 5**.

3.2.3. Stress Nuclear (PET or SPECT) Myocardial Perfusion Imaging

After ACS has been ruled out, rest/stress positron emission tomography (PET) or single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) allows for detection of perfusion abnormalities, measures of left ventricular function, and high-risk findings, such as transient ischemic dilation (1-8). For PET, calculation of myocardial blood flow reserve (MBFR, the ratio of peak hyperemia to resting myocardial blood flow) adds diagnostic and prognostic information over MPI data (9-14). Radiation exposure, as reported by an average effective dose, is ~3 mSv for rest/stress PET with Rb-82 and ~10 mSv for Tc-99m SPECT; dual- isotope SPECT using thallium is not recommended (15-17). SPECT/PET contraindications are and contraindications to type of stress test (exercise versus pharmacologic) are reported in **Table 5**.

3.2.4. Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance (CMR) imaging has the capability to accurately assess global and regional left and right ventricular function, detect and localize myocardial ischemia and infarction, and determine myocardial viability. CMR can also detect myocardial edema and microvascular obstruction, which can help differentiate acute versus chronic MI, as well as other causes of acute chest pain, including myocarditis. CMR contraindications are reported in **Table 5**.

TABLE 5 Contraindication by Type of Imaging Modality and Stress Protocol

Exercise ECG	Stress Nuclear (1)*	Stress Echocardiography (2-5)	Stress CMR (6)	CCTA (7)*
■ Abnormal ST changes on resting ECG, digoxin, left bundle branch block, Wolff-Parkinson-White pattern, ventricular paced rhythm (unless test is performed to establish exercise capacity and not for diagnosis of ischemia) ■ Unable to achieve ≥5 METs or unsafe to exercise ■ High-risk unstable angina or AMI (<2 d) i.e., active ACS ■ Uncontrolled heart failure ■ Significant cardiac arrhythmias (e.g., VT, complete atrioventricular block) or high risk for arrhythmias caused by QT prolongation ■ Severe symptomatic aortic stenosis ■ Severe systemic arterial hypertension (e.g., ≥200/110 mm Hg)	■ High-risk unstable angina, complicated ACS or AMI (<2 d) ■ Contraindications to vasodilator administration ■ Significant arrhythmias (e.g., VT, second- or third-degree atrioventricular block) or sinus bradycardia <45 bpm ■ Significant hypotension (SBP <90 mm Hg) ■ Known or suspected bronchoconstrictive or bronchospastic disease	■ Limited acoustic windows (e.g., in COPD patients) ■ Inability to reach target heart rate ■ Uncontrolled heart failure ■ High-risk unstable angina, active ACS or AMI (<2 d) ■ Serious ventricular arrhythmia or high risk for arrhythmias attributable to QT prolongation ■ Respiratory failure ■ Severe COPD, acute pulmonary emboli, severe pulmonary hypertension ■ Contraindications to dobutamine (if pharmacologic stress test needed)	■ Reduced GFR (<30 mL/min/1.73 m^2) ■ Contraindications to vasodilator administration ■ Implanted devices not safe for CMR or producing artifact limiting scan quality/interpretation ■ Significant claustrophobia ■ Caffeine use within past 12 h	■ Allergy to iodinated contrast ■ Inability to cooperate with scan acquisition and/or breath-hold instructions ■ Clinical instability (e.g., acute respiratory distress, severe hypotension, unstable arrhythmia) ■ Renal impairment as defined by local protocols ■ Contraindication to beta blockade in the presence of an elevated heart rate and no alternative medications available for achieving target heart rate ■ Heart rate variability and arrhythmia ■ Contraindication to nitroglycerin (if indicated)

Continued on the next page

TABLE 5 Continued

Exercise ECG	Stress Nuclear (1)*	Stress Echocardiography (2-5)	Stress CMR (6)	CCTA (7)*
■ Acute illness (e.g., acute PE, acute myocarditis/pericarditis, acute aortic dissection)	■ Recent use of dipyridamole or dipyridamole-containing medications ■ Use of methylxanthines (e.g., aminophylline, caffeine) within 12 h ■ Known hypersensitivity to adenosine, regadenoson ■ Severe systemic arterial hypertension (e.g., ≥200/110 mm Hg)	■ Atrioventricular block, uncontrolled atrial fibrillation ■ Critical aortic stenosis† ■ Acute illness (e.g., acute PE, acute myocarditis/pericarditis, acute aortic dissection) ■ Hemodynamically significant LV outflow tract obstruction ■ Contraindications to atropine use: ■ Narrow-angle glaucoma ■ Myasthenia gravis ■ Obstructive uropathy ■ Obstructive gastrointestinal disorders ■ Severe systemic arterial hypertension (e.g., ≥200/110 mm Hg) Use of Contrast Contraindicated in: ■ Hypersensitivity to perflutren ■ Hypersensitivity to blood, blood products, or albumin (for Optison only)		

For all the imaging modalities, inability to achieve high-quality images should be considered, in particular for obese patients

Readers should also review each imaging society's guidelines for more details on test contraindications (1-14).
*Screening for potential pregnancy by history and/or pregnancy testing should be performed according to the local imaging facilities policies for undertaking radiological examinations that involve ionizing radiation in women of child-bearing age.
†Low-dose dobutamine may be useful for assessing for low-gradient AS.

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; AS, aortic stenosis; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance imaging; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LV, left ventricular; MET, metabolic equivalent; MRI, magnetic resonance imaging; PE, pulmonary embolism; SBP, systolic blood pressure; and VT, ventricular tachycardia.

3.3. Cardiac Testing Considerations for Women Who Are Pregnant, Postpartum, or of Child-Bearing Age

This guideline focuses on elective and urgent cardiac testing and, in both circumstances, imaging using ionizing radiation during pregnancy or postpartum while breast feeding should generally be avoided. When imaging is necessary to guide management, the risks and benefits of invasive angiography, SPECT, PET, or CCTA should be discussed with the patient. In all cases for a test deemed clinically necessary, the lowest effective dose of ionizing radiation should be used, including considerations for tests with no radiation exposure (e.g., echocardiography, CMR imaging) (1). Radiation risk to the fetus is very small. Iodinated contrast enters the fetal circulation through the placenta and should be used with caution in a pregnant woman. The use of gadolinium contrast with CMR should be discouraged and used only when necessary to guide clinical management and is expected to improve fetal or maternal outcome (2-5). If contrast is needed for a postpartum woman, breastfeeding may continue because <1% of iodinated contrast is excreted into the breast milk and absorbed into the infant's gastrointestinal tract (6).

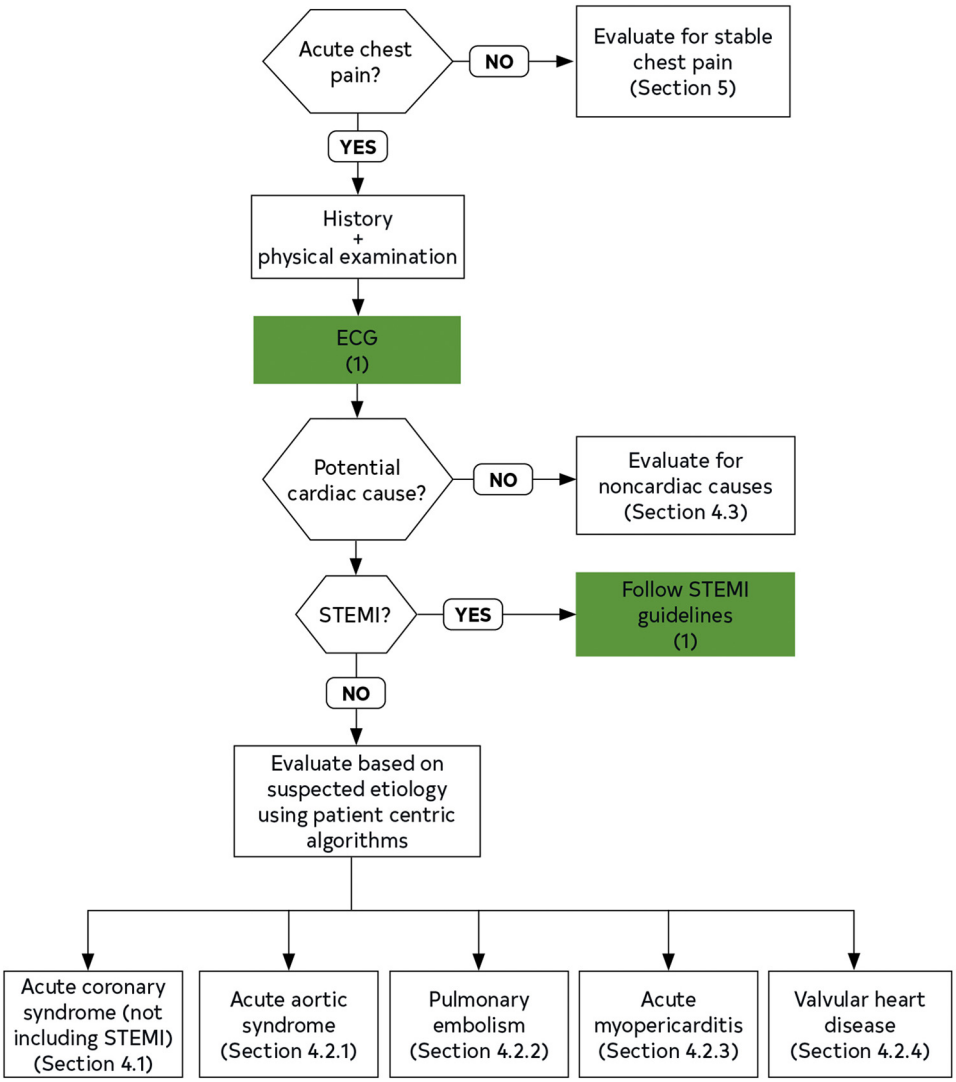
4. CHOOSING THE RIGHT PATHWAY WITH PATIENT-CENTRIC ALGORITHMS FOR ACUTE CHEST PAIN

After initial evaluation, the next step is determining whether further diagnostic testing is needed to establish a diagnosis or formulate a disposition plan. In some cases, there is clearly minimal risk of a serious medical condition although, in others, uncertainty may remain. We provide guidance to help clinicians make this determination within the context of acute and stable chest pain presentations.

The initial assessment of patients presenting with acute chest pain is focused on the rapid identification of patients with immediately life-threatening conditions such that appropriate medical interventions can be initiated. Included among the potentially life-threatening (emergency) causes of chest pain are ACS (Section 4.1), acute aortic syndromes (Section 4.2.1), and PE (Section 4.2.2).

Myopericarditis is heterogeneous in its manifestations but can include fulminant myocarditis, which carries a high mortality rate (Section 4.2.3). A subset of noncardiovascular syndromes are also immediately life-threatening, including esophageal rupture (Section 4.3.1), tension pneumothorax, and sickle cell chest crisis. Nonemergency causes of chest pain, such as costochondritis and other musculoskeletal, or gastrointestinal causes, are discussed in Section 4.3. Such nonemergency causes predominate among patients presenting with acute chest pain; therefore, strategies that incorporate routine, liberal use of testing carry the potential for adverse effects of unnecessary investigations and unnecessary cost. **Figure 7** provides an overview of this approach.

FIGURE 7 Patient-Centric Algorithms for Acute Chest Pain



ECG indicates electrocardiogram; and STEMI, ST-segment–elevation myocardial infarction.

JACC VOL. 78, NO. 22, 2021
NOVEMBER 30, 2021:e187–e285

4.1. Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI)

Recommendations for Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI)
Referenced studies that support the recommendations are summarized in Online Data Supplements 8 and 9.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients presenting with acute chest pain and suspected ACS, clinical decision pathways (CDPs) should categorize patients into low-, intermediate-, and high-risk strata to facilitate disposition and subsequent diagnostic evaluation (1-14).
1	B-NR	2. In the evaluation of patients presenting with acute chest pain and suspected ACS for whom serial troponins are indicated to exclude myocardial injury, recommended time intervals after the initial troponin sample collection (time zero) for repeat measurements are: 1 to 3 hours for high-sensitivity troponin and 3 to 6 hours for conventional troponin assays (15-17).
1	C-LD	3. To standardize the detection and differentiation of myocardial injury in patients presenting with acute chest pain and suspected ACS, institutions should implement a CDP that includes a protocol for troponin sampling based on their particular assay (18,19)
1	C-LD	4. In patients with acute chest pain and suspected ACS, previous testing when available should be considered and incorporated into CDPs (20-24).
2a	B-NR	5. For patients with acute chest pain, a normal ECG, and symptoms suggestive of ACS that began at least 3 hours before ED arrival, a single hs-cTn concentration that is below the limit of detection on initial measurement (time zero) is reasonable to exclude myocardial injury (13,25-29).

Synopsis

Patients with acute chest pain and suspected ACS cover a spectrum of disease likelihood and stratification into low- versus intermediate- or high-risk groups once STEMI has been excluded (**Figure 8**). This stratification is important to guide subsequent management. Although most high-risk patients identified by CDPs should undergo cardiac catheterization, these patients still require a clinical assessment to determine if invasive evaluation is appropriate.

Chest pain risk scores provide a summative assessment combining clinical information, such as age, ST segment changes on ECG, symptoms, CAD risk factors, and cTn (**Table 6**) to estimate a patient's probability of ACS or risk of 30-day major adverse cardiovascular events (MACE) (30-35). Risk scores are essential when conventional cTn assays are used. Based on emerging data, the hs-cTn result may be more predictive than other clinical components of the risk score (36-43).

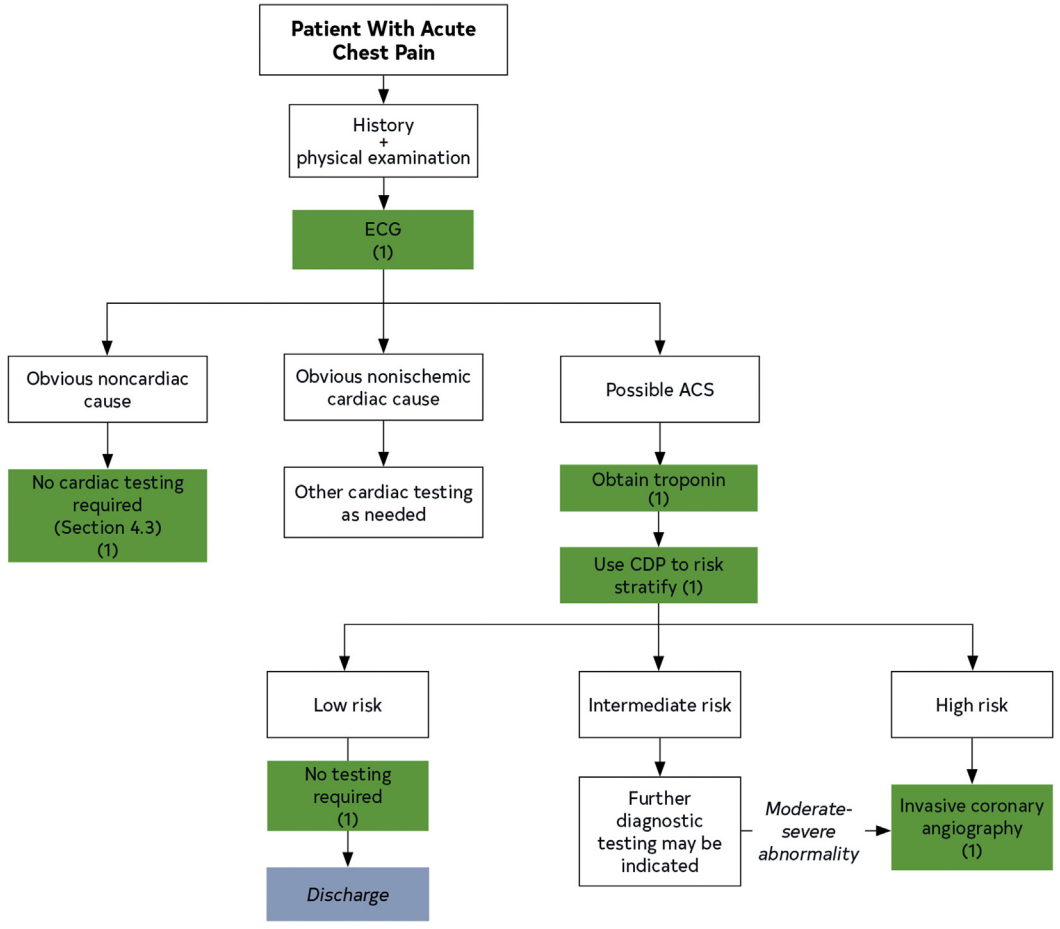
Chest pain protocols are intended to add structure to the process of patient evaluation. Although various terms such as accelerated diagnostic protocols or disposition pathways have been used to describe such protocols, they can collectively be referred to as CDPs. CDPs are generally used to help guide disposition, but some also include guidance for cardiac testing of intermediate-risk patients (30,31,33,34).

Compared with an unstructured clinical assessment, CDPs have been shown to decrease unnecessary testing and reduce admissions while maintaining high sensitivity for detection of acute myocardial injury and 30-day MACE (**Table 6**). The warranty period of prior cardiac testing should be considered when symptoms are unchanged (**Table 7**). Low-risk chest pain has been defined in **Table 8**.

Recommendation-Specific Supportive Text

1. CDPs that are based on cTn results have proven valid and useful in clinical practice (1-14). Use of unstructured assessment for clinical decision-making often leads to both under- and overtesting. To improve on this, protocols have been developed to rapidly detect (rule in) and to rapidly exclude or "rule out" acute myocardial injury, incorporating time-dependent serial cTn sampling. Some protocols include chest pain risk scores while others do not. CDPs have been shown to help avoid admission or further testing in 21.3% to 43% of eligible patients and should be routinely used in clinical practice (31,45,50). To standardize the approach to patient care and ensure consistency in decision-making, CDPs should be implemented at the institution level. There are multiple CDPs from which to choose, and all generally involve single or serial cTn measurement. Because there are several different manufacturers, the

FIGURE 8 General Approach to Risk Stratification of Patients With Suspected ACS



ACS indicates acute coronary syndrome; CDP, clinical decision pathway; and ECG, electrocardiogram.

TABLE 6 Sample Clinical Decision Pathways Used to Define Risk

	HEART Pathway (31)	EDACS (44)	ADAPT (mADAPT) (45)	NOTR (34)	2020 ESC/hs-cTn* (46,47)	2016 ESC/GRACE (11,38)
Target population	Suspected ACS	Suspected ACS, CP >5 min, planned serial troponin	Suspected ACS, CP >5 min, planned observation	Suspected ACS, ECG, troponin ordered	Suspected ACS, stable	Suspected ACS, planned serial troponin
Target outcome	↑ ED discharge without increasing missed 30-d or 1-y MACE	↑ ED discharge rate without increasing missed 30-d MACE	↑ ED discharge rate without increasing missed 30-d MACE	↑ Low-risk classification without increasing missed 30-d MACE	Early detection of AMI; 30-d MACE	Early detection of AMI
Patients with primary outcome in study population, %	6–22	12	15	5–8	9.8	10–17
Troponin	cTn, hs-cTn	hs-cTn	cTn, hs-cTn	cTn, hs-cTn	hs-cTn	cTn, hs-cTn

Continued on the next page

TABLE 6 Continued

	HEART Pathway (31)	EDACS (44)	ADAPT (mADAPT) (45)	NOTR (34)	2020 ESC/hs-cTn* (46,47)	2016 ESC/GRACE (11,38)
Variables used	History ECG Age Risk factors Troponin (0, 3 h)	Age Sex Risk factors History Troponin (0, 2 h)	TIMI score 0-1 No ischemic ECG changes Troponin (0, 2 h)	Age Risk factors Previous AMI or CAD Troponin (0, 2 h)	History ECG hs-cTn (0, 1 or 2 h)	Age HR, SBP Serum Cr Cardiac arrest ECG Cardiac biomarker Killip class
Risk thresholds:						
■ Low risk	HEART score <3 Neg 0, 3-h cTn Neg 0, 2-h hs-cTn	EDACS score <16 Neg 0, 2 h hs-cTn No ischemic ECG Δ	TIMI score 0 (or <1 for mADAPT) ■ Neg 0, 2-h cTn or hs-cTn ■ No ischemic ECG Δ	Age <50 y <3 risk factors Previous AMI or CAD Neg cTn or hs-cTn (0, 2 h)	■ Initial hs-cTn is "very low" and Sx onset >3 h ago **Or** ■ Initial hs-cTn "low" and 1- or 2-h hs-cTn Δ is "low"	Chest pain free, GRACE <140 ■ Sx <6 h - hs-cTn <ULN (0, 3 h) ■ Sx >6 h - hs-cTn <ULN (arrival)
■ Intermediate risk	HEART score 4-6	NA	TIMI score 2-4	NA	■ Initial hs-cTn is between "low" and "high" **And/Or** ■ 1- or 2-h hs-cTn Δ is between low and high thresholds	■ TO hs-cTn = 12–52 ng/L or ■ 1-h Δ = 3–5 ng/L
■ High risk	HEART score 7-10 (48,49)	NA	TIMI score 5-7 (49)	NA	■ Initial hs-cTn is "high" **Or** ■ 1- or 2-h hs-cTn Δ is high	■ TO hs-cTn >52 ng/L **Or** ■ Δ 1 h >5 ng/L
Performance	↑ ED discharges by 21% (40% versus 18%) ↓ 30-d objective testing by 12% (69% versus 57%) ↓ length of stay by 12 h (9.9 versus 21.9 h)	More patients identified as low risk versus ADAPT (42% versus 31%)	ADAPT: More discharged ≤6 h (19% versus 11%)	30-d MACE sensitivity =100% 28% eligible for ED discharge	AMI sensitivity >99% 62% Ruled out (0.2% 30-d MACE) 25% Observe 13% Rule in	AMI sensitivity >99% 30-d MACE not studied
AMI sensitivity, %	100	100	100	100	>99	96.7
cTn accuracy: 30-d MACE sensitivity, %	100	100	100	100	NA	NA
hs-cTn accuracy: 30-d MACE sensitivity, %	95	92	93	99	99	-
ED discharge, %	40	49	19 (ADAPT) 39 (mADAPT)	28	-	-

*The terms "very low," "low," "high," "1 h Δ," and "2 h Δ" refer to hs-cTn assay-specific thresholds published in the ESC guideline (46,47).

ACS indicates acute coronary syndrome; ADAPT, Accelerated Diagnostic protocol to Assess chest Pain using Troponins; AMI, acute myocardial infarction; CP, chest pain or equivalent; Cr, creatinine; cTn, cardiac troponin; hs-cTn, high-sensitivity cardiac troponin; ECG, electrocardiogram; ED, emergency department; EDACS, emergency department ACS; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; HEART, history, ECG, age, risk factors, troponin; HR, heart rate; hs, high sensitivity; MACE, major adverse cardiovascular events; mADAPT, modified (including TIMI scores of 1) ADAPT; NA, not applicable; neg, negative; NICE, National Institute for Health and Clinical Excellence; NOTR, No Objective Testing Rule; SBP, systolic blood pressure; SSACS, symptoms suggestive of ACS; Sx, symptoms; and ULN, upper limit of normal.

CDP should be based on assay-specific performance thresholds (4,5). CDPs are more likely to be successful when they incorporate multidisciplinary teams.

2. There are important differences in the performance of highly sensitive and conventional cTn assays. hs-cTn assays may be used to guide disposition by repeat sampling at 1, 2, or 3 hours from ED arrival using the pattern of rise or fall (i.e., delta) and the repeat value itself, based on assay-specific diagnostic thresholds (37-43). When using conventional cTn assays, the sampling timeframe is extended to 3 to 6 hours from ED arrival (36).
3. CDPs that include risk scores all perform well overall, with 99% to 100% sensitivity for index-visit AMI and 30-day MACE and have been shown to decrease advanced testing to varying degrees and should be used particularly with conventional cTn (2,13,30-35). However, because sex-specific considerations are not included in all scoring systems, their effectiveness in men and women may not be equal (51).
4. Previous test results should always be considered in the evaluation of patients with acute chest pain once ACS has been ruled out. In those with recent cardiac testing and normal findings who do not have biomarker evidence of acute myocardial injury, further testing is of limited value, provided that adequate exercise levels were achieved or pharmacologic stress was performed, imaging was of sufficient quality, and there are no changes in symptom frequency or stability at the new visit. The "warranty" intervals (**Table 7**) for the various cardiac testing modalities differ because of the low number of incident events among patients with a normal CCTA, although patients with normal stress testing may still have significant plaque and a higher event rate (20-22). The warranty period for a normal stress-rest SPECT is highly variable because it is primarily determined by the type of stress, the patient's clinical characteristics, and left ventricular ejection fraction (52).
5. To use cTn properly, an understanding of the assay used (high sensitivity or conventional) and the timing of chest pain onset relative to ED arrival is critical (17,38,39). CDPs that emphasize rapid rule-out based on single hs-cTn concentrations below the limit of detection should be limited to patients whose symptoms started at least 3 hours before ED arrival (2,5,6,11,14,16,25,40-43,53-55). Unlike high-sensitivity assays, clinical decision-making based on single measurement of conventional cTn has not been validated (36). If the clinical presentation is still suspicious for ACS or diagnostic uncertainty remains after serial cTn measurement, it may be reasonable to repeat cTn assay later (i.e., beyond 3 hours for high-sensitivity and beyond 6 hours for conventional assays) (23,40,41).

TABLE 7 Warranty Period for Prior Cardiac Testing

Test Modality	Result	Warranty Period
Anatomic	Normal coronary angiogram CCTA with no stenosis or plaque	2 y
Stress testing	Normal stress test (given adequate stress)	1 y

Table 8 provides a definition used for low-risk chest pain patients.
CCTA indicates coronary computed tomographic angiography.

4.1.1. Low-Risk Patients With Acute Chest Pain

Synopsis

Recommendations for Low-Risk Patients With Acute Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 10 and 11.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. Patients with acute chest pain and a 30-day risk of death or MACE <1% should be designated as low risk (1-11).
2a	B-R	2. In patients with acute chest pain and suspected ACS who are deemed low-risk (<1% 30-day risk of death or MACE), it is reasonable to discharge home without admission or urgent cardiac testing (12-16).

TABLE 8 Definition Used for Low-Risk Patients With Chest Pain

	Low Risk (<1% 30-d Risk for Death or MACE)
hs-cTn Based	
T-0	T-0 hs-cTn below the assay limit of detection or "very low" threshold if symptoms present for at least 3 h
T-0 and 1- or 2-h Delta	T-0 hs-cTn and 1- or 2-h delta are both below the assay "low" thresholds (>99% NPV for 30-d MACE)
Clinical Decision Pathway Based	
HEART Pathway (20)	HEART score ≤3, initial and serial cTn/hs-cTn < assay 99th percentile
EDACS (14)	EDACS score ≤16; initial and serial cTn/hs-cTn < assay 99th percentile
ADAPT (21)	TIMI score 0, initial and serial cTn/hs-cTn < assay 99th percentile
mADAPT	TIMI score 0/1, initial and serial cTn/hs-cTn < assay 99th percentile
NOTR (15)	0 factors

ADAPT indicates 2-hour Accelerated Diagnostic Protocol to Access Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarkers; cTn, cardiac troponin; EDACS, Emergency Department Acute Coronary Syndrome; HEART Pathway, History, ECG, Age, Risk Factors, Troponin; hs-cTn, high-sensitivity cardiac troponin; MACE, major adverse cardiovascular events; mADAPT, modified 2-hour Accelerated Diagnostic Protocol to Access Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarkers; NOTR, No Objective Testing Rule; NPV, negative predictive value; and TIMI, Thrombolysis in Myocardial Infarction.

Low-risk patients are those with symptoms suggestive of ACS and whose probability of MACE within 30 days is ≤1% (17). This estimate is based on clinical information that is readily available during the course of evaluation, typically occurring in the ED. There are several methods to determine that a patient is low risk (**Table 8**) but, invariably, all involve taking an appropriate history and physical examination, demonstration that the ECG is normal, nonischemic, or unchanged from the previous ECG, and cTn measurement at a single point in time (if presentation is >3 hours from symptom onset and using a high-sensitivity assay) or serially (1-11) (with incorporation of a chest pain risk score into the CDP if using a conventional cTn assay). Importantly, there is no evidence to support routine admission or cardiac testing for chest pain patients who are low risk, although outpatient CAC scanning can provide additional information for longer-term risk stratification.

Recommendation-Specific Supportive Text

1. A large proportion of patients presenting to the ED with chest pain are low risk based on a combination of features, including clinical stability, medical history, nonischemic ECG, and absence of acute myocardial injury on cTn measurement. Such individuals have a <1% frequency of ACS or MACE at 30 days (1-11). Although achieving this with conventional cTn assays requires incorporation of risk scores into a CPD, hs-cTn results can be used on their own. This approach has been validated based on 15 studies including a total of >9,600 patients, with a demonstrated negative predictive value for MI or death at 30 days of 99.8% (11). These findings reflect studies involving both hs-cTnI and hs-cTnT using serial measurement algorithms or a single hs-cTn, provided the final measurement is performed ≥3 hours after the onset of symptoms, without incorporation of risk scores.
2. For this low-risk subset of ED patients who have chest pain, there is no evidence that stress testing or cardiac imaging within 30 days of the index ED visit improves their outcomes (18). This represents a change from previous guidelines where stress testing within 72 hours was broadly recommended for patients with acute chest pain (19). However, many of these patients have baseline cardiac risk factors that need to be managed. Pathways to facilitate outpatient follow-up for further evaluation and guideline-directed management of cardiac risk factors should be considered. Among patients presenting to the ED with chest pain, there is a separate group that is at such low risk of having atherosclerotic plaque or 30-day MACE that they do not even need CDP-based risk stratification.

4.1.1.1. Cost-Value Considerations in the Evaluation of Low-Risk Patients

The costs associated with the acute evaluation of chest pain have been examined within systematic reviews, health technology appraisals, and data collected in the observational or randomized clinical trial setting (1-10). The decision analytic models suggest that the use of hs-Tn can be cost effective as a rule-out for ACS, primarily attributable to prompt discharge of patients without hs-Tn elevations (2,8,11,12). Moreover, hs-Tn–guided diagnostic strategies also reduced the use of stress testing by nearly one-third (13). From a large multicenter registry, the reduced time to discharge and use of noninvasive testing contributed to a cost savings of 20% (13). Nonadherence to management recommendations impact the potential for cost savings (5). From a randomized trial applying the HEART Pathway, a modest 30-day cost savings of $216 per

patient (p=0.04) was observed (6). However, the overall reductions in hospital admission and length of stay impacted population estimates for cost savings from 1 ED registry of 30,769 patients presenting before and 23,699 patients presenting after implementation of an accelerated diagnostic pathway and resulted in a total cost reduction of $13.5 million (Australian) (7). Thus, improved process efficiency and discharge of low-risk patients largely results in overall cost reductions.

4.1.2. Intermediate-Risk Patients With Acute Chest Pain

Recommendations for Intermediate-Risk Patients With Acute Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 12 and 13.

COR	LOE	RECOMMENDATIONS
1	C-EO	1. For intermediate-risk patients with acute chest pain, TTE is recommended as a rapid, bedside test to establish baseline ventricular and valvular function, evaluate for wall motion abnormalities, and to assess for pericardial effusion.
2a	A	2. For intermediate-risk patients with acute chest pain, management in an observation unit is reasonable to shorten length of stay and lower cost relative to an inpatient admission (1-7).

Synopsis

Patients in the ED without high-risk features and not classified as low risk by a CDP fall into an intermediate-risk group. Intermediate-risk patients do not have evidence of acute myocardial injury by troponin but remain candidates for additional cardiac testing. Some may have chronic or minor troponin elevations. This testing often requires more time than is appropriate for an ED visit. These patients may be placed in an inpatient bed or managed in a dedicated observation unit using a chest pain protocol.

Recommendation-Specific Supportive Text

1. Prompt use of TTE allows for an evaluation of cardiac cause for symptoms and evaluation of alternative pathologies for acute chest pain (8-13). Rapid echocardiographic assessment may facilitate imaging of patients while they are symptomatic. Point-of-care echocardiograms performed at the bedside by properly trained clinicians and technicians may be particularly useful.
2. The additional testing needed for intermediate-risk patients often requires more time than is appropriate for an ED visit and is often performed under "observation" outpatient status. These patients may be placed in an inpatient bed or managed in a dedicated observation unit. Relative to care in an inpatient bed, dedicated observation units have been shown to decrease hospital admissions, length of stay, and cost while improving inpatient bed availability and chest pain patient satisfaction (1-7).

4.1.2.1. Intermediate-Risk Patients With Acute Chest Pain and No Known (CAD)

Recommendations for Intermediate-Risk Patients With No Known CAD
Referenced studies that support the recommendations are summarized in Online Data Supplements 14 and 15.

COR	LOE	RECOMMENDATIONS
		Index Diagnostic Testing
		Anatomic Testing
1	A	1. For intermediate-risk patients with acute chest pain and no known CAD eligible for diagnostic testing after a negative or inconclusive evaluation for ACS, CCTA is useful for exclusion of atherosclerotic plaque and obstructive CAD (1-11).
1	C-EO	2. For intermediate-risk patients with acute chest pain, moderate-severe ischemia on current or prior (≤1 year) stress testing, and no known CAD established by prior anatomic testing, ICA is recommended.
2a	C-LD	3. For intermediate-risk patients with acute chest pain with evidence of previous mildly abnormal stress test results (≤1 year), CCTA is reasonable for diagnosing obstructive CAD (12,13).

(Continued)

		Stress Testing
1	B-NR	4. For intermediate-risk patients with acute chest pain and no known CAD who are eligible for cardiac testing, either exercise ECG, stress echocardiography, stress PET/SPECT MPI, or stress CMR is useful for the diagnosis of myocardial ischemia (1,4,10,14-36).
		Sequential or Add-on Diagnostic Testing
2a	B-NR	5. For intermediate-risk patients with acute chest pain and no known CAD, with a coronary artery stenosis of 40% to 90% in a proximal or middle coronary artery on CCTA, FFR-CT can be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization (37-43).
2a	C-EO	6. For intermediate-risk patients with acute chest pain and no known CAD, as well as an inconclusive prior stress test, CCTA can be useful for excluding the presence of atherosclerotic plaque and obstructive CAD.
2a	C-EO	7. For intermediate-risk patients with acute chest pain and no known CAD, with an inconclusive CCTA, stress imaging (with echocardiography, PET/SPECT MPI, or CMR) can be useful for the diagnosis of myocardial ischemia.

Synopsis

For patients with recent prior testing and normal findings, no further testing is indicated, given adequate exercise levels were achieved or pharmacologic stress was performed and if imaging was of sufficient quality, provided there are no changes in symptom frequency or stability at the new visit. The intervals (1 year for stress testing, 2 years for CCTA without plaque or stenosis) differ because of a lack of CAD progression and the low number of incident events among patients with a normal CCTA, although patients with normal stress testing may still have significant plaque and a higher event rate (44-46). With a previously inconclusive or mildly abnormal stress test in the past year, CCTA is recommended, avoiding the potential for inconclusive results if the same type of test is repeated and enabling a more definitive rule-out of obstructive CAD. Among patients who present with acute chest pain who have had moderate-severe abnormalities on previous testing, but no interval anatomic testing, direct referral to ICA may be helpful for diagnosis of obstructive CAD.

Among those without a previous diagnostic evaluation and no known CAD, CCTA or stress testing may be the initial method of testing. Second-line testing may be helpful for patients with an initial inconclusive stress test. Similarly, for intermediate-risk patients with an intermediate stenosis on CCTA, FFR-CT, or stress testing may also be indicated.

ICA is indicated for patients categorized as high risk on a validated risk score (**Figure 9**). However, patients with an intermediate-risk score may also be candidates for CCTA or ICA if moderate-severe ischemia or significant left ventricular dysfunction is detected on index diagnostic testing.

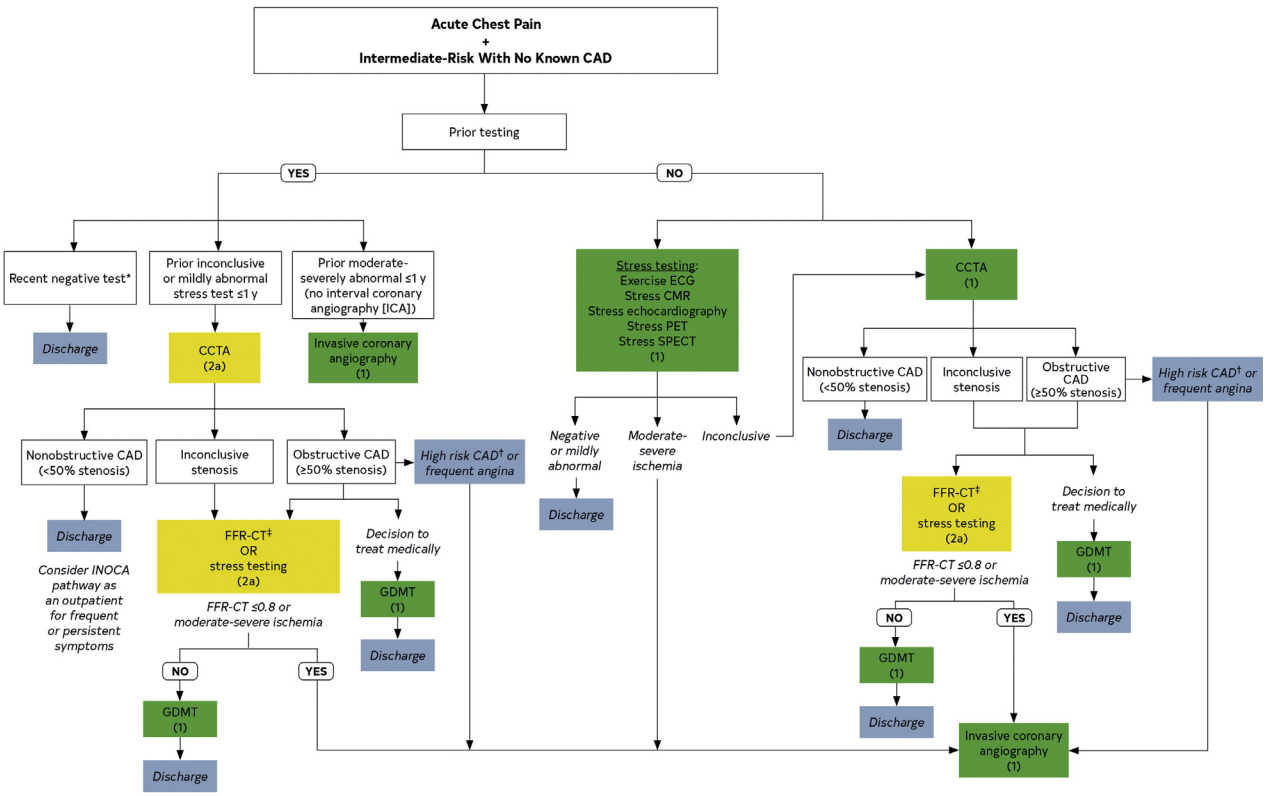
Although there are several acceptable testing modalities for intermediate-risk patients with acute chest pain, the decision to use one versus another should be guided by local expertise and availability.

Recommendation-Specific Supportive Text

Anatomic Testing

1. In the ED evaluation of patients with acute chest pain, CCTA contributes to a reduced time to diagnosis and prompt discharge, without impacting safety (i.e., no difference in death, repeat ED visits, or ACS over 1 to 6 months of follow-up) compared with a standard evaluation including stress testing (1-4,8,47-50). Long-term prognostic data are limited, but the CATCH (Cardiac CT in the Treatment of Acute Chest Pain) trial showed a relative hazard for CAD events at ~18 months of 0.62 (95% CI: 0.40-0.98; p=0.04) for CCTA versus a standard care strategy (48). Similar 40-month MACE rates were reported in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial comparing CCTA- versus MPI-directed strategies (p=0.29) (10). Similar 2-year outcomes were also reported for stress echocardiography and CCTA (p=0.47) (29).
2. In patients who have evidence of moderate or severe ischemia on previous stress testing, who were not revascularized, and who present with acute chest pain, additional noninvasive stress testing is unlikely to result in any change in management. Such patients are assumed to have significant flow-limiting CAD and can proceed directly to an invasive evaluation if coronary revascularization is consistent with the goals of care. A sizeable proportion of patients with moderate-severe ischemia do not undergo ICA (51,52) and may require additional assessment, if repeat symptoms occur.
3. Symptomatic patients with inconclusive or mildly abnormal stress tests often have an increased risk of MACE (53). Patients with previous stress testing often have atherosclerotic plaque and are at risk for obstructive CAD lesions (12,13).

FIGURE 9 Evaluation Algorithm for Patients With Suspected ACS at Intermediate Risk With No Known CAD



Test choice should be guided by local availability and expertise. *Recent negative test: normal CCTA ≤2 years (no plaque/no stenosis) OR negative stress test ≤1 year, given adequate stress. †High-risk CAD means left main stenosis ≥ 50%; anatomically significant 3-vessel disease (≥ 70% stenosis). ‡For FFR-CT, turnaround times may impact prompt clinical care decisions. However, the use of FFR-CT does not require additional testing, as would be the case when adding stress testing. CAD indicates coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; ICA, invasive coronary angiography; INOCA, ischemia and no obstructive coronary artery disease; PET, positron emission tomography; and SPECT, single-photon emission CT.

Stress Testing

4. Among patients evaluated in the ED who need further testing, exercise ECG is safe with most patients having negative studies and a low risk of ACS (1,4,10,14-31, 54). Stress echocardiography is safe and effective for triage and prompt discharge of patients and is associated with few events among those with normal or low-risk findings over near-term follow-up of up to 6 months (17,18,36). Prompt stress echocardiography resulted in a reduction in ED and hospital length of stay, compared with CCTA, with similar 2-year MACE rates (p=0.47) (29). In the ED evaluation of patients with acute chest pain, a nuclear MPI strategy is similarly safe when compared with CCTA with no difference in MACE (death, ACS, or stroke) over follow-up of 6 to 12 months. Longer-term follow-up data from the PROSPECT trial (10) supported that at ~3.5 years, the rate of MACE was similar between MPI and CCTA (p=0.29) (10). Compared with CCTA, use of stress MPI delayed the time to diagnosis by >50% (1,4). Furthermore, recent observation from 213 patients referred for rest-stress MPI with mildly abnormal hs-cTn values reported no adverse events related to the tests and a modest 13.6% yield for ischemic studies (55). Single-center, small (n=105) randomized trial evidence suggests that stress CMR is safe without a near-term (90-day) increase in hospital readmission or additional testing (32-34). From a single-center registry (n=135), stress CMR was associated with a high sensitivity (100%) and specificity (93%) for the detection of obstructive CAD or cardiovascular events at 1 year (35).

Sequential or Add-on Testing

5. Patients with coronary artery stenosis of 40% to 90% in a proximal or middle coronary segment on CCTA may benefit from measurement of FFR-CT (37-43). In a large registry of 555 patients, the addition of FFR-CT was safe with no difference in 90-day MACE compared with CCTA alone (42). No deaths or MI occurred among patients with a negative FFR-CT when revascularization was deferred.
6. CCTA is highly effective at ruling out the presence of plaque or stenosis and may help to clarify risk

assessment and subsequent management decisions in patients with no known CAD who have inconclusive stress test results.

7. Patients with acute chest pain who have indeterminate stenosis on CCTA may benefit from having a stress test with imaging to evaluate for myocardial ischemia (37-43).

4.1.2.1.1. Cost-Value Considerations

Economic evaluations have explored the value of stress echocardiography, CCTA, and stress nuclear imaging. Several observational series report that prompt stress echocardiography in the ED for the evaluation of acute chest pain is associated with significantly lower costs, with no adverse sequelae after early discharge (1,2). In a single-center randomized trial of 400 patients, prompt stress echocardiography was associated with a reduced rate of hospitalization ($p=0.026$) and length of stay in the ED ($p<0.0001$) (3). The CT-STAT (Systematic Triage of Acute Chest Pain Patients to Treatment) trial reported on the use of CCTA (n=361 patients) compared with stress MPI (n=338 patients) in the acute evaluation of chest pain in the ED (4). In the CT-STAT trial, the time to diagnosis was 2.9 hours in the CCTA arm and 6.2 hours in the stress MPI arm ($p<0.0001$). Accordingly, median adjusted ED charges were nearly 40% lower for CCTA, compared with stress MPI ($2,137 for CCTA versus $3,458 for stress MPI; $p<0.001$). Overall, CCTA resulted in improved efficiency with a reduction in length of stay and prompt discharge (5,6), resulting in cost savings from 15% to 38% when compared with standard care strategies (4,7) and a weighted cost savings of $680 (8).

4.1.2.2. Intermediate-Risk Patients With Acute Chest Pain and Known CAD

Recommendations for Intermediate-Risk Patients With Acute Chest Pain and Known CAD
Referenced studies that support the recommendations are summarized in Online Data Supplements 16 and 17.

COR	LOE	RECOMMENDATIONS
1	A	1. For intermediate-risk patients with acute chest pain who have known CAD and present with new onset or worsening symptoms, GDMT should be optimized before additional cardiac testing is performed (1,2).
1	A	2. For intermediate-risk patients with acute chest pain who have worsening frequency of symptoms with significant left main, proximal left anterior descending stenosis, or multivessel CAD on prior anatomic testing or history of prior coronary revascularization, ICA is recommended (3-8).
2a	B-NR	3. For intermediate-risk patients with acute chest pain and known nonobstructive CAD, CCTA can be useful to determine progression of atherosclerotic plaque and obstructive CAD (9-11).
2a	B-NR	4. For intermediate-risk patients with acute chest pain and coronary artery stenosis of 40% to 90% in a proximal or middle segment on CCTA, FFR-CT is reasonable for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization (12-17).
2a	B-NR	5. For intermediate-risk patients with acute chest pain and known CAD who have new onset or worsening symptoms, stress imaging (PET/SPECT MPI, CMR, or stress echocardiography) is reasonable (18-21).

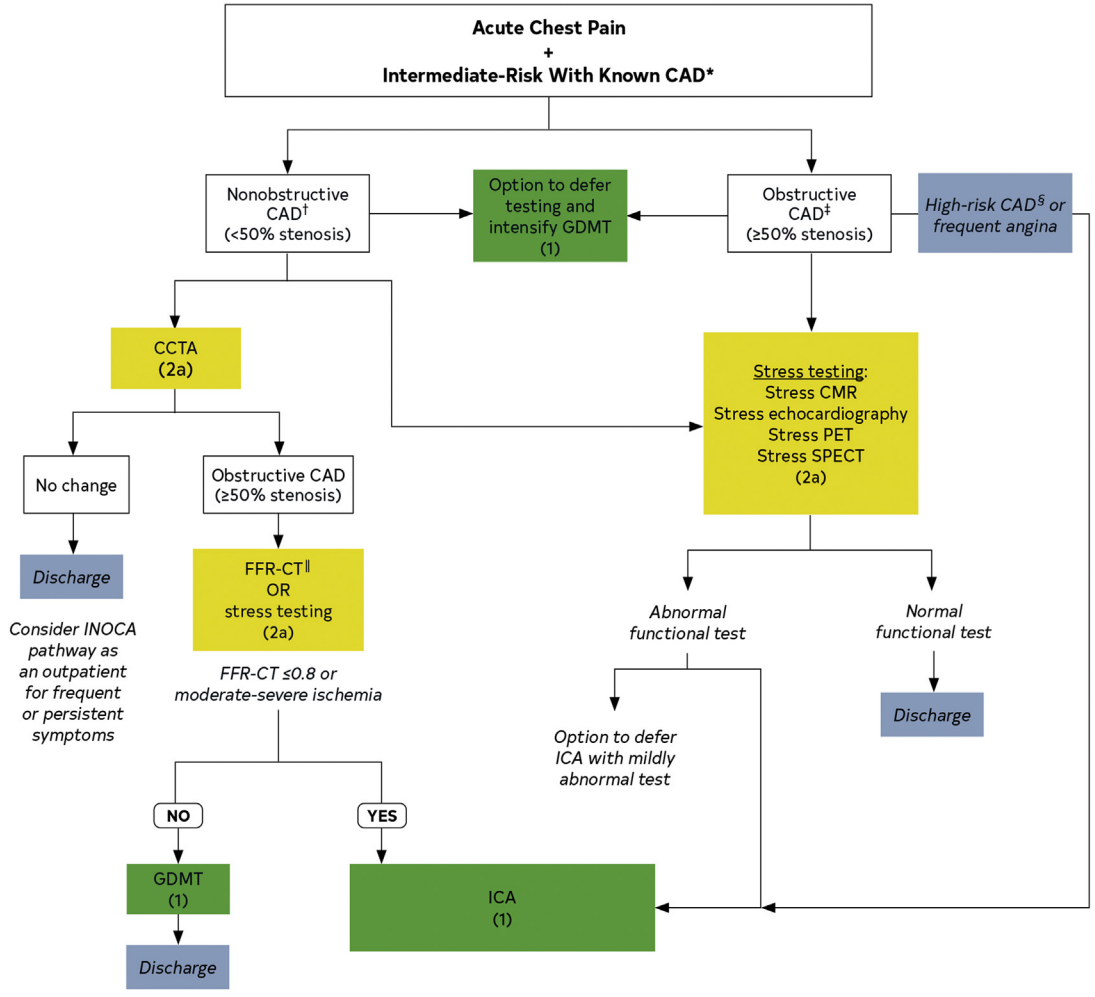
Synopsis

Figure 10 includes the evaluation algorithm for patients with known CAD, including patients with nonobstructive and obstructive CAD. In patents with known nonobstructive CAD (i.e., a luminal stenosis 1% to 49% on CCTA or ICA or calcified plaque on chest CT), repeat CCTA is recommended unless there is a large enough plaque burden where ischemia is suspected. The use of FFR-CT may be helpful to guide clinical decision-making regarding the use of coronary revascularization (16). For all other patients with known CAD, stress testing is recommended to guide decisions on optimizing medical management and revascularization.

Recommendation-Specific Supportive Text

1. As shown in many secondary prevention trials, such as the Veterans Affairs Non-Q-Wave myocardial infarction (VANQUISH), COURAGE and ISCHEMIA, GDMT should be assessed in all patients with known CAD and optimized when symptomatic (2,22,23).
2. ICA is an effective means for diagnosing obstructive CAD and guiding the use of coronary revascularization. For the intermediate-risk patients with a previous history of CAD, ICA is reasonable for patients presenting with frequent weekly or daily symptoms or for those already on GDMT as well as those with high-risk CAD (left main or proximal left anterior descending or multivessel CAD).
3. For patients with previous anatomic testing that revealed nonobstructive CAD, CCTA has been shown to effectively document progressive CAD, including more extensive atherosclerotic plaque or the presence of high-risk plaque features or new obstructive stenosis ≥50% (9-11,24). Patients in this category also

FIGURE 10 Evaluation Algorithm for Patients With Suspected ACS at Intermediate Risk With Known CAD



Test choice should be guided by local availability and expertise. *Known CAD is prior MI, revascularization, known obstructive or nonobstructive CAD on invasive or CCTA. †If extensive plaque is present a high-quality CCTA is unlikely to be achieved, and stress testing is preferred ‡Obstructive CAD includes prior coronary artery bypass graft/percutaneous coronary intervention. §High-risk CAD means left main stenosis ≥50%; anatomically significant 3-vessel disease (≥70% stenosis). ‖FFR-CT turnaround times may impact prompt clinical care decisions. ACS indicates acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance; CT, computed tomography; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; ICA, invasive coronary angiography; INOCA, ischemia and no obstructive coronary artery disease; PET, positron emission tomography; and SPECT, single-photon emission CT.

include those patients with a previous CAC scan (or those for whom coronary artery calcification was noted as an incidental finding on chest CT) who present to an ED for evaluation of chest pain where concern exists with regard to the extent of noncalcified plaque and potential for underlying obstructive stenosis. However, for patients with extensive plaque, a stress test is preferred.

4. Patients with acute chest pain who have coronary artery stenosis from 40% to 90% on CCTA may benefit from measurement of FFR-CT, especially when the stenosis is proximal or mid-coronary artery (12-17,25). From 1 large clinical registry, the deferral of coronary revascularization with a normal FFR-CT was safe, with no difference in MACE at 90 days (16).
5. Most randomized trials that examined the role of stress testing in the ED enrolled patients with no known CAD, with few including patients with obstructive CAD (range: 7%-15%) (18-20). Despite this, assessing the functional significance of obstructive CAD is an important part of ischemia-guided management (26).

4.1.3. High-Risk Patients With Acute Chest Pain

Recommendations for High-Risk Patients With Acute Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 18 and 19.

COR	LOE	RECOMMENDATIONS
		Recommendations for High-Risk Patients, Including Those With High-Risk Findings on CCTA or Stress Testing
1	B-NR	1. For patients with acute chest pain and suspected ACS who have new ischemic changes on electrocardiography, troponin-confirmed acute myocardial injury, new-onset left ventricular systolic dysfunction (ejection fraction <40%), newly diagnosed moderate-severe ischemia on stress testing, hemodynamic instability, and/or a high clinical decision pathway (CDP) risk score should be designated as high risk for short-term MACE (1-3).
1	C-EO	2. For patients with acute chest pain and suspected ACS who are designated as high risk, ICA is recommended (4-7).
2a	B-NR	3. For high-risk patients with acute chest pain who are troponin positive in whom obstructive CAD has been excluded by CCTA or ICA, CMR or echocardiography can be effective in establishing alternative diagnoses (8-12).

Synopsis

Patients with symptoms suggestive of ACS who are at high risk of short-term MACE include those with new ischemic changes on the ECG, troponin-confirmed acute myocardial injury, new-onset left ventricular systolic dysfunction (ejection fraction <40%), newly diagnosed moderate-severe ischemia on stress imaging, and/or a high risk score on CDP (4,13,14). ICA is indicated for patients with confirmed ACS based on a robust body of randomized trial evidence and clinical practice guideline indications (4-7). In the patients with a negative initial evaluation, ICA is also indicated for those categorized as high risk on a validated risk stratification instrument.

For high-risk patients with a documented AMI on the index ED evaluation and who demonstrate on CCTA or ICA normal or nonobstructive CAD, CMR and echocardiography are useful for examining alternative causes for symptoms such as nonischemic cardiomyopathy or myocarditis (8-11).

Recommendation-Specific Supportive Text

1. Patients with acute chest pain and suspected ACS are considered at high risk for short-term MACE if they have new ischemic changes on electrocardiography, troponin-confirmed acute myocardial injury, new-onset left ventricular systolic dysfunction (ejection fraction <40%), newly diagnosed moderate-severe ischemia on stress testing, hemodynamic instability, and/or a high CDP risk score. Risk scores are recommended in guidelines to facilitate the management of patients who present with ACS (3,15,16).
2. Among patients categorized as high risk, ICA provides a comprehensive assessment of the extent and severity of obstructive CAD. Moreover, the determination of the severity of anatomic CAD is critical to guide the use of coronary revascularization (6).
3. Approximately 6% to 15% of troponin-positive ACS occurs in the absence of obstructive CAD (17,18). Additional testing may be helpful to identify the cause that may alter an ensuing therapeutic strategy (19). Evidence supports that CMR can identify wall motion abnormalities and myocardial edema and distinguish infarct-related scar from non-CAD causes such as myocarditis and nonischemic cardiomyopathy. When performed within 2 weeks of ACS, CMR can be useful to identify MI with nonobstructive CAD (MINOCA) from other causes (8-11).

4.1.4. Acute Chest Pain in Patients With Prior Coronary Artery Bypass Graft (CABG) Surgery

Recommendations for Acute Chest Pain in Patients With Prior CABG Surgery

COR	LOE	RECOMMENDATIONS
1	C-LD	1. In patients with prior CABG surgery presenting with acute chest pain who do not have ACS, performing stress imaging is effective to evaluate for myocardial ischemia or CCTA for graft stenosis or occlusion (1-7).
1	C-LD	2. In patients with prior CABG surgery presenting with acute chest pain, who do not have ACS (8-14) or who have an indeterminate/nondiagnostic stress test, ICA is useful (8).

Synopsis

There are many potential causes of acute chest pain in the months after CABG. Musculoskeletal pain from sternotomy remains the most common. However, other causes such as myocardial ischemia from acute graft stenosis or occlusion (1,2), pericarditis, PE, sternal wound infection, or nonunion should also be considered. Post-sternotomy pain syndrome is defined as discomfort after thoracic surgery, persisting for at least 2 months, and without apparent cause (15). The incidence of post-sternotomy pain syndrome has been found to be as low as 7% and as high as 66% (16-19), with a higher prevalence in women compared with men within the first 3 months of thoracic surgery (51.4% versus 31.3%; $p<0.01$) but, after 3 months, postoperative sex difference in prevalence was not seen (20). Graft failure within the first year post-CABG using saphenous venous grafts is usually a result of technical issues, intimal hyperplasia, or thrombosis (5). Internal mammary artery graft failure within the first-year post-CABG is most commonly attributable to issues with the anastomotic site of the graft.

Reasons for acute chest pain several years after CABG include either graft stenosis or occlusion or progression of disease in a non-bypassed vessel. One year after CABG, ~10% to 20% of saphenous vein grafts fail, while by 10 years, only about half of saphenous vein grafts are patent (5). In contrast, the internal mammary artery has patency rates of 90% to 95% 10 to 15 years after CABG (6). Compared with the use of saphenous vein grafts, the use of radial artery grafts for CABG also resulted in a higher rate of patency at 5 years of follow-up (7). In addition, knowledge of the native coronary anatomy and type of revascularization (complete or incomplete) is useful for interpretation of functional testing.

Recommendation-Specific Supportive Text

1. Acute chest pain in patients with prior CABG may be caused by myocardial ischemia as a result of technical errors at the graft anastomotic site, thrombosis within the graft, graft intimal hyperplasia, or vasospasm within arterial grafts. Progressive atherosclerosis within bypass grafts or the native coronary vessels may also result in acute chest pain caused by myocardial ischemia. Noninvasive stress imaging testing is reasonable in these patients as stress imaging will identify ischemic myocardial territories that will further guide revascularization for patients who are amenable to and are candidates for revascularization. CCTA has a great degree of accuracy with a sensitivity and specificity of detecting complete graft occlusions, 99% and 99%, respectively, when compared with the standard of ICA (21). Furthermore, CCTA was ideal in assessing bypass grafts because of the large size of these vessels, decreased vessel calcification, and decreased motion of these vessels when compared with native coronary vessels. Evaluation of bypass grafts has been shown to be successful in 93% to 100% of patients (21). In patients who have acute chest pain without features of ACS, CCTA is especially useful for assessing graft patency and is less robust for assessing native coronary vessel stenosis in this population (1-7).
2. There are clinical features and stress imaging test features in patients with prior CABG presenting with acute chest pain with no ACS that may indicate a high likelihood of severe ischemic heart disease such as new resting left ventricular systolic dysfunction (left ventricular ejection fraction <35%) not readily explained by noncoronary causes, stress electrocardiographic findings including 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/ventricular fibrillation (VF), severe stress-induced left ventricular systolic dysfunction, stress-induced perfusion abnormalities involving ≥10% of the myocardium, or stress-induced left ventricular dilation. In those with prior CABG with high-risk stress imaging features, referral for ICA is useful provided that these patients are amenable to, and are candidates for, coronary revascularization (8-14). Patients with prior CABG presenting with acute chest pain without the presence of ACS may have stress imaging features that are equivocal or nondiagnostic for the presence of myocardial ischemia. Equivocal or nondiagnostic stress

imaging may be as a result of patient's body habitus, inadequate or suboptimal heart rate, arrhythmias such as atrial fibrillation, left bundle branch block, or patient motion. In these patients, performing an ICA is reasonable when the angiographic findings have a high likelihood of impacting therapeutic decisions (8).

4.1.5. Evaluation of Patients With Acute Chest Pain Receiving Dialysis

Recommendation for Evaluation of Patients With Acute Chest Pain Receiving Dialysis
Referenced studies that support the recommendation are summarized in Online Data Supplement 20.

COR	LOE	RECOMMENDATION
1	B-NR	1. In patients who experience acute unremitting chest pain while undergoing dialysis, transfer by EMS to an acute care setting is recommended (1-5).

Synopsis

In 2015, there were nearly 500,000 people in the United States who received maintenance dialysis to treat end-stage renal disease (1). Chest pain occurs during hemodialysis in 2% to 5% of patients (6,7). Causes are numerous and related to the high prevalence of severe cardiovascular disease in this population and the dialysis procedure itself. Causes include AMI or ACS, pericarditis, PE, pleuritis, hemolysis, gastroesophageal reflux, subclavian steal, and musculoskeletal disorders (7). Myocardial ischemia is the most frequent serious cause and can be induced by hypotension (6,7) or tachyarrhythmias (2) occurring during dialysis in patients with CAD. AMI in patients undergoing dialysis is less frequently associated with chest pain than in patients who are not on dialysis, but warning signs may include diaphoresis or dyspnea (3). Unusual but serious causes of chest pain during dialysis are embolism (6) and vessel perforation by catheter (4,5). When indicated, cardiac testing for patients on dialysis should be the same as those who are not on dialysis.

Recommendation-Specific Supportive Text

1. Because the risk of CAD is relatively high in patients undergoing dialysis, when acute unremitting chest pain occurs during dialysis, a 12-lead ECG should be performed and the patient should be urgently transferred by EMS to an acute care setting for evaluation for cause of symptoms and further clinical engagement (3).

4.1.6. Evaluation of Acute Chest Pain in Patients With Cocaine and Methamphetamine Use

Recommendation for Evaluation of Acute Chest Pain in Patients With Cocaine and Methamphetamine Use
Referenced studies that support the recommendation are summarized in Online Data Supplement 21.

COR	LOE	RECOMMENDATION
2a	B-NR	1. In patients presenting with acute chest pain, it is reasonable to consider cocaine and methamphetamine use as a cause of their symptoms (1-3).

Synopsis

The most frequent presenting complaint of cocaine abuse is acute chest pain, resulting from ≥1 of the alkaloid's many cardiovascular actions (1,4,5). Cocaine produces a hyperadrenergic state by blocking neuronal reuptake of norepinephrine and dopamine. The accumulation of these catecholamines increases heart rate and blood pressure, sometimes dramatically. These actions and the drug's simultaneous effect of coronary vasoconstriction and elevated myocardial oxygen demand can produce myocardial ischemia and even infarction in the absence of obstructive CAD. Additional hazardous actions include increased myocardial contractility, cardiac arrhythmias, myocardial toxicity directly or through augmented adrenergic stimulation, increased platelet aggregability, endothelial dysfunction, and hypertensive vascular catastrophes (aortic dissection, cerebrovascular hemorrhage) (4-6).

Methamphetamine has also been shown to lead to myocardial ischemia from mechanisms similar to cocaine. Studies have shown that methamphetamine can result in decreased myocardial perfusion. Like cocaine, methamphetamine also may reduce coronary sinus blood flow (7). It has been reported that up to 70% of methamphetamine users have an abnormal ECG, with the most common finding being tachycardia (8). Additional abnormalities on the ECG have been attributed to presence of hypertension, pulmonary artery hypertension, and cardiomyopathy, all of which have been associated with methamphetamine use (9). General principles for risk stratification of patients with chest pain apply to patients with cocaine or methamphetamine use (4).

Recommendation-Specific Supportive Text

1. Cocaine and methamphetamine use can be considered in young patients presenting with chest pain and evidence of ACS; the frequency of ACS is <10% among cocaine and methamphetamine users in most studies, and death is rare (1-4). A person's urine typically tests positive for cocaine or methamphetamine within 1 to 4 hours of consuming the drug and will continue to test positive for 2 to 4 days.

4.1.7. Shared Decision-Making in Patients With Acute Chest Pain

Recommendations for Shared Decision-Making in Patients With Acute Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplement 22.

COR	LOE	RECOMMENDATIONS
1	B-R	1. For patients with acute chest pain and suspected ACS who are deemed low risk by a CDP, patient decision aids are beneficial to improve understanding and effectively facilitate risk communication (1,2).
1	B-R	2. For patients with acute chest pain and suspected ACS who are deemed intermediate risk by a CDP, shared decision-making between the clinician and patient regarding the need for admission, for observation, discharge, or further evaluation in an outpatient setting is recommended for improving patient understanding and reducing low-value testing (1,2).

Synopsis

Risk communication and shared decision-making using a decision aid such as Chest Pain Choice have been shown to increase patient knowledge, engagement, and satisfaction and decrease the rate of observation unit admission and 30-day cardiac stress testing in both single-center and multicenter randomized trials (1-3). For low-risk patients, decision aids can facilitate risk communication between the clinician and the patient and increase patients' understanding of their risk and the importance of outpatient follow-up after discharge from the ED. For intermediate-risk patients, admission to an observation unit or discharge from the ED with further, timely evaluation in an outpatient setting is acceptable. Decision aids such as Chest Pain Choice can effectively facilitate shared decision-making regarding the need for admission, observation, or discharge for further evaluation in an outpatient setting (3).

Recommendation-Specific Supportive Text

1. Adult ED patients with acute chest pain who are deemed low risk are frequently admitted for observation and cardiac stress testing or CCTA, resulting in increased cost to the patient and the health care system (2). Shared decision-making is the process by which patients and clinicians share information and take steps to build consensus about preferred tests and treatments. In shared decision-making, both parties share information: the clinician offers options and describes the potential harms and benefits, and the patient communicates his or her preferences. Patients are prepared with a better understanding of the relevant factors influencing the decision and share responsibility for deciding how to proceed. Shared decision-making rests on the principles of patient centered care, including respect for patient autonomy (i.e., that a patient's informed preferences should be the basis for medical action) (4). Decision aids are patient-centered tools designed to facilitate shared decision-making between a patient and the clinician such that patients' values and preferences are incorporated into health care decisions (5). Shared decision-making, however, can be performed without a decision aid; lack of a decision aid should not preclude attempts at shared decision-making.
2. In a single-center randomized trial of adults presenting to the ED with a chief complaint of chest pain (n=204) who were being considered by the treating clinician for admission to the observation unit for cardiac stress testing, patients randomized to shared decision-making facilitated by the Chest Pain Choice Decision Aid (2,3) had greater knowledge, were more engaged in the decision-making process, and less frequently decided to be admitted to the observation unit for stress testing (58% versus 77%, absolute difference 19%, 95% CI: 6%-31%) (2). There were no MACE after discharge in either group. The decision aid was subsequently tested in a population of 898 patients with greater socioeconomic diversity recruited from 6 EDs across the United States (1,6). Similar findings were observed. Analysis of health care use in this trial showed fewer cardiac imaging tests and lower overall 45-day health care use in patients randomized to the decision aid (7,8).

4.2. Evaluation of Acute Chest Pain With Nonischemic Cardiac Pathologies

Recommendation for Evaluation of Acute Chest Pain With Nonischemic Cardiac Pathologies

COR	LOE	RECOMMENDATION
1	C-EO	1. In patients with acute chest pain in whom other potentially life-threatening nonischemic cardiac conditions are suspected (e.g., aortic pathology, pericardial effusion, endocarditis), TTE is recommended for diagnosis.

Synopsis

Alternative nonischemic causes for acute chest pain should be considered if an ischemic cause is not suspected based on initial evaluation. Echocardiography, as a portable bedside noninvasive and almost universally available tool, should be used to unmask some imminently dangerous but potentially treatable cardiac conditions.

TTE is the primary tool to diagnose pericardial effusions with and without tamponade, aortic dissections (TTE and transesophageal echocardiography [TEE]), acute right ventricular dysfunction in the setting of PE, as well as mechanical complications of MI (ventricular septal rupture, free wall rupture, papillary muscle dysfunction and rupture).

Echocardiography can also identify cardiac masses, emboli, or clots in transit, intracardiac shunting, or endocarditis. Furthermore, beyond the anatomic findings, echocardiography can be used to noninvasively assess volume status, pulmonary hypertension, valvular stenosis, and regurgitation. Many of these entities may present with acute chest pain as well as shortness of breath.

Recommendation-Specific Supportive Text

1. Prompt use of TTE allows for an evaluation of cardiac cause for symptoms and evaluation of alternative pathologies for acute chest pain (1-6). Rapid echocardiographic assessment may facilitate imaging of the patient while symptomatic.

4.2.1. Acute Chest Pain With Suspected Acute Aortic Syndrome

Recommendations for Acute Chest Pain With Suspected Acute Aortic Syndrome

COR	LOE	RECOMMENDATIONS
1	C-EO	1. In patients with acute chest pain where there is clinical concern for aortic dissection, computed tomography angiography (CTA) of the chest, abdomen, and pelvis is recommended for diagnosis and treatment planning.
1	C-EO	2. In patients with acute chest pain where there is clinical concern for aortic dissection, TEE or CMR should be performed to make the diagnosis if CT is contraindicated or unavailable.

Synopsis

Acute aortic syndrome describes diseases involving disruptions in the aortic wall, including aortic dissection, intramural hematoma, and penetrating aortic ulcer (1). The annual incidence is 2 to 4 cases/100,000, with higher prevalence with genetic conditions that weaken the aortic wall (2). Prominent risk factors include hypertension atherosclerosis and connective tissue disease. Cocaine use may provoke dissection even without other risk factors.

Acute onset of severe chest or back pain heralds acute aortic dissection in 80% to 90% of patients, sometimes characterized as ripping or tearing (3). Progression can produce end-organ hypoperfusion, and proximal extension may cause tamponade, severe acute aortic regurgitation, or rarely, STEMI. Intramural hematomas, which differ from dissection by absence of an identifiable intimal flap, have a lesser understood natural history but are typically evaluated and treated in a similar manner to dissections.

Recommendation-Specific Supportive Text

1. A high index of suspicion in appropriate patients, and a coordinated, multidisciplinary evaluation is needed to optimize outcomes. The diagnostic modality of choice in stable patients is CTA, which is both highly sensitive and specific (4-6). Chest radiographs can show mediastinal widening but may be normal.
2. TTE can show pericardial effusion or aortic regurgitation, and a dissection flap can sometimes be visualized; however, more complete imaging of the aortic arch requires TEE or CT. CMR is sensitive and specific, but CT is usually more expeditious.

4.2.2. Acute Chest Pain With Suspected PE

Recommendations for Acute Chest Pain With Suspected PE
Referenced studies that support the recommendations are summarized in Online Data Supplement 23.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In stable patients with acute chest pain with high clinical suspicion for PE, CTA using a PE protocol is recommended (1-4).
1	C-EO	2. For patients with acute chest pain and possible PE, need for further testing should be guided by pretest probability.

Synopsis

The incidence of PE is estimated at 65 cases per 100,000, but some cases are asymptomatic and others undiagnosed (5,6). One-third of deaths are sudden, and 60% are undiagnosed before death (7). Risk factors for PE are the same for venous thromboembolism and include inherited hypercoagulable states and acquired risk factors (recent surgery, trauma, immobilization, malignancy, smoking, obesity, oral contraception). Recognition of PE can be challenging because symptoms and clinical signs may be nonspecific. Dyspnea followed by chest pain, classically pleuritic, is the most common presenting symptom (1). Signs of deep venous thrombosis may be present on examination (5).

Recommendation-Specific Supportive Text

1. CTA using PE protocol is the diagnostic modality of choice in stable patients; ventilation-perfusion scanning is a second-line alternative in the acute setting (3,4). Use of clinical prediction rules to select patients for imaging can decrease radiation exposure and cost (8). Troponin (and brain natriuretic peptide) can be elevated, and echocardiography may reveal acute right ventricular strain consequent to large PEs; troponin and brain natriuretic peptide are both markers for higher mortality rate (2).
2. Recognition of PE is important because prompt anticoagulation improves outcomes (2). Clinical assessment combined with pretest risk stratification can help select patients appropriate for diagnostic imaging. In the absence of shock, diagnostic evaluation depends on the clinical assessment of pretest probability (3). Several prediction rules are available that add predictive value to clinical assessment (4). D-dimers are highly sensitive but not very specific for the diagnosis of PE in ED patients. Measurement of D-dimers, using age- and sex-specific cutoffs, may be useful in patients at low to intermediate pretest probability; those with negative D-dimers can probably be discharged without further testing, whereas those with positive values should be considered for CTA (2).

4.2.3. Acute Chest Pain With Suspected Myopericarditis

Recommendations for Acute Chest Pain With Suspected Myopericarditis
Referenced studies that support the recommendations are summarized in Online Data Supplement 24.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients with acute chest pain and myocardial injury who have nonobstructive coronary arteries on anatomic testing, CMR with gadolinium contrast is effective to distinguish myopericarditis from other causes, including myocardial infarction and nonobstructive coronary arteries (MINOCA) (1-6).
1	B-NR	2. In patients with acute chest pain with suspected acute myopericarditis, CMR is useful if there is diagnostic uncertainty, or to determine the presence and extent of myocardial and pericardial inflammation and fibrosis (7-12).
1	C-EO	3. In patients with acute chest pain and suspected myopericarditis, TTE is effective to determine the presence of ventricular wall motion abnormalities, pericardial effusion, valvular abnormalities, or restrictive physiology.
2b	C-LD	4. In patients with acute chest pain with suspected acute pericarditis, noncontrast or contrast cardiac CT scanning may be reasonable to determine the presence and degree of pericardial thickening (7,8,13).

Synopsis

Pericarditis and myocarditis share overlapping common causes and likely form a continuum (8). In patients with pericarditis, a minimally elevated troponin does not appear to confer a worse prognosis (14). Most cases of pericarditis in developed nations are viral, although tuberculosis is sometimes a consideration.

Pericarditis classically presents with chest pain that is sharp, pleuritic, and which may be improved by sitting up or leaning forward, although in many instances such findings are not present. A pericardial friction rub may be audible. Widespread ST-elevation with PR depression is the electrocardiographic hallmark, although changes are nonspecific and may be transient.

Clinical manifestations of myocarditis are varied and include chest pain that is often sharp and reflective of epicardial inflammation involving the pericardium. Myocardial dysfunction often causes fatigue and exercise intolerance, and predominance of heart failure distinguishes myocarditis from pericarditis. Troponin is usually elevated (15).

Recommendation-Specific Supportive Text

1. CMR with late gadolinium enhancement imaging can show characteristic changes of acute myopericarditis, especially if performed early, within 2 weeks of the index presentation. CMR can also frequently distinguish between acute myopericarditis, other cardiomyopathies, and occult MI and other causes of MI and nonobstructive coronary arteries (1,2).
2. In patients with suspected acute myopericarditis, or if there is diagnostic uncertainty, CMR is useful to determine myocardial edema, thickening, and late enhancement. CMR may also show evidence of pericardial effusions (2,16). CMR has a sensitivity of 94% to 100% in detecting inflammation of the pericardium (7-10). CMR features that are suggestive of acute pericarditis include enhancement or thickened pericardium, although such findings can also be seen in the presence of pericardial fibrosis. In addition, increased signal on T2-weighted images correlates with edema, which may be seen in acute myopericarditis. The presence of pericardial adhesions between the visceral and parietal pericardium may be useful in patients with suspected acute pericarditis or pericardial constriction (7-10).
3. In patients with suspected myopericarditis, echocardiography may show segmental left ventricular wall hypokinesis, which suggests myocardial involvement in patients with myocarditis and is, therefore, a useful tool in these patients. Patients with acute pericarditis may also have echocardiographic findings such as increased pericardial brightness or pericardial effusion with or without tamponade physiology. Some patients with acute pericarditis may also have normal echocardiographic findings (9,17).
4. In patients with suspected acute pericarditis, cardiac CT with or without contrast may show features that are suggestive of acute pericarditis, such as pericardial thickening or enhancement (after contrast administration). Additionally, CT attenuation values of pericardial effusion can help distinguish between exudative and transudative pericardial fluid. There are limited data on the accuracy of cardiac CT in diagnosing acute pericarditis; a small study showed that pericardial thickening or enhancement was the most accurate single parameter for pericarditis, with sensitivity of 54% to 59% and specificity of 91% to 96%. Therefore, cardiac CT is a reasonable second-line study in these patients (7,8,13).

4.2.4. Acute Chest Pain With Valvular Heart Disease (VHD)

Recommendations for Acute Chest Pain With VHD

COR	LOE	RECOMMENDATIONS
1	C-EO	1. In patients presenting with acute chest pain with suspected or known history of VHD, TTE is useful in determining the presence, severity, and cause of VHD.
1	C-EO	2. In patients presenting with acute chest pain with suspected or known VHD in whom TTE diagnostic quality is inadequate, TEE (with 3D imaging if available) is useful in determining the severity and cause of VHD.
2a	C-EO	3. In patients presenting with acute chest pain with known or suspected VHD, CMR imaging is reasonable as an alternative to TTE and/or TEE is nondiagnostic.

Synopsis

Chest pain may occur in the presence of VHD, particularly stenotic VHD such as aortic valve stenosis and mitral valve stenosis with secondary pulmonary hypertension. Chest pain may also occur after papillary muscle rupture in the setting of MI or in acute degenerative mitral valve disease after spontaneous chordal rupture. Chest pain may also occur in the setting of acute severe aortic insufficiency, which may be related to acute aortic pathology such as an aortic dissection manifesting as severe acute chest pain that may radiate to the back.

The cause of chest pain in patients with aortic valve stenosis may be secondary to coexisting obstructive epicardial CAD (1) or, more commonly, chest pain may occur as a result of coronary microvascular dysfunction (2) in the presence of very elevated left ventricular pressure caused by a high left ventricular afterload, along with the associated left ventricular hypertrophy. The cause of chest pain in patients with severe mitral valve stenosis is more likely to be secondary to epicardial obstructive CAD (1) although, less likely, chest pain may occur in isolated mitral valve stenosis resulting from low cardiac output and decreased coronary perfusion (1).

Recommendation-Specific Supportive Text

1. Patients with VHD may present with chest pain particularly in the setting of stenotic VHD, severe valvular regurgitation in the setting of AMI with ruptured papillary muscle resulting in acute severe mitral valve insufficiency, or acute aortic valve insufficiency in the setting of acute aortic pathology, such as aortic dissection (3,4). TTE is useful in assessing valvular pathologies because it is widely available and is therefore a good first-line test in these patients to determine the presence, severity, and cause of VHD (3).
2. The ability to attain adequate 3-dimensional (3D) transthoracic images depends on the ability to obtain adequate 2-dimensional images (5). In these clinical situations where TTE images are technically inadequate, TEE with 3D images, if required, is useful to determine the severity and cause of VHD (3,6).
3. There may be clinical situations when TTE and TEE may not be technically adequate to assess the severity and cause of VHD. In such circumstances, CMR may be useful to objectively assess the severity and cause of VHD (6). The aorta can also be visualized on CMR and can therefore be used to assess acute aortic pathologies accompanying aortic valve insufficiency such as aortic dissection (4).

4.3. Evaluation of Acute Chest Pain With Suspected Noncardiac Causes

Recommendation for Evaluation of Acute Chest Pain With Suspected Noncardiac Causes

COR	LOE	RECOMMENDATION
1	C-EO	1. Patients with acute chest pain should be evaluated for noncardiac causes if they have persistent or recurring symptoms despite a negative stress test or anatomic cardiac evaluation, or a low-risk designation by a CDP.

TABLE 9 Differential Diagnosis of Noncardiac Chest Pain

Respiratory
Pulmonary embolism
Pneumothorax/hemothorax
Pneumomediastinum
Pneumonia
Bronchitis
Pleural irritation
Malignancy
Gastrointestinal
Cholecystitis
Pancreatitis
Hiatal hernia
Gastroesophageal reflux disease/gastritis/esophagitis
Peptic ulcer disease
Esophageal spasm
Dyspepsia
Chest wall
Costochondritis
Chest wall trauma or inflammation
Herpes zoster (shingles)
Cervical radiculopathy
Breast disease
Rib fracture
Musculoskeletal injury/spasm
Psychological
Panic disorder
Anxiety
Clinical depression
Somatization disorder
Hypochondria
Other
Hyperventilation syndrome
Carbon monoxide poisoning
Sarcoidosis
Lead poisoning
Prolapsed intervertebral disc
Thoracic outlet syndrome
Adverse effect of certain medications (e.g., 5-fluorouracil)
Sickle cell crisis

Synopsis

The differential diagnosis for noncardiac causes of acute chest pain is quite broad and includes respiratory, musculoskeletal, gastrointestinal, psychological, and other causes (Table 9). Of these, musculoskeletal causes are the most common, including costochondritis, muscle strain, and potential consequences of recent or occult chest trauma such as rib fracture. Various gastrointestinal causes, commonly esophageal, can present with chest pain, including gastrointestinal reflux and esophageal dysmotility as well as gastritis from either medications or peptic ulcer disease. Respiratory causes are less frequent but potentially more serious and include PE, pneumonia, and pneumothorax. Many patients will have dyspnea in addition to chest pain. Psychological causes are usually diagnoses of exclusion but merit consideration in the right context.

Recommendation-Specific Supportive Text

1. If acute myocardial injury is ruled out, alternative diagnoses merit consideration in patients with persistent or recurrent symptoms. Clinical risk assessment, with implementation of CDPs when appropriate, is the key to selecting patients for further diagnostic evaluation and also to choosing among potential diagnostic modalities.

4.3.1. Evaluation of Acute Chest Pain With Suspected Gastrointestinal Syndromes

Recommendation for Evaluation of Acute Chest Pain With Suspected Gastrointestinal Syndromes

COR	LOE	RECOMMENDATION
2a	C-LD	1. In patients with recurrent acute chest pain without evidence of a cardiac or pulmonary cause, evaluation for gastrointestinal causes is reasonable.

Synopsis

Among outpatients who present with chest pain, approximately 10% to 20% have a gastrointestinal cause (1). Gastrointestinal pain may result from stimulation of chemoreceptors by acid or hyperosmolar substances, of mechanoreceptors by abnormal contraction or distention, or of thermoreceptors (2). Some patients have abnormal perceptions of otherwise normal stimuli. Gastroesophageal reflux disease is the most likely cause for recurring unexplained chest pain of esophageal origin (3). Chest pain caused by gastroesophageal reflux disease can mimic myocardial ischemia and may be described as squeezing or burning. The duration can be minutes to hours, often occurs after meals or at night, and can worsen with stress. Depending on the severity, it may or may not resolve spontaneously or with antacids. Esophagitis not related to reflux may be caused by medications, underlying infections such as candidiasis, or radiation injury. Allergic conditions are associated with eosinophilic esophagitis, which is diagnosed by biopsy. Esophageal motility disorders such as achalasia, distal esophageal spasm, and nutcracker esophagus are less common but can present as squeezing retrosternal pain or spasm, often accompanied by dysphagia.

Recommendation-Specific Supportive Text

1. The first step in evaluation of potential esophageal chest pain is a careful history. Although the clinical presentation often does not provide adequate clues to distinguish cardiac from esophageal pain, some symptoms may be suggestive of an esophageal cause, such as heartburn, regurgitation, or dysphagia, and relief with antacid or antisecretory agents. These symptoms, however, are not sufficiently specific to be fully diagnostic. A history of use of medications such as nonsteroidal anti-inflammatory agents, potassium supplements, iron, or bisphosphonates should be sought. Physical examination is often unrevealing. When an esophageal cause of chest pain is suspected, upper endoscopy should be considered (4). Symptoms and signs that merit early evaluation (usually within 2 weeks) include dysphagia, odynophagia, gastrointestinal bleeding, unexplained iron deficiency anemia, weight loss, and recurrent vomiting. Patients without these symptoms may merit a trial of empiric acid suppression therapy (5). If an upper endoscopy is normal and the symptoms persist despite a trial of acid suppression, consideration should be given to additional evaluation, such as esophageal function testing and pH monitoring, to exclude other esophageal causes (6).

4.3.2. Evaluation of Acute Chest Pain With Suspected Anxiety and Other Psychosomatic Considerations

Recommendation for Evaluation of Acute Chest Pain With Suspected Anxiety and Other Psychosomatic Considerations
Referenced studies that support the recommendation are summarized in Online Data Supplement 25.

COR	LOE	RECOMMENDATION
2a	B-R	1. For patients with recurrent, similar presentations for acute chest pain with no evidence of a physiological cause on prior diagnostic evaluation including a negative workup for myocardial ischemia, referral to a cognitive-behavioral therapist is reasonable (1-14).

Synopsis

Although the heart-brain relationship is well established (15-17), its clinical relevance has been enhanced by recognition of stress cardiomyopathy (18,19). Less dramatic than the latter syndrome but highly prevalent is recurrent chest pain despite angiographically normal coronary arteries and no definable cardiac disease, including an assessment for INOCA (1-14). Chest pain in these patients has been variously labeled angina, angina-like, “atypical” angina, or noncardiac chest pain based on its deviation from characteristic ischemic cardiac discomfort. Prognosis of patients with noncardiac chest pain is largely devoid of cardiac complications (4,9,20-23). The close association of this symptom with psychological syndromes

such as anxiety, panic attack, depression, somatoform disorder, and cardiophobia suggests that there may be a psychogenic origin in many patients. These factors have also raised consideration of mechanisms for noncardiac chest pain such as central nervous system-visceral interactions, low pain thresholds, hyperbody vigilance, sympathetic activation, as well as anxiety, depression, and panic disorder (6,7,9,14,23-30). It has been reported that these patients undergo extensive and repetitive cardiac testing and have low referral to cognitive-behavioral therapists, suggesting a lost opportunity for pharmacologic or cognitive-behavioral therapy (6).

Recommendation-Specific Supportive Text

1. Most low-risk patients presenting to the ED or office setting with chest pain do not have life-threatening conditions. Diagnoses may include psychological entities such as somatization or noncardiac chest pain (1-13). It has been reported that in low-risk chest pain patients without evidence of cardiac disease, depression, anxiety, and gastroesophageal syndromes each exceeded CAD by almost 10-fold (7). Additionally, care of these patients often includes multiple tests, high cost, and avoidable radiation exposure (5.0 mSv) (6). A low rate (<10%) of clinician inquiry, documentation, or referral has also been noted for psychological factors, even in chest pain patients with self-reported anxiety (6,7). A systematic review of therapy for patients with chest pain, no evidence of cardiac disease, and psychological disorders revealed that antidepressants and anxiolytics had mixed evidence for efficacy (10), but a Cochrane database of psychotherapy (17 RCTs) for such patients revealed a 32% reduction in chest pain frequency (11) for a 3-month interval. Approaches using cognitive-behavioral methods were most effective (11). These results were limited by small study cohorts and patient heterogeneity; however, they do suggest benefit from consideration of psychogenic factors in patients who continue to seek evaluation for chest pain despite previous definitive, negative workups.

4.3.3. Evaluation of Acute Chest Pain in Patients With Sickle Cell Disease

Recommendations for Evaluation of Acute Chest Pain in Patients With Sickle Cell Disease
Referenced studies that support the recommendations are summarized in Online Data Supplement 26.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients with sickle cell disease who report acute chest pain, emergency transfer by EMS to an acute care setting is recommended (1-5).
1	C-LD	2. In patients with sickle cell disease who report acute chest pain, ACS should be excluded (3-5).

Synopsis

Acute chest syndrome is a leading cause of death for patients with sickle cell disease (1,2). Patients with sickle cell disease who are experiencing chest pain require prompt evaluation (3). Although chest pain occurs in most, other manifestations of acute chest syndrome include shortness of breath, fever, arm and leg pain, and the presence of a new density on chest radiography. Older adolescents and adults with sickle cell disease who present with chest pain and shortness of breath should be evaluated for AMI or myocardial ischemia (4). AMI occurs in patients with sickle cell disease at a relatively early age, usually without the traditional risk factors for ACS. Death from ACS in patients with sickle cell disease is significantly high in age-, sex-, and race-matched controls (5).

Recommendation-Specific Supportive Text

1. In patients with sickle cell disease who experience chest pain, ACS is associated with significant morbidity and mortality rates. These patients should be transferred to an acute care setting by EMS when there is clinical suspicion of ACS.
2. The recommended diagnostic evaluation for all adults with sickle cell disease who have a clinical presentation concerning for acute chest syndrome includes an ECG, troponin test, complete blood count with white blood cell differential, reticulocyte count, anteroposterior and lateral chest radiograph, and blood and sputum cultures.

5. EVALUATION OF PATIENTS WITH STABLE CHEST PAIN

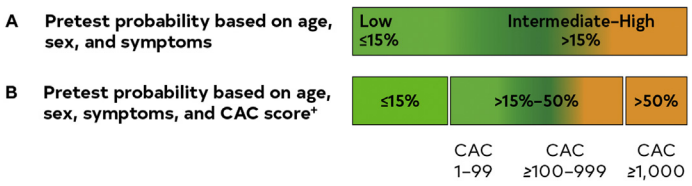
5.1. Patients With No Known CAD Presenting With Stable Chest Pain

Stable chest pain is a symptom of myocardial ischemia characterized by chest pain that is provoked with stress (physical or emotional). Risk status in suspected stable ischemic heart disease (SIHD) is not well defined. **Figure 11** provides a description of SIHD risk estimates (1).

FIGURE 11 Pretest Probabilities of Obstructive CAD in Symptomatic Patients According to Age, Sex, and Symptoms

Pretest Probabilities of Obstructive CAD in Symptomatic Patients
(A) according to age, sex, and symptoms;
(B) according to age, sex, symptoms, and CAC

Age, y	Chest Pain		Dyspnea	
	Men	Women	Men	Women
30–39	≤4	≤5	0	3
40–49	≤22	≤10	12	3
50–59	≤32	≤13	20	9
60–69	≤44	≤16	27	14
70+	≤52	≤27	32	12



Modified from Juarez-Orozco et al. (1) and Winther et al. (2). 1) The pretest probability shown is for patients with anginal symptoms. Patients with lower-risk symptoms would be expected to have lower pretest probability. 2) The darker green- and orange-shaded regions denote the groups in which noninvasive testing is most beneficial (pretest probability >15%). The light green–shaded regions denote the groups with pretest probability of CAD ≤15% in which the testing for diagnosis may be considered based on clinical judgment (1). 3) If CAC is available, it can also be used to estimate the pretest probability based on CAC score (2). CAC indicates coronary artery calcium; and CAD, coronary artery disease.

5.1.1. Pretest Risk Probability to Guide Need for Stress and Anatomic Tests

In the evaluation of symptomatic patients with suspected CAD, use of validated scores to predict the pretest probability of obstructive CAD may be useful to identify low-risk patients for whom testing may be deferred. It is preferable to use contemporary estimates such as those published in the past 10 years, such as the pretest probability proposed by Juarez-Orozco et al. (1) in preference to scores from historical patient series, which may overestimate the frequency of obstructive CAD. Alternatively, low-risk patients may be those <40 years of age or who have symptoms that have a low likelihood of representing ischemia (Section 5.1.2). When available, information on the presence and amount of CAC may be useful for enhancing the pretest probability of obstructive CAD, as shown in **Figure 11** (2). This information can be obtained from performing a CAC scan or, when available, from a visual estimation of CAC based on prior noncardiac chest CT. Among the remaining patients classified as intermediate-high risk, selective testing may improve diagnosis of CAD and for risk stratification purposes (1-5).

5.1.2. Low-Risk Patients With Stable Chest Pain and No Known CAD

Recommendations for Low-Risk Patients With Stable Chest Pain and No Known CAD
Referenced studies that support the recommendations are summarized in Online Data Supplements 27 and 28.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. For patients with stable chest pain and no known CAD presenting to the outpatient clinic, a model to estimate pretest probability of obstructive CAD is effective to identify patients at low risk for obstructive CAD and favorable prognosis in whom additional diagnostic testing can be deferred (1-5).
2a	B-R	2. For patients with stable chest pain and no known CAD categorized as low risk, CAC testing is reasonable as a first-line test for excluding calcified plaque and identifying patients with a low likelihood of obstructive CAD (6-9).
2a	B-NR	3. For patients with stable chest pain and no known CAD categorized as low risk, exercise testing without imaging is reasonable as a first-line test for excluding myocardial ischemia and determining functional capacity in patients with an interpretable ECG (10).

Synopsis

Over the past several decades, patient presentation and observed obstructive CAD prevalence has changed, thus affecting patient selection for diagnostic testing. Current observations in the United States include:

- Typical exertional angina prevalence is generally low (<10%), with more patients presenting without the classic demand-related symptoms (11). Symptoms can be infrequent (i.e., on a weekly or monthly basis) (12,13), which challenges the diagnostic evaluation.
- Among patients undergoing a diagnostic evaluation, there is a relatively low prevalence of obstructive CAD and ischemia (i.e., ~10%) (11,14,15).
- Traditional pretest risk scores largely overestimate disease probability and contribute to overtesting (16-19).
- Current testing patterns result in a high normal coronary angiography rate (upward of 50%-60%) (20,21).

For the aforementioned reasons, use of a contemporary pretest probability estimates to define low-risk patients not requiring additional diagnostic testing is a primary goal of the initial evaluation of symptomatic patients with suspected CAD (5). Even when contemporary pretest probability estimates are used, they have a low specificity for identifying patients with obstructive CAD. A CAC score of zero can be useful to identify patients with stable chest pain who are low risk, have a low likelihood of obstructive CAD, and a low risk of future cardiovascular events (7). Additionally, exercise testing without imaging is also reasonable to perform in low-risk individuals with stable chest pain and no known CAD to exclude myocardial ischemia and assess functional capacity (10) (**Figure 12**).

Recommendation-Specific Supportive Text

1. There are several pretest probability scores for use in symptomatic patients with suspected CAD. Older pretest probability scores, such as the Diamond-Forrester model developed in 1979, estimates the probability of obstructive CAD, resulting in significant overestimation in contemporary patients referred for noninvasive imaging, particularly women (1). Newer pretest probability estimates are available (4). The CAD Consortium models include basic (age, sex, symptoms, and hospital setting); clinical (basic model + risk factors: diabetes, hypertension, hyperlipidemia, and smoking); and extended (clinical model + CAC) versions. Each new variant is better than older models, and the addition of variables within each model level improves prediction (3). A major strength of these models is the extensive validation in different hospitals, settings, and countries. Another updated model to estimate the pretest probability of obstructive CAD was recently developed (4,22) and has been recommended by the ESC guidelines, further reinforcing that the prevalence of obstructive CAD among symptomatic patients is substantially lower than predicted estimates.
2. Among symptomatic patients, a CAC score of zero identifies a low-risk cohort of patients who may not require additional diagnostic testing; most events occur among patients with detectable CAC (e.g., 84% in the PROMISE trial) (7,9). Several randomized trials evaluated the role of CAC in guiding selective use of follow-up testing, including CCTA (6,7). From the CRESCENT 1 (Comprehensive Cardiac CT Versus Exercise Testing in Suspected Coronary Artery Disease) trial, 350 symptomatic patients were randomized to CAC scanning versus exercise ECGs (7). Only patients with detectable CAC or high pretest risk (141/242) underwent follow-up CCTA. At 1 year, the CAC arm was associated with a reduction in cardiovascular disease events when compared with those who underwent exercise testing alone (p=0.011).
3. Exercise testing was shown to be an effective diagnostic strategy in low-risk symptomatic women from the WOMEN (What Is the Optimal Method for Ischemia Evaluation in Women) trial, when compared with exercise MPI (10). Using this approach, there was no significant difference in CAD death or hospitalization for an ACS or heart failure, with either test, but exercise testing alone provided significant cost savings.

5.1.3. Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD

Recommendations for Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD
Referenced studies that support the recommendations are summarized in Online Data Supplements 29 and 30.

COR	LOE	RECOMMENDATIONS
		Index Diagnostic Testing
		Anatomic Testing
1	A	1. For intermediate-high risk patients with stable chest pain and no known CAD, CCTA is effective for diagnosis of CAD, for risk stratification, and for guiding treatment decisions (1-12).
		Stress Testing
1	B-R	2. For intermediate-high risk patients with stable chest pain and no known CAD, stress imaging (stress echocardiography, PET/SPECT MPI or CMR) is effective for diagnosis of myocardial ischemia and for estimating risk of MACE (8,13-35).
2a	B-R	3. For intermediate-high risk patients with stable chest pain and no known CAD for whom rest/stress nuclear MPI is selected, PET is reasonable in preference to SPECT, if available to improve diagnostic accuracy and decrease the rate of nondiagnostic test results (36-39).
2a	B-R	4. For intermediate-high risk patients with stable chest pain and no known CAD with an interpretable ECG and ability to achieve maximal levels of exercise (≥5 METs), exercise electrocardiography is reasonable (8,13,15,40-45).
2b	B-NR	5. In intermediate-high risk patients with stable chest pain selected for stress MPI using SPECT, the use of attenuation correction or prone imaging may be reasonable to decrease the rate of false-positive findings (46-51).
		Assessment of Left Ventricular Function
1	B-NR	6. In intermediate-high risk patients with stable chest pain who have pathological Q waves, symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or a heart murmur with unclear diagnosis, use of TTE is effective for diagnosis of resting left ventricular systolic and diastolic ventricular function and detection of myocardial, valvular, and pericardial abnormalities (13,14,52).
		Sequential or Add-on Testing: What to Do if Index Test Results are Positive or Inconclusive
2a	B-NR	7. For intermediate-high risk patients with stable chest pain and known coronary stenosis of 40% to 90% in a proximal or middle coronary segment on CCTA, FFR-CT can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization (12,53-58).
2a	B-NR	8. For intermediate-high risk patients with stable chest pain after an inconclusive or abnormal exercise ECG or stress imaging study, CCTA is reasonable (5,59-63).
2a	B-NR	9. For intermediate-high risk patients with stable chest pain and no known CAD undergoing stress testing, the addition of CAC testing can be useful (64-70).
2a	B-NR	10. For intermediate-high risk patients with stable chest pain after inconclusive CCTA, stress imaging is reasonable (13,14,20-23, 40,71-76).
2b	C-EO	11. For intermediate-high risk patients with stable chest pain after a negative stress test but with high clinical suspicion of CAD, CCTA or ICA may be reasonable.

Synopsis

The approach to the diagnostic evaluation of patients with no known CAD who are at intermediate to high risk (**Figure 12**) should be guided by the ability to achieve high-quality imaging as well as local availability and expertise. Intermediate-high risk patients have modest rates of obstructive CAD (~10%-20%) and risk of clinical events (~1%-2% per year) (1,5,8,77-80). CCTA is preferable in those <65 years of age and not on optimal preventive therapies, while stress testing may be advantageous in those ≥65 years of age, because they have a higher likelihood of ischemia and obstructive CAD (34-36,81-83). Although previous guidelines supported direct referral to ICA among patients with stable chest pain, contemporary randomized trials support that candidates for elective coronary angiography may be safely triaged using CCTA (1,84) or noninvasive stress testing (34,35).

Patient characteristics and existing contraindications for a given test modality (**Tables 5 and 6**) should be considered when choosing a diagnostic test. Imaging of obese patients, especially those with morbid obesity (body mass index >40), can be challenging and requires careful consideration of available equipment. In obese patients, contrast enhancement is useful to improve imaging quality. In certain patients, it may be important to undergo exercise testing so to collect data on the hemodynamic or symptomatic response to exercise. In patients selected for stress imaging who are able to exercise, exercise testing is preferred over pharmacologic stress to improve the diagnostic and prognostic information of the test. Although PET and SPECT are grouped together, PET has improved diagnostic and prognostic performance, especially when quantitative assessment of MBF can be performed (36-39).

Irrespective of the test performed, an overarching goal of the evaluation of symptomatic patients is to identify those who would benefit from GDMT, as defined by the 2014 SIHD guidelines, the 2018 cholesterol-lowering guidelines, and the 2019 prevention guidelines (13,85-87). For this evaluation, the patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac test modality and in guiding the pathway for treatment decisions.

Recommendation-Specific Supportive Text

Anatomic Testing

1. Clinical trials report a higher diagnostic sensitivity for CCTA compared with stress testing for detecting obstructive CAD on ICA (2-4,37,38,88). CCTA without stenosis or plaque has a low CAD event rate. From the PROMISE trial, the 3-year CAD event rate for negative test findings was 0.9% for CCTA versus 2.1% for stress testing (17).

Randomized trials comparing the effectiveness of CCTA versus stress testing report similar near-term effectiveness (at ~2-3 years of follow-up) (7,8,10-12,89). In the SCOT-HEART (Scottish Computed Tomography of the Heart) trial, the addition of CCTA to standard of care resulted in a reduction in 5-year CAD death or AMI when compared with standard care alone (predominantly exercise ECG) (HR: 0.59; 95% CI: 0.41-0.84; p=0.004) (9). From a prespecified analysis from the PROMISE trial, patients with diabetes who underwent CCTA had a lower risk of cardiovascular death or MI when compared with those randomized to stress testing (adjusted HR: 0.38; 95% CI: 0.18-0.79; p=0.01) (6). Especially for patients with nonobstructive and obstructive CAD, CCTA more often prompts initiation and intensification of preventive and anti-ischemic therapies than other diagnostic strategies (6,89-96). Several randomized trials compared the effectiveness of CCTA versus direct referral to ICA among symptomatic patients (1,5). From the CONSERVE trial, a strategy of initial CCTA was associated with lower cost but similar 1-year MACE rates (death, ACS, stroke, urgent/emergency coronary revascularization, or cardiac hospitalization) as direct ICA (4.6% versus 4.6%) (5).

Stress Testing

2. The prognostic value of stress echocardiography has been demonstrated in large observational series with low rates of CAD events for patients with normal test results, particularly those with good exercise tolerance (71,72,97-99). In the PROMISE trial, patients randomized to stress testing had no difference in the primary outcome of death, ACS, or major procedural complications as compared to CCTA (100). For stress nuclear imaging, multicenter registries support effective risk stratification based on rest/stress measures of MPI and left ventricular function (13,21,27,28,98,101,102), with recent evidence on the prognostic value of stress PET (26,37,38,103,104). Randomized trials have compared the effectiveness of rest/stress MPI with other noninvasive tests, such as CMR (105) and CCTA, revealing similar 1- to 3-year outcomes. Two multicenter trials have evaluated the effectiveness of a CMR-guided strategy as compared to standard testing approaches (34,35). The CE-MARC 2 multicenter trial (n=1,202) revealed that both CMR and SPECT MPI were associated with similar rates (i.e., 7.1%-7.5%) of unnecessary invasive angiography (defined as a no CAD stenosis ≥70% or a normal invasive FFR) compared with standard testing for chest pain (28.8%; p<0.001) (34). The MR-INFORM trial randomized 918 patients with typical angina and multiple risk factors or a positive exercise ECG to a CMR strategy versus invasive FFR strategy (35). The CMR strategy was associated with less coronary revascularization (p=0.005) and a similar event rate (death, AMI, or target vessel revascularization; p=0.91).

3. Although PET and SPECT are grouped together, PET has improved diagnostic and prognostic performance, especially when quantitative assessment of MBF can be performed (36-39). A recent clinical trial (n=475) reported a higher diagnostic accuracy with stress PET MPI compared with other stress test modalities (38).
4. Diagnostic accuracy of the exercise ECG is lower (i.e., sensitivity and specificity range, 60%-77%) than stress imaging, but prognostication remains a useful goal (13,41). In the WOMEN trial including 824 symptomatic women, exercise ECG was equally effective when compared with exercise SPECT MPI, with similar 2-year CAD event rates (2.0% versus 2.3%; p=0.59) (40). Failure to complete the first stage of the Bruce protocol (or <5 METs) or to achieve 85% of age-predicted fitness level increases CAD event risk (13,41-45). Patients exercising to Bruce stage III or >10 METs with a negative ECG have a low risk of CAD events. In patients with submaximal exercise or for those with an ischemic ECG ≥1.0 mm ST depression, additional stress imaging may improve risk detection and guide clinical management (41). Marked ischemia (e.g., ≥2.0 mm at reduced workloads) or high Duke or Lauer scores signify increased risk among women and men (13,41,42,44); such patients may benefit from additional testing (anatomic or stress testing).
5. Use of attenuation correction algorithms and prone imaging can reduce MPI artifacts (46-51).

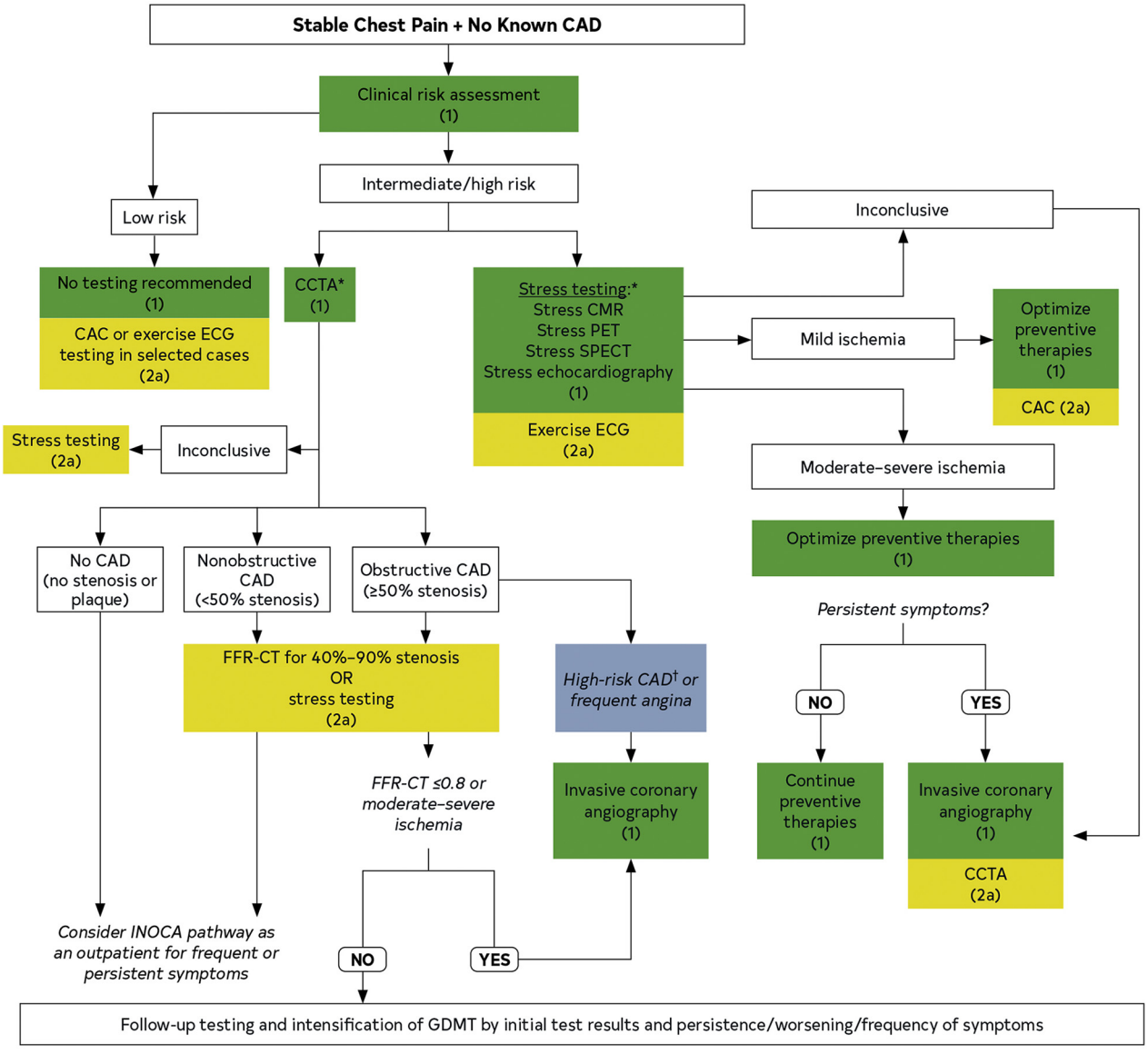
Assessment of Left Ventricular Function

6. Clinical practice guidelines and appropriate use criteria support use of TTE as appropriate for the assessment of regional and global left ventricular function (13,14). The likelihood of abnormal findings increases when TTE is performed selectively among higher risk patients, such as those with electrocardiographic Q waves or heart failure symptoms, complex ventricular arrhythmias, or a heart murmur (52).

Sequential or Add-on Testing

6. The use of FFR-CT is supported by several studies (56,57,104), including one reporting improved diagnostic accuracy with FFR-CT versus coronary CT alone when applying invasive FFR as the gold standard (56). Several multinational registries have examined the utility of FFR-CT with regards to guiding clinical decision-making and the safety of deferring coronary revascularization in patients with a negative FFR-CT (12,26,53,54). In the ADVANCE registry, FFR-CT changed treatment recommendations in two-thirds of 5,083 patients, and there were no MACE at 90 days for patients with a negative FFR-CT (54). FFR-CT is most beneficial when measured in a coronary stenosis of 40% to 90% severity located in a proximal or mid-coronary artery segment (54,106,107).
7. Use of CCTA after stress testing can diagnose or exclude obstructive CAD and identify patients who may benefit from referral to ICA (5,59-61,63). The ISCHEMIA trial used CCTA after site-determined moderate-severe ischemia to exclude patients with nonobstructive CAD and identifying those with significant left main stenosis who benefit from prompt referral to ICA (63,108). Half of the screen failures for the ISCHEMIA trial were identified by CCTA including those with nonobstructive CAD or unprotected left main CAD.
8. Observational registry data suggest that adding CAC can improve risk assessment, reduce diagnostic uncertainty, help detect atherosclerotic plaque, and guide preventive management (64-70,94,109,110).
9. After an initial exercise ECG, data support an improved diagnostic accuracy and improved risk stratification with further stress imaging, such as with stress echocardiography (13,14,71,72), nuclear MPI (20-23,40,73-76), or CMR (35,111-113).
10. For the symptomatic patients with negative stress test findings, selective use of CCTA or invasive coronary angiography can help detect obstructive CAD and atherosclerotic plaque and reduce diagnostic certainty.

FIGURE 12 Clinical Decision Pathway for Patients With Stable Chest Pain and No Known CAD



Test choice should be guided by local availability and expertise. *Test choice guided by patient's exercise capacity, resting electrocardiographic abnormalities; CCTA preferable in those <65 years of age and not on optimal preventive therapies; stress testing favored in those ≥65 years of age (with a higher likelihood of ischemia). †High-risk CAD means left main stenosis ≥50%; anatomically significant 3-vessel disease (≥70% stenosis). CAD indicates coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; INOCA, ischemia and no obstructive CAD; PET, positron emission tomography; and SPECT, single-photon emission CT.

5.2. Patients With Known CAD Presenting With Stable Chest Pain

Recommendations for Patients With Known CAD Presenting With Stable Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplement 31.

COR	LOE	RECOMMENDATIONS
1	A	1. For patients with obstructive CAD and stable chest pain, it is recommended to optimize GDMT (1-3).
1	C-EO	2. For patients with known nonobstructive CAD and stable chest pain, it is recommended to optimize preventive therapies (4,5).

Synopsis

In patients with known CAD, clinicians should opt to intensify GDMT first, if there is an opportunity to do so, and defer testing. Although GDMT exists for obstructive CAD, there are no current guidelines that are specific to nonobstructive CAD. Thus, adhering to atherosclerotic CV prevention guidelines is recommended (4,5).

Recommendation-Specific Supportive Text

1. ACC/AHA clinical practice guidelines for treatment of patients with stable CAD recommend optimization of anti-ischemic and preventive therapies with the goal to reduce the patient's angina burden and improve clinical outcomes (6,7).
2. For all patients with a history of CAD risk factors, optimized preventive therapy should be used according to ACC/AHA clinical practice guidelines (4,5).

5.2.1. Patients With Obstructive CAD Who Present With Stable Chest Pain

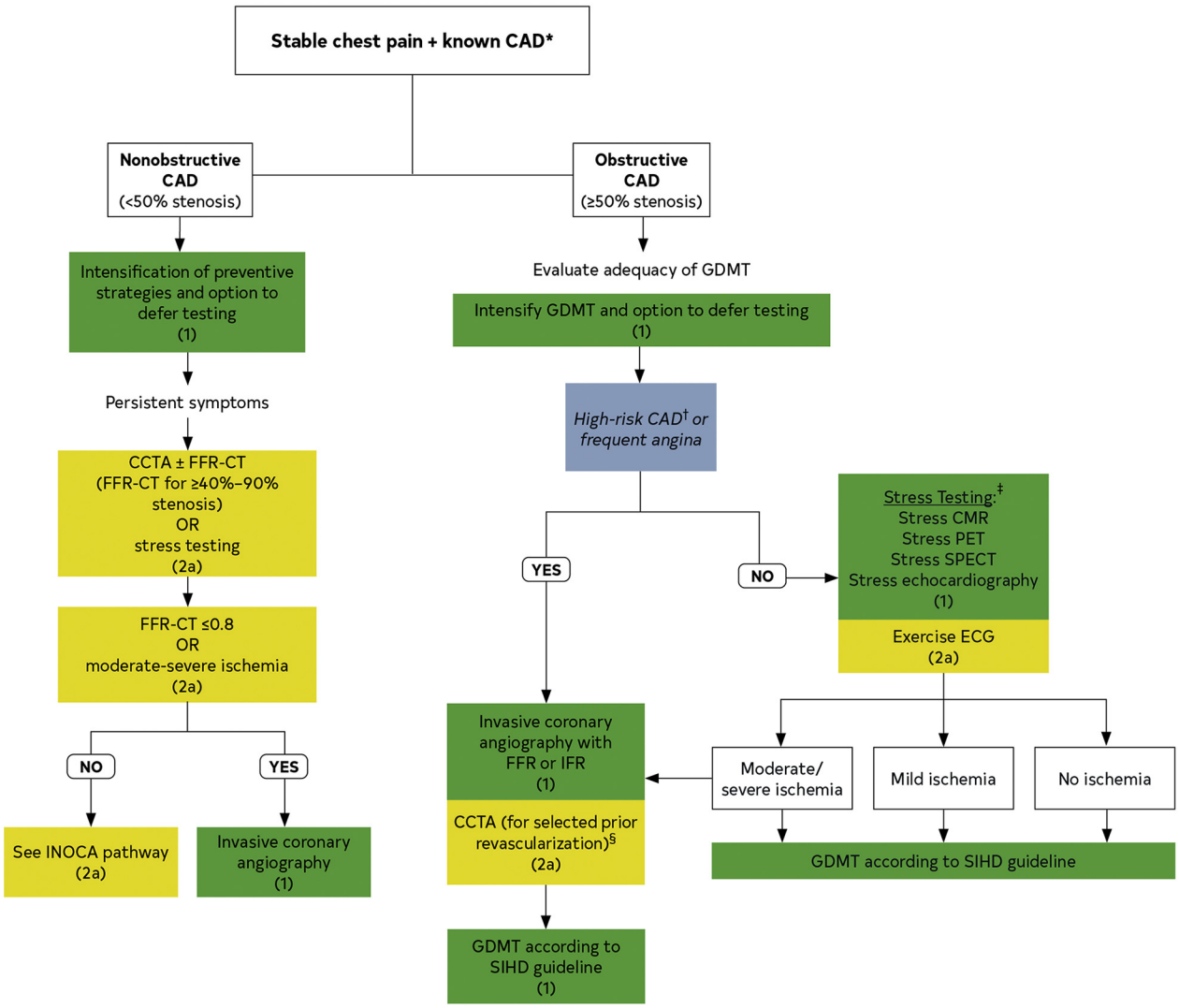
Recommendations for Patients With Obstructive CAD Who Present With Stable Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 32 and 33.

COR	LOE	RECOMMENDATIONS
		Index Diagnostic Testing
		Anatomic Testing
1	A	1. For patients with obstructive CAD who have stable chest pain despite GDMT and moderate-severe ischemia, ICA is recommended for guiding therapeutic decision-making (1-4).
1	A	2. For patients with obstructive CAD who have stable chest pain despite optimal GDMT, those referred for ICA without prior stress testing benefit from FFR or instantaneous wave free ratio (3,5-7).
1	B-R	3. For symptomatic patients with obstructive CAD who have stable chest pain with CCTA-defined ≥50% stenosis in the left main coronary artery, obstructive CAD with FFR with CT ≤0.80, or severe stenosis (≥70%) in all 3 main vessels, ICA is effective for guiding therapeutic decision-making (4,8).
2a	B-NR	4. For patients who have stable chest pain with previous coronary revascularization, CCTA is reasonable to evaluate bypass graft or stent patency (for stents ≥3 mm) (9-13).
		Stress Testing
1	B-NR	5. For patients with obstructive CAD who have stable chest pain despite optimal GDMT, stress PET/SPECT MPI, CMR, or echocardiography is recommended for diagnosis of myocardial ischemia, estimating risk of MACE, and guiding therapeutic decision-making (14-36).
2a	B-R	6. For patients with obstructive CAD who have stable chest pain despite optimal GDMT, when selected for rest/stress nuclear MPI, PET is reasonable in preference to SPECT, if available, to improve diagnostic accuracy and decrease the rate of nondiagnostic test results (37).
2a	B-NR	7. For patients with obstructive CAD who have stable chest pain despite GDMT, exercise treadmill testing can be useful to determine if the symptoms are consistent with angina pectoris, assess the severity of symptoms, evaluate functional capacity and select management, including cardiac rehabilitation (4,38-40).
2a	B-NR	8. For patients with obstructive CAD who have stable chest pain symptoms undergoing stress PET MPI or stress CMR, the addition of MBFR is useful to improve diagnosis accuracy and enhance risk stratification (31-36).

Synopsis

In patients with known CAD, physicians should opt to intensify GDMT first, if there is an opportunity to do so, and defer testing. In patients with a history of obstructive CAD, previous AMI, or previous coronary revascularization, assessing the severity of ischemia may be useful to guide clinical decision-making regarding the use of ICA and intensify preventive and anti-ischemic therapy. Imaging should be considered in those with new onset or persistent stable chest pain (Figure 13). In patients with frequent angina or severe stress-induced ischemia, referral to ICA or CCTA is an option (4). Among individuals with known obstructive CAD or ischemic heart disease who have stable symptoms, exercise treadmill testing may be useful for assessing functional capacity, assessing the type and severity of symptoms, and informing the role of coronary revascularization, cardiac rehabilitation, or anti-anginal therapy (4,38-40).

FIGURE 13 Clinical Decision Pathway for Patients With Stable Chest Pain (or Equivalent) Symptoms With Prior MI, Prior Revascularization, or Known CAD on Invasive Coronary Angiography or CCTA, Including Those With Nonobstructive CAD



Test choice should be guided by local availability and expertise. *Known CAD means prior MI, revascularization, known obstructive CAD, nonobstructive CAD. †High-risk CAD means left main stenosis ≥50%; or obstructive CAD with FFR-CT ≤0.80. ‡Test choice guided by the patient's exercise capacity, resting electrocardiographic abnormalities. §Patients with prior CABG or stents >3.0 mm. *Follow-up Testing and Intensification of GDMT Guided by Initial Test Results and Persistence / Worsening / Frequency of Symptoms and Shared Decision Making*. CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; ECG, electrocardiogram; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; ICA, invasive coronary angiography; iFR, instant wave-free ratio; INOCA, ischemia and no obstructive coronary artery disease; MI, myocardial infarction; MPI, myocardial perfusion imaging; PET, positron emission tomography; SIHD, stable ischemic heart disease; and SPECT, single-photon emission CT.

Recommendation-Specific Supportive Text

Anatomic Testing

1. SIHD randomized trials reveal a pattern that ischemia-guided percutaneous coronary intervention (PCI) results in an improvement in angina when compared with medical therapy alone (1-4,41). In the ISCHEMIA trial, a total of 5,179 patients with stable CAD and site-determined moderate-severe ischemia on stress testing were randomized to invasive versus conservative care strategies (4). No difference in the composite primary MACE endpoint was observed at ~3.3 years of follow-up. Patients presenting with daily, weekly, or monthly angina had a prompt and durable improvement in symptoms when randomized to invasive compared with conservative management (41).
2. Coronary revascularization after identification of suspected lesion-specific ischemia (FFR ≤0.80 or instantaneous wave-free ratio ≤0.89) in obstructive CAD is associated with improved event-free survival compared with the use of PCI determined by anatomy alone (3,5,6,42).
3. In a patient presenting with new or recurrent chest pain symptoms, progression of CAD (i.e., new or worsening stenosis or more extensive nonobstructive atherosclerotic plaque) may be characterized using CCTA (43,44). Detection of nonobstructive CAD often results in prompt initiation and intensification of preventive and anti-ischemic therapies with CCTA (45-50). There is a high degree of concordance between CCTA- and ICA-determined obstructive CAD (33,51-55). CCTA-defined left main stenosis (nonobstructive and ≥50% stenosis) is associated with a high CAD event risk (56,57). Coronary revascularization confers a survival benefit among patients with left main CAD (58). From randomized trials, major clinical outcomes in patients with left main CAD are similar with CABG and PCI at near-term follow-up of 1 to 2 years, although repeat revascularization rates are higher after PCI (58).
4. CCTA has been shown to be accurate for the assessment of native vessel CAD and bypass graft patency with high accuracy (~96%) and concordance (82%->93%) to ICA; it may also be useful to assess patency of proximal large stents (≥3 mm) if such information is known at the time of presentation (9-13). Several controlled clinical trials have evaluated the concordance of FFR-CT with invasive FFR (59-62). Diagnostic sensitivity and specificity of FFR-CT, compared with invasive FFR, is high (>90%) (32,60).

Stress Testing

5. Observational findings reveal that patients with moderate-severe ischemia on PET and SPECT MPI have an improved outcome with early coronary revascularization (20,34,63-65). Patients with moderate-severe ischemia on PET (≥10% ischemic myocardium) treated with PCI reported an improvement in angina when compared with those treated medically (20). Prespecified substudies from therapeutic strategy trials for SIHD also evaluated the role of rest/stress nuclear MPI to assess residual ischemia severity among patients with known CAD who were treated with medical therapy alone or when combined with revascularization (1,2,14-18).

Clinical trials of CMR have included subgroups with obstructive CAD, including 76% and 49% in the MR-IMPACT and MR-IMPACT2 studies, respectively, showing generally comparable diagnostic accuracy to stress SPECT MPI (23,24). Several large, multicenter registries reveal that stress CMR effectively risk stratifies patients with known CAD (27-30). In a multicenter registry of 2,496 patients with a history of CAD, an abnormal stress CMR had a nearly 2-fold increased mortality hazard (27). From the SPINS Registry (Stress CMR Perfusion Imaging in the United States), patients with known CAD with MPI ischemia and scarring by late gadolinium enhancement had a relative hazard of 1.5 to 2.1 for CV death or nonfatal MI (30). Prognosis worsens for patients by the extent and severity of inducible wall motion abnormalities on stress echocardiography (66,67). Recent randomized trial evidence supports the role of stress echocardiography to guide clinical decision-making. From the ORBITA (Objective Randomized Blinded Investigation With Optimal Medical Therapy in Stable Angina) trial, there was a greater reduction in the stress echocardiographic wall motion score among patients with single-vessel CAD treated with PCI compared with placebo ($p<0.0001$) (68). In a secondary analysis, there was an interaction between the baseline stress echocardiographic wall motion score and the efficacy of PCI for improved angina at 6 weeks of follow-up (69). That is, PCI-treated patients with a wall motion score ≥1 were more often angina-free compared with those in the placebo arm.

6. Evidence supports that the improved diagnostic accuracy of PET MPI is helpful in the patient with known CAD. In a randomized trial of 322 symptomatic patients with known CAD, the presence of low- and high-risk stress PET findings was associated with lower and higher rates of ICA when compared with SPECT MPI ($p=0.001$) (37). In this trial, nearly 1 in 5 patients with low-risk SPECT MPI findings underwent ICA, a rate more than twice that of stress PET MPI. Based on such evidence, PET is preferable over SPECT when both are available.
7. Observational studies of patients with CAD and stable chest pain have demonstrated that exercise treadmill testing can be useful by evaluating the relation of

symptoms to graded stress testing, thereby helping to confirm the diagnosis of angina pectoris; assessing symptom severity; and selecting appropriate management: medical therapy, revascularization, and/or cardiac rehabilitation (4,38-40).

Secondary Diagnostic Testing: For the Assessment of Vascular Territory Flow or Vessel-Specific Ischemia

8. Measurement of MBFR, when reduced, reflects abnormalities of flow within the epicardial coronary arteries and/or microvasculature and independently predicts risk of major CAD events. This can be effectively accomplished using PET (31,70,71) or CMR (28). Normal MBFR may be helpful in excluding high risk anatomy, although reduced levels may provide a better estimate of disease extent and severity. In the presence of nonobstructive CAD, reduced MBFR may signify coronary microvascular dysfunction, especially among women (70).

5.2.1.1. Patients With Prior CABG Surgery With Stable Chest Pain

Recommendations for Patients With Prior CABG Surgery With Stable Chest Pain

COR	LOE	RECOMMENDATIONS
1	C-LD	1. In patients who have had prior CABG surgery presenting with stable chest pain whose noninvasive stress test results show moderate-to-severe ischemia (1-7), or in those suspected to have myocardial ischemia with indeterminate/nondiagnostic stress test, ICA is recommended for guiding therapeutic decision-making (1).
2a	C-LD	2. In patients who have had prior CABG surgery presenting with stable chest pain who are suspected to have myocardial ischemia, it is reasonable to perform stress imaging or CCTA to evaluate for myocardial ischemia or graft stenosis or occlusion (8-15).

Synopsis

In patients with prior CABG who have stable chest pain, it is important to assess medical therapies and optimize all guideline-directed therapies (1). ICA can be useful to guide therapeutic decision-making in those with frequent angina that has not improved with medical therapy (1-9). In those whose symptoms do improve after optimizing medical therapy, evaluation with stress testing can be useful to assess the degree of myocardial ischemia and determine which patients may benefit from coronary angiography (6,10). CCTA can also be used to detect graft patency but is often less robust for assessing native coronary vessel stenosis in those with prior CABG, because of high degree of nondiagnostic segments (8-15).

Recommendation-Specific Supportive Text

1. There are stress test features in patients with prior CABG and presenting with stable chest pain that may indicate a high likelihood of severe ischemic heart disease such as stress electrocardiographic 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, severe stress-induced left ventricular systolic dysfunction, stress-induced perfusion abnormalities involving ≥10% myocardium or stress-induced left ventricular dilation. In these patients with prior CABG and high-risk imaging features, referral for ICA is reasonable provided that these patients are amenable to and are candidates for coronary revascularization (1-7). Patients with prior CABG presenting with stable chest pain may have stress imaging features that are equivocal or nondiagnostic for the presence of myocardial ischemia. Equivocal or nondiagnostic stress tests may be a result of patient's body habitus, inadequate or suboptimal heart rate, arrhythmias such as atrial fibrillation, left bundle branch block, or patient motion. In these patients, performing an ICA is reasonable when the angiographic findings have a high likelihood of impacting therapeutic decisions (1).
2. Stable chest pain due to myocardial ischemia may occur in patients with prior CABG because of progression of atherosclerosis in the native coronary arteries or within the bypass grafts. Noninvasive stress imaging testing is reasonable in these patients to identify ischemic myocardial territories that will further guide revascularization for patients who are amenable to and are candidates for revascularization. Furthermore, stress imaging also assists in stratifying patients to determine the degree of likelihood for severe ischemic heart disease, which will assist in therapeutic decisions (8-10,12-14). CCTA has a great degree of accuracy with a sensitivity and specificity of detecting complete graft occlusions, 99% and 99%, respectively, when compared with the standard of ICA (20). Furthermore, CCTA was ideal in assessing bypass grafts attributable to the large size of these vessels, decreased vessel calcification and decreased motion of these vessels when compared with native coronary vessels, with successful

evaluation of bypass grafts in 93% to 100% of patients (15). In patients who have stable chest pain and are previously known to have borderline graft stenosis or are suspected to have new graft stenosis, CCTA is useful for assessing graft patency but less robust for assessing native coronary vessel stenosis in this population because of high degree of non-diagnostic segments (8-15).

5.2.2. Patients With Known Nonobstructive CAD Presenting With Stable Chest Pain

Recommendations for Patients With Known Nonobstructive CAD Presenting With Stable Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 34 and 35.

COR	LOE	RECOMMENDATIONS
		Index Diagnostic Testing
		Anatomic Testing
2a	B-NR	1. For symptomatic patients with known nonobstructive CAD who have stable chest pain, CCTA is reasonable for determining atherosclerotic plaque burden and progression to obstructive CAD, and guiding therapeutic decision-making (1-7).
2a	B-NR	2. For patients with known coronary stenosis from 40% to 90% on CCTA, FFR can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of ICA (8-14).
		Stress Testing
2a	C-LD	3. For patients with known extensive nonobstructive CAD with stable chest pain symptoms, stress imaging (PET/SPECT, CMR, or echocardiography) is reasonable for the diagnosis of myocardial ischemia (15-24).

Synopsis

For patients with known nonobstructive CAD (luminal narrowing 1%–49%), CCTA can be useful for detection of new or worsening obstructive stenosis, atherosclerotic disease progression, and identification of high-risk plaque features, such as low attenuation plaque or positive remodeling (1,2,5-7,25) (**Figure 13**). Similarly, stress imaging is reasonable to detect myocardial ischemia and can help guide further management and treatment of ischemic burden (15-24).

Irrespective of the test performed, an overarching goal of the evaluation of symptomatic patients with known nonobstructive CAD is to identify those who would benefit from intensification of preventive therapy, as defined by the 2018 cholesterol-lowering guidelines and the 2019 prevention guidelines (26-29). For this evaluation, the patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac testing modality and in guiding the pathway for treatment decisions.

Recommendation-Specific Supportive Text

Anatomic Testing

1. Atherosclerosis is a progressive disease that worsens over time (1), with nonobstructive CAD consistently identified as precursor for ACS (3-6). From the PROMISE trial, nonobstructive CAD was associated with a 3-fold increase in MACE risk over ~2 years of follow-up (3). Additional analyses from the SCOT-HEART and PROMISE trials reveal that high-risk atherosclerotic plaque features are associated with an elevated MACE risk among patients with nonobstructive CAD (4,5). CCTA commonly identifies patients with nonobstructive CAD but can further define compositional alterations within the plaque (i.e., noncalcified plaque) and positive remodeling (4,5,7,25,30). These plaque features have been associated with inducible ischemia, identified as precursors for ACS, and independently predict MACE (5,6,31). Recently, Williams et al reported that a low attenuation plaque burden was associated with a >6-fold increase in incident MI for patients with nonobstructive CAD (4).
2. Controlled clinical trials reveal that FFR-CT improves diagnostic accuracy over and above obstructive CAD on CCTA when compared with invasive FFR (12,13). Multinational registries have examined the use of FFR-CT with regards to the use to drive clinical decision-making regarding the use of follow-up ICA and the safety of deferring coronary revascularization in patients with a negative FFR-CT (8-11). From the ADVANCE (Assessing Diagnostic Value of Non-invasive FFR-CT in Coronary Care) registry, FFR-CT changed treatment recommendations in two-thirds of patients, and there were no MACE at 90 days for patients with a negative FFR-CT (10). From the SYNTAX 3 trial (14), FFR-CT was performed in 223 patients. Treatment

recommendations and selection of vessels for revascularization were guided by FFR-CT in ~20% of patients.

Stress Testing

3. Approximately 20% to 30% of patients with nonobstructive CAD will demonstrate ischemia (15-24). Patients who experience ischemia with nonobstructive CAD (INOCA - see section 5.2.3) benefit from assessment of functional significance of an intermediate coronary stenosis as it provides insight into the patient's presenting symptoms and can help guide clinical management.

5.2.3. Patients With Suspected Ischemia and No Obstructive CAD (INOCA)

Recommendations for myocardial blood flow measurements using PET, echocardiography, and CMR are found in Section 5.2.2.

Recommendations for Patients With Suspected INOCA
Referenced studies that support the recommendations are summarized in Online Data Supplements 36 and 37.

COR	LOE	RECOMMENDATIONS
2a	B-NR	1. For patients with persistent stable chest pain and nonobstructive CAD and at least mild myocardial ischemia on imaging, it is reasonable to consider invasive coronary function testing to improve the diagnosis of coronary microvascular dysfunction and to enhance risk stratification (1-4).
2a	B-NR	2. For patients with persistent stable chest pain and nonobstructive CAD, stress PET MPI with MBFR is reasonable to diagnose microvascular dysfunction and enhance risk stratification (5-11).
2a	B-NR	3. For patients with persistent stable chest pain and nonobstructive CAD, stress CMR with the addition of MBFR measurement is reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE (12-14).
2b	C-EO	4. For patients with persistent stable chest pain and nonobstructive CAD, stress echocardiography with the addition of coronary flow velocity reserve measurement may be reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.

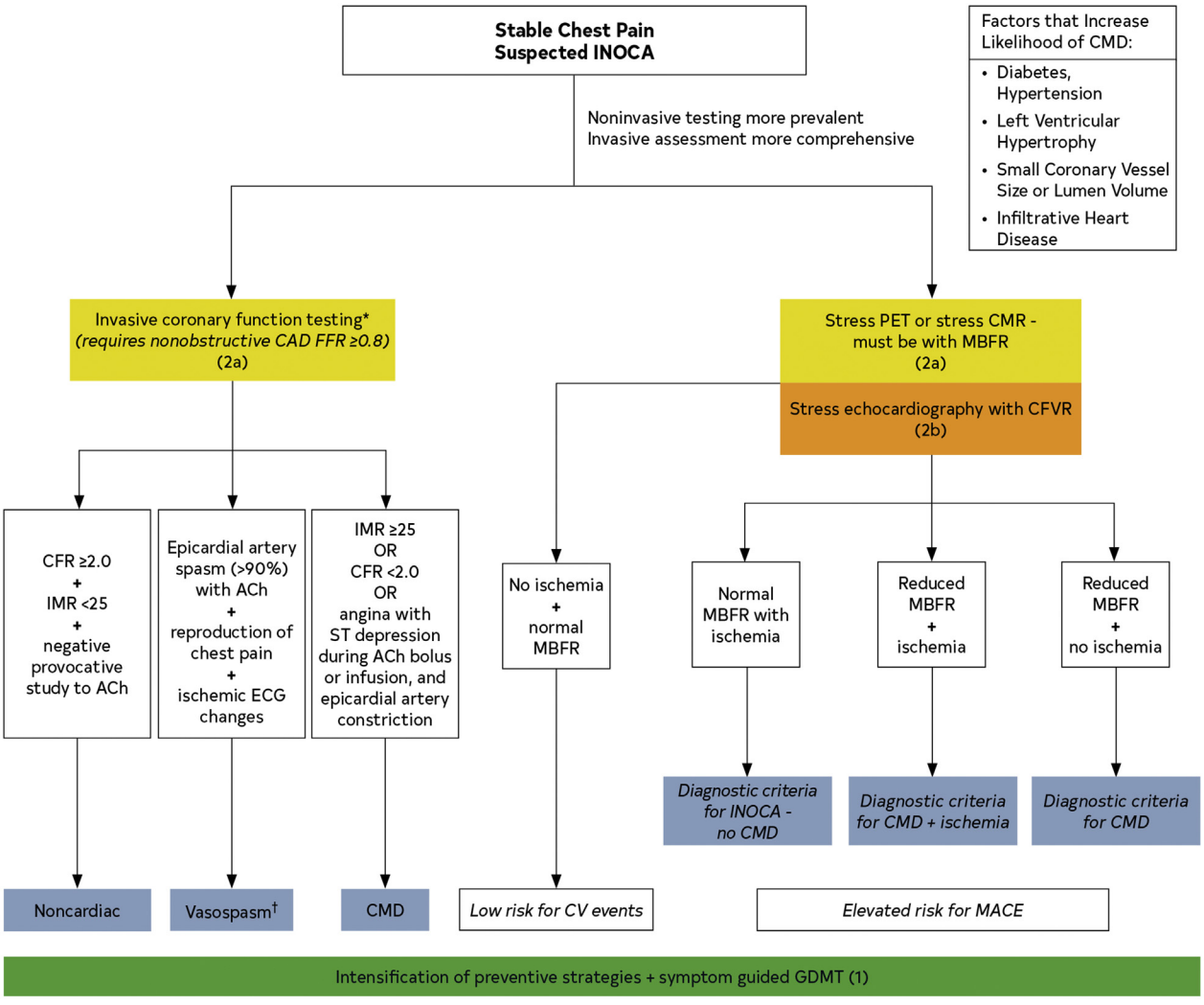
Synopsis

Signs and symptoms of ischemia occur because of focal obstructive CAD, but INOCA is common and may result from alterations in flow within the microvasculature. Thus, many symptomatic patients without obstructive CAD on previous workup may be candidates for assessment of coronary microvascular dysfunction and other causes of INOCA (1). Patients at highest risk for coronary microvascular dysfunction include women, those with hypertension, diabetes, and other insulin-resistant states (15). There is substantive evidence that testing focusing on documentation of coronary or microvascular flow abnormalities can aid in the diagnosis of microvascular angina, and abundant evidence supports that the addition of flow alterations improves risk stratification. Invasive coronary reactivity testing allows for the assessment of vasospasm, in addition to nonendothelial-dependent and endothelium-dependent microvascular reactivity (2,4). From the National Institutes of Health-NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation), impaired coronary flow reserve (i.e., <2.32) among women with no obstructive CAD was associated with an elevated hazard for major CAD events with lengthy follow-up of 10 years (p=0.03) (2). Among women with no obstructive CAD, epicardial vasoconstriction was also significantly associated with higher rates of hospitalization for angina (p=0.0002) (2). Prognostic evidence is available supporting the novel contribution of PET MBFR techniques; several reports also note a benefit using CMR and echocardiographic techniques. A proposed diagnostic evaluation pathway is outlined in Figure 14.

Recommendation-Specific Supportive Text

1. Evidence supports a role for invasive coronary reactivity testing, including prognostic evidence from the WISE study (1,2). The CorMicA (Coronary Microvascular Angina) trial enrolled symptomatic patients (74% women) without obstructive CAD and positive invasive coronary reactivity testing (n=76 patients to intervention and 75 to the blinded control group). The intervention consisted of anti-ischemic therapy using beta-blockers and angiotensin-converting enzyme inhibitors along with preventive care (statins) and lifestyle changes, including smoking cessation, and was associated with a significant improvement in angina and quality of life over 6 months (p=0.001)(4,16). This small trial did not report any differences in 6-month MACE (p=0.8).
2. PET measurement of peak myocardial blood flow and MBFR, when reduced, reflects abnormalities of flow

FIGURE 14 Clinical Decision Pathway for INOCA



Test choice should be guided by local availability and expertise. *Ford T, et al. (16). †Cannot exclude microvascular vasospasm. ACh indicates acetylcholine; CAD, coronary artery disease; CFR, coronary flow reserve; CFVR, coronary flow velocity reserve; CMD, coronary microvascular dysfunction; CV, cardiovascular; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; IMR, index of microcirculatory restriction; INOCA, ischemia and no obstructive CAD; MACE, major adverse cardiovascular events; and MBFR, myocardial blood flow reserve.

within the epicardial coronary arteries and microvasculature and independently predicts risk of major CAD events (5-7,17). PET measurement of MBFR improves risk stratification, including for patients with nonobstructive CAD, especially women, for whom coronary microvascular dysfunction is suspected (18).

3. CMR has been used to evaluate MBFR. When validated against invasive coronary physiology measures, pixel-wise quantitative myocardial perfusion mapping by CMR was able to identify coronary microvascular dysfunction in a small study that included 23 patients with nonobstructive CAD (19). The addition of coronary flow reserve improves prognostication (12-14). Stress CMR studies of MBFR have shown reasonable agreement with PET (n=21) (20).
4. Stress echocardiography assessing coronary flow velocity reserve in the left anterior descending artery with Doppler can currently be combined with wall motion analysis during vasodilator stress echocardiography. Limited data have shown that abnormal coronary flow velocity reserve (≤2) adds incremental value to the prognostic stratification achieved with clinical and angiographic data for events such as death and nonfatal MI in patients with angiographically

normal or near-normal coronary arteries and preserved at-rest regional and global left ventricular function at baseline and during stress (21).

5.3. Cost-Value Considerations in Diagnostic Testing

A general concept regarding cost is that layered testing (i.e., when a test is followed by more tests) leads to higher costs. To minimize the potential needs for downstream testing, clinicians should select the test that is most likely to answer a particular question.

5.3.1. CCTA and CAC Scanning Cost-Value Considerations

In the outpatient setting, long-term costs were generally similar between CCTA and stress testing strategies (1). Higher invasive angiography rates after CCTA are matched by a greater use of downstream stress testing after initial stress testing, resulting in minimal differences in cost at 2 to 3 years of follow-up (1,2). From the CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trial, 823 patients were randomized to a selective versus direct referral strategy to ICA. Enrollment was limited to patients with nonemergent indications for ICA (3). The selective referral arm included CCTA-guided use of ICA. Cumulative diagnostic costs were $1,183 for the selective arm and $2,755 for the direct referral arm of the CONSERVE trial (57% lower costs). In the CCTA-guided arm, follow-up stress testing was applied and contributed to reduced referrals to ICA.

A recent tiered testing strategy was evaluated in both the CRESCENT I and II trials (2,4). From the CRESCENT I trial, CAC was used as the index test, with follow-up CCTA used only in patients with detectable CAC or for those with a high pretest risk (2). In this trial, nearly 40% of patients did not undergo CCTA, which reduced diagnostic evaluation costs; no events were reported in this subgroup. By comparison, nearly half of those randomized to the exercise ECG had additional confirmatory diagnostic testing. Overall, 1-year costs were significantly lower in the CAC tiered testing protocol (16% cost savings; $p<0.0001$) (2). Moreover, 1-year MACE-free survival was higher in the CAC-guided testing arm (97%) compared with exercise ECG (90%; HR: 0.32; $p=0.011$).

5.3.2. Exercise Electrocardiographic Cost-Value Considerations

The economic evidence for the exercise ECG supports that tiered testing may offset its reduced diagnostic accuracy (1,2). In a decision model, tiered testing of exercise ECG followed by selective stress echocardiography resulted in improved diagnostic accuracy and favorable cost-effective ratios when compared with other testing strategies (2). In a Medicare cohort, observed 180-day costs were lowest for the exercise ECG when compared with stress echocardiography, MPI, or CCTA (3). Randomized trial data on cost are available and from the PROMISE trial initial test costs were $174 for exercise ECG, >50% lower than that of other imaging procedures (4). At 3-years of follow-up, the mean cost difference was $1,731 higher for CCTA (n=4818) when compared with the exercise ECG (n=858); however, the 95% CIs for cost differences was wide ($2 to $3,519), and there was no overall difference by randomization (4). Overall, results from the PROMISE trial showed that stress testing was associated with similar costs and CAD outcomes over ~3 years of follow-up (4,5). In a randomized trial of 824 symptomatic women, cumulative procedural costs were nearly 50% lower for exercise ECG versus MPI SPECT ($p<0.0001$), with no difference in 2-year event-free survival ($p=0.59$) (6).

5.3.3. Stress Echocardiographic Cost-Value Considerations

Several cost-effectiveness models have reported an increased incremental cost-effectiveness ratio for stress echocardiography, compared with exercise ECG and other diagnostic procedures (1-4). In these models, cost-effectiveness was influenced by an improved diagnostic accuracy for stress echocardiography, which led to longer life expectancy (1). In a recent systematic review, the evidence supports that stress echocardiography or stress MPI are cost-effective for those patients at intermediate pretest risk (5). The improved CAD detection for exercise echocardiography resulted in fewer office and ED visits and hospital days, yielding a 20% cost savings when compared with the exercise ECG (6). There were 2,204 patients that underwent stress echocardiography in the PROMISE trial, and 3-year mean costs were similar to that of CCTA (CCTA - stress echocardiography mean cost difference: -$363; 95% CI: -$1,562 to $818) (7).

5.3.4. Stress Nuclear MPI Cost-Value Considerations

Among intermediate-risk patients, evidence synthesis supports that stress MPI is a cost-effective test option (1). From the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) registry, observed 2-year mortality rate was highest for PET MPI (5.5%) compared with CCTA (0.7%) or SPECT MPI (1.6%), with 2-year cost highest for patients undergoing PET (2). In the PROMISE trial, nearly two-thirds of patients underwent stress MPI, and the mean cost was similar when compared with CCTA (3). Mean costs were also similar in a randomized trial of 457 patients comparing stress MPI with exercise ECG ($p>0.05$) (4). Among higher-likelihood patients in the UK enrolled in the CECaT (Cost Effectiveness of Noninvasive Cardiac Testing) trial, MPI SPECT was the most cost-effective approach (5).

5.3.5. Stress CMR Cost-Value Considerations

A synthesis of this cost evidence reveals a pattern whereby CMR perfusion and scar imaging is associated with a favorable incremental cost-effectiveness ratio of <$50,000 per quality-adjusted life years saved (1,2). From a single report, a CMR strategy informed by the CE-MARC trial was more cost-effective than stress MPI, largely because of the higher diagnostic accuracy for CMR (2). However, the most cost-effective strategy was that of initial exercise ECG followed by selective stress CMR and invasive angiography; for this tiered testing approach, additional testing was deemed appropriate in the setting of abnormal or inconclusive findings. In a decision model for intermediate pretest risk patients, a strategy of CMR followed by selective ICA had projected reduced costs by ~25% when compared with direct referral to ICA (2,3). From the Stress CMR Perfusion Imaging in the United States registry (4), patients with negative findings for ischemia and scar had low downstream costs (5).

6. EVIDENCE GAPS AND FUTURE RESEARCH

Chest pain is one of the most common symptoms for which a person seeks medical care, and it should therefore be the target of substantial research investigation.

1. For patients with ACS, considerable success has been achieved in reducing door-to-balloon times for STEMI, but little progress has been made in reducing the important delays from symptom onset to presentation. Further research is needed to develop approaches to shorten this interval including studies of other methods of evaluating patients with chest pain using technologies that permit acquisition and transmission of ECGs from home and remote evaluations (e.g., telehealth) for those with acute symptoms (1,2).
2. An important, increasing patient population includes women and men with angina and ACS associated with angiographically normal or nonobstructive coronary arteries (3,4). Prognosis is not benign, pathophysiology has not been clarified, and optimal therapy is unclear in these heterogeneous groups, which are now considered in terms of INOCA (5) and MINOCA (6). Adequately identifying patients with INOCA, and completing an evaluation to make such a diagnosis, is necessary but often not done, regardless of whether chest pain is assessed in the ED, inpatient, or outpatient setting. Further investigation to clarify disease mechanisms in these challenging syndromes is needed to provide the basis for therapeutic advances.
3. One of the initial challenges in the evaluation of patients with chest pain, either in the emergency or office setting, is symptom classification. Methods to elicit symptoms and clusters of symptoms that provide improved pretest probabilities of symptomatic CAD may be aided with machine-learning algorithms. It is already clear that some common dogma about chest pain descriptions, such as differences between men and women, may not be as prevalent as has been reported (7) and may impede care of both sexes if they do not fit preconceived notions of the clinical significance of their symptoms. However, reducing the differences in both sex and racial differences in treatment and outcomes are important future goals of research and clinical care.
4. Clinical risk stratification and decision tools will likely continue to grow in popularity because they are incorporated into electronic health records, but it would be useful to test them in large randomized trials to rigorously determine their benefit in terms of improved outcomes or lower costs before widespread implementation (1). hs-cTn assays are now the global standard of care for identifying myocardial injury, although questions remain about whether minimal elevations, which carry prognostic value, are actionable in a manner that improves outcomes. Trials evaluating various medical and procedural strategies would be useful including diagnostic and therapeutic algorithms for MINOCA. The number of potential questions that could be addressed will demand innovative trial designs to use resources efficiently and meaningfully.
5. Increasingly, randomized trials will be performed to determine which diagnostic tests can be eliminated from initial and follow-up care, both to streamline management algorithms and to decrease health care costs. In part, this approach will encompass evaluation of where patients with chest pain should be initially evaluated and monitored. Comparison of the various imaging modalities in randomized trials should help refine test selection and use (8).

Thus, the diagnosis and management of chest pain will remain a fertile area of investigation, with randomized evaluations complementing insights provided by registries of patients presenting with chest pain (9-12). In the future, registries will more frequently serve as platforms within which to conduct randomized trials. Accreditation activities coupled with registry participation will also need to be evaluated to determine if they not only improve processes of care but also affect clinical endpoints (12). Assessment of long-term outcomes, patient-centered metrics, and cost will be integrated into these studies to enhance the evidence base for care of patients presenting with chest pain with greater precision.

JACC VOL. 78, NO. 22, 2021
NOVEMBER 30, 2021:e187–e285

STAFF

American College of Cardiology

Dipti N. Itchhaporia, MD, FACC, President
Cathleen C. Gates, Chief Executive Officer
MaryAnne Elma, MPH, Senior Director, Enterprise Content and Digital Strategy
Timothy W. Schutt, MA, Clinical Practice Guidelines Analyst
Grace D. Ronan, Team Leader, Clinical Policy Publications

American College of Cardiology/American Heart Association

Thomas S.D. Getchius, Director, Guideline Strategy and Operations
Abdul R. Abdullah, MD, Director, Guideline Science and Methodology
Hannah Planalp, Guideline Advisor
Zainab Shipchandler, MPH, Guideline Advisor

American Heart Association

Mitchell S.V. Elkind, MD, MS, FAAN, FAHA, President
Nancy Brown, Chief Executive Officer
Mariell Jessup, MD, FAHA, Chief Science and Medical Officer
Radhika Rajgopal Singh, PhD, Senior Vice President, Office of Science and Health
Paul St. Laurent, DNP, RN, Senior Science and Medicine Advisor, Office of Science, Medicine and Health
Jody Hundley, Production and Operations Manager, Scientific Publications, Office of Science Operations

REFERENCES

PREAMBLE

1. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press. 2011.

2. Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: National Academies Press. 2011.

3. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2304–2322.

4. ACCF/AHA Task Force on Practice Guidelines. Methodology manual and policies from the ACCF/AHA Task Force on Practice Guidelines. *American College of Cardiology and American Heart Association*. 2010. Available at: https://www.acc.org/Guidelines/About-Guidelines-and-Clinical-Documents/Methodology and https://professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology_manual_and_policies_ucm_319826.pdf. Accessed July 26, 2021.

5. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;67:1572–1574.

6. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. *J Am Coll Cardiol*. 2014;64:1851–1856.

7. Levine GN, O'Gara PT, Beckman JA, et al. Recent innovations, modifications, and evolution of ACC/AHA Clinical Practice Guidelines: an update for our constituencies: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:1990–1998.

1.4. Scope of the Guideline

1. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929–1949.

2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.

3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–e76.

4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74:104–132.

5. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

6. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.

7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239.

8. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70:776–803.

9. Arnett DK, Blumenthal R, Albert M, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:e177–e232.

10. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63:2985–3023.

11. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.

12. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2018;72:e91–e220.

13. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;58:e123–e210.

14. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2020;76:e159–e240.

15. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–e122.

16. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2016;67:1235–1250.

17. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *J Am Coll Cardiol*. 2011;58:2432–2446.

18. Berg KM, Cheng A, Panchal AR, et al. Part 7: systems of care: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142:S580–S604.

19. Panchal AR, Berg KM, Hirsch KG, et al. 2019 American Heart Association focused update on advanced cardiovascular life support: use of advanced airways, vasopressors, and extracorporeal cardiopulmonary resuscitation during cardiac arrest: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2019;140:e881–e894.

20. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248.

21. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756–1776.

22. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2015;132:691–718.

23. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices-United States, 2018-19 Influenza Season. *MMWR Recomm Rep*. 2018;67:1–20.

1.4.1. Scope of the Problem

1. Rui P, Kang K. National Hospital Ambulatory Medical Care Survey: 2017 emergency department summary tables. National Center for Health Statistics. Available at: https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf. Accessed February 12, 2021.

2. Rui P, Okeyode T. National Ambulatory Medical Care Survey: 2016 national summary tables. 2016. Available at: https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2016_namcs_web_tables.pdf. Accessed February 12, 2021.

3. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596.

4. Ruigomez A, Rodriguez LA, Wallander MA, et al. Chest pain in general practice: incidence, comorbidity and mortality. *Fam Pract*. 2006;23:167–174.

5. Bosner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15:141–146.

6. Hsia RY, Hale Z, Tabas JA. A national study of the prevalence of life-threatening diagnoses in patients with chest pain. *JAMA Intern Med*. 2016;176:1029–1032.

1.4.2. Defining Chest Pain

1. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307:813–822.

2. van der Meer MG, Backus BE, van der Graaf Y, et al. The diagnostic value of clinical symptoms in women and men presenting with chest pain at the emergency department, a prospective cohort study. *PLoS One*. 2015;10:e0116431.

3. Hemal K, Pagidipati NJ, Coles A, et al. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE trial. *J Am Coll Cardiol Img*. 2016;9:337–346.

4. Lichtman JH, Leifheit EC, Safdar B, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction: evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). *Circulation*. 2018;137:781–790.

5. Bosner S, Haasenritter J, Hani MA, et al. Gender differences in presentation and diagnosis of chest pain in primary care. *BMC Fam Pract*. 2009;10:79.

6. Ferry AV, Anand A, Strachan FE, et al. Presenting symptoms in men and women diagnosed with myocardial infarction using sex-specific criteria. *J Am Heart Assoc*. 2019;8:e012307.

7. Kreatsoulas C, Fleegler EW, Kubzansky LD, et al. Young adults and adverse childhood events: a potent measure of cardiovascular risk. *Am J Med*. 2019;132:605–613.

2. INITIAL EVALUATION

2.1. History

1. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

2. Lindsell CJ, Anantharaman V, Diercks D, et al. The Internet Tracking Registry of Acute Coronary Syndromes (i*trACS): a multicenter registry of patients with suspicion of acute coronary syndromes reported using the standardized reporting guidelines for emergency department chest pain studies. *Ann Emerg Med*. 2006;48:666–677, 77 e1–9.

3. Hsia RY, Hale Z, Tabas JA. A national study of the prevalence of life-threatening diagnoses in patients with chest pain. *JAMA Intern Med*. 2016;176:1029–1032.

4. Fanaroff AC, Rymer JA, Goldstein SA, et al. Does this patient with chest pain have acute coronary syndrome?: the rational clinical examination systematic review. *JAMA*. 2015;314:1955–1965.

5. Diercks DB, Boghos E, Guzman H, et al. Changes in the numeric descriptive scale for pain after sublingual nitroglycerin do not predict cardiac etiology of chest pain. *Ann Emerg Med*. 2005;45:581–585.

2.1.1. A Focus on the Uniqueness of Chest Pain in Women

1. Hemal K, Pagidipati NJ, Coles A, et al. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE trial. *J Am Coll Cardiol Img*. 2016;9:337–346.

2. Garcia M, Mulvagh SL, Merz CN, et al. Cardiovascular disease in women: clinical perspectives. *Circ Res*. 2016;118:1273–1293.

3. Lichtman JH, Leifheit EC, Safdar B, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction: evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). *Circulation*. 2018;137:781–790.

4. Pelletier R, Khan NA, Cox J, et al. Sex versus gender-related characteristics: which predicts outcome after acute coronary syndrome in the young? *J Am Coll Cardiol*. 2016;67:127–135.

5. Ferry AV, Anand A, Strachan FE, et al. Presenting symptoms in men and women diagnosed with myocardial infarction using sex-specific criteria. *J Am Heart Assoc*. 2019;8:e012307.

6. Kreatsoulas C, Dinakar D, Mehta S, et al. *Machine learning to evaluate gender differences in typical and atypical angina among patients with obstructive coronary artery disease*. ESC Congress 2019. Paris, France. 2019.

7. DeFilippis EM, Collins BL, Singh A, et al. Women who experience a myocardial infarction at a young age have worse outcomes compared with men: the Mass General Brigham YOUNG-MI registry. *Eur Heart J*. 2020;41:4127–4137.

8. Rui P, Kang K, Ashman JJ. National Hospital Ambulatory Medical Care Survey: 2016 Emergency Department Summary Tables. 2016. Available at: https://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2016_ed_web_tables.pdf. Accessed July 26, 2021.

9. Reynolds HR, Shaw LJ, Min JK, et al. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol*. 2020;5:1–14.

10. Meisel ZF, Armstrong K, Mechem CC, et al. Influence of sex on the out-of-hospital management of chest pain. *Acad Emerg Med*. 2010;17:80–87.

11. Khan NA, Daskalopoulou SS, Karp I, et al. Sex differences in prodromal symptoms in acute coronary syndrome in patients aged 55 years or younger. *Heart*. 2017;103:863–869.

12. Roger VL, Farkouh ME, Weston SA, et al. Sex differences in evaluation and outcome of unstable angina. *JAMA*. 2000;283:646–652.

13. McSweeney JC, Cleves MA, Zhao W, et al. Cluster analysis of women's prodromal and acute myocardial infarction symptoms by race and other characteristics. *J Cardiovasc Nurs*. 2010;25:311–322.

14. Safdar B, Nagurney JT, Anise A, et al. Gender-specific research for emergency diagnosis and management of ischemic heart disease: proceedings from the 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Research Workgroup. *Acad Emerg Med*. 2014;21:1350–1360.

15. Khan NA, Daskalopoulou SS, Karp I, et al. Sex differences in acute coronary syndrome symptom presentation in young patients. *JAMA Intern Med*. 2013;173:1863–1871.

16. Tamis-Holland JE, Lu J, Korytkowski M, et al. Sex differences in presentation and outcome among patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with or without prompt revascularization: a report from the BARI 2D Trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes). *J Am Coll Cardiol*. 2013;61:1767–1776.

2.1.2. Considerations for Older Patients With Chest Pain

1. Grosmaitre P, Le Vavasseur O, Yachouh E, et al. Significance of atypical symptoms for the diagnosis and management of myocardial infarction in elderly patients admitted to emergency departments. *Arch Cardiovasc Dis*. 2013;106:586–592.

2. Jokhadar M, Wenger NK. Review of the treatment of acute coronary syndrome in elderly patients. *Clin Interv Aging*. 2009;4:435–444.

3. Gupta R, Munoz R. Evaluation and management of chest pain in the elderly. *Emerg Med Clin North Am*. 2016;34:523–542.

4. Lowenstern A, Alexander KP, Hill CL, et al. Age-related differences in the noninvasive evaluation for possible coronary artery disease: insights from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Trial. *JAMA Cardiol*. 2020;5:193–201.

2.1.3. Considerations for Diverse Patient Populations With Chest Pain

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596.

2. DeVon HA, Burke LA, Nelson H, et al. Disparities in patients presenting to the emergency department with potential acute coronary syndrome: it matters if you are Black or White. *Heart Lung*. 2014;43:270–277.

3. Alrwisan A, Eworuke E. Are discrepancies in waiting time for chest pain at emergency departments between African Americans and Whites improving over time? *J Emerg Med*. 2016;50:349–355.

4. Graham G. Racial and ethnic differences in acute coronary syndrome and myocardial infarction within the United States: from demographics to outcomes. *Clin Cardiol*. 2016;39:299–306.

5. Lopez L, Wilper AP, Cervantes MC, et al. Racial and sex differences in emergency department triage assessment and test ordering for chest pain, 1997-2006. *Acad Emerg Med*. 2010;17:801–808.

6. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–e322.

7. Olson MB, Kelsey SF, Matthews K, et al. Symptoms, myocardial ischaemia and quality of life in women: results from the NHLBI-sponsored WISE Study. *Eur Heart J*. 2003;24:1506–1514.

8. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e1–e34.

9. Kendall H, Marley A, Patel JV, et al. Hospital delay in South Asian patients with acute ST-elevation myocardial infarction in the UK. *Eur J Prev Cardiol*. 2013;20:737–742.

10. Zaman MJ, Junghans C, Sekhri N, et al. Presentation of stable angina pectoris among women and South Asian people. *CMAJ*. 2008;179:659–667.

11. King-Shier K, Quan H, Kapral MK, et al. Acute coronary syndromes presentations and care outcomes in white, South Asian and Chinese patients: a cohort study. *BMJ Open*. 2019;9.e022479.

2.1.4. Patient-Centric Considerations

1. Leifheit-Limson EC, D'Onofrio G, Daneshvar M, et al. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO Study. *J Am Coll Cardiol*. 2015;66:1949–1957.

2. Mathews R, Peterson ED, Li S, et al. Use of emergency medical service transport among patients with ST-segment-elevation myocardial infarction: findings from the National Cardiovascular Data Registry Acute Coronary Treatment Intervention Outcomes Network Registry-Get With The Guidelines. *Circulation*. 2011;124:154–163.

3. Becker L, Larsen MP, Eisenberg MS. Incidence of cardiac arrest during self-transport for chest pain. *Ann Emerg Med*. 1996;28:612–616.

4. Deputy Heart Attack Program with Early Heart Attack Care Education. Available at: https://dha.acc.org/. Accessed September 10, 2020.

5. Merchant RM, Topjian AA, Panchal AR, et al. Part 1: executive summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2020;142:S337–S357.

2.2. Physical Examination

1. Fanaroff AC, Rymer JA, Goldstein SA, et al. Does this patient with chest pain have acute coronary syndrome?: the rational clinical examination systematic review. *JAMA*. 2015;314:1955–1965.

2. McConaghy JR, Oza RS. Outpatient diagnosis of acute chest pain in adults. *Am Fam Physician*. 2013;87:177–182.

3. Ohle R, Um J, Anjum O, et al. High risk clinical features for acute aortic dissection: a case-control study. *Acad Emerg Med*. 2018;25:378–387.

4. Garas G, Zarogoulidis P, Efthymiou A, et al. Spontaneous esophageal rupture as the underlying cause of pneumothorax: early recognition is crucial. *J Thorac Dis*. 2014;6:1655–1658.

5. Grani C, Senn O, Bischof M, et al. Diagnostic performance of reproducible chest wall tenderness to rule out acute coronary syndrome in acute chest pain: a prospective diagnostic study. *BMJ Open*. 2015;5:e007442.

6. Panju AA, Hemmelgarn BR, Guyatt GH, et al. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA*. 1998;280:1256–1263.

7. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet*. 1999;353:190–195.

8. Tsai TT, Trimarchi S, Nienaber CA. Acute aortic dissection: perspectives from the International Registry of Acute Aortic Dissection (IRAD). *Eur J Vasc Endovasc Surg*. 2009;37:149–159.

9. von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Med*. 2000;160:2977–2982.

10. Klompas M. Does this patient have an acute thoracic aortic dissection? *JAMA*. 2002;287:2262–2272.

2.3. Diagnostic Testing

2.3.1. Setting Considerations

1. Diercks DB, Kontos MC, Chen AY, et al. Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction: data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. *J Am Coll Cardiol*. 2009;53:161–166.

2. Puymirat E, Simon T, Steg PG, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012;308:998–1006.

3. Jollis JG, Granger CB, Henry TD, et al. Systems of care for ST-segment-elevation myocardial infarction: a report from the American Heart Association's Mission: Lifeline. *Circ Cardiovasc Qual Outcomes*. 2012;5:423–428.

4. Postma S, Bergmeijer T, ten Berg J, et al. Pre-hospital diagnosis, triage and treatment in patients with ST elevation myocardial infarction. *Heart*. 2012;98:1674–1678.

5. Patel M, Dunford JV, Aguilar S, et al. Pre-hospital electrocardiography by emergency medical personnel: effects on scene and transport times for chest pain and ST-segment elevation myocardial infarction patients. *J Am Coll Cardiol*. 2012;60:806–811.

6. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.

7. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

8. Neumann JT, Twerenbold R, Ojeda F, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med*. 2019;380:2529–2540.

9. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.

10. Becker L, Larsen MP, Eisenberg MS. Incidence of cardiac arrest during self-transport for chest pain. *Ann Emerg Med*. 1996;28:612–616.

11. Hsiao CJ, Cherry DK, Beatty PC, et al. National ambulatory medical care survey: 2007 summary. *Natl Health Stat Report*. 2010:1–32.

2.3.2. Electrocardiogram

1. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.

3. Vogiatzis I, Koulouris E, Ioannidis A, et al. The importance of the 15-lead versus 12-lead ECG recordings in the diagnosis and treatment of right ventricle and left ventricle posterior and lateral wall acute myocardial infarctions. *Acta Inform Med*. 2019;27:35–39.

4. Ashida T, Tani S, Nagao K, et al. Usefulness of synthesized 18-lead electrocardiography in the

diagnosis of ST-elevation myocardial infarction: a pilot study. *Am J Emerg Med*. 2017;35:448–457.

5. Matetzky S, Freimark D, Feinberg MS, et al. Acute myocardial infarction with isolated ST-segment elevation in posterior chest leads V7-9: "hidden" ST-segment elevations revealing acute posterior infarction. *J Am Coll Cardiol*. 1999;34:748–753.

6. Jain S, Ting HT, Bell M, et al. Utility of left bundle branch block as a diagnostic criterion for acute myocardial infarction. *Am J Cardiol*. 2011;107:1111–1116.

7. Ohlsson M, Ohlin H, Wallerstedt SM, et al. Usefulness of serial electrocardiograms for diagnosis of acute myocardial infarction. *Am J Cardiol*. 2001;88:478–481.

8. Mant J, McManus RJ, Oakes RA, et al. Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care. *Health Technol Assess*. 2004;8(iii):1–158.

9. Chase M, Brown AM, Robey JL, et al. Prognostic value of symptoms during a normal or nonspecific electrocardiogram in emergency department patients with potential acute coronary syndrome. *Acad Emerg Med*. 2006;13:1034–1039.

10. Turnipseed SD, Trythall WS, Diercks DB, et al. Frequency of acute coronary syndrome in patients with normal electrocardiogram performed during presence or absence of chest pain. *Acad Emerg Med*. 2009;16:495–499.

11. Pasceri V, Cianflone D, Finocchiaro ML, et al. Relation between myocardial infarction site and pain location in Q-wave acute myocardial infarction. *Am J Cardiol*. 1995;75:224–227.

12. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000;342:1163–1170.

13. McCarthy BD, Beshansky JR, D'Agostino RB, et al. Missed diagnoses of acute myocardial infarction in the emergency department: results from a multicenter study. *Ann Emerg Med*. 1993;22:579–582.

14. Canto JG, Fincher C, Kiefe CI, et al. Atypical presentations among Medicare beneficiaries with unstable angina pectoris. *Am J Cardiol*. 2002;90:248–253.

15. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA*. 1999;281:707–713.

16. Rouan GW, Lee TH, Cook EF, et al. Clinical characteristics and outcome of acute myocardial infarction in patients with initially normal or nonspecific electrocardiograms (a report from the Multicenter Chest Pain Study). *Am J Cardiol*. 1989;64:1087–1092.

17. Slater DK, Hlatky MA, Mark DB, et al. Outcome in suspected acute myocardial infarction with normal or minimally abnormal admission electrocardiographic findings. *Am J Cardiol*. 1987;60:766–770.

18. Fesmire FM. Which chest pain patients potentially benefit from continuous 12-lead ST-segment monitoring with automated serial ECG? *Am J Emerg Med*. 2000;18:773–778.

19. Fesmire FM, Percy RF, Bardoner JB, et al. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. *Ann Emerg Med*. 1998;31:3–11.

20. Challa PK, Smith KM, Conti CR. Initial presenting electrocardiogram as determinant for hospital admission in patients presenting to the emergency department with chest pain: a pilot investigation. *Clin Cardiol*. 2007;30:558–561.

21. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.

22. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2016;67:1235–1250.

2.3.3. Chest Radiography

1. Hess EP, Perry JJ, Ladouceur P, et al. Derivation of a clinical decision rule for chest radiography in emergency department patients with chest pain and possible acute coronary syndrome. *CJEM*. 2010;12:128–134.

2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239.

4. Harris KM, Strauss CE, Eagle KA, et al. Correlates of delayed recognition and treatment of acute type A aortic dissection: the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2011;124:1911–1918.

2.3.4. Biomarkers

1. Apple FS, Jesse RL, Newby LK, et al. National academy of clinical biochemistry and IFCC committee for standardization of markers of cardiac damage laboratory medicine practice guidelines: analytical issues for biochemical markers of acute coronary syndromes. *Circulation*. 2007;115:e352–e355.

2. Bandstein N, Ljung R, Johansson M, et al. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol*. 2014;63:2569–2578.

3. Body R, Burrows G, Carley S, et al. High-sensitivity cardiac troponin t concentrations below the limit of detection to exclude acute myocardial infarction: a prospective evaluation. *Clin Chem*. 2015;61:983–989.

4. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol*. 2011;58:1332–1339.

5. Boeddinghaus J, Nestelberger T, Twerenbold R, et al. Direct comparison of 4 very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I. *Circulation*. 2017;135:1597–1611.

6. Chapman AR, Anand A, Boeddinghaus J, et al. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. *Circulation*. 2017;135:1586–1596.

7. de Lemos JA, Morrow DA, deFilippi CR. Highly sensitive troponin assays and the cardiology community: a love/hate relationship? *Clin Chem*. 2011;57:826–829.

8. Jaffe AS, Apple FS, Morrow DA, et al. Being rational about (im)precision: a statement from the Biochemistry Subcommittee of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Definition of Myocardial Infarction. *Clin Chem*. 2010;56:941–943.

9. Morrow DA, Cannon CP, Jesse RL, et al. National academy of clinical biochemistry laboratory medicine practice guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation*. 2007;115:e356–e375.

10. Mueller C, Giannitsis E, Christ M, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med*. 2016;68:76–87, e4.

11. Odqvist M, Andersson PO, Tygesen H, et al. High-sensitivity troponins and outcomes after myocardial infarction. *J Am Coll Cardiol*. 2018;71:2616–2624.

12. Peacock WF, Baumann BM, Bruton D, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. *JAMA Cardiol*. 2018;3:104–111.

13. Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med*. 2012;172:1211–1218.

14. Reichlin T, Twerenbold R, Maushart C, et al. Risk stratification in patients with unstable angina using absolute serial changes of 3 high-sensitive troponin assays. *Am Heart J*. 2013;165:371–378.e3.

15. Rubini Gimenez M, Hoeller R, Reichlin T, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. *Int J Cardiol*. 2013;168:3896–3901.

16. Rubini Gimenez M, Twerenbold R, Jaeger C, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. *Am J Med*. 2015;128:861–870, e4.

17. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2017;70:996–1012.

18. Twerenbold R, Neumann JT, Sorensen NA, et al. Prospective validation of the 0/1-h algorithm for early diagnosis of myocardial infarction. *J Am Coll Cardiol*. 2018;72:620–632.

19. Wildi K, Nelles B, Twerenbold R, et al. Safety and efficacy of the 0 h/3 h protocol for rapid rule out of myocardial infarction. *Am Heart J*. 2016;181:16–25.

20. Zhelev Z, Hyde C, Youngman E, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. *BMJ*. 2015;350:h15.

21. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.

22. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol*. 2013;62:1242–1249.

23. Lipinski MJ, Baker NC, Escarcega RO, et al. Comparison of conventional and high-sensitivity troponin in patients with chest pain: a collaborative meta-analysis. *Am Heart J*. 2015;169:6–16, e6.

24. Twerenbold R, Wildi K, Jaeger C, et al. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. *Circulation*. 2015;131:2041–2050.

25. van Wijk S, Jacobs L, Eurlings LW, et al. Troponin T measurements by high-sensitivity vs conventional assays for risk stratification in acute dyspnea. *Clin Chem*. 2012;58:284–292.

26. Neumann JT, Twerenbold R, Ojeda F, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med*. 2019;380:2529–2540.

27. Aviles RJ, Wright RS, Aviles JM, et al. Long-term prognosis of patients with clinical unstable angina pectoris without elevation of creatine kinase but with elevation of cardiac troponin I levels. *Am J Cardiol*. 2002;90:875–878.

28. Eggers KM, Oldgren J, Nordenskjold A, et al. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *Am Heart J*. 2004;148:574–581.

29. Kavsak PA, MacRae AR, Newman AM, et al. Effects of contemporary troponin assay sensitivity on the utility of the early markers myoglobin and CKMB isoforms in evaluating patients with possible acute myocardial infarction. *Clin Chim Acta*. 2007;380:213–216.

30. Kontos MC, de Lemos JA, Ou FS, et al. Troponin-positive, MB-negative patients with non-ST-elevation myocardial infarction: an undertreated but high-risk patient group: results from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get With The Guidelines (NCDR ACTION-GWTG) Registry. *Am Heart J*. 2010;160:819–825.

31. Newby LK, Roe MT, Chen AY, et al. Frequency and clinical implications of discordant creatine kinase-MB and troponin measurements in acute coronary syndromes. *J Am Coll Cardiol*. 2006;47:312–318.

32. Volz KA, McGillicuddy DC, Horowitz GL, et al. Creatine kinase-MB does not add additional benefit to a negative troponin in the evaluation of chest pain. *Am J Emerg Med*. 2012;30:188–190.

33. Reichlin T, Twerenbold R, Wildi K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *CMAJ*. 2015;187:E243–E252.

34. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ*. 2015;350:g7873.

35. Morrow DA. The Fourth Universal Definition of Myocardial Infarction and the Emerging Importance of Myocardial Injury. *Circulation*. 2020;141:172–175.

3. CARDIAC TESTING GENERAL CONSIDERATIONS

1. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;63:380–406.

2. Medicare Program: Changes to Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs; Revisions of Organ Procurement Organizations Conditions of Coverage; Prior Authorization Process and Requirements for Certain Covered Outpatient Department Services; Potential Changes to the Laboratory Date of Service Policy; Changes to Grandfathered Children's Hospitals-Within-Hospitals; Notice of Closure of Two Teaching Hospitals and Opportunity To Apply for Available Slots. Available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Hospital-Outpatient-Regulations-and-Notices-Items/CMS-1717-FC. Accessed September 14, 2020.

3.1. Anatomic Testing

3.1.1. Coronary Computed Tomography Angiography

1. Gaur S, Ovrehus KA, Dey D, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. *Eur Heart J*. 2016;37:1220–1227.

2. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol*. 2018;3:144–152.

3. Budoff MJ, Mayrhofer T, Ferencik M, et al. Prognostic value of coronary artery calcium in the PROMISE Study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;136:1993–2005.

4. Ferencik M, Mayrhofer T, Puchner SB, et al. Computed tomography-based high-risk coronary plaque score to predict acute coronary syndrome among patients with acute chest pain-Results from the ROMICAT II trial. *J Cardiovasc Comput Tomogr*. 2015;9:538–545.

5. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol*. 2014;64:684–692.

6. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66:337–346.

7. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:319–326.

8. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54:49–57.

9. Nørgaard BL, Fairbairn TA, Safian RD, et al. Coronary CT angiography-derived fractional flow reserve testing in patients with stable coronary artery disease: recommendations on interpretation and reporting radiology. *Radiology: Cardiothoracic Imaging*. 2019;1:e190050.

10. Stocker TJ, Deseive S, Leipsic J, et al. Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the PROspective multicenter registry on radiaTion dose Estimates of cardiac CT angIOgraphy iN daily practice in 2017 (PROTECTION VI). *Eur Heart J*. 2018;39:3715–3723.

3.1.2. Invasive Coronary Angiography

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.

2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

3. Kobayashi T, Hirshfeld JW Jr. Radiation exposure in cardiac catheterization: operator behavior matters. *Circ Cardiovasc Interv*. 2017;10:e005689.

4. Georges JL, Karam N, Tafflet M, et al. Time-course reduction in patient exposure to radiation from coronary interventional procedures: the Greater Paris Area Percutaneous Coronary Intervention Registry. *Circ Cardiovasc Interv*. 2017;10:e005268.

5. Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. *Heart*. 2018;104:284–292.

6. Taqueti VR, Shaw LJ, Cook NR, et al. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577.

7. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol*. 2018;250:16–20.

8. Ford TJ, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in

angina: the CorMicA Trial. *J Am Coll Cardiol*. 2018;72:2841–2855.

3.2. Diagnostic Testing

3.2.1. Exercise ECG

1. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756–1776.

2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.

3.2.2. Echocardiography/Stress Echocardiography

1. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.

2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

3. Pellikka PA, Arruda-Olson A, Chaudhry FA, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2020;33:1–41.e8.

4. Cortigiani L, Ciampi Q, Rigo F, et al. Prognostic value of dual imaging stress echocardiography following coronary bypass surgery. *Int J Cardiol*. 2019;277:266–271.

5. Cortigiani L, Rigo F, Bovenzi F, et al. The prognostic value of coronary flow velocity reserve in two coronary arteries during vasodilator stress echocardiography. *J Am Soc Echocardiogr*. 2019;32:81–91.

6. Cortigiani L, Ciampi Q, Lombardo A, et al. Age- and gender-specific prognostic cutoff values of coronary flow velocity reserve in vasodilator stress echocardiography. *J Am Soc Echocardiogr*. 2019;32:1307–1317.

3.2.3. Stress Nuclear (PET or SPECT) Myocardial Perfusion Imaging

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.

2. Shaw LJ, Hage FG, Berman DS, et al. Prognosis in the era of comparative effectiveness research: where is nuclear cardiology now and where should it be? *J Nucl Cardiol*. 2012;19:1026–1043.

3. Green R, Cantoni V, Petretta M, et al. Negative predictive value of stress myocardial perfusion imaging and coronary computed tomography angiography: a meta-analysis. *J Nucl Cardiol*. 2017.

4. Rozanski A, Gransar H, Min JK, et al. Long-term mortality following normal exercise myocardial perfusion SPECT according to coronary disease risk factors. *J Nucl Cardiol*. 2014;21:341–350.

5. Metz LD, Beattie M, Hom R, et al. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol*. 2007;49:227–237.

6. Dorbala S, Di Carli MF, Beanlands RS, et al. Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. *J Am Coll Cardiol*. 2013;61:176–184.

7. Kay J, Dorbala S, Goyal A, et al. Influence of sex on risk stratification with stress myocardial perfusion Rb-82 positron emission tomography: results from the PET (Positron Emission Tomography) Prognosis Multicenter Registry. *J Am Coll Cardiol*. 2013;62:1866–1876.

8. Shaw LJ, Cerqueira MD, Brooks MM, et al. Impact of left ventricular function and the extent of ischemia and scar by stress myocardial perfusion imaging on prognosis and therapeutic risk reduction in diabetic patients with coronary artery disease: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *J Nucl Cardiol*. 2012;19:658–669.

9. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol*. 2013;62:1639–1653.

10. Dilsizian V, Bacharach SL, Beanlands RS, et al. ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. *J Nucl Cardiol*. 2016;23:1187–1226.

11. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:840–849.

12. Taqueti VR, Shaw LJ, Cook NR, et al. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577.

13. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation*. 2015;131:19–27.

14. Taqueti VR, Everett BM, Murthy VL, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. *Circulation*. 2015;131:528–535.

15. Einstein AJ, Berman DS, Min JK, et al. Patient-centered imaging: shared decision making for cardiac imaging procedures with exposure to ionizing radiation. *J Am Coll Cardiol*. 2014;63:1480–1489.

16. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? *J Am Coll Cardiol*. 2012;59:553–565.

17. Fazel R, Gerber TC, Balter S, et al. Approaches to enhancing radiation safety in cardiovascular imaging: a scientific statement from the American Heart Association. *Circulation*. 2014;130:1730–1748.

3.2.4. Cardiovascular Magnetic Resonance Imaging

1. Henzlova MJ, Duvall WL, Einstein AJ, et al. ASNC imaging guidelines for SPECT nuclear cardiology procedures: stress, protocols, and tracers. *J Nucl Cardiol*. 2016;23:606–639.

2. Senior R, Becher H, Monaghan M, et al. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. *Eur J Echocardiogr*. 2009;10:194–212.

3. Patil HR, Main M. Revisiting the safety profile of echocardiography contrast agents. Available at: https://www.acc.org/latest-in-cardiology/articles/2016/06/23/08/23/revisiting-the-safety-profile-of-echocardiography-contrast-agents. Accessed August 16, 2020.

4. Porter TR, Abdelmoneim S, Belcik JT, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a focused update from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2014;27:797–810.

5. Pellikka PA, Arruda-Olson A, Chaudhry FA, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2020;33:1–41.e8.

6. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, et al. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson*. 2020;22:17.

7. Narula J, Chandrashekhar Y, Ahmadi A, et al. SCCT 2021 Expert consensus document on coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr*. 2021;15:192–217.

8. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for exercise testing. a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol*. 1997;30:260–311.

9. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128:873–934.

10. Henzlova MJ, Cerqueira MD, Mahmarian JJ, et al. Stress protocols and tracers. *J Nucl Cardiol*. 2006;13:e80–e90.

11. SNM Procedure Guideline for General Imaging 6.0. Available at: https://s3.amazonaws.com/rdcms-snmmi/files/production/public/docs/General_Imaging_Version_6.0.pdf. Accessed July 26, 2021.

12. Committee on Obstetric Practice. Committee Opinion No. 723: Guidelines for diagnostic imaging

during pregnancy and lactation. *Obstet Gynecol*. 2017;130:e210–e216.

13. Ashwath M. Safety of CMR During Pregnancy and Lactation. Available at: https://scmr.org/page/Pregnancy. Accessed November 9, 2020.

14. ACR-SPR practice parameter for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/pregnant-pts.pdf. Accessed November 9, 2020.

3.3. Cardiac Testing Considerations for Women Who Are Pregnant, Postpartum, or of Child-Bearing Age

1. Image Wisely. Available at: https://imagewisely.org. Accessed September 10, 2020.

2. Committee on Obstetric Practice. Committee Opinion No. 723: Guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol*. 2017;130:e210–e216.

3. Ray JG, Vermeulen MJ, Bharatha A, et al. Association between MRI exposure during pregnancy and fetal and childhood outcomes. *JAMA*. 2016;316:952–961.

4. Kodzwa R. ACR manual on contrast media: 2018 updates. *Radiol Technol*. 2019;91:97–100.

5. Expert Panel on MRS, Kanal E, Barkovich AJ, et al. ACR guidance document on MR safe practices: 2013. *J Magn Reson Imaging*. 2013;37:501–530.

6. Truong QA, Rinehart S, Abbara S, et al. Coronary computed tomographic imaging in women: an expert consensus statement from the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr*. 2018;12:451–466.

4. CHOOSING THE RIGHT PATHWAY WITH PATIENT-CENTRIC ALGORITHMS FOR ACUTE CHEST PAIN

4.1. Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI)

1. Apple FS, Jesse RL, Newby LK, et al. National academy of clinical biochemistry and IFCC committee for standardization of markers of cardiac damage laboratory medicine practice guidelines: analytical issues for biochemical markers of acute coronary syndromes. *Circulation*. 2007;115:e352–e355.

2. Bandstein N, Ljung R, Johansson M, et al. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol*. 2014;63:2569–2578.

3. Body R, Burrows G, Carley S, et al. High-sensitivity cardiac troponin t concentrations below the limit of detection to exclude acute myocardial infarction: a prospective evaluation. *Clin Chem*. 2015;61:983–989.

4. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol*. 2011;58:1332–1339.

5. Boeddinghaus J, Nestelberger T, Twerenbold R, et al. Direct comparison of 4 very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I. *Circulation*. 2017;135:1597–1611.

6. Chapman AR, Anand A, Boeddinghaus J, et al. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. *Circulation*. 2017;135:1586–1596.

7. de Lemos JA, Morrow DA, deFilippi CR. Highly sensitive troponin assays and the cardiology community: a love/hate relationship? *Clin Chem*. 2011;57:826–829.

8. Jaffe AS. Chasing troponin: how low can you go if you can see the rise? *J Am Coll Cardiol*. 2006;48:1763–1764.

9. Jaffe AS, Apple FS, Morrow DA, et al. Being rational about (im)precision: a statement from the Biochemistry Subcommittee of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Definition of Myocardial Infarction. *Clin Chem*. 2010;56:941–943.

10. Morrow DA, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation*. 2007;115:e356–e375.

11. Mueller C, Giannitsis E, Christ M, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med*. 2016;68:76–87, e4.

12. Odqvist M, Andersson PO, Tygesen H, et al. High-sensitivity troponins and outcomes after myocardial infarction. *J Am Coll Cardiol*. 2018;71:2616–2624.

13. Peacock WF, Baumann BM, Bruton D, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. *JAMA Cardiol*. 2018;3:104–111.

14. Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med*. 2012;172:1211–1218.

15. Morrow DA. Clinician's guide to early rule-out strategies with high-sensitivity cardiac troponin. *Circulation*. 2017;135:1612–1616.

16. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.

17. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2017;70:996–1012.

18. Januzzi JL Jr, Mahler SA, Christenson RH, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019;73:1059–1077.

19. Huis In 't Veld MA, Cullen L, Mahler SA, et al. The fast and the furious: low-risk chest pain and the rapid rule-out protocol. *West J Emerg Med*. 2017;18:474–478.

20. Schulman-Marcus J, Hartaigh BO, Gransar H, et al. Sex-specific associations between coronary artery plaque extent and risk of major adverse cardiovascular events: the CONFIRM Long-Term Registry. *J Am Coll Cardiol Img*. 2016;9:364–372.

21. Hadamitzky M, Freissmuth B, Meyer T, et al. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. *J Am Coll Cardiol Img*. 2009;2:404–411.

22. Finck T, Hardenberg J, Will A, et al. Ten-year follow-up after coronary computed tomography angiography in patients with suspected coronary artery disease. *J Am Coll Cardiol Img*. 2019;12:1330–1338.

23. Hochman JS, Reynolds HR, Bangalore S, et al. Baseline characteristics and risk profiles of participants in the ISCHEMIA randomized clinical trial. *JAMA Cardiol*. 2019;4:273–286.

24. ISCHEMIA Trial Research Group, Maron DJ, Hochman JS, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. *Am Heart J*. 2018;201:124–135.

25. Pickering JW, Than MP, Cullen L, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. *Ann Intern Med*. 2017;166:715–724.

26. McRae AD, Innes G, Graham M, et al. Undetectable concentrations of a Food and Drug Administration-approved high-sensitivity cardiac troponin T assay to rule out acute myocardial infarction at emergency department arrival. *Acad Emerg Med*. 2017;24:1267–1277.

27. Sandoval Y, Nowak R, deFilippi CR, et al. Myocardial infarction risk stratification with a single measurement of high-sensitivity troponin I. *J Am Coll Cardiol*. 2019;74:271–282.

28. Bularga A, Lee KK, Stewart S, et al. High-sensitivity troponin and the application of risk stratification thresholds in patients with suspected acute coronary syndrome. *Circulation*. 2019;140:1557–1568.

29. Chew DP, Lambrakis K, Blyth A, et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: the Rapid Assessment of Possible Acute Coronary Syndrome in the emergency department with high-sensitivity Troponin T Study (RAPID-TnT). *Circulation*. 2019;140:1543–1556.

30. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol*. 2012;59:2091–2098.

31. Mahler SA, Riley RF, Hiestand BC, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. *Circ Cardiovasc Qual Outcomes*. 2015;8:195–203.

32. Mark DG, Huang J, Chettipally U, et al. Performance of coronary risk scores among patients with chest pain in the emergency department. *J Am Coll Cardiol*. 2018;71:606–616.

33. Stopyra JP, Miller CD, Hiestand BC, et al. Chest pain risk stratification: a comparison of the 2-Hour Accelerated Diagnostic Protocol (ADAPT) and the HEART pathway. *Crit Pathw Cardiol*. 2016;15:46–49.

34. Stopyra JP, Miller CD, Hiestand BC, et al. Validation of the no objective testing rule and comparison to the HEART Pathway. *Acad Emerg Med*. 2017;24:1165–1168.

35. Stopyra JP, Riley RF, Hiestand BC, et al. The HEART Pathway randomized controlled trial one-year outcomes. *Acad Emerg Med*. 2019;26:41–50.

36. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med*. 2009;361:868–877.

37. Neumann JT, Twerenbold R, Ojeda F, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med*. 2019;380:2529–2540.

38. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.

39. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J*. 2012;33:2252–2257.

40. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol*. 2013;62:1242–1249.

41. Reichlin T, Twerenbold R, Wildi K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *CMAJ*. 2015;187:E243–E252.

42. Rubini Gimenez M, Twerenbold R, Jaeger C, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. *Am J Med*. 2015;128:861–870, e4.

43. Twerenbold R, Neumann JT, Sorensen NA, et al. Prospective validation of the 0/1-h algorithm for early diagnosis of myocardial infarction. *J Am Coll Cardiol*. 2018;72:620–632.

44. Than MP, Pickering JW, Aldous SJ, et al. Effectiveness of EDACS versus ADAPT accelerated diagnostic pathways for chest pain: a pragmatic randomized controlled trial embedded within practice. *Ann Emerg Med*. 2016;68:93–102 e1.

45. Than M, Aldous S, Lord SJ, et al. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. *JAMA Intern Med*. 2014;174:51–58.

46. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367.

47. Twerenbold R, Costabel JP, Nestelberger T, et al. Outcome of applying the ESC 0/1-hour algorithm in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2019;74:483–494.

48. Backus BE, Six AJ, Kelder JC, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol*. 2013;168:2153–2158.

49. Fanaroff AC, Rymer JA, Goldstein SA, et al. Does this patient with chest pain have acute coronary syndrome?: the rational clinical examination systematic review. *JAMA*. 2015;314:1955–1965.

50. McCord J, Cabrera R, Lindahl B, et al. Prognostic utility of a modified HEART score in chest pain patients in the emergency department. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003101.

51. Bank IEM, de Hoog VC, de Kleijn DPV, et al. Sex-based differences in the performance of the HEART score in patients presenting to the emergency department with acute chest pain. *J Am Heart Assoc*. 2017;6:e005373.

52. Romero-Farina G, Candell-Riera J, Aguade-Bruix S, et al. Warranty periods for normal myocardial perfusion stress SPECT. *J Nucl Cardiol*. 2015;22:44–54.

53. Twerenbold R, Wildi K, Jaeger C, et al. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. *Circulation*. 2015;131:2041–2050.

54. Wildi K, Nelles B, Twerenbold R, et al. Safety and efficacy of the 0 h/3 h protocol for rapid rule out of myocardial infarction. *Am Heart J*. 2016;181:16–25.

55. Zhelev Z, Hyde C, Youngman E, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. *BMJ*. 2015;350:h15.

4.1.1. Low Risk Patients With Acute Chest Pain

1. Bandstein N, Ljung R, Johansson M, et al. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol*. 2014;63:2569–2578.

2. Chapman AR, Anand A, Boeddinghaus J, et al. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. *Circulation*. 2017;135:1586–1596.

3. Mueller C, Giannitsis E, Christ M, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med*. 2016;68:76–87, e4.

4. Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med*. 2012;172:1211–1218.

5. Reichlin T, Twerenbold R, Wildi K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *CMAJ*. 2015;187:E243–E252.

6. Rubini Gimenez M, Hoeller R, Reichlin T, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. *Int J Cardiol*. 2013;168:3896–3901.

7. Rubini Gimenez M, Twerenbold R, Jaeger C, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. *Am J Med*. 2015;128:861–870, e4.

8. Twerenbold R, Neumann JT, Sorensen NA, et al. Prospective validation of the 0/1-h algorithm for early diagnosis of myocardial infarction. *J Am Coll Cardiol*. 2018;72:620–632.

9. Pickering JW, Than MP, Cullen L, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. *Ann Intern Med*. 2017;166:715–724.

10. Peacock WF, Baumann BM, Bruton D, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. *JAMA Cardiol*. 2018;3:104–111.

11. Neumann JT, Twerenbold R, Ojeda F, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med*. 2019;380:2529–2540.

12. Greenslade JH, Carlton EW, Van Hise C, et al. Diagnostic accuracy of a new high-sensitivity troponin I assay and five accelerated diagnostic pathways for ruling out acute myocardial infarction and acute coronary syndrome. *Ann Emerg Med*. 2018;71:439–451, e3.

13. Cullen L, Mueller C, Parsonage WA, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol*. 2013;62:1242–1249.

14. Flaws D, Than M, Scheuermeyer FX, et al. External validation of the emergency department assessment of chest pain score accelerated diagnostic pathway (EDACS-ADP). *Emerg Med J*. 2016;33:618–625.

15. Stopyra JP, Miller CD, Hiestand BC, et al. Validation of the no objective testing rule and comparison to the HEART Pathway. *Acad Emerg Med*. 2017;24:1165–1168.

16. Than M, Aldous S, Lord SJ, et al. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. *JAMA Intern Med*. 2014;174:51–58.

17. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2017;70:996–1012.

18. Mahler SA, Lenoir KM, Wells BJ, et al. Safely identifying emergency department patients with acute chest pain for early discharge. *Circulation*. 2018;138:2456–2468.

19. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

20. Mahler SA, Riley RF, Hiestand BC, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. *Circ Cardiovasc Qual Outcomes*. 2015;8:195–203.

21. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol*. 2012;59:2091–2098.

4.1.1.1. Cost-Value Considerations in the Evaluation of Low-Risk Patients

1. Velickovic VM, Rochau U, Conrads-Frank A, et al. Systematic assessment of decision-analytic models evaluating diagnostic tests for acute myocardial infarction based on cardiac troponin assays. *Expert Rev Pharmacoecon Outcomes Res*. 2018:1–22.

2. Westwood M, van Asselt T, Ramaekers B, et al. High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-

effectiveness analysis. *Health Technol Assess*. 2015;19:1–234.

3. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess*. 2013;17:v–vi, 1-188.

4. Polanczyk CA, Kuntz KM, Sacks DB, et al. Emergency department triage strategies for acute chest pain using creatine kinase-MB and troponin I assays: a cost-effectiveness analysis. *Ann Intern Med*. 1999;131:909–918.

5. Poldervaart JM, Reitsma JB, Backus BE, et al. Effect of using the HEART score in patients with chest pain in the emergency department: a stepped-wedge, cluster randomized trial. *Ann Intern Med*. 2017;166:689–697.

6. Riley RF, Miller CD, Russell GB, et al. Cost analysis of the History, ECG, Age, Risk factors, and initial Troponin (HEART) Pathway randomized control trial. *Am J Emerg Med*. 2017;35:77–81.

7. Parsonage WA, Milburn T, Ashover S, et al. Implementing change: evaluating the Accelerated Chest pain Risk Evaluation (ACRE) project. *Med J Aust*. 2017;207:201–205.

8. Julicher P, Greenslade JH, Parsonage WA, et al. The organisational value of diagnostic strategies using high-sensitivity troponin for patients with possible acute coronary syndromes: a trial-based cost-effectiveness analysis. *BMJ Open*. 2017;7:e013653.

9. Cheng Q, Greenslade JH, Parsonage WA, et al. Change to costs and lengths of stay in the emergency department and the Brisbane protocol: an observational study. *BMJ Open*. 2016;6:e009746.

10. Roberts RR, Zalenski RJ, Mensah EK, et al. Costs of an emergency department-based accelerated diagnostic protocol vs hospitalization in patients with chest pain: a randomized controlled trial. *JAMA*. 1997;278:1670–1676.

11. Kip MMA, Koffijberg H, Moesker MJ, et al. The cost-utility of point-of-care troponin testing to diagnose acute coronary syndrome in primary care. *BMC Cardiovasc Disord*. 2017;17:213.

12. Vaidya A, Severens JL, Bongaerts BW, et al. High-sensitive troponin T assay for the diagnosis of acute myocardial infarction: an economic evaluation. *BMC Cardiovasc Disord*. 2014;14:77.

13. Twerenbold R, Jaeger C, Rubini Gimenez M, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. *Eur Heart J*. 2016;37:3324–3332.

4.1.2. Intermediate-Risk Patients With Acute Chest Pain

1. Farkouh ME, Smars PA, Reeder GS, et al. A clinical trial of a chest-pain observation unit for patients with unstable angina. Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. *N Engl J Med*. 1998;339:1882–1888.

2. Miller CD, Hwang W, Hoekstra JW, et al. Stress cardiac magnetic resonance imaging with observation unit care reduces cost for patients with emergent chest pain: a randomized trial. *Ann Emerg Med*. 2010;201056:209–219.

3. Roberts RR, Zalenski RJ, Mensah EK, et al. Costs of an emergency department-based accelerated diagnostic protocol vs hospitalization in patients with chest pain: a randomized controlled trial. *JAMA*. 1997;278:1670–1676.

4. Ross MA, Hockenberry JM, Mutter R, et al. Protocol-driven emergency department observation units offer savings, shorter stays, and reduced admissions. *Health Aff (Millwood)*. 2013;32:2149–2156.

5. Rydman RJ, Zalenski RJ, Roberts RR, et al. Patient satisfaction with an emergency department chest pain observation unit. *Ann Emerg Med*. 1997;29:109–115.

6. Miller CD, Hwang W, Case D, et al. Stress CMR imaging observation unit in the emergency department reduces 1-year medical care costs in patients with acute chest pain: a randomized study for comparison with inpatient care. *J Am Coll Cardiol Img*. 2011;4:862–870.

7. Hockenberry JM, Mutter R, Barrett M, et al. Factors associated with prolonged observation services stays and the impact of long stays on patient cost. *Health Serv Res*. 2014;49:893–909.

8. Labovitz AJ, Noble VE, Bierig M, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr*. 2010;23:1225–1230.

9. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.

10. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

11. Douglas PS, Garcia MJ, Haines D, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2011;57:1126–1166.

12. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement—executive summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J*. 2009;30:278–289.

13. Health Quality O. Stress echocardiography for the diagnosis of coronary artery disease: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2010;10:1–61.

4.1.2.1. Intermediate-Risk Patients With Acute Chest Pain and No Known CAD

1. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011;58:1414–1422.

2. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012;366:1393–1403.

3. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess*. 2013;17:v–vi, 1–188.

4. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol*. 2007;49:863–871.

5. Chang SA, Choi SI, Choi EK, et al. Usefulness of 64-slice multidetector computed tomography as an initial diagnostic approach in patients with acute chest pain. *Am Heart J*. 2008;156:375–383.

6. Miller AH, Pepe PE, Peshock R, et al. Is coronary computed tomography angiography a resource sparing strategy in the risk stratification and evaluation of acute chest pain? Results of a randomized controlled trial. *Acad Emerg Med*. 2011;18:458–467.

7. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. 2012;367:299–308.

8. Linde JJ, Kofoed KF, Sorgaard M, et al. Cardiac computed tomography guided treatment strategy in patients with recent acute-onset chest pain: results from the randomised, controlled trial: CArdiac cT in the treatment of acute CHest pain (CATCH). *Int J Cardiol*. 2013;168:5257–5262.

9. Hamilton-Craig C, Fifoot A, Hansen M, et al. Diagnostic performance and cost of CT angiography versus stress ECG—a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). *Int J Cardiol*. 2014;177:867–873.

10. Levsky JM, Spevack DM, Travin MI, et al. Coronary computed tomography angiography versus radionuclide myocardial perfusion imaging in patients with chest pain admitted to telemetry: a randomized trial. *Ann Intern Med*. 2015;163:174–183.

11. Dedic A, Lubbers MM, Schaap J, et al. Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study. *J Am Coll Cardiol*. 2016;67:16–26.

12. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135:2320–2332.

13. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol*. 2011;58:849–860.

14. Blankstein R, Ahmed W, Bamberg F, et al. Comparison of exercise treadmill testing with cardiac computed tomography angiography among patients presenting to the emergency room with chest pain: the Rule Out Myocardial Infarction Using Computer-

Assisted Tomography (ROMICAT) study. *Circ Cardiovasc Imaging*. 2012;5:233–242.

15. Jeetley P, Burden L, Stoykova B, et al. Clinical and economic impact of stress echocardiography compared with exercise electrocardiography in patients with suspected acute coronary syndrome but negative troponin: a prospective randomized controlled study. *Eur Heart J*. 2007;28:204–211.

16. Dadkhah S, Almuwaqqat Z, Sulaiman S, et al. Sensitive troponin I and stress testing in the emergency department for the early management of chest pain using 2-hour protocol. *Crit Pathw Cardiol*. 2017;16:89–92.

17. Nucifora G, Badano LP, Sarraf-Zadegan N, et al. Comparison of early dobutamine stress echocardiography and exercise electrocardiographic testing for management of patients presenting to the emergency department with chest pain. *Am J Cardiol*. 2007;100:1068–1073.

18. Jasani G, Papas M, Patel AJ, et al. Immediate stress echocardiography for low-risk chest pain patients in the emergency department: a prospective observational cohort study. *J Emerg Med*. 2018;54:156–164.

19. Krishnan S, Venn R, Blumenthal DM, et al. Utilization of stress testing for low-risk patients with chest discomfort in the emergency department. *J Nucl Cardiol*. 2019;26:1642–1646.

20. Hermann LK, Newman DH, Pleasant WA, et al. Yield of routine provocative cardiac testing among patients in an emergency department-based chest pain unit. *JAMA Intern Med*. 2013;173:1128–1133.

21. Diercks DB, Mumma BE, Frank Peacock W, et al. Incremental value of objective cardiac testing in addition to physician impression and serial contemporary troponin measurements in women. *Acad Emerg Med*. 2013;20:265–270.

22. Poldervaart JM, Six AJ, Backus BE, et al. The predictive value of the exercise ECG for major adverse cardiac events in patients who presented with chest pain in the emergency department. *Clin Res Cardiol*. 2013;102:305–312.

23. Napoli AM, Tran S, Wang J. Low-risk chest pain patients younger than 40 years do not benefit from admission and stress testing. *Crit Pathw Cardiol*. 2013;12:201–203.

24. Scott AC, Bilesky J, Lamanna A, et al. Limited utility of exercise stress testing in the evaluation of suspected acute coronary syndrome in patients aged less than 40 years with intermediate risk features. *Emerg Med Australas*. 2014;26:170–176.

25. Aldous S, Richards AM, Cullen L, et al. The incremental value of stress testing in patients with acute chest pain beyond serial cardiac troponin testing. *Emerg Med J*. 2016;33:319–324.

26. Greenslade JH, Parsonage W, Ho A, et al. Utility of routine exercise stress testing among intermediate risk chest pain patients attending an emergency department. *Heart Lung Circ*. 2015;24:879–884.

27. Skoien W. Diagnostic Yield of Routine Stress Testing in low and intermediate risk chest pain patients under 40 years: a systematic review. *Crit Pathw Cardiol*. 2016;15:114–120.

28. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

29. Levsky JM, Haramati LB, Spevack DM, et al. Coronary computed tomography angiography versus stress echocardiography in acute chest pain: a randomized controlled trial. *J Am Coll Cardiol Img*. 2018;11:1288–1297.

30. Heitner JF, Klem I, Rasheed D, et al. Stress cardiac MR imaging compared with stress echocardiography in the early evaluation of patients who present to the emergency department with intermediate-risk chest pain. *Radiology*. 2014;271:56–64.

31. Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA*. 2002;288:2693–2700.

32. Miller CD, Case LD, Little WC, et al. Stress CMR reduces revascularization, hospital readmission, and recurrent cardiac testing in intermediate-risk patients with acute chest pain. *J Am Coll Cardiol Img*. 2013;6:785–794.

33. Miller CD, Hwang W, Case D, et al. Stress CMR imaging observation unit in the emergency department reduces 1-year medical care costs in patients with acute chest pain: a randomized study for comparison with inpatient care. *J Am Coll Cardiol Img*. 2011;4:862–870.

34. Miller CD, Hwang W, Hoekstra JW, et al. Stress cardiac magnetic resonance imaging with observation unit care reduces cost for patients with emergent chest pain: a randomized trial. *Ann Emerg Med*. 2010;201056:209–219.

35. Ingkanisorn WP, Kwong RY, Bohme NS, et al. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. *J Am Coll Cardiol*. 2006;47:1427–1432.

36. Siontis GC, Mavridis D, Greenwood JP, et al. Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomised controlled trials. *BMJ*. 2018;360:k504.

37. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63:1145–1155.

38. Sand NPR, Veien KT, Nielsen SS, et al. Prospective comparison of FFR derived from coronary ct angiography with SPECT perfusion imaging in stable coronary artery disease: the ReASSESS study. *J Am Coll Cardiol Img*. 2018;11:1640–1650.

39. Patel MR, Norgaard BL, Fairbairn TA, et al. 1-Year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE registry. *J Am Coll Cardiol Img*. 2020;13:97–105.

40. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J*. 2018;39:3701–3711.

41. Nakanishi R, Osawa K, Ceponiene I, et al. The diagnostic performance of SPECT-MPI to predict functional significant coronary artery disease by fractional flow reserve derived from CCTA (FFRCT): subanalysis from ACCURACY and VCT001 studies. *Int J Cardiovasc Imaging*. 2017;33:2067–2072.

42. Chinnaiyan KM, Safian RD, Gallagher ML, et al. Clinical use of CT-derived fractional flow reserve in the emergency department. *J Am Coll Cardiol Img*. 2020;13:452–461.

43. Ferencik M, Lu MT, Mayrhofer T, et al. Non-invasive fractional flow reserve derived from coronary computed tomography angiography in patients with acute chest pain: subgroup analysis of the ROMICAT II trial. *J Cardiovasc Comput Tomogr*. 2019;13:196–202.

44. Schulman-Marcus J, Hartaigh BO, Gransar H, et al. Sex-specific associations between coronary artery plaque extent and risk of major adverse cardiovascular events: the CONFIRM long-term registry. *J Am Coll Cardiol Img*. 2016;9:364–372.

45. Hadamitzky M, Freissmuth B, Meyer T, et al. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. *J Am Coll Cardiol Img*. 2009;2:404–411.

46. Finck T, Hardenberg J, Will A, et al. Ten-year follow-up after coronary computed tomography angiography in patients with suspected coronary artery disease. *J Am Coll Cardiol Img*. 2019;12:1330–1338.

47. Hulten E, Pickett C, Bittencourt MS, et al. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. *J Am Coll Cardiol*. 2013;61:880–892.

48. Linde JJ, Hove JD, Sorgaard M, et al. Long-term clinical impact of coronary CT angiography in patients with recent acute-onset chest pain: the randomized controlled CATCH trial. *J Am Coll Cardiol Img*. 2015;8:1404–1413.

49. Hulten E, Pickett C, Bittencourt MS, et al. Meta-analysis of coronary CT angiography in the emergency department. *Eur Heart J Cardiovasc Imaging*. 2013;14:607.

50. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials. *Eur Heart J Cardiovasc Imaging*. 2013;14:782–789.

51. Hachamovitch R, Nutter B, Hlatky MA, et al. Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). *J Am Coll Cardiol*. 2012;59:462–474.

52. Shaw LJ, Berman DS, Picard MH, et al. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. *J Am Coll Cardiol Img*. 2014;7:593–604.

53. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography

and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–164.

54. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.

55. Khan A, Engineer R, Wang S, et al. Initial experience regarding the safety and yield of rest-stress myocardial perfusion imaging in emergency department patients with mildly abnormal high-sensitivity cardiac troponins. *J Nucl Cardiol*. 2020. https://doi.org/10.1007/s12350-020-02145-w.

4.1.2.1.1. Cost-Value Considerations

1. Jasani G, Papas M, Patel AJ, et al. Immediate stress echocardiography for low-risk chest pain patients in the emergency department: a prospective observational cohort study. *J Emerg Med*. 2018;54:156–164.

2. Davies R, Liu G, Sciamanna C, et al. Comparison of the effectiveness of stress echocardiography versus myocardial perfusion imaging in patients presenting to the emergency department with low-risk chest pain. *Am J Cardiol*. 2016;118:1786–1791.

3. Levsky JM, Haramati LB, Spevack DM, et al. Coronary computed tomography angiography versus stress echocardiography in acute chest pain: a randomized controlled trial. *J Am Coll Cardiol Img*. 2018;11:1288–1297.

4. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011;58:1414–1422.

5. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012;366:1393–1403.

6. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. 2012;367:299–308.

7. Hulten E, Pickett C, Bittencourt MS, et al. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. *J Am Coll Cardiol*. 2013;61:880–892.

8. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials. *Eur Heart J Cardiovasc Imaging*. 2013;14:782–789.

4.1.2.2. Intermediate-Risk Patients With Acute Chest Pain and Known CAD

1. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.

2. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

3. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. 2012;367:299–308.

4. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011;58:1414–1422.

5. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012;366:1393–1403.

6. Hulten E, Pickett C, Bittencourt MS, et al. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. *J Am Coll Cardiol*. 2013;61:880–892.

7. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess*. 2013;17:v–vi, 1–188.

8. Hulten E, Pickett C, Bittencourt MS, et al. Meta-analysis of coronary CT angiography in the emergency department. *Eur Heart J Cardiovasc Imaging*. 2013;14:607.

9. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol*. 2014;64:684–692.

10. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66:337–346.

11. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018;71:2511–2522.

12. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. *Eur Heart J*. 2015;36:3359–3367.

13. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63:1145–1155.

14. Patel MR, Norgaard BL, Fairbairn TA, et al. 1-Year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE registry. *J Am Coll Cardiol Img*. 2020;13:97–105.

15. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J*. 2018;39:3701–3711.

16. Chinnaiyan KM, Safian RD, Gallagher ML, et al. Clinical use of CT-derived fractional flow reserve in the emergency department. *J Am Coll Cardiol Img*. 2020;13:452–461.

17. Ferencik M, Lu MT, Mayrhofer T, et al. Non-invasive fractional flow reserve derived from coronary computed tomography angiography in patients with acute chest pain: subgroup analysis of the ROMICAT II trial. *J Cardiovasc Comput Tomogr*. 2019;13:196–202.

18. Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA*. 2002;288:2693–2700.

19. Nucifora G, Badano LP, Sarraf-Zadegan N, et al. Comparison of early dobutamine stress echocardiography and exercise electrocardiographic testing for management of patients presenting to the emergency department with chest pain. *Am J Cardiol*. 2007;100:1068–1073.

20. Linde JJ, Kofoed KF, Sorgaard M, et al. Cardiac computed tomography guided treatment strategy in patients with recent acute-onset chest pain: results from the randomised, controlled trial: CArdiac cT in the treatment of acute CHest pain (CATCH). *Int J Cardiol*. 2013;168:5257–5262.

21. Blankstein R, Ahmed W, Bamberg F, et al. Comparison of exercise treadmill testing with cardiac computed tomography angiography among patients presenting to the emergency room with chest pain: the Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT) study. *Circ Cardiovasc Imaging*. 2012;5:233–242.

22. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283–1291.

23. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med*. 1998;338:1785–1792.

24. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *J Am Coll Cardiol Img*. 2018;11:1475–1484.

25. Sand NPR, Veien KT, Nielsen SS, et al. Prospective comparison of FFR derived from coronary ct angiography with SPECT perfusion imaging in stable coronary artery disease: the ReASSESS study. *J Am Coll Cardiol Img*. 2018;11:1640–1650.

26. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–164.

4.1.3. High-Risk Patients With Acute Chest Pain

1. Mahmarian JJ, Shaw LJ, Filipchuk NG, et al. A multinational study to establish the value of early adenosine technetium-99m sestamibi myocardial perfusion imaging in identifying a low-risk group for early hospital discharge after acute myocardial infarction. *J Am Coll Cardiol*. 2006;48:2448–2457.

2. Mahmarian JJ, Dakik HA, Filipchuk NG, et al. An initial strategy of intensive medical therapy is comparable to that of coronary revascularization for suppression of scintigraphic ischemia in high-risk but stable survivors of acute myocardial infarction. *J Am Coll Cardiol*. 2006;48:2458–2467.

3. Yan AT, Yan RT, Tan M, et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. *Eur Heart J*. 2007;28:1072–1078.

4. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

5. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69:2212–2241.

6. Patel MR, Bailey SR, Bonow RO, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;59:1995–2027.

7. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-Elevation myocardial infarction. *J Am Coll Cardiol*. 2016;67:1235–1250.

8. Pathik B, Raman B, Mohd Amin NH, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1146–1152.

9. Dastidar AG, Rodrigues JCL, Johnson TW, et al. Myocardial infarction with nonobstructed coronary arteries: impact of CMR early after presentation. *J Am Coll Cardiol Img*. 2017;10:1204–1206.

10. Assomull RG, Lyne JC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. *Eur Heart J*. 2007;28:1242–1249.

11. Tornvall P, Gerbaud E, Behaghel A, et al. Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: a meta-analysis of individual patient data. *Atherosclerosis*. 2015;241:87–91.

12. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. *J Am Coll Cardiol Img*. 2019;12:1973–1982.

13. Greenslade JH, Carlton EW, Van Hise C, et al. Diagnostic accuracy of a new high-sensitivity troponin I assay and five accelerated diagnostic pathways for ruling out acute myocardial infarction and acute coronary syndrome. *Ann Emerg Med*. 2018;71:439–451, e3.

14. Raff GL, Hoffmann U, Udelson JE. Trials of imaging use in the emergency department for acute chest pain. *J Am Coll Cardiol Img*. 2017;10:338–349.

15. Cohen M. High-risk acute coronary syndrome patients with non-ST-elevation myocardial infarction: definition and treatment. *Cardiovasc Drugs Ther*. 2008;22:407–418.

16. Steg PG, FitzGerald G, Fox KA. Risk stratification in non-ST-segment elevation acute coronary syndromes: troponin alone is not enough. *Am J Med*. 2009;122:107–108.

17. Pasupathy S, Air T, Dreyer RP, et al. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131:861–870.

18. Dastidar AG, Rodrigues JC, Ahmed N, et al. The role of cardiac MRI in patients with troponin-positive chest pain and unobstructed coronary arteries. *Curr Cardiovasc Imaging Rep*. 2015;8:28.

19. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J*. 2015;36:475–481.

4.1.4. Acute Chest Pain in Patients With Prior Coronary Artery Bypass Graft (CABG) Surgery

1. Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol*. 1996;28:616–626.

2. Harskamp RE, Lopes RD, Baisden CE, et al. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. *Ann Surg*. 2013;257:824–833.

3. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;63:380–406.

4. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2010;56:1864–1894.

5. Sabik JF 3rd. Understanding saphenous vein graft patency. *Circulation*. 2011;124:273–275.

6. Taggart DP. Current status of arterial grafts for coronary artery bypass grafting. *Ann Cardiothorac Surg*. 2013;2:427–430.

7. Gaudino M, Benedetto U, Fremes S, et al. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N Engl J Med*. 2018;378:2069–2077.

8. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929–1949.

9. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease. Selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. *Circulation*. 1979;59:421–430.

10. Mark DB, Hlatky MA, Harrell FE Jr, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106:793–800.

11. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–122.

12. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;58:e123–210.

13. Patel MR, Bailey SR, Bonow RO, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;59:1995–2027.

14. Bittl JA, He Y, Jacobs AK, et al. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left

main coronary artery disease. *Circulation*. 2013;127:2177–2185.

15. Costa MA, Trentini CA, Schafranski MD, et al. Factors associated with the development of chronic poststernotomy pain: a case-control study. *Braz J Cardiovasc Surg*. 2015;30:552–556.

16. van Gulik L, Janssen LI, Ahlers SJ, et al. Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur J Cardiothorac Surg*. 2011;40:1309–1313.

17. Kalso E, Mennander S, Tasmuth T, et al. Chronic post-sternotomy pain. *Acta Anaesthesiol Scand*. 2001;45:935–939.

18. Rashidi S, Elenbaas TW, Hamad MA, et al. Does removal of steel wires relieve post-sternotomy pain after cardiac surgery? *Asian Cardiovasc Thorac Ann*. 2013;21:409–413.

19. Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology*. 2006;105:794–800.

20. Marcassa C, Faggiano P, Greco C, et al. A retrospective multicenter study on long-term prevalence of chronic pain after cardiac surgery. *J Cardiovasc Med (Hagerstown)*. 2015;16:768–774.

21. Barbero U, Iannaccone M, d'Ascenzo F, et al. 64 slice-coronary computed tomography sensitivity and specificity in the evaluation of coronary artery bypass graft stenosis: a meta-analysis. *Int J Cardiol*. 2016;216:52–57.

4.1.5. Evaluation of Patients With Acute Chest Pain Receiving Dialysis

1. Saran R, Robinson B, Abbott KC, et al. US renal data system 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2018;71. A7.

2. Voroneanu L, Covic A. Arrhythmias in hemodialysis patients. *J Nephrol*. 2009;22:716–725.

3. Herzog CA, Littrell K, Arko C, et al. Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. *Circulation*. 2007;116:1465–1472.

4. Kielstein JT, Abou-Rebyeh F, Hafer C, et al. Right-sided chest pain at the onset of haemodialysis. *Nephrol Dial Transplant*. 2001;16:1493–1495.

5. Modi KS, Gross D, Davidman M. The patient developing chest pain at the onset of haemodialysis sessions—it is not always angina pectoris. *Nephrol Dial Transplant*. 1999;14:221–223.

6. Merritt B, Naamon E, Morris SA. The influence of an Urgent Care Center on the frequency of ED visits in an urban hospital setting. *Am J Emerg Med*. 2000;18:123–125.

7. Weinick RM, Burns RM, Mehrotra A. Many emergency department visits could be managed at urgent care centers and retail clinics. *Health Aff (Millwood)*. 2010;29:1630–1636.

4.1.6. Evaluation of Acute Chest Pain in Patients With Cocaine and Methamphetamine Use

1. Finkel JB, Marhefka GD. Rethinking cocaine-associated chest pain and acute coronary syndromes. *Mayo Clin Proc*. 2011;86:1198–1207.

2. DeFilippis E, Singh A, Divakaran S, et al. Cocaine and marijuana use among young adults with myocardial infarction. *J Am Coll Cardiol*. 2018;71:2540–2551.

3. Hawley LA, Auten JD, Matteucci MJ, et al. Cardiac complications of adult methamphetamine exposures. *J Emerg Med*. 2013;45:821–827.

4. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*. 2008;117:1897–1907.

5. Rezkalla SH, Kloner RA. Cocaine-induced acute myocardial infarction. *Clin Med Res*. 2007;5:172–176.

6. Richards JR, Hamidi S, Grant CD, et al. Methamphetamine use and emergency department utilization: 20 Years Later. *J Addict*. 2017;2017:4050932.

7. Wei GL, Zheng XZ, Chen KQ, et al. Coronary sinus flow is reduced in methamphetamine abusers: a transthoracic echocardiographic study. *Int J Cardiovasc Imaging*. 2018;34:1889–1894.

8. Paratz ED, Zhao J, Sherwen AK, et al. Is an abnormal ECG just the tip of the ICE-berg? Examining the utility of electrocardiography in detecting methamphetamine-induced cardiac pathology. *Heart Lung Circ*. 2017;26:684–689.

9. Paratz ED, Cunningham NJ, MacIsaac AI. The cardiac complications of methamphetamines. *Heart Lung Circ*. 2016;25:325–332.

4.1.7. Shared Decision-Making in Patients With Acute Chest Pain

1. Hess EP, Hollander JE, Schaffer JT, et al. Shared decision making in patients with low risk chest pain: prospective randomized pragmatic trial. *BMJ*. 2016;355:i6165.

2. Hess EP, Knoedler MA, Shah ND, et al. The chest pain choice decision aid: a randomized trial. *Circ Cardiovasc Qual Outcomes*. 2012;5:251–259.

3. Mayo Clinic. Chest Pain Choice Decision Aid. *YouTube*; 2016. Available at: https://www.youtube.com/watch?v=LgOagKX_-nA. Accessed July 26, 2021.

4. Elwyn G, Tilburt J, Montori VM. The ethical imperative for shared decision-making. *European Journal for Person Centered Healthcare*. 2013;1:129–213.

5. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2017;4:CD001431.

6. Hess EP. Clinical judgment is not passe when it comes to identifying patients with acute myocardial infarction. *Evid Based Med*. 2016;21:117.

7. Hess E. Authority Psychotherapy and the authority of the therapist in the religious Haredi community. *Am J Psychoanal*. 2018;78:137–158.

8. Hess EL, Myers EA, Swithers SE, et al. Associations between nonnutritive sweetener intake and metabolic syndrome in adults. *J Am Coll Nutr*. 2018;37:487–493.

4.2. Evaluation of Acute Chest Pain With Nonischemic Cardiac Pathologies

1. Labovitz AJ, Noble VE, Bierig M, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr*. 2010;23:1225–1230.

2. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.

3. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

4. Douglas PS, Garcia MJ, Haines D, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2011;57:1126–1166.

5. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement—executive summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J*. 2009;30:278–289.

6. Medical Advisory Secretariat. Stress echocardiography for the diagnosis of coronary artery disease: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2010;10:1–61.

4.2.1. Acute Chest Pain With Suspected Acute Aortic Syndrome

1. Vilacosta I, San Roman JA. Acute aortic syndrome. *Heart*. 2001;85:365–368.

2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492.

3. Spittell PC, Spittell JA Jr, Joyce JW, et al. Clinical features and differential diagnosis of aortic dissection: experience with 236 cases (1980 through 1990). *Mayo Clin Proc*. 1993;68:642–651.

4. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55:e27–e129.

5. Mussa FF, Horton JD, Moridzadeh R, et al. Acute aortic dissection and intramural hematoma: a systematic review. *JAMA*. 2016;316:754–763.

6. Vardhanabhuti V, Nicol E, Morgan-Hughes G, et al. Recommendations for accurate CT diagnosis of suspected acute aortic syndrome (AAS)-on behalf of the British Society of Cardiovascular Imaging (BSCI)/British Society of Cardiovascular CT (BSCCT). *Br J Radiol*. 2016;89:20150705.

4.2.2. Acute Chest Pain With Suspected PE

1. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). *J Am Coll Cardiol*. 2011;57:700–706.

2. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35:3033–3069, 69a-69k.

3. Raja AS, Greenberg JO, Qaseem A, et al. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2015;163:701–711.

4. Ceriani E, Combescure C, Le Gal G, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8:957–970.

5. Alotaibi GS, Wu C, Senthilselvan A, et al. Secular trends in incidence and mortality of acute venous thromboembolism: the AB-VTE Population-Based Study. *Am J Med*. 2016;129:879.e19–e25.

6. Smith SB, Geske JB, Kathuria P, et al. Analysis of national trends in admissions for pulmonary embolism. *Chest*. 2016;150:35–45.

7. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost*. 2007;98:756–764.

8. Kline JA, Jones AE, Shapiro NI, et al. Multicenter, randomized trial of quantitative pretest probability to reduce unnecessary medical radiation exposure in emergency department patients with chest pain and dyspnea. *Circ Cardiovasc Imaging*. 2014;7:66–73.

4.2.3. Acute Chest Pain With Suspected Myopericarditis

1. Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e579–e646.

2. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72:3158–3176.

3. Tornvall P, Gerbaud E, Behaghel A, et al. Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: a meta-analysis of individual patient data. *Atherosclerosis*. 2015;241:87–91.

4. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. *J Am Coll Cardiol Img*. 2019;12:1973–1982.

5. Lintingre PF, Nivet H, Clement-Guinaudeau S, et al. High-resolution late gadolinium enhancement magnetic resonance for the diagnosis of myocardial infarction with nonobstructed coronary arteries. *J Am Coll Cardiol Img*. 2020;13:1135–1148.

6. Dastidar AG, Rodrigues JCL, Johnson TW, et al. Myocardial infarction with nonobstructed coronary arteries: impact of CMR early after presentation. *J Am Coll Cardiol Img*. 2017;10:1204–1206.

7. Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26:965–1012, e15.

8. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2015;36:2921–2964.

9. Taylor AM, Dymarkowski S, Verbeken EK, et al. Detection of pericardial inflammation with late-enhancement cardiac magnetic resonance imaging: initial results. *Eur Radiol*. 2006;16:569–574.

10. Young PM, Glockner JF, Williamson EE, et al. MR imaging findings in 76 consecutive surgically proven cases of pericardial disease with CT and pathologic correlation. *Int J Cardiovasc Imaging*. 2012;28:1099–1109.

11. Aquaro GD, Perfetti M, Camastra G, et al. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. *J Am Coll Cardiol*. 2017;70:1977–1987.

12. Grani C, Buechel RR, Kaufmann PA, et al. Multimodality imaging in individuals with anomalous coronary arteries. *J Am Coll Cardiol Img*. 2017;10:471–481.

13. Hammer MM, Raptis CA, Javidan-Nejad C, et al. Accuracy of computed tomography findings in acute pericarditis. *Acta Radiol*. 2014;55:1197–1202.

14. Imazio M, Demichelis B, Cecchi E, et al. Cardiac troponin I in acute pericarditis. *J Am Coll Cardiol*. 2003;42:2144–2148.

15. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34:2636–2648, 48a-48d.

16. Pathik B, Raman B, Mohd Amin NH, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1146–1152.

17. Cosyns B, Plein S, Nihoyanopoulos P, et al. European Association of Cardiovascular Imaging (EACVI) position paper: multimodality imaging in pericardial disease. *Eur Heart J Cardiovasc Imaging*. 2015;16:12–31.

4.2.4. Acute Chest Pain With Valvular Heart Disease

1. Morrison GW, Thomas RD, Grimmer SF, et al. Incidence of coronary artery disease in patients with valvular heart disease. *Br Heart J*. 1980;44:630–637.

2. Ahn JH, Kim SM, Park SJ, et al. Coronary microvascular dysfunction as a mechanism of angina in severe AS: prospective adenosine-stress CMR study. *J Am Coll Cardiol*. 2016;67:1412–1422.

3. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25–e197.

4. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55:e27–e129.

5. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging*. 2012;13:1–46.

6. Doherty JU, Kort S, Mehran R, et al. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2017 appropriate use criteria for multimodality imaging in valvular heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;70:1647–1672.

4.3. Evaluation of Acute Chest Pain With Suspected Noncardiac Causes

4.3.1. Evaluation of Acute Chest Pain With Suspected Gastrointestinal Syndromes

1. Klinkman MS, Stevens D, Gorenflo DW. Episodes of care for chest pain: a preliminary report from MIRNET. Michigan Research Network. *J Fam Pract*. 1994;38:345–352.

2. Sengupta JN. An overview of esophageal sensory receptors. *Am J Med*. 2000;108(suppl 4a):87S–89S.

3. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2005;54:710–717.

4. Richter JE. Typical and atypical presentations of gastroesophageal reflux disease. The role of esophageal testing in diagnosis and management. *Gastroenterol Clin North Am*. 1996;25:75–102.

5. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Practice Parameters Committee of the American College of Gastroenterology. *Arch Intern Med*. 1995;155:2165–2173.

6. Hirano I, Richter JE. Practice parameters committee of the American College of Gasteroenterology. ACG

practice guidelines: esophageal reflux testing. *Am J Gastroenterol*. 2007;102:668–685.

4.3.2. Evaluation of Acute Chest Pain With Suspected Anxiety and Other Psychosomatic Considerations

1. Carter C, Maddock R, Amsterdam E, et al. Panic disorder and chest pain in the coronary care unit. *Psychosomatics*. 1992;33:302–309.

2. Kline JA, Shapiro NI, Jones AE, et al. Outcomes and radiation exposure of emergency department patients with chest pain and shortness of breath and ultralow pretest probability: a multicenter study. *Ann Emerg Med*. 2014;63:281–288.

3. Webster R, Norman P, Goodacre S, et al. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. *Emerg Med J*. 2012;29:267–273.

4. Eslick GD, Talley NJ. Natural history and predictors of outcome for non-cardiac chest pain: a prospective 4-year cohort study. *Neurogastroenterol Motil*. 2008;20:989–997.

5. Foldes-Busque G, Marchand A, Chauny JM, et al. Unexplained chest pain in the ED: could it be panic? *Am J Emerg Med*. 2011;29:743–751.

6. Musey PI Jr, Kline JA. Emergency department cardiopulmonary evaluation of low-risk chest pain patients with self-reported stress and anxiety. *J Emerg Med*. 2017;52:273–279.

7. Al-Ani M, Winchester DE. Prevalence and overlap of noncardiac conditions in the evaluation of low-risk acute chest pain patients. *Crit Pathw Cardiol*. 2015;14:97–102.

8. Czarnecki A, Wang JT, Tu JV, et al. The role of primary care physician and cardiologist follow-up for low-risk patients with chest pain after emergency department assessment. *Am Heart J*. 2014;168:289–295.

9. White KS, Craft JM, Gervino EV. Anxiety and hypervigilance to cardiopulmonary sensations in noncardiac chest pain patients with and without psychiatric disorders. *Behav Res Ther*. 2010;48:394–401.

10. Burgstaller JM, Jenni BF, Steurer J, et al. Treatment efficacy for non-cardiovascular chest pain: a systematic review and meta-analysis. *PLoS One*. 2014;9:e104722.

11. Kisely SR, Campbell LA, Yelland MJ, et al. Psychological interventions for symptomatic management of non-specific chest pain in patients with normal coronary anatomy. *Cochrane Database Syst Rev*. 2015: CD004101.

12. Mitchell AM, Garvey JL, Chandra A, et al. Prospective multicenter study of quantitative pretest probability assessment to exclude acute coronary syndrome for patients evaluated in emergency department chest pain units. *Ann Emerg Med*. 2006;47:447.

13. Hoorweg BB, Willemsen RT, Cleef LE, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart*. 2017;103:1727–1732.

14. Glombiewski JA, Rief W, Bosner S, et al. The course of nonspecific chest pain in primary care: symptom persistence and health care usage. *Arch Intern Med*. 2010;170:251–255.

15. Engel GL. Sudden and rapid death during psychological stress. Folklore or folk wisdom? *Ann Intern Med*. 1971;74:771–782.

16. Samuels MA. The brain-heart connection. *Circulation*. 2007;116:77–84.

17. Rudehill A, Olsson GL, Sundqvist K, et al. ECG abnormalities in patients with subarachnoid haemorrhage and intracranial tumours. *J Neurol Neurosurg Psychiatry*. 1987;50:1375–1381.

18. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352:539–548.

19. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, et al. Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:1955–1971.

20. Bass C, Wade C, Hand D, et al. Patients with angina with normal and near normal coronary arteries: clinical and psychosocial state 12 months after angiography. *Br Med J (Clin Res Ed)*. 1983;287:1505–1508.

21. Mukerji V, Beitman BD, Alpert MA. Chest pain and angiographically normal coronary arteries. Implications for treatment. *Tex Heart Inst J*. 1993;20:170–179.

22. Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol*. 1995;25:1013–1018.

23. Esler JL, Barlow DH, Woolard RH, et al. A brief cognitive-behavioral intervention for patients with noncardiac chest pain. *Behavior Therapy*. 2003;34:129–148.

24. Aikens JE, Zvolensky MJ, Eifert GH. Differential fear of cardiopulmonary sensations in emergency room noncardiac chest pain patients. *J Behav Med*. 2001;24:155–167.

25. Eifert GH, Zvolensky MJ, Lejuez CW. Heart-focused anxiety and chest pain: a conceptual and clinical review. *Clinical Psychology Science and Practice*. 2006;7:403–417.

26. Esler JL, Bock BC. Psychological treatments for noncardiac chest pain: recommendations for a new approach. *J Psychosom Res*. 2004;56:263–269.

27. Altintas E, Yigit F, Taskintuna N. The impact of psychiatric disorders with cardiac syndrome X on quality of life: 3 months prospective study. *Int J Clin Exp Med*. 2014;7:3520–3527.

28. Schwarz J, Prashad A, Winchester DE. Prevalence and implications of severe anxiety in a prospective cohort of acute chest pain patients. *Crit Pathw Cardiol*. 2015;14:44–47.

29. Foldes-Busque G, Denis I, Poitras J, et al. A closer look at the relationships between panic attacks, emergency department visits and non-cardiac chest pain. *J Health Psychol*. 2017:1359105316683785.

30. Campbell KA, Madva EN, Villegas AC, et al. Noncardiac chest pain: a review for the consultation-liaison psychiatrist. *Psychosomatics*. 2017;58:252–265.

4.3.3. Evaluation of Acute Chest Pain in Patients With Sickle Cell Disease

1. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330:1639–1644.

2. Thomas AN, Pattison C, Serjeant GR. Causes of death in sickle-cell disease in Jamaica. *Br Med J (Clin Res Ed)*. 1982;285:633–635.

3. Vichinsky EP, Styles LA, Colangelo LH, et al. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood*. 1997;89:1787–1792.

4. Martin CR, Johnson CS, Cobb C, et al. Myocardial infarction in sickle cell disease. *J Natl Med Assoc*. 1996;88:428–432.

5. Ogunbayo GO, Misumida N, Olorunfemi O, et al. Comparison of outcomes in patients having acute myocardial infarction with versus without sickle-cell anemia. *Am J Cardiol*. 2017;120:1768–1771.

5. EVALUATION OF PATIENTS WITH STABLE CHEST PAIN

5.1. Patients With No Known CAD Presenting With Stable Chest Pain

1. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2019;20:1198–1207.

2. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol*. 2020;76:2421–2432.

5.1.1. Pretest Risk Probability to Guide Need for Stress and Anatomic Tests

1. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2019;20:1198–1207.

2. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol*. 2020;76:2421–2432.

3. Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J*. 2011;32:1316–1330.

4. Fordyce CB, Douglas PS, Roberts RS, et al. Identification of patients with stable chest pain deriving minimal value from noninvasive testing: the PROMISE minimal-risk tool, a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2017;2:400–408.

5. Genders TS, Steyerberg EW, Hunink MG, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ*. 2012;344:e3485.

5.1.2. Low-Risk Patients With Stable Chest Pain and No Known CAD

1. Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J*. 2011;32:1316–1330.

2. Fordyce CB, Douglas PS, Roberts RS, et al. Identification of patients with stable chest pain deriving

minimal value from noninvasive testing: the PROMISE minimal-risk tool, a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2017;2:400–408.

3. Genders TS, Steyerberg EW, Hunink MG, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ*. 2012;344:e3485.

4. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2019;20:1198–1207.

5. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol*. 2020;76:2421–2432.

6. Lubbers M, Coenen A, Kofflard M, et al. Comprehensive cardiac CT with myocardial perfusion imaging versus functional testing in suspected coronary artery disease: the multicenter, randomized CRESCENT-II trial. *J Am Coll Cardiol Img*. 2018;11:1625–1636.

7. Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. *Eur Heart J*. 2016;37:1232–1243.

8. Chang SM, Nabi F, Xu J, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. *J Am Coll Cardiol*. 2009;54:1872–1882.

9. Budoff MJ, Mayrhofer T, Ferencik M, et al. Prognostic value of coronary artery calcium in the PROMISE study (prospective multicenter imaging study for evaluation of chest pain). *Circulation*. 2017;136:1993–2005.

10. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation*. 2011;124:1239–1249.

11. Douglas PS, Hoffmann U. Anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;373:91.

12. Hochman JS, Reynolds HR, Bangalore S, et al. Baseline characteristics and risk profiles of participants in the ISCHEMIA randomized clinical trial. *JAMA Cardiol*. 2019;4:273–286.

13. Spertus JA, Jones PG, Maron DJ, et al. Health status after invasive or conservative care in coronary and advanced kidney disease. *N Engl J Med*. 2020;382:1619–1628.

14. Rozanski A, Gransar H, Hayes SW, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. *J Am Coll Cardiol*. 2013;61:1054–1065.

15. Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). *Circulation*. 2011;124:2423–2432, 1-8.

16. Baskaran L, Danad I, Gransar H, et al. A comparison of the updated Diamond-Forrester, CAD Consortium, and CONFIRM history-based risk scores for predicting obstructive coronary artery disease in patients with stable chest pain: the SCOT-HEART Coronary CTA cohort. *J Am Coll Cardiol Img*. 2019;12:1392–1400.

17. Ferreira AM, Marques H, Tralhao A, et al. Pre-test probability of obstructive coronary stenosis in patients undergoing coronary CT angiography: comparative performance of the modified diamond-Forrester algorithm versus methods incorporating cardiovascular risk factors. *Int J Cardiol*. 2016;222:346–351.

18. Foldyna B, Udelson JE, Karady J, et al. Pretest probability for patients with suspected obstructive coronary artery disease: re-evaluating Diamond-Forrester for the contemporary era and clinical implications: insights from the PROMISE trial. *Eur Heart J Cardiovasc Imaging*. 2019;20:574–581.

19. Bittencourt MS, Hulten E, Polonsky TS, et al. European Society of Cardiology-recommended coronary artery disease consortium pretest probability scores more accurately predict obstructive coronary disease and cardiovascular events than the Diamond and Forrester score: the Partners registry. *Circulation*. 2016;134:201–211.

20. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.

21. Patel MR, Dai D, Hernandez AF, et al. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am Heart J*. 2014;167:846–852 e2.

22. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.

5.1.3. Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD

1. Dewey M, Rief M, Martus P, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. *BMJ*. 2016;355:i5441.

2. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52:2135–2144.

3. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52:1724–1732.

4. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359:2324–2336.

5. Chang H-J, Lin FY, Gebow D, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected CAD: a randomized, controlled, open-label trial. *J Am Coll Cardiol Img*. 2019;12:1303–1312.

6. Sharma A, Coles A, Sekaran NK, et al. Stress testing versus CT angiography in patients with diabetes and suspected coronary artery disease. *J Am Coll Cardiol*. 2019;73:893–902.

7. Min JK, Koduru S, Dunning AM, et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. *J Cardiovasc Comput Tomogr*. 2012;6:274–283.

8. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.

9. SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379:924–933.

10. SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385:2383–2391.

11. McKavanagh P, Lusk L, Ball PA, et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. *Eur Heart J Cardiovasc Imaging*. 2015;16:441–448.

12. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. *Eur Heart J*. 2015;36:3359–3367.

13. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.

14. Douglas PS, Garcia MJ, Haines D, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2011;57:1126–1166.

15. Gurunathan S, Zacharias K, Akhtar M, et al. Cost-effectiveness of a management strategy based on exercise echocardiography versus exercise electrocardiography in patients presenting with suspected angina during long term follow up: a randomized study. *Int J Cardiol*. 2018;259:1–7.

16. Carpeggiani C, Landi P, Michelassi C, et al. Stress echocardiography positivity predicts cancer death. *J Am Heart Assoc*. 2017;6:e007104.

17. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135:2320–2332.

18. Abdelmoneim SS, Ball CA, Mantovani F, et al. Prognostic utility of stress testing and cardiac biomarkers in menopausal women at low to intermediate risk for coronary artery disease (SMART Study): 5-year outcome. *J Womens Health (Larchmt)*. 2018;27:542–551.

19. Cortigiani L, Urluescu ML, Coltelli M, et al. Apparent declining prognostic value of a negative stress echocardiography based on regional wall motion abnormalities in patients with normal resting left ventricular function due to the changing referral profile of the population under study. *Circ Cardiovasc Imaging*. 2019;12:e008564.

20. Gibbons RJ, Hodge DO, Berman DS, et al. Long-term outcome of patients with intermediate-risk exercise electrocardiograms who do not have myocardial perfusion defects on radionuclide imaging. *Circulation*. 1999;100:2140–2145.

21. Rozanski A, Gransar H, Min JK, et al. Long-term mortality following normal exercise myocardial perfusion SPECT according to coronary disease risk factors. *J Nucl Cardiol*. 2014;21:341–350.

22. Bourque JM, Holland BH, Watson DD, et al. Achieving an exercise workload of $>$ or $=$ 10 metabolic equivalents predicts a very low risk of inducible ischemia: does myocardial perfusion imaging have a role? *J Am Coll Cardiol*. 2009;54:538–545.

23. Shaw LJ, Wilson PW, Hachamovitch R, et al. Improved near-term coronary artery disease risk classification with gated stress myocardial perfusion SPECT. *J Am Coll Cardiol Img*. 2010;3:1139–1148.

24. Shaw LJ, Min JK, Hachamovitch R, et al. Nomograms for estimating coronary artery disease prognosis with gated stress myocardial perfusion SPECT. *J Nucl Cardiol*. 2012;19:43–52.

25. Uretsky S, Rozanski A. Long-term outcomes following a normal stress myocardial perfusion scan. *J Nucl Cardiol*. 2013;20:715–718.

26. Patel KK, Al Badarin F, Chan PS, et al. Randomized comparison of clinical effectiveness of pharmacologic SPECT and PET MPI in symptomatic CAD patients. *J Am Coll Cardiol Img*. 2019;12:1821–1831.

27. Dorbala S, Di Carli MF, Beanlands RS, et al. Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. *J Am Coll Cardiol*. 2013;61:176–184.

28. Kay J, Dorbala S, Goyal A, et al. Influence of sex on risk stratification with stress myocardial perfusion Rb-82 positron emission tomography: results from the PET (Positron Emission Tomography) Prognosis Multicenter Registry. *J Am Coll Cardiol*. 2013;62:1866–1876.

29. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet*. 2012;379:453–460.

30. Schwitter J, Wacker CM, Wilke N, et al. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J*. 2013;34:775–781.

31. Hamon M, Fau G, Nee G, et al. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. *J Cardiovasc Magn Reson*. 2010;12:29.

32. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol*. 2012;59:1719–1728.

33. Schwitter J, Wacker CM, Wilke N, et al. Superior diagnostic performance of perfusion-cardiovascular magnetic resonance versus SPECT to detect coronary artery disease: the secondary endpoints of the multicenter multivendor MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial). *J Cardiovasc Magn Reson*. 2012;14:61.

34. Greenwood JP, Ripley DP, Berry C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA*. 2016;316:1051–1060.

35. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med*. 2019;380:2418–2428.

36. Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*. 2018;39:3322–3330.

37. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–1107.

38. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging*. 2015;8:e002179.

39. Danad I, Szymonifka J, Twisk JWR, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J*. 2017;38:991–998.

40. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation*. 2011;124:1239–1249.

41. Mieres JH, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. *Circulation*. 2014;130:350–379.

42. Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med*. 1991;325:849–853.

43. Mark DB, Hlatky MA, Harrell FE Jr, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106:793–800.

44. Lauer MS, Pothier CE, Magid DJ, et al. An externally validated model for predicting long-term survival after exercise treadmill testing in patients with suspected coronary artery disease and a normal electrocardiogram. *Ann Intern Med*. 2007;147:821–828.

45. Gulati M, Black HR, Shaw LJ, et al. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med*. 2005;353:468–475.

46. Ardestani A, Ahlberg AW, Katten DM, et al. Risk stratification using line source attenuation correction with rest/stress Tc-99m sestamibi SPECT myocardial perfusion imaging. *J Nucl Cardiol*. 2014;21:118–126.

47. van Dijk JD, Mouden M, Ottervanger JP, et al. Value of attenuation correction in stress-only myocardial perfusion imaging using CZT-SPECT. *J Nucl Cardiol*. 2017;24:395–401.

48. Gutstein A, Bental T, Solodky A, et al. Prognosis of stress-only SPECT myocardial perfusion imaging with prone imaging. *J Nucl Cardiol*. 2018;25:809–816.

49. Huang JY, Yen RF, Lee WC, et al. Improved diagnostic accuracy of thallium-201 myocardial perfusion single-photon emission computed tomography with CT attenuation correction. *J Nucl Cardiol*. 2019;26:1584–1595.

50. Huang JY, Huang CK, Yen RF, et al. Diagnostic performance of attenuation-corrected myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. *J Nucl Med*. 2016;57:1893–1898.

51. Ito S, Endo A, Okada T, et al. Comparison of CTAC and prone imaging for the detection of coronary artery disease using CZT SPECT. *Ann Nucl Med*. 2017;31:629–635.

52. Gibbons RJ, Carryer D, Liu H, et al. Use of echocardiography in outpatients with chest pain and normal resting electrocardiograms referred to Mayo Clinic Rochester. *Am Heart J*. 2018;196:49–55.

53. Douglas PS, De Bruyne B, Pontone G, et al. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM Study. *J Am Coll Cardiol*. 2016;68:435–445.

54. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J*. 2018;39:3701–3711.

55. Patel MR, Norgaard BL, Fairbairn TA, et al. 1-Year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE registry. *J Am Coll Cardiol Img*. 2019;13:97–105.

56. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*. 2012;308:1237–1245.

57. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT

Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63:1145–1155.

58. Andreini D, Modolo R, Katagiri Y, et al. Impact of fractional flow reserve derived from coronary computed tomography angiography on heart team treatment decision-making in patients with multivessel coronary artery disease: insights from the SYNTAX III REVOLUTION Trial. *Circ Cardiovasc Interv*. 2019;12:e007607.

59. Abidov A, Gallagher MJ, Chinnaiyan KM, et al. Clinical effectiveness of coronary computed tomographic angiography in the triage of patients to cardiac catheterization and revascularization after inconclusive stress testing: results of a 2-year prospective trial. *J Nucl Cardiol*. 2009;16:701–713.

60. Christman MP, Bittencourt MS, Hulten E, et al. Yield of downstream tests after exercise treadmill testing: a prospective cohort study. *J Am Coll Cardiol*. 2014;63:1264–1274.

61. Shaw LJ, Hausleiter J, Achenbach S, et al. Coronary computed tomographic angiography as a gatekeeper to invasive diagnostic and surgical procedures: results from the multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry. *J Am Coll Cardiol*. 2012;60:2103–2114.

62. ISCHEMIA Trial Research Group, Maron DJ, Hochman JS, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. *Am Heart J*. 2018;201:124–135.

63. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

64. Schepis T, Gaemperli O, Koepfli P, et al. Added value of coronary artery calcium score as an adjunct to gated SPECT for the evaluation of coronary artery disease in an intermediate-risk population. *J Nucl Med*. 2007;48:1424–1430.

65. Chang SM, Nabi F, Xu J, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. *J Am Coll Cardiol*. 2009;54:1872–1882.

66. Bavishi C, Argulian E, Chatterjee S, et al. CACS and the frequency of stress-induced myocardial ischemia during MPI: a meta-analysis. *J Am Coll Cardiol Img*. 2016;9:580–589.

67. Rozanski A, Gransar H, Wong ND, et al. Use of coronary calcium scanning for predicting inducible myocardial ischemia: influence of patients' clinical presentation. *J Nucl Cardiol*. 2007;14:669–679.

68. Brodov Y, Gransar H, Dey D, et al. Combined quantitative assessment of myocardial perfusion and coronary artery calcium score by hybrid 82Rb PET/CT improves detection of coronary artery disease. *J Nucl Med*. 2015;56:1345–1350.

69. Ghadri JR, Pazhenkottil AP, Nkoulou RN, et al. Very high coronary calcium score unmasks obstructive coronary artery disease in patients with normal SPECT MPI. *Heart*. 2011;97:998–1003.

70. Schenker MP, Dorbala S, Hong EC, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. *Circulation*. 2008;117:1693–1700.

71. Marwick TH, Case C, Vasey C, et al. Prediction of mortality by exercise echocardiography: a strategy for combination with the Duke Treadmill Score. *Circulation*. 2001;103:2566–2571.

72. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement—executive summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J*. 2009;30:278–289.

73. Vitola JV, Wanderley MR Jr, Cerci RJ, et al. Outcome of patients with high-risk Duke Treadmill Score and normal myocardial perfusion imaging on SPECT. *J Nucl Cardiol*. 2016;23:1291–1300.

74. Boiten HJ, van Domburg RT, Valkema R, et al. Eleven-year prognostic value of dobutamine stress (99m)Tc-sestamibi myocardial perfusion imaging in patients with limited exercise capacity. *Am J Cardiol*. 2015;115:884–889.

75. Uretsky S, Supariwala A, Gurram S, et al. The interaction of exercise ability and body mass index upon long-term outcomes among patients undergoing stress-rest perfusion single-photon emission computed tomography imaging. *Am Heart J*. 2013;166:127–133.

76. Bourque JM, Charlton GT, Holland BH, et al. Prognosis in patients achieving >/=10 METS on exercise stress testing: was SPECT imaging useful? *J Nucl Cardiol*. 2011;18:230–237.

77. Rozanski A, Gransar H, Hayes SW, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. *J Am Coll Cardiol*. 2013;61:1054–1065.

78. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.

79. Patel MR, Dai D, Hernandez AF, et al. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am Heart J*. 2014;167:846–852 e2.

80. Greenwood JP, Ripley DP, Berry C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA*. 2016;316:1051–1060.

81. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2019;20:1198–1207.

82. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol*. 2020;76:2421–2432.

83. Lowenstern A, Alexander KP, Hill CL, et al. Age-related differences in the noninvasive evaluation for possible coronary artery disease: insights from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Trial. *JAMA Cardiol*. 2020;5:193–201.

84. Chang HJ, Lin FY, Gebow D, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected CAD: a randomized, controlled, open-label trial. *J Am Coll Cardiol Img*. 2019;12:1303–1312.

85. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.

86. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929–1949.

87. Arnett DK, Blumenthal R, Albert M, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:e177–e232.

88. Budoff MJ, Li D, Kazerooni EA, et al. Diagnostic accuracy of noninvasive 64-row computed tomographic coronary angiography (CCTA) compared with myocardial perfusion imaging (MPI): the PICTURE study, a prospective multicenter trial. *Acad Radiol*. 2017;24:22–29.

89. SCOT-HEART Investigators, Newby DE, Adamson PD, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379:924–933.

90. Williams MC, Hunter A, Shah ASV, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67:1759–1768.

91. Ladapo JA, Hoffmann U, Lee KL, et al. Changes in medical therapy and lifestyle after anatomical or functional testing for coronary artery disease. *J Am Heart Assoc*. 2016;5:e003807.

92. Mark DB, Anstrom KJ, Sheng S, et al. Quality-of-life outcomes with anatomic versus functional diagnostic testing strategies in symptomatic patients with suspected coronary artery disease: results from the PROMISE randomized trial. *Circulation*. 2016;133:1995–2007.

93. Adamson PD, Williams MC, Dweck MR, et al. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. *J Am Coll Cardiol*. 2019;74:2058–2070.

94. Hulten E, Bittencourt MS, Singh A, et al. Coronary artery disease detected by coronary computed tomographic angiography is associated with intensification of preventive medical therapy and lower low-density lipoprotein cholesterol. *Circ Cardiovasc Imaging*. 2014;7:629–638.

95. Norgaard BL, Terkelsen CJ, Mathiassen ON, et al. Coronary CT angiographic and flow reserve-guided management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2018;72:2123–2134.

96. Bittencourt MS, Hulten EA, Murthy VL, et al. Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: a meta-analysis. *Circ Cardiovasc Imaging*. 2016;9:e004419.

97. McCully RB, Roger VL, Mahoney DW, et al. Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: follow-up of 1,325 patients. *J Am Coll Cardiol*. 1998;31:144–149.

98. Metz LD, Beattie M, Hom R, et al. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol*. 2007;49:227–237.

99. Smulders MW, Jaarsma C, Nelemans PJ, et al. Comparison of the prognostic value of negative non-invasive cardiac investigations in patients with suspected or known coronary artery disease-a meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2017;18:980–987.

100. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.

101. Shaw LJ, Hage FG, Berman DS, et al. Prognosis in the era of comparative effectiveness research: where is nuclear cardiology now and where should it be? *J Nucl Cardiol*. 2012;19:1026–1043.

102. Green R, Cantoni V, Petretta M, et al. Negative predictive value of stress myocardial perfusion imaging and coronary computed tomography angiography: a meta-analysis. *J Nucl Cardiol*. 2018;25:1588–1597.

103. Bom MJ, van Diemen PA, Driessen RS, et al. Prognostic value of [15O]H2O positron emission tomography-derived global and regional myocardial perfusion. *Eur Heart J Cardiovasc Imaging*. 2020;21:777–786.

104. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73:161–173.

105. Greenwood JP, Herzog BA, Brown JM, et al. Prognostic value of cardiovascular magnetic resonance and single-photon emission computed tomography in suspected coronary heart disease: long-term follow-up of a prospective, diagnostic accuracy cohort study. *Ann Intern Med*. 2016;165:1–9.

106. Rabbat M, Leipsic J, Bax J, et al. Fractional flow reserve derived from coronary computed tomography angiography safely defers invasive coronary angiography in patients with stable coronary artery disease. *J Clin Med*. 2020;9:604.

107. Cami E, Tagami T, Raff G, et al. Importance of measurement site on assessment of lesion-specific ischemia and diagnostic performance by coronary computed tomography angiography-derived fractional flow reserve. *J Cardiovasc Comput Tomogr*. 2021;15:114–120.

108. Hochman JS, Reynolds HR, Bangalore S, et al. Baseline characteristics and risk profiles of participants in the ISCHEMIA randomized clinical trial. *JAMA Cardiol*. 2019;4:273–286.

109. Blankstein R, Di Carli MF. Integration of coronary anatomy and myocardial perfusion imaging. *Nat Rev Cardiol*. 2010;7:226–236.

110. Berman DS, Wong ND, Gransar H, et al. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *J Am Coll Cardiol*. 2004;44:923–930.

111. Marcos-Garces V, Gavara J, Monmeneu JV, et al. Vasodilator stress CMR and all-cause mortality in stable ischemic heart disease: a large retrospective registry. *J Am Coll Cardiol Img*. 2020;13:1674–1686.

112. Kwong RY, Ge Y, Steel K, et al. Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. *J Am Coll Cardiol*. 2019;74:1741–1755.

113. Ahmad IG, Abdulla RK, Klem I, et al. Comparison of stress cardiovascular magnetic resonance imaging (CMR) with stress nuclear perfusion for the diagnosis of coronary artery disease. *J Nucl Cardiol*. 2016;23:287–297.

5.2. Patients With Known CAD Presenting With Stable Chest Pain

1. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.

2. BARI 2D Study Group, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.

3. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

4. Arnett DK, Blumenthal R, Albert M, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:e177–232.

5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.

6. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929–1949.

7. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.

5.2.1. Patients With Obstructive CAD Who Present With Stable Chest Pain

1. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.

2. BARI 2D Study Group, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.

3. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.

4. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

5. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371:1208–1217.

6. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.

7. Bhatt DL. Assessment of stable coronary lesions. *N Engl J Med*. 2017;376:1879–1881.

8. Patel MR, Bailey SR, Bonow RO, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;59:1995–2027.

9. Suh YJ, Hong YJ, Lee HJ, et al. Accuracy of CT for selecting candidates for coronary artery bypass graft surgery: combination with the SYNTAX score. *Radiology*. 2015;276:390–399.

10. Chan M, Ridley L, Dunn DJ, et al. A systematic review and meta-analysis of multidetector computed tomography in the assessment of coronary artery bypass grafts. *Int J Cardiol*. 2016;221:898–905.

11. Small GR, Yam Y, Chen L, et al. Prognostic assessment of coronary artery bypass patients with 64-slice computed tomography angiography: anatomical information is incremental to clinical risk prediction. *J Am Coll Cardiol*. 2011;58:2389–2395.

12. Andreini D, Modolo R, Katagiri Y, et al. Impact of fractional flow reserve derived from coronary computed tomography angiography on heart team treatment decision-making in patients with multivessel coronary artery disease: insights from the SYNTAX III REVOLUTION trial. *Circ Cardiovasc Interv*. 2019;12:e007607.

13. Collet C, Onuma Y, Andreini D, et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J*. 2018;39:3689–3698.

14. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283–1291.

15. Shaw LJ, Cerqueira MD, Brooks MM, et al. Impact of left ventricular function and the extent of ischemia and scar by stress myocardial perfusion imaging on

prognosis and therapeutic risk reduction in diabetic patients with coronary artery disease: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *J Nucl Cardiol*. 2012;19:658–669.

16. Zellweger MJ, Fahrni G, Ritter M, et al. Prognostic value of "routine" cardiac stress imaging 5 years after percutaneous coronary intervention: the prospective long-term observational BASKET (Basel Stent Kosteneffektivitats Trial) LATE IMAGING study. *J Am Coll Cardiol Intv*. 2014;7:615–621.

17. Zellweger MJ, Kaiser C, Jeger R, et al. Coronary artery disease progression late after successful stent implantation. *J Am Coll Cardiol*. 2012;59:793–799.

18. Zellweger MJ, Kaiser C, Brunner-La Rocca HP, et al. Value and limitations of target-vessel ischemia in predicting late clinical events after drug-eluting stent implantation. *J Nucl Med*. 2008;49:550–556.

19. Shaw LJ, Weintraub WS, Maron DJ, et al. Baseline stress myocardial perfusion imaging results and outcomes in patients with stable ischemic heart disease randomized to optimal medical therapy with or without percutaneous coronary intervention. *Am Heart J*. 2012;164:243–250.

20. Patel KK, Spertus JA, Arnold SV, et al. Ischemia on PET MPI may identify patients with improvement in angina and health status post-revascularization. *J Am Coll Cardiol*. 2019;74:1734–1736.

21. Patel KK, Spertus JA, Chan PS, et al. Extent of myocardial ischemia on positron emission tomography and survival benefit with early revascularization. *J Am Coll Cardiol*. 2019;74:1645–1654.

22. Reynolds HR, Shaw LJ, Min JK, et al. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol*. 2020;5:1–14.

23. Schwitter J, Wacker CM, van Rossum AC, et al. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. *Eur Heart J*. 2008;29:480–489.

24. Schwitter J, Wacker CM, Wilke N, et al. MR-IMPACT II: Magnetic resonance imaging for myocardial perfusion assessment in coronary artery disease trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J*. 2013;34:775–781.

25. Arai AE, Schulz-Menger J, Berman D, et al. Gadobutrol-enhanced cardiac magnetic resonance imaging for detection of coronary artery disease. *J Am Coll Cardiol*. 2020;76:1536–1547.

26. Takx RA, Blomberg BA, El Aidi H, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. *Circ Cardiovasc Imaging*. 2015;8.

27. Heitner JF, Kim RJ, Kim HW, et al. Prognostic value of vasodilator stress cardiac magnetic resonance imaging: a multicenter study with 48000 patient-years of follow-up. *JAMA Cardiol*. 2019;4:256–264.

28. Kato S, Saito N, Nakachi T, et al. Stress perfusion coronary flow reserve versus cardiac magnetic resonance for known or suspected CAD. *J Am Coll Cardiol*. 2017;70:869–879.

29. Vincenti G, Masci PG, Monney P, et al. Stress perfusion CMR in patients with known and suspected CAD: prognostic value and optimal ischemic threshold for revascularization. *J Am Coll Cardiol Img*. 2017;10:526–537.

30. Kwong RY, Ge Y, Steel K, et al. Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. *J Am Coll Cardiol*. 2019;74:1741–1755.

31. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation*. 2015;131:19–27.

32. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73:161–173.

33. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–1107.

34. Patel KK, Spertus JA, Chan PS, et al. Myocardial blood flow reserve assessed by positron emission tomography myocardial perfusion imaging identifies patients with a survival benefit from early revascularization. *Eur Heart J*. 2020;41:759–768.

35. Bom MJ, van Diemen PA, Driessen RS, et al. Prognostic value of [15O]H2O positron emission tomography-derived global and regional myocardial perfusion. *Eur Heart J Cardiovasc Imaging*. 2020;21:777–786.

36. Knott KD, Seraphim A, Augusto JB, et al. The prognostic significance of quantitative myocardial perfusion: an artificial intelligence-based approach using perfusion mapping. *Circulation*. 2020;141:1282–1291.

37. Patel KK, Al Badarin F, Chan PS, et al. Randomized comparison of clinical effectiveness of pharmacologic SPECT and PET MPI in symptomatic CAD patients. *J Am Coll Cardiol Img*. 2019;12:1821–1831.

38. Ho PM, Rumsfeld JS, Peterson PN, et al. Chest pain on exercise treadmill test predicts future cardiac hospitalizations. *Clin Cardiol*. 2007;30:505–510.

39. Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation*. 2004;109:1371–1378.

40. Jaureguizar KV, Vicente-Campos D, Bautista LR, et al. Effect of high-intensity interval versus continuous exercise training on functional capacity and quality of life in patients with coronary artery disease: a randomized clinical trial. *J Cardiopulm Rehabil Prev*. 2016;36:96–105.

41. Spertus JA, Jones PG, Maron DJ, et al. Health status after invasive or conservative care in coronary and advanced kidney disease. *N Engl J Med*. 2020;382:1619–1628.

42. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med*. 2018;379:250–259.

43. Lee S-E, Sung JM, Andreini D, et al. Differences in progression to obstructive lesions per high-risk plaque features and plaque volumes with CCTA. *J Am Coll Cardiol Img*. 2019;13:1409–1417.

44. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *J Am Coll Cardiol Img*. 2018;11:1475–1484.

45. Williams MC, Hunter A, Shah ASV, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67:1759–1768.

46. Ladapo JA, Hoffmann U, Lee KL, et al. Changes in medical therapy and lifestyle after anatomical or functional testing for coronary artery disease. *J Am Heart Assoc*. 2016;5:e003807.

47. Mark DB, Anstrom KJ, Sheng S, et al. Quality-of-life outcomes with anatomic versus functional diagnostic testing strategies in symptomatic patients with suspected coronary artery disease: results from the PROMISE randomized trial. *Circulation*. 2016;133:1995–2007.

48. Sharma A, Coles A, Sekaran NK, et al. Stress testing versus CT angiography in patients with diabetes and suspected coronary artery disease. *J Am Coll Cardiol*. 2019;73:893–902.

49. SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379:924–933.

50. Adamson PD, Williams MC, Dweck MR, et al. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. *J Am Coll Cardiol*. 2019;74:2058–2070.

51. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52:1724–1732.

52. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52:2135–2144.

53. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359:2324–2336.

54. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging*. 2015;8:e002179.

55. Budoff MJ, Li D, Kazerooni EA, et al. Diagnostic accuracy of noninvasive 64-row computed tomographic coronary angiography (CCTA) compared with myocardial perfusion imaging (MPI): the PICTURE study, a prospective multicenter trial. *Acad Radiol*. 2017;24:22–29.

56. Xie JX, Eshtehardi P, Varghese T, et al. Prognostic significance of nonobstructive left main coronary artery disease in women versus men: long-term outcomes from the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter). *Registry. Circ Cardiovasc Imaging*. 2017;10:e006246.

57. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol*. 2011;58:849–860.

58. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929–1949.

59. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63:1145–1155.

60. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*. 2012;308:1237–1245.

61. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. *Eur Heart J*. 2015;36:3359–3367.

62. Patel MR, Norgaard BL, Fairbairn TA, et al. 1-Year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE registry. *J Am Coll Cardiol Img*. 2019;13:97–105.

63. Hachamovitch R, Rozanski A, Hayes SW, et al. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? *J Nucl Cardiol*. 2006;13:768–778.

64. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900–2907.

65. Hachamovitch R, Rozanski A, Shaw LJ, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J*. 2011;32:1012–1024.

66. Shaw LJ, Vasey C, Sawada S, et al. Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4234 women and 6898 men. *Eur Heart J*. 2005;26:447–456.

67. Yao SS, Bangalore S, Chaudhry FA. Prognostic implications of stress echocardiography and impact on patient outcomes: an effective gatekeeper for coronary angiography and revascularization. *Am Soc Echocardiogr*. 2010;23:832–839.

68. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391:31–40.

69. Al-Lamee RK, Shun-Shin MJ, Howard JP, et al. Dobutamine stress echocardiography ischemia as a predictor of the placebo-controlled efficacy of percutaneous coronary intervention in stable coronary artery disease: the stress echocardiography-stratified analysis of ORBITA. *Circulation*. 2019;140:1971–1980.

70. Taqueti VR, Shaw LJ, Cook NR, et al. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577.

71. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:840–849.

5.2.1.1. Patients With Prior Coronary Artery Bypass With Stable Chest Pain

1. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929–1949.

2. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease. Selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. *Circulation*. 1979;59:421–430.

3. Mark DB, Hlatky MA, Harrell FE Jr, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106:793–800.

4. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–122.

5. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;58:e-123–e-210.

6. Patel MR, Bailey SR, Bonow RO, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;59:1995–2027.

7. Bittl JA, He Y, Jacobs AK, et al. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation*. 2013;127:2177–2185.

8. Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol*. 1996;28:616–626.

9. Harskamp RE, Lopes RD, Baisden CE, et al. Saphenous vein graft failure after coronary artery bypass surgery: pathophysiology, management, and future directions. *Ann Surg*. 2013;257:824–833.

10. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;63:380–406.

11. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2010;56:1864–1894.

12. Sabik JF 3rd. Understanding saphenous vein graft patency. *Circulation*. 2011;124:273–275.

13. Taggart DP. Current status of arterial grafts for coronary artery bypass grafting. *Ann Cardiothorac Surg*. 2013;2:427–430.

14. Gaudino M, Benedetto U, Fremes S, et al. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N Engl J Med*. 2018;378:2069–2077.

15. Barbero U, Iannaccone M, d'Ascenzo F, et al. 64 slice-coronary computed tomography sensitivity and specificity in the evaluation of coronary artery bypass graft stenosis: a meta-analysis. *Int J Cardiol*. 2016;216:52–57.

5.2.2. Patients With Known Nonobstructive CAD Presenting With Stable Chest Pain

1. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *J Am Coll Cardiol Img*. 2018;11:1475–1484.

2. Lee SE, Sung JM, Rizvi A, et al. Quantification of coronary atherosclerosis in the assessment of coronary

artery disease. *Circ Cardiovasc Imaging*. 2018;11:e007562.

3. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135:2320–2332.

4. Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the Multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). *Circulation*. 2020;141:1452–1462.

5. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol*. 2018;3:144–152.

6. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018;71:2511–2522.

7. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66:337–346.

8. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. *Eur Heart J*. 2015;36:3359–3367.

9. Douglas PS, De Bruyne B, Pontone G, et al. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM Study. *J Am Coll Cardiol*. 2016;68:435–445.

10. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J*. 2018;39:3701–3711.

11. Patel MR, Norgaard BL, Fairbairn TA, et al. 1-Year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE registry. *J Am Coll Cardiol Img*. 2019;13:97–105.

12. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*. 2012;308:1237–1245.

13. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63:1145–1155.

14. Andreini D, Modolo R, Katagiri Y, et al. Impact of fractional flow reserve derived from coronary computed tomography angiography on heart team treatment decision-making in patients with multivessel coronary artery disease: insights from the SYNTAX III REVOLUTION trial. *Circ Cardiovasc Interv*. 2019;12:e007607.

15. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:840–849.

16. Taqueti VR, Shaw LJ, Cook NR, et al. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577.

17. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation*. 2015;131:19–27.

18. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73:161–173.

19. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–1107.

20. Patel KK, Spertus JA, Chan PS, et al. Myocardial blood flow reserve assessed by positron emission tomography myocardial perfusion imaging identifies patients with a survival benefit from early revascularization. *Eur Heart J*. 2020;41:759–768.

21. Bom MJ, van Diemen PA, Driessen RS, et al. Prognostic value of [15O]H2O positron emission tomography-derived global and regional myocardial perfusion. *Eur Heart J Cardiovasc Imaging*. 2020;21:777–786.

22. Kato S, Saito N, Nakachi T, et al. Stress perfusion coronary flow reserve versus cardiac magnetic resonance for known or suspected CAD. *J Am Coll Cardiol*. 2017;70:869–879.

23. Indorkar R, Kwong RY, Romano S, et al. Global coronary flow reserve measured during stress cardiac magnetic resonance imaging Is an independent predictor of adverse cardiovascular events. *J Am Coll Cardiol Img*. 2019;12:1686–1695.

24. Zorach B, Shaw PW, Bourque J, et al. Quantitative cardiovascular magnetic resonance perfusion imaging identifies reduced flow reserve in microvascular coronary artery disease. *J Cardiovasc Magn Reson*. 2018;20:14.

25. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol*. 2014;64:684–692.

26. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–164.

27. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.

28. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929–1949.

29. Arnett DK, Blumenthal R, Albert M, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:e177–e232.

30. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54:49–57.

31. Stuijfzand WJ, van Rosendael AR, Lin FY, et al. Stress myocardial perfusion imaging vs coronary computed tomographic angiography for diagnosis of invasive vessel-specific coronary physiology: predictive modeling results from the computed tomographic evaluation of atherosclerotic determinants of myocardial ischemia (CREDENCE) Trial. *JAMA Cardiol*. 2020;5:1338–1348.

5.2.3. Patients With Suspected Ischemia and No Obstructive CAD (INOCA)

1. Bairey Merz CN, Pepine CJ, Walsh MN, et al. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation*. 2017;135:1075–1092.

2. AlBadri A, Bairy Merz CN, Johnson BD, et al. Impact of abnormal coronary reactivity on long-term clinical outcomes in women. *J Am Coll Cardiol*. 2019;73:684–693.

3. AlBadri A, Sharif B, Wei J, et al. Intracoronary bolus injection versus intravenous infusion of adenosine for assessment of coronary flow velocity reserve in women with signs and symptoms of myocardial ischemia and no obstructive coronary artery disease. *J Am Coll Cardiol Intv*. 2018;11:2125–2127.

4. Ford TJ, Stanley B, Sidik N, et al. 1-Year outcomes of angina management guided by invasive coronary function testing (CorMicA). *J Am Coll Cardiol Intv*. 2020;13:33–45.

5. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:840–849.

6. Taqueti VR, Shaw LJ, Cook NR, et al. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577.

7. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of

luminal angiographic severity and modifies the effect of early revascularization. *Circulation*. 2015;131:19–27.

8. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73:161–173.

9. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–1107.

10. Patel KK, Spertus JA, Chan PS, et al. Myocardial blood flow reserve assessed by positron emission tomography myocardial perfusion imaging identifies patients with a survival benefit from early revascularization. *Eur Heart J*. 2020;41:759–768.

11. Bom MJ, van Diemen PA, Driessen RS, et al. Prognostic value of [15O]H2O positron emission tomography-derived global and regional myocardial perfusion. *Eur Heart J Cardiovasc Imaging*. 2020;21:777–786.

12. Kato S, Saito N, Nakachi T, et al. Stress perfusion coronary flow reserve versus cardiac magnetic resonance for known or suspected CAD. *J Am Coll Cardiol*. 2017;70:869–879.

13. Indorkar R, Kwong RY, Romano S, et al. Global coronary flow reserve measured during stress cardiac magnetic resonance imaging Is an independent predictor of adverse cardiovascular events. *J Am Coll Cardiol Img*. 2019;12:1686–1695.

14. Zorach B, Shaw PW, Bourque J, et al. Quantitative cardiovascular magnetic resonance perfusion imaging identifies reduced flow reserve in microvascular coronary artery disease. *J Cardiovasc Magn Reson*. 2018;20:14.

15. Pepine CJ, Ferdinand KC, Shaw LJ, et al. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. *J Am Coll Cardiol*. 2015;66:1918–1933.

16. Ford TJ, Corcoran D, Sidik N, et al. Coronary microvascular dysfunction: assessment of both structure and function. *J Am Coll Cardiol*. 2018;72:584–586.

17. Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. *Circulation*. 2017;136:2325–2336.

18. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI cardiovascular council and the ASNC. *J Nucl Cardiol*. 2018;25:269–297.

19. Kotecha T, Martinez-Naharro A, Boldrini M, et al. Automated pixel-wise quantitative myocardial perfusion mapping by CMR to detect obstructive coronary artery disease and coronary microvascular dysfunction: validation against invasive coronary physiology. *J Am Coll Cardiol Img*. 2019;12:1958–1969.

20. Engblom H, Xue H, Akil S, et al. Fully quantitative cardiovascular magnetic resonance myocardial perfusion ready for clinical use: a comparison between cardiovascular magnetic resonance imaging and positron emission tomography. *J Cardiovasc Magn Reson*. 2017;19:78.

21. Sicari R, Rigo F, Cortigiani L, et al. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. *Am J Cardiol*. 2009;103:626–631.

5.3. Cost-Value Considerations in Diagnostic Testing

5.3.1. CCTA and CAC Scanning Cost-Value Considerations

1. Mark DB, Federspiel JJ, Cowper PA, et al. Economic outcomes with anatomical versus functional diagnostic testing for coronary artery disease. *Ann Intern Med*. 2016;165:94–102.

2. Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. *Eur Heart J*. 2016;37:1232–1243.

3. Chang HJ, Lin FY, Gebow D, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected CAD: a randomized, controlled, open-label trial. *J Am Coll Cardiol Img*. 2019;12:1303–1312.

4. Lubbers M, Coenen A, Kofflard M, et al. Comprehensive cardiac CT with myocardial perfusion imaging versus functional testing in suspected coronary artery disease: the multicenter randomized CRESCENT-II trial. *J Am Coll Cardiol Img*. 2018;11:1625–1636.

5.3.2. Exercise Electrocardiographic Cost-Value Considerations

1. Gurunathan S, Zacharias K, Akhtar M, et al. Cost-effectiveness of a management strategy based on exercise echocardiography versus exercise electrocardiography in patients presenting with suspected angina during long term follow up: a randomized study. *Int J Cardiol*. 2018;259:1–7.

2. Genders TS, Petersen SE, Pugliese F, et al. The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis. *Ann Intern Med*. 2015;162:474–484.

3. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. *JAMA*. 2011;306:2128–2136.

4. Mark DB, Federspiel JJ, Cowper PA, et al. Economic outcomes with anatomical versus functional diagnostic testing for coronary artery disease. *Ann Intern Med*. 2016;165:94–102.

5. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.

6. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation*. 2011;124:1239–1249.

5.3.3. Stress Echocardiographic Cost-Value Considerations

1. Marwick TH, Shaw L, Case C, et al. Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. *Eur Heart J*. 2003;24:1153–1163.

2. Kuntz KM, Fleischmann KE, Hunink MG, et al. Cost-effectiveness of diagnostic strategies for patients with chest pain. *Ann Intern Med*. 1999;130:709–718.

3. Genders TS, Petersen SE, Pugliese F, et al. The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis. *Ann Intern Med*. 2015;162:474–484.

4. Kim C, Kwok YS, Saha S, et al. Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis. *Am Heart J*. 1999;137:1019–1027.

5. van Waardhuizen CN, Khanji MY, Genders TSS, et al. Comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic review. *Eur Heart J Qual Care Clin Outcomes*. 2016;2:245–260.

6. Gurunathan S, Zacharias K, Akhtar M, et al. Cost-effectiveness of a management strategy based on exercise echocardiography versus exercise electrocardiography in patients presenting with suspected angina during long term follow up: a randomized study. *Int J Cardiol*. 2018;259:1–7.

7. Mark DB, Federspiel JJ, Cowper PA, et al. Economic outcomes with anatomical versus functional diagnostic testing for coronary artery disease. *Ann Intern Med*. 2016;165:94–102.

5.3.4. Stress Nuclear MPI Cost-Value Considerations

1. van Waardhuizen CN, Khanji MY, Genders TSS, et al. Comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic review. *Eur Heart J Qual Care Clin Outcomes*. 2016;2:245–260.

2. Hlatky MA, Shilane D, Hachamovitch R, et al. Economic outcomes in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease registry: the SPARC Study. *J Am Coll Cardiol*. 2014;63:1002–1008.

3. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.

4. Sabharwal NK, Stoykova B, Taneja AK, et al. A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD: cost analysis. *J Nucl Cardiol*. 2007;14:174–186.

5. Thom H, West NE, Hughes V, et al. Cost-effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gate-keeper test, compared with upfront invasive coronary angiography in the investigation and management of patients with stable chest pain: mid-term outcomes from the CECaT randomised controlled trial. *BMJ Open*. 2014;4:e003419.

5.3.5. Stress CMR Cost-Value Considerations

1. Pletscher M, Walker S, Moschetti K, et al. Cost-effectiveness of functional cardiac imaging in the diagnostic work-up of coronary heart disease. *Eur Heart J Qual Care Clin Outcomes*. 2016;2:201–207.

2. Walker S, Girardin F, McKenna C, et al. Cost-effectiveness of cardiovascular magnetic resonance in the

diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study. *Heart*. 2013;99:873–881.

3. Moschetti K, Muzzarelli S, Pinget C, et al. Cost evaluation of cardiovascular magnetic resonance versus coronary angiography for the diagnostic work-up of coronary artery disease: application of the European Cardiovascular Magnetic Resonance registry data to the German, United Kingdom, Swiss, and United States health care systems. *J Cardiovasc Magn Reson*. 2012;14:35.

4. Kwong RY, Ge Y, Steel K, et al. Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. *J Am Coll Cardiol*. 2019;74:1741–1755.

5. Ge Y, Pandya A, Steel K, et al. Cost-effectiveness analysis of stress cardiovascular magnetic resonance imaging for stable chest pain syndromes. *J Am Coll Cardiol Img*. 2020;13:1505–1517.

6. EVIDENCE GAPS AND FUTURE RESEARCH

1. Wang X, Bhatt DL. COVID-19: an unintended force for medical revolution? *J Invasive Cardiol*. 2020;32:E81–E82.

2. Roux S, Bhatt DL. Self-treatment for acute coronary syndrome: why not? *Eur Heart J*. 2020;41:2144–2145.

3. Tamis-Holland JE, Jneid H, Reynolds HR, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e891–e908.

4. Gulati M, Shaw LJ. Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. *Clin Cardiol*. 2012;35:141–148.

5. Herscovici R, Sedlak T, Wei J, et al. Ischemia and no obstructive coronary artery disease (INOCA): what is the risk? *J Am Heart Assoc*. 2018;7:e008868.

6. Mukherjee D. Myocardial infarction with non-obstructive coronary arteries: a call for individualized treatment. *J Am Heart Assoc*. 2019;8:e013361.

7. Kreatsoulas C, Dinakar D, Mehta S, et al. *Machine learning to evaluate gender differences in typical and atypical angina among patients with obstructive coronary artery disease. ESC Congress 2019. Paris, France*. 2019.

8. Bhatt DL, Taqueti VR. Out with the old rule-out: raising the bar for acute chest pain evaluation with randomized trials of cardiac imaging. *J Am Coll Cardiol Img*. 2017;10:350–353.

9. Bhatt DL. Advancing the care of cardiac patients using registry data: going where randomized clinical trials dare not. *JAMA*. 2010;303:2188–2189.

10. Ellrodt AG, Fonarow GC, Schwamm LH, et al. Synthesizing lessons learned from get with the guidelines: the value of disease-based registries in improving quality and outcomes. *Circulation*. 2013;128:2447–2460.

11. Bhatt DL, Drozda JP Jr, Shahian DM, et al. ACC/AHA/STS statement on the future of registries and the performance measurement enterprise: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and The Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2015;66:2230–2245.

12. Winchester DE, Osborne A, Peacock WF, et al. Closing gaps in essential chest pain care through accreditation. *J Am Coll Cardiol*. 2020;75:2478–2482.

KEY WORDS ACC/AHA Clinical Practice Guidelines, chest pain, angina, coronary artery disease, acute coronary syndrome, myocardial ischemia, myocardial infarction, myocardial injury, noncardiac, accelerated diagnostic pathway, clinical decision pathway, sex differences, troponins, chest pain syndromes, biomarkers, shared decision-making, noncardiac chest pain, cardiac imaging

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR GUIDELINE FOR THE EVALUATION AND DIAGNOSIS OF CHEST PAIN

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Martha Gulati *(Chair)*	The University of Arizona Phoenix—Professor of Medicine & Chief of Cardiology	None	None	None	None	None	None
Phillip D. Levy *(Vice Chair)*	Wayne State University—Professor and Associate Chair for Research, Department of Emergency Medicine; Assistant Vice President for Translational Science and Clinical Research Innovation	■ Apex Innovation* ■ AstraZeneca ■ AstraZeneca, Hospital Quality Foundation ■ Beckman Coulter ■ Boehringer Ingelheim ■ Bristol-Myers Squibb ■ Cardiorentis ■ Novartis* ■ Ortho Diagnostics* ■ Pfizer ■ Roche* ■ Sciex ■ Shire* ■ Siemens* ■ The Medicines Company ■ Trevena ■ ZS Pharma	None	■ Carbon Life-form Innovations† ■ Mespere†	■ Amgen* ■ Bristol-Myers Squibb* ■ Cardiorentis* ■ Edwards Lifesciences* ■ Gilead Sciences* ■ Novartis* ■ Pfizer* ■ Roche* ■ Shire* ■ Trevena	■ Amgen* ■ Edwards* ■ E.R. Squibb & Sons, L.L.C. ■ Janssen Pharmaceuticals ■ Roche	None
Debabrata Mukherjee *(Vice Chair)*	Texas Tech University Health Sciences Center El Paso—Chairman, Department of Medicine	None	None	None	None	None	None
Ezra Amsterdam	UC Davis Medical Center—Professor, Department of Internal Medicine	None	None	None	None	None	None
Deepak L. Bhatt	Brigham and Women's Hospital Heart & Vascular Center—Executive Director of Interventional Cardiovascular Programs; Harvard Medical School—Professor of Medicine	■ Daiichi Sankyo ■ Pfizer*	None	None	■ Abbott* ■ Amarin* ■ Amgen* ■ AstraZeneca* ■ Bayer* ■ Boehringer Ingelheim* ■ Bristol-Myers Squibb* ■ Cardax* ■ Chiesi* ■ Eisai* ■ Eli Lilly* ■ Ethicon* ■ FlowCo† ■ Forest Laboratories* ■ Idorsia* ■ Ironwood* ■ Ischemix* ■ Medtronic* ■ Merck* ■ Pfizer*	■ Amarin Pharma Inc.* ■ AstraZeneca* ■ Biotronik‡ ■ Boehringer Ingelheim* ■ Boston Scientific‡ ■ Cardax† ■ Merck† ■ Novartis ■ PhaseBio† ■ PLx Pharma† ■ Regado Biosciences† ■ Sanofi-aventis* ■ St. Jude Medical‡ ■ Svelte‡	None

Continued on the next page

APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
					■ PhaseBio* ■ PLx Pharma* ■ Regeneron* ■ Roche* ■ Sanofi-aventis* ■ Synaptic* ■ Takeda† ■ The Medicines Company*		
Kim K. Birtcher	University of Houston College of Pharmacy—Clinical Professor	None	None	None	None	None	None
Ron Blankstein	Harvard Medical School—Associate Professor of Medicine and Radiology, Co-Director, Cardiovascular Imaging Training Program; Brigham and Women's Hospital—Associate Physician, Preventive Cardiology; Director, Cardiac Computed Tomography	■ Amgen ■ Astellas Inc ■ EKOS Corp.	None	None	■ Amgen† ■ Astellas Pharma† ■ Gilead Sciences† ■ Sanofi-aventis†	■ Sanofi US Services*	None
Jack Boyd	Stanford University—Clinical Assistant Professor, Department of Cardiothoracic Surgery	■ Esculon/Centese ■ Sorin	None	None	None	None	None
Renee P. Bullock-Palmer	Deborah Heart & Lung Center—Director, Women's Heart Center; Director, Non-Invasive Cardiac Imaging	None	None	None	None	None	None
Theresa Conejo	Nazareth Hospital—Heart Failure Coordinator	None	None	None	None	None	None
Deborah B. Diercks	UT Southwestern—Professor and Chair, Department of Emergency Medicine	■ ETHealthcare ■ Janssen Pharmaceuticals ■ Novartis*	None	None	■ Abbott* ■ Bristol-Myers Squibb† ■ Ortho Clinical† ■ Roche* ■ Siemens	■ E.R. Squibb & Sons, L.L.C.* ■ Konica Minolta Healthcare Americans, Inc.	None
Federico Gentile	Centro Cardiologico Gentile, Naples, Italy—Director	None	None	None	None	None	None
John P. Greenwood	Leeds Institute of Cardiovascular and Metabolic Medicine—Mautner Chair of Cardiology, Division of Biomedical Imaging	None	None	None	None	None	None
Erik P. Hess	University of Alabama at Birmingham—Professor of Emergency Medicine and Vice Chair for Research, Department of Emergency Medicine	■ Gilead Sciences*	None	None	■ Gilead Sciences*	None	None
Steven M. Hollenberg	Cooper Medical School of Rowan University—Professor of Medicine; Cooper University Hospital—Director, Coronary Care Unit	None	None	None	None	None	None
Wael A. Jaber	Cleveland Clinic Lerner College of Medicine—Professor of Medicine, Department of Cardiovascular Medicine and Fuad Jubran Endowed Chair in Cardiovascular Medicine, Heart and Vascular Institute	None	None	None	None	None	None

Continued on the next page

Continued on the next page

APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Hani Jneid	Baylor College of Medicine—Associate Professor of Medicine; The Michael DeBakey VA Medical Center—Director of Interventional Cardiology Research	None	None	None	None	None	None
José A. Joglar	University of Texas Southwestern Medical Center—Professor of Internal Medicine, Fellowship Program Director, Clinical Cardiac Electrophysiology, Elizabeth Thaxton Page and Ellis Batten Page, Professorship in Clinical Cardiac Electrophysiology Research	None	None	None	None	None	None
David A. Morrow	Brigham and Women's Hospital—Director, Levine Cardiac Intensive Care Unit; Harvard Medical School—Professor of Medicine, Cardiovascular Division	■ Abbott ■ Aralez Pharmaceuticals* ■ AstraZeneca* ■ Bayer* ■ Daiichi Sankyo ■ diaDexus ■ Gilead Sciences ■ GlaxoSmithKline* ■ Merck* ■ Novartis* ■ Pfizer* ■ Roche* ■ Verseon	None	None	■ Abbott* ■ Amgen* ■ AstraZeneca* ■ BRAHMS* ■ Daiichi-Sankyo* ■ Eisai Corporation* ■ GlaxoSmithKline* ■ Johnson & Johnson* ■ Medicines Company* ■ Merck* ■ Novartis* ■ Pfizer* ■ Regeneron* ■ Roche* ■ Singulex* ■ Takeda Pharmaceuticals*	■ Roche*	None
Robert E. O'Connor	University of Virginia—Professor and Chair, Department of Emergency Medicine	None	None	None	None	■ Cardiorentis Ltd.†	None
Michael A. Ross	Emory University School of Medicine—Professor, Department of Emergency Medicine; Emory Healthcare—Chief of Service, Observation Medicine; Emory University Hospital Chest Pain Center— Medical Director	None	None	None	None	None	None
Leslee J. Shaw	Icahn School of Medicine, Mount Sinai—Professor	None	None	None	None	■ Covanos, Inc- Scientific Advisory Board†	None

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

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document;* or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*. Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

*Significant relationship.

†No financial benefit.

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

ACC indicates American College of Cardiology; AHA, American Heart Association; ASE, American Society of Echocardiography; CHEST, American College of Chest Physicians; SAEM, Society for Academic Emergency Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; UC, University of California; UT, University of Texas; and VA, Veterans Affairs.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR GUIDELINE FOR THE EVALUATION AND DIAGNOSIS OF CHEST PAIN

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Sana M. Al-Khatib	Content Reviewer—AHA	Duke University Medical Center	■ Medtronic ■ Milestone Pharmaceuticals	None	None	■ Abbott ■ Medtronic* ■ NHLBI* ■ PCORI* ■ U.S. Food and Drug Administration*	■ Abbott ■ AHA* ■ Bristol-Myers Squibb ■ Medtronic ■ Pfizer	None
Mouaz Al-Mallah	Official Reviewer—American Society of Nuclear Cardiology	Houston Methodist	■ Pfizer	None	None	■ Siemens†	■ Amgen ■ GE Healthcare‡* ■ Pfizer ■ Siemens	None
Jayashri R. Aragam	Official Reviewer—American Society of Echocardiography	West Roxbury VA Hospital, Harvard Medical School	None	None	None	None	None	None
Ragavendra Baliga	Content Reviewer—ACC/AHA	Ohio State University Hospital	None	None	None	None	■ Baliga's *Textbook of Internal Medicine* with 1480 MCQs, Editor-in-Chief† ■ Elsevier, Deputy Editor† ■ Lippincott Williams & Wilkins ■ McGraw-Hill Cardiology Textbook, Editor-in-Chief ■ Oxford University Press & Przewodnik praktyczny jak stosowac statyny, Termedia Wydawnictwa Medyczne, Editor ■ Oxford University Press, Series Editor ■ Springer, Co Editor-in-Chief ■ W.B. Saunders/Elsevier, *250 Cases in Clinical Medicine, Third Edition*	None
Joshua A. Beckman	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Vanderbilt University Medical Center	■ Amgen ■ GlaxoSmithKline* ■ JanOne ■ Janssen ■ Pharmaceuticals* ■ Sanofi-aventis*	None	■ EMX† ■ JanaCare†	■ Bayer (DSMB) ■ Novartis (DSMB)	■ Amgen ■ GlaxoSmithKline ■ Vascular Interventional Advances*	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Daniel S. Berman	Official Reviewer—AHA	Cedars-Sinai Medical Center	■ Bayer* ■ Cedars-Sinai Medical Center* ■ General Electric	None	None	None	■ Amgen* ■ Bayer ■ Cedars-Sinai Medical Center ■ GE Healthcare*	None
Kelley Branch	Content Reviewer—Society of Cardiovascular Computed Tomography	University of Washington	■ Bayer* ■ Janssen Pharmaceuticals*	None	None	■ Bayer* ■ Locke Foundation Grant* ■ Novartis‡	■ AstraZeneca ■ Bayer* ■ Janssen Pharmaceuticals ■ Novartis ■ Sanofi-aventis	None
Andrew Choi	Official Reviewer—Society of Cardiovascular Computed Tomography	The George Washington University School of Medicine	None	None	■ Cleerly, Inc.*	None	None	None
Melissa A. Daubert	Official Reviewer—AHA	Duke University Medical Center	None	None	None	None	■ 4D Molecular Contrafect ■ Heartflow ■ NIH ■ Roche ■ Verliy	None
Lisa de las Fuentes	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Washington University	■ Acceleron ■ Altavant ■ Arena ■ Bayer ■ Express Scripts ■ Gilead Sciences ■ Johnson & Johnson ■ Mentor Planning and Consulting ■ Phase Bio ■ V-wave ■ WebMD*	■ Bayer* ■ Simply Speaking*	None	■ Acceleron* ■ Altavant* ■ Bayer ■ Complexa* ■ Johnson & Johnson* ■ Liquidia* ■ Medtronic* ■ NIH* ■ Reata ■ Trio Analytics* ■ United Therapeutics* ■ University of Kentucky (DSMB) ■ University of Toronto (DSMB)†	■ ACC† ■ AHA† ■ *Circulation* Journals ■ Pulmonary Hypertension Association*	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Anita Deswal	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	UT MD Anderson Cancer Center	None	None	None	None	■ ACC ■ AHA ■ HFSA†	None
Dave L. Dixon	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Virginia Commonwealth University School of Pharmacy	American Pharmacists Association	None	None	■ Centers for Disease Control and Prevention* ■ Community Pharmacy Foundation*	■ Accreditation Council for Clinical Lipidology† ■ American College of Pharmacy Cardiology Practice Research Network† ■ American Pharmacists Association ■ National Lipid Association†	None
John U. Doherty	Official Reviewer—ACC	Jefferson University Hospitals	None	None	None	None	None	None
Maros Ferencik	Content Reviewer—Society of Cardiovascular Computed Tomography	Oregon Health & Science University	■ Biograph*	None	■ AHA, Fellow to Faculty Award*	■ NIH*	■ HeartFlow‡	None
Lee A. Fleisher	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Centers for Medicare & Medicaid Services (CMS)	None	None	None	■ NIH	None	None
Mario Garcia	Content Reviewer—AHA/ACC	Montefiore Medical Center	None	None	None	None	■ Abiomed ■ Medtronic Vascular, Inc. ■ Novartis ■ Philips	None
Seth Gemme	Official Reviewer—American College of Emergency Physicians	Baystate Medical Center	■ Roche Diagnostics	None	None	None	None	None
Zachary D. Goldberger	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	University of Wisconsin School of Medicine and Public Health	None	None	None	None	None	None
Bulent Gorenek	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Eskisehir Osmangazi University	■ AstraZeneca ■ Sandoz	None	None	None	None	None
Norrisa Haynes	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	University of Pennsylvania	None	None	None	None	None	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Adrian F. Hernandez	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Duke University	■ Amgen ■ AstraZeneca* ■ Bayer ■ Biofourmis ■ Boehringer Ingelheim ■ Boston Scientific* ■ Cytokinetics ■ Daiichi Sankyo ■ Eli Lilly ■ Merck* ■ Myokardia ■ Novartis* ■ Pfizer ■ Relypsa ■ Sanofi-aventis* ■ Xogenex	None	None	■ American Regent ■ AstraZeneca* ■ Eidos (DSMB) ■ Genentech ■ GlaxoSmithKline* ■ Janssen Pharmaceuticals ■ Merck ■ NIH† ■ Novartis* ■ PCORI† ■ Verily*	■ AHA† ■ AstraZeneca ■ Boston Scientific ■ CSL Behring ■ Janssen Pharmaceuticals* ■ Merck ■ Novartis ■ Genentech* ■ Relypsa ■ Sanofi-aventis	■ Defendant, Patent Dispute, 2019
Mark A. Hlatky	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Stanford University School of Medicine	■ ACC, Global Advisory Committee ■ Blue Cross Blue Shield Center for Effectiveness Evaluation* ■ The Medicines Company	None	None	■ HeartFlow* ■ NHLBI (DSMB) ■ St. Jude	■ George Institute†	None
Stephen Hoole	Content Reviewer—ACC	Royal Papworth Hospital, UK	■ Abbott* ■ Bayer ■ Boston Scientific	■ AstraZeneca ■ Bayer ■ Novo Nordisk	None	■ Abbott* ■ AstraZeneca*	None	None
W. Schuyler Jones	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Duke University	■ Amgen ■ Bayer* ■ Janssen Pharmaceuticals* ■ Pfizer	None	None	■ Bristol-Myers Squibb ■ Janssen Pharmaceuticals ■ Patient-Centered Outcomes Research Institute	■ Abbott* ■ Amgen ■ AstraZeneca ■ Boehringer Ingelheim ■ Cardiovascular Systems Inc.* ■ Janssen Pharmaceuticals ■ ZOLL Medical	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Michael Kontos	Content Reviewer—ACC	Virginia Commonwealth University Health	None	None	None	None	■ ACC* ■ NIH‡ ■ Society for Academic Emergency Medicine† ■ VCSQUI† ■ VHAC†	None
Raymond Kwong	Official Reviewer—Society for Cardiovascular Magnetic Resonance	Brigham and Women's Hospital	None	None	None	■ Alnylam, Inc* ■ MyoKardia* ■ NIH	■ Bayer ■ Siemens ■ Society for Cardiovascular Magnetic Resonance†	None
Glenn N. Levine	Content Reviewer—Former Chair of the ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine	None	None	None	None	None	■ Defendant, In-hospital death, 2020 ■ Defendant, In-hospital death, 2019*
Jonathan Lindner	Official Reviewer—American Society of Echocardiography	Oregon Health & Science University	None	None	None	■ Bracco† ■ GE Healthcare ■ GE Lifesciences† ■ Pfizer†	■ Lantheus Medical Imaging, Inc.	None
G.B. John Mancini	Content Reviewer—ACC	Vancouver Hospital Research Pavilion, Professor of Medicine	■ Amgen ■ AstraZeneca ■ Bayer ■ Boehringer Ingelheim ■ Eli Lilly ■ Esperion ■ HLS Therapeutics ■ Merck ■ Pfizer ■ Regeneron ■ Sanofi-aventis	■ Amgen ■ HLS Therapeutics ■ Sanofi-aventis	None	■ Novo Nordisk ■ NovartisPle	None	None
Daniel B. Mark	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Duke University	None	None	None	None	■ HeartFlow* ■ Merck*	None
Jim McCord	Content Reviewer—ACC/AHA	Henry Ford Health System	■ Beckman ■ Roche* ■ Siemens*	None	None	■ Abbott* ■ Beckman Diagnostics* ■ Roche* ■ Siemens	■ ACC Accreditation Services, Board Member†	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
C. Noel Bairey Merz	Content Reviewer—ACC/AHA	Cedars-Sinai Heart Institute	■ Med Intelligence	None	None	■ California Institute for Precision Medicine* ■ DOD Warrior* ■ NIH-NIA* ■ Sanofi-aventis* ■ WISE pre-HFpEF*	■ Bayer, Advisory Board ■ iRhythm*	None
Nicholas L. Mills	Content Reviewer—ACC	BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, Scotland	■ Abbott ■ Laboratories ■ LumiraDx ■ Roche Diagnostics ■ Siemens Healthineers	None	None	None	None	None
James Min	Content Reviewer—ACC/AHA	■ Cleerly, Inc.	None	None	■ Cleerly, Inc.	■ NIH	■ Ablative Solutions ■ Arineta ■ Memphis Meats	None
L. Kristin Newby	Content Reviewer—ACC	Duke University	■ Beckman-Coulter ■ BioKier ■ Bristol-Myers Squibb ■ CSL ■ Medtronic ■ NHLBI ■ Quidel ■ Roche Diagnostics	None	None	■ Boehringer Ingelheim ■ David H. Murdock Institute for Business and Culture ■ NIH ■ North Carolina DHHS	■ AHA† ■ ACC, Oregon Chapter ■ AstraZeneca† ■ Boehringer Ingelheim ■ David H. Murdock Research Institute† ■ *JACC*, Deputy Editor* ■ Roche Diagnostics	None
Patrick T. O'Gara	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Brigham and Women's Hospital	None	None	None	None	■ Edwards Lifesciences† ■ *JAMA Cardiology** ■ NIH* ■ Medtrace† ■ Medtronic† ■ Medtronic Vascular, Inc.	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kevin O'Neil	Content Reviewer—American College of Chest Physicians	Wilmington Health, PLLC	None	None	None	None	■ American Board of Internal Medicine ■ Astellas Pharma ■ Commission on Accreditation for Respiratory Care† ■ Genentech ■ Genzyme ■ GlaxoSmithKline ■ Insmed ■ Otsuka ■ America Pharmaceuticals ■ Philips ■ Resmed Corp ■ Sunovion Pharmaceuticals	None
W. Frank Peacock	Content Reviewer—AHA	Baylor College of Medicine	■ Abbott ■ AstraZeneca ■ Instrumentation Laboratories ■ Janssen Pharmaceuticals* ■ Medicure ■ Pharma Inc. ■ Quidel ■ Relypsa ■ Siemens	None	■ Comprehensive Research Associates* ■ Emergencies in Medicine†	■ Roche*	■ Abbott ■ Aseptiscope* ■ Astellas Pharma ■ AstraZeneca ■ Beckman Coulter, Inc.* ■ Boehringer Ingelheim* ■ DiaSorin S.P.A.* ■ E.R. Squibb & Sons, L.L.C.* ■ Instrumentation Laboratory Company* ■ Janssen Pharmaceuticals* ■ Medicure Pharma Inc. ■ Quidel ■ Relypsa ■ Roche* ■ Salix Pharmaceutical Division of Bausch Health US, LLC ■ Siemens*	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Carl Pepine	Content Reviewer—ACC/AHA	University of Florida	■ Caladrius ■ Biosciences ■ Elsevier ■ Slack Inc.* ■ Verily ■ XyloCor	None	None	■ Biocardia* ■ Brigham and Women's Hospital* ■ CSL Behring* ■ Cytori Therapeutics*‡ ■ DCRI* ■ GE Healthcare ■ InVentive Health Clinical, LLC‡ ■ Mesoblast* ■ NIH‡ ■ NIH/NHLBI* ■ Pfizer ■ Sanofi-aventis‡ ■ U.S. Department of Defense*	None	None
Andrea L. Price	Content Reviewer—ACC	Indiana University Health	None	None	■ Quality Informatics Synergies, LLC	■ ACC, Accreditation Foundation Board*	None	None
Susan B. Promes	Official Reviewer—American College of Emergency Physicians	Penn State Health Milton S. Hershey Medical Center	None	None	None	None	None	None
Tanveer Rab	Content Reviewer—ACC	Emory University	None	None	None	None	None	None
Harish Ramakrishna	Content Reviewer—ACC	Mayo Clinic	None	None	None	None	None	None
Basmah Safdar	Official Reviewer—Society for Academic Emergency Medicine	Yale School of Medicine	None	None	None	None	■ OrthoClinical* ■ Roche*	None
Michael Salerno	Content Reviewer—Society for Cardiovascular Magnetic Resonance	University of Virginia	None	None	None	■ NIH*	■ Heartflow ■ Siemens	■ Defendant, SPECT Camera Malfunction, 2020
Ada Stefanescu Schmidt	Content Reviewer—ACC	University of Toronto; Harvard University	None	None	None	None	None	None
Prem Soman	Official Reviewer—American Society of Nuclear Cardiology	University of Pittsburgh Medical Center	■ Alnylam Pharma ■ Eidos ■ Pfizer	None	None	None	■ Astellas ■ Pharma* ■ Pfizer	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Jacqueline Tamis-Holland	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Mount Sinai Morningside Hospital	None	None	None	■ Internal-Minneapolis Heart Institute† ■ The NGS Predict Study‡	■ Abbott† ■ AHA† ■ Bronx Lebanon Hospital, Cardiology Fellowship Program Director† ■ Medscape/Heart.org ■ NIH†‡ ■ NYS†	None
James Thomas	Content Reviewer—ACC/AHA	Northwestern Medicine	■ Abbott ■ Caption Health* ■ Edwards Lifesciences* ■ General Electric ■ Shire North American Group Inc.*	None	None	■ Abbott ■ Caption Health ■ General Electric	■ Abbott ■ Caption Health* ■ Edwards Lifesciences* ■ Medtronic Vascular, Inc. ■ Shire North American Group Inc.	None
Todd Villines	Official Reviewer—Society of Cardiovascular Computed Tomography and ACC	University of Virginia Health System	None	None	None	None	None	None
Andrew R. Waxler	Official Reviewer—ACC	Penn State Health	None	■ Amarin* ■ Regeneron* ■ Sanofi-aventis*	None	None	■ Abbott ■ Amarin* ■ Amgen ■ Boehringer Ingelheim ■ DalCor Pharmaceuticals ■ Janssen Pharmaceuticals ■ Novartis ■ Penn State-St. Joseph Medical Center Foundation, Board Member† ■ Penn State—St. Joseph Medical Center Pharmacy and Therapeutics, Committee Member† ■ Portola ■ Regeneron ■ Sanofi-aventis ■ The Medicines Company ■ ZOLL Medical	None

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nanette K. Wenger	Content Reviewer—AHA	Emory University	■ Amarin Pharma, Inc. ■ AstraZeneca ■ Janssen Pharmaceuticals	None	None	■ AstraZeneca† ■ Boehringer Ingelheim ■ U.S. Department of Defense ■ Duke Clinical Research Institute† ■ NHLBI† ■ ZOLL Medical†	None	None
Joseph Woo	Content Reviewer—ACC/AHA Joint Committee on Clinical Practice Guidelines	Stanford University School of Medicine	None	None	None	None	■ NIH*	None
Sammy Zakaria	Official Reviewer—American College of Chest Physicians	Johns Hopkins University School of Medicine	None	None	None	None	None	None
Mark J. Zucker	Official Reviewer—American College of Chest Physicians	Newark Beth Israel Medical Center	None	None	None	None	None	None

This table represents all relationships of reviewers with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. Please refer to https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

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

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; CHEST, American College of Chest Physicians; DCRI, Duke Clinical Research Institute; DHHS, Department of Health and Human Services; DOD, Department of Defense; DSMB, data and safety monitoring board; HFSA, Heart Failure Society of America; *JACC, Journal of the American College of Cardiology*; NHLBI, National Heart, Lung, and Blood Institute; NIA, National Institute on Aging; NIH, National Institutes of Health; NYS, New York state; PCORI, Patient-Centered Outcomes Research Institute; SAEM, Society for Academic Emergency Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; UT, University of Texas; VCSQI, Virginia Cardiac Services Quality Initiative; VA, Veterans Affairs; and VHAC, Virginia Heart Attack Coalition.