Circulation

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

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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.

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CLINICAL STATEMENTS
AND GUIDELINES

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 pre-test 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
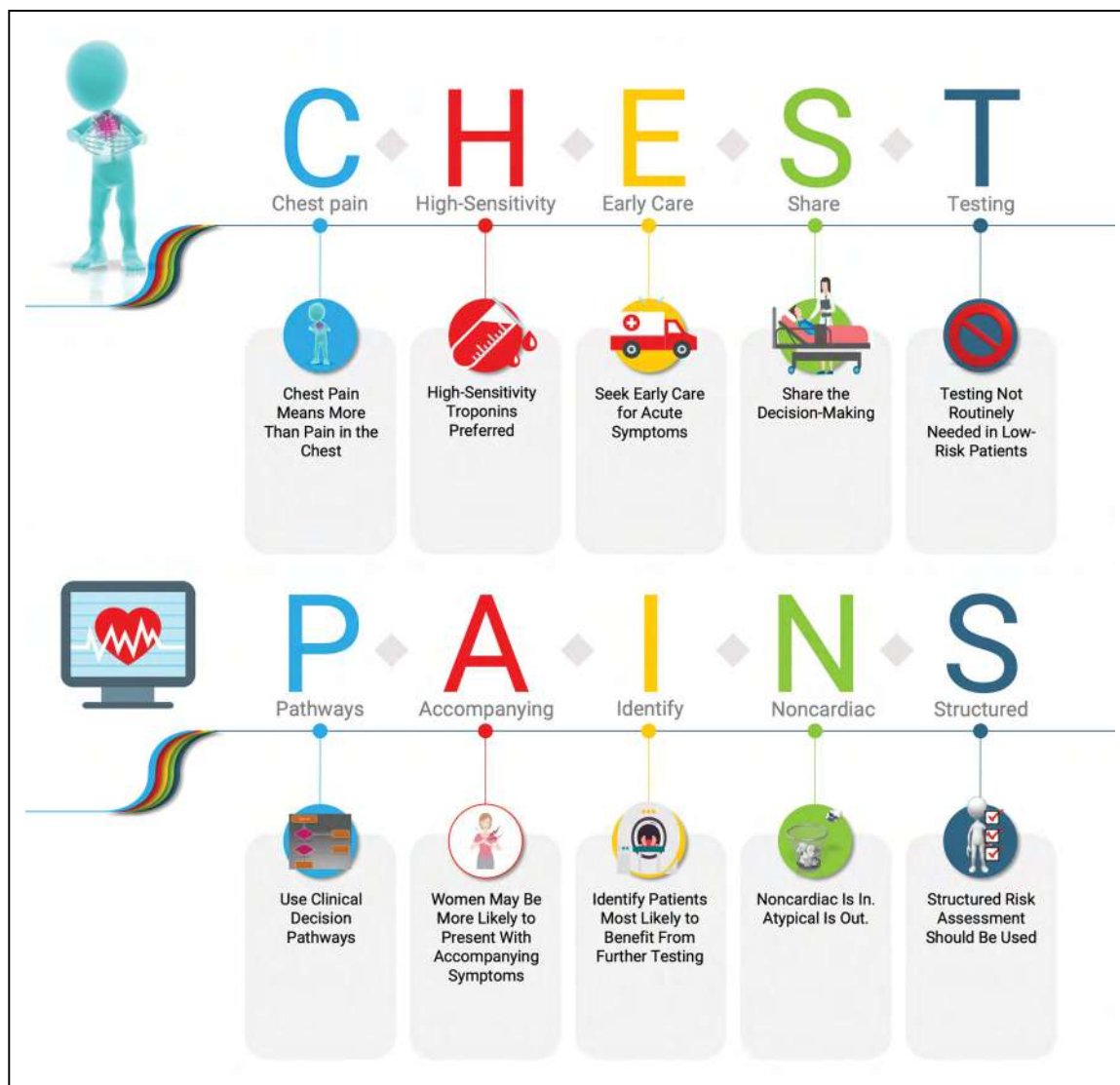
Figure 1. Take-Home Messages for the Evaluation and Diagnosis of Chest Pain

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.

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. Hyper-linked 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 basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1).[4]

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*

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

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

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

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

CLASS 3: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

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 (QUALITY) OF EVIDENCE‡

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

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

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

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

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.

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 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.

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]

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.

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

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.

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

COR	LOE	Recommendations
Recommendations for Defining Chest Pain Referenced studies that support the recommendations are summarized in Online Data Supplements 1 and 2.		
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.
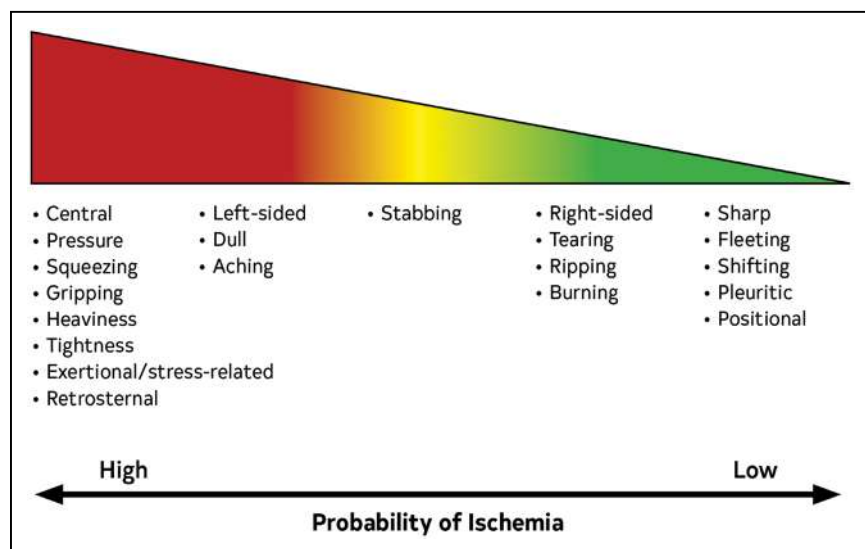
Figure 2. Index of Suspicion That Chest "Pain" Is Ischemic in Origin on the Basis of Commonly Used Descriptors

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 (eg, 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 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
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
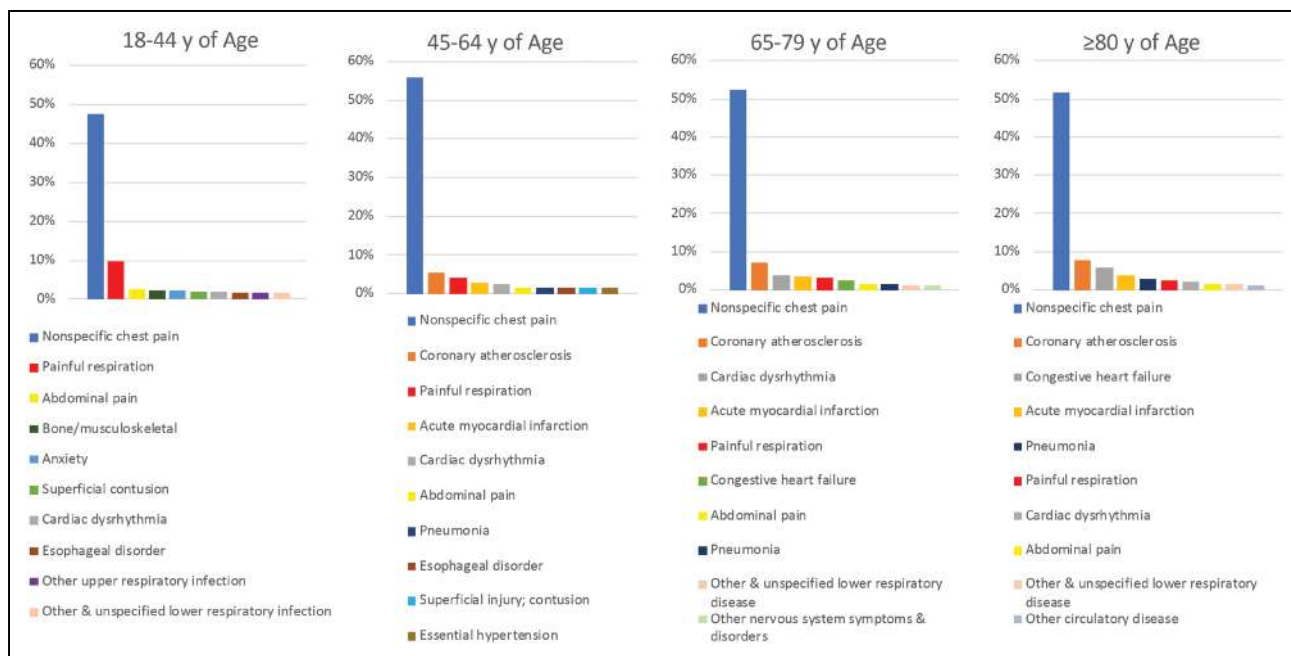
Figure 3. Top 10 Causes of Chest Pain in the ED Based on Age (Weighted Percentage)
Created using data from Hsia RY et al.[3] ED indicates emergency department.

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 (eg, 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 (eg, left arm, neck, jaw) and its associated symptoms (eg, 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 (eg, 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]

Table 3. Chest Pain Characteristics and Corresponding Causes

Nature
Anginal symptoms are perceived as retrosternal chest discomfort (eg, 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 (eg, 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 (eg, 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 (eg, 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.

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 (eg, 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 (eg, 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

COR	LOE	Recommendation
Recommendation for Considerations for Older Patients With Chest Pain		
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

COR	LOE	Recommendations
Recommendations for Considerations for Diverse Patient Populations With Chest Pain		
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 socio-cultural 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 (eg, 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

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 (eg, 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.

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.

2.3. Diagnostic Testing

2.3.1. Setting Considerations

COR	LOE	Recommendations for Setting Considerations Referenced studies that support the recommendations are summarized in Online Data Supplement 5.
		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-threatening 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 (eg, 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

COR	LOE	Recommendations
**Recommendations for Electrocardiogram** **Referenced studies that support the recommendations are** **summarized in Online Data Supplement 6.**
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 (eg, 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 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

COR	LOE	Recommendation
**Recommendation for Chest Radiography**
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.
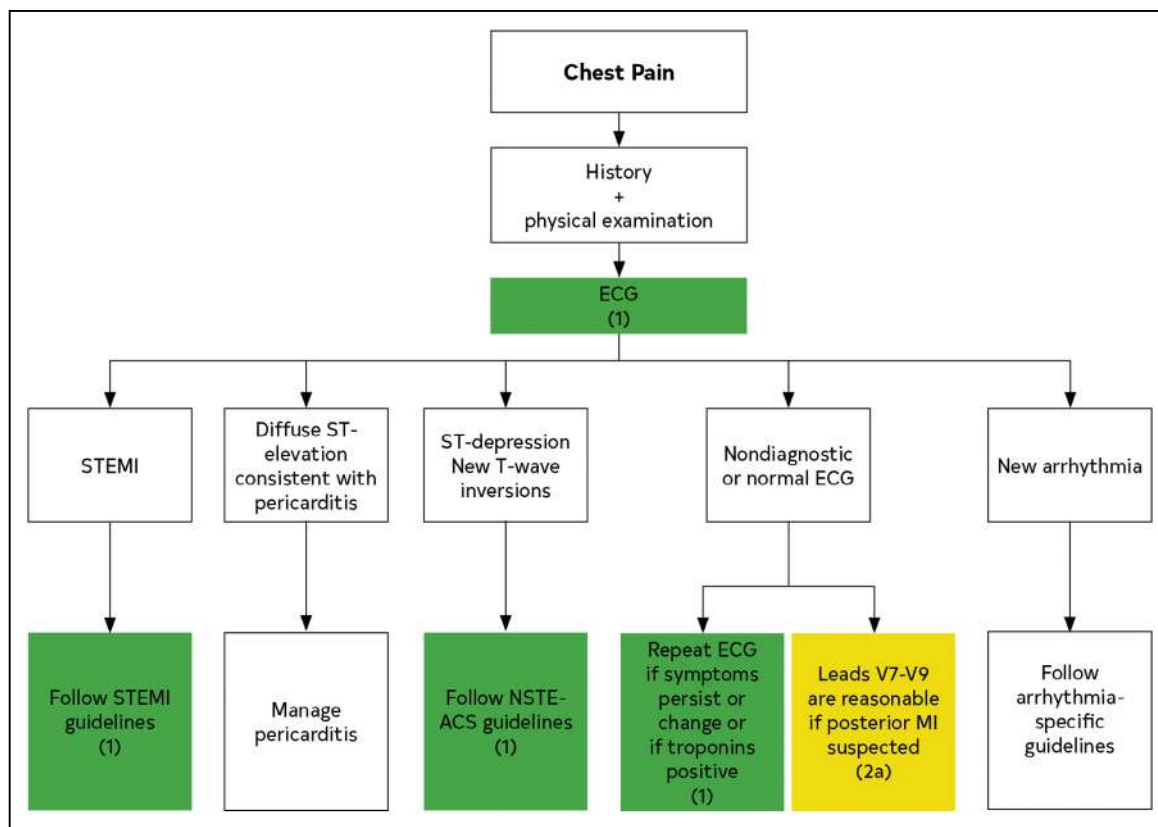
Figure 4. Electrocardiographic-Directed Management of Chest Pain
ECG indicates electrocardiogram; MI, myocardial infarction; NSTE-ACS, non−ST-segment−elevation acute coronary syndrome; and STEMI, ST-segment−elevation myocardial infarction.

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

COR	LOE	Recommendations
Recommendations for Biomarkers Referenced studies that support the recommendations are summarized in Online Data Supplement 7.		
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 (eg, hs-cTnl). 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). 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 (ie, ≥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
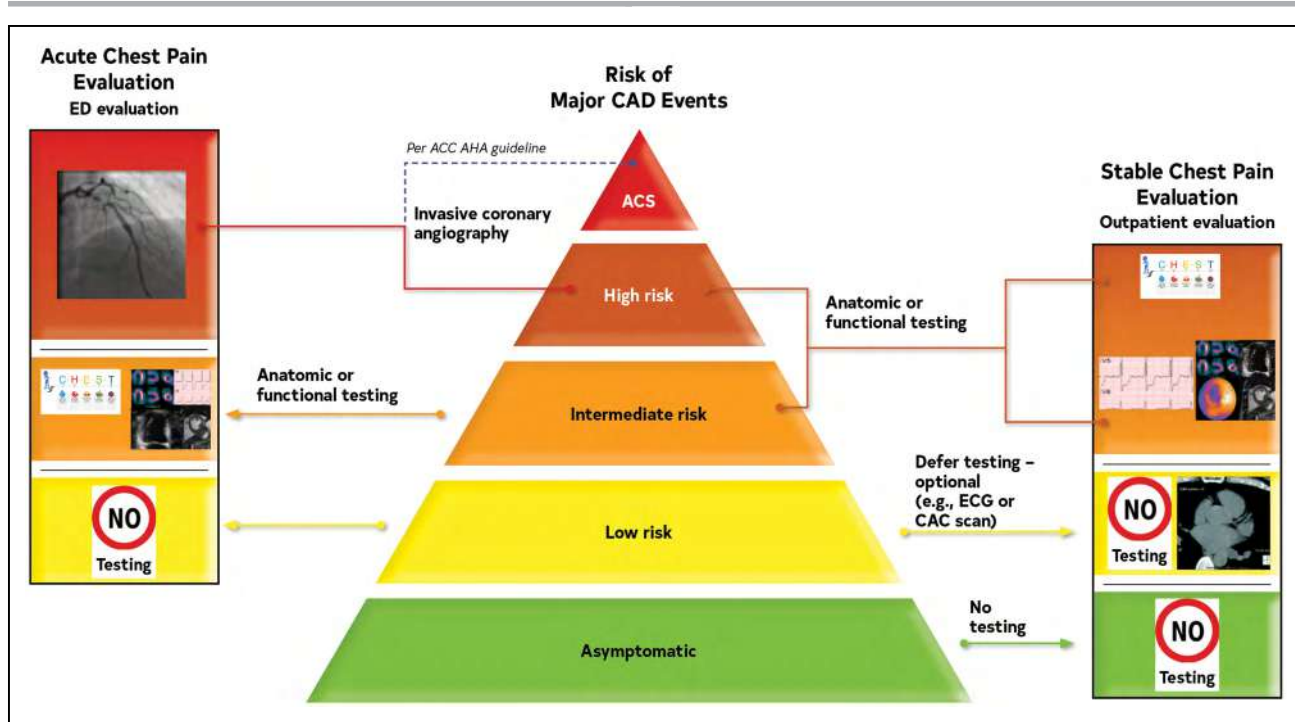
Figure 5. Chest Pain and Cardiac Testing Considerations
The choice of imaging depends on the clinical question of importance, to either a) ascertain the diagnosis of CAD and define coronary anatomy or b) assess ischemia severity among patients with an expected higher likelihood of ischemia with an abnormal 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.

ensure that those with lesser degrees of stenosis who do not require coronary intervention but would benefit from optimized preventive therapy do not get over-looked. However, throughout the document, the term "obstructive," consistent with convention, will be used to indicate CAD with ≥50% stenosis and nonobstruc-tive 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 (eg, 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 pres-ence and severity of a luminal obstruction of an epicar-dial 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 expo-sure 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 vaso-motion. Coronary function testing may assist in manage-

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		✓	✓	✓	✓

Figure 6. Choosing the Right Diagnostic Test
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.

ment 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 dis-comfort), marked ischemia, or a drop in blood pressure occurs.[1] Candidates for exercise ECG are those: a) without disabling comorbidity (eg, 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 (eg, >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.

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.

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 (eg, 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

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)	High-risk unstable angina, complicated ACS or AMI (<2 d)	Limited acoustic windows (eg, in COPD patients)	Reduced GFR (<30 mL/min/1.73 m²)	Allergy to iodinated contrast
Unable to achieve ≥5 METs or unsafe to exercise	Contraindications to vasodilator administration	Inability to reach target heart rate	Contraindications to vasodilator administration	Inability to cooperate with scan acquisition and/or breath-hold instructions
High-risk unstable angina or AMI (<2 d) ie, active ACS	Significant arrhythmias (eg, VT, second- or third-degree atrioventricular block) or sinus bradycardia <45 bpm	Uncontrolled heart failure	Implanted devices not safe for CMR or producing artifact limiting scan quality/interpretation	Clinical instability (eg, acute respiratory distress, severe hypotension, unstable arrhythmia)
Uncontrolled heart failure	Significant hypotension (SBP <90 mm Hg)	High-risk unstable angina, active ACS or AMI (<2 d)	Significant claustrophobia	Renal impairment as defined by local protocols
Significant cardiac arrhythmias (eg, VT, complete atrioventricular block) or high risk for arrhythmias caused by QT prolongation	Known or suspected bronchoconstrictive or bronchospastic disease	Serious ventricular arrhythmia or high risk for arrhythmias attributable to QT prolongation	Caffeine use within past 12 h	Contraindication to beta blockade in the presence of an elevated heart rate and no alternative medications available for achieving target heart rate
Severe symptomatic aortic stenosis	Recent use of dipyridamole or dipyridamole-containing medications	Respiratory failure		Heart rate variability and arrhythmia
Severe systemic arterial hypertension (eg, ≥200/110 mm Hg)	Use of methylxanthines (eg, aminophylline, caffeine) within 12 h	Severe COPD, acute pulmonary emboli, severe pulmonary hypertension		Contraindication to nitroglycerin (if indicated)
Acute illness (eg, acute PE, acute myocarditis/pericarditis, acute aortic dissection)	Known hypersensitivity to adenosine, regadenoson	Contraindications to dobutamine (if pharmacologic stress test needed)		
	Severe systemic arterial hypertension (eg, ≥200/110 mm Hg)	Atrioventricular block, uncontrolled atrial fibrillation		
		Critical aortic stenosis†		
		Acute illness (eg, 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 (eg, ≥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

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. 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.

(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.
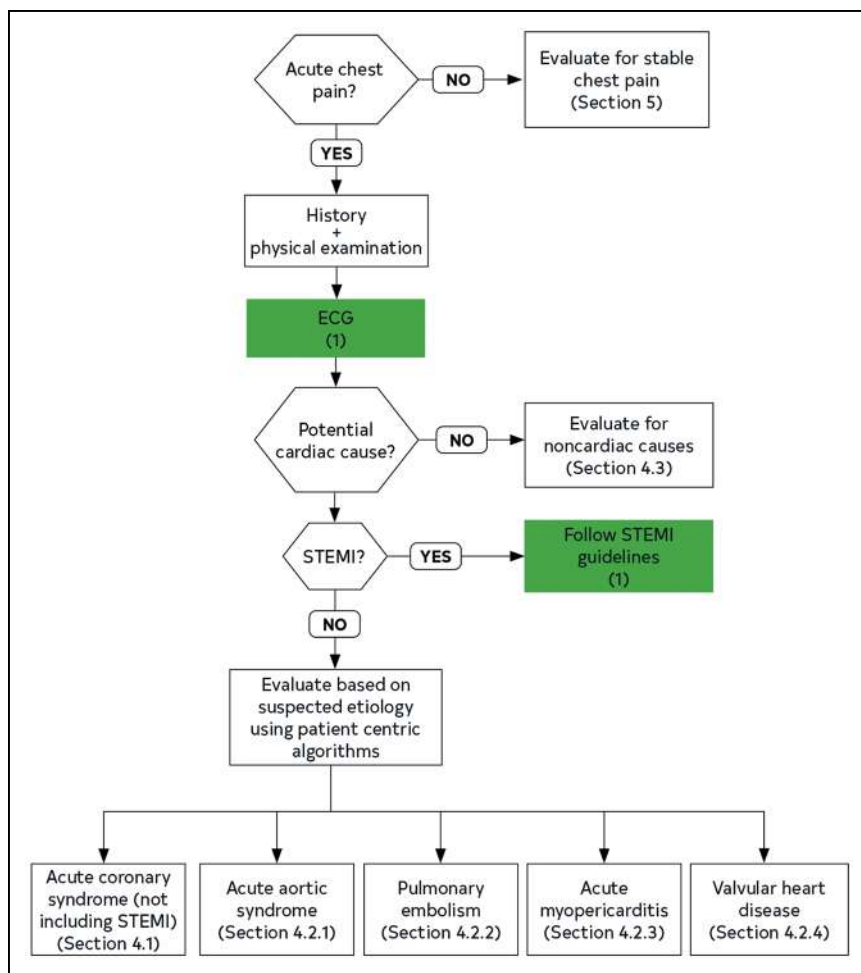
Figure 7. Patient-Centric Algorithms for Acute Chest Pain
ECG indicates electrocardiogram; and STEMI, ST-segment–elevation myocardial infarction.

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

COR	LOE	Recommendations
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.**		
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]

COR	LOE	Recommendations
Recommendations for Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI) (Continued)		
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
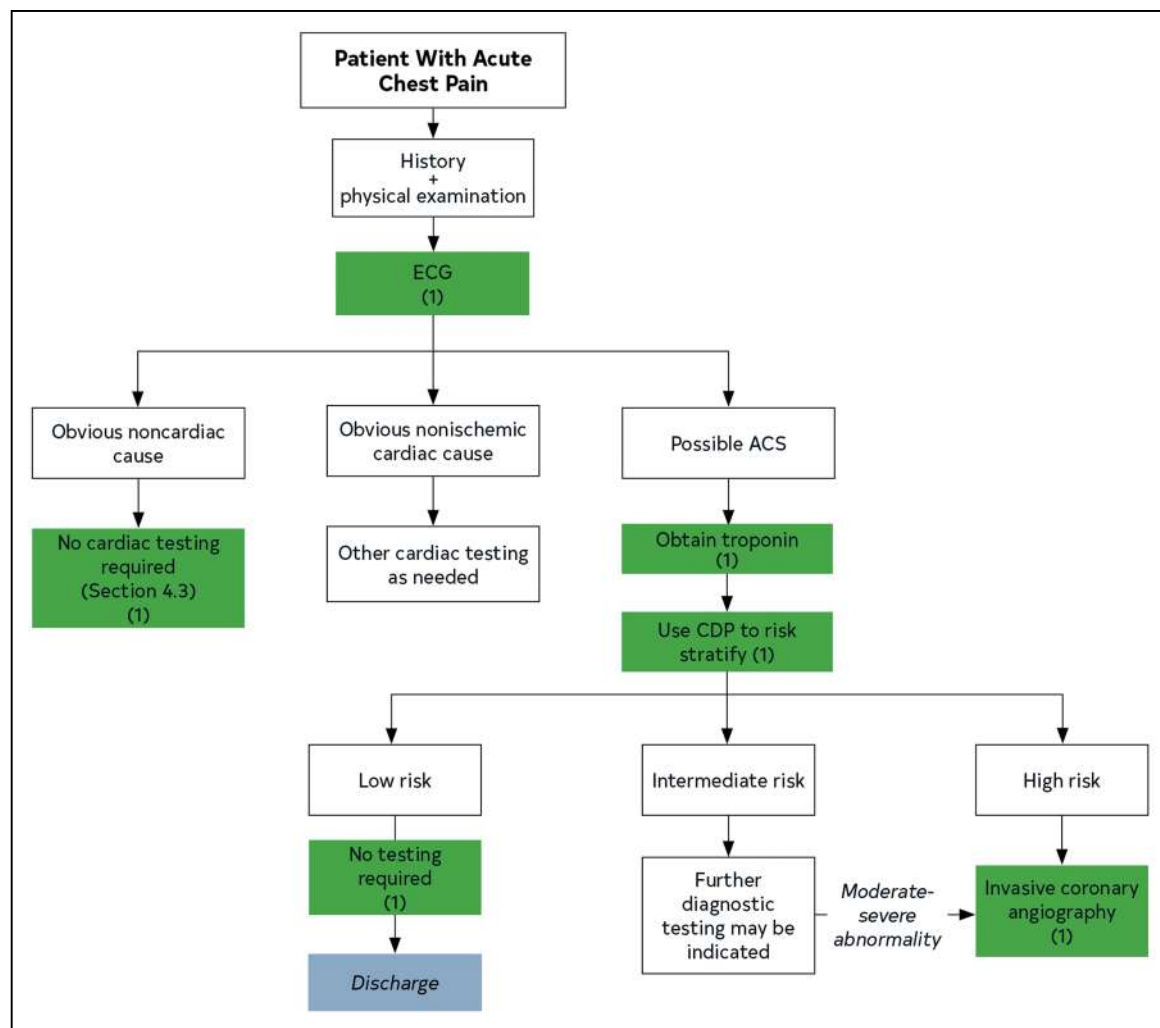
Figure 8. General Approach to Risk Stratification of Patients With Suspected ACS
ACS indicates acute coronary syndrome; CDP, clinical decision pathway; and ECG, electrocardiogram.

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 over-testing. 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

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
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	T0 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	T0 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	--	--

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.

*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]

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.

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.

all generally involve single or serial cTn measurement. Because there are several different manufacturers, the 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 (ie, 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 (ie, beyond 3 hours for high-sensitivity and beyond 6 hours for conventional assays).[23,40,41]

4.1.1. Low-Risk Patients With Acute Chest Pain

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]

Synopsis

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 >9600 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 30769 patients presenting before and 23699 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

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

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

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 ($2137 for CCTA versus $3458 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]
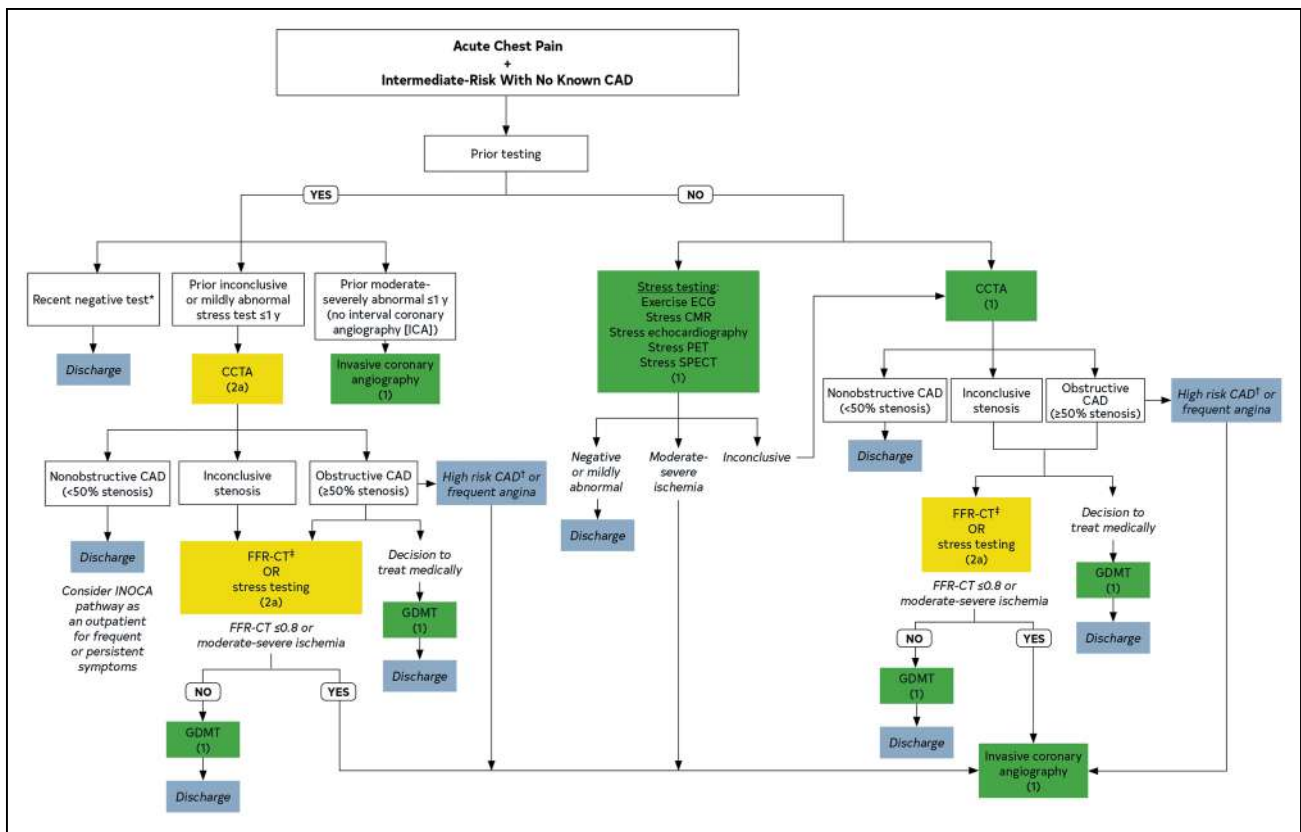
Figure 9. Evaluation Algorithm for Patients With Suspected ACS at Intermediate Risk With No Known CAD
Test choice should be guided by local availability and expertise.
*Recent negative test: normal CCTA ≤2 years (no plaque/no stenosis) OR negative stress test ≤1 year, given adequate stress.
†High-risk 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.

COR	LOE	Recommendations
Recommendations for Intermediate-Risk Patients With Acute Chest Pain and Known CAD (Continued)		
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 (ie, 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]
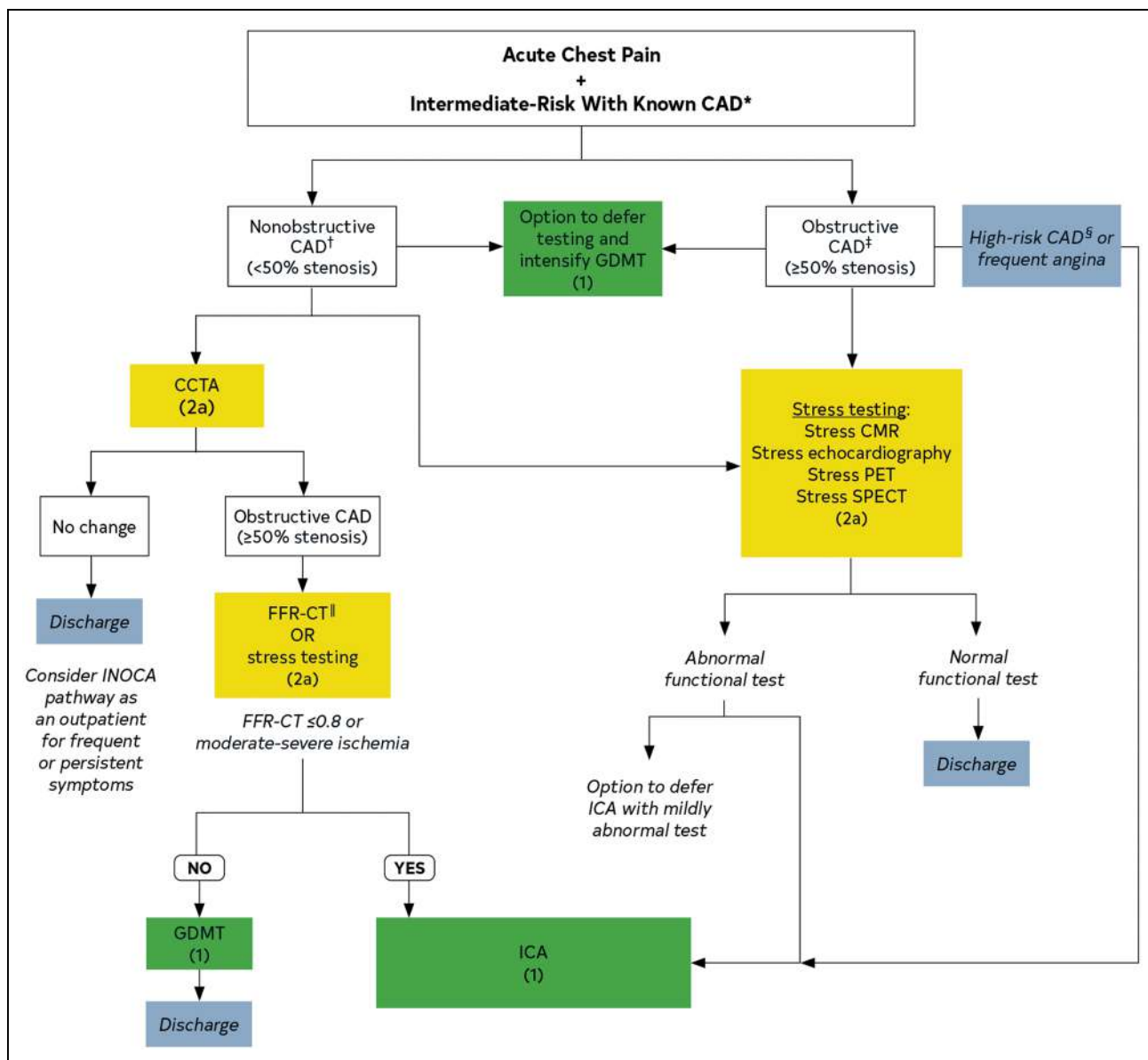
Figure 10. Evaluation Algorithm for Patients With Suspected ACS at Intermediate Risk With Known CAD
Test choice should be guided by local availability and expertise.
*Known CAD is prior MI, revascularization, known obstructive or nonobstructive CAD on invasive or CCTA.
†If extensive plaque is present 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.

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 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

COR	LOE	Recommendations
Recommendations for High-Risk Patients With Acute Chest Pain. Referenced studies that support the recommendations are summarized in Online Data Supplements 1B and 1B.		
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

COR	LOE	Recommendations
Recommendations for Acute Chest Pain in Patients With Prior CABG Surgery		
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

COR	LOE	Recommendation
Recommendation for Evaluation of Patients With Acute Chest Pain Receiving Dialysis Referenced studies that support the recommendation are summarized in Online Data Supplement 26.		
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

COR	LOE	Recommendation
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.**		
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

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

COR	LOE	Recommendation
Recommendation for Evaluation of Acute Chest Pain With Nonischemic Cardiac Pathologies		
1	C-EO	1. In patients with acute chest pain in whom other potentially life-threatening nonischemic cardiac conditions are suspected (eg, 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

COR	LOE	Recommendations
Recommendations for Acute Chest Pain With Suspected Acute Aortic Syndrome		
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

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

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

COR	LOE	Recommendations
Recommendations for Acute Chest Pain With VHD		
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 epi-cardial obstructive CAD[1] although, less likely, chest pain may occur in isolated mitral valve stenosis result-ing 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 pathol-ogy, 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 use-ful 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 circum-stances, 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.

Synopsis

The differential diagnosis for noncardiac causes of acute chest pain is quite broad and includes respiratory, muscu-loskeletal, 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, com-monly 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.

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 (eg, 5-fluorouracil)
Sickle cell crisis

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 28.		
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 inter-

actions, 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

COR	LOE	Recommendations
		**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.
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]

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 ob-

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

A Pretest probability based on age, sex, and symptoms
Low ≤15% — Intermediate–High >15%

B Pretest probability based on age, sex, symptoms, and CAC score+
≤15% — >15%–50% — >50%
CAC 1–99 — CAC ≥100–999 — CAC ≥1,000

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

tained 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

COR	LOE	Recommendations
		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.
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 (ie, 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 (ie, ~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 (eg, 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

COR	LOE	Recommendations
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.		
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]
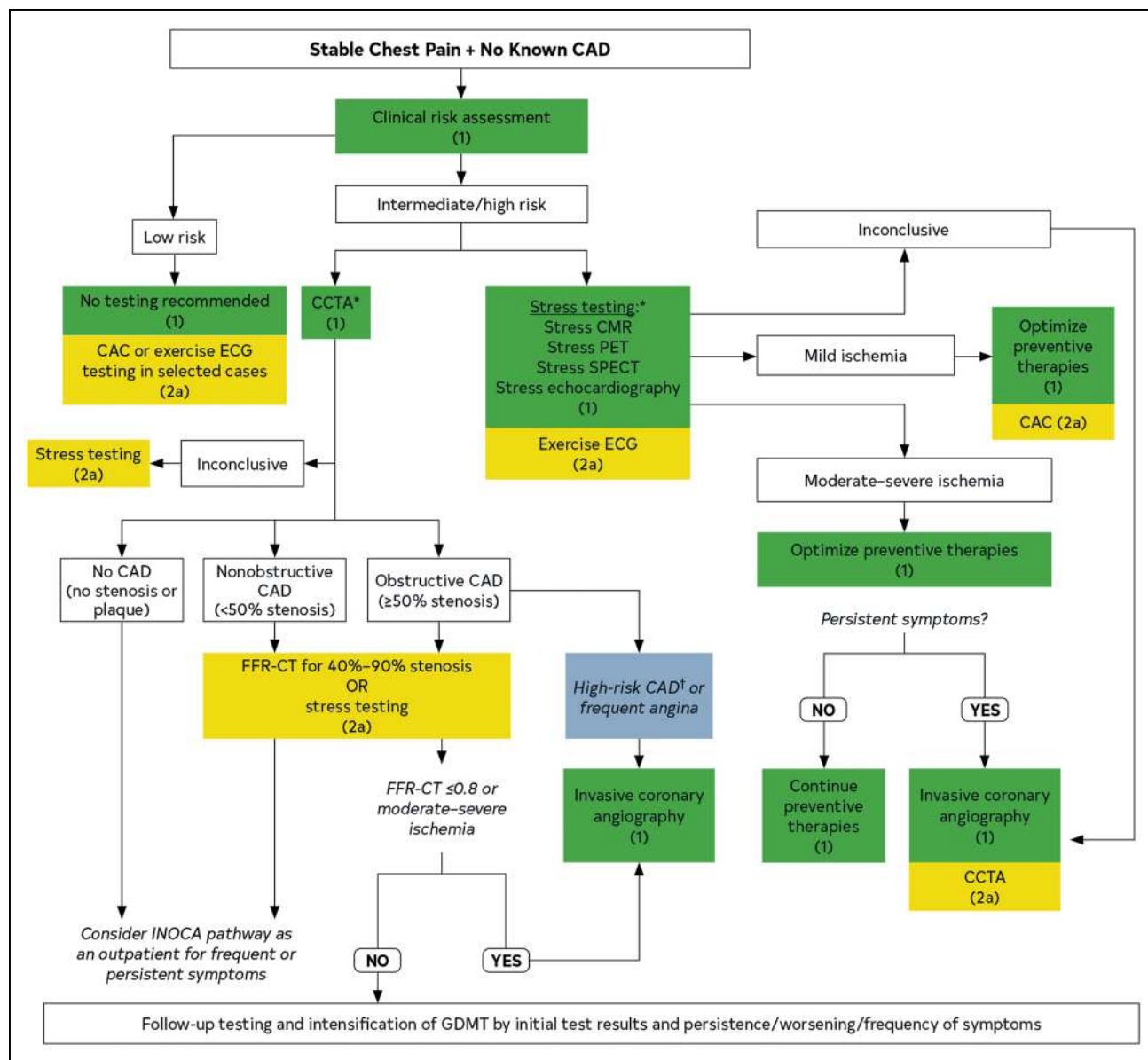
Figure 12. Clinical Decision Pathway for Patients With Stable Chest Pain and No Known CAD
Test choice should be guided by local availability and expertise.
*Test choice guided by patient's exercise capacity, resting electrocardiographic abnormalities; CCTA preferable in those <65 years of age and not 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.

		Recommendations for Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD (Continued)
		Sequential or Add-on Testing: What to Do if Index Test Results are Positive or Inconclusive (continued)
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 (ie, 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 (ie, 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 (eg, ≥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: What to Do if Index Test Results are Positive or Inconclusive

7. 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 5083 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]

8. 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.

9. 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]

10. 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]

11. 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.

5.2. Patients With Known CAD Presenting With Stable Chest Pain

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

COR	LOE	Recommendations
over table		**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]

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 5179 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 (ie, 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]
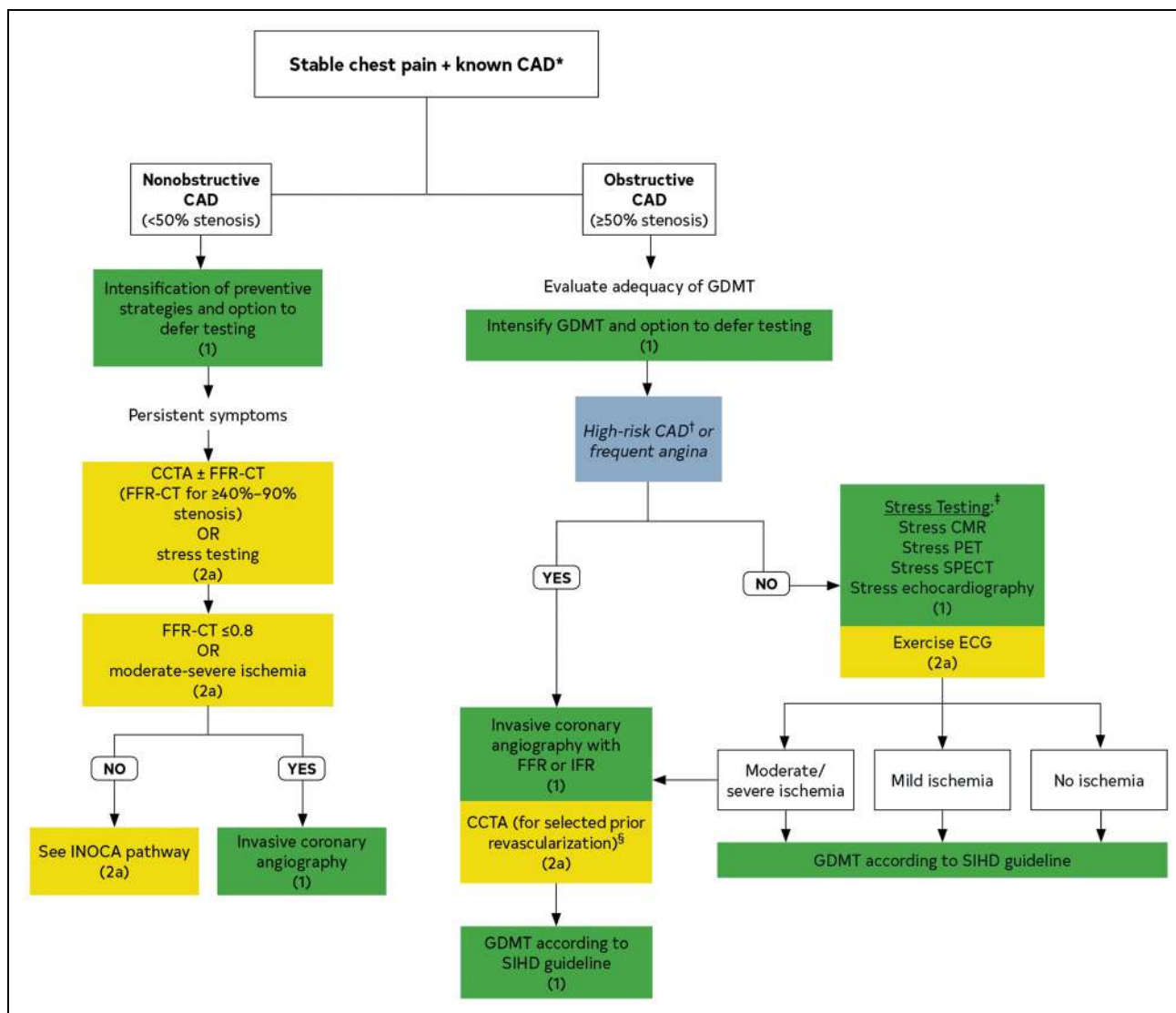
Figure 13. Clinical Decision Pathway for Patients With Stable Chest Pain (or Equivalent) Symptoms With Prior MI, Prior Revascularization, or Known CAD on Invasive Coronary Angiography or CCTA, Including Those With Nonobstructive CAD

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.

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 2496 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.[15] 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 nondiagnostic segments.[8-15]

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

COR	LOE	Recommendations
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.		
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 (ie, 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 Noninvasive 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.

COR	LOE	Recommendations
Recommendations for Patients With INOCA Referenced studies that support the recommendations are summarized in Online Data Supplements 36 and 37.		
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 (ie, <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
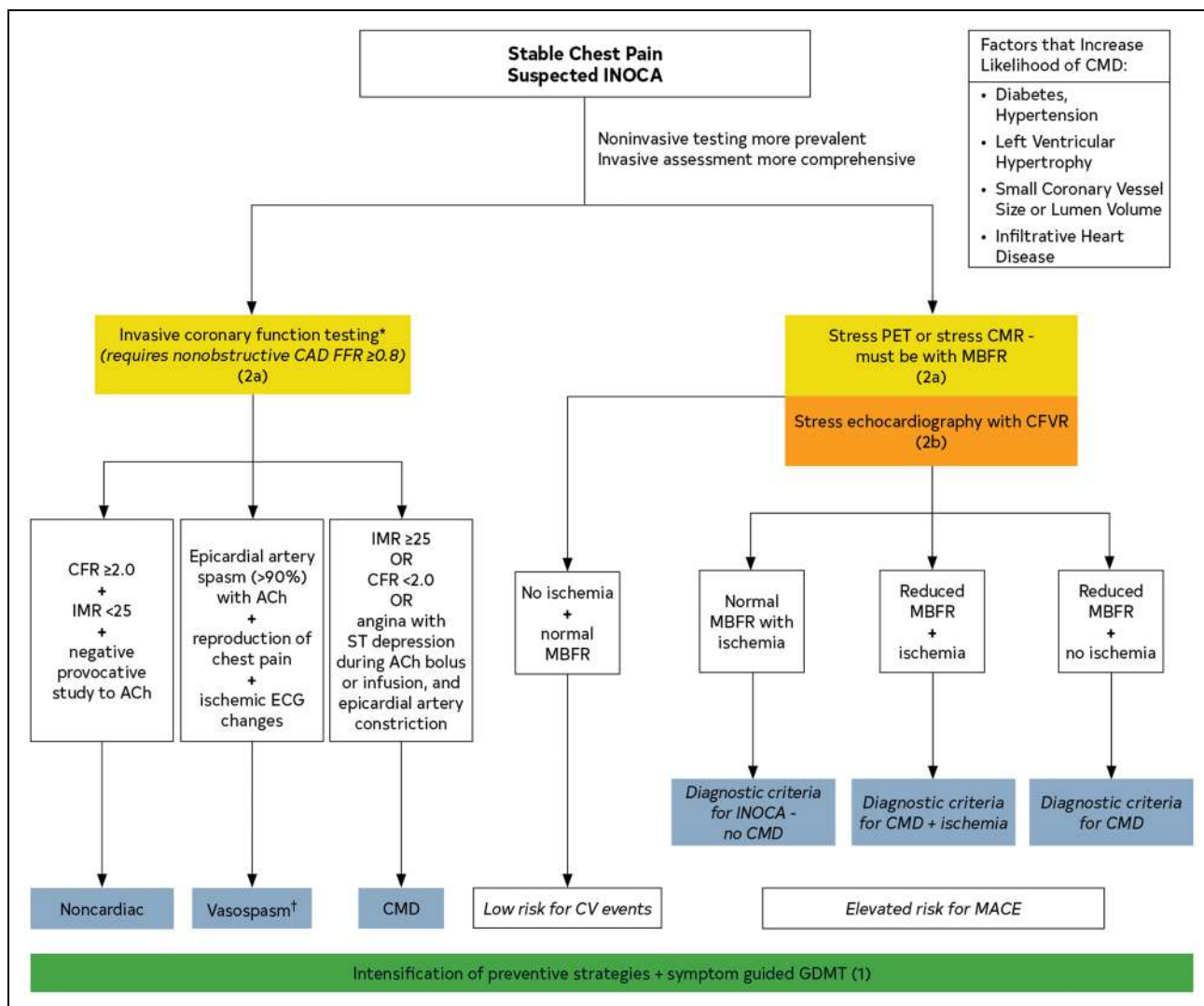
Figure 14. Clinical Decision Pathway for INOCA
Test choice should be guided by local availability and expertise.
*Ford T et al.[16] †Cannot exclude microvascular vasospasm.
ACh indicates acetylcholine; CAD, coronary artery disease; CFR, coronary flow reserve; CFVR, coronary flow velocity reserve; CMD, 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.

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 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 (ie, 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 re-

ferral arm included CCTA-guided use of ICA. Cumulative diagnostic costs were $1183 for the selective arm and $2755 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 $1731 higher for CCTA (n=4818) when compared with the exercise ECG (n=858); however, the 95% CIs for cost differences was wide ($2 to $3519), and there was no overall difference by randomization.[4] Overall, results from the PROMISE trial showed that stress testing was associated with similar costs and CAD outcomes over ~3 years of follow-up.[4,5] In a randomized trial of 824 symptomatic women, cumulative procedural costs were nearly 50% lower for exercise ECG versus MPI SPECT ($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 2204 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: −$1562 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 (eg, 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 non-obstructive 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] hscTn 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.

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ARTICLE INFORMATION

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

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5. EVALUATION OF PATIENTS WITH STABLE CHEST PAIN

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APPENDIX

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 Lifeform 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* • PhaseBio* • PLx Pharma* • Regeneron* • Roche* • Sanofi-aventis* • Synaptic* • Takeda† • The Medicines Company*	• Amarin Pharma Inc.* • AstraZeneca* • Biotronik‡ • Boehringer Ingelheim* • Boston Scientific‡ • Cardax† • Merck† • Novartis • PhaseBio† • PLx Pharma† • Regado Biosciences† • Sanofi-aventis* • St. Jude Medical‡ • Svelte‡	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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 Americas, 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
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

(*Continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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	Employ-ment	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* • US 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
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

Appendix 2.   Continued

Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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
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

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Norrisa Haynes	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	University of Pennsylvania	None	None	None	None	None	None
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
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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Ada Stefanescu Schmidt	Content Reviewer–ACC	University of Toronto; Harvard University	None	None	None	None	None	None
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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

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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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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

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