CLINICAL PRACTICE GUIDELINE

2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

A Report of the American College of Cardiology/American Heart Association
Task Force on Practice Guidelines

Developed in Collaboration With the Society for Cardiovascular Angiography and Interventions
and Society of Thoracic Surgeons

Endorsed by the American Association for Clinical Chemistry

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PREAMBLE

The American College of Cardiology (ACC) and the American Heart Association (AHA) are committed to the prevention and management of cardiovascular diseases through professional education and research for clinicians, providers, and patients. Since 1980, the ACC and AHA have shared a responsibility to translate scientific evidence into clinical practice guidelines (CPGs) with recommendations to standardize and improve cardiovascular health. These CPGs, based on systematic methods to evaluate and classify evidence, provide a cornerstone of quality cardiovascular care.

In response to published reports from the Institute of Medicine (1,2) and the ACC/AHA's mandate to evaluate new knowledge and maintain relevance at the point of care, the ACC/AHA Task Force on Practice Guidelines (Task Force) began modifying its methodology. This modernization effort is published in the 2012 Methodology Summit Report (3) and 2014 perspective article (4). The latter recounts the history of the collaboration, changes over time, current policies, and planned initiatives to meet the needs of an evolving healthcare environment. Recommendations on value in proportion to resource utilization will be incorporated as high-quality

comparative-effectiveness data become available (5). The relationships between CPGs and data standards, appropriate use criteria, and performance measures are addressed elsewhere (4).

Intended Use—CPGs provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but CPGs developed in collaboration with other organizations may have a broader target. Although CPGs may be used to inform regulatory or payer decisions, the intent is to improve the quality of care and be aligned with the patient's best interest.

Evidence Review—Guideline writing committee (GWC) members are charged with reviewing the literature; weighing the strength and quality of evidence for or against particular tests, treatments, or procedures; and estimating expected health outcomes when data exist. In analyzing the data and developing CPGs, the GWC uses evidence-based methodologies developed by the Task Force (6). A key component of the ACC/AHA CPG methodology is the development of recommendations on the basis of all available evidence. 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 opinion. Only selected references are cited in the CPG. To ensure that CPGs remain current, new data are reviewed biannually by the GWCs and the Task Force to determine if recommendations should be updated or modified. In general, a target cycle of 5 years is planned for full revisions (1).

Guideline-Directed Medical Therapy—Recognizing advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force designated the term "guideline-directed medical therapy" (GDMT) to represent recommended medical therapy as defined mainly by Class I measures, generally a combination of lifestyle modification and drug- and device-based therapeutics. As medical science advances, GDMT evolves, and hence GDMT is preferred to "optimal medical therapy." For GDMT and all other recommended drug treatment regimens, the reader should confirm the dosage with product insert material and carefully evaluate for contraindications and possible drug interactions. Recommendations are limited to treatments, drugs, and devices approved for clinical use in the United States.

Class of Recommendation and Level of Evidence—Once recommendations are written, the Class of Recommendation (COR; i.e., the strength the GWC assigns to the recommendation, which encompasses the anticipated magnitude and judged certainty of benefit in proportion to risk) is assigned by the GWC. Concurrently, the Level of Evidence (LOE) rates the scientific evidence supporting the effect of the intervention on the basis on the type, quality, quantity, and consistency of data

TABLE 1   Applying Classification of Recommendations and Level of Evidence

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the clinical practice guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

from clinical trials and other reports (Table 1) (4). Unless otherwise stated, recommendations are presented in order by the COR and then the LOE. Where comparative data exist, preferred strategies take precedence. When more than 1 drug, strategy, or therapy exists within the same COR and LOE and there are no comparative data, options are listed alphabetically. **Relationships With Industry and Other Entities**—The ACC and AHA exclusively sponsor the work of GWCs without commercial support, and members volunteer their time for this activity. The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that might arise through relationships with industry or

other entities (RWI). All GWC members and reviewers are required to fully disclose current industry relationships or personal interests from 12 months before initiation of the writing effort. Management of RWI involves selecting a balanced GWC and requires that both the chair and a majority of GWC members have no relevant RWI (see Appendix 1 for the definition of relevance). GWC members are restricted with regard to writing or voting on sections to which their RWI apply. In addition, for transparency, GWC members' comprehensive disclosure information is available as an online supplement. Comprehensive disclosure information for the Task Force is

available as an additional supplement. The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds representing different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. Selected organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

Individualizing Care in Patients With Associated Conditions and Comorbidities—The ACC and AHA recognize the complexity of managing patients with multiple conditions, compared with managing patients with a single disease, and the challenge is compounded when CPGs for evaluation or treatment of several coexisting illnesses are discordant or interacting (7). CPGs attempt to define practices that meet the needs of patients in most, but not all, circumstances and do not replace clinical judgment.

Clinical Implementation—Management in accordance with CPG recommendations is effective only when followed; therefore, to enhance their commitment to treatment and compliance with lifestyle adjustment, clinicians should engage the patient to participate in selecting interventions on the basis of the patient's individual values and preferences, taking associated conditions and comorbidities into consideration (e.g., shared decision making). Consequently, there are circumstances in which deviations from these guidelines are appropriate.

The recommendations in this CPG are the official policy of the ACC and AHA until they are superseded by a published addendum, focused update, or revised full-text CPG.

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

1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this CPG are, whenever possible, evidence based. An extensive evidence review was conducted through October 2012, and other selected references published through April 2014 were reviewed by the GWC. Literature included was derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this CPG. The relevant data are included in evidence tables in the Online Data Supplement. Key search words included but were not limited to the following: *acute coronary syndrome, anticoagulant therapy, antihypertensives, anti-ischemic therapy, antiplatelet therapy, antithrombotic therapy, beta blockers, biomarkers, calcium channel blockers, cardiac rehabilitation, conservative management, diabetes mellitus, glycoprotein IIb/ IIIa inhibitors, heart failure, invasive strategy, lifestyle modification, myocardial infarction, nitrates, non–ST-elevation, P2Y$_{12}$*

receptor inhibitor, percutaneous coronary intervention, renin-angiotensin-aldosterone inhibitors, secondary prevention, smoking cessation, statins, stent, thienopyridines, troponins, unstable angina, and *weight management.* Additionally, the GWC reviewed documents related to non–ST-elevation acute coronary syndrome (NSTE-ACS) previously published by the ACC and AHA. References selected and published in this document are representative and not all-inclusive.

1.2. Organization of the GWC

The GWC was composed of clinicians, cardiologists, internists, interventionists, surgeons, emergency medicine specialists, family practitioners, and geriatricians. The GWC included representatives from the ACC and AHA, American Academy of Family Physicians, American College of Emergency Physicians, American College of Physicians, Society for Cardiovascular Angiography and Interventions (SCAI), and Society of Thoracic Surgeons (STS).

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC and AHA; 1 reviewer each from the American Academy of Family Physicians, American College of Emergency Physicians, SCAI, and STS; and 37 individual content reviewers (including members of the American Association of Clinical Chemistry, ACC Heart Failure and Transplant Section Leadership Council, ACC Cardiovascular Imaging Section Leadership Council, ACC Interventional Section Leadership Council, ACC Prevention of Cardiovascular Disease Committee, ACC Surgeons' Council, Association of International Governors, and Department of Health and Human Services). Reviewers' RWI information was distributed to the GWC 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 endorsed by the American Association for Clinical Chemistry, SCAI, and the STS.

1.4. Scope of the CPG

The 2014 NSTE-ACS CPG is a full revision of the 2007 ACCF/ AHA CPG for the management of patients with unstable angina (UA) and non–ST-elevation myocardial infarction (NSTEMI) and the 2012 focused update (8). The new title, "Non–ST-Elevation Acute Coronary Syndromes," emphasizes the continuum between UA and NSTEMI. At presentation, patients with UA and NSTEMI can be indistinguishable and are therefore considered together in this CPG.

In the United States, NSTE-ACS affects >625,000 patients annually,* or almost three fourths of all patients with acute coronary syndrome (ACS) (9). In selecting the

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*Estimate includes secondary discharge diagnoses.

initial approach to care, the term "ischemia-guided strategy" has replaced the previous descriptor, "initial conservative management," to more clearly convey the physiological rationale of this approach.

The task of the 2014 GWC was to establish a contemporary CPG for the optimal management of patients with NSTE-ACS. It incorporates both established and new evidence from published clinical trials, as well as information from basic science and comprehensive review articles. These recommendations were developed to guide the clinician in improving outcomes for patients with NSTE-ACS. Table 2 lists documents deemed pertinent to this effort and is intended for use as a resource, thus obviating the need to repeat extant CPG recommendations.

The GWC abbreviated the discussion sections to include an explanation of salient information related to the recommendations. In contrast to textbook declaratory presentations, explanations were supplemented with evidence tables. The GWC also provided a brief summary

TABLE 2	Associated CPGs and Statements		
Title		**Organization**	**Publication Year (Reference)**
CPGs			
Stable ischemic heart disease		ACC/AHA/AATS/PCNA/SCAI/STS	2014 (10)* 2012 (11)
Atrial fibrillation		AHA/ACC/HRS	2014 (12)
Assessment of cardiovascular risk		ACC/AHA	2013 (13)
Heart failure		ACC/AHA	2013 (14)
Lifestyle management to reduce cardiovascular risk		AHA/ACC	2013 (15)
Management of overweight and obesity in adults		AHA/ACC/TOS	2013 (16)
ST-elevation myocardial infarction		ACC/AHA	2013 (17)
Treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults		ACC/AHA	2013 (18)
Acute myocardial infarction in patients presenting with ST-segment elevation		ESC	2012 (19)
Device-based therapy		ACC/AHA/HRS	2013 (20)
Third universal definition of myocardial infarction		ESC/ACC/AHA/WHF	2012 (21)
Acute coronary syndromes in patients presenting without persistent ST-segment elevation		ESC	2011 (22)
Coronary artery bypass graft surgery		ACC/AHA	2011 (23)
Hypertrophic cardiomyopathy		ACC/AHA	2011 (24)
Effectiveness-based guidelines for the prevention of cardiovascular disease in women		AHA/ACC	2011 (25)
Percutaneous coronary intervention		ACC/AHA/SCAI	2011 (26)
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease		AHA/ACC	2011 (27)
Assessment of cardiovascular risk in asymptomatic adults		ACC/AHA	2010 (28)
Myocardial revascularization		ESC	2010 (29)
Unstable angina and non–ST-elevation myocardial infarction		NICE	2010 (30)†
Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care—part 9: postcardiac arrest care		AHA	2010 (31)
Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure		NHLBI	2003 (32)
Statements			
Key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease		ACC/AHA	2013 (33)
Practical clinical considerations in the interpretation of troponin elevations		ACC	2012 (34)
Testing of low-risk patients presenting to the emergency department with chest pain		AHA	2010 (35)
Primary prevention of cardiovascular diseases in people with diabetes mellitus		AHA/ADA	2007 (36)
Prevention and control of influenza		CDC	2005 (37)

*The full-text SIHD CPG is from 2012 (11). A focused update was published in 2014 (10).

†Minor modifications were made in 2013. For a full explanation of the changes, see http://publications.nice.org.uk/unstable-angina-and-nstemi-cg94/changes-after-publication.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; CDC, Centers for Disease Control and Prevention; CPG, clinical practice guideline; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; NHLBI, National Heart, Lung, and Blood Institute; NICE, National Institute for Health and Clinical Excellence; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; SIHD, stable ischemic heart disease; STS, Society of Thoracic Surgeons; TOS, The Obesity Society; and WHF, World Heart Federation.

of the relevant recommendations and references related to secondary prevention rather than detailed reiteration. Throughout, the goal was to provide the clinician with concise, evidence-based contemporary recommendations and the supporting documentation to encourage their application.

2. OVERVIEW OF ACS

2.1. Definition of Terms

ACS has evolved as a useful operational term that refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow (Figure 1). A key branch point is ST-segment elevation (ST-elevation) or new left bundle-branch block on the electrocardiogram (ECG), which is an indication for immediate coronary angiography to determine if there is an indication for reperfusion therapy to open a likely completely occluded coronary artery. Separate CPGs have been developed for ST-elevation myocardial infarction (STEMI) (17).

The absence of persistent ST-elevation is suggestive of NSTE-ACS (except in patients with true posterior myocardial infarction [MI], Sections 3.3.2.4, 4.3.2, and 7.2.2). NSTE-ACS can be further subdivided on the basis of cardiac biomarkers of necrosis (e.g., cardiac troponin, Sections 3.2.4 and 3.4). If cardiac biomarkers are elevated and the clinical context is appropriate, the patient is considered to have NSTEMI (34); otherwise, the patient is deemed to have UA. ST depression, transient ST-elevation, and/or prominent T-wave inversions may be present but are not required for a diagnosis of NSTEMI. Abnormalities on the ECG and elevated troponins in isolation are insufficient to make the diagnosis of ACS but must be interpreted in the appropriate clinical context. Thus, UA and NSTEMI are closely related conditions whose pathogenesis and clinical presentations are similar but vary in severity. The conditions differ primarily by whether the ischemia is severe enough to cause myocardial damage leading to detectable quantities of myocardial injury biomarkers. The term "possible ACS" is often assigned during initial evaluation if the ECG is unrevealing and troponin data are not yet available. UA can present without any objective data of myocardial ischemic injury (normal ECG and normal troponin), in which case the initial diagnosis depends solely on the patient's clinical history and the clinician's interpretation and judgment. However, with the increasing sensitivity of troponin assays, biomarker-negative ACS (i.e., UA) is becoming rarer (39). The pathogenesis of ACS is considered in the "Third Universal Definition of Myocardial Infarction" (21). This statement defines MI caused by a primary coronary artery process such as spontaneous plaque rupture as MI type 1 and one related to reduced myocardial oxygen supply and/or increased myocardial oxygen demand (in the absence of a direct coronary artery process) as a MI type 2 (Appendix 4, Table A and Section 3.4 for an additional discussion on the diagnosis of MI).

2.2. Epidemiology and Pathogenesis

2.2.1. Epidemiology

In the United States, the median age at ACS presentation is 68 years (interquartile range 56 to 79), and the male-to-female ratio is approximately 3:2 (40). Some patients have a history of stable angina, whereas in others, ACS is the initial presentation of coronary artery disease (CAD). It is estimated that in the United States, each year, >780,000 persons will experience an ACS. Approximately 70% of these will have NSTE-ACS (9). Patients with NSTE-ACS typically have more comorbidities, both cardiac and noncardiac, than patients with STEMI.

2.2.2. Pathogenesis

The hallmark of ACS is the sudden imbalance between myocardial oxygen consumption (MVO_2) and demand, which is usually the result of coronary artery obstruction. The imbalance may also be caused by other conditions, including excessive myocardial oxygen demand in the setting of a stable flow-limiting lesion; acute coronary insufficiency due to other causes (e.g., vasospastic [Prinzmetal] angina [Section 7.11], coronary embolism, coronary arteritis); noncoronary causes of myocardial oxygen supply-demand mismatch (e.g., hypotension, severe anemia, hypertension, tachycardia, hypertrophic cardiomyopathy, severe aortic stenosis); nonischemic myocardial injury (e.g., myocarditis, cardiac contusion, cardiotoxic drugs); and multifactorial causes that are not mutually exclusive (e.g., stress [Takotsubo] cardiomyopathy [Section 7.13], pulmonary embolism, severe heart failure [HF], sepsis) (41).

3. INITIAL EVALUATION AND MANAGEMENT

3.1. Clinical Assessment and Initial Evaluation: Recommendation

CLASS I

1. **Patients with suspected ACS should be risk stratified based on the likelihood of ACS and adverse outcome(s) to decide on the need for hospitalization and assist in the selection of treatment options (42–44).** *(Level of Evidence: B)*

Patients with suspected ACS must be evaluated rapidly to identify those with a life-threatening emergency versus those with a more benign condition. The goal of the initial evaluation focuses on answering 2 questions:

1. What is the likelihood that the symptoms and signs represent ACS?
2. What is the likelihood of adverse clinical outcome(s)?

FIGURE 1 Acute Coronary Syndromes

The top half of the figure illustrates the progression of plaque formation and onset and complications of NSTE-ACS, with management at each stage. The numbered section of an artery depicts the process of atherogenesis from 1) normal artery to 2) extracellular lipid in the subintima to 3) fibrofatty stage to 4) procoagulant expression and weakening of the fibrous cap. ACS develops with 5) disruption of the fibrous cap, which is the stimulus for thrombogenesis. 6) Thrombus resorption may be followed by collagen accumulation and smooth muscle cell growth. Thrombus formation and possible coronary vasospasm reduce blood flow in the affected coronary artery and cause ischemic chest pain. The bottom half of the figure illustrates the clinical, pathological, electrocardiographic, and biomarker correlates in ACS and the general approach to management. Flow reduction may be related to a completely occlusive thrombus (bottom half, right side) or subtotally occlusive thrombus (bottom half, left side). Most patients with ST-elevation (thick white arrow in bottom panel) develop QwMI, and a few (thin white arrow) develop NQMI. Those without ST-elevation have either UA or NSTEMI (thick red arrows), a distinction based on cardiac biomarkers. Most patients presenting with NSTEMI develop NQMI; a few may develop QwMI. The spectrum of clinical presentations including UA, NSTEMI, and STEMI is referred to as ACS. This NSTE-ACS CPG includes sections on initial management before NSTE-ACS, at the onset of NSTE-ACS, and during the hospital phase. Secondary prevention and plans for long-term management begin early during the hospital phase. Patients with noncardiac etiologies make up the largest group presenting to the ED with chest pain (dashed arrow).
  *Elevated cardiac biomarker (e.g., troponin), Section 3.4.
 ACS indicates acute coronary syndrome; CPG, clinical practice guideline; Dx, diagnosis; ECG, electrocardiogram; ED, emergency department; MI, myocardial infarction; NQMI, non-Q-wave myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndromes; NSTEMI, non–ST-elevation myocardial infarction; QwMI, Q-wave myocardial infarction; STEMI, ST-elevation myocardial infarction; and UA, unstable angina.
Modified with permission from Libby et al. (38).

Risk assessment scores and clinical prediction algorithms using clinical history, physical examination, ECG, and cardiac troponins have been developed to help identify patients with ACS at increased risk of adverse outcome(s). Common risk assessment tools include the TIMI (Thrombolysis In Myocardial Infarction) risk score (42), the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk score (43), the GRACE (Global Registry of Acute Coronary Events) risk score (44), and the NCDR-ACTION (National Cardiovascular Data Registry-Acute Coronary Treatment and Intervention Outcomes Network) registry (https://www.ncdr.com/webncdr/action/). These assessment tools have been applied with variable efficacy to predict outcomes in patients presenting to the emergency department (ED) with undifferentiated chest pain ("pain" encompasses not only pain, but also symptoms such as discomfort, pressure, and squeezing) (45-48). The Sanchis score (49), Vancouver rule (50), Heart (History, ECG, Age, Risk Factors, and Troponin) score (51), HEARTS$_3$ score (52), and Hess prediction rule (53) were developed specifically for patients in the ED with chest pain. Although no definitive study has demonstrated the superiority of risk assessment scores or clinical prediction rules over clinician judgment, determination of the level of risk on initial evaluation is imperative to guide patient management, including the need for additional diagnostic testing and treatment. See Section 3.2.2 for a discussion of risk stratification variables.

See Online Data Supplement 1 for additional information on clinical assessment and initial evaluation.

3.1.1. ED or Outpatient Facility Presentation: Recommendations

CLASS I

1. **Patients with suspected ACS and high-risk features such as continuing chest pain, severe dyspnea, syncope/presyncope, or palpitations should be referred immediately to the ED and transported by emergency medical services when available.** *(Level of Evidence: C)*

CLASS IIb

1. **Patients with less severe symptoms may be considered for referral to the ED, a chest pain unit, or a facility capable of performing adequate evaluation depending on clinical circumstances.** *(Level of Evidence: C)*

Patients with suspected ACS and high-risk features should be transported to the ED by emergency medical services when available. Hospitals and outpatient facilities should provide clearly visible signage directing patients transported by private vehicle to the appropriate triage area. Outpatient facilities should have the capacity for ECG and cardiac troponin measurements with immediate ED referral for those considered to have ACS.

3.2. Diagnosis of NSTE-ACS

Differential diagnosis of NSTE-ACS includes (41):

- Nonischemic cardiovascular causes of chest pain (e.g., aortic dissection, expanding aortic aneurysm, pericarditis, pulmonary embolism)
- Noncardiovascular causes of chest, back, or upper abdominal discomfort include:
  o Pulmonary causes (e.g., pneumonia, pleuritis, pneumothorax)
  o Gastrointestinal causes (e.g., gastroesophageal reflux, esophageal spasm, peptic ulcer, pancreatitis, biliary disease)
  o Musculoskeletal causes (e.g., costochondritis, cervical radiculopathy)
  o Psychiatric disorders
  o Other etiologies (e.g., sickle cell crisis, herpes zoster)

In addition, the clinician should differentiate NSTE-ACS from acute coronary insufficiency due to a nonatherosclerotic cause and noncoronary causes of myocardial oxygen supply-demand mismatch (41) (Section 2.2.2).

3.2.1. History

NSTE-ACS most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion lasting ≥10 minutes (41). The pain most frequently starts in the retrosternal area and can radiate to either or both arms, the neck, or the jaw. Pain may also occur in these areas independent of chest pain. Patients with NSTE-ACS may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope. Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent. Less common presentations include nausea and vomiting, diaphoresis, unexplained fatigue, and syncope. Factors that increase the probability of NSTE-ACS are older age, male sex, positive family history of CAD, and the presence of peripheral arterial disease, diabetes mellitus, renal insufficiency, prior MI, and prior coronary revascularization. Although older patients (≥75 years of age) and women usually present with typical symptoms of ACS, the frequency of atypical presentations is increased in these groups as well as in patients with diabetes mellitus, impaired renal function, and dementia (54,55). Atypical symptoms, including epigastric pain, indigestion, stabbing or pleuritic pain, and increasing dyspnea in the absence of chest pain should raise concern for NSTE-ACS (56). Psychiatric disorders (e.g., somatoform disorders, panic attack, anxiety disorders) are noncardiac causes of chest pain that can mimic ACS (57).

3.2.2. Physical Examination

The physical examination in NSTE-ACS can be normal, but signs of HF should expedite the diagnosis and treatment

of this condition. Acute myocardial ischemia may cause a S_4, a paradoxical splitting of S_2, or a new murmur of mitral regurgitation due to papillary muscle dysfunction. However, these signs may also exist without NSTE-ACS and thus are nonspecific. The coupling of pain on palpation suggesting musculoskeletal disease or inflammation with a pulsatile abdominal mass suggesting abdominal aortic aneurysm raises concern for nonischemic causes of NSTE-ACS. The physical examination can indicate alternative diagnoses in patients with chest pain, several of which are life threatening. Aortic dissection is suggested by back pain, unequal palpated pulse volume, a difference of ≥15 mm Hg between both arms in systolic blood pressure (BP), or a murmur of aortic regurgitation. Acute pericarditis is suggested by a pericardial friction rub. Cardiac tamponade can be reflected by pulsus paradoxus. Pneumothorax is suspected when acute dyspnea, pleuritic chest pain, and differential breath sounds are present. A pleural friction rub may indicate pneumonitis or pleuritis.

3.2.3. Electrocardiogram

A 12-lead ECG should be performed and interpreted within 10 minutes of the patient's arrival at an emergency facility to assess for cardiac ischemia or injury (21). Changes on ECG in patients with NSTE-ACS include ST depression, transient ST-elevation, or new T-wave inversion (21,58). Persistent ST-elevation or anterior ST depression indicative of true posterior MI should be treated according to the STEMI CPG (17). The ECG can be relatively normal or initially nondiagnostic; if this is the case, the ECG should be repeated (e.g., at 15- to 30-minute intervals during the first hour), especially if symptoms recur (21). A normal ECG does not exclude ACS and occurs in 1% to 6% of such patients (59-61). A normal ECG may also be associated with left circumflex or right coronary artery occlusions, which can be electrically silent (in which case posterior electrocardiographic leads [V_7 to V_9] may be helpful). Right-sided leads (V_3R to V_4R) are typically performed in the case of inferior STEMI to detect evidence of right ventricular infarction. Left ventricular (LV) hypertrophy, bundle-branch blocks with repolarization abnormalities, and ventricular pacing may mask signs of ischemia/injury (62).

3.2.4. Biomarkers of Myocardial Necrosis

Cardiac troponins are the most sensitive and specific biomarkers for NSTE-ACS. They rise within a few hours of symptom onset and typically remain elevated for several days (but may remain elevated for up to 2 weeks with a large infarction). A negative cardiac troponin obtained with more sensitive cardiac troponin assays on admission confers a >95% negative predictive value for MI compared with high-sensitivity assays that confer a negative predictive value ≥99% (63-65). See Section 3.4 for a detailed review of biomarkers for the diagnosis of MI.

3.2.5. Imaging

A chest roentgenogram is useful to identify potential pulmonary causes of chest pain and may show a widened mediastinum in patients with aortic dissection. Computed tomography (CT) of the chest with intravenous contrast can help exclude pulmonary embolism and aortic dissection. Transthoracic echocardiography can identify a pericardial effusion and tamponade physiology and may also be useful to detect regional wall motion abnormalities. Transesophageal echocardiography can identify a proximal aortic dissection. In low-risk patients with chest pain, coronary CT angiography can result in a more rapid, more cost-effective diagnosis than stress myocardial perfusion imaging (66).

3.3. Prognosis—Early Risk Stratification: Recommendations

See Table 4 for a summary of recommendations from this section.

CLASS I

1. In patients with chest pain or other symptoms suggestive of ACS, a 12-lead ECG should be performed and evaluated for ischemic changes within 10 minutes of the patient's arrival at an emergency facility (21). *(Level of Evidence: C)*

2. If the initial ECG is not diagnostic but the patient remains symptomatic and there is a high clinical suspicion for ACS, serial ECGs (e.g., 15- to 30-minute intervals during the first hour) should be performed to detect ischemic changes. *(Level of Evidence: C)*

3. Serial cardiac troponin I or T levels (when a contemporary assay is used) should be obtained at presentation and 3 to 6 hours after symptom onset (see Section 3.4, Class I, #3 recommendation if time of symptom onset is unclear) in all patients who present with symptoms consistent with ACS to identify a rising and/or falling pattern of values (21,64,67-71). *(Level of Evidence: A)*

4. Additional troponin levels should be obtained beyond 6 hours after symptom onset (see Section 3.4, Class I, #3 recommendation if time of symptom onset is unclear) in patients with normal troponin levels on serial examination when changes on ECG and/or clinical presentation confer an intermediate or high index of suspicion for ACS (21,72-74). *(Level of Evidence: A)*

5. Risk scores should be used to assess prognosis in patients with NSTE-ACS (42-44,75-80). *(Level of Evidence: A)*

CLASS IIa

1. Risk-stratification models can be useful in management (42-44,75-81). *(Level of Evidence: B)*

2. It is reasonable to obtain supplemental electrocardiographic leads V_7 to V_9 in patients whose initial ECG is nondiagnostic and who are at intermediate/high risk of ACS (82-84). *(Level of Evidence: B)*

CLASS IIb

1. Continuous monitoring with 12-lead ECG may be a reasonable alternative in patients whose initial ECG is non-diagnostic and who are at intermediate/high risk of ACS (85,86). *(Level of Evidence: B)*

2. Measurement of B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide may be considered to assess risk in patients with suspected ACS (87–91). *(Level of Evidence: B)*

3.3.1. Rationale for Risk Stratification and Spectrum of Risk: High, Intermediate, and Low

Assessment of prognosis guides initial clinical evaluation and treatment and is useful for selecting the site of care (coronary care unit, monitored step-down unit, or outpatient monitored unit), antithrombotic therapies (e.g., P2Y$_{12}$ inhibitors, platelet glycoprotein [GP] IIb/IIIa inhibitors [Sections 4.3.1.2 and 5.1.2.2]), and invasive management (Sections 4.4.2.1, 4.3.1, 4.4, 4.4.4, 4.4.5). There is a strong relationship between indicators of ischemia due to CAD and prognosis (Table 3 and Figure 2). Patients with a high likelihood of ischemia due to CAD are at greater risk of a major adverse cardiac event (MACE) than patients with a lower likelihood of ischemia due to CAD. Risk is highest at the time of presentation but remains elevated past the acute phase. By 6 months, NSTE-ACS mortality rates may equal or exceed those of STEMI (58). By 12 months, rates of death, MI, and recurrent instability in contemporary registries are >10%. Early events are related to the ruptured coronary plaque and thrombosis, and later events are more closely associated with the pathophysiology of chronic atherosclerosis and LV systolic function (92-98).

3.3.2. Estimation of Level of Risk

At initial presentation, the clinical history, anginal symptoms and equivalents, physical examination, ECG,

TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %
0-1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6-7	40.9

TABLE 3   TIMI Risk Score* for NSTE-ACS

*The TIMI risk score is determined by the sum of the presence of 7 variables at admission; 1 point is given for each of the following variables: ≥65 y of age; ≥3 risk factors for CAD; prior coronary stenosis ≥50%; ST deviation on ECG; ≥2 anginal events in prior 24 h; use of aspirin in prior 7 d; and elevated cardiac biomarkers.

CAD indicates coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndromes; and TIMI, Thrombolysis In Myocardial Infarction.
Modified with permission from Antman et al. (42).

renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events (Table 3 and Figure 2) (42,78).

3.3.2.1. History: Angina Symptoms and Angina Equivalents

In patients with or without known CAD, clinicians must determine whether the presentation is consistent with acute ischemia, stable ischemic heart disease, or an alternative etiology. Factors in the initial clinical history related to the likelihood of acute ischemia include age, sex, symptoms, prior history of CAD, and the number of traditional risk factors (99-105).

The characteristics of angina include deep, poorly localized chest or arm pain that is reproducibly associated with exertion or emotional stress (106). Angina is relieved promptly (i.e., in <5 minutes) with rest and/or short-acting nitroglycerin. Patients with NSTE-ACS may have typical or atypical anginal symptoms, but episodes are more severe and prolonged, may occur at rest, or may be precipitated by less exertion than the patient previously experienced. Some patients have no chest pain but present solely with dyspnea or with arm, shoulder, back, jaw, neck, epigastric, or ear discomfort (107-109).

Features not characteristic of myocardial ischemia include:

- Pleuritic pain (sharp or knifelike pain provoked by respiration or cough);
- Primary or sole location of discomfort in the middle or lower abdomen;
- Pain localized by the tip of 1 finger, particularly at the LV apex or costochondral junction;
- Pain reproduced with movement or palpation of the chest wall or arms;
- Brief episodes of pain lasting a few seconds or less;
- Pain that is of maximal intensity at onset; and
- Pain that radiates into the lower extremities.

Evaluation should include the clinician's impression of whether the pain represents a high, intermediate, or low likelihood of acute ischemia.

Although typical characteristics increase the probability of CAD, atypical features do not exclude ACS. In the Multicenter Chest Pain Study, acute ischemia was diagnosed in 22% of patients who presented to the ED with sharp or stabbing pain and in 13% of those with pleuritic pain (110). Seven percent of patients whose pain was reproduced with palpation had ACS. The ACI-TIPI (Acute Cardiac Ischemia Time-Insensitive Predictive Instrument) project found that older age, male sex, chest or left arm pain, and chest pain or pressure were the most important findings, and each increased the likelihood of ACS (111,112).

The relief of chest pain with nitroglycerin is not predictive of ACS. One study reported that sublingual

TABLE 4	Summary of Recommendations for Prognosis: Early Risk Stratification			
Recommendations		COR	LOE	References
Perform rapid determination of likelihood of ACS, including a 12-lead ECG within 10 min of arrival at an emergency facility, in patients whose symptoms suggest ACS		I	C	(21)
Perform serial ECGs at 15- to 30-min intervals during the first hour in symptomatic patients with initial nondiagnostic ECG		I	C	N/A
Measure cardiac troponin (cTnI or cTnT) in all patients with symptoms consistent with ACS*		I	A	(21,64,67–71)
Measure serial cardiac troponin I or T at presentation and 3–6 h after symptom onset* in all patients with symptoms consistent with ACS		I	A	(21,72–74)
Use risk scores to assess prognosis in patients with NSTE-ACS		I	A	(42–44,75–80)
Risk-stratification models can be useful in management		IIa	B	(42–44,75–81)
Obtain supplemental electrocardiographic leads V_7 to V_9 in patients with initial nondiagnostic ECG at intermediate/high risk for ACS		IIa	B	(82–84)
Continuous monitoring with 12-lead ECG may be a reasonable alternative with initial nondiagnostic ECG in patients at intermediate/high risk for ACS		IIb	B	(85,86)
BNP or NT–pro-BNP may be considered to assess risk in patients with suspected ACS		IIb	B	(87–91)

*See Section 3.4, Class I, #3 recommendation if time of symptom onset is unclear.

   ACS indicates acute coronary syndromes; BNP, B-type natriuretic peptide; COR, Class of Recommendation; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ECG, electrocardiogram; LOE, Level of Evidence; N/A, not available; NSTE-ACS, non−ST-elevation acute coronary syndromes; and NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

nitroglycerin relieved symptoms in 35% of patients with documented ACS compared with 41% of patients without ACS (113). The relief of chest pain by "gastrointestinal cocktails" (e.g., mixtures of liquid antacids, and/or viscous lidocaine, and/or anticholinergic agents) does not predict the absence of ACS (114).

3.3.2.2. Demographics and History in Diagnosis and Risk Stratification

A prior history of MI is associated with a high risk of obstructive and multivessel CAD (115). Women with suspected ACS are less likely to have obstructive CAD than men. When obstructive CAD is present in women, it tends to be less severe than it is in men (116). It has been suggested that coronary microvascular disease and endothelial dysfunction play a role in the pathophysiology of NSTE-ACS in patients with nonobstructive CAD (116). Older adults have increased risks of underlying CAD (117,118), multivessel CAD, and a worse prognosis (Section 7.1).

A family history of premature CAD is associated with increased coronary artery calcium scores (119) and increased risk of 30-day cardiac events in patients with ACS (120,121). Diabetes mellitus, extracardiac (carotid, aortic, or peripheral) arterial disease, and hypertension are major risk factors for poor outcomes in patients with ACS (Section 6.2) with both STEMI (122) and NSTE-ACS (92).

The current or prior use of aspirin at presentation is associated with increased cardiovascular risk (42), likely reflecting the greater probability that patients who have been prescribed aspirin have an increased cardiovascular risk profile and/or prior vascular disease. Smoking is associated with a lower risk of death in ACS (42,123,124), primarily because of the younger age of smokers with ACS

and less severe CAD. Overweight and/or obesity at ACS presentation are associated with lower short-term risk of death. The "obesity paradox" may be a function of younger age at presentation, referral for angiography at an earlier stage of disease, and more aggressive management of ACS (123). These individuals, especially those with severe obesity (body mass index >35), have a higher long-term total mortality risk (124–129).

Cocaine use can cause ACS by inducing coronary vasospasm, dissection, thrombosis, positive chronotropic and hypertensive actions, and direct myocardial toxicity (Section 7.10) (130). Methamphetamines are also associated with ACS (131). Urine toxicology screening should be considered when substance abuse is suspected as a cause of or contributor to ACS, especially in younger patients (<50 years of age) (132).

3.3.2.3. Early Estimation of Risk

The TIMI risk score is composed of 7, 1-point risk indicators rated on presentation (**Table 3**) (42). The composite endpoints increase as the score increases. The TIMI risk score has been validated internally within the TIMI 11B trial and in 2 separate cohorts of patients from the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Event) trial (133). The TIMI risk score calculator is available at www.timi.org. The TIMI risk index is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS (134). For patients with a TIMI risk score of 0 and normal high-sensitivity cardiac troponin 2 hours after presentation, accelerated diagnostic protocols have been developed that predict a very low rate of 30-day MACE (Section 3.4.3) (65).

A. GRACE Risk Model Nomogram

1. Find Points for Each Predictive Factor.

Killip Class	Points		SBP, mm Hg	Points		Heart Rate Beats/min	Points		Age, y	Points		Creatinine Level, mg/dL	Points
I	0		≤80	58		≤50	0		≤30	0		0-0.39	1
II	20		80-99	53		50-69	3		30-39	8		0.40-0.79	4
III	39		100-119	43		70-89	9		40-49	25		0.80-1.19	7
IV	59		120-139	34		90-109	15		50-59	41		1.20-1.59	10
			140-159	24		110-149	13		60-69	58		1.60-1.99	13
			160-199	10		150-199	38		70-79	75		2.00-3.99	21
			≥200	0		≥200	46		80-89	91		>4.0	28
									≥90	100			

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum Points for All Predictive Factors:

Killip Class + SBP + Heart Rate + Age + Creatinine Level + Cardiac Arrest at Admission + ST-Segment Deviation + Elevated Cardiac Enzyme Levels = Total Points

3. Look Up Risk Corresponding to Total Points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.
His score would be: 20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196
This person would have about a 16% risk of having an in-hospital death.

Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4, and no risk factors would have the following score:
0 + 58 + 3 + 41 + 1 = 103, which gives approximately a 0.9% risk of having an in-hospital death.

To convert serum creatinine level to micromoles per liter, multiply by 88.4

SBP indicates systolic blood pressure.
Reprinted with permission from Granger et al. (44).

B. Calibration of Simplified Global Registry of ACS Mortality Model

c statistic = 0.83

ACS indicates acute coronary syndrome.
Reprinted with permission from Granger et al. (44).

FIGURE 2 Global Registry of Acute Coronary Events Risk Calculator for In-Hospital Mortality for Acute Coronary Syndrome

The GRACE risk model predicts in-hospital and post-discharge mortality or MI (44,78,79,81). The GRACE tool was developed from 11,389 patients in GRACE and validated in subsequent GRACE and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) IIb cohorts. The sum of scores is applied to a reference nomogram to determine all-cause mortality from hospital discharge to 6 months. The GRACE clinical application tool is a web-based downloadable application available at http://www.outcomes-umassmed.org/grace/ (**Figure 2**) (44,135).

Among patients with a higher TIMI risk score (e.g., ≥3), there is a greater benefit from therapies such as low-molecular-weight heparin (LMWH) (133,136), platelet GP IIb/IIIa inhibitors (137), and an invasive strategy (138). Similarly, the GRACE risk model can identify patients who would benefit from an early invasive strategy (139). Patients with elevated cardiac troponin benefit from more aggressive therapy, whereas those without elevated cardiac troponins may not (140). This is especially true for women in whom some data suggest adverse effects from invasive therapies in the absence of an elevated cardiac troponin value (141). Although B-type natriuretic peptide and N-terminal pro–B-type natriuretic peptide are not useful for the diagnosis of ACS per se (but rather HF, which has many etiologies), they add prognostic value (87-91).

3.3.2.4. Electrocardiogram

The 12-lead ECG is pivotal in the decision pathway for the evaluation and management of patients presenting with symptoms suggestive of ACS (58,59,85). Transient ST changes (≥0.5 mm [0.05 mV]) during symptoms at rest strongly suggest ischemia and underlying severe CAD. Patients without acute ischemic changes on ECG have a reduced risk of MI and a very low risk of in-hospital life-threatening complications, even in the presence of confounding electrocardiographic patterns such as LV hypertrophy (143-145). ST depression (especially horizontal or downsloping) is highly suggestive of NSTE-ACS (21,146,147). Marked symmetrical precordial T-wave inversion (≥2 mm [0.2 mV]) suggests acute ischemia, particularly due to a critical stenosis of the left anterior descending coronary artery (148,149); it may also be seen with acute pulmonary embolism and right-sided ST-T changes.

Nonspecific ST-T changes (usually defined as ST deviation of <0.5 mm [0.05 mV] or T-wave inversion of <2 mm [0.2 mV]) are less helpful diagnostically. Significant Q waves are less helpful, although by suggesting prior MI, they indicate a high likelihood of significant CAD. Isolated Q waves in lead 3 are a normal finding. A completely normal ECG in a patient with chest pain does not exclude ACS, because 1% to 6% of such patients will have a MI,

and at least 4% will have UA (59-61). Fibrinolytic therapy is contraindicated for patients with ACS without ST-elevation, except for those with electrocardiographic evidence of true posterior MI (i.e., ST-elevation in posterior chest leads [V_7 to V_9]). This can be evaluated when acute myocardial infarction (AMI) is suspected but electrocardiographic changes are modest or not present (82-84); a transthoracic echocardiogram to evaluate for posterior wall motion abnormalities may also be helpful in this setting.

Alternative causes of ST-T changes include LV aneurysm, pericarditis, myocarditis, bundle-branch block, LV hypertrophy, hyperkalemia, Prinzmetal angina, early repolarization, apical LV ballooning syndrome (Takotsubo cardiomyopathy, Section 7.13), and Wolff-Parkinson-White conduction. Central nervous system events and therapy with tricyclic antidepressants or phenothiazines can cause deep T-wave inversion.

3.3.2.5. Physical Examination

The physical examination is helpful in assessing the hemodynamic impact of an ischemic event. Patients with suspected ACS should have vital signs measured (BP in both arms if dissection is suspected) and should undergo a thorough cardiovascular examination. Patients with evidence of LV dysfunction on examination (e.g., rales, S_3 gallop) or acute mitral regurgitation have a higher likelihood of severe underlying CAD and are at high risk of a poor outcome. In the SHOCK (Should we Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) study, NSTEMI accounted for approximately 20% of cardiogenic shock complicating MI (150). Other trials have reported lower percentages (92,151). The physical examination may also help identify comorbid conditions (e.g., occult GI bleeding) that could impact therapeutic risk and decision making.

See *Online Data Supplement 2 for additional information on risk stratification.*

3.4. Cardiac Biomarkers and the Universal Definition of MI: Recommendations

See **Table 5** for a summary of recommendations from this section and Online Data Supplement 3 for additional information on cardiac injury markers and the universal definition of AMI.

3.4.1. Biomarkers: Diagnosis

CLASS I

1. **Cardiac-specific troponin (troponin I or T when a contemporary assay is used) levels should be measured at presentation and 3 to 6 hours after symptom onset in all patients who present with symptoms consistent with ACS to identify a rising and/or falling pattern (21,64,67-71,152-156). (Level of Evidence: A)**

TABLE 5	Summary of Recommendations for Cardiac Biomarkers and the Universal Definition of MI			
Recommendations		**COR**	**LOE**	**References**
Diagnosis				
Measure cardiac-specific troponin (troponin I or T) at presentation and 3–6 h after symptom onset in all patients with suspected ACS to identify pattern of values		I	A	(21,64,67–71,152–156)
Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features		I	A	(21,72–74,157)
Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values		I	A	(67,68,72)
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS		III: No Benefit	A	(158–164)
Prognosis				
Troponin elevations are useful for short- and long-term prognosis		I	B	(71,73,165,166)
Remeasurement of troponin value once on d 3 or 4 in patients with MI may be reasonable as an index of infarct size and dynamics of necrosis		IIb	B	(164,165)
BNP may be reasonable for additional prognostic information		IIb	B	(87,88,167–171)

ACS indicates acute coronary syndromes; BNP, B-type natriuretic peptide; CK-MB, creatine kinase myocardial isoenzyme; COR, Class of Recommendation; LOE, Level of Evidence; and MI, myocardial infarction.

2. **Additional troponin levels should be obtained beyond 6 hours after symptom onset in patients with normal troponins on serial examination when electrocardiographic changes and/or clinical presentation confer an intermediate or high index of suspicion for ACS (21,72–74,157). (Level of Evidence: A)**

3. **If the time of symptom onset is ambiguous, the time of presentation should be considered the time of onset for assessing troponin values (67,68,72). (Level of Evidence: A)**

CLASS III: NO BENEFIT

1. **With contemporary troponin assays, creatine kinase myocardial isoenzyme (CK-MB) and myoglobin are not useful for diagnosis of ACS (158–164). (Level of Evidence: A)**

3.4.2. Biomarkers: Prognosis

CLASS I

1. **The presence and magnitude of troponin elevations are useful for short- and long-term prognosis (71,73,165,166). (Level of Evidence: B)**

CLASS IIb

1. **It may be reasonable to remeasure troponin once on day 3 or day 4 in patients with MI as an index of infarct size and dynamics of necrosis (164,165). (Level of Evidence: B)**

2. **Use of selected newer biomarkers, especially B-type natriuretic peptide, may be reasonable to provide additional prognostic information (87,88,167–171). (Level of Evidence: B)**

Cardiac troponins are the mainstay for diagnosis of ACS and for risk stratification in patients with ACS. The primary diagnostic biomarkers of myocardial necrosis are cardiac troponin I and cardiac troponin T. Features that favor troponins for detection of ACS include high concentrations of troponins in the myocardium; virtual absence of troponins in

nonmyocardial tissue; high-release ratio into the systemic circulation (amount found in blood relative to amount depleted from myocardium); rapid release into the blood in proportion to the extent of myocardial injury; and the ability to quantify values with reproducible, inexpensive, rapid, and easily applied assays. The 2012 Third Universal Definition of MI provides criteria that classify 5 clinical presentations of MI on the basis of pathological, clinical, and prognostic factors (21). In the appropriate clinical context, MI is indicated by a rising and/or falling pattern of troponin with ≥1 value above the 99th percentile of the upper reference level and evidence for serial increases or decreases in the levels of troponins (67,68,156). The potential consequences of emerging high-sensitivity troponin assays include increases in the diagnosis of NSTEMI (152,172,173) influenced by the definition of an abnormal troponin (67,153,174,175). The recommendations in this section are formulated from studies predicated on both the new European Society of Cardiology/ACC/AHA/World Health Organization criteria (21) and previous criteria/redefinitions of MI based on earlier-generation troponin assays (Appendix 4, Table A).

3.4.3. Cardiac Troponins

See Online Data Supplement 4 for additional information on cardiac troponins.

Of the 3 troponin subunits, 2 subunits (troponin I and troponin T) are derived from genes specifically expressed in the myocardium. Cardiac troponin measurements provide highly sensitive results specific for detecting cardiomyocyte necrosis (34,173). Highly sensitive assays can identify cardiac troponin not only in the blood of patients with acute cardiac injury, but also in the blood of most healthy people (64,68,70,166,176,177). As assay sensitivity increases, a greater proportion of patients will have detectable long-term elevations in troponin, thus

requiring consideration of serial changes for the diagnosis of MI. Clinicians should be aware of the sensitivity of the tests used for troponin evaluation in their hospitals and cutpoint concentrations for clinical decisions. Markedly elevated values are usually related to MI, myocarditis, rare analytical factors, or chronic elevations in patients with renal failure and in some patients with HF.

CPGs endorse the 99th percentile of the upper reference level as the appropriate cutpoint for considering myocardial necrosis (21,22). For the diagnosis of acute myocardial necrosis, it is important to determine not only the peak troponin value, but also serial changes:

1. A troponin value above the 99th percentile of the upper reference level is required. Additionally, evidence for a serial increase or decrease ≥20% is required if the initial value is elevated (21,178).
2. For any troponin values below or close to the 99th percentile, evidence for acute myocardial necrosis is indicated by a change of ≥3 standard deviations of the variation around the initial value as determined by the individual laboratory (21,179).
3. Clinical laboratory reports should indicate whether significant changes in cardiac troponin values for the particular assay have occurred.

Absolute changes in nanograms per liter of high-sensitivity cardiac troponin T levels appear to have a significantly higher diagnostic accuracy for AMI than relative changes and may distinguish AMI from other causes of high-sensitivity cardiac troponin T elevations (71). This has also been suggested for some contemporary assays (71). Troponins are elevated in MI as early as 2 to 4 hours after symptom onset (64,70), and many medical centers obtain troponins at 3 hours. Depending on the assay, values may not become abnormal for up to 12 hours. In the vast majority of patients with symptoms suggestive of ACS, MI can be excluded or confirmed within 6 hours, because very few patients present immediately after symptom onset. In high-risk patients, measurements after 6 hours may be required to identify ACS.

Solitary elevations of troponin cannot be assumed to be due to MI, because troponin elevations can be due to tachyarrhythmia, hypotension or hypertension, cardiac trauma, acute HF, myocarditis and pericarditis, acute pulmonary thromboembolic disease, and severe noncardiac conditions such as sepsis, burns, respiratory failure, acute neurological diseases, and drug toxicity (including cancer chemotherapy). Chronic elevations can result from structural cardiac abnormalities such as LV hypertrophy or ventricular dilatation and are also common in patients with renal insufficiency (34). Patients with end-stage renal disease and no clinical evidence of ACS frequently have elevations of cardiac troponin (180-182). With conventional assays, this is more common with cardiac troponin T than with cardiac troponin I (180).

In the diagnosis of NSTEMI, cardiac troponin values must manifest an acute pattern consistent with the clinical events, including ischemic symptoms and electrocardiographic changes. Troponin elevations may persist for up to 14 days or occasionally longer. There is a paucity of guidelines for establishment of reinfarction during the acute infarct period on the basis of troponin measurements. References suggest that an increase of >20% of previous troponin levels or an absolute increase of high-sensitivity cardiac troponin T values (e.g., >7 ng/L over 2 hours) may indicate reinfarction (183-185).

During pregnancy, troponin values are within the normal range in the absence of cardiovascular morbidities. There is controversy as to whether troponin levels are elevated in pre-eclampsia, eclampsia, or gestational hypertension (186-189). When present, cardiac troponin elevations reflect myocardial necrosis.

Point-of-care troponin values may provide initial diagnostic information, although their sensitivity is substantially below that of central laboratory methods (154,155,190-192). In addition, the rigorous quantitative assay standardization needed for routine diagnosis favors central laboratory testing.

3.4.3.1. Prognosis

Troponin elevations convey prognostic assessment beyond that of clinical information, the initial ECG, and the predischarge stress test (71). In addition, troponin elevations may provide information to direct therapy. Patients with cardiac troponin elevations are at high risk and benefit from intensive management and early revascularization (193-195). High risk is optimally defined by the changing pattern as described in Section 3.4.3. Cardiac troponin elevations correlate with estimation of infarct size and risk of death; persistent elevation 72 to 96 hours after symptom onset may afford relevant information in this regard (164). Elevations of cardiac troponin can occur for multiple reasons other than MI. In these cases, there is often substantial risk of adverse outcomes, as troponin elevation indicates cardiomyocyte necrosis (181).

3.4.4. CK-MB and Myoglobin Compared With Troponin

Previously, CK-MB was used for early evidence of myocardial injury. Because myoglobin is a relatively small molecule, it is rapidly released from infarcted myocardium. CK-MB is much less sensitive for detection of myocardial injury than troponin, and substantially more tissue injury is required for its detection. With the availability of cardiac troponin, CK-MB, myoglobin, and other diagnostic biomarkers are no longer necessary (158,160-163,196-198). CK-MB may be used to estimate MI size. Detection of MI after percutaneous coronary intervention (PCI) remains an area of controversy. Because of the increased sensitivity of cardiac troponin, the

prognostic value associated with varying degrees of elevation remains unclear.

See Online Data Supplements 5, 6, and 7 for additional information on cardiac injury markers.

3.5. Immediate Management

3.5.1. Discharge From the ED or Chest Pain Unit: Recommendations

CLASS IIa

1. It is reasonable to observe patients with symptoms consistent with ACS without objective evidence of myocardial ischemia (nonischemic initial ECG and normal cardiac troponin) in a chest pain unit or telemetry unit with serial ECGs and cardiac troponin at 3- to 6-hour intervals (196,197,199-201). *(Level of Evidence: B)*

2. It is reasonable for patients with possible ACS who have normal serial ECGs and cardiac troponins to have a treadmill ECG (200-202) *(Level of Evidence: A)*, stress myocardial perfusion imaging (200), or stress echocardiography (203,204) before discharge or within 72 hours after discharge. *(Level of Evidence: B)*

3. In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary CT angiography to assess coronary artery anatomy (205-207) *(Level of Evidence: A)* or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia (208,209). *(Level of Evidence: B)*

4. It is reasonable to give low-risk patients who are referred for outpatient testing daily aspirin, short-acting nitroglycerin, and other medication if appropriate (e.g., beta blockers), with instructions about activity level and clinician follow-up. *(Level of Evidence: C)*

The majority of patients presenting to the ED with chest pain do not have ACS (**Figure 1**), and most are at low risk for major morbidity and mortality (35). Low-risk patients are usually identified by an absence of history of cardiovascular disease, normal or near-normal initial ECG, normal initial troponin, and clinical stability (35,202). The utility of an accelerated diagnostic protocol for detecting patients with benign conditions versus those who require admission for serious disease has been established (35). At minimum, these protocols involve serial ECGs and troponin measurements, both of which can be performed in the ED, a separate chest pain unit, or a telemetry unit. A 30-day negative predictive value >99% for ACS has been reported for patients presenting to the ED with chest pain who undergo a 2-hour accelerated diagnostic protocol composed of a TIMI risk score of 0, normal ECG, and normal high-sensitivity troponin at 0 hours and 2 hours (assuming appropriate follow-up care) (65,210). Some protocols also call for a functional or anatomic test (e.g., treadmill test, rest

scintigraphy, coronary CT angiography, stress imaging). Coronary CT angiography is associated with rapid assessment, high negative predictive value, decreased length of stay, and reduced costs (205-207); however, in the latter studies, it increased the rate of invasive coronary angiography and revascularization with uncertain long-term benefits in low-risk patients without ECG or troponin alterations (211). Accelerated diagnostic protocols are also potentially applicable in intermediate-risk patients, whose presentation includes a history of cardiovascular disease, diabetes mellitus, chronic kidney disease (CKD), and/or advanced age (202).

See Online Data Supplement 8 for additional information on discharge from the ED or chest pain unit.

4. EARLY HOSPITAL CARE

The standard of care for patients who present with NSTE-ACS, including those with recurrent symptoms, ischemic electrocardiographic changes, or positive cardiac troponins, is admission for inpatient management. The goals of treatment are the immediate relief of ischemia and the prevention of MI and death. Initially, stabilized patients with NSTE-ACS are admitted to an intermediate (or step-down) care unit. Patients undergo continuous electrocardiographic rhythm monitoring and observation for recurrent ischemia. Bed or chair rest is recommended for patients admitted with NSTE-ACS. Patients with NSTE-ACS should be treated with antianginal (Section 4.1.2.5), antiplatelet, and anticoagulant therapy (Section 4.3). Patients are managed with either an early invasive strategy or an ischemia-guided strategy (Section 4.4).

Patients with continuing angina, hemodynamic instability, uncontrolled arrhythmias, or a large MI should be admitted to a coronary care unit. The nurse-to-patient ratio should be sufficient to provide 1) continuous electrocardiographic rhythm monitoring, 2) frequent assessment of vital signs and mental status, and 3) ability to perform rapid cardioversion and defibrillation. These patients are usually observed in the coronary care unit for at least 24 hours. Those without recurrent ischemia, significant arrhythmias, pulmonary edema, or hemodynamic instability can be considered for admission or transfer to an intermediate care or telemetry unit.

An assessment of LV function is recommended because depressed LV function will likely influence pharmacological therapies (e.g., angiotensin-converting enzyme [ACE] inhibitors for depressed left ventricular ejection fraction [LVEF]), may suggest the presence of more extensive CAD, and may influence the choice of revascularization (PCI versus coronary artery bypass graft surgery [CABG]). Because significant valvular disease may also influence the type of revascularization, echocardiography

rather than ventriculography is often preferred for assessment of LV function.

4.1. Standard Medical Therapies.

See Table 6 for a summary of recommendations from this section.

4.1.1. Oxygen: Recommendation

CLASS I

1. Supplemental oxygen should be administered to patients with NSTE-ACS with arterial oxygen saturation less than 90%, respiratory distress, or other high-risk features of hypoxemia. *(Level of Evidence: C)*

Patients with cyanosis, arterial oxygen saturation <90%, respiratory distress, or other high-risk features of hypoxemia are treated with supplemental oxygen. The 2007 UA/NSTEMI CPG recommended the routine administration of supplemental oxygen to all patients with NSTE-ACS during the first 6 hours after presentation on the premise that it is safe and may alleviate hypoxemia (212). The benefit of routine supplemental oxygen administration in normoxic patients with NSTE-ACS has never been demonstrated. At the time of GWC deliberations, data emerged that routine use of supplemental oxygen in cardiac patients may have untoward effects, including increased coronary vascular resistance, reduced coronary blood flow, and increased risk of mortality (213–215).

TABLE 6	Summary of Recommendations for Early Hospital Care			
Recommendations		**COR**	**LOE**	**References**
Oxygen				
Administer supplemental oxygen only with oxygen saturation <90%, respiratory distress, or other high-risk features for hypoxemia		I	C	N/A
Nitrates				
Administer sublingual NTG every 5 min × 3 for continuing ischemic pain and then assess need for IV NTG		I	C	(216–218)
Administer IV NTG for persistent ischemia, HF, or hypertension		I	B	(219–224)
Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor		III: Harm	B	(225–227)
Analgesic therapy				
IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications		IIb	B	(232,233)
NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of MACE associated with their use		III: Harm	B	(234,35)
Beta-adrenergic blockers				
Initiate oral beta blockers within the first 24 h in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade		I	A	(240–242)
Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant NSTE-ACS, *stabilized* HF, and reduced systolic function		I	C	N/A
Re-evaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers		I	C	N/A
It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS		IIa	C	(241,243)
IV beta blockers are potentially harmful when risk factors for shock are present		III: Harm	B	(244)
CCBs				
Administer initial therapy with nondihydropyridine CCBs with recurrent ischemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 s, or second- or third-degree atrioventricular block without a cardiac pacemaker		I	B	(248–250)
Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications		I	C	N/A
CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects*		I	C	N/A
Long-acting CCBs and nitrates are recommended for patients with coronary artery spasm		I	C	N/A
Immediate-release nifedipine is contraindicated in the absence of a beta blocker		III: Harm	B	(251,252)
Cholesterol management				
Initiate or continue high-intensity statin therapy in patients with no contraindications		I	A	(269–273)
Obtain a fasting lipid profile, preferably within 24 h		IIa	C	N/A

*Short-acting dihydropyridine calcium channel antagonists should be avoided.

CCB indicates calcium channel blocker; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; MACE, major adverse cardiac event; N/A, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-elevation acute coronary syndromes; and NTG, nitroglycerin.

4.1.2. Anti-Ischemic and Analgesic Medications

4.1.2.1. Nitrates: Recommendations

CLASS I

1. Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 mg to 0.4 mg) every 5 minutes for up to 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin if not contraindicated (216–218). *(Level of Evidence: C)*

2. Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, HF, or hypertension (219-224). *(Level of Evidence: B)*

CLASS III: HARM

1. Nitrates should not be administered to patients with NSTE-ACS who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil (225–227). *(Level of Evidence: B)*

Nitrates are endothelium-independent vasodilators with peripheral and coronary vascular effects. By dilating the capacitance vessels, nitrates decrease cardiac preload and reduce ventricular wall tension. More modest effects on the arterial circulation result in afterload reduction and further decrease in MVO_2. This may be partially offset by reflex increases in heart rate and contractility, which counteract the reduction in MVO_2 unless a beta blocker is concurrently administered. Nitrates also dilate normal and atherosclerotic coronary arteries and increase coronary collateral flow. Nitrates may also inhibit platelet aggregation (228).

RCTs have not shown a reduction in MACE with nitrates. The rationale for nitrate use in NSTE-ACS is extrapolated from pathophysiological principles and extensive (although uncontrolled) clinical observations, experimental studies, and clinical experience. The decision to administer nitrates should not preclude therapy with other proven mortality-reducing interventions such as beta blockers.

Intravenous nitroglycerin is beneficial in patients with HF, hypertension, or symptoms that are not relieved with sublingual nitroglycerin and administration of a beta blocker (219,221-224). Patients who require intravenous nitroglycerin for >24 hours may require periodic increases in the infusion rate and use of nontolerance-producing regimens (e.g., intermittent dosing) to maintain efficacy. In current practice, most patients who require continued intravenous nitroglycerin for the relief of angina undergo prompt coronary angiography and revascularization. Topical or oral nitrates are acceptable alternatives to intravenous nitroglycerin for patients who do not have refractory or recurrent ischemia (229,230). Side effects of nitrates include headache and hypotension. Nitrates should not be administered to patients with hypotension or to

those who received a phosphodiesterase inhibitor and are administered with caution to patients with right ventricular infarction (231).

See Online Data Supplement 9 for additional information on nitrates.

4.1.2.2. Analgesic Therapy: Recommendations

CLASS IIb

1. In the absence of contraindications, it may be reasonable to administer morphine sulfate intravenously to patients with NSTE-ACS if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications (232,233). *(Level of Evidence: B)*

CLASS III: HARM

1. Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of MACE associated with their use (234,235). *(Level of Evidence: B)*

The role of morphine sulfate was re-evaluated for this CPG revision, including studies that suggest the potential for adverse events with its use (232). Morphine sulfate has potent analgesic and anxiolytic effects, as well as hemodynamic actions, that are potentially beneficial in NSTE-ACS. It causes venodilation and produces modest reductions in heart rate (through increased vagal tone) and systolic BP. In patients with symptoms despite antianginal treatment, morphine (1 mg to 5 mg IV) may be administered during intravenous nitroglycerin therapy with BP monitoring. The morphine dose may be repeated every 5 to 30 minutes to relieve symptoms and maintain the patient's comfort. Its use should not preclude the use of other anti-ischemic therapies with proven benefits in patients with NSTE-ACS. To our knowledge, no RCTs have assessed the use of morphine in patients with NSTE-ACS or defined its optimal administration schedule. Observational studies have demonstrated increased adverse events associated with the use of morphine sulfate in patients with ACS and acute decompensated HF (232,233,236). Although these reports were observational, uncontrolled studies limited by selection bias, they raised important safety concerns.

Although constipation, nausea, and/or vomiting occur in >20% of patients, hypotension and respiratory depression are the most serious complications of excessive use of morphine. Naloxone (0.4 mg to 2.0 mg IV) may be administered for morphine overdose with respiratory or circulatory depression.

Traditional NSAIDs and selective cyclooxygenase (COX)-2 inhibitors markedly block endothelial prostacyclin production, which leads to unopposed platelet aggregation by platelet-derived thromboxane A_2. Both

types of NSAIDs prevent the beneficial actions of aspirin and interfere with the inhibition of COX-1, thromboxane A_2 production, and platelet aggregation. Because of their inhibitory activity on the ubiquitous COXs, NSAIDs have an extensive adverse side effect profile, particularly renal and gastrointestinal. The increased cardiovascular hazards associated with NSAIDs have been observed in several studies of patients without ACS (234,235,237,238). The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen Or Naproxen) trial, in progress at the time of publication, is the first study of patients with high cardiovascular risk who are receiving long-term treatment with a selective COX-2 inhibitor or traditional NSAIDs. PRECISION will examine the relative cardiovascular safety profiles of celecoxib, ibuprofen, and naproxen in patients without ACS (239).

See Online Data Supplement 10 *for additional information on analgesic therapy.*

4.1.2.3. Beta-Adrenergic Blockers: Recommendations

CLASS I

1. Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) (240–242). *(Level of Evidence: A)*

2. In patients with concomitant NSTE-ACS, *stabilized* HF, and reduced systolic function, it is recommended to continue beta-blocker therapy with 1 of the 3 drugs proven to reduce mortality in patients with HF: sustained-release metoprolol succinate, carvedilol, or bisoprolol. *(Level of Evidence: C)*

3. Patients with documented contraindications to beta blockers in the first 24 hours of NSTE-ACS should be re-evaluated to determine their subsequent eligibility. *(Level of Evidence: C)*

CLASS IIa

1. It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS (241,243). *(Level of Evidence: C)*

CLASS III: HARM

1. Administration of intravenous beta blockers is potentially harmful in patients with NSTE-ACS who have risk factors for shock (244). *(Level of Evidence: B)*

Beta blockers decrease heart rate, contractility, and BP, resulting in decreased MVO_2. Beta blockers without increased sympathomimetic activity should be administered orally in the absence of contraindications. Although early

administration does not reduce short-term mortality (241,244), beta blockers decrease myocardial ischemia, reinfarction, and the frequency of complex ventricular dysrhythmias (240,245), and they increase long-term survival. Early beta blockade, particularly if given intravenously, can increase the likelihood of shock in patients with risk factors. Risk factors for shock include patients >70 years of age, heart rate >110 beats per minute, systolic BP <120 mm Hg, and late presentation (244). In patients with LV dysfunction (LVEF <0.40) with or without pulmonary congestion, beta blockers are strongly recommended before discharge. Beta blockers should be used prudently with ACE inhibitors or angiotensin-receptor blockers (ARBs) in patients with HF. Renin-angiotensin-aldosterone system blocking agents should be cautiously added in patients with decompensated HF (246). Beta blockers without intrinsic sympathomimetic activity should be used, especially beta-1 blockers such as sustained-release metoprolol succinate, bisoprolol, or carvedilol, a beta-1 and alpha-1 blocker. This is because of their mortality benefit in patients with HF and systolic dysfunction (246,247). In patients with chronic obstructive lung disease or a history of asthma, beta blockers are not contraindicated in the absence of active bronchospasm. Beta-1 selective beta blockers are preferred and should be initiated at a low dosage.

See Online Data Supplement 11 *for additional information on beta blockers, including risk factors for shock.*

4.1.2.4. Calcium Channel Blockers: Recommendations

CLASS I

1. In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta blockers, a non-dihydropyridine calcium channel blocker (CCB) (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval greater than 0.24 second, or second- or third-degree atrioventricular block without a cardiac pacemaker (248–250). *(Level of Evidence: B)*

2. Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta blockers and nitrates. *(Level of Evidence: C)*

3. CCBs† are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects. *(Level of Evidence: C)*

4. Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. *(Level of Evidence: C)*

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†Short-acting dihydropyridine calcium channel antagonists should be avoided.

CLASS III: HARM

1. Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy (251,252). *(Level of Evidence: B)*

CCBs include dihydropyridines and nondihydropyridines. The dihydropyridines (nifedipine and amlodipine) produce the most marked peripheral vasodilation and have little direct effect on contractility, atrioventricular conduction, and heart rate. The nondihydropyridines (diltiazem and verapamil) have significant negative inotropic actions and negative chronotropic and dromotropic effects. All CCBs cause similar coronary vasodilation and are preferred in vasospastic angina (253). They also alleviate ischemia due to obstructive CAD by decreasing heart rate and BP. Verapamil and diltiazem decreased reinfarction in patients without LV dysfunction in some (248,249,254) but not all studies (255,256). Verapamil may be beneficial in reducing long-term events after AMI in hypertensive patients without LV dysfunction (250) and in patients with MI and HF receiving an ACE inhibitor (257). Immediate-release nifedipine causes a dose-related increase in mortality in patients with CAD and harm in ACS and is not recommended for routine use in patients with ACS (251,258). Long-acting preparations may be useful in older patients with systolic hypertension (259). There are no significant trial data on efficacy of amlodipine or felodipine in patients with NSTE-ACS.

See *Online Data Supplement 12* for additional information on CCBs.

4.1.2.5. Other Anti-Ischemic Interventions

Ranolazine
Ranolazine is an antianginal medication with minimal effects on heart rate and BP (260,261). It inhibits the late inward sodium current and reduces the deleterious effects of intracellular sodium and calcium overload that accompany myocardial ischemia (262). Ranolazine is currently indicated for treatment of chronic angina. The MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes-Thrombosis In Myocardial Infarction) 36 trial examined the efficacy and safety of ranolazine in 6,560 patients with NSTE-ACS who presented within 48 hours of ischemic symptoms (263). In a post hoc analysis in women, ranolazine was associated with a reduced incidence of the primary endpoint (cardiovascular death, MI, or recurrent ischemia), principally owing to a 29% reduction in recurrent ischemia (116). In the subgroup with prior chronic angina (n=3,565), ranolazine was associated with a lower primary composite endpoint, a significant reduction of worsening angina, and increased exercise duration (264). Because the primary endpoint of the original MERLIN-TIMI

36 trial was not met, all additional analyses should be interpreted with caution. The recommended initial dose is 500 mg orally twice daily, which can be uptitrated to a maximum of 1,000 mg orally twice daily. Ranolazine is usually well tolerated; its major adverse effects are constipation, nausea, dizziness, and headache. Ranolazine prolongs the QTc interval in a dose-related manner, but QTc prolongation requiring dose reduction was comparable with ranolazine and placebo in the MERLIN-TIMI 36 trial (263).

See *Online Data Supplement 13* for additional information on ranolazine.

Intra-Aortic Balloon Pump (IABP) Counterpulsation
IABP counterpulsation may be used in patients with NSTE-ACS to treat severe persistent or recurrent ischemia, especially in patients awaiting invasive angiography and revascularization, despite intensive medical therapy. In experimental studies, IABP counterpulsation increases diastolic BP and coronary blood flow and potentially augments cardiac output while diminishing LV end-diastolic pressure. The use of IABP for refractory ischemia dates back several decades, and its current application is predominantly driven by clinical experience and nonrandomized observational studies (265). When studied in rigorous RCTs, IABP counterpulsation failed to reduce MACE in high-risk elective PCI (266), decrease infarct size after primary PCI for acute STEMI (267), or diminish early mortality in patients with cardiogenic shock complicating AMI (268).

4.1.2.6. Cholesterol Management

CLASS I

1. High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use (269–273). *(Level of Evidence: A)*

CLASS IIa

1. It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. *(Level of Evidence: C)*

Therapy with statins in patients with NSTE-ACS reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. High-risk patients, such as those with NSTE-ACS, derive more benefit in reducing these events from high-intensity statins, such as atorvastatin which lower low-density lipoprotein cholesterol levels by ≥50% as in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) and MIRACL (Myocardial Ischemia Reduction With Acute Cholesterol Lowering) trials (273,274), than from moderate- or low-intensity statins (18,272). These findings provide the basis for high-intensity statin therapy

after stabilization of patients with NSTE-ACS. In addition, early introduction of this approach can promote improved compliance with this regimen.

4.2. Inhibitors of the Renin-Angiotensin-Aldosterone System: Recommendations

CLASS I

1. ACE inhibitors should be started and continued indefinitely in all patients with LVEF less than 0.40 and in those with hypertension, diabetes mellitus, or stable CKD (Section 7.6), unless contraindicated (275,276). *(Level of Evidence: A)*

2. ARBs are recommended in patients with HF or MI with LVEF less than 0.40 who are ACE inhibitor intolerant (277,278). *(Level of Evidence: A)*

3. Aldosterone blockade is recommended in patients post–MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K+ >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta blocker and have a LVEF 0.40 or less, diabetes mellitus, or HF (279). *(Level of Evidence: A)*

CLASS IIa

1. ARBs are reasonable in other patients with cardiac or other vascular disease who are ACE inhibitor intolerant (280). *(Level of Evidence: B)*

CLASS IIb

1. ACE inhibitors may be reasonable in all other patients with cardiac or other vascular disease (281,282). *(Level of Evidence: B)*

ACE inhibitors reduce mortality in patients with recent MI, primarily those with LV dysfunction (LVEF <0.40) with or without pulmonary congestion (283-285). In patients with normal LV function (including patients with diabetes mellitus), total mortality and MACE (including HF) are reduced. It has been found that approximately 15% of patients with NSTEMI develop HF during hospitalization, with the rate increasing to 24% of patients 1 year later (286). A meta-analysis demonstrated a small but significant (0.48%) absolute benefit of early initiation of an ACE inhibitor on survival at 30 days, with benefit seen as early as 24 hours after admission for AMI (283). An ACE inhibitor should be used cautiously in the first 24 hours of AMI, because it may result in hypotension or renal dysfunction (283). It may be prudent to initially use a short-acting ACE inhibitor, such as captopril or enalapril, in patients at increased risk of these adverse events. In patients with significant renal dysfunction, it is sensible to stabilize renal function before initiating an ACE inhibitor or an ARB, with re-evaluation of creatinine levels after drug initiation. An ARB may be substituted for an ACE inhibitor with similar benefits on survival (277,278). Combining an ACE inhibitor and an ARB

may result in an increase in adverse events (277,278). In a study in which patients with AMI with LV dysfunction (LVEF <0.40) with or without HF were randomized 3 to 14 days after AMI to receive eplerenone (a selective aldosterone blocker), eplerenone was efficacious as an adjunct to ACE inhibitors and beta blockers in decreasing long-term mortality (279,287). In a study of patients with HF, >50% of whom had an ischemic etiology, spironolactone (a nonselective aldosterone inhibitor) was beneficial (279); however, RCT data on MI are not available.

See Online Data Supplement 14 for additional information on inhibitors of the renin-angiotensin-aldosterone system.

4.3. Initial Antiplatelet/Anticoagulant Therapy in Patients With Definite or Likely NSTE-ACS

4.3.1. Initial Oral and Intravenous Antiplatelet Therapy in Patients With Definite or Likely NSTE-ACS Treated With an Initial Invasive or Ischemia-Guided Strategy: Recommendations

See Table 7 for a summary of recommendations from this section and Online Data Supplement 15 for additional information on initial oral and intravenous antiplatelet therapy in patients with definite or likely NSTE-ACS treated with an early invasive or an ischemia-guided strategy.

CLASS I‡

1. Non–enteric-coated, chewable aspirin (162 mg to 325 mg) should be given to *all* patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 mg/d to 325 mg/d) should be continued indefinitely (288–290,293,391). *(Level of Evidence: A)*

2. In patients with NSTE-ACS who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered (291). *(Level of Evidence: B)*

3. A P2Y$_{12}$ inhibitor (either clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with either an early invasive§ or ischemia-guided strategy. Options include:
   - Clopidogrel: 300-mg or 600-mg loading dose, then 75 mg daily (289,292) *(Level of Evidence: B)*
   - Ticagrelor‖: 180-mg loading dose, then 90 mg twice daily (293,294) *(Level of Evidence: B)*

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‡See Section 5.1.2.1 for recommendations at the time of PCI.

§See Section 4.3.1.2 for prasugrel indications in either an early invasive or ischemia-guided strategy.

‖The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

TABLE 7   Summary of Recommendations for Initial Antiplatelet/Anticoagulant Therapy in Patients With Definite or Likely NSTE-ACS and PCI

Recommendations	Dosing and Special Considerations	COR	LOE	References
Aspirin				
• Non-enteric-coated aspirin to *all* patients promptly after presentation	162 mg-325 mg	I	A	(288-290)
• Aspirin maintenance dose continued indefinitely	81 mg/d-325 mg/d*	I	A	(288-290, 293,391)
P2Y$_{12}$ inhibitors				
• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B	(291)
• P2Y$_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: – Clopidogrel – Ticagrelor*	300-mg or 600-mg loading dose, then 75 mg/d 180-mg loading dose, then 90 mg BID	I	B	(289,292) (293,294)
• P2Y$_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	N/A	I	B	(293,296,302, 330,331)
• Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B	(293,294)
GP IIb/IIIa inhibitors				
• GP IIb/IIIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin)	Preferred options are eptifibatide or tirofiban	IIb	B	(43,94,295)
Parenteral anticoagulant and fibrinolytic therapy				
• SC enoxaparin for duration of hospitalization or until PCI is performed	• 1 mg/kg SC every 12 h (reduce dose to 1 mg/kg/d SC in patients with CrCl <30 mL/min) • Initial 30 mg IV loading dose in selected patients	I	A	(133,136,309)
• Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only	• Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h • Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT	I	B	(292,293, 310,311)
• SC fondaparinux for the duration of hospitalization or until PCI is performed	2.5 mg SC daily	I	B	(312-314)
• Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux	N/A	I	B	(313-315)
• IV UFH for 48 h or until PCI is performed	• Initial loading dose 60 IU/kg (max 4,000 IU) with initial infusion 12 IU/kg/h (max 1,000 IU/ h) • Adjusted to therapeutic aPTT range	I	B	(316-322)
• IV fibrinolytic treatment not recommended in patients with NSTE-ACS	N/A	III: Harm	A	(93,329)

See Section 5.1.2.1 for recommendations on antiplatelet/anticoagulant therapy at the time of PCI and Sections 6.2.1 and 6.3 for recommendations on posthospital therapy.
*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

aPTT indicates activated partial thromboplastin time; BID, twice daily; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; GP, glycoprotein; IV, intravenous; LOE, Level of Evidence; max, maximum; N/A, not available; NSTE-ACS, non-ST-elevation acute coronary syndromes; PCI, percutaneous coronary intervention; SC, subcutaneous; and UFH, unfractionated heparin.

CLASS IIa

1. It is reasonable to use ticagrelor in preference to clopidogrel for P2Y$_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy (293,294). *(Level of Evidence: B)*

CLASS IIb

1. In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban (43,94,295). *(Level of Evidence: B)*

Despite the large number of new antiplatelet and antithrombotic agents, aspirin, which targets COX and subsequent thromboxane A$_2$ inhibition, is the mainstay of antiplatelet therapy. Multiple other pathways of platelet activation can be targeted by agents that inhibit the platelet P2Y$_{12}$ receptor, including thienopyridine prodrug agents, such as clopidogrel

and prasugrel, which require conversion into molecules that bind irreversibly to the P2Y$_{12}$ receptor. Additional pyrimidine derivatives, including ticagrelor, do not require biotransformation and bind reversibly to the P2Y$_{12}$ receptor, antagonizing adenosine diphosphate platelet activation. In addition to these oral agents, intravenous GP IIb/IIIa receptor inhibitors, including abciximab, eptifibatide, and tirofiban, target the final common pathway of platelet aggregation. In the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome) trial, patients were randomly assigned to either early, pre-PCI double-bolus eptifibatide or delayed, provisional eptifibatide. Seventy-five percent of the patients received upstream, preprocedure clopidogrel. The risk of TIMI major bleeding in the early eptifibatide group was 2.6% compared with 1.8% (p=0.02) in the delayed provisional group (295). In the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV-Acute Coronary Syndromes) trial, there was no clinical benefit of abciximab in this population; in troponin-negative patients, mortality was 8.5% compared with 5.8% in controls (p=0.002) (288,289,296,297).

4.3.1.1. Aspirin

Aspirin is the established first-line therapy in patients with NSTE-ACS and reduces the incidence of recurrent MI and death (288,289). A loading dose of non–enteric-coated aspirin 162 mg to 325 mg is the initial antiplatelet therapy. The subsequent maintenance dose is 81 mg per day to 162 mg per day; in special circumstances, a higher maintenance dose up to 325 mg daily has been used (391). The lower dose is favored and all patients treated with ticagrelor should receive only 81 mg per day (290). In other countries, available low-dose aspirin formations may include 75 mg and 100 mg. High-dose (≥160 mg) versus low-dose (<160 mg) aspirin is associated with increased bleeding risk in the absence of improved outcomes (298). Most NSAIDs reversibly bind to COX-1, preventing inhibition by aspirin and by COX-2 and may cause prothrombotic effects. Enteric-coated aspirin should be avoided initially because of its delayed and reduced absorption (299).

4.3.1.2. P2Y$_{12}$ Receptor Inhibitors

Three P2Y$_{12}$ receptor inhibitors are approved in the United States for treatment of ischemic myocardial disorders, including NSTE-ACS. For discontinuation before surgery, see Section 5.

Clopidogrel

Administration of clopidogrel with aspirin was superior to administration of aspirin alone in reducing the incidence of cardiovascular death and nonfatal MI or stroke both acutely and over the following 11 months (289,296). There was a slight increase in major bleeding

events with clopidogrel, including a nonsignificant increase in life-threatening bleeding and fatal bleeding (289). An initial loading dose of 300 mg to 600 mg is recommended (289,296,300). A 600-mg loading dose results in a greater, more rapid, and more reliable platelet inhibition compared with a 300-mg loading dose (301). Use of clopidogrel for patients with NSTE-ACS who are aspirin intolerant is based on a study in patients with stable ischemic heart disease (291). When possible, discontinue clopidogrel at least 5 days before surgery (301).

Prasugrel

The metabolic conversion pathways of prasugrel produce more rapid and consistent platelet inhibition than clopidogrel (300). In patients with NSTE-ACS and defined coronary anatomy undergoing planned PCI, a 60-mg loading dose of prasugrel followed by 10 mg daily was compared with a 300-mg loading dose and 75 mg daily of clopidogrel. The composite primary endpoint (cardiovascular death, nonfatal MI, and stroke) was reduced in patients treated with prasugrel (hazard ratio [HR]: 0.81; p=0.001). This was driven by a risk reduction for MI and stent thrombosis with no difference in mortality (302). Counterbalancing the salutary effects of prasugrel was a significant increase in spontaneous bleeding, life-threatening bleeding, and fatal bleeding in the patients treated with prasugrel compared with patients treated with clopidogrel. There was net harm in patients with a history of cerebrovascular events and no clinical benefit in patients >75 years of age or those with low body weight (<60 kg) (302). In patients with NSTE-ACS treated with an ischemia-guided strategy, 1 RCT comparing aspirin and either clopidogrel or prasugrel evaluated the primary endpoint of death from cardiovascular causes, MI, or stroke for up to 30 months; there were similar bleeding rates and no benefit of treatment with prasugrel when compared with treatment with clopidogrel (303). The ACCOAST (A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST-Elevation Myocardial Infarction) RCT of high-risk patients with NSTE-ACS scheduled to undergo early coronary angiography found that a strategy of administration of prasugrel at the time of randomization before angiography did not lead to a reduction in the composite primary endpoint when compared with a strategy of administration of prasugrel only at the time of PCI; however, it did lead to an increase in bleeding complications (304). On the basis of TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study design and the results of TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) and ACCOAST, prasugrel is not recommended for "upfront" therapy in patients with

NSTE-ACS. The use of prasugrel in patients undergoing PCI is addressed in Section 5.

Ticagrelor

Ticagrelor is an oral, reversibly binding P2Y$_{12}$ inhibitor with a relatively short plasma half-life (12 hours). Compared with clopidogrel, ticagrelor has a more rapid and consistent onset of action and, because it is reversible, it has a faster recovery of platelet function. The loading dose of ticagrelor for patients treated either invasively or with an ischemia-guided strategy is 180 mg followed by a maintenance dose of 90 mg twice daily (293,294). In patients with NSTE-ACS treated with ticagrelor compared with clopidogrel, there was a reduction in the composite outcome of death from vascular causes, MI, or stroke (reduction: 11.7% to 9.8%; HR: 0.84; p<0.001) (293). The mortality rate was also lower in those patients treated with ticagrelor. Although overall major bleeding was not increased with ticagrelor, a modest increase in major bleeding and non-procedure-related bleeding occurred in the subgroup of patients who did not undergo CABG (major bleeding: 4.5% versus 3.8%; p=0.02; non-procedure major bleeding: 3.1% versus 2.3%; p=0.05); however, there was no difference in blood transfusion or fatal bleeding (305). Side effects unique to ticagrelor include dyspnea (which occurs in up to 15% of patients within the first week of treatment but is rarely severe enough to cause discontinuation of treatment) (293) and bradycardia. The benefit of ticagrelor over clopidogrel was limited to patients taking 75 mg to 100 mg of aspirin (290). The short half-life requires twice-daily administration, which could potentially result in adverse events in non-compliant patients, particularly after stent implantation. When possible, ticagrelor should be discontinued at least 5 days before surgery (306). Although ticagrelor has not been studied in the absence of aspirin, its use in aspirin-intolerant patients is a reasonable alternative.

Intravenous GP IIb/IIIa Receptor Inhibitors

The small molecule GP IIb/IIIa receptor antagonists, tirofiban and eptifibatide, bind reversibly to the GP IIb/IIIa receptor. Because the drug-to-receptor ratio is high, platelet infusion is not effective in cases of severe bleeding after use of eptifibatide or tirofiban, and they must be cleared from the circulation to reduce bleeding. In contrast, with abciximab, the drug-to-receptor ratio is low, and platelet infusion may be effective.

Several large RCTs evaluated the impact of GP IIb/IIIa receptor inhibitors in patients with NSTE-ACS who were committed to an invasive strategy (295,296,306). The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial evaluated unfractionated heparin (UFH) versus bivalirudin with or without GP IIb/IIIa inhibitors (295,307). The rates of composite ischemia (death, MI, unplanned revascularization) in patients who received bivalirudin alone compared with those who received UFH plus GP IIb/IIIa inhibitors were similar (9% versus 8%; p=0.45) (307). Fewer patients experienced major bleeding with bivalirudin alone than did with heparin plus GP IIb/IIIa inhibitors (4% versus 7%; relative risk [RR]: 0.52; 95% confidence interval [CI]: 0.40 to 0.66; p<0.0001) (307). The ACUITY Timing trial evaluated the benefit of upstream GP IIb/IIIa receptor antagonist compared with its deferred use, testing the hypothesis that earlier administration of GP IIb/IIIa inhibitors in patients destined for PCI would be superior (308). Composite ischemia at 30 days occurred in 7.9% of patients assigned to deferred use compared with 7.1% assigned to upstream administration (RR: 1.12; 95% CI: 0.97 to 1.29; p=0.044 for noninferiority; p=0.13 for superiority). Deferred GP IIb/IIIa inhibitors reduced the 30-day rates of major bleeding compared with upstream use (4.9% versus 6.1%; p<0.001) (308). Similar results were reported by the EARLY ACS investigators, who evaluated eptifibatide given upstream versus delayed, provisional administration in >9,000 patients with NSTE-ACS (295). The composite endpoint of death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic complications occurred in 9.3% of patients in the early-eptifibatide group compared with 10% in the delayed-eptifibatide group (odds ratio [OR]: 0.92; 95% CI: 0.80 to 1.06; p=0.23) (308). As in the ACUITY Timing trial, the early-eptifibatide group had significantly higher rates of bleeding and red cell transfusions (295,308).

4.3.2. Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS: Recommendations

See Table 7 for a summary of recommendations regarding antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS and Online Data Supplement 16 for additional information on combined oral anticoagulant therapy and antiplatelet therapy in patients with definite NSTE-ACS.

CLASS I‡

1. In patients with NSTE-ACS, anticoagulation, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy. Treatment options include:
   - Enoxaparin: 1 mg/kg subcutaneous (SC) every 12 hours (reduce dose to 1 mg/kg SC once daily in patients with creatinine clearance [CrCl] <30 mL/min), continued for the duration of hospitalization or until PCI is performed. An initial intravenous loading dose of 30 mg has been used in selected patients (133,136,309). *(Level of Evidence: A)*

‡See Section 5.1.2.1 for recommendations at the time of PCI.

- Bivalirudin: 0.10 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients managed with an early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor, provided the patient is also treated with DAPT (292,293,310,311). (*Level of Evidence: B*)

- Fondaparinux: 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed (312–314). (*Level of Evidence: B*)

- If PCI is performed while the patient is on fondaparinux, an additional anticoagulant with anti-IIa activity (either UFH or bivalirudin) should be administered because of the risk of catheter thrombosis (313–315). (*Level of Evidence: B*)

- UFH IV: initial loading dose of 60 IU/kg (maximum 4,000 IU) with initial infusion of 12 IU/kg per hour (maximum 1,000 IU/h) adjusted per activated partial thromboplastin time to maintain therapeutic anticoagulation according to the specific hospital protocol, continued for 48 hours or until PCI is performed (316–322). (*Level of Evidence: B*)

4.3.2.1. Low-Molecular-Weight Heparin

LMWHs have a molecular weight approximately one third that of UFH and have balanced anti-Xa and anti-IIa activity. LMWHs are readily absorbed after subcutaneous administration and have less platelet activation (323). The anticoagulant activity of LMWH does not require routine monitoring. The dose of enoxaparin is 1 mg/kg SC every 12 hours for NSTE-ACS; an initial intravenous loading dose of 30 mg has been used in selected patients. In the presence of impaired renal function (CrCl <30 mL per minute), which is a common finding in older patients, the dose should be reduced to 1 mg/kg SC once daily, and strong consideration should be given to UFH as an alternative. Calculation of CrCl is prudent in patients considered for enoxaparin therapy.

In the ESSENCE trial, in patients with UA or non-Q-wave MI, the rates of recurrent ischemic events and invasive diagnostic and therapeutic procedures were significantly reduced by enoxaparin therapy in the short term, and benefit was sustained at 1 year (324).

In the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial of high-risk patients with NSTE-ACS treated with an early invasive strategy, there was no significant difference in death or MI at 30 days between those randomized to enoxaparin versus UFH. There was more TIMI major bleeding in those treated with enoxaparin without statistically significant increase in GUSTO severe bleeding or transfusion. Some of the increased bleeding may have been related to patients randomized to enoxaparin who received additional UFH at the time of PCI (325,326).

4.3.2.2. Bivalirudin

The direct thrombin inhibitor bivalirudin is administered intravenously. Bivalirudin was evaluated in the ACUITY trial, a randomized open-label trial, in 13,819 moderate- to high-risk patients with NSTE-ACS with a planned invasive strategy. Three treatment arms were tested, including UFH or LMWH with a GP IIb/IIIa receptor inhibitor, bivalirudin with a GP IIb/IIIa receptor inhibitor, or bivalirudin alone. The majority of patients received clopidogrel (300 mg) before intervention, in addition to aspirin, anticoagulants, and GP IIb/IIIa inhibitors. Bivalirudin alone was noninferior to the standard UFH/LMWH combined with GP IIb/IIIa inhibitor (composite ischemia endpoint 7.8% versus 7.3%; HR: 1.08; p=0.32), but there was a significantly lower rate of major bleeding with bivalirudin (3.0% versus 5.7%; HR: 0.53; p<0.001) (310). The anticoagulant effect of bivalirudin can be monitored in the catheterization laboratory by the activated clotting time.

4.3.2.3. Fondaparinux

Fondaparinux is a synthetic polysaccharide molecule and the only selective inhibitor of activated factor X available for clinical use. Fondaparinux is well absorbed when given subcutaneously and has a half-life of 17 hours, enabling once-daily administration. Because it is excreted by the kidneys, it is contraindicated if CrCl is <30 mL per minute. Monitoring of anti-Xa activity is not required, and fondaparinux does not affect usual anticoagulant parameters such as activated partial thromboplastin time or activated clotting time. In NSTE-ACS, the dose of fondaparinux is 2.5 mg SC administered daily and continued for the duration of hospitalization or until PCI is performed (312–314). In the OASIS (Organization to Assess Strategies in Ischemic Syndromes)-5 study, patients with NSTE-ACS were randomized to receive 2.5 mg SC fondaparinux daily or enoxaparin 1 mg/kg SC twice daily for 8 days. The incidence of the primary composite ischemic endpoint at 9 days was similar between fondaparinux and enoxaparin, but major bleeding was significantly less frequent with fondaparinux. To avert catheter thrombosis when fondaparinux is used alone in patients undergoing PCI, an anticoagulant with anti-IIa activity is also administered (313–315). One regimen is 85 IU/kg of UFH loading dose at the time of PCI (reduced to 60 IU/kg if a GP IIb/IIIa inhibitor is used concomitantly) (314).

4.3.2.4. Unfractionated Heparin

Studies supporting the addition of a parenteral anticoagulant to aspirin in patients with NSTE-ACS were performed primarily on patients with a diagnosis of "unstable angina" in the era before DAPT and early catheterization and revascularization. In general, those studies found a strong trend for reduction in composite

adverse events with the addition of parenteral UFH to aspirin therapy (316-322).

Clinical trials indicate that a weight-adjusted dosing regimen of UFH can provide more predictable anticoagulation (327) than a fixed initial dose (e.g., 5,000 IU loading dose, 1,000 IU/h initial infusion). The recommended weight-adjusted regimen is an initial loading dose of 60 IU/kg (maximum 4,000 IU) and an initial infusion of 12 IU/kg/h (maximum 1,000 IU/h), adjusted using a standardized nomogram.

4.3.2.5. Argatroban

Argatroban, a direct thrombin inhibitor, is indicated for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia, including those undergoing PCI (328). Steady state plasma concentrations are achieved in 1 to 3 hours after intravenous administration. Because of its hepatic metabolism, argatroban can be used in patients with renal insufficiency. The usual dose is 2 mcg/kg per minute by continuous intravenous infusion, adjusted to maintain the activated partial thromboplastin time at 1.5 to 3 times baseline (but not >100 s).

4.3.3. Fibrinolytic Therapy in Patients With Definite NSTE-ACS: Recommendation

CLASS III: HARM

1. **In patients with NSTE-ACS (i.e., without ST-elevation, true posterior MI, or left bundle-branch block not known to be old), intravenous fibrinolytic therapy should not be used (93,329).** *(Level of Evidence: A)*

There is no role for fibrinolytic therapy in patients with NSTE-ACS. Fibrinolysis with or without subsequent PCI in patients with NSTE-ACS was evaluated by the Fibrinolytic Trialists and TIMI investigators (93,329). There was no benefit for mortality or MI. Intracranial hemorrhage and fatal and nonfatal MI occurred more frequently in patients treated with fibrinolytic therapy.

See Online Data Supplement 17 for additional information on parenteral anticoagulant and fibrinolytic therapy in patients with definite NSTE-ACS.

4.4. Ischemia-Guided Strategy Versus Early Invasive Strategies
See **Figure 3** for the management algorithm for ischemia-guided versus early invasive strategy.

4.4.1. General Principles

Two treatment pathways have emerged for all patients with NSTE-ACS. The invasive strategy triages patients to an invasive diagnostic evaluation (i.e., coronary angiography). In contrast, the initial ischemia-guided strategy calls for an invasive evaluation for those patients who 1) fail medical therapy (refractory angina or angina at rest

or with minimal activity despite vigorous medical therapy), 2) have objective evidence of ischemia (dynamic electrocardiographic changes, myocardial perfusion defect) as identified on a noninvasive stress test, or 3) have clinical indicators of very high prognostic risk (e.g., high TIMI or GRACE scores). In both strategies, patients should receive optimal anti-ischemic and antithrombotic medical therapy as outlined in Section 4.1. A subgroup of patients with refractory ischemic symptoms or hemodynamic or rhythm instability are candidates for urgent coronary angiography and revascularization.

4.4.2. Rationale and Timing for Early Invasive Strategy

This strategy seeks to rapidly risk stratify patients by assessing their coronary anatomy. The major advantages of invasive therapy when appropriate are 1) the rapid and definitive nature of the evaluation, 2) the potential for earlier revascularization in appropriate patients that might prevent occurrence of further complications of ACS that could ensue during medical therapy, and 3) facilitation of earlier discharge from a facility.

4.4.2.1. Routine Invasive Strategy Timing

The optimal timing of angiography has not been conclusively defined. In general, 2 options have emerged: early invasive (i.e., within 24 hours) or delayed invasive (i.e., within 25 to 72 hours). In most studies using the invasive strategy, angiography was deferred for 12 to 72 hours while antithrombotic and anti-ischemic therapies were intensified (138,332-337). The concept of deferred angiography espouses that revascularization may be safer once plaque is stabilized with optimal antithrombotic and/or anti-ischemic therapies. Conversely, early angiography facilitates earlier risk stratification and consequently speeds revascularization and discharge but can place greater logistic demands on a healthcare system.

4.4.3. Rationale for Ischemia-Guided Strategy

The ischemia-guided strategy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability. When the ischemia-guided strategy is chosen, a plan for noninvasive evaluation is required to detect severe ischemia that occurs at a low threshold of stress and to promptly refer these patients for coronary angiography and revascularization as indicated. The major advantage offered by the ischemia-guided strategy is that some patients' conditions stabilize during medical therapy and will not require coronary angiography and revascularization. Consequently, the ischemia-guided strategy may potentially avoid costly and possibly unnecessary invasive procedures.

FIGURE 3 **Algorithm for Management of Patients With Definite or Likely NSTE-ACS***

*See corresponding full-sentence recommendations and their explanatory footnotes.

†In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis.

ASA indicates aspirin; CABG, coronary artery bypass graft; cath, catheter; COR, Class of Recommendation; DAPT, dual antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; LOE, Level of Evidence; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; pts, patients; and UFH, unfractionated heparin.

4.4.4. Early Invasive and Ischemia-Guided Strategies: Recommendations

CLASS I

1. An urgent/immediate invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in patients (men and women¶) with NSTE-ACS who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures) (42,44,138,338). *(Level of Evidence: A)*

2. An early invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in initially stabilized patients with NSTE-ACS (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (Table 8) (42,44,138,333,334,338,339). *(Level of Evidence: B)*

CLASS IIa

1. It is reasonable to choose an early invasive strategy (within 24 hours of admission) over a delayed invasive strategy (within 25 to 72 hours) for initially stabilized high-risk patients with NSTE-ACS. For those not at high/intermediate risk, a delayed invasive approach is reasonable (139). *(Level of Evidence: B)*

CLASS IIb

1. In initially stabilized patients, an ischemia-guided strategy may be considered for patients with NSTE-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events (333,334,338). *(Level of Evidence: B)*

2. The decision to implement an ischemia-guided strategy in initially stabilized patients (without serious comorbidities or contraindications to this approach) may be reasonable after considering clinician and patient preference. *(Level of Evidence: C)*

CLASS III: NO BENEFIT

1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with:
   a. Extensive comorbidities (e.g., hepatic, renal, pulmonary failure; cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. *(Level of Evidence: C)*
   b. Acute chest pain and a low likelihood of ACS who are troponin-negative *(Level of Evidence: C)*, especially women (141). *(Level of Evidence: B)*

¶See Section 7.7 for additional information on women.

TABLE 8	Factors Associated With Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients With NSTE-ACS
Immediate invasive (within 2 h)	Refractory angina
	Signs or symptoms of HF or new or worsening mitral regurgitation
	Hemodynamic instability
	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Sustained VT or VF
Ischemia-guided strategy	Low-risk score (e.g., TIMI [0 or 1], GRACE [<109]) Low-risk Tn-negative female patients
	Patient or clinician preference in the absence of high-risk features
Early invasive (within 24 h)	None of the above, but GRACE risk score >140 Temporal change in Tn (Section 3.4)
	New or presumably new ST depression
Delayed invasive (within 25–72 h)	None of the above but diabetes mellitus Renal insufficiency (GFR <60 mL/min/1.73 m^2)
	Reduced LV systolic function (EF <0.40)
	Early postinfarction angina
	PCI within 6 mo
	Prior CABG
	GRACE risk score 109–140; TIMI score ≥2

CABG indicates coronary artery bypass graft; EF, ejection fraction; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; Tn, troponin; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Several studies (93,138,334-337) and meta-analyses (141,340) have concluded that a strategy of routine invasive therapy is generally superior to an ischemia-guided strategy or selectively invasive approach. One study reported that the routine invasive strategy resulted in an 18% relative reduction in death or MI, including a significant reduction in MI alone (341). The routine invasive arm was associated with higher in-hospital mortality (1.8% versus 1.1%), but this disadvantage was more than compensated for by a significant reduction in mortality between discharge and the end of follow-up (3.8% versus 4.9%). The invasive strategy was also associated with less angina and fewer rehospitalizations. Patients undergoing routine invasive treatment also had improved quality of life. In an analysis of individual patient data (340) that reported 5-year outcomes from the FRISC (Framingham and Fast Revascularization During Instability in Coronary Artery Disease)-II trial (339), ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial (338), and RITA (Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina)-3 trial (334), 14.7% of patients (389 of 2,721) randomized to a routine invasive strategy experienced cardiovascular death or nonfatal MI versus 17.9% of patients (475 of 2,746) in the selective invasive strategy (HR: 0.81; 95% CI: 0.71 to 0.93; p=0.002). The most marked treatment effect was on MI

(10.0% routine invasive strategy versus 12.9% selective invasive strategy), and there were consistent trends for fewer cardiovascular deaths (HR: 0.83; 95% CI: 0.68 to 1.01; p=0.068) and all-cause mortality (HR: 0.90; 95% CI: 0.77 to 1.05). There were absolute reductions of 2.0% to 3.8% in cardiovascular death or MI in the low- and intermediate-risk groups and an 11.1% absolute risk reduction in the highest-risk patients. The invasive strategy demonstrated its greatest advantage in the highest-risk stratum of patients with no significant benefit on mortality over the noninvasive approach in moderate- and low-risk patients (342). An ischemia-guided strategy has been used with favorable results in initially stabilized patients with NSTE-ACS at elevated risk for clinical events, including those with positive troponin levels (338). One limitation of these studies is the absence of adherence to optimal medical therapy in noninvasively treated patients during long-term management. In addition, in FRISC-II, invasive management was delayed and patients with markedly positive stress tests (up to 2.9-mm exercise-induced ST depression) were randomized to noninvasive or invasive therapy (338).

See *Online Data Supplement 18* for additional information on comparison of early invasive strategy and ischemia-guided strategy.

4.4.4.1. Comparison of Early Versus Delayed Angiography

In some studies, early angiography and coronary intervention have been more effective in reducing ischemic complications than delayed interventions, particularly in patients at high risk (defined by a GRACE score >140) (139,336). A more delayed strategy is also reasonable in low- to intermediate-risk patients. The advantage of early intervention was achieved in the context of intensive background antithrombotic and anti-ischemic therapy. However, this question was also assessed by a meta-analysis of 11 trials (7 RCTs and 4 observational studies) (343). Meta-analysis of the RCTs was inconclusive for a survival benefit of the early invasive strategy (OR: 0.83 [95% CI: 0.64 to 1.09]; p=0.180), and there were no significant differences in MI or major bleeding; a similar result was found with the observational studies. These data are limited by the small sample size of the individual trials, low event rates, inconsistency in timing of intervention, and heterogeneous patient profiles.

See *Online Data Supplement 19* for additional information on comparison of early versus delayed angiography.

4.4.5. Subgroups: Early Invasive Strategy Versus Ischemia-Guided Strategy

The TACTICS-TIMI (Treat Angina With Tirofiban and Determine Cost of Therapy With an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction) 18 trial demonstrated a reduction in the 6-month endpoint of death or MI in older adults with ACS (138). Controversy exists over revascularization treatment differences between men and women with ACS. The FRISC-II trial showed a benefit of revascularization in men for death or MI that was not observed for women (344). In contrast, death, MI, or rehospitalization rates were reduced for both men and women in TACTICS-TIMI 18 (138). RITA-3 showed that the routine strategy of invasive evaluation resulted in a beneficial effect in high-risk men that was not seen in women (342). A meta-analysis suggests that in NSTE-ACS, an invasive strategy has a comparable benefit in men and high-risk women for reducing the composite endpoint of death, MI, or rehospitalization (141,345,346). In contrast, an ischemia-guided strategy is preferred in low-risk women (141). Another collaborative meta-analysis of randomized trials reported that an early invasive strategy yielded similar RR reductions in overall cardiovascular events in patients with and without diabetes mellitus (347). However, an invasive strategy appeared to reduce recurrent nonfatal MI to a greater extent in patients with diabetes mellitus.

4.4.6. Care Objectives

Coronary angiography is designed to provide detailed information about the size and distribution of coronary vessels, the location and extent of atherosclerotic obstruction, and the suitability for revascularization. The LV angiogram, usually performed with coronary angiography, provides an assessment of the extent of focal and global LV dysfunction and of the presence and severity of coexisting disorders (e.g., valvular or other associated lesions). Patients with NSTE-ACS can be divided into risk groups on the basis of their initial clinical presentation. The TIMI, PURSUIT, and GRACE scores are useful tools for assigning risk to patients with NSTE-ACS.

Risk stratification identifies patients who are most likely to benefit from subsequent revascularization. Patients with left main disease or multivessel CAD with reduced LV function are at high risk for adverse outcomes and are likely to benefit from CABG. Clinical evaluation and noninvasive testing aid in the identification of most patients at high risk because they often have ≥1 of the following high-risk features: advanced age (>70 years of age), prior MI, revascularization, ST deviation, HF, depressed resting LV function (i.e., LVEF ≤0.40) on noninvasive study, or noninvasive stress test findings, including magnetic resonance imaging (348). Any of these risk factors or diabetes mellitus may aid in the identification of high-risk patients who could benefit from an invasive strategy.

Some patients with NSTE-ACS are not in the very high-risk group and do not have findings that portend a high

risk for adverse outcomes. They are not likely to receive the same degree of benefit from routine revascularization afforded to high-risk patients, and an invasive study is optional for those at lower risk and can be safely deferred pending further clinical evidence. Decisions about coronary angiography in patients who are not at high risk according to findings on clinical examination and noninvasive testing can be individualized on the basis of patient preferences and/or symptoms.

4.5. Risk Stratification Before Discharge for Patients With an Ischemia-Guided Strategy of NSTE-ACS: Recommendations

CLASS I

1. Noninvasive stress testing is recommended in low- and intermediate-risk patients who have been free of ischemia at rest or with low-level activity for a minimum of 12 to 24 hours (349–353). *(Level of Evidence: B)*

2. Treadmill exercise testing is useful in patients able to exercise in whom the ECG is free of resting ST changes that may interfere with interpretation (349–352). *(Level of Evidence: C)*

3. Stress testing with an imaging modality should be used in patients who are able to exercise but have ST changes on resting ECG that may interfere with interpretation. In patients undergoing a low-level exercise test, an imaging modality can add prognostic information (349–352). *(Level of Evidence: B)*

4. Pharmacological stress testing with imaging is recommended when physical limitations preclude adequate exercise stress. *(Level of Evidence: C)*

5. A noninvasive imaging test is recommended to evaluate LV function in patients with definite ACS (349–352). *(Level of Evidence: C)*

The management of patients with NSTE-ACS requires continuous risk stratification. Important prognostic information is derived from initial assessment, the patient's course during the early days of management, and the response to anti-ischemic and antithrombotic therapy. The choice of stress test is based on the patient's resting ECG and ability to exercise, local expertise, and available technologies. The exercise intensity of the treadmill test (low level or symptom-limited) is used at the discretion of the attending clinician based on individual patient assessment. For invasively managed patients with residual nonculprit lesions, additional evaluation may be indicated to ascertain the significance of such lesions. Refer to the PCI CPG for additional details (26).

4.5.1. Noninvasive Test Selection

The goals of noninvasive testing in patients with a low or intermediate likelihood of CAD and high-risk patients who did not have an early invasive strategy are to detect ischemia and estimate prognosis. This information guides further diagnostic steps and therapeutic measures.

Because of its simplicity, lower cost, and widespread familiarity with its performance and interpretation, the standard low-level exercise electrocardiographic stress test remains the most reasonable test in patients who are able to exercise and who have a resting ECG that is interpretable for ST shifts. There is evidence that imaging studies are superior to exercise electrocardiographic evaluation in women for diagnosis of CAD (350). However, for prognostic assessment in women, treadmill exercise testing has provided comparable results to stress imaging (354). Patients with an electrocardiographic pattern that would interfere with interpretation of the ST segment (baseline ST abnormalities, bundle-branch block, LV hypertrophy with ST-T changes, intraventricular conduction defect, paced rhythm, pre-excitation, and digoxin) should have an exercise test with imaging. Patients who are unable to exercise should have a pharmacological stress test with imaging. Low- and intermediate-risk patients with NSTE-ACS may undergo symptom-limited stress testing, provided they have been asymptomatic and clinically stable at 12 to 24 hours for those with UA and 2 to 5 days for patients at similar risk with NSTEMI (349). The optimal testing strategy in women is less well defined than in men.

4.5.2. Selection for Coronary Angiography

In contrast to noninvasive tests, coronary angiography provides detailed structural information for assessment of prognosis and appropriate management. When combined with LV angiography, it also provides an assessment of global and regional LV function. Coronary angiography is usually indicated in patients with NSTE-ACS who have recurrent symptoms or ischemia despite adequate medical therapy or who are at high risk as categorized by clinical findings (HF, serious ventricular arrhythmias), noninvasive test findings (significant LV dysfunction with EF <0.40, large anterior or multiple perfusion defects or wall motion abnormalities on echocardiography, high-risk Duke treadmill score ≤−11), high-risk TIMI or GRACE scores, or markedly elevated troponin levels. Patients with NSTE-ACS who have had previous PCI or CABG should also be considered for early coronary angiography, unless prior coronary angiography data indicate that no further revascularization is feasible.

The general indications for coronary angiography and revascularization should be tempered by individual patient characteristics and preferences (a patient-centered approach). Patient and clinician judgments about risks and benefits are important for patients who might not be candidates for coronary revascularization, such as very frail older adults and those with serious

comorbid conditions (e.g., severe hepatic, pulmonary, or renal failure; active or inoperable cancer).

See Online Data Supplement 20 for additional information on risk stratification.

5. MYOCARDIAL REVASCULARIZATION

Recommendations about coronary artery revascularization indications, benefits, and choice of revascularization procedure (PCI or CABG) for all anatomic subsets have been published in the 2011 PCI CPG (26), the 2011 CABG CPG (23), and the 2012 stable ischemic heart disease CPG and its 2014 focused update (10,11). The main difference between management of patients with stable ischemic heart disease and NSTE-ACS is a stronger impetus for revascularization in those with NSTE-ACS. Myocardial ischemia in ACS may progress to MI and is potentially life threatening. In addition, in patients with ACS, angina (including recurrent angina) is more likely to be reduced by revascularization than by medical therapy (26).

A "heart team" approach to revascularization decisions, involving an interventional cardiologist and cardiothoracic surgeon, is used in patients with unprotected left main or complex CAD. Calculation of SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) and STS scores is reasonable in these patients to guide the choice of revascularization (23,26,355).

Factors that influence the choice of revascularization procedure include the extent and complexity of CAD; short-term risk and long-term durability of PCI; operative mortality (which can be estimated by the STS score); diabetes mellitus; CKD; completeness of revascularization; LV systolic dysfunction; previous CABG; and the ability of the patient to tolerate and comply with DAPT. In general, the greater the extent and complexity of the multivessel disease, the more compelling the choice of CABG over multivessel PCI (23,26,356–358). In patients with NSTE-ACS, PCI of a culprit unprotected left main coronary artery lesion is an option if the patient is not a candidate for CABG (23,26).

See Online Data Supplements 21 and 22 for additional information on myocardial revascularization.

5.1. Percutaneous Coronary Intervention

5.1.1. PCI—General Considerations: Recommendation

CLASS IIb

1. A strategy of multivessel PCI, in contrast to culprit lesion—only PCI, may be reasonable in patients undergoing coronary revascularization as part of treatment for NSTE-ACS (330,359–364). *(Level of Evidence: B)*

Approximately half of all PCI procedures are performed in patients with UA or NSTEMI, and approximately 32% to 40% of patients with NSTE-ACS will undergo PCI (365). As discussed previously, in patients with NSTE-ACS, a strategy of early angiography and revascularization (primarily with PCI) results in lower rates of recurrent UA, recurrent rehospitalization, MI, and death (366,367). Although PCI of a nonculprit lesion is not advocated in patients with STEMI (26), there is less agreement on whether nonculprit lesions should undergo intervention at the time of culprit-lesion PCI for NSTE-ACS. Most reports (359–364), but not all (330), comparing culprit lesion—only PCI with multivessel PCI (e.g., PCI of multiple vessels performed at the same time) in patients with NSTE-ACS did not find an increased risk of MACE with multivessel PCI and found a reduction in the need for repeat revascularization. However, the data consist predominantly of post hoc analysis of nonrandomized data with variable duration of follow-up. This question has not been resolved and is an area of current investigation.

5.1.2. PCI—Antiplatelet and Anticoagulant Therapy

5.1.2.1. Oral and Intravenous Antiplatelet Agents: Recommendations

CLASS I

1. Patients already taking daily aspirin before PCI should take 81 mg to 325 mg non–enteric-coated aspirin before PCI (26,368–370). *(Level of Evidence: B)*

2. Patients not on aspirin therapy should be given non–enteric-coated aspirin 325 mg as soon as possible before PCI (26,368–370). *(Level of Evidence: B)*

3. After PCI, aspirin should be continued indefinitely at a dose of 81 mg to 325 mg daily (27,288,371). *(Level of Evidence: B)*

4. A loading dose of a $P2Y_{12}$ receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting (26,293,302,331,372–375). *(Level of Evidence: A)* Options include:

   a. Clopidogrel: 600 mg (331,372–374,376–378) *(Level of Evidence: B)* or

   b. Prasugrel#: 60 mg (302) *(Level of Evidence: B)* or

   c. Ticagrelor‖: 180 mg (293) *(Level of Evidence: B)*

5. In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI (379–382). *(Level of Evidence: A)*

#Patients should receive a loading dose of prasugrel, provided that they were not pretreated with another $P2Y_{12}$ receptor inhibitor.
‖The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

6. In patients receiving a stent (bare-metal stent or drug-eluting stent [DES]) during PCI for NSTE-ACS, P2Y$_{12}$ inhibitor therapy should be given for at least 12 months (330). Options include:

    a. Clopidogrel: 75 mg daily (296,331) *(Level of Evidence: B)* or

    b. Prasugrel#: 10 mg daily (302) *(Level of Evidence: B)* or

    c. Ticagrelor‖: 90 mg twice daily (293) *(Level of Evidence: B)*

CLASS IIa

1. It is reasonable to choose ticagrelor over clopidogrel for P2Y$_{12}$ inhibition treatment in patients with NSTE-ACS treated with an early invasive strategy and/or coronary stenting (293,294). *(Level of Evidence: B)*

2. It is reasonable to choose prasugrel over clopidogrel for P2Y$_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications (302,303). *(Level of Evidence: B)*

3. In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI (195,383,384). *(Level of Evidence: B)*

4. After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses (331,368,385–388). *(Level of Evidence: B)*

5. If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of P2Y$_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of P2Y$_{12}$ inhibitor therapy is reasonable (330). *(Level of Evidence: C)*

CLASS IIb

1. Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation. *(Level of Evidence: C)*

CLASS III: HARM

1. Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack (302). *(Level of Evidence: B)*

Comprehensive recommendations on the use of antiplatelet and anticoagulant therapy in patients with NSTE-ACS undergoing PCI are given in the 2011 PCI CPG (26). Aspirin reduces the frequency of ischemic complications after PCI and is ideally administered at least 2 hours, and preferably 24 hours,

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#Patients should receive a loading dose of prasugrel, provided that they were not pretreated with another P2Y$_{12}$ receptor inhibitor.
‖The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

before PCI (26,368,369). DAPT, consisting of aspirin and a P2Y$_{12}$ inhibitor, in patients treated with coronary stents reduces the risk of stent thrombosis and composite ischemic events (296,331,372–375,389,390). Compared with a loading dose of 300 mg of clopidogrel, a loading dose of 600 mg of clopidogrel in patients undergoing PCI achieves greater platelet inhibition with fewer low responders and decreases the incidence of MACE (376-378). In patients with ACS who have undergone coronary stenting, treatment with prasugrel or ticagrelor, compared with treatment with clopidogrel, results in a greater reduction in composite ischemic events and the incidence of stent thrombosis, although at a risk of increased non-CABG bleeding (293,302). The optimal duration of DAPT therapy in patients treated with DES is not well established (26). However, aspirin is continued indefinitely in all patients managed with a bare-metal stent or DES, and DAPT is an option for >12 months in patients who have received a DES. This determination should balance the risks of stent thrombosis and ischemic complications versus bleeding and should be jointly made by the clinician and the patient.

Loading and short-term maintenance doses of clopidogrel were studied in CURRENT-OASIS (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Organization to Assess Strategies in Ischemic Syndromes) 7, which demonstrated a potential benefit of higher-dose clopidogrel (600-mg loading dose, 150 mg daily for 6 days, 75 mg daily thereafter) in patients with NSTE-ACS undergoing an invasive management strategy (292,391). Although the overall trial (292) failed to demonstrate a significant difference in the primary endpoint between the clopidogrel and aspirin groups (4.2% versus 4.4%), the PCI subset (n=17,263) showed significant differences in the clopidogrel arm (391). Notably, the higher-dose clopidogrel therapy increased major bleeding in the entire group (2.5% versus 2.0%; p=0.012) and the PCI subgroup (1.1% versus 0.7%; p=0.008). In addition, during the period of several hours required for conversion of clopidogrel to its active metabolite, there is reduced effectiveness. However, efficacy is restored following conversion.

Patients undergoing PCI who have previously received a loading dose of 300 mg of clopidogrel and are on a 75-mg daily maintenance dose should receive another 300-mg loading dose (315). There are no data appropriate for prasugrel because this drug is administered before PCI. For ticagrelor, there are no data on additional loading.

5.1.2.2. GP IIb/IIIa Inhibitors: Recommendations

CLASS I

1. In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) who are not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI (379–382). *(Level of Evidence: A)*

CLASS IIa

1. In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pre-treated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI (195,383). *(Level of Evidence: B)*

GP IIb/IIIa receptor antagonist therapy in patients with NSTE-ACS undergoing PCI reduced the incidence of composite ischemic events, primarily through a decrease in documented MI, although in some trials this is counterbalanced by an increased rate of bleeding (193,195,310,379-382,392). Most, but not all, randomized trials of the use of GP IIb/IIIa inhibitor were conducted in the era before clopidogrel therapy (193,195,310,379-383,392). Abciximab, double-bolus eptifibatide, and high-bolus dose tirofiban result in a high degree of platelet inhibition, reduce ischemic complications in patients undergoing PCI, and appear to afford comparable angiographic and clinical outcomes (26). As trials of the GP IIb/IIIa inhibitors generally excluded patients at high risk of bleeding, recommendations for the use of GP IIb/IIIa inhibitors are best understood as applying to patients not at high risk of bleeding complications. Although GP IIb/IIIa inhibitors were used in 27% and 55% of patients, respectively, in the PLATO (Platelet Inhibition and Patient Outcomes) and TRITON studies of ticagrelor and prasugrel, there are insufficient data (293,302,393) (and no RCT data) from which to make specific recommendations about GP IIb/IIIa inhibitor use in patients treated with either of these P2Y$_{12}$ inhibitors.

See *Online Data Supplement 21* for additional information on GP IIb/IIIa inhibitors.

5.1.2.3. Anticoagulant Therapy in Patients Undergoing PCI: Recommendations

CLASS I

1. An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. *(Level of Evidence: C)*

2. Intravenous UFH is useful in patients with NSTE-ACS undergoing PCI. *(Level of Evidence: C)*

3. Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH in patients with NSTE-ACS undergoing PCI (310,394-398). *(Level of Evidence: B)*

4. An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than 2 therapeutic subcutaneous doses (e.g., 1 mg/kg SC) or received the last subcutaneous enoxaparin dose 8 to 12 hours before PCI (309,399-403). *(Level of Evidence: B)*

5. If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter

thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time) (26,313-315,404). *(Level of Evidence: B)*

6. In patients with NSTE-ACS, anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue such therapy. *(Level of Evidence: C)*

CLASS IIa

1. In patients with NSTE-ACS undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist (310,396). *(Level of Evidence: B)*

CLASS IIb

1. Performance of PCI with enoxaparin may be reasonable in patients treated with upstream subcutaneous enoxaparin for NSTE-ACS (26,309,399-402,405,406). *(Level of Evidence: B)*

CLASS III: HARM

1. Fondaparinux should not be used as the sole anticoagulant to support PCI in patients with NSTE-ACS due to an increased risk of catheter thrombosis (26,313-315). *(Level of Evidence: B)*

Anticoagulant therapy prevents thrombus formation at the site of arterial injury, on the coronary guide wire, and in the catheters used for PCI (26,407). With rare exceptions, all PCI studies have used some form of anticoagulant at the time of PCI (26). Intravenous UFH and bivalirudin both have Class I recommendations in patients undergoing PCI in the 2011 PCI CPG (26). Patients who have received multiple doses of subcutaneously-administered enoxaparin who undergo PCI within 8 hours of the last subcutaneous dose generally have received adequate anticoagulation to undergo PCI, but the degree of anticoagulation may diminish 8 to 12 hours after the last subcutaneous dose. In such patients, as well as in patients who have received fewer than 2 subcutaneous doses of enoxaparin, the addition of enoxaparin (0.3 mg/kg IV) at the time of PCI provides additional anticoagulation and has become standard practice (26,309,399-403). Patients who undergo PCI >12 hours after the last subcutaneous dose of enoxaparin are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose UFH or bivalirudin). Fondaparinux as the sole anticoagulant during PCI has been associated with catheter thrombosis, and use of an anticoagulant with anti-IIa activity is recommended when patients treated with fondaparinux undergo PCI (313-315). One suggested regimen is UFH 85 IU/kg IV if no GP IIb/IIIa inhibitor is used and 60 IU/kg IV if a GP IIb/IIIa inhibitor is used with UFH dosing based on the target-activated clotting time (314,404) (**Table 9**) (26,313-315).

TABLE 9	Dosing of Parenteral Anticoagulants During PCI	
Drug*	**In Patients Who Have Received Prior Anticoagulant Therapy**	**In Patients Who Have Not Received Prior Anticoagulant Therapy**
Enoxaparin	• For prior treatment with enoxaparin, if last SC dose was administered 8–12 h earlier or if <2 therapeutic SC doses of enoxaparin have been administered, an IV dose of enoxaparin 0.3 mg/kg should be given • If the last SC dose was administered within prior 8 h, no additional enoxaparin should be given	• 0.5 mg/kg–0.75 mg/kg IV loading dose
Bivalirudin	• For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV loading dose, then 1.75 mg/kg/h IV infusion • For patients already receiving bivalirudin infusion, give additional loading dose 0.5 mg/kg and increase infusion to 1.75 mg/kg/h during PCI	• 0.75 mg/kg loading dose, 1.75 mg/kg/h IV infusion
Fondaparinux	• For prior treatment with fondaparinux, administer additional IV treatment with anticoagulant possessing anti-IIa activity, considering whether GPI receptor antagonists have been administered	N/A
UFH	• IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve ACT of 200–250 s • No IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve ACT of 250–300 s for HemoTec, 300–350 s for Hemochron	• IV GPI planned: 50–70 U/kg loading dose to achieve ACT of 200–250 s • No IV GPI planned: 70–100 U/kg loading dose to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron

*Drugs presented in order of the COR and then the LOE as noted in the Preamble. When more than 1 drug exists within the same LOE, and there are no comparative data, then the drugs are listed alphabetically.

ACT indicates activated clotting time; COR, Class of Recommendation; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; LOE, Level of Evidence; N/A, not applicable; PCI, percutaneous coronary intervention; SC, subcutaneous; and UFH, unfractionated heparin.
Modified from Levine et al. (26).

5.2. Timing of Urgent CABG in Patients With NSTE-ACS in Relation to Use of Antiplatelet Agents: Recommendations

CLASS I

1. Non-enteric-coated aspirin (81 mg to 325 mg daily) should be administered preoperatively to patients undergoing CABG (408-410). *(Level of Evidence: B)*

2. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (23,411–413) *(Level of Evidence: B)* and prasugrel for at least 7 days before surgery (8,414). *(Level of Evidence: C)*

3. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding (8,412,415-417). *(Level of Evidence: B)*

4. In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery (418,419) and abciximab for at least 12 hours before to limit blood loss and transfusion (389). *(Level of Evidence: B)*

CLASS IIb

1. In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued. *(Level of Evidence: C)*

In-hospital CABG is performed in 7% to 13% of patients hospitalized with NSTE-ACS (420-422). Approximately one third of patients with NSTEMI undergo CABG within 48 hours of hospital admission (421). In these patients, CABG was performed at a median time of 73 hours after admission (interquartile range: 42 to 122 hours) (421). In-hospital mortality in patients with NSTEMI undergoing CABG is approximately 3.7% (421).

Recommendations for management of patients treated with oral and intravenous antiplatelet agents who undergo CABG are given in the 2011 CABG CPG (23). Preoperative aspirin reduces operative morbidity and mortality, and CABG can be performed safely in patients on aspirin therapy with only a modest increase in bleeding risk (23,408-410). The use of $P2Y_{12}$ inhibitors in patients with NSTE-ACS is associated with an increase in post-CABG bleeding and the need for transfusion (293,302,411,413,423-425). Although it is recommended that clopidogrel and ticagrelor be discontinued at least 5 days before surgery and prasugrel at least 7 days before surgery in patients referred for elective CABG (23,411-413), the timing of CABG in patients with NSTE-ACS treated with a $P2Y_{12}$ inhibitor (330) should reflect a balance of the potential increase in bleeding against the potential benefits of not delaying surgery 5 to 7 days. The risk of major bleeding complications is increased when CABG is performed <24 hours after discontinuation of clopidogrel (23,416,417). In patients who undergo CABG 1 to 4 days after discontinuation of clopidogrel, it appears that the incidence of life-threatening bleeding is not significantly increased, but an increase in blood transfusions is likely (23,415,416,425,426). In the TRITON-TIMI 38 trial (302), the incidence of CABG-related major bleeding was higher in patients treated with prasugrel than in patients treated with clopidogrel (23,386). In the PLATO trial, the rates of major bleeding and transfusion requirements were similar

between patients treated with ticagrelor and patients treated with clopidogrel (294). The more rapid recovery of platelet function in pharmacokinetic studies of ticagrelor did not translate to a lower risk of bleeding or lessen the need for transfusion compared with clopidogrel when CABG was performed early (i.e., <5 days) after drug discontinuation (23,293,412).

See *Online Data Supplements 21 and 22 for more information on myocardial revascularization.*

6. LATE HOSPITAL CARE, HOSPITAL DISCHARGE, AND POSTHOSPITAL DISCHARGE CARE

6.1. General Principles (Cardioprotective Therapy and Symptom Management)

The goals of therapy after NSTE-ACS are to restore the patient to normal activities to the extent possible and to use the acute event to re-evaluate the plan of care, particularly lifestyle and risk factor modification. Aggressive risk factor modifications that can prolong survival should be the main goal of long-term management of patients with stable CAD. Patients presenting with NSTE-ACS represent a high-risk cohort in whom secondary cardiovascular disease prevention is likely to be particularly effective (Table 10). Clinicians have an opportunity to provide evidence-based care to this high-risk cohort and to aggressively treat the underlying atherosclerotic process through lifestyle modification and effective pharmacological therapies (427). In most cases, the inpatient anti-ischemic medical regimen should be continued after discharge, and the antiplatelet/anticoagulant medications should be changed to an outpatient regimen. The goals for continued medical therapy after discharge relate to potential prognostic benefits (primarily shown for antiplatelet agents, beta blockers, statins, and inhibitors of the renin-angiotensin aldosterone system, especially for LVEF <0.40). Added benefits are control of ischemic symptoms (nitrates, beta blockers, CCBs, and ranolazine) and treatment of major risk factors such as smoking, hypertension, dyslipidemia, physical inactivity, obesity, and diabetes mellitus (427). Selection of a medical regimen should be individualized to each patient on the basis of in-hospital findings, risk factors for CAD, drug tolerability, and recent procedural interventions. The mnemonic "ABCDE" (Aspirin, Antianginals, and ACE Inhibitors; Beta Blockers and BP; Cholesterol and Cigarettes; Diet and Diabetes Mellitus; Education and Exercise) is useful in guiding treatment (428).

6.2. Medical Regimen and Use of Medications at Discharge: Recommendations

CLASS I

1. Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization,

and patients with recurrent symptoms after revascularization. Titration of the doses may be required (427,428). *(Level of Evidence: C)*

2. All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use (429). *(Level of Evidence: C)*

3. Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms (429). *(Level of Evidence: C)*

4. Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use (429). *(Level of Evidence: C)*

5. For patients who are post–NSTE-ACS and have initial angina lasting more than 1 minute, nitroglycerin (1 dose sublingual or spray) is recommended if angina does not subside within 3 to 5 minutes; call 9-1-1 immediately to access emergency medical services (429). *(Level of Evidence: C)*

6. If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing (429). *(Level of Evidence: C)*

7. Before discharge, patients should be educated about modification of cardiovascular risk factors (428). *(Level of Evidence: C)*

6.2.1. Late Hospital and Posthospital Oral Antiplatelet Therapy: Recommendations

CLASS I

1. Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients (288-290). *(Level of Evidence: A)*

2. In addition to aspirin, a P2Y$_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. Options include:

- Clopidogrel: 75 mg daily (289,296) *(Level of Evidence: B)* or

- Ticagrelor‖: 90 mg twice daily (293,294) *(Level of Evidence: B)*

‖The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

TABLE 10	Plan of Care for Patients With NSTE-ACS
Plan of Care	**Resources/References**
Medications	
Antithrombotic therapies	• Sections 6.2.1 and 6.2.2
Beta blockers	• Section 4.1.2.3
ACE inhibitors/ARBs/aldosterone antagonists	• Section 4.2
CCBs	• Section 4.1.2.4
Statins	• 2013 Blood cholesterol CPG (18)
Discontinuation of antithrombotic therapies for elective surgical and medical procedures with increased risk of bleeding	• 2014 SIHD focused update (10) • 2012 SIHD CPG (11) • 2012 Management of AMI in patients with persistent STEMI CPG (19) • 2011 Secondary prevention CPG (27) • 2007 Science Advisory on the prevention of premature discontinuation of DAPT in patients with coronary artery stents (504)
Inappropriate use of analgesics (NSAIDs)	• 2010 Expert consensus document on PPIs and thienopyridines (430)
Use of PPIs	• 2011 PCI CPG (26)
Risk factor modification/lifestyle interventions and physical activity/cardiac rehabilitation	
Smoking cessation	• Tobacco cessation toolkit (505)
Diet nutrition	• 2013 Lifestyle CPG (15)
Physical activity	• 2013 Lifestyle CPG (15) • 2011 Secondary prevention CPG (27)
Cardiorespiratory fitness (MET capacity)	• 2011 Secondary prevention CPG (27) • 2010 Performance measures on cardiac rehabilitation (454) • 2012 Scientific statement on sexual activity and cardiovascular disease (231)
Management of comorbidities	
Overweight/obesity	• 2013 Obesity CPG (16) • 2011 Secondary prevention CPG (27)
Statins	• 2013 Lifestyle CPG (15) • 2013 Blood cholesterol CPG (18)
Hypertension	• 2014 Report on high BP (501) • 2013 Science advisory on high BP control (506)
Diabetes mellitus	• 2013 Position statement on standards of medical care in diabetes (507)
HF	• 2013 HF CPG (14)
Arrhythmia/Arrhythmia risk	• 2012 Focused update incorporated into the 2008 DBT CPG (20) • 2014 AF CPG (12)
Psychosocial factors	
Sexual activity	• 2012 Scientific statement on sexual activity and cardiovascular disease (231) • 2013 Consensus document on sexual counseling for individuals with cardiovascular disease and their partners (508)
Gender-Specific issues	• 2007 Cardiovascular disease prevention in women CPG (475)
Depression, stress, and anxiety	• 2008 Science advisory on depression and coronary heart disease (509)
Alcohol use	• 2011 Secondary prevention CPG (27)
Culturally sensitive issues	• 2009 Consensus report on a comprehensive framework and preferred practices for measuring and reporting cultural competency (510)
Return to work schedule	
Clinician follow-up	
Cardiologist	• 2011 Secondary prevention CPG (27) • 2013 Hospital to Home Quality Initiative (511)
Primary care clinician	
Advanced practice nurse/physician assistant	
Pharmacists	• 2013 Discharge counseling for patients with HF or MI (512)
Other relevant medical specialists	
Electronic personal health records	
Influenza vaccination	• 2005 Recommendations for prevention and control of influenza (37)

TABLE 10 Continued	
Plan of Care	**Resources/References**
Patient/family education	
Plan of care for AMI	• 2010 CPG for cardiopulmonary resuscitation and emergency cardiovascular care—part 9: postcardiac arrest care (31) • 2013 STEMI CPG (17)
Recognizing symptoms of MI	
Activating EMS, signs and symptoms for urgent vs. emergency evaluations	
CPR training for family members	
Risk assessment and prognosis	
Advanced directives	
Social networks/social isolation	
Socioeconomic factors	
Access to health insurance coverage	
Access to clinicians	• Effective communication and care coordination (513)
Disability	• Cardiovascular disability: updating Social Security listings (514)
Social services	
Community services	

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CPG, clinical practice guideline; CPR, cardiopulmonary resuscitation; DAPT, dual antiplatelet therapy; DBT, device-based therapy; ECC, emergency cardiovascular care; EMS, emergency medical services; HF, heart failure; MET, metabolic equivalent; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; NSTE-ACS, non–ST-elevation acute coronary syndromes; PCI, percutaneous coronary intervention; PPI, protein pump inhibitor; SIHD, stable ischemic heart disease; and STEMI, ST-elevation myocardial infarction.

3. In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months (330). Options include:
   • Clopidogrel: 75 mg daily (296,331) *(Level of Evidence: B)* or
   • Prasugrel#: 10 mg daily (302) *(Level of Evidence: B)* or
   • Ticagrelor‖: 90 mg twice daily (293) *(Level of Evidence: B)*

CLASS IIa

1. It is reasonable to use an aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients with NSTE-ACS treated either invasively or with coronary stent implantation (26,331,368,385–388). *(Level of Evidence: B)*

2. It is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy (293,294). *(Level of Evidence: B)*

3. It is reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk for bleeding complications (302,303). *(Level of Evidence: B)*

4. If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable (330). *(Level of Evidence: C)*

#Patients should receive a loading dose of prasugrel, provided they were not pretreated with another PY_{12} receptor inhibitor.

‖The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

CLASS IIb

1. Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation. *(Level of Evidence: C)*

6.2.2. Combined Oral Anticoagulant Therapy and Antiplatelet Therapy in Patients With NSTE-ACS

CLASS I

1. The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. *(Level of Evidence: C)*

2. Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor (26,430,431). *(Level of Evidence: C)*

CLASS IIa

1. Proton pump inhibitor use is reasonable in patients with NSTE-ACS *without* a known history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor (26,430,431). *(Level of Evidence: C)*

CLASS IIb

1. Targeting oral anticoagulant therapy to a lower international normalized ratio (INR) (e.g., 2.0 to 2.5) may be reasonable in patients with NSTE-ACS managed with aspirin and a $P2Y_{12}$ inhibitor. *(Level of Evidence: C)*

The combination of oral antiplatelet therapy and oral anticoagulant therapy significantly increases the risk of bleeding. This risk varies widely, but on average, the addition of a single antiplatelet agent increased the risk of bleeding from a range of 2% to 3% to a range of 4% to 6%, whereas the addition of DAPT to oral anticoagulant therapy ("triple therapy") increased the risk of bleeding from a range of 4% to 6% to a range of 10% to 14% (432–435). This risk was also related to the duration of triple therapy.

In patients with NSTE-ACS in whom there are indications for triple therapy, the benefit of such therapy in terms of prevention of stent thrombosis, thromboembolic events, and recurrent MI must be weighed against the risk of bleeding complications. Similarly, DAPT, in addition to anticoagulant therapy, requires consideration of the increased risk of bleeding. It is essential that therapeutic decision making in this critical area include discussion with the patient about the options, advantages, and limitations of available approaches.

Recommendations about the management of patients treated with triple therapy have been published in ACC/AHA CPGs and by other organizations (17,26,430,433,436). Although some organizations have recommended a target INR of 2.0 to 2.5 in patients with atrial fibrillation (AF) who require triple therapy (437), others continue to recommend a target INR of 2.0 to 3.0 (12,436). The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score has relevance in these deliberations (439). No prospective study to date has demonstrated that a target INR of 2.0 to 2.5 reduces bleeding complications.

Whenever possible, shorter durations of triple therapy are favored in preference to longer durations of triple therapy. In patients with NSTE-ACS who require oral anticoagulation for AF, mechanical heart valve, deep venous thrombosis, or other conditions, a bare-metal stent may offer the advantages of lower bleeding risk over a DES because of the potentially shorter duration of triple antithrombotic therapy. The WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial is the first published study to address the question of optimal antiplatelet therapy in patients taking oral anticoagulant medication (440). WOEST was a randomized, open-label trial of 563 patients (approximately 25% of whom had NSTE-ACS) receiving oral anticoagulant therapy and undergoing coronary stenting. Patients randomized to single antiplatelet treatment with clopidogrel had significantly fewer bleeding complications and no increase in

thrombotic events compared with those randomized to DAPT with aspirin and clopidogrel. Larger clinical trials are needed to compare double versus triple therapy in the setting of coronary stenting and NSTE-ACS. One such study that has been initiated is PIONEER AF-PCI (an Open-Label, Randomized, Controlled, Multicenter Study Exploring two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation who Undergo Percutaneous Coronary Intervention).

Although there are some data on therapy with aspirin, clopidogrel, and warfarin, there is sparse information on the use of newer $P2Y_{12}$ inhibitors (prasugrel, ticagrelor), direct thrombin inhibitor (dabigatran), or factor-Xa inhibitors (rivaroxaban, apixaban) in patients receiving triple therapy. Prasugrel (302) and ticagrelor (412) produce a greater degree of platelet inhibition than clopidogrel and are associated with greater rates of bleeding (300,302,412,441). These are important potential disadvantages in patients requiring triple therapy, a group in which the inherent risks of bleeding are significantly increased. (Overall bleeding risk was not increased with ticagrelor, although there was increased bleeding in certain subgroups on this drug (412)). Because there are no well-established therapies to reverse the anticoagulant effects of the newer oral antiplatelet agents, caution is required when considering the use of these agents in patients who require triple therapy and are at significantly increased risk of bleeding. This admonition is especially important in elderly patients, a group in which bleeding risk is inherently increased (Section 7.1).

Proton pump inhibitors decrease the risk of gastrointestinal bleeding in patients treated with DAPT (431) and are used in patients treated with DAPT who have a history of gastrointestinal bleeding and those at increased risk of bleeding, which is associated with oral anticoagulation therapy even if there is no history of gastrointestinal bleeding (430). On the basis of these results, proton pump inhibitors are also used in patients receiving triple antithrombotic therapy who have a history of gastrointestinal bleeding. Although the clinical evidence that omeprazole and esomeprazole diminish the antiplatelet efficacy of clopidogrel is weak (430), the U.S. Food and Drug Administration has issued a warning to avoid concomitant use of these 2 proton pump inhibitors with clopidogrel (442).

6.2.3. Platelet Function and Genetic Phenotype Testing

Although higher platelet reactivity has been associated with a greater incidence of adverse events in patients undergoing stent implantation, a strategy of adjusting

antiplatelet therapy based on routine platelet function testing has not been beneficial in reducing ischemic complications (26,443-445). Similarly, a strategy of routine genetic phenotype testing has also not been beneficial and thus is not recommended (26,446-448). A more detailed discussion of these issues and current recommendations about platelet function testing and genetic testing are in the 2011 PCI CPG (26).

6.3. Risk Reduction Strategies for Secondary Prevention

Secondary prevention is a critical aspect of the management of care for the survivor of NSTE-ACS. It has been clearly established that in this high-risk cohort, subsequent cardiovascular morbidity and mortality can be reduced by a comprehensive approach to favorably modifying patients' risk profiles (27).

Secondary prevention comprises lifestyle changes, risk factor education, medical therapy, and, where appropriate, revascularization. These elements are discussed in Section 6.4. Despite the proven utility of secondary prevention, its implementation remains suboptimal, and enhanced application is a major goal in this patient population.

See Online Data Supplement 23 for additional information on risk reduction strategies.

6.3.1. Cardiac Rehabilitation and Physical Activity: Recommendation

CLASS I

1. **All eligible patients with NSTE-ACS should be referred to a comprehensive cardiovascular rehabilitation program either before hospital discharge or during the first outpatient visit (449-452).** *(Level of Evidence: B)*

The U.S. Public Health Service emphasizes comprehensive cardiac rehabilitation programs (449), and the 2011 secondary prevention CPG underscores referral to cardiac rehabilitation for survivors of ACS (27). Since 2007, referral to these programs has been designated a quality performance measure (453-455). Barriers to referral can be obviated by discussion with the patient and referral by the patient's primary care clinician and/or cardiovascular caregiver. These comprehensive programs provide patient education, enhance regular exercise, monitor risk factors, and address lifestyle modification (456). Aerobic exercise training can generally begin 1 to 2 weeks after discharge in patients treated with PCI or CABG (457). Mild-to-moderate resistance training can be considered and started 2 to 4 weeks after aerobic training (458). Unsupervised exercise may target a heart rate range of 60% to 75% of maximum age-predicted heart rate based on the patient's exercise stress test. Supervised training may target a higher heart rate (70% to 85% of age-predicted maximum) (457). Additional restrictions apply when residual ischemia is present.

Daily walking can be encouraged soon after discharge for most patients. Resource publications on exercise prescription in cardiovascular patients are available (456,457). Regular physical activity reduces symptoms in patients with cardiovascular disease, enhances functional capacity, improves other risk factors such as insulin resistance and glucose control, and is important in weight control (456). Questionnaires and nomograms for cardiac patients have been developed to guide exercise prescription if an exercise test is unavailable (459-462). See Section 6.4 and **Table 10** for more information.

6.3.2. Patient Education: Recommendations

CLASS I

1. **Patients should be educated about appropriate cholesterol management, BP, smoking cessation, and lifestyle management (15,16,18).** *(Level of Evidence: C)*

2. **Patients who have undergone PCI or CABG derive benefit from risk factor modification and should receive counseling that revascularization does not obviate the need for lifestyle changes (463).** *(Level of Evidence: C)*

Results of testing should be discussed with the patient, the patient's family, and/or the patient's advocate in an understandable manner. Test results should be used to help determine the advisability of coronary angiography, the need for adjustments in the medical regimen, and the specifics for secondary prevention measures. See Section 6.4 and **Table 10** for more information on plan of care.

6.3.3. Pneumococcal Pneumonia: Recommendation

CLASS I

1. **The pneumococcal vaccine is recommended for patients 65 years of age and older and in high-risk patients with cardiovascular disease (464-466).** *(Level of Evidence: B)*

Vaccination with the 23-valent pneumococcal polysaccharide vaccine is recommended for all adults ≥65 years of age. Adults of any age who are at increased risk, including smokers and those with asthma, should also be given the vaccine. Immunocompromised adults should receive the 13-valent conjugate vaccine in addition to the 23-valent vaccine (464-466). The influenza vaccine is discussed in Section 6.4.

6.3.4. NSAIDs: Recommendations

CLASS I

1. **Before hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed, and a stepped-care approach should be used for selection of treatments. Pain treatment before consideration of NSAIDs should begin with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics if these medications are not adequate (17,237).** *(Level of Evidence: C)*

CLASS IIa

1. It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics is insufficient (237). *(Level of Evidence: C)*

CLASS IIb

1. NSAIDs with increasing degrees of relative COX-2 selectivity may be considered for pain relief only for situations in which intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, nonacetylated salicylates, tramadol, small doses of narcotics, or nonselective NSAIDs. In all cases, use of the lowest effective doses for the shortest possible time is encouraged (234,235,237,467). *(Level of Evidence: C)*

CLASS III: HARM

1. NSAIDs with increasing degrees of relative COX-2 selectivity should not be administered to patients with NSTE-ACS and chronic musculoskeletal discomfort when therapy with acetaminophen, nonacetylated salicylates, tramadol, small doses of narcotics, or nonselective NSAIDs provide acceptable pain relief (234,235,237,467). *(Level of Evidence: B)*

Selective COX-2 inhibitors and other nonselective NSAIDs have been associated with increased cardiovascular risk, and the risk appears to be amplified in patients with established cardiovascular disease (17,234,235,467,469). In a large Danish observational study of patients with first MI (n=58,432), the HR and 95% CI for death were 2.80 (2.41 to 3.25) for rofecoxib, 2.57 (2.15 to 3.08) for celecoxib, 1.50 (1.36 to 1.67) for ibuprofen, 2.40 (2.09 to 2.80) for diclofenac, and 1.29 (1.16 to

1.43) for other NSAIDs (234). There were dose-related increases in risk of death and non-dose-dependent trends for rehospitalization for MI for all drugs (234,467). An AHA scientific statement on the use of NSAIDs concluded that the risk of cardiovascular events is proportional to COX-2 selectivity and the underlying risk in the patient (237). Non-pharmacological approaches were recommended as the first line of treatment, followed by the stepped-care approach to pharmacological therapy, as shown in **Figure 4**.

6.3.5. Hormone Therapy: Recommendation

CLASS III: HARM

1. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given as new drugs for secondary prevention of coronary events to postmenopausal women after NSTE-ACS and should not be continued in previous users unless the benefits outweigh the estimated risks (17,470–472). *(Level of Evidence: A)*

Although prior observational data suggested a protective effect of hormone therapy for coronary events, a randomized trial of hormone therapy for secondary prevention of death and MI (the HERS [Heart and Estrogen/Progestin Replacement] study) failed to demonstrate a beneficial effect (473). There was an excess risk for death and MI early after initiation of hormone therapy. The Women's Health Initiative included randomized primary prevention trials of estrogen plus progestin and estrogen alone (472). Both trials were stopped early owing to an increased risk related to hormone therapy that was believed to outweigh the potential benefits of further study (470-472). It is recommended that post-menopausal women receiving hormone therapy at the time

- Acetaminophen, ASA, tramadol, narcotic analgesics (short-term)
- Nonacetylated salicylates

- Non-COX-2 selective NSAIDs
- NSAIDs with some COX-2 selectivity
- COX-2 selective NSAIDs

- Select patients at low risk of thrombotic events
- Prescribe lowest dose required to control symptoms
- ASA 81 mg in all patients with PPI added in patients on ASA and NSAIDs to decrease risk of upper GI bleeding

- Regular monitoring for sustained hypertension (or worsening of prior blood pressure control), edema, worsening renal function, or GI bleeding
- If these occur, consider reduction of dose or discontinuation of the offending drug, a different drug, or alternative therapeutic modalities, as dictated by clinical circumstances

FIGURE 4   Stepped-Care Approach to Pharmacological Therapy for Musculoskeletal Symptoms in Patients With Known Cardiovascular Disease or Risk Factors for Ischemic Heart Disease

ASA indicates aspirin; COX-2, cyclooxygenase-2; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; and PPI, proton-pump inhibitor. Modified from Jneid et al. (8).

of a cardiovascular event discontinue its use and that hormone therapy should not be initiated for the primary or secondary prevention of coronary events. However, there may be other permissible indications for hormone therapy in postmenopausal women (e.g., treatment of perimenopausal symptoms such as flushing or prevention of osteoporosis) if the benefits are believed to outweigh the increased cardiovascular risk. Postmenopausal women who are >1 to 2 years past the initiation of hormone therapy who wish to continue such therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of cardiovascular events and breast cancer (combination therapy) or stroke (estrogen) (473).

6.3.6. Antioxidant Vitamins and Folic Acid: Recommendations

CLASS III: NO BENEFIT

1. Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) should not be used for secondary prevention in patients with NSTE-ACS (474,475). *(Level of Evidence: A)*

2. Folic acid, with or without vitamins B_6 and B_{12}, should not be used for secondary prevention in patients with NSTE-ACS (476,477). *(Level of Evidence: A)*

Although there is an association of elevated homocysteine blood levels and CAD, a reduction in homocysteine levels with routine folate supplementation did not reduce the risk of CAD events in 2 trials (the NORVIT [Norwegian Vitamin Trial] and the HOPE [Heart Outcomes Prevention Evaluation] study) that included post–MI or high-risk stable patients (476–478) and produced poorer outcomes in another study (479). Additionally, in the NORVIT trial, there was a trend toward increased cardiovascular events (95% CI: 1.00 to 1.50; p=0.05) in the cohort receiving the combination of folic acid, vitamin B6, and vitamin B12; the authors cautioned against using the treatment for secondary prevention (476). Similarly, experience in large clinical trials with antioxidant vitamins has failed to demonstrate benefit for primary or secondary prevention (474,475,480).

See *Online Data Supplement 23* for additional information on antioxidant vitamins and folic acid.

6.4. Plan of Care for Patients With NSTE-ACS: Recommendations

CLASS I

1. Posthospital systems of care designed to prevent hospital readmissions should be used to facilitate the transition to effective, coordinated outpatient care for all patients with NSTE-ACS (481–485). *(Level of Evidence: B)*

2. An evidence-based plan of care (e.g., GDMT) that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with NSTE-ACS. *(Level of Evidence: C)*

3. In addition to detailed instructions for daily exercise, patients should be given specific instruction on activities (e.g., lifting, climbing stairs, yard work, and household activities) that are permissible and those to avoid. Specific mention should be made of resumption of driving, return to work, and sexual activity (452,486,487). *(Level of Evidence: B)*

4. An annual influenza vaccination is recommended for patients with cardiovascular disease (27,488). *(Level of Evidence: C)*

Education of patients with NSTEMI and their families is critical and often challenging, especially during transitions of care. Failure to understand and comply with a plan of care may account for the high rate of AMI rehospitalization rates in the United States (489,490). An important intervention to promote coordination is to provide patients and caregivers with a comprehensive plan of care and educational materials during the hospital stay that support compliance with evidence-based therapies (491–493). The posthospitalization plan of care for patients with NSTE-ACS (**Table 10**) should address in detail several complex issues, including medication adherence and titration, timely follow-up, dietary interventions, physical and sexual activities, cardiac rehabilitation, compliance with interventions for secondary prevention, and reassessment of arrhythmic and HF risks. In addition, clinicians should pay close attention to psychosocial and socioeconomic issues, including access to care, risk of depression, social isolation, and healthcare disparities (494–496).

6.4.1. Systems to Promote Care Coordination

There has been improved understanding of the system changes necessary to achieve safer care (497). This includes adoption by all U.S. hospitals of a standardized set of "Safe Practices" endorsed by the National Quality Forum (498), which overlap with the National Patient Safety Goals espoused by The Joint Commission (499). Examples of patient safety standards for all patients after AMI include improved communication among clinicians, nurses, and pharmacists; medication reconciliation; careful transitions between care settings; and consistent documentation. The National Quality Forum has also endorsed a set of patient-centered "Preferred Practices for Care Coordination" (500), which detail comprehensive specifications that are necessary to achieve successful care coordination for patients and their families. Systems of care designed to support patients with NSTE-ACS, STEMI, and other cardiac diseases can result in significant improvement in patient outcomes. **Table 10** provides reference documents for multiple risk-reduction strategies for secondary prevention in the posthospital phase of NSTE-ACS. These include the 2013 ACC/AHA CPGs on management of blood cholesterol (18), obesity (16), and lifestyle (15) and the 2014 recommendations for management of hypertension (501), which were published during

the development of this CPG. To provide the interventions and services listed in Table 10, appropriate resources must be used so that patients with MI have full access to evidence-based therapies and follow-up care. There is a growing emphasis on penalizing hospitals for avoidable hospital readmissions. It is imperative for health systems to work with clinicians, nurses, pharmacists, communities, payers, and public agencies to support the interventions that achieve comprehensive care. Several patient characteristics have been predictors of readmission after AMI (502,503).

7. SPECIAL PATIENT GROUPS

See Table 11 for summary of recommendations for this section.

7.1. NSTE-ACS in Older Patients: Recommendations

CLASS I

1. Older patients** with NSTE-ACS should be treated with GDMT, an early invasive strategy, and revascularization as appropriate (515–519). *(Level of Evidence: A)*

2. Pharmacotherapy in older patients** with NSTE-ACS should be individualized and dose adjusted by weight and/or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity (515,520–522). *(Level of Evidence: A)*

3. Management decisions for older patients** with NSTE-ACS should be patient centered, and consider patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy (515,523–525). *(Level of Evidence: B)*

CLASS IIa

1. Bivalirudin, rather than a GP IIb/IIIa inhibitor plus UFH, is reasonable in older patients** with NSTE-ACS, both initially and at PCI, given similar efficacy but less bleeding risk (396,526–528). *(Level of Evidence: B)*

2. It is reasonable to choose CABG over PCI in older patients** with NSTE-ACS who are appropriate candidates, particularly those with diabetes mellitus or complex 3-vessel CAD (e.g., SYNTAX score >22), with or without involvement of the proximal LAD artery, to reduce cardiovascular disease events and readmission and to improve survival (529–534). *(Level of Evidence: B)*

In this CPG, "older adults" refers to patients ≥75 years of age (515). Older adults have the highest incidence, prevalence, and adverse outcomes of NSTE-ACS (9,515–517,535,536). Older age is accompanied by comorbidities, polypharmacy, and age- and disease-related physiological changes that

adversely impact NSTE-ACS presentation, management, and outcome. As older patients are under-represented in clinical trials, the recommendations in this CPG are largely supported by registry data and meta-analyses (516,537).

Older patients with NSTE-ACS primarily present with chest pain but frequently have atypical symptoms. ECGs may be less diagnostic than in younger patients (517,538). Older patients with NSTE-ACS derive the same or greater benefit from pharmacological therapies, interventional therapies, and cardiac rehabilitation as younger patients, but older patients receive significantly less GDMT than younger patients, even when adjusted for comorbidities (515–517,535,538,539). In the ACSIS (Acute Coronary Syndrome Israeli Survey) registry, patients >80 years of age referred for early coronary angiography, compared with no angiography, had lower 30-day and 1-year mortality rates (540).

Age-related pharmacokinetics and pharmacodynamic changes can alter drug dosing, efficacy, and safety of many NSTE-ACS therapies, as can drug–drug interactions (Appendix 4, Table B) (515,520,521,541,542). CrCl or glomerular filtration rate (GFR) should be estimated initially and throughout care for all older patients with NSTE-ACS, and pharmaceutical agents should be renally and weight dose-adjusted to limit drug toxicity (especially bleeding risk), given the unreliability of serum creatinine to assess age-related renal dysfunction (515,522,526,543–545) (Appendix 4, Table C). Bleeding in older patients with NSTE-ACS is multifactorial, resulting in narrower therapeutic windows (541,542,544,546,547).

In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) study, excessive doses of UFH, LMWH, and GP IIb/IIIa inhibitors accounted for 15% of major bleeding, longer lengths of stay, and increased mortality (522,548). Aspirin should be maintained at 81 mg per day (after initial stent implantation). Owing to excess bleeding without clinical benefit, the U.S. Food and Drug Administration lists a Black Box warning that does not recommend administration of prasugrel to patients with NSTE-ACS who are ≥75 years of age or weigh <60 kg except in those at very high risk. A meta-analysis of 6 RCTs about the use of GP IIb/IIIa inhibitors in patients with NSTE-ACS reported no significant age-treatment interaction, although older women had significantly more adverse events (549). Bivalirudin appears safer for older patients with NSTE-ACS ± PCI than GP IIb/IIIa inhibitors plus UFH, with less bleeding and similar efficacy (526,550). AF is more common in older patients with NSTE-ACS, and triple therapy (DAPT and warfarin) entails a marked bleeding risk (551). In the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in

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**Those ≥75 years of age (see text).

Patients With Oral Anticoagulation and Coronary Stenting) study, it was found that in patients taking oral coagulants who required PCI, use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in thrombotic events (440). Nonetheless, practice should not be changed on the basis of this limited study alone.

Older patients with NSTE-ACS benefit as much or more than younger patients from an early invasive strategy compared with an ischemia-guided strategy (340,341,515,518,519). In a 5-year follow-up meta-analysis of FRISC-II and RITA-3, an early invasive strategy versus an ischemia-guided strategy was associated with a significant reduction in death/MI and MI in patients ≥75 years of age but not in patients <65 years of age (518). Although the highest risk reduction in death/MI with an early invasive strategy occurred in those ≥75 years of age, this strategy was associated with a 3-fold bleeding risk (552). However, despite the overall favorable evidence for an early invasive strategy in older patients, age is the strongest risk factor for this group not undergoing an early invasive strategy (553).

PCI has increased in older patients, including the very elderly (≥90 years of age), with success rates similar to younger patients and declining complication rates, including major bleeding (515,517,526–528,554). Several large registries report a greater RR reduction in mortality of older patients treated with revascularization versus medical therapy compared with those ≤65 years of age, despite increased comorbidities (517,540,554–556).

Operative mortality rates for CABG in patients ≥80 years of age with NSTE-ACS range from 5% to 8% (11% for urgent cases) and increase to approximately 13% at ≥90 years of age. Complications occur more frequently in older patients with CABG (557,558). Length of stay averages 6 days longer in older patients than in patients <50 years of age, and discharge (to home [52%]) is less frequent than in younger patients (557). In a meta-analysis, off-pump CABG appeared to offer a potentially safer and more effective revascularization technique compared with on-pump CABG in older patients with NSTE-ACS (559). Older patients with NSTE-ACS with diabetes mellitus had a greater survival advantage with CABG (529). Evaluation tools can help identify older patients with NSTE-ACS whose risk and comorbidity profile predict mortality within 6 to 12 months and possibly guide a palliative approach (524).

See *Online Data Supplement 24* for additional information on older patients.

7.2. HF: Recommendations

CLASS I

1. Patients with a history of HF and NSTE-ACS should be treated according to the same risk stratification guidelines and recommendations for patients without HF (14,42–44,75–81). *(Level of Evidence: B)*

2. Selection of a specific revascularization strategy should be based on the degree, severity, and extent of CAD; associated cardiac lesions; the extent of LV dysfunction; and the history of prior revascularization procedures (14,138,141,333,334, 337,341,560,561). *(Level of Evidence: B)*

In patients with HF and NSTE-ACS, the plan of care should be implemented as in patients without HF using medical therapy and an early invasive approach, because patients with abnormal LV function are at increased risk of mortality and morbidity (562). HF itself may be associated with elevated serum troponin in the presence or absence of obstructive CAD. After angiography, risk stratification can be used to select revascularization strategies. The effect of surgical revascularization on improving survival has been most clearly demonstrated in patients with both extensive CAD and LV dysfunction (356,357,563–567). Such patients should undergo testing to identify the severity and extent of ischemia and should in general be referred for coronary angiography. In selected patients with appropriate anatomy, PCI has been used (23,568). In patients who have already undergone CABG or in whom the anatomy is not favorable for CABG, PCI has been performed using CPG-based PCI performance strategies if specific targeted areas that are amenable to PCI can be identified (26). If there is a large amount of ischemic territory and very poor LV function, percutaneous ventricular assist devices or, in less severe cases, an IABP can be used for support during the procedure (266,569–573).

See *Online Data Supplement 25* for additional information on HF.

7.2.1. Arrhythmias

Ventricular arrhythmias are common early after onset of NSTE-ACS, and not all require intervention. The mechanisms for these arrhythmias include continuing ischemia, hemodynamic and electrolyte abnormalities, reentry, and enhanced automaticity. Approximately 5% to 10% of hospitalized patients may develop ventricular tachycardia (VT)/ventricular fibrillation (VF), usually within 48 hours of presentation (574). The incidence of VF in otherwise uncomplicated AMI appears to have decreased within the past few years from >4% to <2%, of which 59% of patients had non-Q-wave MI (574). A study of 277 consecutive patients with NSTE-ACS who underwent cardiac catheterization within 48 hours found VT/VF occurring in 7.6% of patients, 60% of which developed within 48 hours after admission (575). Risk factors for VT/VF include HF, hypotension, tachycardia, shock, and low TIMI flow grade. Treatment consists of immediate defibrillation or cardioversion for VF or pulseless sustained VT. Early administration of beta

TABLE 11	Summary of Recommendations for Special Patient Groups			
Recommendations		**COR**	**LOE**	**References**
NSTE-ACS in older patients				
Treat older patients (≥75 y of age) with GDMT, early invasive strategy, and revascularization as appropriate		I	A	(515–519)
Individualize pharmacotherapy in older patients, with dose adjusted by weight and/or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics, volume of distribution, comorbidity, drug interactions, and increased drug sensitivity		I	A	(515,520–522)
Undertake patient-centered management for older patients, considering patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy		I	B	(515,523–525)
Bivalirudin rather than GP IIb/IIIa inhibitor plus UFH is reasonable for older patients (≥75 y of age), given similar efficacy but less bleeding risk		IIa	B	(396,526–528)
It is reasonable to choose CABG over PCI in older patients, particularly those with DM or multivessel disease, because of the potential for improved survival and reduced CVD events		IIa	B	(529–534)
HF				
Treat patients with a history of HF according to the same risk stratification guidelines and recommendations for patients without HF		I	B	(14,42–44,75–81)
Select a revascularization strategy based on the extent of CAD, associated cardiac lesions, LV dysfunction, and prior revascularization		I	B	(14,138,141,333,334, 337,341,560,561)
Cardiogenic shock				
Recommend early revascularization for cardiogenic shock due to cardiac pump failure		I	B	(560,588,589)
DM				
Recommend medical treatment and decisions for testing and revascularization similar to those for patients without DM		I	A	(138,339,601)
Post−CABG				
Recommend GDMT antiplatelet and anticoagulant therapy and early invasive strategy because of increased risk with prior CABG		I	B	(67,68,141,340–342)
Perioperative NSTE-ACS				
Administer GDMT to perioperative patients with limitations imposed by noncardiac surgery		I	C	(626,627)
Direct management at underlying cause of perioperative NSTE-ACS		I	C	(21,626–634)
CKD				
Estimate CrCl and adjust doses of renally cleared medications according to pharmacokinetic data		I	B	(649,650)
Administer adequate hydration to patients undergoing coronary and LV angiography		I	C	N/A
Invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD		IIa	B	(649–652)
Women				
Manage women with the same pharmacological therapy as that for men for acute care and secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk		I	B	(669–673)
Early invasive strategy is recommended in women with NSTE-ACS and high-risk features (troponin positive)		I	A	(141,345,346,561)
Myocardial revascularization is reasonable for pregnant women if ischemia-guided strategy is ineffective for management of life-threatening complications		IIa	C	(674)
Women with low-risk features (Section 3.3.1) should not undergo early invasive treatment because of lack of benefit and the possibility of harm		III: No Benefit	B	(141,345,346)
Anemia, bleeding, and transfusion				
Evaluate all patients for risk of bleeding		I	C	N/A
Recommend that anticoagulant and antiplatelet therapy be weight-based where appropriate and adjusted for CKD to decrease the risk of bleeding		I	B	(522,697,698)
There is no benefit of routine blood transfusion in hemodynamically stable patients with hemoglobin levels >8 g/dL		III: No Benefit	B	(699–703)
Cocaine and methamphetamine users				
Manage patients with recent cocaine or methamphetamine use similarly to those without cocaine- or methamphetamine-related NSTE-ACS. The exception is in patients with signs of acute intoxication (e.g., euphoria, tachycardia, and hypertension) and beta-blocker use unless patients are receiving coronary vasodilator therapy		I	C	N/A
It is reasonable to use benzodiazepines alone or in combination with NTG to manage hypertension and tachycardia and signs of acute cocaine or methamphetamine intoxication		IIa	C	(741–744)
Do not administer beta blockers to patients with recent cocaine or methamphetamine use who have signs of acute intoxication due to risk of potentiating coronary spasm		III: Harm	C	N/A

TABLE 11	Continued			
Recommendations		COR	LOE	References
Vasospastic (Prinzmetal) angina				
Recommend CCBs alone or in combination with nitrates		I	B	(753–758)
Recommend HMG-CoA reductase inhibitor, cessation of tobacco use, and atherosclerosis risk factor modification		I	B	(759–763)
Recommend coronary angiography (invasive or noninvasive) for episodic chest pain with transient ST-elevation to detect severe CAD		I	C	N/A
Provocative testing during invasive coronary angiography* may be considered for suspected vasospastic angina when clinical criteria and noninvasive assessment fail to determine diagnosis		IIb	B	(764–767)
ACS with angiographically normal coronary arteries				
Invasive physiological assessment (coronary flow reserve measurement) may be considered with normal coronary arteries if endothelial dysfunction is suspected		IIb	B	(629,773–776)
Stress (Takotsubo) cardiomyopathy				
Consider stress-induced cardiomyopathy in patients with apparent ACS and nonobstructive CAD		I	C	N/A
Perform ventriculography, echocardiography, or MRI to confirm or exclude diagnosis		I	B	(795–798)
Treat with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) if hemodynamically stable		I	C	N/A
Administer anticoagulant therapy for LV thrombi		I	C	N/A
It is reasonable to administer catecholamines for symptomatic hypotension in the absence of LV outflow tract obstruction		IIa	C	N/A
It is reasonable to use IABP for refractory shock		IIa	C	N/A
It is reasonable to use beta blockers and alpha-adrenergic agents for LV outflow tract obstruction		IIa	C	N/A
Prophylactic anticoagulation may be considered to prevent LV thrombi		IIb	C	N/A

*Provocative testing during invasive coronary angiography (e.g., using ergonovine, acetylcholine, methylergonovine) is relatively safe, especially when performed in a controlled manner by experienced operators. However, sustained spasm, serious arrhythmias, and even death can also occur but very infrequently. Therefore, provocative tests should be avoided in patients with significant left main disease, advanced 3-vessel disease, presence of high-grade obstructive lesions, significant valvular stenosis, significant LV systolic dysfunction, and advanced HF.

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; COR, Class of Recommendation; CrCl, creatinine clearance; CVD, cardiovascular disease; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; GP, glycoprotein; HF, heart failure; IABP, intra-aortic balloon pump; LOE, Level of Evidence; LV, left ventricular; MRI, magnetic resonance imaging; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndrome; NTG, nitroglycerin; PCI, percutaneous coronary intervention; and UFH, unfractionated heparin.

blockers has been associated with reduction in incidence of VF (576). The prophylactic use of lidocaine is not recommended. Although VT/VF is associated with higher 90-day mortality risk, premature ventricular contractions not associated with hemodynamic compromise and accelerated ventricular rhythms do not confer higher mortality risks and do not require specific therapy other than maintaining electrolyte balance. NSTE-ACS nonsustained VT occurring >48 hours after admission indicates an increased risk of cardiac and sudden death, especially when associated with accompanying myocardial ischemia (577). Life-threatening ventricular arrhythmias that occur >48 hours after NSTE-ACS are usually associated with LV dysfunction and signify poor prognosis. RCTs in patients with ACS have shown consistent benefit of implantable cardioverter-defibrillator therapy for survivors of VT or VF arrest (578–582). For other at-risk patients, especially those with significantly reduced LVEF, candidacy for primary prevention of sudden cardiac death with an implantable cardioverter-defibrillator should be readdressed ≥40 days after discharge (583). A life vest may be considered in the interim.

AF, atrial flutter, and other supraventricular arrhythmias may be triggered by excessive sympathetic stimulation, atrial stress due to volume overload, atrial infarction, pericarditis, electrolyte abnormalities, hypoxia, or pulmonary disease. AF is the most common of these arrhythmias and may develop in >20% of patients. AF is associated with shock, HF, stroke, and increased 90-day mortality (584). Management of AF requires rate control and adequate anticoagulation according to the 2014 AF CPG (12). For hemodynamically unstable patients and those with continuing ischemia, treatment should be implemented according to the 2010 advanced cardiac life support CPGs (585).

Sinus bradycardia is especially common with inferior NSTEMI. Symptomatic or hemodynamically significant sinus bradycardia should be treated with atropine and, if not responsive, temporary pacing. The incidence of complete heart block is 1.0% to 3.7% in NSTEMI, based on anterior or posterior/inferior location, respectively (586). Atrioventricular block and bundle-branch block develop in approximately 5% of patients (587). High-degree atrioventricular block or bundle-branch block in anterior NSTEMI is more ominous because of a greater extent of

myocardial injury and involvement of the conduction system (587).

First-degree atrioventricular block does not require treatment. High-grade atrioventricular block after inferior NSTEMI usually is transient, with a narrow QRS complex and a junctional escape rhythm that can be managed with an ischemia-guided strategy. Prophylactic placement of a temporary pacemaker is recommended for high-grade atrioventricular block, new bundle-branch block, or bifascicular block with anterior infarction. Indications for permanent pacing are reviewed in the 2012 device-based therapy CPG (20).

7.2.2. Cardiogenic Shock: Recommendation

CLASS I

1. Early revascularization is recommended in suitable patients with cardiogenic shock due to cardiac pump failure after NSTE-ACS (560,588,589). *(Level of Evidence: B)*

AMI is the leading cause of cardiogenic shock. Early revascularization is a mainstay in the treatment of cardiogenic shock (560,589). Compared with medical therapy, early revascularization is associated with improved 6-month mortality (560) and 13% absolute mortality reduction at 6 years (588). Urgent revascularization with CABG may be indicated for failed PCI, coronary anatomy not amenable to PCI, and at the time of surgical repair of a mechanical defect (e.g., septal, papillary muscle, free-wall rupture). Age alone is not a contraindication to urgent revascularization for cardiogenic shock (589,590). Mortality after cardiogenic shock has steadily improved (591), including in older adults (589,590), with 30-day mortality ranging from approximately 40% with milder forms of shock (268) to >45% with refractory shock (592). Approximately 30% of patients in the IABP-SHOCK (Intra-Aortic Balloon Pump in Cardiogenic Shock) II trial presented with NSTEMI (268), and 22% of patients in the TRIUMPH (Tilarginine Acetate Injection in a Randomized International Study in Unstable Acute Myocardial Infarction Patients With Cardiogenic Shock) trial had ST depression on presentation (592). Of the 23% of patients with ACS who had NSTEMI in the GRACE registry, 4.6% of patients experienced cardiogenic shock (593). Of the 2,992 patients in shock, 57% underwent cardiac catheterization, and in-hospital revascularization was performed in 47% of this group.

In-hospital mortality of all patients with shock was 59% (594). Patients with NSTEMI developed cardiogenic shock later than patients with STEMI, and had higher-risk clinical characteristics, more extensive CAD, and more recurrent ischemia and infarction before developing shock compared with patients with STEMI, and shock developed later in patients with NSTEMI (151). Patients with NSTEMI constituted >17% of those in the SHOCK trial registry (595). They were also older and had more comorbidities but had comparable mortality to patients with STEMI. The left circumflex coronary artery was the culprit vessel in 30% of patients with NSTEMI, suggesting the presence of true posterior MI (595). Dopamine in patients with cardiogenic shock may be associated with increased mortality compared with norepinephrine (596). The use of percutaneous ventricular assist devices has been hampered by the need for interventional expertise, cost, and lack of supportive evidence (597). IABP has been used for decades (265,598), and it may facilitate intervention in patients who are hemodynamically unstable, but it did not reduce mortality or secondary endpoints in 1 RCT of 598 patients with cardiogenic shock complicating AMI (268). Newer devices with higher levels of support have provided better hemodynamic support but without improved clinical outcomes compared with IABP (599,600).

See Online Data Supplement 26 for additional information on cardiogenic shock.

7.3. Diabetes Mellitus: Recommendation

CLASS I

1. Medical treatment in the acute phase of NSTE-ACS and decisions to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus (138,339,601). *(Level of Evidence: A)*

CAD accounts for 75% of deaths in patients with diabetes mellitus; >30% of patients with NSTE-ACS have diabetes mellitus; and patients with NSTE-ACS and diabetes mellitus have more adverse outcomes (e.g., death, MI, readmission with ACS, or HF) during follow up (593,602,603). The latter may be related to increased plaque instability and comorbidities, including hypertension, LV hypertrophy, cardiomyopathy, HF, and autonomic dysfunction (603-605). Patients with diabetes mellitus and ACS have longer delays from symptom onset to presentation (593,606,607), which may be attributable to their atypical symptoms.

There is a U-shaped relationship between glucose levels and mortality in patients with diabetes mellitus and ACS (543). Both hyperglycemia and hypoglycemia have similar adverse effects on in-hospital and 6-month mortality. The urgency to aggressively control blood glucose has been moderated by the results of the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regimen) trial (608). In this study of patients admitted to medical and surgical intensive care units, intensive glucose control (target 81 mg/dL to 108 mg/dL) resulted in increased all-cause mortality and hypoglycemia compared with moderate glucose control (target <180 mg/dL). Blood glucose should be maintained at <180 mg/dL while avoiding hypoglycemia. There is no established role for the administration of glucose-insulin-potassium infusions in NSTE-ACS (609-611).

Although patients with diabetes mellitus and NSTE-ACS are at higher risk for in-hospital and longer-term events, they undergo less frequent revascularization procedures. In a multinational study of 6,385 patients with ACS, 25% of whom had diabetes mellitus, those with diabetes mellitus had more adverse risk profiles, more atypical presentations, longer treatment delays, more HF, and renal insufficiency but underwent less angiography and revascularization (607). In the GRACE Registry (593) and other studies (606), patients with diabetes mellitus and NSTE-ACS in the United Kingdom (603) and Finland (612) had higher baseline risk profiles but received effective medical cardiac therapies and revascularization less frequently.

Although there are no RCTs of patients specifically diagnosed with diabetes mellitus and ACS, there are ample data on patients with diabetes mellitus treated with PCI or CABG (564,565,613-615). The largest RCT, the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (616), evaluated 1,900 patients (approximately 30% with "recent" [interval unspecified] ACS) with 2- or 3-vessel CAD randomized to a DES or CABG. At 5 years, there was a significant decrease in all-cause mortality (p=0.049; MI: p<0.001) associated with CABG. There was no specific analysis of outcomes in patients with "recent" (interval unspecified) ACS. CABG was also superior to PCI in reducing MACE in other trials (564,613-615) (Appendix 4, Table D).

The importance of the severity and complexity of CAD was underscored in the SYNTAX trial, in which those with less severe and complex CAD had similar outcomes with PCI and CABG compared with those with more severe and complex disease, in which CABG improved outcomes, including survival (355,565).

7.3.1. Adjunctive Therapy

A meta-analysis (6 trials: 23,072 patients without diabetes mellitus, 6,458 patients with diabetes mellitus) of the effect of GP IIb/IIIa platelet receptor inhibitors (abciximab, eptifibatide, and tirofiban) on mortality in NSTEMI revealed that for the entire patient group, a GP IIb/IIIa inhibitor was associated with reduced 30-day mortality (6.2% to 4.6%; p=0.007) (392). This benefit was particularly large in the 1,279 patients with diabetes mellitus who underwent PCI (4.0% to 1.2%; p=0.002). The ACUITY trial in ACS (13,819 patients, 3,852 with diabetes mellitus) reported that 30-day adverse clinical outcomes (death, MI, or unplanned revascularization) or major bleeding were increased in patients with diabetes mellitus (12.9% versus 10.6%; p<0.001) (617). Bivalirudin plus a GP IIb/IIIa inhibitor resulted in increased similar rates of the composite ischemia compared with heparin plus a GP IIb/IIIa inhibitor. Bivalirudin alone was associated with a similar increased rate of composite ischemia but less major bleeding (3.7% versus 7.1%; p<0.001).

Several studies evaluated the benefit of oral antiplatelet therapy during ACS in patients with diabetes mellitus. In TRITON-TIMI 38, patients with diabetes mellitus had a greater reduction in ischemic events without an observed increase in TIMI major bleeding with prasugrel compared with clopidogrel (618). In PLATO, ticagrelor compared with clopidogrel reduced ischemic events irrespective of diabetic status and glycemic control, without an increase in major bleeding (619).

See *Online Data Supplement 27* for additional information on diabetes mellitus.

7.4. Post–CABG: Recommendation

CLASS I

1. Patients with prior CABG and NSTE-ACS should receive antiplatelet and anticoagulant therapy according to GDMT and should be strongly considered for early invasive strategy because of their increased risk (67,68,141,340–342). *(Level of Evidence: B)*

Although CABG reduces morbidity and mortality in selected patients with complex CAD, they remain at risk for development of disease progression of ungrafted native vessels or significant atherothrombotic disease in saphenous vein grafts and subsequent ACS. These patients constitute a higher-risk group because they have already undergone CABG, typically for more extensive CAD, and they have more comorbidities (620-624).

In the PURSUIT trial, 12% (1,134) of the patients had prior CABG and more adverse follow-up outcomes, including increased mortality, but had a benefit with eptifibatide similar to those without prior CABG (622). Patients with prior CABG are less likely to undergo early catheterization after NSTEMI. In the Get With The Guidelines study of patients with NSTEMI, 18.5% had prior CABG and a lower likelihood of early invasive evaluation but had higher rates of guideline-recommended clopidogrel and bivalirudin therapy and lower rates of GP IIb/IIIa and anticoagulant therapy (625). In patients with prior CABG who develop NSTE-ACS that is related to an ungrafted native coronary vessel, treatment should follow GDMT (26).

Because patients with prior CABG presenting with ACS are a high-risk group with increased comorbid characteristics and high-risk anatomy, a strategy of early angiography should be implemented (unless clinically contraindicated), and these patients should receive optimal antiplatelet and anticoagulant therapy.

See *Online Data Supplement 28* for additional information on post-CABG.

7.5. Perioperative NSTE-ACS Related to Noncardiac Surgery: Recommendations

CLASS I

1. Patients who develop NSTE-ACS following noncardiac surgery should receive GDMT as recommended for patients in the general population but with the modifications imposed by the specific noncardiac surgical procedure and the severity of the NSTE-ACS (626,627). *(Level of Evidence: C)*

2. In patients who develop NSTE-ACS after noncardiac surgery, management should be directed at the underlying cause (21,626–634). *(Level of Evidence: C)*

Patients with NSTE-ACS following noncardiac surgery should be managed according to the guidelines for patients in the general population, with risk stratification and guideline-based pharmacological and invasive management directed at the etiology (e.g., hypertension, tachycardia, HF, hypotension, sepsis, and anemia) with modifications based on the severity of NSTE-ACS and the limitations imposed by the noncardiac surgical procedure.

The definition of ACS has a substantial effect on reported incidence (178,184,635–644). Some patients may not be able to give a history of ischemic symptoms because of the noncardiac surgery. The criteria in the 2012 Third Universal Definition of MI should be applied (21). In patients at risk of ACS following noncardiac surgery, routine monitoring of troponins and ECGs may be performed. As the sensitivity of troponin assays improves, the frequency of identifying perioperative MI will increase. In the POISE (Perioperative Ischemic Study Evaluation) trial (645), of 8,351 patients randomized to extended-release metoprolol versus placebo, 5.7% of patients in the control group had a perioperative MI typically occurring within 48 hours and often not associated with ischemic symptoms.

ACS in the setting of noncardiac surgery is associated with increased mortality. Several risk scores have been developed to determine the probability of mortality (646–648). A meta-analysis of the prognostic value of troponin and CK-MB after noncardiac surgery that included 14 studies enrolling 3,318 patients demonstrated that elevated troponin after surgery was an independent predictor of mortality both in the hospital and at 1-year follow-up (639). Markedly elevated troponins are associated with increased mortality compared with minimal troponin elevation, even though the latter still indicates a postoperative MI (184,639,641,642). In patients with UA in whom the risks of bleeding with antiplatelet therapy outweigh the benefits, GDMT with beta blockers, nitrates, and ACE inhibitors should be optimized to achieve symptom control. In patients with a relative or absolute contraindication to antiplatelet or anticoagulant therapy, coronary angiography may be helpful to identify anatomy requiring revascularization after recovery from the noncardiac surgery.

7.6. CKD: Recommendations

CLASS I

1. CrCl should be estimated in patients with NSTE-ACS, and doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications (649,650). *(Level of Evidence: B)*

2. Patients undergoing coronary and LV angiography should receive adequate hydration. *(Level of Evidence: C)*

CLASS IIa

1. An invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD (649–652). *(Level of Evidence: B)*

CKD is a major risk factor for poor outcomes in patients with NSTEMI (652–657). Patients with impaired renal function have additional adverse baseline characteristics, including older age, a history of prior HF, and peripheral arterial disease. It is prudent to omit LV angiography in patients with CKD and assess LV function with echocardiography.

In an analysis from 3 ACS trial databases of 19,304 patients with NSTEMI, 42% (8,152 patients) had abnormal renal function on the basis of serum creatinine and calculated CrCl; total mortality and mortality/MI were increased at 30 days and 180 days. CrCl was independently associated with mortality (HR: 0.81) and the risk of mortality/MI (HR: 0.93) (656). The VALIANT (Valsartan in Acute Myocardial Infarction) trial included 14,527 high-risk patients with AMI with LV dysfunction or HF and a serum creatinine level $\geq$1.5 mg/dL (658,659). The Modification of Diet in Renal Disease equation was used, and patients were analyzed based on their estimated GFR. There was an increasing adjusted HR for both death and the composite endpoint of cardiovascular death, reinfarction, HF, stroke, or resuscitation after cardiac arrest with decreasing estimated GFR. For death, with a GFR <45.0 mL per minute/1.73 m^2, the adjusted HR was 1.70 compared with patients with a GFR of 60.0 mL per minute/1.73 m^2 to 74.9 mL per minute/1.73 m^2 in whom the adjusted HR was 1.14. There are insufficient data on the benefit-to-risk ratio of an invasive strategy in patients with NSTE-ACS and advanced CKD (stages 4 and 5) (652). There is also less evidence-based medical therapy and revascularization data in patients with CKD because of the risk for contrast-induced nephropathy, increased need for dialysis, and increased mortality. Multiple studies have evaluated radiographic agents, including ionic versus nonionic media and isosmolar or low-osmolar agents.

The strength and consistency of relationships between specific isosmolar or low-osmolar agents and contrast-induced nephropathy or renal failure are insufficient

for selection of low-osmolar and isosmolar media. Limitation of the risk of contrast-induced nephropathy is based on reduced contrast volume (660) and adequate hydration (661).

A recent meta-analysis of 5 RCTs evaluated 1,453 patients with NSTE-ACS and CKD, all with GFR <60 mL per minute/1.73 m² (651). Patients were analyzed according to baseline renal function: stage 3a, 3b, and 4 to 5. An invasive strategy was associated with a nonsignificant reduction in all-cause mortality and the composite of death or nonfatal MI. An early invasive strategy in patients with CKD and ACS reduced rehospitalization and resulted in a trend toward lower mortality and nonfatal reinfarction. The increased risk of mortality associated with mild, moderate, and severe CKD is evident across studies, and risks are increased as the gradient of renal dysfunction worsens (649-651,662).

See Online Data Supplement 29 for additional information on CKD.

7.6.1. Antiplatelet Therapy

Patients with CKD with ACS are at increased risk for ischemic complications, including stent thrombosis and post–PCI ischemic events (663). They are also predisposed to higher bleeding complications, which, in addition to the lack of clinical trial data, result in their undertreatment with antiplatelet therapy. Patients with advanced CKD exhibit high residual platelet reactivity despite treatment with clopidogrel independent of the presence of diabetes mellitus (664). Hyporesponsiveness to thienopyridines is associated with increased adverse cardiovascular outcomes, including cardiovascular mortality (665), and higher dosing regimens of clopidogrel do not appear to further suppress adenosine diphosphate-induced platelet aggregation (664,666).

Although prasugrel may be more efficient than doubling the dose of clopidogrel in achieving adequate platelet inhibition (667), no clinical studies have demonstrated its efficacy in patients with CKD with ACS. Ticagrelor, however, was studied in a prespecified analysis from the PLATO trial (668). In patients with an estimated GFR <60 mL per minute (nearly 21% of patients in PLATO with available central laboratory serum creatinine levels), ticagrelor significantly reduced the primary cardiovascular endpoint (17.3% versus 22.0%; HR: 0.77; 95% CI: 0.65 to 0.90) compared with clopidogrel (667). Notably, this was associated with a 4% absolute risk reduction in all-cause mortality favoring ticagrelor and with no differences in major bleeding, fatal bleeding, and non–CABG-related major bleeding events, demonstrating its utility in patients with renal insufficiency.

7.7. Women: Recommendations

CLASS I

1. Women with NSTE-ACS should be managed with the same pharmacological therapy as that for men for acute care and for secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk (669-673). *(Level of Evidence: B)*

2. Women with NSTE-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy (141,345,346,561). *(Level of Evidence: A)*

CLASS IIa

1. Myocardial revascularization is reasonable in pregnant women with NSTE-ACS if an ischemia-guided strategy is ineffective for management of life-threatening complications (674). *(Level of Evidence: C)*

CLASS III: NO BENEFIT

1. Women with NSTE-ACS and low-risk features (see Section 3.3.1) should not undergo early invasive treatment because of the lack of benefit (141,345,346) and the possibility of harm (141). *(Level of Evidence: B)*

Women of all ages have higher rates of in-hospital and long-term complications of NSTE-ACS than men, including bleeding, HF, cardiogenic shock, acute renal failure, recurrent MI, stroke, and readmissions (670,675,676).

Women present later after symptom onset of NSTE-ACS and have higher rates of inappropriate discharges from the ED (671,677,678). Women more commonly report atypical symptoms than men (675,679). Women presenting with chest pain are more likely than men to have either a noncardiac cause or cardiac causes other than obstructive epicardial coronary disease (108,677,680,681). Women with NSTE-ACS with no apparent obstructive epicardial disease have a 2% risk of death or MI within 30 days and require secondary prevention and symptom management (682).

Women derive the same treatment benefit as men from aspirin, clopidogrel, anticoagulants, beta blockers, ACE inhibitors, and statins (385,670-672,675,676,683,684). Despite worse outcomes, women with NSTE-ACS are underprescribed guideline-directed pharmacological therapy, both during the acute illness and at discharge (538,685,686). The basis for pharmacotherapy for women with NSTE-ACS with abnormal biomarkers and/or functional tests, but without significant obstructive epicardial disease, remains unclear (Section 7.13). In addition to risk factor modification, some studies support the benefit of imipramine, ranolazine, beta blockers, and/or ACE inhibitors to reduce adverse outcomes (687). Women with NSTE-ACS incur a higher rate of bleeding complications

(672,673) (Section 7.8) and renal failure. A risk score has been developed to attempt to reduce the bleeding risk in women with NSTE-ACS (688).

The decision for an early invasive versus an ischemia-guided strategy in women with NSTE-ACS is based on a meta-analysis (366) and post hoc gender analyses of clinical trials, including FRISC II, RITA-3, and TACTICS-TIMI 18 (344,346,689). The Agency for Healthcare Research and Quality analysis of an early invasive versus ischemia-guided strategy (345) provides further evidence that an early invasive strategy should be reserved for women with positive troponins, as shown in TACTICS-TIMI 18 (346). Such women had a significant reduction of death and MI at 1 year with an early invasive versus ischemia-guided strategy. Women with NSTE-ACS and no elevation in troponin who underwent an early invasive strategy had a nonsignificant increase in events, as did women with a low-risk TIMI score (OR: 1.59 for early invasive versus ischemia-guided strategy), prompting the Class III recommendation in this CPG.

The NCDR-ACTION registry reported increased complication rates of myocardial revascularization in women (https://www.ncdr.com/webncdr/action/). Women also have higher rates of contrast-induced nephropathy and vascular complications (673,690,691). Despite having fewer high-risk angiographic lesions, a higher percentage of normal LV function, and up to 25% angiographically normal coronary arteries, women with NSTE-ACS have a paradoxically higher rate of persistent angina, reinfarction, functional decline, and depression after PCI (141,675,677,680,682). Clinical trials (692,693), and a meta-analysis (694) of DES for NSTE-ACS reported no gender differences in short- and long-term (up to 5 years) outcome, including target vessel revascularization, MACE, cardiac death, or MI. However, women were older and had more comorbidities than men at enrollment.

Women with NSTE-ACS referred for CABG are older with more comorbidities, which is reflected by higher periprocedural mortality, HF, bleeding, MI, and renal failure (686,695,696). Women required more periprocedural IABP, vasopressors, mechanical ventilation, dialysis, and blood products and had longer stays in the intensive care unit and hospital, higher rates of wound infection, depression, and longer recovery (549,677).

An Agency for Healthcare Research and Quality meta-analysis of 10 RCTs through December 2011 reported no efficacy or safety difference between PCI and CABG for NSTE-ACS in men or women in 30-day or 1-year MACE (death/MI/stroke). At 2 years, the procedural success remained equal in women but favored CABG in men (p=0.002) (345,564). The Agency for Healthcare Research and Quality reported similar outcomes in women with

diabetes mellitus with PCI and CABG for NSTE-ACS at 7 years, but men with diabetes mellitus had fewer events with CABG. A prespecified gender analysis of the FREEDOM trial favored CABG over PCI for women with diabetes mellitus, although the difference was not as significant as it was for men (616).

Consistent with the European Society of Cardiology recommendations, myocardial revascularization should be reserved for pregnant women with NSTE-ACS and very serious complications unresponsive to medical therapy (674).

See Online Data Supplement 30 for more information on women.

7.8. Anemia, Bleeding, and Transfusion: Recommendations

CLASS I

1. All patients with NSTE-ACS should be evaluated for the risk of bleeding. (Level of Evidence: C)

2. Anticoagulant and antiplatelet therapy should be weight-based where appropriate and should be adjusted when necessary for CKD to decrease the risk of bleeding in patients with NSTE-ACS (522,697,698). (Level of Evidence: B)

CLASS III: NO BENEFIT

1. A strategy of routine blood transfusion in hemodynamically stable patients with NSTE-ACS and hemoglobin levels greater than 8 g/dL is not recommended (699-703). (Level of Evidence: B)

Anemia in patients with ACS is associated with an increased risk for Holter monitor−detected recurrent ischemia and for MACE, with greater anemia correlating with greater risk (704-708). In 1 large analysis of multiple studies, the risk of adverse outcome was higher in patients with NSTE-ACS with hemoglobin levels <11 g/dL (704). The potentially detrimental effects of severe anemia include decreased myocardial oxygen delivery and increased MVO_2 related to maintenance of a higher cardiac output (704,709,710). Patients with anemia are less likely to be treated with aspirin, and patients with ACS and anemia are likely to have more bleeding complications with PCI (711). This has been correlated with increased short-term risk of MACE outcomes, including mortality; long-term risk remains controversial (712-717). The ACUITY study suggests that the risk of mortality associated with bleeding is at least as great as that associated with procedure-related or spontaneous MI (718).

Major bleeding is a coprimary endpoint in many trials and is a consideration when assessing the "net clinical benefit" of a new drug. A "universal definition of bleeding" has been proposed to assist clinicians (547,719-721). The incidence of major bleeding in patients with ACS varies widely (0.4% to 10%) (715,722) owing to differing definitions of major bleeding, patient populations, anticoagulation regimens, and PCI or CABG. Factors in patients with ACS related to an increased

bleeding risk include older age, female sex, lower body weight, history of prior bleeding and/or invasive procedures, anemia, use of GP IIb/IIIa inhibitors or thrombolytics, and CKD (522,711,713-715,722,723). Non-weight-based dosing of anticoagulants and dosing of antithrombin and antiplatelet medications that are not adjusted for CKD are associated with an increased risk of bleeding (522,697,698). Bleeding is related to adverse outcomes because it may be a marker of underlying disease, such as occult malignancy; leads to cessation of antithrombin and antiplatelet therapy; may prompt transfusion, which itself may have adverse effects; can cause hypotension; and, if intracranial, can be fatal (724). Proton pump inhibitors decrease the risk of upper GI bleeding, including in patients treated with DAPT. Proton pump inhibitors are used in patients with a history of prior GI bleeding who require DAPT and are an option in patients at increased risk of GI bleeding (26,430).

Evaluation of the risk of bleeding includes a focused history of bleeding symptoms, identification of predisposing comorbidities, evaluation of laboratory data, and calculation of a bleeding risk score (688,716,725). Approximately 15% of all patients with NSTE-ACS and 3% to 12% of those not undergoing CABG receive blood transfusion (702). Rates vary widely and are closer to the lower figure but increase in association with factors such as coronary intervention, anticoagulant/antithrombotic therapy, older age, female sex, anemia, renal insufficiency, and frailty. Tissue oxygenation does not change or may actually decrease with transfusion (722). Blood transfusion in patients with ACS is associated with an increased risk of adverse outcome, including death (702-704). A restrictive transfusion strategy leads to an outcome that is at least as good, if not better, than a liberal transfusion strategy (699,700). An analysis of a large ACS registry found no benefit from blood transfusion in patients with a nadir hematocrit >24% (702). In a meta-analysis of 10 studies of patients with AMI, transfusion versus no transfusion was associated with an increase in all-cause mortality (18.2% versus 10.2%; p<0.001) and subsequent MI rate (RR: 2.0; 95% CI: 1.06 to 3.93; p=0.03) (726). A restrictive approach to transfusion generally consists of no routine transfusion for a hemoglobin level >7 g/dL to 8 g/dL (699,700,727). A restrictive approach to blood transfusion is advocated by the American Association of Blood Banks (700) and the European Society of Cardiology (727). On the basis of data available at the time of publication, a strategy of routine liberal blood transfusion in hemodynamically stable patients with NSTE-ACS and mild to moderate anemia is not recommended.

See Online Data Supplement 31 for more information on anemia, bleeding, and transfusion.

7.9. Thrombocytopenia

The incidence of thrombocytopenia in patients with ACS varies from 1% to 13%. In 1 large prospective registry, one third of patients treated with prolonged heparin therapy developed some degree of thrombocytopenia (728). Independent risk factors for the development of thrombocytopenia include lower baseline platelet count, older age, ACS, cardiac or vascular surgery, intravenous UFH or both UFH and LMWH, duration of heparin therapy, and low body mass index (728-730). The risk of thrombocytopenia is increased in patients treated with abciximab and, to a lesser degree, with eptifibatide or tirofiban (731-734).

Thrombocytopenia on presentation or related to antithrombotic therapy is associated with significantly increased risk of thrombotic events, MI, major bleeding, and in-hospital mortality in patients with and without ACS (728-731,735-739). The OR for development of these endpoints with thrombocytopenia (compared to without thrombocytopenia) is 2 to 8. Data from the CATCH (Complications After Thrombocytopenia Caused by Heparin) registry identified a platelet count nadir of 125 × 109/L as a threshold, below which there is a linear augmentation in probability of bleeding (740). Results from CATCH highlighted that thrombocytopenia and heparin-induced thrombocytopenia are often not diagnosed (728). Thrombocytopenia is generally a contraindication for GP IIb/IIIa inhibitor therapy; direct thrombin inhibitors are often considered in preference to UFH or LMWH in patients with thrombocytopenia.

See Online Data Supplements 31 and 32 for additional information on anemia, bleeding, and transfusion.

7.10. Cocaine and Methamphetamine Users: Recommendations

CLASS I

1. Patients with NSTE-ACS and a recent history of cocaine or methamphetamine use should be treated in the same manner as patients without cocaine- or methamphetamine-related NSTE-ACS. The only exception is in patients with signs of acute intoxication (e.g., euphoria, tachycardia, and/or hypertension) and beta-blocker use, unless patients are receiving coronary vasodilator therapy. *(Level of Evidence: C)*

CLASS IIa

1. Benzodiazepines alone or in combination with nitroglycerin are reasonable for management of hypertension and tachycardia in patients with NSTE-ACS and signs of acute cocaine or methamphetamine intoxication (741-744). *(Level of Evidence: C)*

CLASS III: HARM

1. Beta blockers should not be administered to patients with ACS with a recent history of cocaine or methamphetamine

use who demonstrate signs of acute intoxication due to the risk of potentiating coronary spasm. *(Level of Evidence: C)*

Cocaine exerts multiple effects on the cardiovascular system, which may precipitate ACS (48,744,745). Acute cocaine exposure results in increased BP, heart rate, endothelial dysfunction, and platelet aggregation, all of which may precipitate ACS. Cocaine's direct vasoconstrictor effect can produce coronary vasospasm. Long-term use of cocaine results in progressive myocyte damage and accelerated atherosclerosis (48,744,745).

ACS in patients with a history of cocaine use should be treated in the same manner as patients without cocaine use (744). The exception is in patients with ACS in the presence of acute cocaine intoxication. Because cocaine stimulates both alpha- and beta-adrenergic receptors, administration of intravenous beta blockers may result in unopposed alpha stimulation with worsening coronary spasm (48,132,744-746). Evidence suggests it is safe to administer intravenous beta blockers in patients with chest pain and recent cocaine ingestion, although information is lacking about the effects of beta-blocker administration during the acute stages of cocaine intoxication (747,748). Intravenous beta blockers should be avoided in patients with NSTE-ACS with signs of acute cocaine intoxication (euphoria, tachycardia, and/or hypertension). In these patients, benzodiazepines alone or in combination with nitroglycerin have been useful for management of hypertension and tachycardia owing to their effects on the central and peripheral manifestations of acute cocaine intoxication (741-744).

Methamphetamine abuse is becoming increasingly common in the United States owing to the ease of manufacturing and the lower cost of methamphetamines compared with cocaine (131,749,750). Methamphetamines may be ingested orally, inhaled, or used intravenously. Methamphetamine affects the central nervous system by simultaneously stimulating the release and blocking the reuptake of dopamine and norepinephrine (751). Like cocaine, methamphetamine exerts multiple effects on the cardiovascular system, all of which may precipitate ACS (131,750-752). The acute effects of methamphetamine are euphoria, tachycardia, hypertension, and arrhythmias. MI may result from coronary spasm or plaque rupture in the presence of enhanced platelet aggregation. Long-term use of methamphetamine has been associated with myocarditis, necrotizing vasculitis, pulmonary hypertension, and cardiomyopathy (750-752). Because methamphetamine and cocaine have similar pathophysiological effects, treatment of patients with ACS associated with methamphetamine and cocaine use should theoretically be similar.

See *Online Data Supplement 33 for additional information about cocaine and methamphetamine users.*

7.11. Vasospastic (Prinzmetal) Angina: Recommendations

CLASS I

1. CCBs alone (753-757) or in combination with long-acting nitrates (755,758) are useful to treat and reduce the frequency of vasospastic angina. *(Level of Evidence: B)*

2. Treatment with HMG-CoA reductase inhibitor (759,760), cessation of tobacco use (761,762), and additional atherosclerosis risk factor modification (762,763) are useful in patients with vasospastic angina. *(Level of Evidence: B)*

3. Coronary angiography (invasive or noninvasive) is recommended in patients with episodic chest pain accompanied by transient ST-elevation to rule out severe obstructive CAD. *(Level of Evidence: C)*

CLASS IIb

1. Provocative testing during invasive coronary angiography†† may be considered in patients with suspected vasospastic angina when clinical criteria and noninvasive testing fail to establish the diagnosis (764-767). *(Level of Evidence: B)*

Vasospastic (Prinzmetal) angina chest pain typically occurs without provocation, is associated with ST-elevation, and usually resolves spontaneously or with rapid-acting nitroglycerin. Vasospastic angina may also be precipitated by emotional stress, hyperventilation, exercise, or the cold. It results from coronary vasomotor dysfunction leading to focal spasm (768), which may occasionally be multifocal within a single vessel and rarely involves >1 vessel. Vasospastic angina occurs with normal coronary arteries, nonobstructive CAD, and obstructive CAD, but prognosis is least favorable with the latter. ST-elevation indicates transmural ischemia and corresponds to the distribution of the involved artery (769). A circadian variation is often present; most attacks occur in the early morning (770,771). The most prominent coronary risk factor is smoking. Most episodes resolve without complications, but arrhythmias, syncope, MI, and sudden death can occur (772).

Nonpharmacological provocative tests, such as cold pressor and hyperventilation, have been used diagnostically; potent vasoconstrictors (e.g., acetylcholine) may be useful when noninvasive assessment is uninformative (764-767). Smoking, which exacerbates coronary vasospasm, should be proscribed, and CCBs are first-line therapies (642); long-acting nitrates are also effective when combined with CCBs (755,758). Statins improve

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††Provocative testing during invasive coronary angiography (e.g., using ergonovine, acetylcholine, methylergonovine) is relatively safe, especially when performed in a controlled manner by experienced operators. However, sustained spasm, serious arrhythmias, and even death can also occur very infrequently. Therefore, provocative testing should be avoided in patients with significant left main disease, advanced 3-vessel disease, presence of high-grade obstructive lesions, significant valvular stenosis, significant LV systolic dysfunction, and advanced HF.

endothelium-dependent vasodilation and can be useful in vasospastic angina (759,760). Magnesium supplementation and alpha-receptor blockers may be effective and can be added (755,758).

7.12. ACS With Angiographically Normal Coronary Arteries: Recommendation

CLASS IIb

1. If coronary angiography reveals normal coronary arteries and endothelial dysfunction is suspected, invasive physiological assessment such as coronary flow reserve measurement may be considered (629,773-776). *(Level of Evidence: B)*

ACS associated with angiographically normal or non-obstructive (<50% stenosis) coronary arteries (also referred to as syndrome X) may be related to coronary endothelial dysfunction (777); plaque rupture that may be evident only with intracoronary ultrasound (778); coronary vasospasm (779); and coronary artery dissection (780). Myocarditis may present with electrocardiographic and biomarker findings similar to ACS and can be distinguished by magnetic resonance imaging (781-783). Intracoronary ultrasound and/or optical coherence tomography to assess the extent of atherosclerosis and exclude obstructive lesions may be considered in patients with possible ACS and angiographically normal coronary arteries (778). If ECGs during chest pain are not available and coronary spasm cannot be ruled out, coronary angiography and provocative testing with acetylcholine, adenosine, or methacholine and 24-hour ambulatory ECG may be undertaken after a period of stabilization. Endothelial dysfunction is more common in women than in men (679,777,784-786), and chest pain is typical or atypical (785,786). In the absence of a culprit coronary lesion, prognosis of coronary endothelial dysfunction and/or occult plaque rupture is favorable (765,787).

Risk factor reduction and medical therapy with nitrates, beta blockers, and CCBs alone or in combination are considered for endothelial dysfunction (788-790). High doses of arginine have also been given (791). Imipramine or aminophylline have been used in patients with endothelial dysfunction for continued pain despite optimal medical therapy. In postmenopausal women, estrogen reverses acetylcholine-induced coronary arterial vasoconstriction, presumably by improving endothelium-dependent coronary vasomotion, and reduces frequency of chest pain (792). However, estrogen is not recommended because of its demonstrated increase in cardiovascular and other risks (793).

Spontaneous coronary artery dissection affects a young, predominantly female population. Treatment of spontaneous coronary artery dissection with CABG or stenting is described to improve outcome (794), but high rates of stenting complications are reported (780).

7.13. Stress (Takotsubo) Cardiomyopathy: Recommendations

CLASS I

1. Stress (Takotsubo) cardiomyopathy should be considered in patients who present with apparent ACS and nonobstructive CAD at angiography. *(Level of Evidence: C)*

2. Imaging with ventriculography, echocardiography, or magnetic resonance imaging should be performed to confirm or exclude the diagnosis of stress (Takotsubo) cardiomyopathy (795-798). *(Level of Evidence: B)*

3. Patients should be treated with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) as otherwise indicated if hemodynamically stable. *(Level of Evidence: C)*

4. Anticoagulation should be administered in patients who develop LV thrombi. *(Level of Evidence: C)*

CLASS IIa

1. It is reasonable to use catecholamines for patients with symptomatic hypotension if outflow tract obstruction is not present. *(Level of Evidence: C)*

2. The use of IABP is reasonable for patients with refractory shock. *(Level of Evidence: C)*

3. It is reasonable to use beta blockers and alpha-adrenergic agents in patients with outflow tract obstruction. *(Level of Evidence: C)*

CLASS IIb

1. Prophylactic anticoagulation may be considered to inhibit the development of LV thrombi. *(Level of Evidence: C)*

Stress (Takotsubo) cardiomyopathy (also referred to as transient LV apical ballooning or Takotsubo cardiomyopathy) mimics NSTE or STEMI (799-803). There is no obstructive CAD, and the distribution of electrocardiographic changes and LV wall motion abnormalities usually includes >1 coronary artery territory (801). Cardiac troponin elevations are usually modest (798). The majority of cases occur in postmenopausal women, and presentation is typically precipitated by emotional or physical stress. Imaging by echocardiography, ventriculography (696), or magnetic resonance imaging (699) demonstrates characteristic hypokinesis or dyskinesis of the LV apex with basilar increased contractility. Variants include hypokinesis of the mid or base of the left ventricle (795), and right ventricular involvement is common (804). In the vast majority of patients, electrocardiographic and LV wall motion abnormalities normalize within 1 to 4 weeks, and recurrences are uncommon (805). The pathogenesis has been attributed to excess catecholamine release (803), coronary spasm, or small coronary vessel hypoperfusion (806).

Care is predominantly supportive and includes beta blockers, vasodilators, and catecholamines. The latter 2 interventions must be used cautiously, because they may induce outflow tract obstruction (800). If shock is present,

IABP can be used. Prophylactic anticoagulation should be considered to prevent or treat LV thrombus (798).

7.14. Obesity

Obesity is associated with conditions such as dyslipidemia, diabetes mellitus, hypertension, arrhythmias, and HF that adversely affect ACS outcomes. In the MADIT (Multicenter Automatic Defibrillator Implantation)-II trial, there was an inverse relation between body mass index and both all-cause mortality and sudden cardiac death in patients with LV dysfunction after MI (807). In the SYNERGY trial of 9,837 patients with NSTEMI, mortality was lower in morbidly obese patients, consistent with the "obesity paradox" (808). The "obesity paradox" has not been clarified and is under continuing investigation. Standard approaches to weight reduction in obese patients are usually unsuccessful in producing large decreases in weight. A weight reduction study of obese and morbidly obese patients following AMI resulted in weight loss of only 0.5% in obese patients and 3.5% in morbidly obese patients after 1 year (809). Two drugs, controlled-release phentermine/topiramate (810) and lorcaserin (811), are available for weight reduction but have not been studied in patients following NSTE-ACS. Bariatric surgery has been successful in reducing cardiovascular risk factors, including diabetes mellitus, hypertension, and dyslipidemia but has not been evaluated in post–ACS patients (812). The 2013 obesity CPG provides comprehensive strategies for weight reduction (16).

7.15. Patients Taking Antineoplastic/Immunosuppressive Therapy

Antineoplastic or immunosuppressive therapy may contribute to the development of NSTE-ACS. For example, antineoplastic agents such as gemcitabine, sorafenib sunitinib, and 5-fluorouracil have been associated with coronary artery spasm or stenosis (813,814). Trastuzumab and possibly other anticancer drugs may alter biomarker levels (815). Antineoplastic agents can induce changes in the arterial wall (813), and modulators of inflammation may promote atherogenesis (816). In patients receiving these agents, it is prudent to communicate with the prescribing clinician about the necessity of their continuation during NSTE-ACS and future resumption.

8. QUALITY OF CARE AND OUTCOMES FOR ACS—USE OF PERFORMANCE MEASURES AND REGISTRIES

8.1. Use of Performance Measures and Registries: Recommendation

CLASS IIa

1. Participation in a standardized quality-of-care data registry designed to track and measure outcomes, complications, and

performance measures can be beneficial in improving the quality of NSTE-ACS care (817–825). *(Level of Evidence: B)*

The development of national systems for ACS is crucial and includes the participation of key stakeholders to evaluate care using standardized performance and quality-improvement measures for ACS (819,821). Standardized quality-of-care data registries include the NCDR Registry–Get With the Guidelines, the Get With the Guidelines quality-improvement program, the Acute Myocardial Infarction Core Measure Set, and performance measures required by The Joint Commission and the Centers for Medicare and Medicaid Services (817,823-825). The AHA has promoted its Mission: Lifeline initiative to encourage cooperation among prehospital emergency medical services personnel and cardiac care professionals (817). The evaluation of ACS care delivery across traditional boundaries can identify problems with systems and enable application of modern quality-improvement methods (818,820,822). On a local level, registries as part of the Chronic Care Model were associated with improved outcomes in chronic diseases, including cardiovascular disease (826,827).

9. SUMMARY AND EVIDENCE GAPS

Despite landmark advances in the care of patients with NSTE-ACS since the publication of the 2007 UA/NSTEMI CPG (212), many emerging diagnostic and therapeutic strategies have posed new challenges. There is general acceptance of an early invasive strategy for patients with NSTE-ACS in whom significant coronary vascular obstruction has been precisely quantified. Low-risk patients with NSTE-ACS are documented to benefit substantially from GDMT, but this is often suboptimally used. Advances in noninvasive testing have the potential to identify patients with NSTE-ACS who are at intermediate risk and are candidates for invasive versus medical therapy.

Newer, more potent antiplatelet agents in addition to anticoagulant therapy are indicated irrespective of initial treatment strategy. Evidence-based decisions will require comparative-effectiveness studies of available and novel agents. The paradox of newer and more potent antithrombotic and anticoagulant drugs that reduce major adverse cardiac outcomes but increase bleeding risk occurs with greater frequency in patients with AF. Patients with AF who develop NSTE-ACS and receive a coronary stent are the population at risk from triple anticoagulant/antiplatelet therapy. This regimen has been reported to be safely modified by elimination of aspirin, a finding that requires confirmation.

Among the most rapidly evolving areas in NSTE-ACS diagnosis is the use of cardiac troponin, the preferred biomarker of myocardial necrosis. Although a truly

high-sensitivity cardiac troponin is not available in the United States at the time this CPG was prepared, the sensitivity of contemporary assays continues to increase. This change is accompanied by higher rates of elevated cardiac troponin unrelated to coronary plaque rupture. The diagnostic quandary posed by these findings necessitates investigation to elucidate the optimal utility of this advanced biomarker. A promising approach to improve the diagnostic accuracy for detecting myocardial necrosis is measurement of absolute cardiac troponin change, which may be more accurate than the traditional analysis of relative alterations.

Special populations are addressed in this CPG, the most numerous of which are older persons and women. More than half of the mortality in NSTE-ACS occurs in older patients, and this high-risk cohort will increase as our population ages. An unmet need is to more clearly distinguish which older patients are candidates for an ischemia-guided strategy compared with an early invasive management strategy. An appreciable number of patients with NSTE-ACS have angiographically normal or nonobstructive CAD, a group in which women predominate. Their prognosis is not benign, and the multiple mechanisms of ACS postulated for these patients remain largely speculative. Clinical advances are predicated on clarification of the pathophysiology of this challenging syndrome.

A fundamental aspect of all CPGs is that these carefully developed, evidence-based documents cannot encompass all clinical circumstances, nor can they replace the judgment of individual physicians in management of each patient. The science of medicine is rooted in evidence, and the art of medicine is based on the application of this evidence to the individual patient. This CPG has adhered to these principles for optimal management of patients with NSTE-ACS.

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2014 AHA/ACC GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Ezra A. Amsterdam *(Chair)*	University of California (Davis) Medical Center, Division of Cardiology—Professor	None	None	None	None	None	None	None
Nanette K. Wenger *(Vice Chair)*	Emory University, School of Medicine—Professor of Medicine (Cardiology)	• Abbott • Amgen • AstraZeneca • Gilead Sciences† • Janssen Pharmaceuticals • Medtronic • Merck • Pfizer	None	None	• Abbott† • Eli Lilly† • Gilead Sciences† • Merck • Pfizer†	None	None	All sections except 3.1.1, 3.4, 5.2, 6.3.1, 6.3.2, 6.3.6, 7.5, 7.6, 7.8, and 8.
Ralph G. Brindis	University of California, San Francisco Department of Medicine and the Phillip R. Lee Institute for Health Policy Studies—Clinical Professor of Medicine	None	• Volcano	None	None	None	None	None
Donald E. Casey, Jr	Atlantic Health—Vice President of Health and Chief Medical Officer	None	None	None	None	None	None	None
Theodore G. Ganiats	University of California, San Diego School of Medicine—Executive Director of Health Services Research Center	None	None	None	None	None	None	None
David R. Holmes, Jr	Mayo Clinic—Consultant, Cardiovascular Diseases	None	None	None	None	None	None	None
Allan S. Jaffe	Mayo Clinic, Cardiovascular Division—Professor of Medicine	• Abbott • Alere • Amgen • Beckman-Coulter • Critical Diagnostics • ET Healthcare • Ortho Clinical Diagnostic • Radiometer† • Roche‡ • Thermo-Fisher‡ • Trinity	None	None	None	None	None	All sections except 3.1, 3.1.1, 3.3, 4.1.2.1-4.1.2.3, 4.2, 4.3.1, 4.3.2, 4.5, 5.1, 5.2, 6.2.1, 6.3.1, 6.3.3, 6.3.6, 7.2.2, 7.5, 7.6, and 8.
Hani Jneid	Baylor College of Medicine—The Michael E. DeBakey VA Medical Center—Assistant Professor of Medicine	None	None	None	None	None	None	None

APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Rosemary F. Kelly	University of Minnesota— Professor of Surgery; VA Medical Center— Chief, Cardiothoracic Surgery	None	None	None	None	None	None	None
Michael C. Kontos	Virginia Commonwealth University, Pauley Heart Center— Medical Director, Coronary Intensive Care Unit, and Associate Professor, Internal Medicine	• Astellas • General Electric • Ikaria • Prevencio • Sanofi-aventis • Wellpoint/ Anthem	• Astellas • AstraZeneca	None	None	• Astellas • Eli Lilly‡ • Merck‡ • Novartis‡	None	All sections
Glenn N. Levine	Baylor College of Medicine— Professor of Medicine; Director, Cardiac Care Unit	None	None	None	None	None	None	None
Philip R. Liebson	Rush University Medical Center— McMullan-Eybel Chair of Excellence in Clinical Cardiology and Professor of Medicine and Preventive Medicine	None	None	None	None	None	None	None
Debabrata Mukherjee	Texas Tech University Health Sciences Center—Chief, Cardiovascular Medicine	None	None	None	None	None	None	None
Eric D. Peterson	Duke University Medical Center— Fred Cobb, MD, Distinguished Professor of Medicine; Duke Clinical Research Institute—Director	• Boehringer Ingelheim • Genentech • Janssen Pharmaceuticals • Johnson & Johnson • Merck	None	None	• Eli Lilly† • Johnson & Johnson† • Janssen Pharmaceuticals†	DCRI has numerous grants and contracts sponsored by industry that are relevant to the content of this CPG. Dr. Peterson participated in discussions but recused himself from writing or voting, in accordance with ACC/AHA policy. See comprehensive RWI table for a complete list of companies pertaining to this organization.	None	All sections

APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Marc S. Sabatine	Brigham and Women's Hospital, Chairman—TIMI Study Group, Division of Cardiovascular Medicine; Harvard Medical School—Professor of Medicine	• Amgen • AstraZeneca • Bristol-Myers Squibb • Merck • Pfizer • Sanofi-aventis	None	None	• Abbott Laboratories† • Amgen† • AstraZeneca† • Bristol-Myers Squibb† • BRAHMS† • Critical Diagnostics† • Daiichi-Sankyo† • Genzyme† • GlaxoSmithKline† • Nanosphere† • Roche Diagnostics† • Sanofi-aventis† • Takeda†	• AstraZeneca† • Daiichi-Sankyo† • Gilead† • Johnson & Johnson† • Merck† • Proventys† • Siemens† • Singulex†	None	All sections except 3.1.1, 5.2, 6.3.1, 6.3.2, 7.5, 7.8, and 8.
Richard W. Smalling	University of Texas, Health Science Center at Houston—Professor and Director of Interventional Cardiovascular Medicine; James D. Woods Distinguished Chair in Cardiovascular Medicine	• Gilead • Maquet	None	None	• Cordis • E-valve Abbott Vascular • Edwards Lifesciences • Gilead • Maquet Datascope	• Cordis† • E-valve†	None	All sections except 3.1, 3.1.1, 3.3, 3.4, 3.5.1, 4.1.2.1-4.1.2.3, 4.2, 4.3.1, 4.3.2, 5.2, 6.2.1, 6.3.1, 6.3.2, 6.3.3, 6.3.6, 7.2.2, 7.5, 7.8, and 8.
Susan J. Zieman	National Institute on Aging/NIH, Geriatrics Branch, Division of Geriatrics and Clinical Gerontology—Medical Officer	None	None	None	None	None	None	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 GWC during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

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*Writing members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

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ACC indicates American College of Cardiology, AHA, American Heart Association, BMS, Bristol-Myers Squibb; CPG, clinical practice guideline; DCRI, Duke Clinical Research Institute; NIH, National Institutes of Health; NYU, New York University; RWI, relationships with industry and other entities; TIMI, Thrombolysis In Myocardial Infarction; and VA, Veterans Affairs.

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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APPENDIX 3. ABBREVIATIONS

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome

AF = atrial fibrillation

AMI = acute myocardial infarction

BP = blood pressure

CABG = coronary artery bypass graft

CAD = coronary artery disease

CKD = chronic kidney disease

CK-MB = creatine kinase myocardial isoenzyme

COX = cyclooxygenase

CPG = clinical practice guideline

CrCl = creatinine clearance

CT = computed tomography

DAPT = dual antiplatelet therapy

DES = drug-eluting stent

ECG = electrocardiogram

ED = emergency department

GDMT = guideline-directed medical therapy

GP = glycoprotein

GFR = glomerular filtration rate

GWC = guideline writing committee

HF = heart failure

IABP = intra-aortic balloon pump

IV = intravenous

LMWH = low-molecular-weight heparin

LV = left ventricular

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac event

MI = myocardial infarction

MVO_2 = myocardial oxygen consumption

NSAID = nonsteroidal anti-inflammatory drug

NSTE-ACS = non-ST-elevation acute coronary syndromes

NSTEMI = non-ST-elevation myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

SC = subcutaneous

STEMI = ST-elevation myocardial infarction

UA = unstable angina

UFH = unfractionated heparin

VF = ventricular fibrillation

VT = ventricular tachycardia

APPENDIX 4. ADDITIONAL TABLES

TABLE A   Universal Classification of MI

Type 1: Spontaneous MI

Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in ≥1 of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD, but on occasion nonobstructive or no CAD.

Type 2: MI secondary to ischemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between MVO_2, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: MI resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiographic changes or new LBBB, but death occurred before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases where blood was not collected for cardiac biomarker testing.

Type 4a: MI related to PCI

MI associated with PCI is arbitrarily defined by elevation of cTn values >5 × 99th percentile URL in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% if baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic electrocardiographic changes or new LBBB, (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.

Type 4b: MI related to stent thrombosis

MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with ≥1 value above the 99th percentile URL.

Type 5: MI related to CABG

MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 × 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographically documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; cTn, cardiac troponin; LBBB, left bundle-branch block; LVH, left ventricular hypertrophy; MI, myocardial infarction; MVO_2, myocardial oxygen consumption; PCI, percutaneous coronary intervention; and URL, upper reference limit.
Modified from Thygesen et al. (21).

TABLE B   Pharmacological Therapy in Older Patients With NSTE-ACS

	Age-Related Pharmacological Change	Clinical Effect	Dose-Adjustment Recommendations	Additional Precautions
General principles	• ↓In renal function (CrCl*): drug clearance, water/electrolyte balance • SCr unreliable measure of renal function in older adults • Change in body composition • ↑Fat, ↓lean body mass/total water • ↓GI absorption	• ↑Levels renally cleared drug • Risk high/low electrolyte levels • ↑Levels hydrophilic agents • ↓Levels lipophilic agents • Longer time to reach steady-state lipophilic agents	• Calculate CrCl in all pts—renal-dose accordingly • Start at lowest recommended dose, titrate up slowly • Avoid interacting drugs • Consider ↓doses in women, malnourished, hypovolemic	• Caution fall risk with ↓BP agents and diuretics • Monitor for ADR, especially delirium • Frequent monitoring of renal function/electrolytes • Minimize polypharmacy—watch for drug-drug interactions
ASA	Hydrophilic; levels ↑with ↓total body water; age-related ↑plasma concentration for similar dose	↑Bleeding risk with ↑age, dehydration, frailty, diuretics	• Maintenance=81 mg/d (lowest possible dose)	↑Bleeding with NSAIDs, other AP, AC, AT; ↑risk peptic ulcer with NSAIDs
Nitrates	↑Sensitivity	↑Hypotensive response with ↓baroreceptor response	Lowest dose possible, especially if hypovolemic	↑Risk OH, syncope, falls
ACE inhibitors	↓First-pass metabolism (some) with ↓effect; enalapril ↑effect	May have ↓effect	May need ↑dose	↑Risk AKI and ↑K^+ and ↓effect with NSAIDs; avoid K-sparing diuretics
ARBs	No significant age-related changes	No age-related clinical changes	None	↑Risk AKI and ↑K^+ and ↓effect with NSAIDs; avoid K-sparing diuretics
Alpha blockers	↑Sensitivity; ↓BP with ↓baroreceptor response	↓BP; OH	Avoid when possible	↑Risk OH, falls, syncope, especially with loop diuretics

TABLE B	Continued			
	Age-Related Pharmacological Change	**Clinical Effect**	**Dose-Adjustment Recommendations**	**Additional Precautions**
Beta blockers	↓Myocardial sensitivity (↓postreceptor signaling), ↑conduction system sensitivity	Bradycardia/heart block; ↓BP effect vs. younger pts	May need ↑dose with age	Caution conduction system blocks
CCBs				
• **DHPs (amlodipine; nifedipine)**	Lipophilic; ↓hepatic and overall clearance; ↑fat storage; ↑sinus node sensitivity; ↓baroreceptor response to ↓BP	↓BP more than non-DHP and with ↑age; edema hypotension, bradycardia	Initiate low dose, titrate cautiously	Inhibits clopidogrel; ↑risk OH, falls, syncope; most potent ↓BP first 3 mo, then less
• **Non-DHP (verapamil; diltiazem)**	↓Hepatic and overall clearance; less PR prolongation than DHP and with ↑age; negative inotropy; ↑SA node sensitivity and ↓HR than DHP and with ↑age; ↓AV conduction with ↑age; ↓baroreceptor response to ↓BP	↓BP more with ↑age; edema; ↑heart block; hypotension; ↑bradycardia and bradyarrhythmias with ↑age	Initiate low dose, titrate cautiously	↑Risk OH, falls, syncope; consider rhythm monitoring
Diuretics	↓Diuretic/natriuretic response, ↓EC space, ↑drug concentration if ↓GFR; ↓baroreceptor response to volume shifts	↑Sensitivity; ↑hypotension; risk hypokalemia/hypomagnesemia/hyponatremia; ↓diuretic effect with ↓GFR; risk hypovolemia- ↓thirst	May need ↑doses if ↓GFR; may need ↑dose if cotreating with NSAIDs	• Monitor Na⁺, K⁺, Mg²⁺ levels; ↑risk OH/falls; • With NSAIDs: ↓natriuretic and diuretic effect, ↑K⁺, ↓Mg²⁺
Heparins				
• **UFH**	Hydrophilic; ↑concentration, especially if ↓lean body mass or ↓plasma proteins; ↑levels with ↑age	↑Bleeding risk with age; more potent anticoagulation per dose with ↑age; weight-based dosing but with precautions for shift in body composition	Weight-based 60 U/kg loading dose + 12 U/kg/h INF. Suggested max loading dose: 400 U and 900 U/h INF or 5,000 U loading dose/1,000 U/h if pt weight >100 kg	↑Bleeding with ASA; ↑bleeding risk with other AP, AT, and GP IIb/IIIa; vigilantly monitor aPTT
• **LMWH**	Cleared renally; more predictable dose response than UFH; not dependent on plasma protein levels; ↑levels with ↓lean body mass; ↑effect with ↑age	↑Bleeding risk with age and weight and renally dosed	Enoxaparin: Weight-based 1 mg/kg SC q 12 h; CrCl* <30 mL/min— avoid or 1 mg/kg SC q 24 h; CrCl 30-60 mL/min: ↓75%; Dalteparin: Use caution in older pts with low body weight or renal insufficiency	• ↑Bleed with ASA • Monitor anti-Xa; ↑bleeding with GP IIb/IIIa with ↑age
Direct Thrombin Inhibitors				
• **Bivalirudin**	Cleared renally; more predictable dose response; not dependent on plasma protein levels	Significantly less bleeding in older pts, even with renal dysfunction vs. UFH + GP IIb/IIIa with similar efficacy	CrCl <30 mL/min: 1 mg/kg/h; CrCl: 30 to 60 mL/min—less bleeding than UFH	Less bleeding than GP IIb/IIIa inhibitor + heparin
• **Fondaparinux**	Cleared renally	Renal/weight adjust; less bleeding but similar efficacy vs. enoxaparin in older pts with NSTE-ACS, even with mild to moderate renal dysfunction	Renal adjustment: CrCl <30— contraindicated; CrCl 30 to 60— preferred over enoxaparin	↓Bleeding vs. enoxaparin; good safety profile vs. UFH/LMWH
P2Y₁₂ Inhibitors				
• **Clopidogrel**	Lipophilic; ↑HPR; ↑metabolism; ↑fat distribution; ↑to steady state (↑fat distribution/T¹/₂)	↓Antiplatelet effect in some older pts	Maintenance: 75 mg (no ↑response to higher dose)	↓Effect with proton pump inhibitors; if HPR—may respond to prasugrel or ticagrelor
• **Prasugrel**	↑19% Active metabolite >75 y of age	↑Bleeding risk	Avoid in pts ≥75 y of age or if weight ≤60 kg; 10 mg in very high-risk pts	N/A
• **Ticagrelor**	None known	N/A	None	Reversible
GP IIb/IIIa Inhibitors				
• **Abciximab**	N/A	• ↑Bleeding with ↑age • ↑Bleeding risk without clinical benefit	Not recommended	N/A

TABLE B	Continued			
	Age-Related Pharmacological Change	**Clinical Effect**	**Dose-Adjustment Recommendations**	**Additional Precautions**
• **Eptifibatide**	Weight/renally dosed	↑Bleeding risk	Weight-based: 180 mcg/kg loading dose + 2 mcg/kg/min INF; CrCl ≤50 mL/min: 1.0 mcg/kg/min INF	Less benefit/more bleeding with ↑age
• **Tirofiban**	Weight/renally dosed	↑Bleeding risk	Weight-based: 12 mcg/kg loading dose + 0.14 mcg/kg/min INF; CrCl <30 mL/min: 6 mcg/kg loading dose + 0.05 mcg/kg/min INF	In older pts with high bleeding risk, low-dose INF effective with ↓bleeding
Warfarin	↑Sensitivity; ↓20%–40% clearance; protein binding; ↑inhibition vitamin K-dependent clotting factors at same plasma levels with ↑age	↑Bleeding risk at lower INR; higher INR/dose with ↑age; ↑risk GI bleeding	• Loading: 4 mg/d × 4 d • Maintain mean dose ↓0.4 mg/w/y of age	Multiple drug interactions, ↑frequency of monitoring; ASA potentiates effect
New Oral AC†	N/A	N/A	Contraindicated if CrCl <15 mL/min	If pt taking when admitted, stop—consider delaying angiogram/PCI until effect wanes, switch to UFH/dalteparin/bivalirudin/fondaparinux; AP and DAPT ↑bleeding 2× post-ACS—consider BMS and radial access. Avoid GP IIb/IIIa inhibitor if possible; ↑thrombotic risk following discontinuation.
• **Rivaroxaban**	35% cleared renally; 65% hepatic (CYP3A4); ↑levels in hepatic and/or renal dysfunction and ↑age	↑Bleeding risk; not reversible	CrCl 15–49 mL/min: 15 mg QD; consider avoiding if CrCl 15–30 mL/min if ↑bleeding risk; CrCl >50 mL/min: 20 mg QD	Some drug interactions
• **Dabigatran**	80% cleared renally; ↑plasma level with ↑age, especially ≥75 y	↑Bleeding risk; not reversible	CrCl 15–30 mL/min: 75 mg BID with caution; CrCl 30–49 mL/min: 75 mg BID; CrCl >50 mL/min: 150 mg BID	Monitor pt and renal function frequently; longest for effect to wane with ↓CrCl; ↑risk dyspepsia, GI bleeding
• **Apixaban**	Hepatically cleared (minor CYP3A4); dose adjust if weight ≤60 kg; highly protein bound	↑Bleeding risk; not reversible	CrCl 15–29 mL/min: 2.5 mg BID or with 2 of the following: age ≥80 y/weight ≤60 kg/SCr ≥1.5 mg/dL: SCr <1.5: 5 mg BID	↑Risk abnormal liver function tests

*CrCl should be calculated for all older pts because SCr level does not accurately reflect renal dysfunction: CrCl decreases with age 0.7 mL/min/y.

†These agents are not approved for NSTE-ACS but are included for management of pts with nonvalvular chronic atrial fibrillation.

AC indicates anticoagulants; ACE, angiotensin-converting-enzyme; ACS, acute coronary syndromes; ADR, adverse drug reactions; AKI, acute kidney injury; AP, antiplatelets; aPTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; ASA, aspirin; AT, antithrombins; AV, atrioventricular; BID, twice daily; BMS, bare-metal stent; BP, blood pressure; CCBs, calcium channel blockers; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; DHP, dihydropyridine; EC, extracellular; GFR, glomerular filtration rate; GI, gastrointestinal; GP, glycoprotein; HPR, high platelet reactivity; HR, heart rate; INF, infusion; INR, international normalized ratio; K⁺, potassium; LMWH, low-molecular-weight heparin; max, maximum; Mg, magnesium; N/A, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non-ST-elevation acute coronary syndromes; OH, orthostatic hypotension; PCI, percutaneous coronary intervention; pts, patients; QD; once daily; SA, sinoatrial; SC, subcutaneous; SCr, serum creatinine; T½, half-life; and UFH, unfractionated heparin.

TABLE C	Age-Related Physiological Changes: Clinical Impact in Older Patients With NSTE-ACS	
Age-Related Change	**Clinical Alteration**	**Clinical Impact in NSTE-ACS**
↑**Central arterial stiffness**	↑SBP/↓DBP; ↑LVH; ↓diastolic function; ↓coronary perfusion pressure; ↓ischemia/infarct threshold for tachycardia/hypertension with and without coronary obstructive disease; ↑PA pressure	↑Risk end-organ damage (cerebrovascular accident, AKI); ↑BP lability; ↑reinfarction/ischemia; orthostatic hypotension; ↑HF; ↑pulmonary edema
LV diastolic function	↑LA size; ↓early passive LV filling; ↑late LV filling and ↑LV EDP; ↑PA pressure	↑Risk AF; (↑pulmonary edema/↓CO), ↑DOE; ↑pulmonary edema with ↑HR/↑BP
↓**Response to beta-adrenergic stimulation**	↓HR/↓inotropic responsiveness to stress; resting systolic LV function unchanged with age	Hypotension, HF, ↓HR response
Conduction system changes	↓Sinus node cells; ↓AV conduction; ↑LBBB; and ↑RBBB	Difficult to interpret electrocardiographic MI/ischemia; ↑heart block; SSS; ↑SVT, ↑sensitivity to conduction system drugs
↓**Volume regulating hormones**	↓Na, K, and water regulation—BP lability	Altered electrolytes, ↑sensitivity to fluid therapy/diuretics
Renal changes	↓GFR (0.8 mL/min/y), ↓Na/K clearance, normal serum creatinine despite moderate to severe CKD, altered drug clearance; ↓urine concentrating ability	CrCl or eGFR must be calculated for drug dosing, ↑sensitivity to contrast nephropathy, ↑risk AKI
Fat-muscle redistribution	↑Third spacing of fluid, may alter drug storage; ↓Vo$_{2max}$	May alter fluid/drug dosing, decreased CO; DOE; early fatigability
↓**Baroreceptor sensitivity**	↑BP lability	Orthostatic hypotension, fall risk
Clotting factor/platelet function/hemostasis	↑Bleeding and clotting risk, ↑sensitivity to anticoagulants/antithrombins	↑Risk cerebrovascular accident/reinfarction/recurrent ischemia, bleeding, thrombosis, PE, DVT; may alter drug dosing/sensitivity;↑stent thrombosis

AF indicates atrial fibrillation; AKI, acute kidney injury; AV, atrioventricular; BP, blood pressure; CKD, chronic kidney disease; CO, cardiac output; CrCl, creatinine clearance; DBP, diastolic blood pressure; DOE, dyspnea on exertion; DVT, deep vein thrombosis; EDP, end-diastolic pressure; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HR, heart rate; K, potassium; LA, left atrium; LBBB, left bundle-branch block; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; NA, sodium; Na/K sodium and potassium clearance; NTSE-ACS, non–ST-elevation acute coronary syndrome; PA, pulmonary artery; PE, pulmonary embolism; RBBB, right bundle-branch block; SBP, systolic blood pressure; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; and Vo$_{2\ max}$, maximum oxygen consumption.

TABLE D	FREEDOM Trial: Key Outcomes at 2 Years and 5 Years After Randomization				
	2 y		**5 y**		
	PCI	**CABG**	**PCI**	**CABG**	
Outcome	Number (%)				**p Value***
Primary composite†	121 (13.0)	108 (11.9)	200 (26.6)	146 (18.7)	0.005‡
Death from any cause	62 (6.7)	57 (6.3)	114 (16.3)	83 (10.9)	0.049
MI	62 (6.7)	42 (4.7)	98 (13.9)	48 (6.0)	<0.001
Stroke	14 (1.5)	24 (2.7)	20 (2.4)	37 (5.2)	0.03§
Cardiovascular death	9 (0.9)	12 (1.3)	73 (10.9)	52 (6.8)	0.12

*P values were calculated with the log-rank test on the basis of all available follow-up data (i.e., >5 y).
†The primary composite outcome was rate of death from any cause, MI, or stroke.
‡p=0.006 in the as-treated (non-intention-to-treat) analysis.
§p=0.16 by the Wald test of the Cox regression estimate for study-group assignment in 1,712 patients after adjustment for average glucose level after procedure.
CABG indicates coronary artery bypass graft; FREEDOM, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; MI, myocardial infarction; and PCI, percutaneous coronary intervention.
Modified with permission from Farkouh et al. (616).