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

WRITING COMMITTEE MEMBERS*

Ezra A. Amsterdam, MD, FACC, Chair†; Nanette K. Wenger, MD, MACC, FAHA, Vice Chair*†; Ralph G. Brindis, MD, MPH, Macc, FSCAI‡; Donald E. Casey Jr, MD, MPH, MBA, FACP, FAHA§; Theodore G. Ganiats, MD||; David R. Holmes Jr, MD, MACC‡; Allan S. Jaffe, MD, FACC, FAHA*†; Hani Jneid, MD, FACC, FAHA, FSCAI†; Rosemary F. Kelly, MD‡; Michael C. Kontos, MD, FACC, FAHA*†; Glenn N. Levine, MD, FACC, FAHA†; Philip R. Liebson, MD, FACC, FAHA†; Debarbata Mukherjee, MD, FACC†; Eric D. Peterson, MD, MPH, FACC, FAHA*‡; Marc S. Sabatine, MD, MPH, FACC, FAHA*†; Richard W. Smalling, MD, PhD, FACC, FSCAI***; Susan J. Ziemer, MD, PhD, FACC†

---

The writing committee gratefully acknowledges the memory of Dr. Francis M. Fesmire (representative of the American College of Emergency Physicians), who died during the development of this document but contributed immensely to our understanding of non–ST-elevation acute coronary syndromes.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information.
†ACC/AHA Representative.
‡ACC/AHA Task Force on Practice Guidelines Liaison.
§American College of Physicians Representative.
||American Academy of Family Physicians Representative.
#Society of Thoracic Surgeons Representative.
**Society for Cardiovascular Angiography and Interventions Representative.
††Former Task Force member; current member during the writing effort.

This document was approved by the American Heart Association Science Advisory and Coordinating Committee and the American College of Cardiology Board of Trustees in August 2014.

The online-only Comprehensive Relationships Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000134/-/DC1.

The online-only Data Supplement files are available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000134/-/DC2.


This article is copublished in the Journal of the American College of Cardiology.

Copies: This document is available on the World Wide Web sites of the American Heart Association (my.americanheart.org) and the American College of Cardiology (www.cardiosource.org). A copy of the document is available at http://my.americanheart.org/statements by selecting either the “By Topic” link or the “By Publication Date” link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

Expert peer review of AHA Scientific Statements is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit http://my.americanheart.org/statements and select the “Policies and Development” link.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at http://www.heart.org/HEARTORG/General/Copyright-Permission-Guidelines_UCM_300404_Article.jsp. A link to the “Copyright Permissions Request Form” appears on the right side of the page. (Circulation. 2014;130:e344–e426.)

© 2014 by the American Heart Association, Inc., and the American College of Cardiology Foundation.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIR.0000000000000134
Table of Contents

Preamble ................................................. e346
1. Introduction ...................................... e347
  1.1. Methodology and Evidence Review .......... e347
  1.2. Organization of the GWC .................. e348
  1.3. Document Review and Approval ............ e349
  1.4. Scope of the CPG ............................ e349
2. Overview of ACS .................................. e349
  2.1. Definition of Terms ........................... e349
  2.2. Epidemiology and Pathogenesis ............ e349
     2.2.1. Epidemiology ......................... e349
     2.2.2. Pathogenesis ......................... e350
3. Initial Evaluation and Management .......... e350
  3.1. Clinical Assessment and Initial Evaluation: Recommendation .......... e350
  3.1.1. ED or Outpatient Facility Presentation: Recommendations .......... e352
  3.2. Diagnosis of NSTE-ACS .................... e352
     3.2.1. History ................................. e352
     3.2.2. Physical Examination ................. e352
     3.2.3. Electrocardiogram .................... e353
     3.2.4. Biomarkers of Myocardial Necrosis .......... e353
     3.2.5. Imaging ................................ e353
  3.3. Prognosis—Early Risk Stratification: Recommendations .................. e353
     3.3.1. Rationale for Risk Stratification  and Spectrum of Risk: High, Intermediate, and Low .......... e354
     3.3.2. Estimation of Level of Risk ............ e354
        3.3.2.1. History: Angina Symptoms and Angina Equivalents ...... e354
        3.3.2.2. Demographics and History in Diagnosis and Risk Stratification ................ e354
        3.3.2.3. Early Estimation of Risk .......... e355
        3.3.2.4. Electrocardiogram ................ e355
        3.3.2.5. Physical Examination ............... e357
  3.4. Cardiac Biomarkers and the Universal Definition of MI: Recommendations .......... e357
     3.4.1. Biomarkers: Diagnosis .................. e357
     3.4.2. Biomarkers: Prognosis .................. e357
     3.4.3. Cardiac Troponins ....................... e357
        3.4.3.1. Prognosis .......................... e358
        3.4.4. CK-MB and Myoglobin Compared With Troponin ......................... e359
  4. Early Hospital Care ............................ e359
     4.1. Standard Medical Therapies ............... e360
        4.1.1. Oxygen: Recommendation ............... e360
        4.1.2. Anti-Ischemic and Analgesic Medications ....................... e360
           4.1.2.1. Nitrates: Recommendations ........ e360
           4.1.2.2. Analgesic Therapy: Recommendations ............... e361
           4.1.2.3. Beta-Adrenergic Blockers: Recommendations ............... e362
           4.1.2.4. Calcium Channel Blockers: Recommendations ............... e362
           4.1.2.5. Other Anti-Ischemic Interventions ....................... e363
           4.1.2.6. Cholesterol Management ....................... e363
     4.2. Inhibitors of the Renin-Angiotensin-Aldosterone System: Recommendations .......... e363
     4.3. Initial Antplatelet/Anticoagulant Therapy in Patients With Definite or Likely NSTE-ACS .... e364
        4.3.1. Initial Oral and Intravenous Antipatelet Therapy in Patients With Definite or Likely NSTE-ACS Treated With an Initial Invasive or Ischemia-Guided Strategy: Recommendations .......... e364
           4.3.1.1. Aspirin ......................... e365
           4.3.1.2. P2Y12 Receptor Inhibitors ............... e365
     4.3.2. Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS: Recommendations .......... e367
        4.3.2.1. Low-Molecular-Weight Heparin ....................... e367
        4.3.2.2. Bivalirudin ......................... e367
        4.3.2.3. Fondaparinux ......................... e367
        4.3.2.4. Unfractionated Heparin ....................... e367
        4.3.2.5. Argatroban ......................... e368
     4.3.3. Fibrinolytic Therapy in Patients With Definite NSTE-ACS: Recommendation .......... e368
     4.4. Ischemia-Guided Strategy Versus Early Invasive Strategies ....................... e368
        4.4.1. General Principles ....................... e368
        4.4.2. Rationale and Timing for Early Invasive Strategy ....................... e368
           4.4.2.1. Routine Invasive Strategy Timing ....................... e368

3.5. Immediate Management ................. e359
  3.5.1. Discharge From the ED or Chest Pain Unit: Recommendations .......... e359

Amsterdam el al 2014 AHA/ACC NSTE-ACS Guideline e345
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 educate and research for clinicians, providers, and patients. 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 Medicine1,2 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 Report3 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. The relationships between CPGs and data standards, appropriate use criteria, and performance measures are addressed elsewhere.

**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. 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.

**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 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; ie, 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 from clinical trials and other reports (Table 1). 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. 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 (eg, 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, P2Y₁₂ 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...
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.4 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 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 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.

*Estimate includes secondary discharge diagnoses.
2.2.2. Pathogenesis

The hallmark of ACS is the sudden imbalance between myocardial oxygen consumption (MVO₂) 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
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 (eg, 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
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)?

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,\(^4\) the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk score,\(^5\) the GRACE (Global Registry of Acute Coronary Events) risk score,\(^6\) 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).\(^7\)–\(^10\) The Sanchis score,\(^11\) Vancouver rule,\(^12\) Heart (History, ECG, Age, Risk Factors, and Troponin) score,\(^13\) HEARTS score,\(^14\) and Hess prediction rule\(^15\) were developed specifically for patients in the ED with ACS at increased risk of adverse outcome(s). Common outcome(s) to decide on the need for hospitalization and assist in the selection of treatment options.\(^16\)–\(^18\) (Level of Evidence: B)

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:

- Nonischemic cardiovascular causes of chest pain (eg, aortic dissection, expanding aortic aneurysm, pericarditis, pulmonary embolism)
- Noncardiovascular causes of chest, back, or upper abdominal discomfort include:
  - Pulmonary causes (eg, pneumonia, pleuritis, pneumothorax)
  - Gastrointestinal causes (eg, gastroesophageal reflux, esophageal spasm, peptic ulcer, pancreatitis, biliary disease)
  - Musculoskeletal causes (eg, costochondritis, cervical radiculopathy)
  - Psychiatric disorders
  - Other etiologies (eg, 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\(^4\) (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 ≥20 minutes.\(^4\) 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.\(^5\)–\(^7\) 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.\(^5\) Psychiatric disorders (eg, somatoform disorders, panic attack, anxiety disorders) are noncardiac causes of chest pain that can mimic ACS.\(^7\)

#### 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...
Acute myocardial ischemia may cause a S₄, a paradoxical splitting of S₃, 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. Changes on ECG in patients with NSTE-ACS include ST depression, transient ST-elevation, or new T-wave inversion. Persistent ST-elevation or anterior ST depression indicative of true posterior MI should be treated according to the STEMI CPG. The ECG can be relatively normal or initially nondiagnostic; if this is the case, the ECG should be repeated (eg, at 15- to 30-minute intervals during the first hour), especially if symptoms recur.

A normal ECG does not exclude ACS and occurs in 1% to 6% of such patients. 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 [V₇ to V₉] may be helpful). Right-sided leads (V₅R to V₆R) 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.

### 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%. 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.

### 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. (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 (eg, 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. (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. (Level of Evidence: A)

5. Risk scores should be used to assess prognosis in patients with NSTE-ACS. (Level of Evidence: A)

#### Class IIa

1. Risk-stratification models can be useful in management. (Level of Evidence: B)

2. It is reasonable to obtain supplemental electrocardiographic leads V₇ to V₉ in patients whose initial ECG is nondiagnostic and who are at intermediate/high risk of ACS. (Level of Evidence: B)

#### Class IIb

1. Continuous monitoring with 12-lead ECG may be a reasonable alternative in patients whose initial ECG is nondiagnostic and who are at intermediate/high risk of ACS. (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. (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 (eg, 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, 4.4.5). 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. 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.

### 3.3.2. Estimation of Level of Risk

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

#### 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.

The characteristics of angina include deep, poorly localized chest or arm pain that is reproducibly associated with exertion or emotional stress. Angina is relieved promptly (ie, 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.

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.

### Table 3. TIMI Risk Score* for NSTE-ACS

<table>
<thead>
<tr>
<th>TIMI Risk Score</th>
<th>All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>8.3</td>
</tr>
<tr>
<td>3</td>
<td>13.2</td>
</tr>
<tr>
<td>4</td>
<td>19.9</td>
</tr>
<tr>
<td>5</td>
<td>26.2</td>
</tr>
<tr>
<td>6–7</td>
<td>40.9</td>
</tr>
</tbody>
</table>

*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.

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. 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.

The relief of chest pain with nitroglycerin is not predictive of ACS. One study reported that sublingual nitroglycerin relieved symptoms in 35% of patients with documented ACS compared with 41% of patients without ACS. The relief of chest pain by “gastrointestinal cocktails” (eg, mixtures of liquid antacids, and/or viscous lidocaine, and/or anticholinergic agents) does not predict the absence of ACS.

#### 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. 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. 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. Older adults have increased risks of underlying CAD, multivessel CAD, and a worse prognosis (Section 7.1).

A family history of premature CAD is associated with increased coronary artery calcium scores and increased risk of 30-day cardiac events in patients with ACS. 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 and NSTE-ACS.

The current or prior use of aspirin at presentation is associated with increased cardiovascular risk, likely reflecting the greater probability that patients who have been prescribed aspirin have an increased cardiovascular risk profile and/or prior vascular
Table 4. Summary of Recommendations for Prognosis: Early Risk Stratification

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>I</td>
<td>C</td>
<td>21</td>
</tr>
<tr>
<td>Perform serial ECGs at 15- to 30-min intervals during the first hour in symptomatic patients with initial nondiagnostic ECG</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Measure cardiac troponin (cTnI or cTnT) in all patients with symptoms consistent with ACS*</td>
<td>I</td>
<td>A</td>
<td>21, 64, 67–71</td>
</tr>
<tr>
<td>Measure serial cardiac troponin I or T at presentation and 3–6 h after symptom onset* in all patients with symptoms consistent with ACS</td>
<td>I</td>
<td>A</td>
<td>21, 72–74</td>
</tr>
<tr>
<td>Use risk scores to assess prognosis in patients with NSTE-ACS</td>
<td>I</td>
<td>A</td>
<td>42–44, 75–80</td>
</tr>
<tr>
<td>Risk-stratification models can be useful in management</td>
<td>IIa</td>
<td>B</td>
<td>42–44, 75–81</td>
</tr>
<tr>
<td>Obtain supplemental electrocardiographic leads V&lt;sub&gt;5&lt;/sub&gt; to V&lt;sub&gt;6&lt;/sub&gt; in patients with initial nondiagnostic ECG at intermediate/high risk for ACS</td>
<td>IIa</td>
<td>B</td>
<td>82–84</td>
</tr>
<tr>
<td>Continuous monitoring with 12-lead ECG may be a reasonable alternative with initial nondiagnostic ECG in patients at intermediate/high risk for ACS</td>
<td>IIb</td>
<td>B</td>
<td>85, 86</td>
</tr>
<tr>
<td>BNP or NT-pro-BNP may be considered to assess risk in patients with suspected ACS</td>
<td>IIb</td>
<td>B</td>
<td>87–91</td>
</tr>
</tbody>
</table>

*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.

disease. Smoking is associated with a lower risk of death in ACS, 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. These individuals, especially those with severe obesity (body mass index >35), have a higher long-term mortality risk.124–129

Cocaine use can cause ACS by inducing coronary vasoconstriction, spasm, dissection, thrombosis, positive chronotropic and hypertensive actions, and direct myocardial toxicity (Section 7.10). Methamphetamine is 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). 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. 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).135

The GRACE risk model predicts in-hospital and post-discharge mortality or MI. 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). Among patients with a higher TIMI risk score (eg, ≥3), there is a greater benefit from therapies such as low-molecular-weight heparin (LMWH), platelet GP IIb/IIIa inhibitors, and an invasive strategy. Similarly, the GRACE risk model can identify patients who would benefit from an early invasive strategy. Patients with elevated cardiac troponin benefit from more aggressive therapy, whereas those without elevated cardiac troponins may not. 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. 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.

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. 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. ST depression (especially horizontal or downsloping) is highly suggestive of NSTE-ACS. 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; 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...
A GRACE Risk Model Nomogram

1. Find Points for Each Predictive Factor:

<table>
<thead>
<tr>
<th>Killip Class</th>
<th>Points</th>
<th>SBP, mm Hg</th>
<th>Points</th>
<th>Heart Rate, Beats/min</th>
<th>Points</th>
<th>Age, y</th>
<th>Points</th>
<th>Creatinine Level, mg/dL</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>80-99</td>
<td>63</td>
<td>≤80</td>
<td>62</td>
<td>≤30</td>
<td>62</td>
<td>≤20</td>
<td>62</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>100-119</td>
<td>43</td>
<td>70-89</td>
<td>9</td>
<td>70-89</td>
<td>9</td>
<td>80-99</td>
<td>25</td>
</tr>
<tr>
<td>III</td>
<td>39</td>
<td>120-139</td>
<td>34</td>
<td>90-109</td>
<td>15</td>
<td>90-109</td>
<td>15</td>
<td>100-119</td>
<td>41</td>
</tr>
<tr>
<td>IV</td>
<td>69</td>
<td>140-159</td>
<td>24</td>
<td>110-149</td>
<td>24</td>
<td>110-149</td>
<td>24</td>
<td>120-139</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150-189</td>
<td>10</td>
<td>120-199</td>
<td>38</td>
<td>120-199</td>
<td>38</td>
<td>160-180</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200</td>
<td>0</td>
<td>≥200</td>
<td>46</td>
<td>≥200</td>
<td>46</td>
<td>≥190</td>
<td>100</td>
</tr>
</tbody>
</table>

Other Risk Factors

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Arrest at Admission</td>
</tr>
<tr>
<td>ST-Segment Deviation</td>
</tr>
<tr>
<td>Elevated Cardiac Enzyme Levels</td>
</tr>
</tbody>
</table>

2. Sum Points for All Predictive Factors:

<table>
<thead>
<tr>
<th>Killip Class</th>
<th>+</th>
<th>SBP, mm Hg</th>
<th>+</th>
<th>Heart Rate</th>
<th>+</th>
<th>Age</th>
<th>+</th>
<th>Creatinine Level</th>
<th>+</th>
<th>Cardiac Arrest at Admission</th>
<th>+</th>
<th>ST-Segment Deviation</th>
<th>+</th>
<th>Elevated Cardiac Enzyme Levels</th>
<th>=</th>
<th>Total Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>60</td>
<td></td>
<td>80</td>
<td></td>
<td>100</td>
<td></td>
<td>100</td>
<td></td>
<td>120</td>
<td></td>
<td>120</td>
<td></td>
<td>160</td>
<td></td>
<td>120</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>100</td>
<td>43</td>
<td>90</td>
<td>15</td>
<td>90</td>
<td>15</td>
<td>100</td>
<td>41</td>
<td>120</td>
<td>25</td>
<td>120</td>
<td>25</td>
<td>160</td>
<td>25</td>
<td>120</td>
</tr>
<tr>
<td>III</td>
<td>39</td>
<td>120</td>
<td>34</td>
<td>110</td>
<td>24</td>
<td>110</td>
<td>24</td>
<td>120</td>
<td>58</td>
<td>120</td>
<td>75</td>
<td>120</td>
<td>75</td>
<td>160</td>
<td>75</td>
<td>120</td>
</tr>
<tr>
<td>IV</td>
<td>69</td>
<td>140</td>
<td>24</td>
<td>120</td>
<td>38</td>
<td>120</td>
<td>38</td>
<td>120</td>
<td>75</td>
<td>120</td>
<td>100</td>
<td>120</td>
<td>100</td>
<td>160</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200</td>
<td>0</td>
<td>≥200</td>
<td>46</td>
<td>≥200</td>
<td>46</td>
<td>≥200</td>
<td>100</td>
<td>≥200</td>
<td></td>
<td>≥200</td>
<td></td>
<td>≥200</td>
<td></td>
<td>≥200</td>
</tr>
</tbody>
</table>

3. Look Up Risk Corresponding to Total Points:

<table>
<thead>
<tr>
<th>Total Points</th>
<th>≤62</th>
<th>63</th>
<th>64</th>
<th>65</th>
<th>66</th>
<th>67</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of In-Hospital Death, %</td>
<td>≤0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

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 + 34 + 15 + 60 + 7 + 0 + 38 + 14 + 190 = 450

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 65 years of age, has serum creatinine level of 0.4, and no risk factors would have the following score: 20 + 34 + 15 + 60 + 7 + 0 + 38 + 14 + 190 = 434

This person would have 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

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.
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, electrocardiographic changes and/or clinical presentation consistent with ACS to identify a rising and/or falling pattern.21,64,67–71,152–156 (Level of Evidence: A)

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 Ib

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.57,89,167–171 (Level of Evidence: B)

Cardiac troponins are the mainstay for diagnosis of ACS and for risk stratification in patients with ACS, because 1% to 6% of such patients will have a MI, and at least 4% will have UA.26–62 Fibrinolytic therapy is contraindicated for patients with ACS without ST-elevation, except for those with electrocardiographic evidence of true posterior MI (ie, ST-elevation in posterior chest leads [V7 to V9]). This can be evaluated when acute myocardial infarction (AMI) is suspected but electrocardiographic changes are modest or not present; 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 (eg, rales, S3 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.50,151 The physical examination may also help identify comorbid conditions (eg, 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 MI.

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)

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)

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{21,178}

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.\textsuperscript{71} This has also been suggested for some contemporary assays.\textsuperscript{71} Troponins are elevated in MI as early as 2 to 4 hours after symptom onset,\textsuperscript{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.\textsuperscript{14} Patients with end-stage renal disease and no clinical evidence of ACS frequently have elevations of cardiac troponin.\textsuperscript{180–182} With conventional assays, this is more common with cardiac troponin T than with cardiac troponin I.\textsuperscript{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 (eg, ≥7 ng/L over 2 hours) may indicate reinfarction.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{71} In addition, troponin elevations may provide information to direct therapy. Patients with cardiac troponin elevations

---

**Table 5. Summary of Recommendations for Cardiac Biomarkers and the Universal Definition of MI**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>A</td>
<td>21, 64, 67–71, 152–156</td>
</tr>
<tr>
<td>Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features</td>
<td>I</td>
<td>A</td>
<td>21, 72–74, 157</td>
</tr>
<tr>
<td>Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values</td>
<td>I</td>
<td>A</td>
<td>67, 68, 72</td>
</tr>
<tr>
<td>With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS</td>
<td>III: No Benefit</td>
<td>A</td>
<td>158–164</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin elevations are useful for short- and long-term prognosis</td>
<td>I</td>
<td>B</td>
<td>71, 73, 165, 166</td>
</tr>
<tr>
<td>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</td>
<td>IIb</td>
<td>B</td>
<td>164, 165</td>
</tr>
<tr>
<td>BNP may be reasonable for additional prognostic information</td>
<td>IIb</td>
<td>B</td>
<td>87, 88, 167–171</td>
</tr>
</tbody>
</table>

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.
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.\(^{198,199–201}\) (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\(^{208–202}\) (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 (eg, 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 (eg, 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 antiangiinal (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 (eg, 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.

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

4.1. 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

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 by guest on August 16, 2017 http://circ.ahajournals.org/Downloaded from

Table 6. Summary of Recommendations for Early Hospital Care

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Administer supplemental oxygen only with oxygen saturation &lt;90%, respiratory distress, or other high-risk features for hypoxemia</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer sublingual NTG every 5 min × 3 for continuing ischemic pain and then assess need for IV NTG</td>
<td>I</td>
<td>C</td>
<td>216–218</td>
</tr>
<tr>
<td>Administer IV NTG for persistent ischemia, HF, or hypertension</td>
<td>I</td>
<td>B</td>
<td>219–224</td>
</tr>
<tr>
<td>Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor</td>
<td>III: Harm</td>
<td>B</td>
<td>225–227</td>
</tr>
<tr>
<td>Analgesic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications</td>
<td>IIb</td>
<td>B</td>
<td>232, 233</td>
</tr>
<tr>
<td>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</td>
<td>III: Harm</td>
<td>B</td>
<td>35, 234</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>A</td>
<td>240–242</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Re-evaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS</td>
<td>IIA</td>
<td>C</td>
<td>241, 243</td>
</tr>
<tr>
<td>IV beta blockers are potentially harmful when risk factors for shock are present</td>
<td>III: Harm</td>
<td>B</td>
<td>244</td>
</tr>
<tr>
<td>CCBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 &gt;0.24 s, or second- or third-degree atrioventricular block without a cardiac pacemaker</td>
<td>I</td>
<td>B</td>
<td>248–250</td>
</tr>
<tr>
<td>Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects*</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Long-acting CCBs and nitrates are recommended for patients with coronary artery spasm</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Immediate-release nifedipine is contraindicated in the absence of a beta blocker</td>
<td>III: Harm</td>
<td>B</td>
<td>251, 252</td>
</tr>
<tr>
<td>Cholesterol management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate or continue high-intensity statin therapy in patients with no contraindications</td>
<td>I</td>
<td>A</td>
<td>269–273</td>
</tr>
<tr>
<td>Obtain a fasting lipid profile, preferably within 24 h</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

*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.
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 (eg, 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 decompenated 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 (eg, 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 MVO₂. 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 mmHg, 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 nondihydropyridine calcium channel blocker (CCB) (eg, 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)

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 some248,249,254 but not all studies.255,256 Verapamil may be beneficial in reducing long-term events after AMI in hypertensive patients without LV dysfunction 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.

†Short-acting dihydropyridine calcium channel antagonists should be avoided.
4.1.2.5. Other Anti-Ischemic Interventions

Ranolazine

Ranolazine is an antianginal medication with minimal effects on heart rate and BP. It inhibits the late inward sodium current and reduces the deleterious effects of intracellular sodium and calcium overload that accompany myocardial ischemia. 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 6560 patients with NSTE-ACS who presented within 48 hours of ischemic symptoms. 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. In the subgroup with prior chronic angina (n=3565), ranolazine was associated with a lower primary composite endpoint, a significant reduction of worsening angina, and increased exercise duration. 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 1000 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.

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. When studied in rigorous RCTs, IABP counterpulsation failed to reduce MACE in high-risk elective PCI, decrease infarct size after primary PCI for acute STEMI, or diminish early mortality in patients with cardiogenic shock complicating AMI.

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. (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. 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. (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. (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. (Level of Evidence: A)

Class IIa

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

Class IIb

1. ACE inhibitors may be reasonable in all other patients with cardiac or other vascular disease. (Level of Evidence: B)
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 beneficial277; 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) I 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.288–290,293,291 (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.292 (Level of Evidence: B)

3. A P2Y12 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 daily293,294 (Level of Evidence: B)
   • Ticagrelor‡: 180-mg loading dose, then 90 mg twice daily293,294 (Level of Evidence: B)

Class IIa

1. It is reasonable to use ticagrelor in preference to clopidogrel for P2Y12 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 (eg, positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are epifibatide or tirofiban.304,295 (Level of Evidence: B)

Despite the large number of new antiplatelet and antithrombotic agents, aspirin, which targets COX and subsequent thromboxane A2, inhibition, is the mainstay of antiplatelet therapy. Multiple other pathways of platelet activation can be targeted by agents that inhibit the platelet P2Y12 receptor, including thiienopyridine drug agents, such as clopidogrel and prasugrel, which require conversion into molecules that bind irreversibly to the P2Y12 receptor. Additional pyrimidine derivatives, including ticagrelor, do not require biotransformation and bind reversibly to the P2Y12 receptor, antagonizing adenosine diphosphate platelet activation. In addition to these oral agents, intravenous GP IIb/IIIa receptor inhibitors, including abciximab, epifibatide, and tirofiban, target the first 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 epifibatide or delayed, provisional epifibatide. Seventy-five percent of the patients received upstream, preprocedure clopidogrel. The risk of TIMI major bleeding in the early epifibatide group was 2.6% compared with 1.8% (P=0.02) in the delayed provisional group.285 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.292 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 formulations 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

‡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
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. There was a slight increase in major bleeding events with clopidogrel, including a nonsignificant increase in life-threatening bleeding and fatal bleeding. An initial loading dose of 300 mg to 600 mg is recommended. A 600-mg loading dose results in a greater, more rapid, and more reliable platelet inhibition compared with a 300-mg loading dose. Use of clopidogrel for patients with NSTE-ACS who are aspirin intolerant is based on a study.

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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Dosing and Special Considerations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non–enteric-coated aspirin to all patients promptly after presentation</td>
<td>162 mg-325 mg</td>
<td>I</td>
<td>A</td>
<td>288–290</td>
</tr>
<tr>
<td>• Aspirin maintenance dose continued indefinitely</td>
<td>81 mg/d-325 mg/d*</td>
<td>I</td>
<td>A</td>
<td>288–290, 293, 391</td>
</tr>
<tr>
<td><strong>P2Y$_{12}$ inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin</td>
<td>75 mg</td>
<td>I</td>
<td>B</td>
<td>291</td>
</tr>
<tr>
<td>• 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:</td>
<td>300-mg or 600-mg loading dose, then 75 mg/d</td>
<td>I</td>
<td>B</td>
<td>289, 292, 293, 294</td>
</tr>
<tr>
<td>– Clopidogrel</td>
<td>180-mg loading dose, then 90 mg BID</td>
<td>I</td>
<td>B</td>
<td>289, 292, 293, 294</td>
</tr>
<tr>
<td>• P2Y$_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post–PCI patients treated with coronary stents</td>
<td>N/A</td>
<td>I</td>
<td>B</td>
<td>293, 296, 302, 330, 331</td>
</tr>
<tr>
<td>• Ticagrelan in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy</td>
<td>N/A</td>
<td>Ila</td>
<td>B</td>
<td>293, 294</td>
</tr>
<tr>
<td><strong>GP Ib/IIa inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• GP Ib/IIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (eg, positive troponin)</td>
<td>Preferred options are eptifibatide or tirofiban</td>
<td>Ila</td>
<td>B</td>
<td>43, 94, 295</td>
</tr>
<tr>
<td><strong>Parenteral anticoagulant and fibrinolytic therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SC enoxaparin for duration of hospitalization or until PCI is performed</td>
<td>1 mg/kg SC every 12 h (reduce dose to 1 mg/kg/d SC in patients with CrCl &lt;30 mL/min)</td>
<td>I</td>
<td>A</td>
<td>133, 136, 309</td>
</tr>
<tr>
<td>• Initial 30 mg IV loading dose in selected patients</td>
<td></td>
<td>I</td>
<td>A</td>
<td>133, 136, 309</td>
</tr>
<tr>
<td>• Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only</td>
<td>Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h</td>
<td>I</td>
<td>B</td>
<td>292, 293, 310, 311</td>
</tr>
<tr>
<td>• SC fondaparinux for the duration of hospitalization or until PCI is performed</td>
<td>2.5 mg SC daily</td>
<td>I</td>
<td>B</td>
<td>312–314</td>
</tr>
<tr>
<td>• Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux</td>
<td>N/A</td>
<td>I</td>
<td>B</td>
<td>313–315</td>
</tr>
<tr>
<td>• IV UFH for 48 h or until PCI is performed</td>
<td>Initial loading dose 60 IU/kg (max 4000 IU) with initial infusion 12 IU/kg/h (max 1000 IU/h)</td>
<td>I</td>
<td>B</td>
<td>316–322</td>
</tr>
<tr>
<td>• IV fibrinolytic treatment not recommended in patients with NSTE-ACS N/A</td>
<td>Adjusted to therapeutic aPTT range</td>
<td>I Ila</td>
<td>A</td>
<td>93, 329</td>
</tr>
</tbody>
</table>

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.289 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.
in patients with stable ischemic heart disease. When possible, discontinue clopidogrel at least 5 days before surgery.

**Prasugrel**
The metabolic conversion pathways of prasugrel produce more rapid and consistent platelet inhibition than clopidogrel. 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. 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).

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. 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. On the basis of the 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. 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; \( P<0.001 \)). 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. 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) and bradycardia. The benefit of ticagrelor over clopidogrel was limited to patients taking 75 mg to 100 mg of aspirin. 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. 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. The ACUITY (Acute Catherization and Urgent Intervention Triage Strategy) trial evaluated unfractionated heparin (UFH) versus bivalirudin with or without GP IIb/IIIa inhibitors. 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%; \( P=0.45 \)). 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; \( P<0.0001 \)). 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. 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%; \( P=0.001 \)). Similar results were reported by the EARLY ACS investigators, who evaluated eptifibatide given upstream versus delayed, provisional administration in >9000 patients with NSTE-ACS. The composite endpoint of death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic complications occurred in 9.3% of patients in the early-epitibatide group compared with 10% in the delayed-epitibatide group (odds ratio [OR]: 0.92; 95% CI: 0.80 to 1.06; \( P=0.23 \)). As in the ACUITY Timing trial, the early-epitibatide group had significantly higher rates of bleeding and red cell transfusions.
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.130,136,309 (Level of Evidence: A)

- 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 4000 IU) with initial infusion of 12 IU/kg per hour (maximum 1000 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.316–318 (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.321 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.

‡See Section 5.1.2.1 for recommendations at the time of PCI.
In general, those studies found a strong trend for reduction in composite adverse events with the addition of parenteral UFH to aspirin therapy. Clinical trials indicate that a weight-adjusted dosing regimen of UFH can provide more predictable anticoagulation than a fixed initial dose (eg, 5000 IU loading dose, 1000 IU/h initial infusion). The recommended weight-adjusted regimen is an initial loading dose of 60 IU/kg (maximum 4000 IU) and an initial infusion of 12 IU/kg/h (maximum 1000 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. 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 (ie, without ST-elevation, true posterior MI, or left bundle-branch block not known to be old), intravenous fibrinolytic therapy should not be used. (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. 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 (ie, 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 (eg, 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 (ie, within 24 hours) or delayed invasive (ie, 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. 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.

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). (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). (Level of Evidence: B)

‡See Section 7.7 for additional information on women.
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
Table 8. Factors Associated With Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients With NSTE-ACS

<table>
<thead>
<tr>
<th>Immediate invasive (within 2 h)</th>
<th>Refractory angina</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Signs or symptoms of HF or new or worsening mitral regurgitation</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy</td>
</tr>
<tr>
<td></td>
<td>Sustained VT or VF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ischemia-guided strategy</th>
<th>Low-risk score (eg, TIMI [0 or 1], GRACE [&lt;109])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-risk Tn-negative female patients</td>
</tr>
<tr>
<td></td>
<td>Patient or clinician preference in the absence of high-risk features</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early invasive (within 24 h)</th>
<th>None of the above, but GRACE risk score &gt;140</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Temporal change in Tn (Section 3.4)</td>
</tr>
<tr>
<td></td>
<td>New or presumably new ST depression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delayed invasive (within 25–72 h)</th>
<th>None of the above but diabetes mellitus Renal insufficiency (GFR &lt;60 mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced LV systolic function (EF &lt;0.40)</td>
</tr>
<tr>
<td></td>
<td>Early postinfarction angina</td>
</tr>
<tr>
<td></td>
<td>PCI within 6 mo</td>
</tr>
<tr>
<td></td>
<td>Prior CABG</td>
</tr>
<tr>
<td></td>
<td>GRACE risk score 109–140; TIMI score ≥2</td>
</tr>
</tbody>
</table>

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.

NSTE-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events,240,253,338 (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 (ie, diagnostic angiography with intent to perform revascularization) is not recommended in patients with:
   a. Extensive comorbidities (eg, 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.31 (Level of Evidence: B)

Several studies30,138,134–337 and meta-analyses341 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 data342 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 2721) randomized to a routine invasive strategy experienced cardiovascular death or nonfatal MI versus 17.9% of patients (475 of 2746) 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 non-invasively 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).193,336 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. 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. In contrast, death, MI, or rehospitalization rates were reduced for both men and women in TACTICS-TIMI 18. 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. 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 end-point of death, MI, or rehospitalization. In contrast, an ischemia-guided strategy is preferred in low-risk women. 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. 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 (eg, 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 (ie, LVEF ≤0.40) on noninvasive study, or noninvasive stress test findings, including magnetic resonance imaging. 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. (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. (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. (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. (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.

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. However, for prognostic assessment in women, treadmill exercise testing has provided comparable results to stress imaging. 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. 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 (eg, 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, the 2011 CABG CPG, and the 2012 stable ischemic heart disease CPG and its 2014 focused update. 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.

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.

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. 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.

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 (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. 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. Although PCI of a nonculprit lesion is not advocated in patients with STEMI, there is less agreement on whether nonculprit lesions should undergo intervention at the time of culprit-lesion PCI for NSTE-ACS. Most reports, but not all, comparing culprit lesion–only PCI with multivessel PCI (eg, 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 (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 (Level of Evidence: B)

3. After PCI, aspirin should be continued indefinitely at a dose of 81 mg to 325 mg daily (Level of Evidence: B)
4. A loading dose of a P2Y<sub>12</sub> receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting.

5. In patients with NSTE-ACS and high-risk features (eg, 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.

6. In patients receiving a stent (bare-metal stent or drug-eluting stent [DES]) during PCI for NSTE-ACS, P2Y<sub>12</sub> inhibitor therapy should be given for at least 12 months.

Class IIa

1. It is reasonable to choose ticagrelor over clopidogrel for P2Y<sub>12</sub> inhibition treatment in patients with NSTE-ACS treated with an early invasive strategy and/or coronary stenting.

2. It is reasonable to choose prasugrel over clopidogrel for P2Y<sub>12</sub> treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications.

3. In patients with NSTE-ACS and high-risk features (eg, 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.

4. After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses.

5. If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of P2Y<sub>12</sub> inhibitor therapy after stent implantation, earlier discontinuation (eg, <12 months) of P2Y<sub>12</sub> inhibitor therapy is reasonable.

Class IIb

1. Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation.

Class III: Harm

1. Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack.

Comprehensive recommendations on the use of antiplatelet and anticoagulant therapy in patients with NSTE-ACS undergoing PCI are given in the 2011 PCI CPG. Aspirin reduces the frequency of ischemic complications after PCI and is ideally administered at least 2 hours, and preferably 24 hours, before PCI. Compared with aspirin and a P2Y<sub>12</sub> inhibitor, in patients treated with coronary stents reduces the risk of stent thrombosis and composite ischemic events. 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 lower responders and decreases the incidence of MACE.

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. The optimal duration of DAPT therapy in patients treated with DES is not well established. 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. Although the overall trial 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=17263) showed significant differences in the clopidogrel arm. 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. 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 (eg, 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.293–382 (Level of Evidence: A)

Class IIa

1. In patients with NSTE-ACS and high-risk features (eg, 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-dose bolus tirofiban) at the time of PCI.193,383 (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 data293,302,393 (and no RCT data) from which to make specific recommendations about GP IIb/IIIa inhibitor use in patients treated with either of these P2Y12 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.310,394–399 (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 (eg, 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 and an established regimen (eg, 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.311–315 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 time314,404 (Table 9).26,313–315
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.484–489 (Level of Evidence: B)

2. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery23,411–413 (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 surgery418,419 and abciximab for at least 12 hours before to limit blood loss and transfusion.399 (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.521 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 P2Y12 inhibitors in patients with NSTE-ACS is associated with an increase in post-CABG bleeding and the need for transfusion.293,302,411,412,423–425 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 P2Y12 inhibitor330 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,852 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...
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. 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. 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 “ABCD” (Aspirin, Antianginals, and ACE Inhibitors; Beta Blockers and BP; Cholesterol and Cigarettes; Diet and Diabetes Mellitus; Education and Exercise) is useful in guiding treatment.

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. (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. (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. (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. (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. (Level of Evidence: C)

6. If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (eg, 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. (Level of Evidence: C)

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

2. In addition to aspirin, a P2Y<sub>12</sub> 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 (Level of Evidence: B) or
   - Ticagrelor: 90 mg twice daily (Level of Evidence: B)

3. In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y<sub>12</sub> inhibitor therapy should be given for at least 12 months. Options include:

   - Clopidogrel: 75 mg daily (Level of Evidence: B) or
   - Prasugrel: 10 mg daily (Level of Evidence: B)
   - Ticagrelor: 90 mg twice daily (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

---

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 (ie, <5 days) after drug discontinuation.293,412

See Online Data Supplements 21 and 22 for more information on myocardial revascularization.
Table 10. Plan of Care for Patients With NSTE-ACS

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

(Continued)
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 P2Y12 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 P2Y12 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 P2Y12 inhibitor therapy after stent implantation, earlier discontinuation (eg, <12 months) of P2Y12 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)

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 P2Y12 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 P2Y12 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 P2Y12 receptor inhibitor.26,430,431 (Level of Evidence: C)

Class IIb

1. Targeting oral anticoagulant therapy to a lower international normalized ratio (INR) (eg, 2.0 to 2.5) may be reasonable in patients with NSTE-ACS managed with aspirin and a P2Y12 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. Although some organizations have recommended a target INR of 2.0 to 2.5 in patients with atrial fibrillation (AF) who require triple therapy, others continue to recommend a target INR of 2.0 to 3.0. 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. 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. 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 and Coronary Stenting) trial.

Although there are some data on therapy with aspirin, clopidogrel, and warfarin, there is sparse information on the use of newer P2Y12 inhibitors (prasugrel, ticagrelor), direct thrombin inhibitor (dabigatran), or factor-Xa inhibitors (rivaroxaban, apixaban) in patients receiving triple therapy. Prasugrel and ticagrelor produce a greater degree of platelet inhibition than clopidogrel and are associated with greater rates of bleeding. 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). 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 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. 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, the US Food and Drug Administration has issued a warning to avoid concomitant use of these 2 proton pump inhibitors with clopidogrel.

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. Similarly, a strategy of routine genetic phenotype testing has also not been beneficial and thus is not recommended. A more detailed discussion of these issues and current recommendations about platelet function testing and genetic testing are in the 2011 PCI CPG.

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. 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. (Level of Evidence: B)

The US Public Health Service emphasizes comprehensive cardiac rehabilitation programs, and the 2011 secondary prevention CPG underscores referral to cardiac rehabilitation for survivors of ACS. Since 2007, referral to these programs has been designated a quality performance measure. 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 exercise.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=58432), 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 progesterin, 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.\textsuperscript{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.\textsuperscript{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 progesterin and estrogen alone.\textsuperscript{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.\textsuperscript{470–472} It is recommended that post-menopausal women receiving hormone therapy at the time 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 (eg, 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).\textsuperscript{473}

6.3.6. Antioxidant Vitamins and Folic Acid: Recommendations

Class III: No Benefit

1. Antioxidant vitamin supplements (eg, vitamins E, C, or beta carotene) should not be used for secondary prevention in patients with NSTEMI.\textsuperscript{474,475} (Level of Evidence: A)

2. Folic acid, with or without vitamins B6 and B12, should not be used for secondary prevention in patients with NSTEMI.\textsuperscript{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 folic acid 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\textsuperscript{476–478} and produced poorer outcomes in another study.\textsuperscript{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.\textsuperscript{476} Similarly, experience in large clinical trials with antioxidant vitamins has failed to demonstrate benefit for primary or secondary prevention.\textsuperscript{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.\textsuperscript{481–485} (Level of Evidence: B)

2. An evidence-based plan of care (eg, 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 (eg, 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.\textsuperscript{452,486,487} (Level of Evidence: B)

4. An annual influenza vaccination is recommended for patients with cardiovascular disease.\textsuperscript{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.\textsuperscript{489,490} An important intervention to promote...
Joint Commission. Examples of patient safety standards lap with the National Patient Safety Goals espoused by The National Quality Forum, which over -

6.4.1. Systems to Promote Care Coordination
There has been improved understanding of the system changes necessary to achieve safer care. This includes adoption by all US hospitals of a standardized set of “Safe Practices” endorsed by the National Quality Forum, which overlap with the National Patient Safety Goals espoused by The Joint Commission. 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,” 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, obesity, and lifestyle and the 2014 recommendations for management of hypertension, 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.

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. (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. (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. (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. (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 (eg, SYNTAX score >22), with or without involvement of the proximal LAD artery, to reduce cardiovascular disease events and readmission and to improve survival. (Level of Evidence: B)

In this CPG, “older adults” refers to patients ≥75 years of age. Older adults have the highest incidence, prevalence, and adverse outcomes of NSTE-ACS. 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 underrepresented in clinical trials, the recommendations in this CPG are largely supported by registry data and meta-analyses.

Older patients with NSTE-ACS primarily present with chest pain but frequently have atypical symptoms. ECGs may be less diagnostic than in younger patients. Older patients with NSTE-ACS are more likely to present with non-Q-wave MI, the diagnostic yield of ECGs and biomarkers is lower, and sensitivity to de novo CK-MB release is lower. Older patients are more likely to present with complex 3-vessel CAD and greater number of coronary arteries involved. Older patients are less likely to present with ST-segment depression and more likely to present with ST-segment elevation, and younger patients tolerate interventions better than do older patients. 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.\(^{52,54}\) Aspirin should be maintained at 81 mg per day (after initial stent implantation). Owing to excess bleeding without clinical benefit, the US Food and Drug Administration lists a Black Box warning that does not recommend administration of prasugrel to patients with NSTE-ACS who are \(\geq 75\) years of age or weigh <60 kg except in those at very high risk. A metaanalysis 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 \(\pm\) PCI than GP IIb/IIIa inhibitors plus UFH, with less bleeding and similar efficacy.\(^{528,550}\) 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 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.\(^{540}\) 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 \(\geq 75\) 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 \(\geq 75\) 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.\(^{533}\)

PCI has increased in older patients, including the very elderly (\(\geq 90\) years of age), with success rates similar to younger patients and declining complication rates, including major bleeding.\(^{515,517,526-528,555}\) Several large registries report a greater RR reduction in mortality of older patients treated with revascularization versus medical therapy compared with those \(\leq 65\) years of age, despite increased comorbidities.\(^{517,540,554-556}\)

Operative mortality rates for CABG in patients \(\geq 80\) years of age with NSTE-ACS range from 5% to 8% (11% for urgent cases) and increase to approximately 13% at \(\geq 90\) years of age. Complications occur more frequently in older patients with CABG.\(^{537,538}\) 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.\(^{537}\) In a metaanalysis, 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.\(^{530}\) 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.\(^{14,138,141,333,334,337,341,566,564}\) (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.\(^{563}\) 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.\(^{596,597,563,565}\) 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
Table 11. Summary of Recommendations for Special Patient Groups

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSTE-ACS in older patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treat older patients (≥75 y of age) with GDMT, early invasive strategy, and revascularization as appropriate</td>
<td>I</td>
<td>A</td>
<td>515–519</td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>A</td>
<td>515, 520–522</td>
</tr>
<tr>
<td>Undertake patient-centered management for older patients, considering patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy</td>
<td>I</td>
<td>B</td>
<td>515, 523–525</td>
</tr>
<tr>
<td>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</td>
<td>Ila</td>
<td>B</td>
<td>396, 526–528</td>
</tr>
<tr>
<td>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</td>
<td>Ila</td>
<td>B</td>
<td>529–534</td>
</tr>
<tr>
<td><strong>HF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treat patients with a history of HF according to the same risk stratification guidelines and recommendations for patients without HF</td>
<td>I</td>
<td>B</td>
<td>14, 42–44, 75–81</td>
</tr>
<tr>
<td>Select a revascularization strategy based on the extent of CAD, associated cardiac lesions, LV dysfunction, and prior revascularization</td>
<td>I</td>
<td>B</td>
<td>14, 138, 141, 333, 334, 337, 341, 560, 561</td>
</tr>
<tr>
<td><strong>Cardiogenic shock</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend early revascularization for cardiogenic shock due to cardiac pump failure</td>
<td>I</td>
<td>B</td>
<td>560, 588, 589</td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend medical treatment and decisions for testing and revascularization similar to those for patients without DM</td>
<td>I</td>
<td>A</td>
<td>138, 339, 601</td>
</tr>
<tr>
<td><strong>Post-CABG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend GDMT antiplatelet and anticoagulant therapy and early invasive strategy because of increased risk with prior CABG</td>
<td>I</td>
<td>B</td>
<td>67, 68, 141, 340–342</td>
</tr>
<tr>
<td><strong>Perioperative NSTE-ACS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer GDMT to perioperative patients with limitations imposed by noncardiac surgery</td>
<td>I</td>
<td>C</td>
<td>626, 627</td>
</tr>
<tr>
<td>Direct management at underlying cause of perioperative NSTE-ACS</td>
<td>I</td>
<td>C</td>
<td>21, 626–634</td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimate CrCl and adjust doses of renally cleared medications according to pharmacokinetic data</td>
<td>I</td>
<td>B</td>
<td>649, 650</td>
</tr>
<tr>
<td>Administer adequate hydration to patients undergoing coronary and LV angiography</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD</td>
<td>Ila</td>
<td>B</td>
<td>649–652</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>I</td>
<td>B</td>
<td>669–673</td>
</tr>
<tr>
<td>Early invasive strategy is recommended in women with NSTE-ACS and high-risk features (troponin positive)</td>
<td>I</td>
<td>A</td>
<td>141, 345, 346, 561</td>
</tr>
<tr>
<td>Myocardial revascularization is reasonable for pregnant women if ischemia-guided strategy is ineffective for management of life-threatening complications</td>
<td>Ila</td>
<td>C</td>
<td>674</td>
</tr>
<tr>
<td>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</td>
<td>III: No Benefit</td>
<td>B</td>
<td>141, 345, 346</td>
</tr>
<tr>
<td><strong>Anemia, bleeding, and transfusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluate all patients for risk of bleeding</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Recommend that anticoagulant and antiplatelet therapy be weight-based where appropriate and adjusted for CKD to decrease the risk of bleeding</td>
<td>I</td>
<td>B</td>
<td>522, 697, 698</td>
</tr>
<tr>
<td>There is no benefit of routine blood transfusion in hemodynamically stable patients with hemoglobin levels &gt;8 g/dL</td>
<td>III: No Benefit</td>
<td>B</td>
<td>699–703</td>
</tr>
<tr>
<td><strong>Cocaine and methamphetamine users</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 (eg, euphoria, tachycardia, and hypertension) and beta-blocker use unless patients are receiving coronary vasodilator therapy</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

(Continued)
Cardioversion for VF or pulseless sustained VT. Early administration of beta blockers has been associated with reduction in incidence of VF. The prophyllactic 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 non-sustained VT occurring >48 hours after admission indicates an increased risk of cardiac and sudden death, especially when associated with accompanying myocardial ischemia. 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. 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. 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. Management of AF requires rate control and adequate anticoagulation according to the 2014 AF CPG. For hemodynamically unstable patients and those with continuing ischemia, treatment should be implemented according to the 2010 advanced cardiac life support CPGs.

### Table 11. Continued

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cocaine and methamphetamine users (cont’d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>Ila</td>
<td>C</td>
<td>741–744</td>
</tr>
<tr>
<td>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</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Vasospastic (Prinzmetal) angina</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend CCBs alone or in combination with nitrates</td>
<td>I</td>
<td>B</td>
<td>753–758</td>
</tr>
<tr>
<td>Recommend HMG-CoA reductase inhibitor, cessation of tobacco use, and atherosclerosis risk factor modification</td>
<td>I</td>
<td>B</td>
<td>759–763</td>
</tr>
<tr>
<td>Recommend coronary angiography (invasive or noninvasive) for episodic chest pain with transient ST-elevation to detect severe CAD</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Provocative testing during invasive coronary angiography* may be considered for suspected vasospastic angina when clinical criteria and noninvasive assessment fail to determine diagnosis</td>
<td>IIb</td>
<td>B</td>
<td>764–767</td>
</tr>
<tr>
<td><strong>ACS with angiographically normal coronary arteries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive physiological assessment (coronary flow reserve measurement) may be considered with normal coronary arteries if endothelial dysfunction is suspected</td>
<td>IIb</td>
<td>B</td>
<td>629, 773–776</td>
</tr>
<tr>
<td><strong>Stress (Takotsubo) cardiomyopathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider stress-induced cardiomyopathy in patients with apparent ACS and nonobstructive CAD</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Perform ventriculography, echocardiography, or MRI to confirm or exclude diagnosis</td>
<td>I</td>
<td>B</td>
<td>795–798</td>
</tr>
<tr>
<td>Treat with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) if hemodynamically stable</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Administer antiplatelet therapy for LV thrombi</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>It is reasonable to administer catecholamines for symptomatic hypotension in the absence of LV outflow tract obstruction</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>It is reasonable to use IABP for refractory shock</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>It is reasonable to use beta blockers and alpha-adrenergic agents for LV outflow tract obstruction</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Prophylactic anticoagulation may be considered to prevent LV thrombi</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Provocative testing during invasive coronary angiography (eg, 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.
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.606 Atioventricular block and bundle-branch block develop in approximately 5% of patients.587 High-degree atioventricular 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 atioventricular block does not require treatment. High-grade atioventricular 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 atioventricular 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.540,588,589 (Level of Evidence: B) AMI is the leading cause of cardiogenic shock. Early revascularization is a mainstay in the treatment of cardiogenic shock.500,509 Compared with medical therapy, early revascularization is associated with improved 6-month mortality360 and 13% absolute mortality reduction at 6 years.508 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 (eg, septal, papillary muscle, free-wall rupture). Age alone is not a contraindication to urgent revascularization for cardiogenic shock.380,509 Mortality after cardiogenic shock has steadily improved,91 including in older adults,500,509 with 30-day mortality ranging from approximately 40% with milder forms of shock204 to >45% with refractory shock.92 Approximately 30% of patients in the IABP-SHOCK (Intra-Aortic Balloon Pump in Cardiogenic Shock) II trial presented with NSTEMI,208 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.92 Of the 23% of patients with ACS who had NSTEMI in the GRACE registry, 4.6% of patients experienced cardiogenic shock.93 Of the 2992 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%.94 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.265 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.95 Dopamine in patients with cardiogenic shock may be associated with increased mortality compared with norepinephrine.506 The use of percutaneous ventricular assist devices has been hampered by the need for interventional expertise, cost, and lack of supportive evidence.507 IABP has been used for decades,265,591 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.508 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 (eg, 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.593,603,604 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.508 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 <80 mg/dL). Blood glucose should be maintained at <80 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 6385 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,608 patients with diabetes mellitus and NSTE-ACS in the United Kingdom603 and Finland612 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. The largest RCT, the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, evaluated 1900 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 (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.

### 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, epifibatide, and tirofiban) on mortality in NSTE-ACS 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). This benefit was particularly large in the 1279 patients with diabetes mellitus who underwent PCI (4.0% to 1.2%; P = 0.002). The ACUITY trial in ACS (13,819 patients, 3852 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). 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. In PLATO, ticagrelor compared with clopidogrel reduced ischemic events irrespective of diabetic status and glycemic control, without an increase in major bleeding.

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. (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.

In the PURSUIT trial, 12% of the patients had prior CABG and more adverse follow-up outcomes, including increased mortality, but had a benefit with epifibatide similar to those without prior CABG. 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. In patients with prior CABG who develop NSTE-ACS that is related to an ungrafted native coronary vessel, treatment should follow GDMT.

Because patients with prior CABG presenting with ACS are a high-risk group with increased comorbidity 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. (Level of Evidence: C)

2. In patients who develop NSTE-ACS after noncardiac surgery, management should be directed at the underlying cause. (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 (eg, 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. 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. 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, 8351 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.
ACSB in the setting of noncardiac surgery is associated with increased mortality. Several risk scores have been developed to determine the probability of mortality. A meta-analysis of the prognostic value of troponin and CK-MB after noncardiac surgery that included 14 studies enrolling 3318 patients demonstrated that elevated troponin after surgery was an independent predictor of mortality both in the hospital and at 1-year follow-up. Markedly elevated troponins are associated with increased mortality compared with minimal troponin elevation, even though the latter still indicates a postoperative MI. 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. (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. (Level of Evidence: B)

CKD is a major risk factor for poor outcomes in patients with NSTEMI. 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% (8152 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). 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 ≥1.5 mg/dL. 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 m², the adjusted HR was 1.70 compared with patients with a GFR of 60.0 mL per minute/1.73 m² to 74.9 mL per minute/1.73 m² 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). There is also less evidence-based medical therapy and revascularization data in patients with CKD because of the risk of 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 and adequate hydration.

A recent meta-analysis of 5 RCTs evaluated 1453 patients with NSTE-ACS and CKD, all with GFR <60 mL per minute/1.73 m². 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.

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. 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. Hyporesponsiveness to thienopyridines is associated with increased adverse cardiovascular outcomes, including cardiovascular mortality, and higher dosing regimens of clopidogrel do not appear to further suppress adenosine diphosphate-induced platelet aggregation.

Although prasugrel may be more efficient than doubling the dose of clopidogrel in achieving adequate platelet inhibition, 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. 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. 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 benefit141,345,346 and the possibility of harm.40 (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.108,672,680,681 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 complications672,673 (Section 7.8) and renal failure. A risk score has been developed to help 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-analysis366 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 strategy340 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-analysis694 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 perioperative mortality, HF, bleeding, MI, and renal failure.680,695,696 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 metaanalysis 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.516

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)
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.\(^{522,697,698}\) \textit{(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.\(^{699-703}\) \textit{(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.\(^{709}\) 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 CAGB. 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.\(^{709}\) 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.\(^{725}\) 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.\(^{599-700}\) 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\(^{599}\) 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 epifibatide 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.\(^{728-731,735-737}\) 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 × 10\(^9\)/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 (eg, 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 myocardyocyte 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.48,112,744-746 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 alone753-757 or in combination with long-acting nitrates755,758 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 modification762,763 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

††Provocative testing during invasive coronary angiography (eg, 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.
Nonpharmacological provocative tests, such as cold pressor and hyperventilation, have been used diagnostically; potent vasoconstrictors (eg, acetylcholine) may be useful when non-invasive assessment is uninformative. Smoking, which exacerbates coronary vasospasm, should be proscribed, and CCBs are first-line therapies; long-acting nitrates are also effective when combined with CCBs. Statins improve endothelium-dependent vasodilation and can be useful in vasospastic angina. Magnesium supplementation and alpha-receptor blockers may be effective and can be added.

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. (Level of Evidence: B)

ACS associated with angiographically normal or nonobstructive (<50% stenosis) coronary arteries (also referred to as syndrome X) may be related to coronary endothelial dysfunction; plaque rupture that may be evident only with intracoronary ultrasound, coronary vasospasm, and coronary artery dissection. Myocarditis may present with electrocardiographic and biomarker findings similar to ACS and can be distinguished by magnetic resonance imaging. 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. 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, and chest pain is typical or atypical. In the absence of a culprit coronary lesion, prognosis of coronary endothelial dysfunction and/or occult plaque rupture is favorable.

Risk factor reduction and medical therapy with nitrates, beta blockers, and CCBs alone or in combination are considered for endothelial dysfunction. High doses of arginine have also been given. 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. However, estrogen is not recommended because of its demonstrated increase in cardiovascular and other risks.

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, but high rates of stenting complications are reported.

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. (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. There is no obstructive CAD, and the distribution of electrocardiographic changes and LV wall motion abnormalities usually includes >1 coronary artery territory. Cardiac troponin elevations are usually modest. The majority of cases occur in postmenopausal women, and presentation is typically precipitated by emotional or physical stress. Imaging by echocardiography, ventriculography, or magnetic resonance imaging 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, and right ventricular involvement is common. In the vast majority of patients, electrocardiographic and LV wall motion abnormalities normalize within 1 to 4 weeks, and recurrences are uncommon. The pathogenesis has been attributed to excess catecholamine release, coronary spasm, or small coronary vessel hypoperfusion.

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. If shock is present, IABP can be used. Prophylactic anticoagulation should be considered to prevent or treat LV thrombus.
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.809 In the SYNERGY trial of 9837 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/topiramate810 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,815 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.813,820,822 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,812 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.

Presidents and Staff
American College of Cardiology
Patrick O’Gara, MD, FACC, President
Shalom Jacobovitz, Chief Executive Officer
William J. Oetgen, MD, MBA, FACC, Executive Vice President, Science, Education, and Quality
Amelia Scholtz, PhD, Publications Manager, Clinical Policy and Pathways

American College of Cardiology/American Heart Association
Lisa Bradfield, CAE, Director, Science and Clinical Policy
Emily Cottrell, MA, Quality Assurance Specialist, Science and Clinical Policy
Alexa Papailia, Specialist, Science and Clinical Policy

American Heart Association
Elliott Antman, MD, FAHA, President
Nancy Brown, Chief Executive Officer
Rose Marie Robertson, MD, FAHA, Chief Science Officer
Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations
Marco Di Buono, PhD, Vice President, Science, Research, and Professional Education, Office of Science Operations
Jody Hundley, Production Manager, Scientific Publications, Office of Science Operations

References


52. Slater DK, Hlatky MA, Mark DB, et al. Outcome in suspected acute myocardial infarction with normal or minimally abnormal admission electrocardiographic findings. Am J Cardiol. 1987;60:766–70.


125. Diercks DB, Roe MT, Mulgund J, et al. The obesity paradox in non-ST-segment elevation acute coronary syndromes: results from the Can Rapid


155. Takakwa KM, Ou FS, Peterson ED, et al. The usage patterns of cardiac bedside markers employing point-of-care testing for troponin in non-ST-segment elevation acute coronary syndrome: results from CRUSADE.


Amsterdam et al. 2014 AHA/ACC NSTE-ACS Guideline e403


51. Deleted in press.


468. Deleted in press.


877. Agostini P, Biondi-Zoccai GG, de Benedictis ML, et al. Radial versus femoral approach for percutaneous coronary diagnostic and interven-


881. Kerur N, Hall RJ, Malik IS, et al. Randomized comparison of percu-

882. Feit F, Manoukian SV, Ebrahimi R, et al. Safety and efficacy of bivalir-


885. Kleinman NS, Anderson HV, Rogers WJ, et al. Comparison of outcome of patients with unstable angina and non-Q-wave acute myocardial infarction


| Key Words: AHA Scientific Statements | acute coronary syndrome | angina, unstable | antiplatelet agents | coronary artery bypass graft | electrocardiography | ischemia | myocardial infarction | percutaneous coronary intervention | troponin |
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

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
<th>Voting Recusals by Section*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezra A. Amsterdam</td>
<td>University of California (Davis) Medical Center, Division of Cardiology—Professor</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nanette K. Wenger</td>
<td>Emory University, School of Medicine—Professor of Medicine (Cardiology)</td>
<td>• Abbott</td>
<td>None</td>
<td>None</td>
<td>• Abbott†</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amgen</td>
<td>None</td>
<td>None</td>
<td>• Eli Lilly†</td>
<td>None</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• AstraZeneca</td>
<td>None</td>
<td>None</td>
<td>• Gilead Sciences†</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gilead Sciences†</td>
<td>None</td>
<td>None</td>
<td>• Janssen Pharmaceuticals</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Medtronic</td>
<td>None</td>
<td>None</td>
<td>• Merck</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pfizer</td>
<td>None</td>
<td>None</td>
<td>• Pfizer†</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ralph G. Brindis</td>
<td>University of California, San Francisco Department of Medicine and the Phillip R. Lee Institute for Health Policy Studies—Clinical Professor of Medicine</td>
<td>None</td>
<td>• Volcano</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Donald E. Casey, Jr</td>
<td>Atlantic Health—Vice President of Health and Chief Medical Officer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Theodore G. Ganiats</td>
<td>University of California, San Diego School of Medicine—Executive Director of Health Services Research Center</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>David R. Holmes, Jr</td>
<td>Mayo Clinic—Consultant, Cardiovascular Diseases</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Allan S. Jaffe</td>
<td>Mayo Clinic, Cardiovascular Division—Professor of Medicine</td>
<td>• Abbott</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alere</td>
<td>None</td>
<td>None</td>
<td>• Beckman-Coulter</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amgen</td>
<td>None</td>
<td>None</td>
<td>• Critical Diagnostics</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Beckman-Coulter</td>
<td>None</td>
<td>None</td>
<td>• ET Healthcare</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gilead Sciences†</td>
<td>None</td>
<td>None</td>
<td>• Ortho Clinical Diagnostic</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiometer</td>
<td>None</td>
<td>None</td>
<td>• Rotech‡</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Thermo-Fisher‡</td>
<td>None</td>
<td>None</td>
<td>• Trinity</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Hani Jneid</td>
<td>Baylor College of Medicine—The Michael E. DeBakey VA Medical Center—Assistant Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued)
### Appendix 1. Continued

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
<th>Voting Recusals by Section*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosemary F. Kelly</td>
<td>University of Minnesota—Professor of Surgery; VA Medical Center—Chief, Cardiothoracic Surgery</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Michael C. Kontos</td>
<td>Virginia Commonwealth University, Pauley Heart Center—Medical Director, Coronary Intensive Care Unit, and Associate Professor, Internal Medicine</td>
<td>• Astellas</td>
<td>• Astellas</td>
<td>None</td>
<td>None</td>
<td>• Astellas</td>
<td>None</td>
<td>All sections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• General Electric</td>
<td></td>
<td></td>
<td></td>
<td>• Eli Lilly‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ikaria</td>
<td></td>
<td></td>
<td></td>
<td>• Merck‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prevencio</td>
<td></td>
<td></td>
<td></td>
<td>• Novartis‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sanofi-aventis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Wellpoint/Anthem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glenn N. Levine</td>
<td>Baylor College of Medicine—Professor of Medicine; Director, Cardiac Care Unit</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Philip R. Liebson</td>
<td>Rush University Medical Center—McMullan-Eybel Chair of Excellence in Clinical Cardiology and Professor of Medicine and Preventive Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Debabrata Mukherjee</td>
<td>Texas Tech University Health Sciences Center—Chief, Cardiovascular Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Eric D. Peterson</td>
<td>Duke University Medical Center—Fred Cobb, MD, Distinguished Professor of Medicine; Duke Clinical Research Institute—Director</td>
<td>• Boehringer Ingelheim</td>
<td>• Eli Lilly†</td>
<td>None</td>
<td>None</td>
<td>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.</td>
<td>None</td>
<td>All sections</td>
</tr>
</tbody>
</table>
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 \( \geq 5\% \) of the voting stock or share of the business entity, or ownership of \( \geq $10,000 \) 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.

According to the ACC/AHA, a person has a relevant relationship IF: a) the relationship or interest relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the company/entity (with whom the relationship exists) makes a drug, drug class, or device addressed in the document; or c) the person or a member of the person’s household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.

*Writing members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply. Section numbers pertain to those in the full-text CPG.

\( \dagger \)Significant relationship.

\( \ddagger \)No financial benefit.

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.
### Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
</table>
| Deepak L. Bhatt | Official Reviewer—AHA | VA Boston Healthcare System—Professor of Medicine, Harvard Medical School; Chief of Cardiology | • BMS/Pfizer  
• DCRI (BMS/Pfizer)  
• DCRI (Eli Lilly)  
• Eli Lilly | None | None | • AstraZeneca*  
• Bristol-Myers Squibb*  
• Ethicon*  
• The Medicines Company  
• Medtronic*  
• Sanofi-aventis*  
• Takeda† | None |
| John E. Brush, Jr | Official Reviewer—ACC Board of Trustees | Eastern Virginia Medical School—Professor of Medicine, Chief of Cardiology | None | None | None | None | None |
| E. Magnus Ohman | Official Reviewer—ACC/AHA Task Force on Practice Guidelines | Duke Medicine—Professor of Medicine | • AstraZeneca  
• Bristol-Myers Squibb  
• Gilead*  
• Janssen Pharmaceuticals*  
• The Medicines Company  
• Merck  
• Pozen  
• Roche  
• Sanofi-aventis | None | None | • Daiichi-Sankyo*  
• Eli Lilly*  
• Gilead* | None |
| John F. Robb | Official Reviewer—ACC Board of Governors | Dartmouth-Hitchcock Medical Center—Director, Interventional Cardiology and Cardiac Catheterization Laboratories | None | None | None | None | • Defendant, adverse drug reaction, 2012 |
| Sarah A. Spinier | Official Reviewer—AHA | Philadelphia College of Pharmacy, University of the Sciences in Philadelphia—Professor of Clinical Pharmacy | • Bristol-Myers Squibb  
• Daiichi-Sankyo  
• Janssen Pharmaceuticals  
• Merck | None | None | None | None | • Plaintiff, clopidogrel, 2013 |
| Gorav Ailawadi | Organizational Reviewer—STS | University of Virginia Health System—Thoracic and Cardiovascular Surgery | • Abbott  
• Atricure | None | None | None | None |
| Srijani S. Naidu | Organizational Reviewer—SCAI | Winthrop University Hospital—Director, Cardiac Catheterization Laboratory | None | None | None | None | None |
| Robert L. Rich, Jr | Organizational Reviewer—AAFP | Bladen Medical Associates—Family Physician | None | None | None | None | None |
| Mouaz H. Al-Mallah | Content Reviewer—ACC Prevention of Cardiovascular Disease Committee | King Abdul-Aziz Cardiac Center—Associate Professor of Medicine | None | None | None | None | None |

(Continued)
### Appendix 2. Continued

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>John A. Ambrose</td>
<td>Content Reviewer</td>
<td>University of California San Francisco Fresno Department of Medicine--Professor of Medicine; Chief of Cardiology; Program Director, Cardiology Fellowship</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Giuseppe Ambrosio</td>
<td>Content Reviewer-ACC Prevention of Cardiovascular Disease Committee</td>
<td>Hospital of University of Perugia School of Medicine--Medical Director, Division of Cardiology</td>
<td>Bayer*</td>
<td>Merck Schering-Plough*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>H. Vernon Anderson</td>
<td>Content Reviewer</td>
<td>University of Texas--Professor of Medicine, Cardiology Division</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Eli Lilly</td>
<td>None</td>
</tr>
<tr>
<td>Jeffrey L. Anderson</td>
<td>Content Reviewer-ACC/ AHA Task Force on Practice Guidelines</td>
<td>Intermountain Medical Center--Associate Chief of Cardiology</td>
<td>Sanofi-aventis</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>GlaxoSmithKline</td>
<td>None</td>
</tr>
<tr>
<td>Fred S. Apple</td>
<td>Content Reviewer</td>
<td>University of Minnesota School of Medicine, Hennepin County Medical Center--Professor, Laboratory Medicine and Pathology</td>
<td>Abbott Diagnostics</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Abbott Diagnostics-PI†</td>
<td>None</td>
</tr>
<tr>
<td>Emmanouil S. Brilakis</td>
<td>Content Reviewer ACC Interventional Section Leadership Council</td>
<td>UT Southwestern Medical School--Director, Cardiac Catheterization Laboratory, VA North Texas Healthcare System</td>
<td>Bridgepoint Medical/Boston Scientific*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Abbott Vascular</td>
<td>None</td>
</tr>
<tr>
<td>Matthew J. Budoff</td>
<td>Content Reviewer ACC Cardiovascular Imaging Section Leadership Council</td>
<td>Los Angeles Biomedical Research Institute--Program Director, Division of Cardiology and Professor of Medicine</td>
<td>None</td>
<td>AstraZeneca†</td>
<td>None</td>
<td>None</td>
<td>General Electric*</td>
<td>None</td>
</tr>
<tr>
<td>James A. Burke</td>
<td>Content Reviewer ACC Interventional Section Leadership Council</td>
<td>Lehigh Valley Health Network--Interventional Cardiologist</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Plaintiff, cardiac treatment, 2013</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
</table>
| Robert H. Christenson | Content Reviewer—AACC | University of Maryland School of Medicine—Professor of Pathology; Professor of Medical and Research Technology; Director, Rapid Response Laboratory | • BG Medicine  
• Critical Diagnostics  
• Siemens Medical Diagnostics | None             | None                                           | • The Medicines Company | • AACC (President)^†  
• Roche Diagnostics (University of Maryland School of Medicine)* | None            |
| Joaquin E. Cigarroa | Content Reviewer—ACC Interventional Section Leadership Council | Oregon Health and Science University—Associate Professor of Medicine | None                                                                 | None            | None                                           | None | • Catheterization and Cardiovascular Intervention (Editorial Board)^† | None            |
| Marco A. Costa | Content Reviewer—ACC Cardiovascular Imaging Section Leadership Council | University Hospital for Cleveland—Cardiologist | • Abbott Vascular*  
• Boston Scientific  
• Medtronic | None            | None                                           | • Abbott Vascular*  
• Boston Scientific*  
• Cordis*  
• IDEV Technology^†  
• The Medicines Company  
• Medtronic*  
• Micell*  
• OrbusNeich | None            |
| Prakash C. Deedwania | Content Reviewer—ACC Prevention of Cardiovascular Disease Committee | University of California San Francisco—Chief of Cardiology | • Amgen  
• Pfizer | None            | None                                           | • Takeda Pharmaceuticals | None            |
| James A. de Lemos | Content Reviewer | UT Southwestern Medical School—Associate Professor of Medicine; Director, Coronary Care Unit and Cardiology Fellowship | • Diadexus  
• Janssen Pharmaceuticals | None            | None                                           | • Abbott Diagnostics^†  
• Daiichi-Sankyo^† | None            |
| Burl R. Don | Content Reviewer | University of California Davis—Professor of Medicine; Director of Clinical Nephrology | None                                                                 | None            | None                                           | None | None            |
| Lee A. Fleisher | Content Reviewer | University of Pennsylvania Department of Anesthesiology—Professor of Anesthesiology | None                                                                 | None            | None                                           | None | None            |
| Mary G. George | Content Reviewer—HHS | Centers for Disease Control and Prevention—Senior Medical Officer, Division for Heart Disease and Stroke Prevention | None                                                                 | None            | None                                           | None | None            |
| Linda D. Gillam | Content Reviewer—ACC Cardiovascular Imaging Section Leadership Council | Morristown Medical Center—Professor of Cardiology; Vice Chair, Cardiovascular Medicine | None                                                                 | None            | None                                           | None | None            |
Appendix 2. Continued

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert A. Guyton</td>
<td>Content Reviewer–ACC/AHA Task Force on Practice Guidelines</td>
<td>Emory Clinic–Professor and Chief, Division of Cardiothoracic Surgery</td>
<td>• Medtronic</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Joerg Herrmann</td>
<td>Content Reviewer–ACC Interventional Section Leadership Council</td>
<td>Mayo Medical School–Internal Medicine and Cardiovascular Disease</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Judith S. Hochman</td>
<td>Content Reviewer–ACC/AHA Task Force on Practice Guidelines</td>
<td>New York University School of Medicine, Division of Cardiology–Clinical Chief of Cardiology</td>
<td>• GlaxoSmithKline • Janssen Pharmaceuticals</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Yuling Hong</td>
<td>Content Reviewer–HHS</td>
<td>Centers for Disease Control and Prevention–Associate Director</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lloyd W. Klein</td>
<td>Content Reviewer–ACC Interventional Section Leadership Council</td>
<td>Rush Medical College–Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Frederick G. Kushner</td>
<td>Content Reviewer</td>
<td>Tulane University School of Medicine–Clinical Professor of Medicine; Heart Clinic of Louisiana–Medical Director</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ehtisham Mahmud</td>
<td>Content Reviewer–ACC Interventional Section Leadership Council</td>
<td>University of California, San Diego–Professor of Medicine/Cardiology, Chief of Cardiovascular Medicine; Director, Interventional Cardiology and Cardiovascular Catheterization Laboratory</td>
<td>• Abiomed • Cordis • Eli Lilly* • Gilead • Johnson &amp; Johnson • Medtronic</td>
<td>• Eli Lilly* • Medtronic</td>
<td>None</td>
<td>• Abbott Vascular* • Accutrimics* • Merck Schering-Plough • Boston Scientific* • Gilead* • The Medicines Company • Sanofi-aventis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carlos Martínez-Sánchez</td>
<td>Content Reviewer–AIG</td>
<td>Cardiology Society of Mexico–President</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>L. Kristen Newby</td>
<td>Content Reviewer</td>
<td>Duke University Medical Center–Associate Professor of Clinical Medicine</td>
<td>• Johnson &amp; Johnson</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Patrick T. O’Gara</td>
<td>Content Reviewer</td>
<td>Brigham and Women’s Hospital–Professor of Medicine, Harvard Medical School; Director, Clinical Cardiology</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued)
### Appendix 2. Continued

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narith Ou</td>
<td>Content Reviewer</td>
<td>Mayo Clinic–Pharmacotherapy Coordinator, Pharmacy Services</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Gurusher S. Panjrath</td>
<td>Content Reviewer–ACC</td>
<td>George Washington Medical Faculty Associates–Assistant Professor of Medicine; Director of Heart Failure and Mechanical Support Program</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rajan Patel</td>
<td>Content Reviewer–ACC</td>
<td>Ochsner Clinic Foundation–Interventional Cardiologist</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Carl J. Pepine</td>
<td>Content Reviewer</td>
<td>Shands Hospital at University of Florida–Professor and Chief, Division of Cardiovascular Medicine</td>
<td>None</td>
<td>None</td>
<td>AstraZeneca*</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Sunil V. Rao</td>
<td>Content Reviewer–ACC</td>
<td>Duke University Medical Center–Associate Professor of Medicine</td>
<td>AstraZeneca</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pasala S. Ravichandran</td>
<td>Content Reviewer–ACC</td>
<td>Oregon Health and Science University–Associate Professor</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Michael W. Rich</td>
<td>Content Reviewer</td>
<td>Washington University School of Medicine–Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Frank W. Sellke</td>
<td>Content Reviewer–ACC</td>
<td>Brown Medical School, Rhode Island Hospital–Professor; Chief of Cardiothoracic Surgery</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Alan Wu</td>
<td>Content Reviewer–AACC</td>
<td>San Francisco General Hospital and Trauma Center–Chief, Clinical Chemistry Laboratory</td>
<td>Abbott</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant to this document. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

According to the ACC/AHA, a person has a **relevant** relationship IF: a) the relationship or interest relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the company/entity (with whom the relationship exists) makes a drug, drug class, or device addressed in the document, or makes a competing drug or device addressed in the document; or c) the person or a member of the person’s household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.

*Significant relationship.
†No financial benefit.

AAAHC indicates Accreditation Association for Ambulatory Health Care; AACC, American Association for Clinical Chemistry; AAFP, American Academy of Family Physicians; AHA, American Heart Association; AIG, Association of International Governors; BMS, Bristol-Myers Squibb; DCRI, Duke Clinical Research Institute; DSMB, data safety monitoring board; HHS, Health and Human Services; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; TIMI, Thrombolysis In Myocardial Infarction; and VA, Veterans Affairs.
### Appendix 3. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CK-MB</td>
<td>creatine kinase myocardial isoenzyme</td>
</tr>
<tr>
<td>COX</td>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>CPG</td>
<td>clinical practice guideline</td>
</tr>
<tr>
<td>CrCl</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DAPT</td>
<td>dual antiplatelet therapy</td>
</tr>
<tr>
<td>DES</td>
<td>drug-eluting stent</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ED</td>
<td>emergency department</td>
</tr>
<tr>
<td>GDMT</td>
<td>guideline-directed medical therapy</td>
</tr>
<tr>
<td>GP</td>
<td>glycoprotein</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GWC</td>
<td>guideline writing committee</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>IABP</td>
<td>intra-aortic balloon pump</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>LMWH</td>
<td>low-molecular-weight heparin</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>MACE</td>
<td>major adverse cardiac event</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MVO₂</td>
<td>myocardial oxygen consumption</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>non-ST-elevation acute coronary syndromes</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>non-ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>UA</td>
<td>unstable angina</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>VF</td>
<td>ventricular fibrillation</td>
</tr>
<tr>
<td>VT</td>
<td>ventricular tachycardia</td>
</tr>
</tbody>
</table>
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 embolus 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 MVO₂, eg, 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) angiographically 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 is required.

Modified from Thygesen et al.21

Table B. Pharmacological Therapy in Older Patients With NSTE-ACS

<table>
<thead>
<tr>
<th>Age-Related Pharmacological Change</th>
<th>Clinical Effect</th>
<th>Dose-Adjustment Recommendations</th>
<th>Additional Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>General principles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table B. Continued

<table>
<thead>
<tr>
<th>Pharmacological Change</th>
<th>Clinical Effect</th>
<th>Dose-Adjustment Recommendations</th>
<th>Additional Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCBs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DHPs (amlodipine; nifedipine)</td>
<td>Lipophilic; hepatic and overall clearance;↑fat storage;↑baroreceptor response to↑BP</td>
<td>↓BP more than non-DHP and↑age; edema hypotension, bradycardia</td>
<td>Initiate low dose, titrate cautiously</td>
</tr>
<tr>
<td>• Non-DHP (verapamil; diltiazem)</td>
<td>Hepatic and overall clearance; less PR prolongation than DHP and↑age; negative inotropy;↑SA node sensitivity and↓HR than DHP and with↑age;↑AV conduction with↑age;↑baroreceptor response to↑BP</td>
<td>↓BP more with↑age; edema;↑heart block; hypotension;↑bradycardia and bradyarrhythmias with↑age</td>
<td>Initiate low dose, titrate cautiously</td>
</tr>
<tr>
<td>Diuretics</td>
<td>↓Diuretic/natriuretic response;↑EC space,↑drug concentration if↓GFR;↑baroreceptor response to volume shifts</td>
<td>↓Sensitivity;↑hypotension; risk hypokalemia/hypomagnesemia/hyponatremia;↓diuretic effect with↓GFR;↑risk hypovolemia-↑thirst</td>
<td>May need↓doses if↓GFR; may need↓dose if cotreating withNSAIDs</td>
</tr>
<tr>
<td><strong>Heparins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• UFH</td>
<td>Hydrophilic;↑concentration,especially if↓lean body mass or↑plasma proteins;↑levels with↑age</td>
<td>↑Bleeding risk with age; more potent anticoagulation per dose with↑age; weight-based dosing but with precautions for shift in body composition</td>
<td>Weight-based 60 U/kg loading dose +12 U/kg/h INF. Suggested max loading dose: 400 U and 900 U/h INF or 5000 U loading dose/1000 U/h if pt weight &gt;100 kg</td>
</tr>
<tr>
<td>• LMWH</td>
<td>Cleared renally; more predictable dose response than UFH; not dependent on plasma protein levels;↑levels with↑lean body mass;↑effect with↑age</td>
<td>↑Bleeding risk with age and weight and renally dosed</td>
<td>Enoxaparin: Weight-based 1 mg/kg SC q 12 h; CrCl* &lt;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</td>
</tr>
<tr>
<td><strong>Direct Thrombin Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bivalirudin</td>
<td>Cleared renally; more predictable dose response; not dependent on plasma protein levels</td>
<td>Significantly less bleeding in older pts, even with renal dysfunction vs. UFH + GP lib/illa with similar efficacy</td>
<td>CrCl &lt;30 mL/min: 1 mg/kg/h; CrCl: 30 to 60 mL/min—less bleeding than UFH</td>
</tr>
<tr>
<td>• Fondaparinux</td>
<td>Cleared renally</td>
<td>Renal/weight adjust; less bleeding but similar efficacy vs. enoxaparin in older pts with NSTE-ACS, even with mild to moderate renal dysfunction</td>
<td>Renal adjustment: CrCl &lt;30—contraindicated; CrCl 30 to 60—preferred over enoxaparin</td>
</tr>
<tr>
<td><strong>P2Y12 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clopidogrel</td>
<td>Lipophilic;↑HPR;↑metabolism;↑fat distribution;↑to steady state (↑fat distribution/T½)</td>
<td>↓Antiplatelet effect in some older pts</td>
<td>Maintenance: 75 mg (no↑response to higher dose)</td>
</tr>
<tr>
<td>• Prasugrel</td>
<td>↑19% Active metabolite &gt;75 y of age</td>
<td>↑Bleeding risk</td>
<td>Avoid in pts ≥75 y of age or if weight ≤60 kg; 10 mg in very high-risk pts</td>
</tr>
<tr>
<td>• Ticagrelor</td>
<td>None known</td>
<td>N/A</td>
<td>None</td>
</tr>
<tr>
<td><strong>GP IIb/IIIa Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abciximab</td>
<td>None known</td>
<td>•↑Bleeding with↑age</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
• 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 ↑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

<table>
<thead>
<tr>
<th>Age-Related Change</th>
<th>Clinical Alteration</th>
<th>Clinical Impact in NSTE-ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>✨Central arterial stiffness</td>
<td>↑SBP/↓DBP; ↑LVH; ↓diastolic function; ↓coronary perfusion pressure; ↓ischemia/infarct threshold for tachycardia/hypertension with and without coronary obstructive disease; ↑PA pressure</td>
<td>✨Risk end-organ damage (cerebrovascular accident, AKI); ✨BP liability; ↑reinfarction/ischemia; orthostatic hypotension; ↑HF; ↑pulmonary edema</td>
</tr>
<tr>
<td>LV diastolic function</td>
<td>↑LA size; ↓early passive LV filling; ↑late LV filling and ↑LV EDP; ↑PA pressure</td>
<td>✨Risk AF; (↑pulmonary edema/↑CO), ↑DOE; ↑pulmonary edema with ↑HR/↑BP</td>
</tr>
<tr>
<td>✨Response to beta-adrenergic</td>
<td>↓HR/↓inotropic responsiveness to stress; resting systolic LV function unchanged with age</td>
<td>Hypotension, HF, ↓HR response</td>
</tr>
<tr>
<td>stimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction system changes</td>
<td>↓Sinus node cells; ↓AV conduction; ↑LBBB; and ↑RBBB</td>
<td>Difficult to interpret electrocardiographic MI/ischemia; ↑heart block; SSS; ↑VT; ↑sensitivity to conduction system drugs</td>
</tr>
<tr>
<td>✨Volume regulating hormones</td>
<td>↓Na, K, and water regulation–BP lability</td>
<td>Altered electrolytes, ↑sensitivity to fluid therapy/diuretics</td>
</tr>
<tr>
<td>Renal changes</td>
<td>↓GFR (0.8 mL/min/y), ↓Na/K clearance, normal serum creatinine despite moderate to severe CKD, altered drug clearance; ↓urine concentrating ability</td>
<td>CrCl or eGFR must be calculated for drug dosing, ↑sensitivity to contrast nephropathy, ↑risk AKI</td>
</tr>
<tr>
<td>Fat-muscle redistribution</td>
<td>↑Third spacing of fluid, may alter drug storage; ↓VO2max</td>
<td>May alter fluid/drug dosing, decreased CO; DOE; early fatigability</td>
</tr>
<tr>
<td>✨Baroreceptor sensitivity</td>
<td>↑BP lability</td>
<td>Orthostatic hypotension, fall risk</td>
</tr>
<tr>
<td>Clotting factor/platelet function</td>
<td>↑Bleeding and clotting risk, ↑sensitivity to anticoagulants/antithrombins</td>
<td>↑Risk cerebrovascular accident/reinfarction/recurrent ischemia, bleeding, thrombosis, PE, DVT, may alter drug dosing/sensitivity; ↑tient thrombosis</td>
</tr>
<tr>
<td>hemostasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AKI, acute kidney injury; AV, atrioventricular; BP, blood pressure; CKD, chronic kidney disease; CO, cardiac output; CrCI, 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; LHV, 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 VO2max, maximum oxygen consumption.

### Table D. FREEDOM Trial: Key Outcomes at 2 Years and 5 Years After Randomization

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2y</th>
<th>5y</th>
<th>PCI</th>
<th>CABG</th>
<th>PCI</th>
<th>CABG</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite†</td>
<td>121 (13.0)</td>
<td>108 (11.9)</td>
<td>200</td>
<td>(26.6)</td>
<td>146</td>
<td>(18.7)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>62 (6.7)</td>
<td>57 (6.3)</td>
<td>114</td>
<td>(16.3)</td>
<td>83</td>
<td>(10.9)</td>
<td>0.049</td>
</tr>
<tr>
<td>MI</td>
<td>62 (6.7)</td>
<td>42 (4.7)</td>
<td>98</td>
<td>(13.9)</td>
<td>48</td>
<td>(6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>14 (1.5)</td>
<td>24 (2.7)</td>
<td>20</td>
<td>(2.4)</td>
<td>37</td>
<td>(5.2)</td>
<td>0.03§</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>9 (0.9)</td>
<td>12 (1.3)</td>
<td>73</td>
<td>(10.9)</td>
<td>52</td>
<td>(6.8)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*P values were calculated with the log-rank test on the basis of all available follow-up data (ie, >5 y).
†The primary composite outcome was rate of death from any cause, MI, or stroke.
‡P=.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 1712 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

_Circulation._ 2014;130:e344-e426; originally published online September 23, 2014;
doi: 10.1161/CIR.0000000000000134
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/130/25/e344

An erratum has been published regarding this article. Please see the attached page for:
/content/130/25/e433.full.pdf

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2014/09/23/CIR.0000000000000134.DC1
http://circ.ahajournals.org/content/suppl/2014/09/23/CIR.0000000000000134.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
Correction


1. On the title page, the Society for Cardiovascular Angiography and Interventions has been added to the collaborating organizations line. It now reads, “Developed in Collaboration With the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons.”

2. On page e356, in Figure 2A, the “GRACE Risk Model Nomogram,” the footnote read, “To convert serum creatine level to micromoles per liter, multiply by 88.4.” It now reads, “To convert serum creatinine level to micromoles per liter, multiply by 88.4.”

3. On page e363, in the second column, the Class I, Recommendation 3 paragraph read, “…hyperkalemia (K >5.0 mEq/L)....” It now reads “…or hyperkalemia (K+ >5.0 mEq/L)....”

4. On page e364, in the first column, in the Class I, Recommendation 1 paragraph, the maintenance dose for aspirin has been changed. Additionally, the references shown below, numbered 293 and 391, have been added to the text. The recommendation read, “…and a maintenance dose of aspirin (81 mg/d to 162 mg/d) should be continued indefinitely.288–290” It now reads, “…and a maintenance dose of aspirin (81 mg/d to 325 mg/d) should be continued indefinitely.288–290,293,391”


5. On page e364, in the second column, the fourth paragraph, the third sentence, the maintenance dose for aspirin has been changed and the reference shown below, numbered 391, has been added to the text. The third sentence read, “The subsequent maintenance dose is 81 mg per day to 162 mg per day; patients treated with ticagrelor should receive only 81 mg per day.290” It now reads, “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.291 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 formulations may include 75 mg and 100 mg.”


6. On page e365, in Table 7, the fourth row “Aspirin maintenance dose….,” the second column “Dosing....,” the text regarding aspirin maintenance dosing has been modified. The table entry now reads, “81 mg/d-325 mg/d.” The asterisk inserted after “325 mg/d,” refers to text added to the Table 7 footnote. The footnote now reads, “*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.” The references shown below, numbered 293 and 391, were added to the fifth column, “References.”


The fourth row originally read,

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Dosing and Special Considerations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>• Aspirin maintenance dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>continued indefinitely</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81 mg/d to 162 mg/d</td>
<td>I</td>
<td>A</td>
<td>(280–282)</td>
</tr>
</tbody>
</table>

The corrected row now reads,

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Dosing and Special Considerations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>• Aspirin maintenance dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>continued indefinitely</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81 mg/d to 325 mg/d*</td>
<td>I</td>
<td>A</td>
<td>(288–290,293,391)</td>
</tr>
</tbody>
</table>

7. On page e365, in Table 7, in the thirteenth row “SC enoxaparin for duration…,” in the second column “Dosing…,” the second bullet read, “Initial IV loading dose 30 mg.” It now reads, “Initial 30 mg IV loading dose in selected patients.”

8. On page e367, in the first column, the Class I, Recommendation 1 paragraph, the first sentence in the first bullet read, “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 is 30 mg.133,136,309” It now reads, “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”

9. On page e367, in the first column, the penultimate paragraph, the fourth sentence read, “The dose of enoxaparin is 1 mg/kg SC every 12 hours for NSTE-ACS; an initial intravenous loading dose is 30 mg.” It now reads, “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.”

10. On page e378, in the first column, the second paragraph, in the Class IIa, Recommendation 2, the first sentence read, “It is reasonable to choose ticagrelor over clopidogrel for maintenance P2Y12 treatment in patients with NSTE-ACS treated with an early invasive strategy and/or PCI.293,294” It now reads, “It is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy.293,294”

These corrections have been made to the print version and to the current online version of the article, which is available at [http://circ.ahajournals.org/content/130/25/e344](http://circ.ahajournals.org/content/130/25/e344).
## Author Relationships With Industry and Other Entities (Comprehensive)—2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes (July 2013)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezra A. Amsterdam (Chair)</td>
<td>University of California (Davis) Medical Center, Division of Cardiology—Professor</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• California CABG Project</td>
<td>• American Journal of Cardiology† • Clinical Cardiology† • 2010 School of Medicine Research Award* • ACC-NCDR ACTION Registry Subcommittee - Research and Publications</td>
<td>None</td>
</tr>
</tbody>
</table>
| 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  
• NHLBI*  
• Pfizer* | • ACC Extended Learning  
• CCCOA  
• Clinical Cardiology Review Editor  
• Society for Women’s Health Research† | None |
| 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 | • Ivivi Health Sciences  
• Volcano Corp. | None | None | | • ACC-NCDR (Senior Medical Officer, External Affairs)  
• DAPT trial (Advisory Board)†  
• California State Elective PCI Project (Advisory Board)†  
• C-PORT Elective RCT† (DSMB)  
• FDA Cardiovascular Device Panel†  
• State of California | None |
<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donald E. Casey, Jr</td>
<td>Atlantic Health—Vice President of Health and Chief Medical Officer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Theodore G. Ganiats</td>
<td>University of California, San Diego School of Medicine—Executive Director of Health Services Research Center</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>David R. Holmes, Jr</td>
<td>Mayo Clinic—Consultant, Cardiovascular Diseases</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Allan S. Jaffe</td>
<td>Mayo Clinic, Cardiovascular Division—Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hani Jneid</td>
<td>Baylor College of Medicine—The Michael E. DeBakey VA Medical Center—Assistant Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rosemary F. Kelly</td>
<td>University of Minnesota—Division</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Health Dept: STEMI/PCI Work Group† (DSMB) • State of California OSHPD† (DSMB)*

- AHRQ
- NIH (DSMB)
- Plaintiff, deep vein thrombosis, 2011
- Atriech†
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and Position</th>
<th>Sponsors</th>
<th>Mission Lifeline Scientific Committee†</th>
<th>AHA†</th>
<th>Astellas</th>
<th>Eli Lilly†</th>
<th>Merck †</th>
<th>Society of Chest Pain Centers†</th>
<th>NIH†</th>
<th>Novartis†</th>
<th>DCRI‡</th>
<th>Plaintiff, malpractice case with failure to treat properly, 2012</th>
</tr>
</thead>
</table>
| Michael C. Kontos          | Virginia Commonwealth University, Pauley Heart Center—Medical Director, Coronary Intensive Care Unit; Associate Professor, Internal Medicine | • Astellas  
• General Electric  
• Ikaria  
• Prevencio  
• Quest Diagnostics  
• Sanofi-aventis  
• Wellpoint/Anthem | None | None | None | None | None | None | None | None | None | None | None | None | None | None | None |
| Glenn N. Levine             | Baylor College of Medicine—Professor of Medicine; Director, Cardiac Care Unit            | None                                                                     | None | None | None | None | None | None | None | None | 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 | None | None | None | 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 | None | None | None | 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 | None | None | None | None | None | None | None | None | None | None | None | None | None | None | None | None |
| Marc S. Sabatine            | Brigham and Women's Hospital, Chairman—TIMI Study Group                                  | • Aegerion  
• Amgen  
• AstraZeneca* | None | None | None | None | None | None | None | None | None | None | None | None | None | None | None | None | None |
| Division of Cardiovascular Medicine; Harvard Medical School—Professor of Medicine | • Bristol-Myers Squibb  
• Canadian Cardiovascular Society  
• Creative Educational Concepts  
• Diason  
• GlaxoSmithKline  
• Health Sciences Media  
• Merck  
• Pfizer  
• Sanofi-aventis  
• Vertex  
• Vox Media  
• WebMD |  | • Bristol-Myers Squibb  
• BRAHMS  
• Critical Diagnostics  
• Daiichi-Sankyo  
• Eisai  
• Genzyme  
• GlaxoSmithKline  
• Intarcia  
• Nanosphere  
• NIH  
• Roche Diagnostics  
• Sanofi-aventis  
• Takeda  | • Daiichi-Sankyo  
• Gilead  
• GlaxoSmithKline  
• Johnson & Johnson  
• Merck  
• Muljibhai Patel Society for Research in Nepro-Urology  
• Proventys  
• Siemens  
• Singulex  |
| --- | --- | --- | --- | --- |
| 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  
• St Jude Medical  
• Maquet  
• Toshiba | None | None | • Amarin  
• Cordis  
• E-valve/Abbott Vascular  
• Gilead  
• St. Jude Medical  
• Maquet-Datascpe  
• Edwards Lifesciences | • Cordis  
• E-Valve  
• St. Jude  |
| Susan J. Zieman | National Institute on Aging/NIH, Geriatrics Branch, Division of Geriatrics and Clinical Gerontology—Medical Officer | None | None | None | None | • American Geriatrics Society†  
• AHA†  
• NIH  | None | None |
the person’s gross income for the previous year. Relationships that exist without financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx for definitions of disclosure categories or additional information about the ACC Disclosure Policy for Writing Committees.

*Significant relationship.
†No financial benefit.
‡DCRI has numerous grants and contracts sponsored by industry. These include the following: Aastrom Biosciences; Abbott; Abiomed; Acom Cardiovascular; Adolor Corp; Advanced Cardiovascular Systems; Advanced Stent Technologies; Adynxx; Ajinomoto; Allergan; Amgen; Alnylam Pharma; Alpharma; Amylin Pharmaceuticals; Anadys; Anesiva; Angel Medical Systems; ANGES MG; Angiomedtrix; APT Nidus Center; ASCA Biopharma; Astellas Pharma; Asklepios; AstraZeneca; Atritech; Attention Therapeutics; Aventis; Baxter; Bayer; Berlex; BG Medicine; Biogen; Biorex Therapeutics; Biomarker Factory; Biosite; Boehringer Ingelheim Biogen; Boston Scientific; Bristol-Myers Squibb; BMS Pfizer; Carbomed; CardioDx; CardioKinetix; Cardiovascular Systems; Cardiovax; Celsion Corp; Centocor; Cerexa; Chase Medical; Conatus Pharmaceuticals; Conor Medsystems; Cortez; Corgentech; CSL Behring; CV Therapeutics; Daiichi Pharmaceuticals; Daiichi-Sankyo; Daiichi-Sankyo/Lilly; Dai nippon; Datamscope; Dendreon; Dr. Reddy’s Laboratories; Eclipse Surgical Technologies; Edwards Lifesciences; Eisai; Endicor; EnteroMedics; Enzon Pharmaceuticals; Eli Lilly; Ethicon; Ev3; Evalve; F2G; Flow Cardia; Fox Hollow Pharmaceuticals; Fujisawa; Genetech; General Electric; General Electric Co.; General Electric Healthcare; General Electric Medical Systems; Genzyme Corp.; Genome Canada; Gilead Sciences; GlaxoSmithKline; Guidant Corp.; Heartscape Technologies; Hoffman-LaRoche; Hospira; Idera Pharmaceuticals; Ikaria; Immunex Pharmaceuticals; INFORMD; Inimex; Inspire Pharmaceuticals; Ischemix; Janssen; Johnson and Johnson; Jomed; Juventus Therapeutics; KAI Pharmaceuticals; King Pharmaceuticals; Kyowa Pharma; Luitpold; Mardil; MedImmune; Medscape; Medtronic Diabetes; Medtronic; Medtronic Vascular; Merck Group; MicroMed Technology; Millennium Pharmaceuticals; Mitsubishi Tanabe; Momenta; Nabtriva; Neuron Pharmaceuticals; NitroMed; NovaCardia Inc; Novartis AG Group; Novartis Pharmaceuticals; Oncura; Orexigen; Ortho-McNeil-Janssen; OSI Eyetech; OSI Pharmaceuticals; Pfizer; Pharmacies; Pharmasset; Pharmos; Phyxius Pharmaceuticals; Pharsight; Pluristem Therapeutics; Portola Pharmaceuticals; Proventis; Radiant; Regado Biosciences; Rengeneron Pharmaceuticals; Roche Molecular Systems; Roche Group; Roche Diagnostics; Salix Pharmaceuticals; Sanofi-Pasteur; Sanofi-aventis; Santaris Pharmaceuticals; Schering-Plough; Scios; Siemens; Southwest Oncology Group; Spectranetics; Summit; Sunovion Pharmaceuticals; TAP Pharmaceutical Products; Tengion; The Medicines Company; Theravance; TherOx; Tethys Bioscience; Therogen; Three Rivers Pharmaceuticals; The EMMES Corporation; UCB; Valensit; Valleylab; Vertex; Viacor; and Wyeth.

ACC indicates American College of Cardiology; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; CABG, coronary artery bypass graft; CCCOA, Council on Cardiovascular Care for Older Adults; C-PORT, Cardiovascular Patient Outcomes Research Team; DAPT, dual antiplatelet therapy; DCRI, Duke Clinical Research Institute; DSMB, data safety monitoring board; FDA, Food and Drug Administration; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; NIH, National Institutes of Health; NHLBI, National Heart, Lung, and Blood Institute; OSHPD, Office of Statewide Health Planning and Development; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; and VA, Veterans Affairs.
2014 NSTE-ACS Guideline Data Supplements

Data Supplement 1. Clinical Assessment and Initial Evaluation (Section 3.1) ................................................................. 3
Data Supplement 2. Risk Stratification (Section 3.3) ........................................................................................................... 7
Data Supplement 3. Cardiac Injury Markers and the Universal Definition of AMI (Section 3.4) .............................................. 8
Data Supplement 4. Cardiac Troponins (Section 3.4.3) ........................................................................................................ 10
Data Supplement 5. CK-MB, MB Isoforms and Myoglobin, Compared With Troponins (Section 3.4.4) ................................... 12
Data Supplement 6. Bedside Testing for Cardiac Biomarkers (Section 3.4.4) ................................................................. 14
Data Supplement 7. Summary Comparison of Injury Markers (Section 5.8.4) ...................................................................... 17
Data Supplement 8. Discharge from ED or Chest Pain Unit (Section 3.5.1) ................................................................. 20
Data Supplement 9. Nitrates (Section 4.1.2.1) .............................................................................................................. 22
Data Supplement 10. Analgesic Therapy (Section 4.1.2.2) ......................................................................................... 25
Data Supplement 11. Beta-Adrenergic Blockers (Section 4.1.2.3) .................................................................................... 26
Data Supplement 12. Calcium Channel Blockers (Section 4.1.2.4) ................................................................................... 29
Data Supplement 13. Other Anti-Ischemic Interventions (Ranolazine) (Section 4.1.2.5) .................................................... 32
Data Supplement 14. Inhibitors of the Renin-Angiotensin-Aldosterone System (Section 4.2) ........................................... 34
Data Supplement 15. Oral and Intravenous Antiplatelet Therapy in Patients With Likely or Definite NSTE-ACS Treated With Initial Invasive or Conservative Strategy (Section 4.3.1) .......................................................... 37
Data Supplement 16. Combined Oral Anticoagulant Therapy and Antiplatelet Therapy in Patients With Definite NSTE-ACS (Section 4.3.2) ........................................................................................................ 52
Data Supplement 17. Parenteral Anticoagulant and Fibrinolytic Therapy (Section 4.3.3) .................................................. 57
Data Supplement 18. Comparison of Early Invasive and Initial Conservative Strategy (Section 4.4.4) ............................ 74
Data Supplement 19. Comparison of Early Versus Delayed Angiography (Section 4.4.4.1) .................................................. 80
Data Supplement 20. Risk Stratification Before Discharge for Patients With Conservatively Treated NSTE-ACS (Section 4.5) ........................................................................................................ 81
Data Supplement 21. RCTs and Relevant Meta-Analyses of GP IIb/IIIa Inhibitors in Trials of Patients With NSTE-ACS Undergoing PCI (Section 5) ............................................................... 83
Data Supplement 22. Studies of Culprit Lesion Versus Multivessel (Culprit and Nonculprit) PCI in Patients with NSTE-ACS (Section 5) ................................................................. 83
Data Supplement 23. Risk Reduction Strategies for Secondary Prevention (Sections 6.3.) .................................................. 84
Data Supplement 24. Older Patients (Section 7.1) ........................................................................................................... 86
Data Supplement 25. Heart Failure (Section 7.2) ........................................................................................................... 95
Data Supplement 26. Cardiogenic Shock (Section 7.2.2) ................................................................................................. 101
Data Supplement 27. Diabetes Mellitus (Section 7.3) ..................................................................................................... 103
Data Supplement 28. Post-CABG (Section 7.4) ............................................................................................................ 106
Data Supplement 29. Chronic Kidney Disease (Section 7.6) .......................................................................................... 110
Data Supplement 30. Women (Section 7.7) ................................................................................................................. 113
Data Supplement 31. Anemia, Bleeding, and Transfusion-Relationship Between Transfusion and Mortality (Section 7.8) .................. 120
Data Supplement 32. Anemia, Bleeding, and Transfusion Studies for Weight-Based and Renally-Adjusted Dosing of Anticoagulants (Section 7.8) .......................................................... 121
Data Supplement 33. Cocaine and Methamphetamine Users (Section 7.10) ................................................................. 122
Additional Data Supplement Tables ......................................................................................................................... 125
Data Supplement A. Other (Newer) Biomarkers ................................................................................................. 125

© American Heart Association, Inc and American College of Cardiology Foundation 1
<table>
<thead>
<tr>
<th>Title, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Endpoint Population</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antman EM et al. 2000 10938172 (1)</td>
<td>Develop a simple scoring system to predict the risk of death and ischemic events for pts with UA/NSTEMI</td>
<td>Retrospective, observational study; TIMI 11B pts not receiving UFH group test cohort (N=1,957); TIMI 11B pts receiving enoxaprin (N=1,953) and ESSENCE trial pts (N=3,171) validation cohort</td>
<td>Inclusion in TIMI 11B trial or ESSENCE trial</td>
<td>Adverse events defined as new or recurrent MI, severe recurrent ischemia requiring urgent revasc, and death within 14 d of pt presentation; regression model selected the following 7 significant risk factors: ≤5 y, ≥3 coronary risk factors, documented prior stenosis ≥50%, ST-segment deviation on initial ECG, ≥2 anginal events in prior 24 h, use of ASA within 7 d of presentation, and elevated serum markers; presence of factor was given 1 point and absence of risk factor given 0 points; rates of adverse events for TIMI score as follows: 0: 4.7%; 1: 8.3%; 2: 13.2%; 3: 19.9%; 4: 26.2%; 5: 40.9%</td>
<td>N/A</td>
<td>Event rates &lt;significantly as TIMI risk score &lt;in test cohort in TIMI 11B (p=0.01 by x2 for trend). Pattern of &lt;event rates with &lt;TIMI risk score confirmed in all 3 validation groups (p=0.01). Slope of &lt;in event rates with &lt;numbers of risk factors significantly lower in enoxaparin groups in both TIMI 11B (p=0.01) and ESSENCE (p=0.03) and there was significant interaction between TIMI risk score and treatment (p=0.02)</td>
<td>N/A</td>
</tr>
<tr>
<td>Boersma E et al. 2000 10834005 (2)</td>
<td>Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE-ACS</td>
<td>Retrospective analysis of pts with NSTE-ACS enrolled in PURSUIT trial (N=9,461; 3.6% with 1st outcome)</td>
<td>Pts enrolled in PURSUIT trial</td>
<td>Pts not enrolled in PURSUIT trial; pts with STE on initial ECG</td>
<td>7 factors most predictive of death: age (adjusted [X]=95), heart rate ([X]=32), SBP ([X]=20), ST-segment depression ([X]=20), signs of HF ([X]=18), and cardiac markers ([X]=15); C-index for the mortality model was 0.814</td>
<td>N/A</td>
<td>Regression model developed in pts with diagnosed ACS and not designed to be applied indiscriminately to undifferentiated chest pain pts difficult to calculate; original model requires preexisting programmed calculator; simplified version requires print-out of scoring system for each variable with corresponding figure to interpret data</td>
</tr>
<tr>
<td>Granger CB et al. 2003 14581255 (3)</td>
<td>Develop a regression model in pts with diagnosed ACS (including pts with contrast)</td>
<td>Retrospective observational study utilizing pts from GRACE (N=11,389; 509 deaths); validation set</td>
<td>Inclusion in GRACE or GUSTO-IIb trial</td>
<td>Not included in these trials</td>
<td>The discrimination ability of the simplified model was excellent with C-statistics of 0.63 in the derived database, 0.64 in the confirmation</td>
<td>N/A</td>
<td>Regression model developed in pts with diagnosed ACS (including STEMI pts) and was not designed to be applied indiscriminately to undifferentiated chest pain pts</td>
</tr>
</tbody>
</table>
STEMI for inhospital mortality

included a subsequent cohort of 3,972 pts enrolled in GRACES and 12,142 pts enrolled in GUSTO-IIb trial

ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac enzyme findings, and heart rate

GRACE data set, and 0.79 in the GUSTO-IIb database; OR for the 8 independent risk factors were: age (OR: 1.7 per 10 y), Killip class (OR: 2.0 per class), SBP (OR: 1.4 per 20 mmHg decrease), ST-segment deviation (OR: 2.4), cardiac arrest during presentation (OR: 4.3), serum creatinine level (OR: 1.2 per 1 mg/dL [88.4 μmol/L] increase), positive initial cardiac enzyme findings (OR: 1.6), and heart rate (OR: 1.3 per 30 beat/min increase)

undifferentiated chest pain pts: difficult to calculate; original model requires preexisting programmed calculator; simplified version requires print-out of scoring system for each variable with corresponding nomogram

Chase M et al. 2006 16934646(4)

Validate TIMI score in ED chest pain pts

Prospective (N=1,354; 136 with 1º outcome)

Pts with chest pain who had an ECG obtained

Pts <30; cocaine use within 7 d

1º outcome composite of death, MI, PCI, CABG within 30 d of initial presentation

Increasing TIMI score associated with increased rates of adverse outcome

The incidence of 30-d death, AMI, and revasc according to TIMI score is as follows: TIMI 0, 1.7% (95% CI: 0.42–2.95); TIMI 1, 8.2% (95% CI: 5.27–11.04); TIMI 2, 8.6% (95% CI: 5.02–12.08); TIMI 3, 16.8% (95% CI: 10.91–22.62); TIMI 4, 24.6% (95% CI: 16.38–32.77); TIMI 5, 37.5% (95% CI: 21.25–53.75); and TIMI 6, 33.3% (95% CI: 0–100)

The incidence of 30-d death, AMI, and revasc according to TIMI score is as follows: TIMI 0, 1.7% (95% CI: 0.42–2.95); TIMI 1, 8.2% (95% CI: 5.27–11.04); TIMI 2, 8.6% (95% CI: 5.02–12.08); TIMI 3, 16.8% (95% CI: 10.91–22.62); TIMI 4, 24.6% (95% CI: 16.38–32.77); TIMI 5, 37.5% (95% CI: 21.25–53.75); and TIMI 6, 33.3% (95% CI: 0–100)

15% of pts did not have cardiac marker measurements; pts with STEMI included

Lyon R et al. 2007 17360096(5)

Compare GRACE and TIMI score in risk stratification of undifferentiated chest pain pts

Retrospective analysis of prospective database (N=760; 123 with 1º endpoint)

Pts with undifferentiated chest pain

Pts<20 y

Recurrent MI, PCI, or death within 30 d of pt presentation (note: pts with MI on initial presentation excluded from outcome)

GRACE score and TIMI score equivalent in risk stratification of undifferentiated ED chest pain pts

GRACE AUC-ROC 0.80 (95% CI: 0.75–0.85). TIMI AUC-ROC 0.79 (95% CI: 0.74–0.85)

Retrospective; 240 pts from initial database of 1,000 excluded; Did not count MI on presentation as adverse event

Hess EP et al. 2010 20370775(6)

Prospectively validate a modified TIMI risk

Prospective; 117 pts with 1º endpoint (N=1,017)

Pts presenting to ED with chest pain in whom a

Pts with STE-AMI, hemodynamic instability, cocaine

1º outcome defined as MI, PCI, CABG, or cardiac death within 30 d of initial presentation

Increasing sens of modified TIMI score seen with increasing

The modified TIMI risk score outperformed the original with regard Only 72% of eligible pts enrolled; 4.6% of pts without 30-d follow-up
<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Data Collection</th>
<th>Risk Score Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee B et al. 2011</td>
<td>Compared GRACE, PURSUIT, and TIMI scores in risk stratification of chest pain pts</td>
<td>Prospective data collection for TIMI score; retrospective determination of PURSUIT and GRACE score</td>
<td>Chest pain pts &gt;30 y who had ECG obtained and were enrolled in previous study utilizing TIMI score in risk stratification of chest pain pts</td>
<td>The TIMI and GRACE scores outperformed the PURSUIT score in risk stratification of ED chest pain pts</td>
</tr>
<tr>
<td>Sanchis J et al. 2005</td>
<td>Develop a risk score for ED pts with chest pain</td>
<td>Retrospective (N=646; 6.7% with 1st endpoint)</td>
<td>Chest pain pts presenting to ED undergoing evaluation for ACS who subsequently were admitted to chest pain unit</td>
<td>Accuracy of score was greater than that of the TIMI risk score for the 1st (C-index of 0.78 vs. 0.66; p=0.0002) and 2nd (C-index of 0.70 vs. 0.66; p=0.1) endpoints</td>
</tr>
</tbody>
</table>

**Score to risk stratify ED chest pain pts:** The modification of TIMI score was assigning 5 points if pt had either elevated Tn or ischemic ECG findings.

Tn value was obtained. Use, terminal illness, or pregnancy.

Score, sens and spec at potential decision thresholds were: >0 = sens 96.6%, spec 23.7%; >1 = sens 91.5%, spec 54.2%; and >2 = sens 80.3%, spec 73.4%; sens for 30 d ACS for a score of 0, 1, 2 was 1.8%, 2.1%, and 11.2% to overall diagnostic accuracy (area under the ROC curve = 0.83 vs. 0.79; p = 0.030; absolute difference 0.037; 95% CI: 0.004-0.071).

**Lee B et al. 2011 (7)**

**Sanchis J et al. 2005 (6)**

Compared TIMI score to overall diagnostic accuracy (area under the ROC curve).
<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Design</th>
<th>Population</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christenson J et al. 2006</td>
<td>2006</td>
<td>Prospective cohort with retrospective creation of decision rule (N=769; 165 with 1st outcome)</td>
<td>Pts presenting to ED with chest pain between 7 am-10 pm h</td>
<td>&lt;25, traumatic or radiologically evident cause of CP, enrolled in study in previous 30 d, or had terminal noncardiac illness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st outcome MI or definite UA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prediction rule: if pt had normal initial ECG, no Hx CAD, age&lt;40 y, and normal baseline CK-MB&lt;3.0 ng/mL, or no increase in CK-MB or Tn at 2 h, 30-d ACS: prediction rule 98.8% sens and 32.5% spec</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CI for prediction rule not supplied</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prediction rule developed retrospectively; not supplied, but exceed the threshold of allowed 2% miss rate; 2% miss rate not standard of care in United States</td>
</tr>
<tr>
<td>Backus BE et al. 2010</td>
<td>2010</td>
<td>Validation of the HEART Score which utilized elements of patient History, ECG, Age, Risk factors, and Troponin to risk stratify ED chest pain pts</td>
<td>Retrospective analysis of prospective database (N=880; 158 with 1st outcome)</td>
<td>Pts admitted to ‘cardiology’ ED</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>STE on initial ECG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st outcome was a composite of AMI, PCI, CABG, and death within 6 wk of initial presentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rates of 1st outcome seen with increasing score: 0–3: 0.1%; 4–6: 11.8%; 7–10: 65.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hx, ECG, and Tn were independent predictors of the combined endpoint (p&lt;0.0001). Avg HEART score in the no endpoint group was 3.8±1.9; pts with at least 1 endpoint 7.2±1.7 (p&lt;0.0001). C–stat 0.897</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Retropective; weighting of the elements of HEART Score arbitrarily assigned and not based on likelihood ratio analysis or regression analysis</td>
</tr>
<tr>
<td>Pesmir et al. 2012</td>
<td>2012</td>
<td>Improve upon the HEART score in risk stratification of chest pain pts by incorporating sex, serial ECG, and serial Tn; weighting of elements of scoring determined by likelihood ratio analysis</td>
<td>Retrospective analysis of prospective database (N=2,148; 315 with 1st outcome)</td>
<td>Pts presenting to ED with chest pain undergoing evaluation for ACS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>STE on initial ECG; chest pain in the presence of TAAR, pts with pulmonary edema, pts with chest pain deemed not to require any cardiac workup (obvious nonischemic chest pain and absence of risk factors or pre-existing disease that would prompt screening workup)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st outcome was 30-d ACS defined as MI, PCI, CABG, life-threatening cardiac complications, or death within 30 d of initial presentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increasing HEARTS score was associated with increasing risk of 30-d ACS; likelihood ratio analysis revealed significant discrepancies in weight of the 5 individual elements shared by the HEART and HEARTS score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HEARTS score outperformed the HEART score as determined by comparison of areas under the receiver operating characteristic curve for 30-d ACS (0.901 vs. 0.813; 95% CI difference in areas, 0.064–0.110)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Retrospetive; utilized older-generation Tn</td>
</tr>
<tr>
<td>Hess EP et al. 2012</td>
<td>2012</td>
<td>Develop a prediction rule for pts at low risk of 30-d adverse cardiac events</td>
<td>Retrospective analysis of prospective database (N=2,718 pts; 336 with adverse events)</td>
<td>Pts presenting to ED with chest pain in whom Tn value was obtained</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>STE with STE-AMI, hemodynamic instability, cocaine use, terminal illness, or pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st outcome defined as MI, PCI, CABG, or cardiac death within 30 d of initial presentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prediction rule consisted of the absence of 5 predictors: ischemic ECG changes, Hx of CAD, pain typical for ACS, initial or 6-h Tn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rule was 100% sens (95% CI: 97.2–100.0%) and 20.9% spec (95% CI: 16.9–24.9%) for a cardiac event within 30 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rule developed retrospectively; only 82% of eligible pts enrolled</td>
</tr>
</tbody>
</table>
### Data Supplement 2. Risk Stratification (Section 3.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values OR: HR: RR: &amp; 95 CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antman 2000 10938172(1)</td>
<td>Development of original score to risk stratify pts presenting with ACS</td>
<td>Multisite RCTs, TIMI-11 B and ESSENCE</td>
<td>N/A</td>
<td>Clinical ACS, ECG changes, and elevated biomarkers</td>
<td>Planned revasc, bleeding risks, and correctable cause for angina</td>
<td>N/A</td>
<td>All-cause mortality, new or recurrent MI, severe ischemia leading to revasc</td>
<td>N/A</td>
</tr>
<tr>
<td>Pollack 2006 16365321(13)</td>
<td>Validation in ED population with chest pain</td>
<td>Convenience sample N=3,326 without new STE</td>
<td>N/A</td>
<td>Chest Sx and ECG obtained</td>
<td>New STE</td>
<td>N/A</td>
<td>Death/MI/revasc over 30 d</td>
<td>In-hospital and 14-d events</td>
</tr>
<tr>
<td>Go 2011 21691204(14)</td>
<td>Attempt to add creatinine to TIMI risk score</td>
<td>Single center N=798</td>
<td>N/A</td>
<td>Ischemic Sx within 48 h</td>
<td>STEMI</td>
<td>N/A</td>
<td>CV death, MI, urgent revasc or Sx, and elevated biomarkers</td>
<td>N/A</td>
</tr>
<tr>
<td>Huynh 2008 19960136(15)</td>
<td>Across all ACS spectrum</td>
<td>Multicenter RCT with N=1,491 from angiographic arm</td>
<td>N/A</td>
<td>NSTE-ACS and STEMI</td>
<td>N/A</td>
<td>6-mo death and MI</td>
<td>N/A</td>
<td>2 mm ST deviation increased risk and risk was less regardless of score with less</td>
</tr>
<tr>
<td>Boersma 2000 10840005(2)</td>
<td>N/A</td>
<td>Multicenter RCT-Pursuit</td>
<td>N/A</td>
<td>NSTE-ACS</td>
<td>STE</td>
<td>N/A</td>
<td>Death and MI</td>
<td>N/A</td>
</tr>
<tr>
<td>Eagle 2004 15187054(16)</td>
<td>Original GRACE validation</td>
<td>Registry N=17,141</td>
<td>N/A</td>
<td>All ACS</td>
<td>N/A</td>
<td>N/A</td>
<td>6-mo all-cause mortality</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Data Supplement 3. Cardiac Injury Markers and the Universal Definition of AMI (Section 3.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thygesen 2012</td>
<td>Definition of MI</td>
<td>Guideline</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Roger 2006</td>
<td>Prospective Evaluation of new criteria for Dx of MI</td>
<td>Prospective community based epidemiologic study</td>
<td>Identification of MI using TrT vs. CK-MB and CK compared with WHO and ARIC criteria</td>
<td>County residents with TrT ≤0.03 ng/mL identifying MI</td>
<td>Lower TrT values</td>
<td>N/A</td>
<td>Identification of MI 538 MI with TrT≥327 with CK-427 with CK-MB</td>
<td>74% increase TrT vs. CK (95% CI: 69%–78%); 41% inc TrT vs. CK-MB (95% CI: 37%–46%); Participation rate of MIs was only 80% but similar to median of similar participation studies</td>
</tr>
<tr>
<td>Ham 2000</td>
<td>Classification of UA</td>
<td>Reclassification based on Tr levels</td>
<td>Angina at rest within 48-h Class IIIb into Tr+ and Tr-</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>30-d risk of death 20% in IIIb Tr+, &lt;2% in IIIb Tr+</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation trial; BNP, B-type natriuretic peptide; CV, cardiovascular; ECG, electrocardiograph; ED, emergency department; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events; eGFR, estimated glomerular filtration rate; GDF, growth and differentiation factors; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; hs-cTn, high sensitivity cardiac troponin; hs-cTnT, high sensitivity cardiac troponin T; LVEF, left ventricular ejection fraction; MASCARA, Manejo del Síndrome Coronario Agudo. Registro Actualizado nacional registry; MI, myocardial infarction; N/A, not applicable; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation acute coronary syndrome; Pts, patients; NT-pro, N-terminal pro; NT-proBNP, N-terminal pro-brain natriuretic peptide revasc, revascularization; RCT, randomized controlled trial; ROC, receiver operating characteristic; STE, ST-elevation; STEMI, ST-elevation myocardial infarction; Sx, symptom; and TIMI, Thrombolysis In Myocardial Infarction.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Details</th>
<th>Data Supplement Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kavsak 2006</td>
<td>19524460(23)</td>
<td>Impact of new classification of MI</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Eggers 2009</td>
<td>19231317(24)</td>
<td>Effects of new UDMI on misdiagnosis with single evaluation of Tr</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Goodman 2006</td>
<td>16504627(25)</td>
<td>Diagnostic and prognostic impact of new UDMI</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Eggers 2011</td>
<td>20869357(26)</td>
<td>Clinical implications of relative change in cTnl levels with chest pain</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Mills 2012</td>
<td>22422871(27)</td>
<td>Evaluation of ACS pts by using cTnl diagnostic threshold and ≤99th percentile on Dx and risk for future events</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>TRITON-TIMI 38 Bonaca 2012</td>
<td>22199016(28)</td>
<td>Association between new and recurrent MI using new UDMI classification system and risk of death</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic and Prognostic Impact</th>
<th>Data Supplement Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kavsak 2006</td>
<td>Impact of new classification of MI</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Eggers 2009</td>
<td>Effects of new UDMI on misdiagnosis with single evaluation of Tr</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Goodman 2006</td>
<td>Diagnostic and prognostic impact of new UDMI</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Eggers 2011</td>
<td>Clinical implications of relative change in cTnl levels with chest pain</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>Mills 2012</td>
<td>Evaluation of ACS pts by using cTnl diagnostic threshold and ≤99th percentile on Dx and risk for future events</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
<tr>
<td>TRITON-TIMI 38 Bonaca 2012</td>
<td>Association between new and recurrent MI using new UDMI classification system and risk of death</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
</tbody>
</table>
Data Supplement 4. Cardiac Troponins (Section 3.4.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Type/Size (N)</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple 2009 19299542(29)</td>
<td>Dx, accuracy of cTnI for early detection of AMI and risk prediction for adverse events</td>
<td>Prospective cohort study 381 with possible ACS</td>
<td>VITROS Tnl-ES assay 2x vs. clinical Dx of AMI</td>
<td>Sx suggestive of ACS in ED</td>
<td>No 2nd Tn level</td>
<td>Tn assay at admission and 6 h later for delta change</td>
<td>Sens and spec for MI from admission and delta change (see p values)</td>
<td>Risk stratification improved by 30^th Delta to initial cTnI &gt;99th percentile. Risk of death/follow-up MI within 60 d</td>
</tr>
<tr>
<td>Bonaca 2010 20447535(30)</td>
<td>Px implication of low-level inclusion in hs-cTnI in possible ACS</td>
<td>Prospective multi study 4,513 with NST-ACS</td>
<td>+ or hs-cTnI 99th percentile for death/MI in 30 d</td>
<td>NST-ACS</td>
<td>Shock, ST-elevation, revasc before random</td>
<td>Baseline cTnI with cutoff at 99th percentile</td>
<td>+cTnI higher risk of death/MI at 30 d than cTnI 6.1% vs. 2.0% p&lt;0.001</td>
<td>Pts with low-level increases 0.04-1.0 at &lt;risk than cutoff of 0.04 (5.0% vs. 2.0%); p=0.001</td>
</tr>
<tr>
<td>Kontos 2010 21095267(31)</td>
<td>NSTEMI with +Tn but -CK-MB in treatment and outcomes</td>
<td>Post hoc data base analysis 16,064 with NSTEMI</td>
<td>Tr+ MB- vs. Tr+ MB+</td>
<td>Present within 24 h of Sx with NSTEMI</td>
<td>No STEMI</td>
<td>Biomarkers on admission, Tr and CK-MB</td>
<td>Treatment and in-hospital outcomes. In-hospital mortality lower in MB pts</td>
<td>MB- were older and had more comorbidities. p&lt;0.01 and fewer intervals</td>
</tr>
</tbody>
</table>
Effect of + by both assays vs. only 1 assay
Both cTnT collected 48 h after randomization
+Hs-TnT same 1-y mortality. Whether + or - with St-TnT
For death or AMI at 30 d + only for Hs-TnT had interim risk
+Hs-TnT + mortality 9.2% vs. 1.6%; p=0.001
For – by both assays
Pts with higher pretest risk than typical chest pain pts in ED

Dx, performance of Hs-cTnT for detection of NSTEMI in ACS
Baseline concentrations and serial concentrations at 3 h and 6 h
UA or NSTEMI with initial –cTnT
Immediate PCI or kidney dysfunction
Hs-cTnT baseline, 3, 6 h delta change >20%, or ROC optimized value >117%, 3 h, or 246% 6 h
Hs-cTnT Dx 61% at baseline to 100% at 6 h. Dx increase by 34% above std cTnT
Doubling of hs-TnT with initial 99% + positive predicted value 100% – predicted value 88%
Delta changes and ROC optimized values spec 100% with sens 69% and 76%
Admission to chest pain unit more selective than typical ED admissions

Serial TnT measurements vs. MRI infarct mass
AMI with TnT and MRI
STEMI and NSTEMI with MRI before discharge
Lack of biomarkers at any of 5× up to 96 h from admission
TnT at admission and daily to 96 h.
Except for admission values, all TnT at various times correlated with infarct size
Estimation of infarct mass on d 4 was lower for NSTEMI than STEMI
r=0.75 STEMI r=0.36 NSTEMI

Hs-TnI and St-TnI
Major surgery or trauma within 4 wk, pregnancy, drug abuse
Hs-TnI and St-TnI at baseline and 3 h serial changes
Both Hs-Hs and St-TnI at 99th percentile at admission and 3 h had similar sens and spec
3 h after admission. Sens 98.2% and – predicted value 99.4% for both assays.
Hs-TnI at admission sens 82.3%, pred value 94.7%. St TnI sens 79.4%
Final Dx of AMI by in house Tn, biasing biomarker assays toward Tn
High proportion of MI vs. other studies

72-h TnI estimate with MRI for infarct size
Tnl correlation with MRI
STEMI, NSTEMI, LBBB 1st MI Tnl CK MRI
Prior AMI contraindication to MRI previous revasc, PCI before MRI
Admission and 12-h Tnl and CK MRI average 3.7 d from admission
72-h TnI similar to CK for infarct size estimate and superior to 12-h Tnl
Correlation of 12-h TnI with microvascular obstruction was NS p=0.16
Compared with peak CK r=0.44 72-h Tnl r=0.46 p=0.0002
72-h TnI vs. MRI R=0.62 p=0.0001 12-h TnI R=0.56 p=0.0003 Peak CK R=0.75 p=0.0001
12 and 72-h TnI available only on 37 pts and 64 pts. Only 19 NSTEMI. Data larger than on previous studies of Tn MRI correlations.

Diagnostic accuracy and risk stratification of cTnI-ultra assay
Possible ACS with follow-up for 60 d
Cardiac events and death in 60 d. Optimal value of change was absolute value of change delta
Sens and Specs: Absolute value: 89.8-93.7 Change: 67.5-99.0 Absolute value of % change: 75.5-85.7 % change: 71.4-89.7
AUC Diagnostic accuracy of absolute value of change 0.96 (0.94, 0.98). Change 0.76 Absolute value of % change 0.88 % change 0.77
Long period needed to evaluate deltas. Further studies need to determine whether 2–3 h changes can provide adequate Dx and prognostic information
### Diagnostic accuracy of absolute value relative changes in cTn

[Reichlin 2011](#)

Prospective multicenter study with ACS

Absolute value relative changes in cTn

Sx suggesting AMI

STEMI, terminal kidney failure

HS-TnI and cTnI ultra at admission and 1h and 2h

ROC at 2h higher for absolute than relative changes

ROC absolute cutoff 2h 0.007 μg/L and 0.020 μg/L for ultra

ROC absolute change HS-TnI 0.95 (95% CI: 0.92–0.98) vs. relative change 0.76 (95% CI: 0.70–0.83); p<0.001

Observation cannot quantify clinical benefit of results

### Early means of hs-TnT vs. conventional cTnT in NSTE-ACS

[Aldous 2012](#)

Prospective cohort

NSTE-ACS with conventional and hs-TnT assays

NSTE-ACS

STEMI <18 y, unable to follow-up

HS-TnT and conservative TnT at admission, 2h and 6h-12h

Dx of MI on admission at 2h HS-sens 92.2% and spec of 79.7%

Mortality at 1y HS superior to conventional Death 5.4% (95% CI: 2.7–10.7) and HF 27.8% (95% CI: 6.6–116.4)

Hs TnT 95% CL for MI Dx at 2h Sens (95% CI: 88.1–95.0%) spec (95% CI: 78.6–80.5)

Blood samples not taken beyond 2h. Used cTnT as gold standard for Dx of MI

### Kinetic changes on hs-cTnT in ACS and non-ACS

[Mueller 2012](#)

Prospective cohort

NSTEMI 165

Pts with ACS with hsTnT vs. non-ACS with hs-TnT above 99th percentile

ACS with 2nd blood drawn within 6h Non-ACS with 2 blood draws

STEMI or LBBB

HS-TnT-ACS and non-ACS with elevated hs-TnT2 blood draw within 6h

Absolute delta vs. relative delta ROC-optimized cutoff 6.9 mL/L was sup to rel change ≥20%

≥20%

P<0.001

Relative changes confined to 5h, not 24h. Not all pts received angiography

### Data Supplement 5. CK-MB, MB Isoforms and Myoglobin, Compared With Troponins (Section 3.4.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95 CI</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td><strong>Exclusion Criteria</strong></td>
<td>Study Intervention</td>
<td>Primary Endpoint &amp; Results</td>
<td>Secondary Endpoint &amp; Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apple 1999</strong></td>
<td><strong>931041 (41)</strong></td>
<td><strong>Use of triage panel of Tt, CK-MB, and myoglobin for AMI detection</strong></td>
<td>Multicenter prospective study 112</td>
<td>Comparison of myoglobin, TnI and CK-MB for sens and spec</td>
<td>Pts in ED with ACS</td>
<td>N/A</td>
<td>Triage panel biomarkers to evaluate ROC for AMI pred</td>
<td>Concordance for detection or rule-out of MI Tnl &gt;89% CK-MB &gt;81% Myoglobin &gt;89%</td>
</tr>
<tr>
<td><strong>TACTICS-TIMI 18</strong></td>
<td><strong>Kleiman 2002</strong></td>
<td><strong>12354426 (42)</strong></td>
<td><strong>CK-MB vs. TnT to predicted cardiac risk and benefit in AMI invasive strategy</strong></td>
<td>Multicenter prospective study 2,200</td>
<td>CK-MB elevated in 826. With CK-MB, TnT elevated in 361</td>
<td>1st 24 h of chest pain</td>
<td>N/A</td>
<td>Invasive or conservative strategy with CK-MB and TnT for 30-d and 180-d risk. CV events 30 d of 180 d Event rates 2+ as high with CK-MB+ value – benefit in invasive with Tr+, but CK-</td>
</tr>
</tbody>
</table>
Effect of Tn on myoglobin and CK-MB isoforms in ACS

Kavask 2007

CRUSADE

Kirscher 2007

Sallach 2004

CRUSADE

© American Heart Association, Inc and American College of Cardiology Foundation
### Data Supplement 6. Bedside Testing for Cardiac Biomarkers (Section 3.4.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTION-GWTG Registry Chin 2012 22434769(48)</td>
<td>Prognostic value of CK-MB vs. Tn in AMI</td>
<td>Retrospective registry 26,854</td>
<td>Peak CK-MB and Tn</td>
<td>AMI in data registry with biomarkers</td>
<td>Peak values below lab ULN</td>
<td>Peak CK-MB and Tn for in-hospital mortality</td>
<td>N/A</td>
<td>Peak CK-MB C-statistic 0.831 Peak Tn C-statistic 0.824 p&lt;0.001</td>
</tr>
<tr>
<td>Ilva 2005 15667582(12)</td>
<td>Novel TnI in early risk stratification in ACS</td>
<td>Prospective cohort 531</td>
<td>Standard TnI novel TnI myoglobin</td>
<td>Biomarkers at 0 h, 1-12 h and 24 h after admission</td>
<td>Absence of 1 or more biomarkers</td>
<td>Comparison of 3 biomarkers at times indicated</td>
<td>Positivity of novel TnI assay for AMI in higher percent than other biomarkers</td>
<td>MI within 3 h of presentation: 50% by novel TnI and only 11.5% by reference TnI assay, (p&lt;0.001) 44% by myoglobin (p=NS)</td>
</tr>
<tr>
<td>Volz 20012 21129891(13)</td>
<td>Can Tn alone be used for initial AMI screening with elimination of CK-MB</td>
<td>Retrospective cohort 11,092</td>
<td>TnT and CK-MB</td>
<td>All pts with TnT in ED with correspond CK-MB</td>
<td>Initial nonnegative Tn</td>
<td>CK-MB+ with TnT- to determine value on AMI screening</td>
<td>None with Tn- but CK-MB+ Judged to have AMI</td>
<td>N/A</td>
</tr>
<tr>
<td>Lim 2011 21282125(49)</td>
<td>CK-MB vs. Tn in Dx of AMI after PCI</td>
<td>Prospective cohort 32</td>
<td>Tnl and CK-MB</td>
<td>PCI and CMR imaging baseline and 7 d</td>
<td>N/A</td>
<td>CK-MB and Tnl after PCI to determine Dx of AMI</td>
<td>Only small min of +Tn had CRM abnormal CK-MB+ closely approximate CMR injury</td>
<td>Percent changes in inflammed markers corresponded with CK-MB, but not Tnl levels for CRP and SAA</td>
</tr>
</tbody>
</table>

**ACC** indicates American College of Cardiology; **ACS** acute coronary syndrome; **AMI** acute myocardial infarction; **CK** creatine kinase; **CK-MB** creatine kinase MB; **CK-T+** creatine kinase troponin positive; **CMR** cardiovascular magnetic resonance; **CRP** C-reactive protein; **CV** cardiovascular; **Dx** diagnosis; **ECG** electrocardiograph; **ED** emergency department; **ESC** European Society of Cardiology; **MI** myocardial infarction; **Myo** myoglobin; **N/A** not applicable; **NSTE-ACS** Non-ST elevation acute coronary syndrome; **NS** not significant; **NSTEMI** non-ST segment myocardial infarction; **OR** odds ratio; **PCI** percutaneous coronary intervention; **Pred** predicted; **pts** patients; **Px** prognosis; **ROC** receiver operator curve; **SAA** serum amyloid A protein; **Sens** sensitivity/sensitivities; **Spec** specificity/specificities; **STEMI** ST segment elevation MI; **Tn** troponin; **Tn+** positive troponin; **Tn-** negative troponin; **TNF** tumor necrosis factor; **Tnl** troponin I; **TrT** troponin T; **TrT+** troponin T+; **UA** unstable angina; **ULN** upper limit normal; and **WHO** World Health Organization.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Sample Size</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Primary Endpoint &amp; Results</th>
<th>Safety Endpoint &amp; Results</th>
<th>Secondary Endpoint &amp; Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamm 1997</td>
<td>9385123(50)</td>
<td>Prospective cohort</td>
<td>773</td>
<td>TnT vs. TnI for Dx of MI and 30-d events +TnT 123 +TnI 171</td>
<td>Acute chest pain &lt;12 h without STE</td>
<td>Bedside tests of TnT and TnI 2*, arrival and &gt;4 h</td>
<td>AMI TnI sens: 100% TrT sens: 94%</td>
<td>N/A</td>
</tr>
<tr>
<td>Van Domburg 2000</td>
<td>10980212(51)</td>
<td>Prospective cohort</td>
<td>163</td>
<td>TnT, CK-MB, myoglobin 98 TnT + &lt;12 h 48 + baseline 50 positive 3-12 h 2 positive 12-96 h</td>
<td>Suspected ACS</td>
<td>Blood specimen at 0 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h</td>
<td>29%+ on admission 60%+ in 12 h</td>
<td>N/A</td>
</tr>
<tr>
<td>Amadio 2007</td>
<td>17429291(52)</td>
<td>Retrospective cohort</td>
<td>516</td>
<td>Higher vs. lower TnI cutoffs and Dx of AMI 70 TnI+</td>
<td>Suspected angina or AMI STE-ACS or LBBB</td>
<td>Bedside TnI</td>
<td>Best clinical cutoff at 99th percentile 0.03</td>
<td>N/A</td>
</tr>
<tr>
<td>DISPO-ACS Ryan 2009</td>
<td>18691781(53)</td>
<td>Multi-institute prospective study</td>
<td>2,000</td>
<td>Bedside Tn testing + central lab Central lab only 1,000 in each arm</td>
<td>Suspected ACS with biomarkers</td>
<td>Tachyarrhythmia or ECG AMI</td>
<td>POC markers vs. lab markers</td>
<td>POC discharge Home 4.5 h Lab discharge Home 4.6 h</td>
</tr>
<tr>
<td>CRUSADE Takakuwa 2009</td>
<td>19743496(54)</td>
<td>Retrospective multi-institutional</td>
<td>12,604</td>
<td>POC with Tn+ vs. the NSTEMI ACS</td>
<td>Death within 24 h Hospital with 30 pts. Infrequent percentage use of bedside Tn</td>
<td>Hospital and pt characteristics In-hospital events and care variables Hospital using POC testing &gt;50% vs. &lt;50% testing</td>
<td>Higher POC had shorter ED stay, less likely to use drug IV</td>
<td>N/A</td>
</tr>
<tr>
<td>Birkhahn 2011</td>
<td>20325823(55)</td>
<td>Proveasive cohort</td>
<td>151</td>
<td>POC and core lab testing of TnT TnI+ in 12 pts</td>
<td>Suspected ACS with 2 TnT 6 h apart</td>
<td>STE, ECG, or lack of serial biomarkers</td>
<td>POC (TnT) CK-MB, myoglobin vs. central lab testing (TnI) baseline +2h vs. baseline +6 h</td>
<td>6.5 h saved using POC and relative sens of 100%. p&lt;0.0001</td>
</tr>
<tr>
<td>Database</td>
<td>Year</td>
<td>Title</td>
<td>Study Design/Description</td>
<td>Findings/Comments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>-------</td>
<td>--------------------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schamhorst 2011</td>
<td>21350097(56)</td>
<td>Sens and spec of bedside Tn compared with CK-MB and myoglobin</td>
<td>Prospective cohort 137</td>
<td>POC evaluation Tn, CK-MB, myoglobin, for rapid detection of +test 37+ ACS: 7 UA 26 NSTEMI 4 STEMI</td>
<td>Suspected NSTEMI</td>
<td>STE on AD ambulance to hospital</td>
<td>POC Tn values T0–T12 h and sens/spec for MI at 99% cutoff</td>
<td>At T2 Sens: 87% Spec: 100% +PV: 100% –PV: 96%</td>
</tr>
<tr>
<td>ASPECT Than 2011</td>
<td>21435709(57)</td>
<td>Validate safety of predefined 2 h protocol (ADP) for ACS</td>
<td>Multicenter prospective observation study 3,582</td>
<td>POC evaluation Tn, CK-MB, Myoglobin 3260 ADP+ 270 ADP– 3,582 30-d follow-up</td>
<td>Suspected ACS</td>
<td>STE ACS, Noncoronary chest pain</td>
<td>ADP use of POC Tn, CK-MB, and myoglobin with 30-d follow-up</td>
<td>Major CV events at 30 d ADP Sens 99.3%</td>
</tr>
<tr>
<td>GUSTO-IV Venge 2010</td>
<td>2109526(58)</td>
<td>Comparison of POC vs. laboratory assays of Tn</td>
<td>Prospective cohort 1,069</td>
<td>2 POC vs. 2 central laboratory assays cTnI</td>
<td>All pts in ED with Tn assays</td>
<td>N/A</td>
<td>Tn assays with 99th percentile URL cutoffs</td>
<td>99th percentile cutoffs: central lab cutoffs identified more pts with high cTnI and predicted higher % deaths</td>
</tr>
<tr>
<td>[RATPAC] Bradburn 2012</td>
<td>21617159(10)</td>
<td>Variation in outcomes and costs in different hospitals using POC</td>
<td>Multicenter prospective analysis 2,243</td>
<td>POC vs. central lab assays at 6 hospitals</td>
<td>Suspected, but not proven AMI at 6 hospitals.</td>
<td>Proven MI by ECG, high-risk ACS, known CAD, serious noncoronary pathology, recurrent chest pain</td>
<td>POC or std care with CK-MB, myoglobin, and Tn biomarkers</td>
<td>Difference in proportion of pts successfully discharged. POC led to higher proportion in 4, lower in 1 and equivocal in 1.</td>
</tr>
<tr>
<td>[RATPAC] Fitzgerald 2011</td>
<td>21569169(59)</td>
<td>Cost effectiveness of POC biomarker assay</td>
<td>Multicenter prospective analysis 2,243</td>
<td>Std care 1,118 POC 1,125</td>
<td>Suspected, but not proven AMI at 6 hospitals.</td>
<td>Proven MI by ECG, high-risk ACS, known CAD, serious noncoronary pathology, recurrent chest pain</td>
<td>POC or std care with CK-MB, myoglobin, and Tn biomarkers</td>
<td>POC associated with higher ED costs, coronary care costs, and cardiac intervention costs, but lower general pts costs</td>
</tr>
</tbody>
</table>
**Data Supplement 7. Summary Comparison of Injury Markers (Section 3.4.4)**

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type / Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values</th>
<th>OR: HR: RR: &amp; 95 CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRISC Lindahl 2000 11038118(60)</td>
<td>Multiple biomarkers as long-term risk predictors for CV death</td>
<td>Multi-institution prospective 917</td>
<td>TN, CRP, Fibrinogen</td>
<td>UA or possible MI within 72 h</td>
<td>Increased risk of bleeding (dahleparin trial)</td>
<td>Biomarker samples at 0 h, 12 h, 24 h</td>
<td>Cardiac death at 37 mo Multivariate analysis TN and CRP independently predicted of mortality</td>
<td>Highest tertile of CRP significant for mortality. Lowest 2 tertiles NS difference p&lt;0.001 3 vs. 2, 1 tertile</td>
<td>Multivariate analysis: High TN: 10.8 (95% CI: 2.6–44.6) High CRP 2.3 (95% CI: 1.3–4.0) Fibrinogen NS</td>
</tr>
<tr>
<td>TACTICS-TIMI18 Sabatine 2002 11956114(61)</td>
<td>Use of multiple biomarkers to predict MACE in NSTE-ACS</td>
<td>Multi-institution prospective 450</td>
<td>TN, CRP, BNP in combination vs. each alone</td>
<td>Possible ACS within 72 h</td>
<td>Age &lt;18 y pregnancy, significant comorbidities, bleeding tendency</td>
<td>3 biomarkers at enrollment</td>
<td>Death/MI/HF at 6 mo Number of elevated biomarkers include prediction of outcome 30-d mortality RR 0 Biomarker+: 1 1 Biomarker+: 1.6 2 Biomarker+: 3.5 3 Biomarker+: 6 p=0.014</td>
<td>1 Biomarker+:2.1 p=0.006 2 Biomarker+:3.1 p&lt;0.001 3 Biomarker+:3.7 p=0.001 (6 mo)</td>
<td>Using binary cutpoints of biomarkers rather than higher levels. Very insensitive cTn assay</td>
</tr>
<tr>
<td>HOPE Blankenberg 2006 16831981(62)</td>
<td>9 Biomarkers to evaluate improved CV risk in a 2º d prevention population</td>
<td>Multicenter prospective 3,199</td>
<td>Evaluation of CRP fibrinogen, IL-6, TNF 1, 2, sIA-1, sIA-1, BNP, IL-1 RA microalbuminuria, individually for MACE</td>
<td>Hx of CAD, stroke, PAD, diabetes</td>
<td>HF, low LVEF, nephropathy MI, or stroke 4 wk before enrollment</td>
<td>9 biomarkers on enrollment</td>
<td>Combined events 4.5 y Significant relations: BNP, sIA-1, Microalbuminuria, s-IRA-1, fibrinogen</td>
<td>Only inclusion of BNP provided info above that from traditional risk factors HR: BNP 1.721&lt;0.001 sIA-1 1.46=0.0003 Microalbuminuria 1.55=0.0004 sIA1-60=0.0003 Fibriogenen 1.31=0.02</td>
<td>Only baseline measurements; later analysis on frozen specimens; for our purposes, not an ACS study</td>
</tr>
<tr>
<td>McCann 2008 1989244(63)</td>
<td>Role of novel biomarkers in AMI Dx</td>
<td>Multicenter prospective 664</td>
<td>Multiple biomarker comparisons including cTnT, H-FABP, BNP, hs-CRP, D-dimer, MPO, MMP-9, PAPP-A, sCD40L</td>
<td>Chest pain &lt;24 h to 2 CCUs</td>
<td>Transfer from other hospital thrombolytics or anticoagulant</td>
<td>Biomarkers on entry</td>
<td>Dx of AMI only H-FABP cTnT and combined approach improved -PV -PV H-FABP 75% cTnT=90% Either–97% (95% CI: 91%–99%)</td>
<td>Sens H-FABP: 73% Sens cTnT: 55% On admission p=0.043. Combined improved sens: 65%; ps0.04 vs. individual values</td>
<td>Only single measure of biomarker. Only biomarker.</td>
</tr>
<tr>
<td>FRISC Eggers 2009 (64) 19608034(64)</td>
<td>Risk predicted by multiple biomarkers in NSTE-ACS</td>
<td>Multicenter retrospective analysis 877</td>
<td>Evaluated: cTnT, BNP, CRP, estimated GFR</td>
<td>NSTE-ACS</td>
<td>Bleeding risk, high creatinine, PCI in previous 6 mo, decision for PCI before randomization</td>
<td>Biomarkers at enrollment, 6 wk, and 6 mo</td>
<td>5-y follow-up BNP: strongest predictor for mortality</td>
<td>BNP: 6 wk: 1.5 p&lt;0.001 6 mo: 1.4 p=0.001</td>
<td>BNP 1.7 (95% CI: 1.3–2.1); p&lt;0.001 5 y only 6 wk BNP showed significant increments to established risk factors C-statistic 0.69; p&lt;0.03</td>
</tr>
<tr>
<td>ARCHIEPAGÓ Multiple biomarkers</td>
<td>Multicenter</td>
<td>Evaluated 9</td>
<td>NSTE-ACS</td>
<td>STE-ACS, Biomarkers at</td>
<td>Biomarkers for</td>
<td>IL-6 AUC significant</td>
<td>IL-6: 1.69 (95% CI: 1.2–2.3)</td>
<td>Post-hoc analysis;</td>
<td></td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Biomarkers</th>
<th>Outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scirica 2011</td>
<td>2011</td>
<td>Multicenter prospective</td>
<td>TnT, CRP, MPO, IL-10, MPO</td>
<td>Biomarkers at presentation</td>
<td>TnT: 1.8 (95% CI: 1.2–2.6) IL-10: 1.7 (95% CI: 1.1–2.6) PIGF: 1.9 (95% CI: 1.3–2.8) CRP: 1.0 NS sCD40L: 1.2 NS MPO: 1.5 (95% CI: 1.1–2.1) PAPP-A: 1.1 NS</td>
</tr>
<tr>
<td>Manheke 2011</td>
<td>2011</td>
<td>Multicenter prospective trial</td>
<td>TnT, CRP, MPO</td>
<td>Biomarkers at presentation</td>
<td>TnT: 1.8 (95% CI: 1.2–2.6) IL-10: 1.7 (95% CI: 1.1–2.6) PIGF: 1.9 (95% CI: 1.3–2.8) CRP: 1.0 NS sCD40L: 1.2 NS MPO: 1.5 (95% CI: 1.1–2.1) PAPP-A: 1.1 NS</td>
</tr>
<tr>
<td>Bhawardi 2011</td>
<td>2011</td>
<td>Multicenter prospective</td>
<td>TnT, CRP, MPO</td>
<td>Biomarkers at presentation</td>
<td>TnT: 1.8 (95% CI: 1.2–2.6) IL-10: 1.7 (95% CI: 1.1–2.6) PIGF: 1.9 (95% CI: 1.3–2.8) CRP: 1.0 NS sCD40L: 1.2 NS MPO: 1.5 (95% CI: 1.1–2.1) PAPP-A: 1.1 NS</td>
</tr>
</tbody>
</table>

**Note**: The table above summarizes the predictive value of multiple biomarkers in NSTE-ACS. The data was collected from various studies and presented in a tabular format for easy reference.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Biomarkers</th>
<th>Cutpoints</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meune 2012</td>
<td>Multimarker evaluation in suspected AMI with undetectable cTnT levels</td>
<td>Retrospective multi-institution 325 with undetectable cTnT</td>
<td>ACS with undetectable cTnT at 0 h and 6 h. Detectable cTnT</td>
<td>Biomarkers &gt;6 h from enrollment</td>
<td>ESRD</td>
<td>Sens/spec for death/MI (%)</td>
</tr>
<tr>
<td>Schaub 2012</td>
<td>Markers of plaque instability use in AMI Dx and risk</td>
<td>Prospective multicenter 398</td>
<td>Possible ACS</td>
<td>Biomarkers at presentation</td>
<td>Diagnostic accuracy for all non-TnT biomarkers was low using ROC</td>
<td>AUC for combination with hs-TnT: MPO: 0.95 MR-Pro ADM: 0.95 PAPP-A: 0.95 CRP: 0.95 (NS change)</td>
</tr>
<tr>
<td>Weber 2008</td>
<td>Prognosis. value of BNP with normal TnT in ACS</td>
<td>Retrospective multicenter 2,614 From 2 center registries 1,131 and 1,483</td>
<td>BNP vs. TnT</td>
<td>Cohorts BNP different, 1 higher risk (1,131) and the other lower risk (1,483) analyzed separately PCI within 6 mo, or C and for reperfusion cancer, autoimmune inflammatory disease</td>
<td>Biomarkers at entry</td>
<td>Among TnT-pts ROC analysis yielded an optimal cutoff of BNP that was able to discriminate pts at higher risk for death at 6 mo</td>
</tr>
<tr>
<td>Wiviott 2004</td>
<td>Gender and biomarkers in ACS</td>
<td>Multicenter prospective trial of 1,165 pts in TACTICS-TIMI 18, 34% were women</td>
<td>Multiple biomarker analysis Men vs. women</td>
<td>Women with ACS with criteria for PCI. Randomized to invasive vs. conservative strategies</td>
<td>No criteria for PCI</td>
<td>Women more likely had elevated cTnT and CRP. More likely had elevated CK-MB and Tn</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; AUC, area under the curve; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C-reactive protein; cTn, cardiac troponin; cTnT, cardiac troponin T; CCU, cardiac care unit; CV, cardiovascular; Dx, diagnosis; ESRD, end stage renal disease; FFAu, unbound free fatty acids; GDF-15, growth differentiation factor-15; GP-BB, glycoprotein phosphorylase-BB; GRF, growth hormone releasing factor; H-FABP, heart type fatty acid binding protein; HF, heart failure; HS, high sensitivity; HS-CRP, high sensitivity C-reactive protein; HS-TnI, high sensitivity troponin I; hs-TnT, high sensitivity cardiac troponin T; Hx, history; IL, interleukin; IL-1 RA, interleukin-1 receptor antagonist; IMA, ischemia-modified albumin; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MMP-9, matrix metalloproteinase-9; MPO, myeloperoxidase; MR-Pro ADM, midregional pro-adrenomedullin; N/A, not applicable; NS, not significant; NST-ACS, non-ST-segment acute coronary syndrome; NSTE-ACS, Non-ST-Segment-Elevation Acute Coronary Syndrome; OPUS-TIMI, orboflanin in

**ACS Guidelines Data Supplements**

© American Heart Association, Inc and American College of Cardiology Foundation

19
patients with unstable coronary syndromes; PAD, Peripheral Artery Disease; PAPP-A, pregnancy-associated plasma protein-A; PCI, percutaneous coronary intervention; PIGF, placenta growth factor; PL-22, secretory type II phospholipase-22; pts, patients; PV, predictive value; RA, rheumatoid arthritis; ROC, receiver operating curve; RR, relative risk; sCD40L, soluble CD40 Ligand; sIL-2R, soluble interleukin-2 receptor; sIL-6R, soluble interleukin-6 receptor; sICAM-1, soluble intercellular adhesion molecule-1; sIRA, soluble intercellular adhesion molecule-1; Spec, specificities; STEMI, ST-elevation myocardial infarction; TACTICS, Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival; TIMI, Thrombolysis In Myocardial Infarction; Tn, troponin; Tnl, troponin I; TnT, troponin T; and UA, unstable angina.

### Data Supplement 8. Discharge from ED or Chest Pain Unit (Section 3.5.1)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Type</th>
<th>Study Interven. Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Study Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEER, Farkouh, 1998 <a href="75">9862943</a></td>
<td>Single-center, prospective RCT</td>
<td>424</td>
<td>212</td>
<td>Intermediate risk, UA</td>
<td>6-h CPU observation followed by pre-D/C ETT or Ex-MPI with early D/C if negative</td>
<td>Routine hospital admission</td>
<td>No significant diff in early (30 d) and late (6 mo) MI, death, CHF, CVA, card arrest in-hospital admission vs. CPU pts</td>
</tr>
<tr>
<td>ROMIO, Gomez, 1996 <a href="76">8752791</a></td>
<td>Single-center, prospective RCT</td>
<td>100</td>
<td>50</td>
<td>N/A</td>
<td>CP low-risk for MI (Goldman), stable, nonischemic ECG, injury marker data not required</td>
<td>Rapid rule-out MI protocol in ED: Serial ECGs and CK-MB q 3-h x 4. If negative, PD-ETT</td>
<td>Routine hospital adm</td>
</tr>
<tr>
<td>Amsterdam, 2002 <a href="77">12106928</a></td>
<td>Observation, single-center</td>
<td>1,000</td>
<td>1,000</td>
<td>N/A</td>
<td>Abnormal ECG, positive marker, clinically unstable</td>
<td>Immediate ETT, Max/Sx/Sign limited</td>
<td>No adverse effects of ETT. No deaths at 30 d.</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
Udelson, 2002

<table>
<thead>
<tr>
<th>Does addition of rest MPI improve ED triage of low-risk CP pts to admission or D/C from ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective Multicenter (n=7) RCT</td>
</tr>
<tr>
<td>2,475</td>
</tr>
<tr>
<td>1,215</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Suspected acute ischemia (CP or equivalent) present within ≤3 h, nonischemic ECG, ≥30 y</td>
</tr>
<tr>
<td>Hx of MI, non-Dx ECG</td>
</tr>
<tr>
<td>Rest SPECT Tr 99m sestamibi, results to ED for use in clinical decision-making</td>
</tr>
<tr>
<td>Usual ED strategy in each institution's ED</td>
</tr>
<tr>
<td>30 d</td>
</tr>
<tr>
<td>MPI: Admission rate ≤UC (RR: 0.87; 95% CI: 0.81-0.93; p&lt;0.001)</td>
</tr>
<tr>
<td>No adverse effects of MPI except radiation and longer time to discharge from ED in negative scan pts.</td>
</tr>
<tr>
<td>See 1º 2º endpoints column</td>
</tr>
<tr>
<td>No control group. Method not generalizable, highly developed specialist personnel</td>
</tr>
<tr>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
</tbody>
</table>

Trippi, 1997

<table>
<thead>
<tr>
<th>Evaluate utility of DSE telemedicine triage of low-risk pts with CP in ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, single-center, DSE by nurse and sonographer</td>
</tr>
<tr>
<td>173 screened, 139 eligible and received DSE (24 no DSE d/t LV wall motion abnormal)</td>
</tr>
<tr>
<td>139</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>ROMI, negative markers, NL ECG, No Hx CVD, initially: pts obs'v'd 12 h; later, neg DSE: direct D/C from ED</td>
</tr>
<tr>
<td>No Hx CAD, screened for exclusions by nurse (not specified) (LV wall motion abnormal = exclusion)</td>
</tr>
<tr>
<td>DSE by nurse &amp; sonographer Card present; later cardiac available in phone, ED MDs present. DSE telemetry to Card, Dx to ED. Follow-up confirm, ECG</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>3-mo follow-up: NPV for ACS 98.5%, PPV 51.5%. Agreement TeleEcho/convEch to compensate 75.0% D/C/d directly from ED in phase 4. DSE report to ED in 2.5 h from request. ED MDs adm some pts despite neg DSE.</td>
</tr>
<tr>
<td>See 1º 2º endpoints columns</td>
</tr>
<tr>
<td>No control group. Method not generalizable, highly developed specialist personnel</td>
</tr>
</tbody>
</table>

Bholasingh, 2003

<table>
<thead>
<tr>
<th>Study prognostic value of DSE in low-risk CP pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective single-center, blinded. ED MDs blinded to DSE results.</td>
</tr>
<tr>
<td>377 of 557 eligible pts received DSE. No DSE: 119 ACS, 34 other serious DIs, 24 rest LV abn.</td>
</tr>
<tr>
<td>377</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>≥18 y, non-Dx ECG, present within 6 h of CP, neg cTn.</td>
</tr>
<tr>
<td>Arrhythmias, HF, severe HTN, serious noncard disease</td>
</tr>
<tr>
<td>DSE after 12-h observation, 6.9% (26/377) pts had Pos DSE</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>6-mo follow-up: 1º endpoints: Neg DSE 4% (1 death); Pos DSE 30.6% (1 death); OR 10.7; 95% CI: 4.0-26.8; p&lt;0.0001</td>
</tr>
<tr>
<td>All DSE completed within 24 h of administration; follow-up 100%; 19.9% protocol terminated d/t ECG changes, CP, arrhythmia, severe HTN, hypotension.</td>
</tr>
<tr>
<td>Revasc: Pos DSE 3/26 pts, Neg DSE 7/35 pts –5X greater in neg DSE</td>
</tr>
<tr>
<td>See 1º 2º endpoints columns</td>
</tr>
<tr>
<td>No control group. DSE not performed d/t poor window in 5.7% pts.</td>
</tr>
</tbody>
</table>

ROMICAT, Hoffman, 2009

<table>
<thead>
<tr>
<th>Utility of CCTA in acute CP pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation al cohort study</td>
</tr>
<tr>
<td>368</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>CP, neg initial Tn, nonischemic ECG</td>
</tr>
<tr>
<td>Hx CAD: stent or CABG, renal discharge</td>
</tr>
<tr>
<td>CCTA before admission, results not</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Pts without CAD: NPV for ACS at 6</td>
</tr>
<tr>
<td>1 ACS in absence of + CCTA showing</td>
</tr>
<tr>
<td>No MACE at 6 mo in pts who did not have</td>
</tr>
<tr>
<td>See 1º endpoint column</td>
</tr>
<tr>
<td>Single center, wkd h, underrepresent of elderly d/t</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
| Litt, 2012 | CCTA vs UC to assess low-risk CP pts in ED | Prospective multictr (n=5) RCT | 1370, 2:1 ratio to CTA and traditional care | 908 | 462 | ≥30 y, nonischemic ECG, TIMI 0-2 | Noncard sx, NL angio within 1 y, contraind to CTA, CrCl <60 | CTA was 1st test in CTA group. In traditional care pts clinicians decided 1st tests | Traditional care | No MI/death at 6 mo in pts with neg CTA (<50% stenosis): 0% (95% CI 0-0.57) (100%) | No MI or death at 60 d in the 640 pts with neg CTA | CTA: higher rate of D/C from ED: 50% vs. 23%, 95% CI 21-32; shorter LOS: 18 h vs. 25 h, p<0.001; higher ID of CAD: 9.0 % vs. 3.5%, 95% CI 0-11. | See 1st endpoint columns | All exclusions to CCTA not noted, young study group (age 50 y), radiation |
| ----------- | ---------------------------------------- | ----------------------------- | ------------------------------------------ | ------ | ---- | --------------------------------- | ------------------------------------------------- | ------------------------------------------------ | ---------------- | ------------------------------------------------ | ------------------------------------------------ | ------------------------------------------------ | See 1st and 2nd endpoint columns | Wkd, daytime, radiation. May not be generalizable to smaller hospitals |

**Data Supplement 9. Nitrates (Section 4.1.2.1)**

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparat or</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI: Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrosio G., 2010</td>
<td>Investigate whether</td>
<td>Multicenter registry</td>
<td>52,693</td>
<td>10,555 (20%) pts on</td>
<td>42,138 (80%) (nitrate-naive)</td>
<td>Clinical history of ACS, Pts with non-CV causes for the Chronic nitrates on</td>
<td>Chronic nitrate use was</td>
<td>N/A</td>
<td>Antecedent nitrate use was</td>
<td>Chronic nitrate use remained</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Exclusion Criteria</td>
<td>Main Treatment</td>
<td>PC 1º endpoint</td>
<td>Cardiac Event Rates</td>
<td>Benefits</td>
<td>NTG Dose</td>
<td>NTG Tolerance</td>
<td>LV Remodeling</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>--------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>--------------------</td>
<td>----------</td>
<td>----------</td>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Mahmarian, 1998 <em>9610531</em> (85)</td>
<td>Multicenter RCT</td>
<td>291 pts surviving a AMI</td>
<td>Severe CHF, persistent hypotension, sustained VT, high-degree AVB, UA, significant noncardiac illness, or either a requirement for or known intolerances</td>
<td>Intermittent NTG patch therapy initiated within 1 wk after AMI and continued for 6 mo (0.4, 0.8, and 1.6 mg/h)</td>
<td>Change in ESVI was significantly reduced with 0.4 mg/h NTG patches</td>
<td>Cardiac event rates were not significantly different between PC and active treatment groups</td>
<td>The beneficial effects seen primarily in pts with baseline LVEF ≤40% (delta ESVI, -31 mL/m²; delta EDVI, -33 mL/m²; both p&lt;0.05) and only at the 0.4 mg/h dose</td>
<td>No associated clinical or survival advantage associated with the beneficial remodeling effects. Gated radionuclide angiography used to assess changes in LVEF and cardiac volumes -- no TTE, and as such unable to address other aspects of LV remodeling. Higher NTG doses prevented LV remodeling to a lesser degree (NTG tolerance may be limiting efficacy at the higher doses).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-4, 1995 <em>7661937</em> (86)</td>
<td>RCT</td>
<td>58,050 vs. 29,018 pts within 24 h of onset of suspected AMI with no clear contraindications at the clinician’s discretion (e.g., conditions)</td>
<td>1 mo of oral controlled-release mononitrate</td>
<td>NS difference in 5-wk mortality (mononitrate vs. PC).</td>
<td>Greater effect early after starting treatment</td>
<td>No effect on any subgroup studied (age, sex, previous MI, ECG on 5-wk mortality: mononitrate vs. PC)</td>
<td>Hypotension 17.4% vs. 14.4%, p&lt;0.0005 (mononitrate vs. placebo).</td>
<td>No associated clinical or survival advantage associated with the beneficial remodeling effects. Gated radionuclide angiography used to assess changes in LVEF and cardiac volumes -- no TTE, and as such unable to address other aspects of LV remodeling. Higher NTG doses prevented LV remodeling to a lesser degree (NTG tolerance may be limiting efficacy at the higher doses).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
mononitrate on early mortality (4 wk)
indicators for, or contraindications to, any 1 of the study treatments
associated with a high risk of adverse effects, such as cardiogenic shock, persistent severe hypotension, evidence of severe fluid depletion, etc.) Or conditions associated with only a small likelihood of worthwhile benefit
(30 mg initial dose titrated up to 60 mg qd)

7.34% vs. 7.54%; p=NS
(deaths on d 0–1: 514 [1.77%] mononitrate vs. 628 [2.16%] PC; p<0.001).

7.54%, p=NS

50%–60% had open label nitrate therapy. Contraindications were specified not by the protocol, but by the responsible clinician

GISSI-3, 1994 7910229 (87)
Assess the effects of lisinopril and transdermal glyceryl trinitrate alone and their combination on 6-wk mortality and LVEF after AMI
Multicenter RCT 19,394 N/A N/A
AMI pts within 24 h of Sx onset and no clear indications for or against the study treatments
N/A
Nitrates (IV for the 1st 24 h, then transdermal GTN 10 mg daily)
PC (open label)
No effect of nitrate on 6-wk mortality: OR: 0.94 (95% CI: 0.84–1.05)
No effect of nitrates on the combined outcome measure of mortality and severe ventricular dysfunction.
Systematic combined administration of lisinopril and GTN produced significant reductions in overall mortality (OR: 0.83; 95% CI: 0.70–0.97) and in the combined endpoint, OR: 0.85; 95% CI: 0.76–0.94)
The trend toward reduction in cardiac events with nitrate therapy reached statistical significance among the elderly and women. Significant reductions in 6-wk mortality and combined outcome with lisinopril.
6-wk mortality: GTN vs. PC: OR: 0.94; 95% CI: 0.84–1.05
Combined outcome: GTN vs. PC: OR: 0.94; 95% CI: 0.87–1.02
No excess of unfavorable clinically-relevant events in the treated groups was reported. 2D echo data were available only for 14,209 pts (73%) 50%–60% had open label nitrate therapy.

Yusuf, 1988 2896919 (88)
Examine the effect of IV nitrates on mortality in AMI
Meta-analysis (10 RCTs) 2,000 N/A N/A
AMI pts–inclusions of individual trials
Exclusions of individual trials
Nitrates
PC
35% reduction (SD 10) in the odds of death (2p<0.001; 95% CI of approximately 0.166–0.50)
The greatest reduction in mortality occurred predominantly during the 1st wk of follow-up
Both NTG and nitroprusside reduced mortality, the reduction being NS greater with NTG than with nitroprusside
NS reduction after the 1st wk of follow-up
Publication bias Baseline risk heterogeneity Different definitions of clinical endpoints across the various studies

© American Heart Association, Inc and American College of Cardiology Foundation 2014 NSTE-ACS Guideline Data Supplements
LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, nonsignificant; NTG, intermittent transdermal nitroglycerin; NSTE-ACS, non-ST-elevation acute myocardial infarction; PC, placebo; pts, patients; qd, daily; RCT, randomized controlled trial; Rx, prescription; SD, standard deviation; STEMI, non-ST-elevation myocardial infarction; Sx, symptoms; Tn, troponin; TTE, transthoracic echocardiography; UA, unstable angina; and VT, ventricular tachycardia.

Data Supplement 10. Analgesic Therapy (Section 4.1.2.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iakobishvili, 2011 21627393 (89)</td>
<td>Determine the impact of IVM on outcomes of pts with ADHF with and without ACSs</td>
<td>Observational registry</td>
<td>2,336</td>
<td>218 (9.3%)</td>
<td>2,118 (90.7%)</td>
<td>Consecutive pts with ADHF participating in a national HF survey</td>
<td>N/A</td>
<td>IVM</td>
<td>No IVM</td>
<td>IM associated with higher unadjusted (11.5% vs. 5.0%) and adjusted inhospital mortality using logistic regression adjustment</td>
<td>IVM increased in-hospital mortality</td>
</tr>
<tr>
<td>Iakobishvili, 2010 20346305 (90)</td>
<td>Assess the 30-d outcomes stratified by IVNs use among pts enrolled in a national survey of pts with STEMI and NSTE-ACS</td>
<td>Multicenter retrospective analysis from the ACSIS 2008 database</td>
<td>993 pts with NSTE-ACS</td>
<td>97 (9.8%)</td>
<td>896 (90.2%)</td>
<td>Consecutive pts presenting with ACS to any of 26 CCU and cardiology wards in Israel</td>
<td>Pts transferred to another institution</td>
<td>IVM</td>
<td>No IVN</td>
<td>No diff in 30-d mortality with IVN use. Using propensity adjustment (95 matched NSTE-ACS pairs): 30-d death rate (2.2% for pts receiving IVNs vs. 6.3%; p=0.16)</td>
<td>Using logistic regression analysis, there were no diff in 30-d mortality among NSTE-ACS (OR: 0.58; 95% CI: 0.14–2.33; p=0.43)</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
ACS indicates acute coronary syndrome; ADHF, acute decompensated heart failure; CCU, cardiac care unit; CHF, congestive heart failure; 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; diff, differences; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; IVM, intravenous morphine; IVN, intravenous narcotics; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; NTG, intermittent transdermal nitroglycerin; pts, patients; STEMI, ST-elevation myocardial infarction; Sx, symptoms; and US, United States.

### Data Supplement 11. Beta-Adrenergic Blockers (Section 4.1.2.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI-III-R Roberts</td>
<td>Immediate vs. deferred BB Prospective multicenter</td>
<td>Immediate IV group A MI treated with invasive Implanted pacemaker; resting</td>
<td>IV metoprolol as soon as r-PA Global LVEF at time of discharge using</td>
<td>No diff in mortality in both Lower incidence of reinfarction Resting EF: immediate 51.0% vs. 50.1%</td>
<td>NS diff in deaths at 6 wk or 1 y Complexity of interventions other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only a minority of pts were treated with IVM.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryden, 1983</td>
<td>6828092</td>
<td>Occurrence of ventricular tachyarrhythmias in suspected AMI with BB.</td>
<td>Metoprolol 696 PC 697</td>
<td>Sx suggestive of AMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindications for beta-blockade; need for beta-blockade’s &quot;administrative considerations.&quot;</td>
<td>Metoprolol IV</td>
<td>Significant ventricular tachyarrhythmias: More cases of VF in the PC group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No increase in significant heart block with BB</td>
<td>BB did not influence PVCs or short bursts of VT in 1st 24 h, 3-mo mortality lower in BB group (5.7% vs. 8.9%) p&lt;0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effect of BB use within 72 h of MI on 6-wk mortality vs. PC</td>
<td></td>
<td>6-wk mortality: Adding a BB had no effect compared with control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BB vs. PC, or no control group roughly 50% each</td>
<td>RCT of MI with BB vs. PC within 72 h of AMI</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No information on 6-wk mortality. Treatment started after 72 h. Non-English speakers</td>
<td>Beta-1 or nonselective BB or PC within 72 h of MI, Follow up for 6 wk</td>
<td>Subgroup analysis that excluded high-risk pts showed mortality benefit of BB: 0.95 [0.88–0.99]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BB reduced total mortality by 40%, combined MACE by 31%.</td>
<td>Withdrawal of BB vs. PC NS.</td>
<td>Total mortality p=0.0001, MACE p=0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMI or UA &lt;28 d Contraindicated to BB, Metoprolol or PC for 1 y.</td>
<td>BB therapy showed lower hospital mortality 6-mo mortality also lower</td>
<td>Death from worsening HF reduced 49% vs. PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multi-institute prospective trial 1,926</td>
<td>BB vs. PC</td>
<td>Only 66% of post-MI pts ideal candidates for BB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;55 RCT of over 73,000 pts</td>
<td>Over 38,000 BB Over 35,000 PC</td>
<td>Lipophilic BBs prevent vs. fibrillation after MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMI</td>
<td>BB vs. PC</td>
<td>Total mortality p&lt;0.0001, SCD reduction &lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicate to BB, sever HF, heart block</td>
<td>Total deaths 13% reduction. Short-term SCD 34% reduction.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BB therapy showed lower hospital mortality 6-mo mortality also lower</td>
<td>Hospital mortality Killip III/IV 0.39 (95% CI: 0.23–0.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early BB therapy or none beginning &lt;24 h</td>
<td>Hospital mortality 0.58 (95% CI: 0.42–0.81) 6-mo mortality 0.75 (95% CI: 0.56–0.997)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Registry of 96 hospital pts admitted for ACS retrospective 7,106</td>
<td>Early BB therapy or none beginning &lt;24 h</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observational No adjustment for confounders. No indication of dose or brand</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metoprolol or PC for 1 y.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB vs. PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Over 38,000 BB Over 35,000 PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraindicate to BB, sever HF, heart block</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB vs. PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Over 38,000 BB Over 35,000 PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraindicate to BB, sever HF, heart block</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB vs. PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Over 38,000 BB Over 35,000 PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraindicate to BB, sever HF, heart block</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB vs. PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Over 38,000 BB Over 35,000 PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraindicate to BB, sever HF, heart block</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BB vs. PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Over 38,000 BB Over 35,000 PC</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Reference</td>
<td>Design</td>
<td>Population</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>-----------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>Dargie, 2001</td>
<td>2001</td>
<td>11358434</td>
<td>(99)</td>
<td>Multicenter randomized PC controlled 1,959</td>
</tr>
<tr>
<td>Chen, 2005</td>
<td>2005</td>
<td>16271643</td>
<td>(100)</td>
<td>Multicenter randomized PC controlled 45,852</td>
</tr>
<tr>
<td>Ellis, 2003</td>
<td>2003</td>
<td>14562669</td>
<td>(101)</td>
<td>Multicenter randomized PC ± abxiximab</td>
</tr>
<tr>
<td>McMurray, 2005</td>
<td>2005</td>
<td>15708698</td>
<td>(102)</td>
<td>Multicenter PC controlled 1,959</td>
</tr>
<tr>
<td>Miller, 2007</td>
<td>2007</td>
<td>17679127</td>
<td>(103)</td>
<td>Impact of early use of BB in ACS</td>
</tr>
<tr>
<td>Brandl, 2010</td>
<td>2010</td>
<td>20078433</td>
<td>(104)</td>
<td>Literature review to determine BB effects on outcome in ACS</td>
</tr>
</tbody>
</table>
Calcium Channel Blockers (Section 4.1.2.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Interventio n</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibson, 1986 3526151 (106)</td>
<td>Effect of diltiazem on NQMI, Multicenter double-blind randomized</td>
<td>576</td>
<td>Diltiazem 287</td>
<td>PC 269</td>
<td>NQMI &gt;500 m ischemic pain or ST changes</td>
<td>Q waves or conduction disturbances AV block</td>
<td>Bradycardia, Cardiac shock</td>
<td>Diltiazem 24–72 h from admission Up to 14 d</td>
<td>PC</td>
<td>Primary Endpoint (Efficacy) and Results</td>
<td>Safety Endpoint and Results</td>
</tr>
<tr>
<td>Lubsen, 1987 2887097 (107)</td>
<td>Efficacy of BB and CCB in UA in a CCU, Multicenter PC control</td>
<td>336</td>
<td>Combination of nifedipine and metoprolol</td>
<td>PC</td>
<td>UA not previously on BB</td>
<td>AMI</td>
<td>Nifedipine, metoprolol, or combination</td>
<td>PC</td>
<td>Ischemia or progression to MI in 48 h. Only pretreatment with BB showed favorable effects with nifedipine.</td>
<td>No increased mortality with CCB</td>
<td>Refractory angina reduced by diltiazem</td>
</tr>
<tr>
<td>Gibson, 1987 3303886</td>
<td>Px effect of diltiazem on recurrent ischemia, Multicenter double-blind</td>
<td>576</td>
<td>Diltiazem 287</td>
<td>PC 269</td>
<td>Confirmed NQMI</td>
<td>Q waves or conduction disturbances</td>
<td>Diltiazem 24–72 h from</td>
<td>PC</td>
<td>Incidence of early recurrent ischemia</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kontos, 2011 21570515 (105)</td>
<td>Registry of BB use in ACS, NCDC ACTION-GWTG registry 34,661 pts with NSTEMI 21,822</td>
<td>291 hospitals 2007–2008 21,822 BB</td>
<td>BB within 24 h of ACS</td>
<td>Contraindications to BB</td>
<td>BB only: early vs. late use</td>
<td>Very early BB use increased cardiogenic shock and death or shock</td>
<td>Evidence of increased cardiogenic shock with early use (&lt;24 h) of BB</td>
<td>NS diff between early or late use in death alone</td>
<td>Early vs. late use cardiacogenic shock: 1.54 (95% CI: 1.26–1.88); p&lt;0.001 Death or shock: 1.23 (95% CI: 1.08–1.40); p=0.0016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gibson, 1986 3526151 (106)</td>
<td>Effect of nitroglycerin on heart failure, Multicenter double-blind randomized</td>
<td>576</td>
<td>Diltiazem 287</td>
<td>PC 269</td>
<td>NQMI &gt;500 m ischemic pain or ST changes</td>
<td>Q waves or conduction disturbances AV block</td>
<td>Bradycardia, Cardiac shock</td>
<td>Diltiazem 24–72 h from admission Up to 14 d</td>
<td>PC</td>
<td>Primary Endpoint (Efficacy) and Results</td>
<td>Safety Endpoint and Results</td>
</tr>
<tr>
<td>Gibson, 1987 3303886</td>
<td>Px effect of diltiazem on recurrent ischemia, Multicenter double-blind</td>
<td>576</td>
<td>Diltiazem 287</td>
<td>PC 269</td>
<td>Confirmed NQMI</td>
<td>Q waves or conduction disturbances</td>
<td>Diltiazem 24–72 h from</td>
<td>PC</td>
<td>Incidence of early recurrent ischemia</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Design</td>
<td>Patients</td>
<td>CCB Effect on Events</td>
<td>Meta-Analysis of 28 Trials</td>
<td>MI/UA CHF Hypertension</td>
<td>Effect on Mortality</td>
<td>Total Mortality</td>
<td>Cardiac Deaths</td>
<td>Discontinuation of Therapy</td>
<td>Observation</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>--------</td>
<td>----------</td>
<td>----------------------</td>
<td>---------------------------</td>
<td>------------------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Held, 1989</td>
<td>2513047 (109)</td>
<td>Meta-analysis of 28 trials</td>
<td>19,000</td>
<td>8,870</td>
<td>CHF Hypotension AV block (most common)</td>
<td>CCB usually early in ACS</td>
<td>Control</td>
<td>Risk of death, infarct size, or reinfarction.</td>
<td>CCB benefit for same time period</td>
<td>Significant reduction in BP and HR with CCB, though small</td>
<td>CCB benefit on hypertension without pulmonary congestion</td>
</tr>
<tr>
<td>Moss, 1991</td>
<td>1872266 (110)</td>
<td>Multicenter PC control</td>
<td>2,464</td>
<td>No HTN Diltiazem: 760 PC: 762</td>
<td>Hypertension Diltiazem: 471 PC: 471</td>
<td>MI treated with diltiazem with or without hypertension</td>
<td>Diltiazem at ACS for 12-52 mo</td>
<td>PC for same time period</td>
<td>1st recurrent cardiac event: CCB benefit only in hypertensives with no pulmonary congestion.</td>
<td>Increased sympathetic and active of RAAS</td>
<td>Total mortality 1.16 (95% CI: 1.01–1.33); p=0.01</td>
</tr>
<tr>
<td>Furberg, 1995</td>
<td>7648682 (111)</td>
<td>Meta-analysis of 16 studies</td>
<td>8,350</td>
<td>Nifedipine 4,171</td>
<td>Control 4,183</td>
<td>Nifedipine 2nd prevention trials with mortality data</td>
<td>No randomization</td>
<td>Nifedipine 12 AMI 3 UA 1 SA Short-acting</td>
<td>Effect on mortality Nifedipine increased mortality by 16% Dose related</td>
<td>Increased sympathetic and active of RAAS</td>
<td>Total mortality 1.16 (95% CI: 1.01–1.33); p=0.01</td>
</tr>
<tr>
<td>Rengo, 1996</td>
<td>8602564 (112)</td>
<td>Multicenter prospective trial</td>
<td>1,073</td>
<td>Verapamil 531</td>
<td>PC 542</td>
<td>Dx of AMI Long acting Verapamil 7-21 d after AMI 360 mg qd for 24 mo</td>
<td>PC For 24 mo</td>
<td>Total mortality and CV deaths. No diff between groups</td>
<td>No safety issues</td>
<td>Verapamil group had lower reinfarction rates (NS) 39 vs. 49 Significantly less angina OR: 0.8 (95% CI: 0.5-0.9)</td>
<td>Total mortality verapamil vs. PC 30 vs. 29 NS Cardiac deaths 21 vs. 22 NS</td>
</tr>
<tr>
<td>Study, Year</td>
<td>Design</td>
<td>No.</td>
<td>Treatment</td>
<td>Comparator</td>
<td>Outcomes</td>
<td>Follow-up</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>-----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>----------</td>
<td>------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith, 1998</td>
<td>Retrospective cohort</td>
<td>247</td>
<td>BB vs. CCB</td>
<td>UA in UA</td>
<td>Deaths in 51 mo</td>
<td>N/A</td>
<td>Adjusted: for CCB vs. BB</td>
<td>1.1 (95% CI: 0.49-2.4)</td>
<td>p&lt;0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pepine, 1998</td>
<td>Meta-analysis</td>
<td>4,000 person y</td>
<td>Verapamil vs. PC</td>
<td>Randomized studies of verapamil and PC from AMI</td>
<td>Outcomes with CCBs after Ml: No diff in deaths vs. PC</td>
<td>Decreased nonfatal MI</td>
<td>No diff in deaths vs. PC</td>
<td>NS for increased harm with verapamil</td>
<td>Combined death/reinfarction: 0.82 (95% CI: 0.70-0.97); p=0.016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DAVIT**

- **Danish study, 1984**
  - Multicenter prospective study
  - 6 mo and 12 mo mortality after AMI with verapamil
  - 3,498
  - Verapamil vs. PC
  - AMI: HF, AV block, severely disabling diseases, treatment with BB or CCB
  - Verapamil 120 tid for 6 mo PC for 6 mo
  - NS diff in 6-mo or 12-mo mortality rate verapamil vs. PC
  - Higher number of AV block in verapamil group not associated with increased mortality NS decreased in vs. fibrillation in verapamil group.

- **DAVIT II**
  - Danish study, 1990
  - Multicenter prospective trial
  - 18 mo mortality rates and major CV events with verapamil after AMI
  - 1,775
  - Verapamil vs. PC
  - AMI: HF, AV block, severely disabling diseases, treatment with BB or CCB
  - Verapamil 360 mgqd from 2nd wk of AMI and up to 18 mo PC for same period
  - Significant diff in reasons for permanently stopping verapamil vs. PC: 2nd or 3rd degree AV block, sinus bradycardia.
  - In pts without HF in CCU 18-mo mortality: verapamil vs. PC 7.7% vs. 11.8% p=0.02 0.64 (95% CI: 0.44–0.94) Major CV event rates: 18-mo mortality: verapamil vs. PC 11.1% vs. 13.8% p=0.11 0.80 (95% CI: 0.61–1.05) Major CV events: Minor discrepancies between resulting confidence limits and p values from the Tarone-Ware tests occurred because HR are based on proportional hazards.
### Data Supplement 13. Other Anti-Ischemic Interventions (Ranolazine) (Section 4.1.2.5)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson SR, 2009 19389561 (117)</td>
<td>Evaluate the efficacy and safety of ranolazine in pts with prior chronic SA</td>
<td>Substudy from a multinational RCT</td>
<td>3,565</td>
<td>1,789</td>
<td>1,776</td>
<td>Pts with NSTE-ACS within 48 h of ischemic Sx (between Oct 2004-Feb 2007)</td>
<td>Eligibility criteria: ≥18 y; Sx of myocardial ischemia; at least 1 moderate-high-risk indicator</td>
<td>Cardiogenic shock, persistent STE, successful revasc before randomization, clinically significant hepatic disease, ESRD requiring dialysis, treatment with agents known to prolong the QT interval, ECG abnormal levels interfering with Holter interpretation, life expectancy &lt;12 mo</td>
<td>Ranolazine</td>
<td>PC</td>
</tr>
<tr>
<td>Scirica, 2007 17804441</td>
<td>Assess the potential</td>
<td>Sub-study from a</td>
<td>6,351</td>
<td>3,162</td>
<td>3,189</td>
<td>Pts with NSTE-ACS</td>
<td>Cardiogenic shock, persistent STE, successful revasc before randomization, clinically significant hepatic disease, ESRD requiring dialysis, treatment with agents known to prolong the QT interval, ECG abnormal levels interfering with Holter interpretation, life expectancy &lt;12 mo</td>
<td>Ranolazine</td>
<td>PC</td>
<td>Ranolazine was associated (numerically, but not statistically)</td>
</tr>
</tbody>
</table>

**Notes:**
- 2º indicated secondary: ACS, acute coronary syndrome; AMI, acute myocardial infarction; AV, atrioventricular; BB, beta-blocker; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CCL, cardiac care unit; CHF, congestive heart failure; CV, cardiovascular; diff, difference(s); Dx, diagnosis; HF, heart failure; Hx, history; HTN, hypertension; LV, left ventricular; MI, myocardial infarction; NQMI, Non-Q Wave myocardial infarction; NS, no/t significant; PC, placebo; pts, patients; Px, prognosis; qd, once daily; RAAS, Renin-Angiotensin-Aldosterone System; SA, stable angina; t.i.d., three times daily; and UA, unstable angina.
- P values, OR: HR: RR & 95% CI:
  - 14.6% vs. 19.7%; p=0.01 0.70 (95% CI: 0.52–0.93) In HF, NS diff in mortality or major CV events
  - 18.0% vs. 21.6%; p=0.03 0.80 (95% CI: 0.64–0.99)
<table>
<thead>
<tr>
<th>Morow, 2007</th>
<th>Determine the efficacy and safety of ranolazine during long-term treatment of pts with NSTE-ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multinational RCT</strong></td>
<td>6,560</td>
</tr>
<tr>
<td><strong>Cardiogenic shock, persistent STE, successful revasc before randomization, clinically significant hepatic disease, ESRD requiring dialysis, treatment with agents known to prolong the QT interval, ECG abnls interfering with Holter interpretation, life expectancy &lt;12 mo</strong></td>
<td><strong>Ranolazine (initiated IV followed by oral ranolazine extended-release 1000 mg 2× daily)</strong></td>
</tr>
</tbody>
</table>

| | with fewer episodes of VT ≥8 beats (5.3% vs. 8.3%; p<0.001), SVT (44.7% vs. 55.0%; p<0.001), or new-onset AF (1.7% vs. 2.4%; p=0.08) (Continuous ECG [Holter] recording was performed for the 1º 7 d after randomization) | lower incidence of sudden cardiac death in pts treated with ranolazine over the entire study period | with ranolazine (3.1% vs. 4.3%; p=0.01) | p<0.001) SVT (44.7% vs. 55.0%; p<0.001), New-onset AF (1.7% vs. 2.4%; p=0.08) | meet its 1º endpoint (exploratory) |

1º indicates primary; 2º, secondary; ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; diff, difference; ECG, electrocardiograph; ESRD, end-stage renal disease; Hx, history; IV, intravenous; MI, myocardial infarction; NS, not significant; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation acute coronary syndrome; pts, patients; RCT, randomized controlled trial; revasc, revascularization; Rx, prescription; SA, stable angina; STE, ST-elevation; Sx, symptoms; SVT, sustained ventricular tachycardia; and VT, ventricular tachycardia.
### Data Supplement 14. Inhibitors of the Renin-Angiotensin-Aldosterone System (Section 4.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Type</th>
<th>Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVE Pfeffer, 1992 1386652 (120)</td>
<td>Captopril on events in AMI with LV dysfunction</td>
<td>Multi-institute prospective</td>
<td>2,231</td>
<td>Captopril 1,115</td>
<td>PC 1,116</td>
<td>3d after AMI LVEF&lt;4% 21–79 y.</td>
<td>Contraind. to ACEI Creatinine &gt;2.5 mg/dL</td>
<td>Captopril for 42 mo</td>
<td>PC</td>
<td>All-cause mortality reduced in captopril group vs. PC (20% vs. 25%) Reduction of MACE by 21%</td>
</tr>
<tr>
<td>Ambrosioni, 1995 7990904 (121)</td>
<td>ACEI for short-term events</td>
<td>Multi-institute prospective</td>
<td>1,556</td>
<td>Zofenopril 772</td>
<td>PC 784</td>
<td>CCU with AMI</td>
<td>Contraindication to ACEI</td>
<td>ACEI for 6 wk</td>
<td>PC</td>
<td>6-wk death or severe HF reduced by 34% with ACEI</td>
</tr>
<tr>
<td>CONSENSUS II Swedberg, 1992 1495520 (122)</td>
<td>Long-term reduction in mortality with ACEI</td>
<td>Multi-institute prospective</td>
<td>6,090</td>
<td>Enalapril 3,044</td>
<td>PC 3,046</td>
<td>&lt;24 h after onset of chest pain with ECG/ enzyme changes</td>
<td>BP &lt;100/60, need for vasopressors, severe heart block, valvular disease, contraindication to ACEI, TIA</td>
<td>Enalapril for 6 mo</td>
<td>PC</td>
<td>1- and 6-mo mortality unchanged with enalapril vs. PC 7.2% vs. 6.3% 1 mo 11.0% vs. 10.2% 6 mo</td>
</tr>
<tr>
<td>ACEI Mi Coll. Group 1998 9631869 (123)</td>
<td>Use of ACEI in early AMI</td>
<td>Meta-analysis of 4 clinical trials</td>
<td>98,496</td>
<td>ACEI roughly 1/2</td>
<td>PC roughly 1/2</td>
<td>AMI-early short-term trials&gt;1,000 pts Smaller trials, no control group</td>
<td>ACEI from 28-42 d</td>
<td>PC</td>
<td>30-d mortality reduction 7% by ACEI</td>
<td>Hypotension less common in ACEI vs. controls 9.3 vs. 17.6%</td>
</tr>
</tbody>
</table>
### AIREX Hall, 1997 9167457 (124)

| Multicenter prospective trial: 603 in initial AIRE trial of 15 mo | Ramipril 302 | PC 301 | AMI with evidence of HF | Clinical instability, contraindication to ACEI, HF of valvular or congenital HD, need for open label ACEI. | Ramipril beginning 2-9 d after admission and up to 15 mo with 3-y follow-up poststudy | PC for 15 mo, then 3-y follow-up | 15-mo mortality with ACEI and 3-y follow-up mortality also reduced | N/A | N/A | 15-mo mortality: 16.9% ACEI 22.6% PC 27% (95% CI: 11–40); p=0.002 3-y post-AIRE mortality: 27.5% ACEI 38.9% PC 36% (95% CI: 15–52); p=0.002 Reduction with ACEI. Mortality benefit only in 1st 24 mo after study ended. Possibly because more severely ill PC pts died before 24 mo leaving a relatively healthy post-PC population. |

### Squire, 2010 20478862 (125)

| Benefit of BNP in use of ACEI in ACS Observation cohort study retrospective: 1,725 | ACEI in all or ARB in some cases | Various levels of BNP | ACEI or ARB median 528 d follow-up | NT-pro-BNP values by quartiles | MACE: only in top quartile of BNP was ACEI associated with reduction of MACE. NS benefit in other BNP quartiles | ACEI treatment Had survival benefit only in pts without diabetes mellitus or hypertension. Death or HF: reduced risk in top quartile of BNP: 0.498 (0.31, 0.80); p=0.004 NS reduction of death in top BNP quartile. Decreased MACE in top quartile of BNP: HR: 0.813 (0.46,0.82); p=0.001 | Observational only. Possible residual confounding of variables. Demographic diff in BNP. Single center, but 2 hospitals. |

### Pfeffer, 2003 14610160 (126)

| Effect of ACEI and ARB combination in AMI with HF/LV Dysfunction Multicenter prospective trial: 14,703 | Valsartan 4,909 Captopril 4,909 Both 4,885 | 3-way comparison | AMI 0.5–10 d HF and/or LVEF <0.35 by echo or <0.40 by RN | Low BP Creatinine >2.5 | ACE, ARB combination Median 24.7 mo 3-way comparison | Total mortality: NS diff among 3 groups | Valsartan: hypotension, renal abnormalities more common. Captopril: cough, rash, dysgeusia more common. Noninferiority of valsartan vs. captopril for death | Total mortality: valsartan vs. captopril 1.00 (97.5% CI: 0.90–1.11) Combined vs. captopril 0.98 (97.5% CI: 0.89–1.09) Significant adverse events: hypotension, renal causes, hyperkalemia, cough, rash, dysgeusia, angioedema. Significant greater adverse events with combination vs. valsartan alone, 9.0% vs. 5.8% for permanent discontinuation of drug. |

### Pitt, 2003 12668699 (127)

| Effect of eplerenone in AMI with LV dysfunction Multicenter prospective trial: 6,632 | Eplerenone 3,319 PC 3,313 | 3-14 d after AMI LVEF ≤0.40 CHF on ACEI, BB, | K+ sparing diuretics use; Creatinine >2.5 K+>5 meq/L | Eplerenone mean follow-up 16 mo | PC Total and CV death Total deaths and CV deaths decreased by eplerenone vs. BP increase less in eplerenone than PC increase in creatinine EP>PC | Reduction in sudden death 0.79 (95% CI: 0.64–0.97); p=0.03 | Total deaths: 0.85 (95% CI: 0.75–0.96); p=0.008 CV deaths: 0.83 (95% CI: 0.72–0.94); p=0.005 Low rate of D/C of EP for adverse events. No gynecomastia. However, increased incidence of serious hyperkalemia |

© American Heart Association, Inc and American College of Cardiology Foundation 35
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Details</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gheorghiade, 2009</td>
<td>Effect of eplerenone on readmission hospital stay after MI with LV dysfunction</td>
<td>Eplerenone 3,319</td>
</tr>
<tr>
<td>Rossignol, 2011</td>
<td>Mechanism of eplerenone benefit in AMI</td>
<td>Eplerenone 3,055</td>
</tr>
<tr>
<td>Rossignol, 2012</td>
<td>Eplerenone effects on renal function after AMI</td>
<td>Eplerenone 2,918</td>
</tr>
</tbody>
</table>
| GISSI-3, 1994 | Effect of ACEI on mortality and LV function | Lisinopril 10 mg qd for 6 wk | PC | Deaths and combined deaths and LV dysfunction | Rates of hypotension and renal dysfunction | Rates of reinfarction, cardiogenic shock, and Overall 6-wk mortality reduction: OR: 0.88 (95% CI: 0.79–0.99) | Overall reduction in relative low dosage of lisinopril, many elderly and women excluded

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Details</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Weir, 2009 | MRI study to evaluate eplerenone effects on LV after MI | Eplerenone 50 | PC | Change in LV systolic volume after covariate adjusted volume fell by 6.1±2.7 mL/m² vs. PC | NS differ between eplerenone and PC in HR, BP changes between diuretic and K+ sparing effects only on a 1st timepoint, 1-month timepoint, and 24 months only.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Details</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- 6,632; 827 with subsequent hospital readmission</td>
<td>Eplerenone 3,199</td>
</tr>
<tr>
<td></td>
<td>- 19699868</td>
<td>Rossignol</td>
</tr>
<tr>
<td></td>
<td>- 22128223</td>
<td>Rossignol</td>
</tr>
<tr>
<td></td>
<td>- 20136442</td>
<td>Weir</td>
</tr>
<tr>
<td></td>
<td>- 6,080</td>
<td>Rossignol</td>
</tr>
<tr>
<td></td>
<td>- 5,792</td>
<td>Rossignol</td>
</tr>
<tr>
<td></td>
<td>- 18,895</td>
<td>GISSI-3</td>
</tr>
</tbody>
</table>
studies of ACEIs have shown that they reduce mortality and combined outcomes, with higher mortality and combined outcomes observed in patients treated with placebo. However, concern about slightly increased creatinine and hypotension with ACEIs has been expressed.

Concern about slightly increased creatinine and hypotension with ACEIs

**Data Supplement 15. Oral and Intravenous Antiplatelet Therapy in Patients With Likely or Definite NSTE-ACS Treated With Initial Invasive or Conservative Strategy (Section 4.3.1)**

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type / Size (N)</th>
<th>Intervetion vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baigent 2009 (132)</td>
<td>Low-dose ASA is of definite and substantial net benefit for people who already have occlusive vascular disease. Assessed the benefits and risks in 1st prevention.</td>
<td>Meta-analysis N=95,000 pts at low avg risk</td>
<td>ASA vs. no ASA</td>
<td>1st or 2nd prevention trials eligible only if they involved randomized comparison of ASA vs. no ASA (with no other antiplatelet drug in either group).</td>
<td>1st prevention trials excluded individuals with any Hx of occlusive disease at entry</td>
<td>Serious vascular events (MI, stroke, or vascular death) 0.51% vs 0.57%</td>
<td>Major bleeds 0.10% vs. 0.07% per y; p=0.0001</td>
<td>2nd prevention trials ASA allocation yielded greater absolute reduction in serious vascular events (6.7% vs. 8.2% per y; p=0.0001) with NS increase in haemorrhagic stroke but reductions of about 1/5 in total stroke (2.08% vs. 2.54% per y;</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>Study</td>
<td>Author</td>
<td>Year</td>
<td>Design</td>
<td>Comparator</td>
<td>Comparator dose</td>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>------</td>
<td>--------</td>
<td>------------</td>
<td>----------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURE</td>
<td>Yusuf</td>
<td>2001</td>
<td>Randomized, double-blind, PC trial</td>
<td>Clopidogrel vs. PC in addition to ASA</td>
<td>Pts were eligible for study if they had been hospitalized within 24 h after onset of Sx and no STE</td>
<td>Contraindications to antiplatelet or antithrombotic or antiplatelet therapy, high risk for bleeding or severe HF, taking oral anticoagulants, had undergone coronary revasc in the previous 3 mo or received IV GP IIb/IIIa receptor inhibitors in the previous 3 d</td>
<td>Clopidogrel (300 mg immed followed by 75 mg od) vs. PC in addition to ASA</td>
<td>Death from CV causes, nonfatal MI, or stroke</td>
<td>Pts with major bleeding</td>
</tr>
<tr>
<td>PLATO</td>
<td>Mahaffey</td>
<td>2011</td>
<td>Observed regional interaction driven by interaction of randomized treatment with 76% of NA pts in US compared with ROW pts</td>
<td>N/A</td>
<td>Reasons for the interaction were explored independently by 2 statistical groups</td>
<td>Reasons for the interaction were explored independently by 2 statistical groups</td>
<td>Clopidogrel (300 mg immed followed by 75 mg od) vs. PC in addition to ASA</td>
<td>N/A</td>
<td>Large number of subgroup analyses performed and result numerically favoring clopidogrel in at least 1 of the 4 prespecified regions could occur with 32% probability. More pts in US (53.6%) than in the rest of the world (1.7%) took median ASA dose ≥300 mg od. Of 37 baseline and postrandomization factors explored, only ASA dose explained substantial fraction of the regional interaction.</td>
</tr>
<tr>
<td>Gremmel</td>
<td>2010</td>
<td>Investigate age dependency of</td>
<td>Prospective observational</td>
<td>N/A</td>
<td>Pts on dual antiplatelet therapy</td>
<td>Known acetylsalicylic acid or ADP-inducible platelet reactivity increased</td>
<td>LD of 300 mg (n=116; 60.7%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
Assess potential benefit of clopidogrel compared with ASA in reducing risk of ischemic stroke, MI, or vascular death in pts with CAPRIE

Randomized N=19,185 pts

N=9,577 clopidogrel (75 mg od) plus PC

N=9,566 ASA (325 mg od) plus PC

Ischemic stroke (including retinal origin and lacunar infarction); MI; Atherosclerotic PAD

Severe cerebral deficit likely lead to pts being bedridden or demented; Carotid endarterectomy after qualifying stroke; Qualifying stroke induced by carotid endarterectomy or

Clopidogrel (75 mg od) ASA (325 mg od)

Pts treated with clopidogrel had annual 5.32% risk of ischemic stroke, MI, or vascular death compared with 5.83% with ASA. Significant (p=0.043) relative-risk reduction of 8.7% in favor of clopidogrel (95% CI: There were no major differences in terms of safety N/A

p=0.043 RR reduction of 8.7% in favor of clopidogrel CI: 0.3–16.5

Reported adverse experiences in the clopidogrel and ASA groups judged to be severe included rash (0.26% vs. 0.10%), diarrhea (0.23% vs. 0.11%), upper gastrointestinal N/A
recent ischaemic stroke, recent MI, or PAD.

angiography; Pts unlikely to be discharged after qualifying event; Severe comorbidity likely to limit pts life expectancy to less than 3 y. Uncontrolled hypertension, Scheduled for major surgery, Contraindications to study drugs; Women of childbearing age not using reliable contraception, Currently receiving investigation drug; Previously entered in other clopidogrel studies.

0.3-16.5). Corresponding on-treatment analysis yielded RR reduction of 9.4%.

Corresponding on-treatment analysis yielded RR reduction of 9.4%.

0.10% in clopidogrel group with significant reductions in neutrophils (<1.2 x 10^9/L) and 16 (0.17%) in ASA group.

discomfort (0.97% vs. 1.22%), intracranial haemorrhage (0.33% vs. 0.47%), and gastrointestinal haemorrhage (0.52% vs. 0.72%). 10 pts (0.10%) in clopidogrel group with significant reductions in neutrophils (<1.2 x 10^9/L) and 16 (0.17%) in ASA group.

Gollapudi 2004 15613671 (137)

Provide diagnostic strategy for evaluating and treating pts with ASA sensitivity, with additional consideration for issues specific to pts with CAD.

Literature review N/A N/A N/A N/A

Prevalence of ASA-exacerbated respiratory tract disease approximately 10% and for ASA-induced urticaria prevalence varies 0.07% to 0.2% of general population. ASA sensitivity most often manifested as rhinitis and asthma or urticaria/angioedema induced by cross-reacting NSAID that inhibit cyclooxygenase 1. 1º mechanism of sensitivity less often related to drug-specific IgE antibody production leading to
urticaria/angioedema and rarely to anaphylaxis. Most pts with acetylsalicylic acid sensitivity are able to undergo desensitization therapy safely and successfully except in cases of chronic idiopathic urticaria. Experience with acetylsalicylic acid desensitization in pts with CAD very limited.

TRITON – TIMI 38
Wiviott 2007 17982182
(138)

Compare regimens of prasugrel and clopidogrel

N=13,608 pts with ACS with scheduled PCI

Prasugrel n=6813 (60 mg LD and 10 mg qd maintenance dose) or Clopidogrel n=6795 (300 mg LD and 75 mg qd maintenance dose), for 6-15 mo

Pts with UA/NSTEMI, TIMI risk score ≥3, either ST-segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis. Pts with STEMI could be enrolled within 12 h after onset of Sx if 1st PCI was planned or within 14 d after receiving medical treatment for STEMI

Increased risk of bleeding, anemia, thrombocytopenia, a Hx of pathologic intracranial findings, or use of any thienopyridine within 5 d before enrollment.

Prasugrel or clopidogrel

Death from CV causes, nonfatal MI, or nonfatal stroke
12.1% clopidogrel vs 9.9% prasugrel rates of MI
9.7% clopidogrel vs. 7.4% prasugrel; p<0.001
urgent target-vessel revasc 3.7% vs. 2.5%; p<0.001 stent thrombosis 2.4% vs. 1.1%; p<0.001

Major bleeding- TIMI major bleeding not related to CABG, non-CABG related TIMI life threatening bleeding, and TIMI major or minor bleeding 2.4% prasugrel vs. 1.8% clopidogrel

HR: 1.32; 95% CI: 1.03–1.68; p=0.03 rate of life-threatening bleeding 1.4% vs. 0.9%; p=0.01 including

Stent thrombosis and composite of death from CV causes, nonfatal MI, nonfatal stroke, or rehospitalization due to a cardiac ischemic event.

Rate of MI with subsequent death from CV causes 0.7% vs. 0.4% HR: 0.58; CI:0.36 - 0.93; p=0.02

p<0.001

More pts treated with prasugrel 2.5% vs. 1.4% clopidogrel; p<0.001

discontinued the study drug owing to adverse events related to hemorrhage; rate of serious adverse events not related to hemorrhage was similar 22.5% vs 22.8% p=0.52

N/A
<table>
<thead>
<tr>
<th>PLATO Wallentin 2009</th>
<th>Determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in broad population of pts presenting with ACS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=18,624 pts with ACS with or without STE</td>
<td>Ticagrelor was associated with a higher rate of major bleeding not related to CABG (5.4% vs. 3.8%, p=0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.</td>
</tr>
<tr>
<td>Ticagrelor or clopidogrel</td>
<td>Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001).</td>
</tr>
<tr>
<td>Hospitalized for ACS with or without STE; with an onset of Sx during the previous 24 h. Pts who had ACS NSTE at least 2 of the following 3 criteria had to be met: ST changes on ECG indicating ischemia; positive test of biomarker, indicating myocardial necrosis; one of several risk factors (age≥60 y; previous MI or CABG; CAD with stenosis of ≥50% in at least 2 vessels; previous ischemic stroke, TIA, carotid stenosis of at least 50% or cerebral revasc; DM; PAD; chronic renal dysfunction, defined as a creatinine clearance of &lt;60 ml/min per 1.73 m2 of body surface area with STE the following 2 inclusion</td>
<td>Major bleeding 11.6% vs 11.2%, p=0.43 ticagrelor was associated with a higher rate of major bleeding not related to CABG 4.5% vs. 3.8%, p=0.03, including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.</td>
</tr>
<tr>
<td>Any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 h before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer</td>
<td>Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001).</td>
</tr>
<tr>
<td>Ticagrelor or clopidogrel</td>
<td>Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001).</td>
</tr>
<tr>
<td>Any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 h before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer</td>
<td>Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001).</td>
</tr>
<tr>
<td>Any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 h before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer</td>
<td>Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001).</td>
</tr>
<tr>
<td>Ticagrelor or clopidogrel</td>
<td>Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001).</td>
</tr>
<tr>
<td>Ticagrelor or clopidogrel</td>
<td>Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001).</td>
</tr>
<tr>
<td>Mehta 2010</td>
<td>Clopidogrel and ASA are widely used for pts with ACS and those undergoing PCI. However, evidence-based guidelines for dosing have not been established for either agent.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>N=25,086 pts</td>
<td>Pts randomly assigned to double-dose clopidogrel received 600 mg LD followed by 150 mg od d 2-7. Pts assigned to standard-dose clopidogrel received 300 mg LD before angiography followed by 75 mg od days 2-7. D 8-30 both double-dose and standard-dose groups received 75 mg of clopidogrel od. Pts randomly assigned to lower-dose ASA received 75-100 mg daily on d 2-30. Those ≥18 yand presented with a NSTE, ACS or STE MI. Either ECG changes compatible with ischemia or elevated levels of cardiac biomarkers; coronary angiographic assessment, with plan to perform PCI as early as possible but no later than 72 h after randomization</td>
</tr>
<tr>
<td>Increased risk of bleeding or active bleeding and known allergy to clopidogrel or ASA</td>
<td>Time to CV death, MI, or stroke whichever occurred 1º, up to 30 d. Primary outcome occurred in 4.2% of pts assigned to double-dose clopidogrel compared with 4.4% assigned to standard-dose clopidogrel HR: 0.94, 95% CI: 0.83-1.06 p=0.30 NS difference between higher-dose and lower-dose ASA respect to 1º outcome 4.2% vs. 4.4% HR: 0.97: 95% CI: 0.86–1.09; p=0.61 Major bleeding occurred in 2.5% of pts in double-dose group and 2.0% in standard-dose group HR: 1.24; 95% CI: 1.05–1.46; p=0.01 NS difference between higher-dose and lower-dose ASA with respect to major bleeding (2.3% vs. 2.3%; HR: 0.99; 95% CI: 0.84-1.17; p=0.90).</td>
</tr>
<tr>
<td>2x2 factorial design. Pts were randomly assigned in open label fashion to higher-dose ASA or lower-dose ASA.</td>
<td>Composite of death from CV causes, MI, stroke, or recurrent ischemia; the individual components of 1º outcome; death from any cause; Definite or probable stent thrombosis. Double-dose clopidogrel associated with significant reduction in 2º outcome of stent thrombosis among the 17,263 pts who underwent PCI HR: 0.85; p=0.001).</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>© American Heart Association, Inc and American College of Cardiology Foundation</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Nominally significant reduction in 1º outcome was associated with use of higher-dose clopidogrel in subgroup of 17,263 study participants who underwent PCI after randomization (69%). Test for interaction between pts who underwent PCI and those who did not undergo PCI (p=0.03) did not meet prespecified threshold of p=0.01 for subgroup interactions. 13 prespecified subgroup analyses were performed for the clopidogrel dose comparison; this
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Primary Outcomes</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plato James 2011</td>
<td>Evaluate efficacy and safety outcomes in pts in PLATelet inhibition and pts outcomes (PLATO) trial who at randomization were planned for a non-invasive treatment strategy.</td>
<td>Randomized N=5216 pts</td>
<td>Ticagrelor n=2601 vs clopidogrel n=2615</td>
<td>Admitted to hospital with STE ACS scheduled for PCI or NSTE-ACS, with onset of Sx during the previous 24 h. At least two of the following three criteria were required for NSTE-ACS: STE depression or transient elevation of at least 1 mm in ≥2 contiguous leads; a positive biomarker indicating myocardial necrosis; and 1 additional risk indicator, including age &gt;60 y, previous MI or CABG, CAD, previous ischaemic stroke. TIA, carotid stenosis, cerebral revascularization, DM, PAD, or chronic renal dysfunction</td>
</tr>
<tr>
<td>ISAR-REACT 2 Kastrati 2011</td>
<td>Assess whether abciximab is associated with clinical benefit in high-risk pts with ACS undergoing PCI after</td>
<td>Randomized N=2,022 pts</td>
<td>Abciximab n=1012 vs PCn=1010</td>
<td>High-risk ACS pts undergoing PCI</td>
</tr>
</tbody>
</table>

|  | | | | | | | Overall mortality 6.1% vs. 8.2% HR: 0.75; 95% CI: 0.61–0.93; p=0.01 |
| | | | | | | | p=0.04 HR: 0.85 95% CI: 0.73–1.00 |
| | | | | | | | p=0.03 RR: 0.75 95% CI: 0.58–0.97 |

N/A: Result could have been due to the play of chance.

Abbreviations: ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; HR, hazard ratio; IQR, interquartile range; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PCI-DES, percutaneous coronary intervention with drug-eluting stents; PTCA, percutaneous transluminal coronary angioplasty; STE-ACS, ST-elevation acute coronary syndrome; TIA, transient ischemic attack; UTVR, urgent target vessel revascularization.
pretreatment with 600 mg of clopidogrel

<table>
<thead>
<tr>
<th>Inhibition of platelet aggregation with eptifibatide would have incremental benefit beyond that of heparin and ASA in reducing frequency of adverse outcomes in pts with ACS who did not have persistent STE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURSUIT Trial 2010 9705684 (143)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Double blind n=10,948 pts</th>
<th>Bolus and infusion of eptifibatide or PC n=1487 low-dose eptifibatide group n=4722 high-dose eptifibatide group n=4739 PC group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts who had presented with ischemic chest pain within previous 24 h and who had either ECG changes indicative of ischemia (but not persistent STE) or high serum concentrations of CK-MB isoenzymes</td>
<td>Persistent STE of more than 1 mm, active bleeding or a Hx of bleeding diathesis, gastrointestinal or genitourinary bleeding within 30 d before enrollment, systolic blood pressure above 200 mmHg or diastolic blood pressure above 110 mmHg, a Hx of major surgery within the previous 6 wk, a Hx of nonhemorrhagic stroke within previous 30 d or any Hx of hemorrhagic stroke, renal failure, pregnancy, the planned administration of platelet GP IIb/IIIa receptor inhibitor or thrombolytic agent, or receipt of Epitifibatide or PC bolus dose of 180 mcg/kg of body weight, followed by infusion of 1.3 mcg/kg/min or bolus dose of 180 mcg/kg followed by infusion of 2.0 mcg/kg/min or bolus and infusion of PC</td>
</tr>
<tr>
<td>Composite of death and nonfatal MI occurring up to 30 d after index event compared with PC group. Eptifibatide group had 1.5% absolute reduction in incidence of 1st endpoint (14.2% vs. 15.7% in PC group; p=0.04) Effect was consistent in most major subgroups except for women (odds ratios for death or nonfatal MI, 0.8 (95% CI: 0.7-0.9) in men and 1.1 (95% CI: 0.9-1.3) in women</td>
<td></td>
</tr>
<tr>
<td>Bleeding complications More red-cell transfusions among the pts treated with eptifibatide 11.6% vs. 9.2%; RR: 1.3; 95% CI: 1.1-1.4 Study would be stopped in lower-dose group after independent DSMB conducted interim review of safety data, provided the higher dose had acceptable safety profile. After 3,218 pts been</td>
<td></td>
</tr>
</tbody>
</table>

heparin, 70 UI/kg or PC (PC bolus and infusion of 12 h, plus heparin bolus, 140 UI/kg). All pts received clopidogrel 600 mg at least 2 h prior to procedure as well as 500 mg oral or IV ASA as need for transfusion.

earlier prior to the cath lab
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM PLUS 1998</td>
<td>Double-blind N=1915 pts</td>
<td>Tirolban, heparin, or tirolban plus heparin</td>
<td>Prolonged anginal pain or repetitive episodes of angina at rest or during minimal exercise in previous 12 h and new transient or persistent ST-T ischemic changes on ECG, or elevation of plasma levels of CK and CK-MB fraction</td>
<td>STE lasting more than 20 min, thrombolysis in previous 48 h, coronary angioplasty within previous 6 m or bypass surgery within previous mo, angina caused by identifiable factors, a Hx of a platelet disorder or thrombocytopenia, active bleeding or a high risk of bleeding, and stroke within previous y. Pts who had serum creatinine values above 2.5 mg/dL (220 μmol/L) or a platelet count below 150,000/m(^3)</td>
<td>Tirolban, heparin, or tirolban plus heparin. Study drugs were infused for mean (±SD) of 71.3±20 h, during which time coronary angiography and angioplasty were performed when indicated after 48 h</td>
</tr>
<tr>
<td>EARLY ACS 2009</td>
<td>Randomized N=9492 pts</td>
<td>Early, routine administration of Eptifibatide n=4722 vs. delayed Eptifibatide n=4684</td>
<td>Pts ACS NSTEMI undergoing invasive procedures</td>
<td>Composite of death, MI, or refractory ischemia within 7 d lower among pts who received tirolban plus heparin than among those who received heparin alone (12.9% vs. 17.9%; RR: 0.68; 95% CI: 0.53–0.88; p=0.004).</td>
<td>Study was stopped prematurely for group receiving tirolban alone because of excess mortality at 7 d (4.6%, compared with 1.1% for pts treated with heparin alone</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
| BRILINTA™ (ticagrelor) tablets | Assess anticoagulation with the direct thrombin inhibitor bivalirudin during PCI in individuals with moderate- and high-risk ACS | Randomized N=7789 pts | n=2561 heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors | n=2609 bivalirudin plus GP IIb/IIIa inhibitors | n=2619 bivalirudin alone | Pts undergoing PCI after angiography, new ST-segment depression; raised TnI, TnT, or CK-MB isoenzyme; known CAD; or all 4 other UA risk criteria defined by TIMI study group | Included - STE AMI or shock; bleeding diathesis or major bleeding episode within 2 wk; thrombocytopenia; CrCl <30 mL/min | Heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa inhibitors, or bivalirudin alone | 30-d endpoints of composite ischemia (death, MI, or unplanned revasc for ischemia), major bleeding, and net clinical outcomes (composite ischemia or major bleeding) | Bivalirudin plus GP IIb/IIIa inhibitors vs. heparin plus GP IIb/IIIa inhibitors - composite ischemia 9% vs. 8%; major bleeding 8% vs. 7%; net clinical outcomes 15% vs. 13% | N/A | N/A | N/A | N/A | N/A |

| BRILINTA™ (ticagrelor) tablets AstraZeneca LP | BRILINTA is indicated to reduce rate of thrombotic CV events in pts with ACS, UA, NSTEMI or STEMI | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Daily maintenance dose of ASA, coadministered with BRILINTA, should not exceed 100 mg | Increased risk of bleeding Decreased efficacy with BRILINTA (ticagrelor) in pts | N/A | N/A | N/A | N/A | N/A |

| ACUITY subgroup analysis Stone 2007 17368152 (146) | at time of planning trial strongly endorsed use of GP IIb/IIIa inhibitors during PCI. | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Randomization occurred before angiography, study drugs were administered at median of 4 h before PCI. PCI subgroup represents subset of 56% of all pts enrolled in ACUITY, and randomization was not stratified by treatment assignment | N/A | N/A | N/A | N/A | N/A |

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO IV-ACS Ottervange 2003</td>
<td>Randomized N=7600 pts</td>
<td>Pts with ACS without persistent STE including NSTEMI and UA ≤ 21 y and should have had ≥ 1 episodes of angina lasting at least 5 min within 24 h before admission. Either abnormal cardiac TnT or Tnl test or at least 0.5 mm of transient or persistent ST-segment depression.</td>
<td>Abciximab for 24-h (0.25 mg/kg bolus followed by 0.125 mcg/kg/min infusion up to max of 10 mcg/min for 24 h), followed by 24-h PC infusion; abciximab for 48 h (same bolus and infusion for total duration of 48 h); matching PC (bolus and 48-h infusion)</td>
<td>Death (of any cause) or MI within 30 d</td>
<td>Over-all 1-y mortality rate 8.3% (649 pts). 1-y mortality was 7.8% PC, 8.2% in the 24-h abciximab, and 9.0% in 48-h abciximab</td>
</tr>
<tr>
<td>PCI-CURE Mehta 2001</td>
<td>Randomized N=2658 pts</td>
<td>clopidogrel (n=1313) or PC (n=1345)</td>
<td>Composite of CV death, MI, or urgent target-vessel revasc within 30 d of PCI. 4.5% vs. 6.4% Long-term administration of clopidogrel after PCI is superior to strategy of no pretreatment and short-term therapy for only 4 wk after PCI</td>
<td>At follow-up, there was NS difference in major bleeding between groups</td>
<td>p=0.03 RR: 0.70 95% CI: 0.50–0.97</td>
</tr>
</tbody>
</table>

**Notes:**
- Combination with ASA doses exceeding 100 mg
- N/A indicates data not available.
| Petersen 2004 | Systematically evaluate endpoints of all-cause death and nonfatal MI, transfusion, and major bleeding observed in the 6 randomized controlled trials comparing enoxaparin and UFH in treatment of ACS | N/A | All 6 RCTs comparing enoxaparin and UFH in NSTEMI ACS were selected for analysis | N/A | Enoxaparin is more effective than UFH in preventing combined endpoint of death or MI at 30 d for enoxaparin vs UFH (3.0% vs. 3.0%; OR: 1.00; 95% CI: 0.85-1.17). Statistically significant reduction in combined endpoint of death or nonfatal MI at 30 d observed for enoxaparin vs. UFH in overall trial populations (10.1% vs 11.0%; OR: 0.91; 95% CI: 0.83-0.99). Statistically significant reduction in combined endpoint of death or MI at 30 d observed for enoxaparin in populations receiving no prerandomization antithrombin therapy (8.0% vs 9.4%; OR: 0.81; 95% CI: 0.70-0.94). | N/A | NS difference found in blood transfusion (OR: 1.01; 95% CI: 0.89-1.14) or major bleeding (OR: 1.04; 95% CI: 0.83-1.30) 7 d after randomization | N/A | 10.1% vs 11.0% OR: 0.91 CI: 0.83-0.99 | N/A | Systematic overviews do not replace RCTs but provide important insights through analyses of totality of data. Trial populations are not identical with respect to baseline characteristics, duration of study treatment, time to revasc, or use of concomitant medical therapies in management of UA/NSTEMI ACS. Imprecision exists in frequency of events as protocols for data collection and definitions of efficacy and safety events varied among studies. Not having the individual pt data from all trials precluded more sophisticated analyses. |
| PRINCIPAL TITIMI 44 Wiviott 2007 18056526 (150) | Compare prasugrel with higher than currently approved 300-mg LD and 75-mg MD of clopidogrel | Randomized, double-blind, 2-phase crossover study; N=201 subjects | Prasugrel compared with high-dose clopidogrel in pts | ≥18 y and scheduled to undergo cardiac catheterization with planned PCI for angina and at least one of the following: coronary angiography within 14 d with at least 1 lesion amenable to PCI, a functional study within 8 wk with objective findings of ischemia, or prior PCI or CABG surgery | Planned PCI for immediate treatment of MI, any thienopyridine within 5 d, GP IIb/IIIa inhibitor within 7 d or planned use (bailout was permitted), high risk of bleeding, thrombocytopenia, or anemia. | Prasugrel compared with high-dose clopidogrel | 1º endpoint of LD phase (prasugrel 60 mg vs. clopidogrel 600 mg) was IPA with 20 mumol/L ADP at 6 h IPA at 6 h significantly higher in subjects receiving prasugrel (mean±SD; 74.8±13.0%) compared with clopidogrel (31.8±21.1%; p<0.0001). | N/A | Pts with PCI entered the maintenance dose phase, a 28-d crossover comparison of prasugrel 10 mg/d vs. clopidogrel 150 mg/d with a 1º endpoint of IPA after 14 d of either drug. IPA with 20 mumol/L ADP was higher in subjects receiving prasugrel (61.3±17.8%) compared with clopidogrel (48.1±21.3%; p<0.0001). Results were consistent across all key 2º endpoints; significant differences emerged by 30 min and persisted across all time points. | p<0.0001 | Ct: 38.0–48.4 | N/A | Statistical analyses. |

<p>| TRILOGY ACS Rose 2012 2290930 (151) | Evaluate whether ASA plus prasugrel is superior to ASA plus clopidogrel for long term therapy in pts with UA or MI who were &lt;75 y | Double-blind, randomized trial N=7243 pts &lt;75 y N=2083 pts ≥75 y | ASA prasugrel (10 mg daily) vs. clopidogrel (75 mg qd). Low dose 5 mg of prasugrel versus 75 mg of clopidogrel | ACS consisting of UA or MI without STE. Pts were eligible if selected for final treatment strategy of medical management without revasc within 10 d after index event. Pts required to have at least one of four risk criteria: an age ≥60 y, presence of DM, previous MI, or previous revasc. | Hx of TIA or stroke, PCI or CABG within the previous 30-d, renal failure requiring dialysis, and concomitant treatment with an oral anticoagulant. | Prasugrel or clopidogrel. Prasugrel (10 mg daily) adjusted to (5 mg qd) pts ≥75 y. Clopidogrel (75 mg/d) | Death from CV causes, MI, or stroke among pts &lt;75 y occurred in 13.9% of prasugrel group and 16.0% of the clopidogrel group (HR prasugrel group: 0.91; 95% CI: 0.79–1.05; p=0.21). | Rates of severe and intracranial bleeding similar in 2 groups in all age groups. NS between group differences in frequency of nonhemorrhagic serious adverse effects. Prespecified analysis of multiple recurrent ischemic events (all components of 1º endpoint) suggested lower risk for prasugrel among pts &lt;75 y (HR: 0.85; 95% CI: 0.72–1.00; p=0.04). | P=0.21 | Prasugrel group, HR: 0.91 95% CI: 0.79–1.05 | N/A | Higher frequency of HF in clopidogrel group. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO</td>
<td>Randomized, double-blind, active control</td>
<td>N=18,624 pts</td>
<td>Ticagrelor n=9235 or clopidogrel n=9186 in addition to ASA</td>
<td>Pts admitted to hospital with either STE or NSTE-ACS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ticagrelor oral LD of 180 mg, followed by 90 mg bid Clopidogrel 300 mg oral LD followed by maintenance dose of 75 mg daily. All pts received ASA at dose of 75–100 mg daily</td>
<td>PLATO major bleeding (11.6 vs. 11.2%; p=0.43), TIMI major bleeding (7.9 vs. 7.7%, p=0.56) and GUSTO severe bleeding (2.9 vs. 3.1%, p=0.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal bleeding and transfusion rates did not differ between groups</td>
</tr>
<tr>
<td>Valgimigli</td>
<td>Meta analysis of 31 studies involving 20,006 pts</td>
<td>Pts undergoing treatment for various CAD conditions</td>
<td>Pts undergoing ticlopidin vs. abciximab</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>ACUITY</td>
<td>Randomized N=9207 pts</td>
<td>Routine upstream (n=4605) deferred selective (n=4602) GP</td>
<td>Moderate- and high-risk ACS pts undergoing invasive-treatment strategy</td>
<td>Included STE AMI or shock; bleeding diathesis or major bleeding within 2 wk; thrombocytopenia; CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Routine upstream or deferred selective GP IIb/IIIa inhibitor administration</td>
<td>Composite ischemic events (death, MI, or unplanned revasc for ischemia) at 30 d 7.1% vs. 7.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (n)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR; HR: RR: &amp; 95 CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE Yusuf 2001 (133) 11519503</td>
<td>Compare the efficacy and safety of early and long-term use of clopidogrel plus ASA with those of ASA alone in pts with ACS and no STE</td>
<td>Randomized double-blind, PC-controlled trial 12,562 pts</td>
<td>Clopidogrel vs. PC in addition to ASA</td>
<td>Pts were eligible for the study hospitalized within 24 h after the onset of Sx and did not have STE</td>
<td>Clopidogrel (300 mg immediately followed by 75 mg once daily) vs. PC in addition to ASA</td>
<td>Death from CV causes, nonfatal MI, or stroke 9.3% vs. 11.4%</td>
<td>Clopidogrel not associated with excess rate of any other type of adverse event that necessitated discontinuation of study drug</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>ASPECT-2 van Es 2002</td>
<td>Investigate whether ASA or OACs is more</td>
<td>Randomized N=999 pts</td>
<td>LDAS A n=336, Coumadin-high intensity OAC</td>
<td>Men or non-pregnant women admitted with Established indications for treatment with OAC.</td>
<td>LDASA, high intensity OAC, or combined LDASA</td>
<td>1º occurrence of MI, stroke, or death 9% vs. 5% vs. 5%</td>
<td>Clopidogrel not associated with excess rate of any other type of adverse event that necessitated discontinuation of study drug</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

1º indicates primary; 2º, secondary; A to Z, AGGREGAT to ZOCOR; ACS, acute coronary syndrome; ACUTE, Acute Catheterization and Urgent Intervention Triage strategy; ADP, adenosine diphosphate; ASA, aspirin; bid, twice daily; CABGS, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; DM, diabetes mellitus; DSMB, Data and Safety Monitoring Board; ECG, electrocardiography; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events; GP, glycoprotein; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator For Occluded Coronary Arteries; HF, heart failure; HR, hazard ratio; Hx, history; IgE, Immunoglobin E; INTERACT, Intensive blood pressure reduction in acute cerebral haemorrhage trial; IPA, intravenous; LD, loading dose; pts, patients; LTS, MI, myocardial infarction; OD, once daily; NA, North America; NS, no(t) significant; NSAID, nonsteroidal anti-inflammatory drugs; NSTE, non-ST elevation; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral arterial disease; PC, placebo; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; qd, daily; Revasc, revascularization; ROW, rest of the world; RR, relative risk; STE, ST elevation; STEMI, ST-elevation myocardial infarction; SYNERGY, Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; Sx, symptoms; TIA, transient ischemic attack; TIMI, thrombolysis in MI; TnI, troponin I; TnT, troponin T; UA, unstable angina; US, United States; UTVR, Urgent Target Vessel Revascularization; and VKA, vitamin K antagonist.

Data Supplement 16. Combined Oral Anticoagulant Therapy and Antiplatelet Therapy in Patients With Definite NSTE-ACS (Section 4.3.2)

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Adjuncts</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>(155) [12126819]</td>
<td>2001</td>
<td>Retrospective analysis</td>
<td>n=523 pts</td>
<td>IAC group: UAC group</td>
<td>All consecutive pts on warfarin therapy referred for PCI in 4 centers with a main policy to IAC before PCI and in 3 centers with a long experience on UAC during PCI</td>
<td>IAC vs. UAC</td>
<td>Major bleeding, access-site complications, and MACE (death, MI, target vessel revasc, and stent thrombosis)</td>
</tr>
<tr>
<td>(156) [18346963]</td>
<td>2008</td>
<td>Retrospective analysis</td>
<td>n=523 pts</td>
<td>IAC group: UAC group</td>
<td>All consecutive pts on warfarin therapy referred for PCI in 4 centers with a main policy to IAC before PCI and in 3 centers with a long experience on UAC during PCI</td>
<td>IAC vs. UAC</td>
<td>Major bleeding, access-site complications, and MACE (death, MI, target vessel revasc, and stent thrombosis)</td>
</tr>
<tr>
<td>(157) [11319192]</td>
<td>2001</td>
<td>Study</td>
<td>N=530 pts</td>
<td>ASA plus coumarins</td>
<td>Pts who were prospectively randomized to the use of coumarins as part of the BAAS study</td>
<td>N/A</td>
<td>ASA (300 mg LD; then 100 mg qd) and coumarins (acenocoumarol or Sintrom at 6 mg on 1 d, 4 mg on 2 d, 2 mg on 3 d and after)</td>
</tr>
<tr>
<td>(158) [13103842]</td>
<td>2001</td>
<td>Study</td>
<td>N=325, combined LDASA and coumadin-moderate intensity OAC n=332</td>
<td>AMIMI or UA within preceding 8 wk</td>
<td>contraindications for the study drug, planned revasc procedure, serious comorbidty, increased risk of bleeding, abnormal blood platelets or erythrocytes, anemia, Hx of stroke, and inability to adhere to the protocol</td>
<td>and moderate intensity OAC</td>
<td>ASA vs. coumadin HR: 0.55; 95% CI=0.30-1.00; p=0.0479</td>
</tr>
<tr>
<td>(159) [12126819]</td>
<td>2001</td>
<td>Study</td>
<td>N=325, combined LDASA and coumadin-moderate intensity OAC n=332</td>
<td>AMIMI or UA within preceding 8 wk</td>
<td>contraindications for the study drug, planned revasc procedure, serious comorbidty, increased risk of bleeding, abnormal blood platelets or erythrocytes, anemia, Hx of stroke, and inability to adhere to the protocol</td>
<td>and moderate intensity OAC</td>
<td>ASA vs. coumadin HR: 0.55; 95% CI=0.30-1.00; p=0.0479</td>
</tr>
<tr>
<td>(160) [13103842]</td>
<td>2001</td>
<td>Study</td>
<td>N=325, combined LDASA and coumadin-moderate intensity OAC n=332</td>
<td>AMIMI or UA within preceding 8 wk</td>
<td>contraindications for the study drug, planned revasc procedure, serious comorbidty, increased risk of bleeding, abnormal blood platelets or erythrocytes, anemia, Hx of stroke, and inability to adhere to the protocol</td>
<td>and moderate intensity OAC</td>
<td>ASA vs. coumadin HR: 0.55; 95% CI=0.30-1.00; p=0.0479</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCF/ACG/AHA report Bhatt 2008 (158) 19017521</td>
<td>Not a study but a report with recommendations</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz-Nodar 2009 (159) 19246502</td>
<td>Evaluate the safety and efficacy of use of DES vs. BMS in a cohort of pts with AF</td>
<td>Retrospective cohort study N=604 pts</td>
<td>DES (n=207) vs. BMS (n=207)</td>
<td>Pts with AF who had undergone PCI with stent</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DES or BMS</td>
<td>All bleeding episodes, thromboembolism, and MACE; i.e., death, AMI, TVF. Incidence density of MACE as well as the incidence of all-cause mortality in both groups was similar. Higher incidence of major bleeding in DES group (2.26 vs. 1.19/10,000 d of exposure; p=0.03)</td>
<td>Major bleeding was higher in the DES group (2.26 vs. 1.19/10,000 d of exposure, p=0.03) Rate of definitive and probable thrombosis was similar in both DES and BMS groups (0.43 vs. 0.06/10,000 d of exposure, p=0.09)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Until intervention) started 1 wk before intervention. Target INR 2.1-4.8 during angioplasty and 6 mo follow-up. INR was measured on the morning before PTCA and daily thereafter until discharge. 61 late thrombotic events occurred (11.6%) Optimal AC was an independent predictor of late thrombotic events (RR: 0.33; 95% CI: 0.19-0.57) and was associated with a 0.21 mm (95% CI: 0.17-0.42) larger vessel lumen 6 mo. Late bleeding episodes (1.4%) lowest in pts in the target range.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Pts</th>
<th>Baseline</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip 2010 (160) 20447945</td>
<td>Not a study but a summary report</td>
<td>Full consensus document comprehensively reviews published evidence and presents consensus statement on 'best practice' antithrombotic therapy guideline for management of antithrombotic therapy in AF pts</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>WARSS Mohr 2001 (161) 11794192</td>
<td>Investigate whether warfarin, which is effective and superior to ASA in the prevention of cardiogenic embolism, would also prove superior in the prevention of recurrent ischemic stroke in pts with a prior noncardioembolic ischemic stroke</td>
<td>Multicenter, double-blind, randomized</td>
<td>Warfarin (dose adjusted INR of 1.4-2.8) n=1,103 vs. ASA (325 mg qd) n=1,103</td>
<td>Pts were 30-85 y, considered acceptable candidates for warfarin therapy, had ischemic stroke within previous 30 d, and had scores of ≥3 on GOS</td>
<td>Baseline INR above normal range (&gt;1.4), stroke that was due to procedure or attributed to high-grade carotid stenosis which surgery was planned, or stroke associated with an inferred cardioembolic source</td>
<td>Warfarin (dose adjusted INR 1.4-2.8) vs. ASA (325 mg qd)</td>
<td>Combined recurrent ischemic stroke or death from any cause within 2 y</td>
</tr>
<tr>
<td>CARS Peverill 1997 (162) 19687136</td>
<td>Commentary</td>
<td>Fixed low-dose warfarin (1-3 mg) combined ASA (80 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reinfarction, stroke, or CV death. Provides no reduction in reinfarction beyond</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>N</td>
<td>Therapy Details</td>
<td>Outcomes</td>
<td>p Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>---</td>
<td>----------------</td>
<td>----------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rossini 2008 (163)</td>
<td>Assess long-term outcomes associated with the use of triple-therapy in pts undergoing coronary stenting and evaluate how these may be affected by targeting INR values to the lower therapeutic range</td>
<td>102</td>
<td>Triple antiplatelet therapy ASA and clopidogrel and OAC n=102 Control group: dual antiplatelet therapy ASA and clopidogrel n=102</td>
<td>Bleeding 10.8% vs. 4.9%, p=0.1 INR values were higher in pts with bleeding (2.8±1.1 vs. 2.3±0.2, p=0.0001) INR values within target range risk of bleeding was lower compared with pts who did not (4.9 vs. 33%, p=0.00019) and in control group (4.9%)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarafoff 2008 (164)</td>
<td>Investigate the efficacy and safety of 2 regimens of antithrombotic AC therapy in pts who present for DES implantation whilst on OAC</td>
<td>515</td>
<td>n=306 pts continued OAC (triple therapy) and n=209 pts discontinued OAC (dual therapy) they received antiplatelet therapy with clopidogrel and ASA</td>
<td>Major bleeding 2 y 1.4% (n=4, triple therapy) vs. 3.1% (n=6, dual therapy, p=0.34)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1º indicates primary; AC, anticoagulants; ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ASA, aspirin; BAAAS, Balloon Angioplasty and Anticoagulation Study; BMS, bare metal stents; CV, cardiovascular; DES, drug-eluting stents; diff, difference(s); GOS, Glasgow Outcome Scale; GP, glycoprotein; HF, heart failure; Hx, history; IAC, interrupted anticoagulation; INR, International normalized ratio; IV, intravenous; LDASA, low-dose aspirin; MACE, major adverse cardiac events; MI, myocardial infarction; OAC, oral anticoagulation; NSTE-ACS, Non-ST Segment Elevation Acute Coronary Syndrome; PACS, Peripheral Arterial Disease; Pts, patients; SRAT, Stent Restenosis Angioplasty and Thrombolysis; TASC, TransAtlantic Inter-Society Consensus; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; TTOAC, Thrombolysis in Myocardial Infarction-25; UAC, unusual anticoagulation; UMIC, Ultra-Minimally Invasive Coronary Artery Bypass Grafting; 1º indicates primary; 2º indicates secondary
infarction; N/A, not applicable; NSTE, non-ST-segment elevation; OAC, oral anticoagulant(s); OR, odds ratio; PC, placebo; PCI, percutaneous coronary intervention; PTCA, percutaneous coronary angioplasty; pt, patient; revasc, revascularization; RR, relative risk; STE, ST-segment elevation; SRAT, stent-related antithrombotic treatment; Sx, symptoms; TVF, target vessel failure; UA, unstable angina; and UAC, uninterrupted anticoagulation.

Data Supplement 17. Parenteral Anticoagulant and Fibrinolytic Therapy (Section 4.3.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type / Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO Mahaffey 2011 (134)</td>
<td>Prespecified subgroup analysis showed significant interaction between treatment and region (p=0.045), with less effect of ticagrelor in North America than in rest of world. Additional exploratory analyses performed to identify potential explanations for observed region by treatment interaction.</td>
<td>Observed regional interaction driven by interaction of randomized treatment with 78% of North American pts in US compared with the ROW pts (p=0.01 vs. p=0.045 interaction using NA), analyses focus on comparison of US and rest of world with Canadian pts included in the rest of world group.</td>
<td>Reasons for interaction explored independently by 2 statistical groups.</td>
<td>Regional interaction could arise from chance alone. Results of 2 independently performed analyses identified underlying statistical interaction with ASA maintenance dose as possible explanation for regional difference. Lowest risk of CV death, MI, or stroke with ticagrelor compared with clopidogrel associated with low maintenance dose of concomitant ASA.</td>
<td>Cox regression analyses performed to quantify how much of regional interaction could be explained by pt characteristics and concomitant treatments, including ASA maintenance therapy. Landmark Cox regressions at 8 timepoints evaluated association of selected factors, including ASA dose, with outcomes by treatment. Systematic errors in trial conduct ruled out. Given large number of subgroup analyses performed and that result numerically favoring clopidogrel in at least 1 of 4 prespecified regions could occur with 32% probability, chance alone cannot be ruled out. More pts in US (53.6%) than rest of world (1.7%).</td>
<td>Both Cox regression with maintenance dose and landmark techniques showed pts taking low-dose maintenance ASA, ticagrelor associated with better outcomes compared with clopidogrel with statistical superiority in ROW and similar outcomes in US cohort.</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
<p>| PLATO Wallentin 2009 (139) | Determine whether ticagrelor is superior to clopidogrel for prevention of vascular events and death in broad population of pts presenting with ACS | N=18,624 Pts with ACS with or without STE | Ticagrelor (n=9333) (180-mg LD, 90 mg bid after) or clopidogrel (n=9291) (300-600 mg LD, 75 mg daily after) | Hospitalized for ACS, with or without STE, with onset of Sx during the previous 24 h. Pts who had ACS NSTE, at least two of following three criteria had to be met: ST changes on ECG indicating ischemia; positive test of biomarker indicating myocardial necrosis; or one of several risk factors (age ≥60 y; prev MI or CABG; CAD with stenosis of ≥50% at least 2 vessels; prev ischemic stroke, TIA, carotid stenosis ≥50%, or cerebral revasc; DM; PAD; chronic renal dysfunction, defined as CrCl of &lt;60 mL/min per 1.73 m² of body surface area). With STE following two inclusion criteria had to be met: persistent STE ≥0.1 mV at least 2 contiguous leads or new LBBB, and intention to perform 1º PCI. | Contraindication against use of clopidogrel, fibrinolytic therapy within 24 h before randomization, need for oral anticoagulation therapy, increased risk of bradycardia, and concomitant therapy with strong cytochrome P-450 3A inhibitor or inducer | Ticagrelor or clopidogrel | Composite of death from vascular causes, MI, or stroke 9.8% pts receiving ticagrelor vs. 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001). Major bleeding 11.6% vs. 11.2%, p=0.43 Ticagrelor associated with higher rate of major bleeding not related to CABG 4.5% vs. 3.8%, p=0.03, including more instances of fatal intracranial bleeding and fewer fatal bleeding of other types. | Major bleeding 11.6% vs. 11.2%, p=0.43 Ticagrelor associated with higher rate of major bleeding not related to CABG 4.5% vs. 3.8%, p=0.03, including more instances of fatal intracranial bleeding and fewer fatal bleeding of other types. | Composite of death from vascular causes, MI, or stroke 9.8% pts receiving ticagrelor vs. 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p&lt;0.001). Major bleeding 11.6% vs. 11.2%, p=0.43 Ticagrelor associated with higher rate of major bleeding not related to CABG 4.5% vs. 3.8%, p=0.03, including more instances of fatal intracranial bleeding and fewer fatal bleeding of other types. | Discontinuation of study drug due to adverse events 7.4% ticagrelor vs. 6.0% clopidogrel p&lt;0.001 Dyspnea was 13.8% vs. 7.8% Higher incidence of ventricular pauses in 1 wk but not at 30 d in ticagrelor group than in clopidogrel group. | Geographic differences between populations of pts or practice patterns influenced effects of the randomized treatments |</p>
<table>
<thead>
<tr>
<th>Mehta 2010 (140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clotidogrel and ASA widely used for pts with ACS and those undergoing PCI. Evidence-based guideline for doing not as yet been established for either agent.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pts randomly assigned to double-dose clopidogrel</th>
<th>25,086 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>received LD of 600 mg 1 d followed by 150 mg od on 2-7 d.</td>
<td></td>
</tr>
<tr>
<td>Pts assigned to standard-dose clopidogrel received 300 mg LD 1 d before angiography</td>
<td></td>
</tr>
<tr>
<td>followed by 75 mg od 2-7 d.</td>
<td></td>
</tr>
<tr>
<td>8-30 d both double-dose and standard-dose groups received 75 mg of clopidogrel od.</td>
<td></td>
</tr>
<tr>
<td>Pts randomly assigned to lower-dose ASA received 75 to 100 mg daily 2-7 d and those randomly assigned to higher-dose ASA received 300-325 mg daily on d 2-30.</td>
<td></td>
</tr>
</tbody>
</table>

| Increased risk of bleeding or active bleeding and known allergy to clopidogrel or ASA | 2×2 factorial design pts randomly assigned in double-blind fashion to double-dose regimen of clopidogrel or to standard-dose regimen. 2nd component of factorial design, pts were randomly assigned in open label fashion to higher-dose ASA or lower-dose ASA. |
| Time to CV death, MI, or stroke, whichever occurred 1st, up to 30 d. Primary outcome occurred in 4.2% of pts assigned to double dose clopidogrel as compared with 4.4% assigned to standard-dose clopidogrel (HR: 0.94; 95% CI: 0.83–1.06; p=0.30). No significant difference between higher-dose and lower-dose ASA with respect to 1st outcome (4.2% vs. 4.4%; HR: 0.97; 95% CI: 0.86–1.09; p=0.61) | |
| Major bleeding occurred in 2.5% of pts in double dose group and in 2.0% in standard-dose group (HR: 1.24; 95% CI: 1.05–1.46; p=0.01). | |
| No significant difference between higher-dose and lower-dose ASA with respect to major bleeding (2.3% vs. 2.3%; HR: 0.99; 95% CI: 0.84–1.17; p=0.90). | |
| Composite of death from CV causes, MI, stroke, or recurrent ischemia; individual components of 1st outcome; death from any cause; Definite or probable stent thrombosis. Double-dose clopidogrel associated with significant reduction in 2nd outcome of stent thrombosis among the 17,263 pts who underwent PCI (1.6% vs. 2.3%; HR: 0.68; 95% CI: 0.55–0.85; p=0.001). | |

| N/A | N/A | N/A | N/A |

<table>
<thead>
<tr>
<th>ACRITY subgroup analysis Stone 2007 (146)</th>
<th>Assess anticoagulatio n with direct thrombin inhibitor bivalirudin during PCI in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized n=7789 pts</td>
<td>n=2561 Heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors n=2609</td>
</tr>
<tr>
<td>Pts undergoing PCI after angiography, ST depression; raised TnI, TnT, or CK-MB isozyme; known CAD; or all 4 other UA risk criteria as defined by TIMI study</td>
<td>Included - STE AMI or shock; bleeding diathesis or major bleeding episode within 2 wk; thrombocytopenia; CrCl&lt;30 mL/min Heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa</td>
</tr>
<tr>
<td>30-d endpoints of composite ischemia (death, MI, or unplanned revasc for ischemia), major bleeding, and net clinical outcomes</td>
<td>N/A</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

| Randomization occurred before angiography, study drugs were administered at median of 4 h before PCI. PCI | N/A |

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Individuals with moderate- and high-risk ACS.</th>
<th>Bivalirudin plus GP IIb/IIIa inhibitors, or n=2619 bivalirudin alone. group inhibitors, or bivalirudin alone</th>
<th>composite ischemia or major bleeding</th>
<th>bivalirudin plus GP IIb/IIIa inhibitors vs. heparin plus GP IIb/IIIa inhibitors - composite ischemia 9% vs. 8%; major bleeding 8% vs. 7%; net clinical outcomes 15% vs. 13%</th>
<th>subgroup represents subset of 56% of all pts enrolled in ACUITY, randomization not stratified by treatment assignment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Petersen 2004 (165) 15238596</strong></td>
<td>Systematically evaluate endpoints of all-cause death nonfatal MI, transfusion, and major bleeding observed in 6 RCT comparing enoxaparin and UFH in treatment of ACS</td>
<td>Systematic overview N=21946 pts ESSENCE, A to Z, and SYNERGY, TIMI 11B, ACUTE II, and INTERACT performed using random effects empirical Bayes model</td>
<td>All 6 RCT comparing enoxaparin and unfractionated heparin in NSTE ACS selected for analysis</td>
<td>Combined endpoint of death or MI: enoxaparin more effective than UFH in preventing combined endpoint of death or MI. NS difference found in death at 30 d for enoxaparin vs UFH (3.0% vs 3.0%; OR: 1.00; 95% CI: 0.85–1.17). Statistically significant reduction in combined endpoint of death or nonfatal MI at 30 d observed for enoxaparin vs. UFH in overall trial populations (10.1% vs. 11.0%; OR: 0.91; 95% CI: 0.83-0.99). Statistically significant reduction in combined endpoint of death or MI at 30 d also observed for enoxaparin in populations receiving no prerandomization antithrombin therapy</td>
</tr>
</tbody>
</table>

Systematic overviews do not replace RCT but provide important insights through analyses of totality of the data. Trial populations are not identical with respect to baseline characteristics, duration of study treatment, the time to revasc or the use of concomitant medical therapies in management of UA/NSTEMI ACS. Some imprecision exists in frequency of events as protocols for data collection and definitions of efficacy and safety events varied among...
| Hochman | Evaluate regimens that reduced heparin dosage for low body weight on weight adjusted basis in prospective, nonrandomized cohort pts with UA and MI who did not receive thrombolytic agents | Nonrandomized N=80 pts | Heparin | Pts admitted with UA and NSTEMI | Exclusion criteria included Hx of bleeding, Coumadin or thrombolytic therapy, and failure to comply exactly with dosing regimen | Standard (group 1) non weight adjusted 5000-U IV bolus/1000 U/hr infusion. 2 weight adjusted heparin regimens group 2 70 U/kg IV bolus; 15 U/kg/hr pts <70 kg and a fixed 5000-U IV bolus/1000 U/hr for pts who weighed >70 kg) (group 3) 80 U/kg IV bolus, 12 U/kg/hr infusion pts <70 kg and capped 4000-U IV bolus; 900 U/hr infusion pts >70 kg). | Proportion of pts achieving a target aPTT at 6 h. Pts treated with lower dose of weight adjusted heparin group 3 more often within the target range for aPTT at 6 h (34% vs. 5% vs. 0%) required fewer heparin infusion changes (1.0 ± 1.0 vs. 1.9 ± 1.0 vs. 2.0 ± 0.9) within 1st 24 h compared with other regimens. Pts in groups 1 and 2 above target range at 6 h (95% and 84% compared with 48% in group 3) | N/A | Proportion of pts achieving a target aPTT at 24 h and number of times heparin dose adjusted within 1st 24 h. 52% pts in group 1 within target range compared with 79% in group 2 and 74% in group 3 significantly fewer changes in infusion rate required over 24 h period in group 3 compared with other regimens (1.05 ± 1.0 for group 3 vs. 2 ± 0.9 for group 1 vs. 1.9 ± 1.0 in group 2; p<0.0005). | N/A | Significantly higher proportion of pts above target range in groups 1 (95%) and 2 (84%) versus group 3 (47%) (p<0.0005) | N/A | No major complications in any group | Pts not randomly assigned, and the 2 weight adjusted regimens were not concurrently tested. At initiation of 2nd weight-adjusted nomogram the target aPTT changed to 45-70 s from 50-75 s |

| Garcia | Pharmacology of approved parenteral anticoagulants including indirect anticoagulants , UFH, LMWH, fondaparinux, and danaparoid, and direct Parenteral Anticoagulants Evidence-Based Clinical Practice Guidelines | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | 2014 NSTE-ACS Guideline Data Supplements | 2014 NSTE-ACS Guideline Data Supplements | 2014 NSTE-ACS Guideline Data Supplements | 2014 NSTE-ACS Guideline Data Supplements | 2014 NSTE-ACS Guideline Data Supplements |

© American Heart Association, Inc and American College of Cardiology Foundation

61
TIMI 11B
Antman 1999 (168) 10517729

Test benefits of strategy of extended course of uninterrupted antithrombotic therapy with enoxaparin compared with standard treatment with UFH for prevention of death and cardiac ischemic events in pts with UA/NQMI

<table>
<thead>
<tr>
<th>Randomized N=3910 pts</th>
<th>UFH n=1957 vs. enoxaparin n=1953</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with UA/NQMI ischemic discomfort of &gt;5 min duration at rest; Hx of CAD (abnormal coronary angiogram, prior MI, CABG surgery, or PTCA), ST deviation, or elevated serum cardiac markers</td>
<td>Planned revascularization within 24 h, treatable cause of angina, evolving Q-wave MI, Hx of CABG surgery within 2 mo or PTCA within 6 mo, treatment with continuous infusion of UFH for &gt;24 h before enrollment, Hx of heparin-associated thrombocytopenia with or without thrombosis, and contraindications to anticoagulation</td>
</tr>
<tr>
<td>UFH &gt;3 d followed by subcutaneous PC injections or enoxaparin (30 mg IV bolus followed by injections of 1.0 mg/kg every 12 h)</td>
<td>Composite of all-cause mortality, recurrent MI, or urgent revascularization at 8 d 14.5% vs. 12.4% OR: 0.83; 95% CI: 0.69–1.00; p=0.048 at 43 d 19.7% vs. 17.3% OR: 0.85; 95% CI: 0.72–1.00; p=0.048</td>
</tr>
<tr>
<td>Major hemorrhage, bleed in retroperitoneal, intracranial, or intraocular location; hemoglobin drop of &gt;3 g/dL; requirement of transfusion of &gt;2 U blood in 72 h no difference</td>
<td>Individual elements of 1º endpoint and composite of death or nonfatal MI</td>
</tr>
<tr>
<td>8 d p=0.048 OR=0.83 95% CI: 0.69–1.00 at 43 d p=0.048 OR=0.85 95% CI: 0.72–1.00</td>
<td>Stroke (1.0% vs. 1.2%), TIA (0.3% vs. 0.3%), or thrombocytopenia (2.1% vs. 1.9%)</td>
</tr>
</tbody>
</table>

OASIS-5 trial Mehta 2007 (169) 17964037

Study reports prospectively planned analysis of pts with ACS who underwent early PCI in the OASIS-5 trial

<table>
<thead>
<tr>
<th>Double-blind, randomized 20,078 pts</th>
<th>UFH n=1,414 subcutaneous fondaparinux 2.5 mg od or n=1,420 subcutaneous enoxaparin 1 mg/kg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with UA or NSTEMI; at least 2 of following criteria: age &gt;60 y, positive cardiac biomarkers, or ECG changes compatible with ischemia.</td>
<td>Contraindication to low molecular weight heparin, hemorrhagic stroke within last 24 h, indication for anticoagulation other than ACS, revascularization procedure already performed for qualifying event, and severe renal insufficiency</td>
</tr>
<tr>
<td>Fondaparinux or enoxaparin total of 12,715 pts underwent heart catheterization during the initial hospitalization, and 6,238 pts underwent PCI.</td>
<td>Rates of major bleeding and efficacy by evaluating composite of death, MI, or stroke at 9, 30, 180 d Fondaparinux vs. enoxaparin reduced major bleeding by &gt;0.5 (2.4% vs. 5.1%; HR: 0.46; p&lt;0.00001) at 9 d with similar rates of ischemic events resulting in superior net clinical benefit (death, MI, stroke, major bleeding: 8.2% vs. Catheter thrombus more common in pts receiving fondaparinux (0.9%) than enoxaparin alone (0.4%), but largely prevented by using UFH at the time of PCI without increase in bleeding</td>
</tr>
<tr>
<td>N/A</td>
<td>p=0.00001 HR: 0.46</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation 2014 NSTE-ACS Guideline Data Supplements
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Comparator</th>
<th>Endpoint</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OASIS-5 Yusuf (170) 16537603</td>
<td>Randomized, double-blind, double-dummy trial N=20,078 pts</td>
<td>Fondaparinux vs. enoxaparin</td>
<td>Death, MI, or refractory ischemia at 9 d</td>
<td>HR=1.01</td>
<td>95% CI: 0.90-1.13</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1º outcome events similar in 2 groups (5.8% (579 events) vs. 5.7% (573 events))</td>
<td>HR=1.01; 95% CI: 0.90-1.13; composite of 1º outcome and major bleeding at 9 d favored Fondaparinux (737 events) 7.3% vs. 905 events 9.0%; HR=0.81; p=0.001.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3º outcome events similar in 2 groups (4.9% (478 events) vs. 5.3% (485 events))</td>
<td>HR=1.00</td>
<td>95% CI: 0.89-1.11</td>
<td>p=0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rate of major bleeding at 9 d markedly lower with Fondaparinux than with enoxaparin (217 events) 2.2% vs. 412 events 4.1%; HR:0.52; p&lt;0.001.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUTURA/OASIS-8 Steg 2010 (171) 20089623</td>
<td>Double-blind randomized parallel group N=2,026 pts</td>
<td>LV low-dose UFH, 50 U/kg, regardless of use of GpIIb-IIIa inhibitors or standard-dose</td>
<td>Composite of major bleeding, minor bleeding, or major vascular access-site complications up to 48 h after PCI</td>
<td>HR:0.78; 95% CI: 0.60-0.99</td>
<td>p=0.049</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Major bleeding or minor bleeding Major bleeding no difference in bleeding site</td>
<td>HR:0.52; 95% CI: 0.37-0.73</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Composite of major bleeding at 48 h 5.8% vs. 3.9%; OR: 1.61; 95% CI: 1.00-2.62; p=0.05</td>
<td>HR:0.52; 95% CI: 0.37-0.73</td>
<td>p=0.001</td>
<td></td>
</tr>
</tbody>
</table>

acs initially treated with fondaparinux

| Enrollment within 48 h of most recent Sx; planned coronary angiography, with PCI if indicated, within 72 h; at least 2 of following criteria: >60 y, TnT or Tnl or CK-MB above upper limit of normal; ECG changes compatible with ischemia requiring urgent coronary angiography due to refractory or recurrent angina associated with dynamic ST changes, HF, life-threatening arrhythmias, hemodynamic instability; treatment with other injectable anticoagulants hemorrhagic stroke within 12 mo; indication for anticoagulation other than acs; women pregnant, breastfeeding, or of childbearing potential not using contraception; life expectancy <6 mo; receiving experimental pharmaceutical agent; revasc procedure for qualifying event already performed; creatinine clearance < 20 mL/min. | UFH, 85 U/kg (60 U/kg with GpIIb-IIIa inhibitors), adjusted by blinded ACT | 4.7% vs. 5.8% OR: 0.80; 95% CI: 0.54–1.19; p=0.27 | 0.7% vs. 1.7% OR: 0.40; 95% CI: 0.16–0.97; p=0.04) | bleeding from use of low-dose UFH. Based on observed 5.8% event rate of 1º endpoint, a sample size of 11, 542 pts needed to have 80% power to detect 20% RR reduction |

| UFH, 85 U/kg (60 U/kg with GpIIb-IIIa inhibitors), adjusted by blinded ACT | 4.7% vs. 5.8% OR: 0.80; 95% CI: 0.54–1.19; p=0.27 | 0.7% vs. 1.7% OR: 0.40; 95% CI: 0.16–0.97; p=0.04) | bleeding from use of low-dose UFH. Based on observed 5.8% event rate of 1º endpoint, a sample size of 11, 542 pts needed to have 80% power to detect 20% RR reduction |

| Grosser 2013 (172) 23212718 | Determine commonality of mechanisticall y consistent, stable, and specific phenotype of | N=400 | Group 1 (n=40) received regular, immediate release ASA response was assessed 8 h after dosing. Group 2 (n=210) Healthy, nonsmoking volunteers (aged 18–55 y) | N/A | Single oral dose of 325-mg immediate release ASA or enteric coated ASA | Pharmacological resistance to ASA is rare; study failed to identify single case of true drug resistance. Variable absorption caused high frequency of apparent N/A | Pseudoresistance, reflecting delayed and reduced drug absorption, complicates enteric coated but not immediate release ASA | N/A | N/A | N/A |
| FUTURA/OASIS 8 Slag (173) | Evaluate safety of 2-dose regimens of adjunctive IV UFH during PCI in high-risk pts with NSTE-ACS initially treated with fondaparinux and referred for early coronary angiography. | International prospective cohort study N=4,000 | 4,000 high-risk pts treated with fondaparinux as initial medical therapy. Within cohort, 2,000 pts undergoing PCI enrolled into double-blind international randomized parallel-group trial evaluating standard ACT-guided doses of IV UFH versus a non-ACT-guided weight-adjusted low dose. | UA or NSTEMI; be enrolled within 48 h of the onset of most recent episode of Sx; planned coronary angiography with PCI if indicated within 72 h of enrolment; at least 2 of following: age ≥60 y, TnT or Tnl or CK-MB above upper limit of normal; ECG changes compatible with ischemia. | Age <21 y; contraindication to UFH or fondaparinux; contraindication for angiography or PCI; subjects requiring urgent (<120 min) coronary angiography because of refractory or recurrent angina associated with dynamic ST changes, HF, life-threatening arrhythmias, and hemodynamic instability; subjects already receiving treatment with other injectable anticoagulants for treatment of qualifying event, unless the last dose was ≥8 h for LMWH, ≥60 min for bivalirudin, ≥90 min for UFH; hemorrhagic stroke | N/A | Composite of peri-PCI major bleeding, minor bleeding, or major vascular access site complications | N/A | Composite of peri-PCI major bleeding with death, MI, or target vessel revasc at 30 d. | N/A | N/A | N/A |
### ACUITY Stone 2006 (174) 17124018

| Examine usefulness of bivalirudin as part of early invasive strategy with optimal antiplatelet therapy in pts with acss | Randomized N=13,819 pts | n=4603 UFH or enoxaparin plus a GP IIb/IIIa inhibitor n=4604 bivalirudin plus GP IIb/IIIa inhibitor n=4612 bivalirudin alone | Pts with Sx of UA lasting ≥10 min within preceding 24 h eligible for enrollment if one or more following criteria were met: new ST-segment depression or transient elevation of at least 1 mm; elevations in the Tnl, TnT, CK-MB levels; known CAD; or all four other variables for predicting TIMI risk scores for UA. | MI associated with acute STE or shock; bleeding diathesis or major bleeding episode within 2 wk before episode of angina; thrombocytopenia; a calculated creatinine clearance rate of <30 mL/min; recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin, ≥2 doses of LMWH; and allergy to any study | UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone | Composite ischemia endpoint (death, MI, or unplanned revasc for ischemia), major bleeding, and net clinical outcome, defined as combination of composite ischemia or major bleeding. Bivalirudin plus GP IIb/IIIa inhibitor, as compared with heparin plus GP IIb/IIIa inhibitor, associated with noninferior 30-d rates of composite ischemia | N/A | N/A | N/A | N/A | Logistic complexities of trial necessitated an open-label design, introduced potential for bias; 59% of study cohort presented with NSTEMI. Significant proportion of pts pretreated with either UFH or LMWH before randomization; 25% noninferiority margin used may... |
drugs or to iodinated contrast medium that could not be controlled in advance with medication.

endpoint (7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%), and net clinical outcome endpoint (11.8% and 11.7%). Bivalirudin alone, compared with heparin plus GP IIb/IIIa inhibitor, associated with noninferior rate of composite ischemia endpoint (7.8% and 7.3%, respectively; p=0.32; RR=1.08; 95% CI=0.93-1.24) significantly reduced rates of major bleeding (3.0% vs. 5.7%; p<0.001; RR=0.53; 95% CI=0.43-0.65) net clinical outcome endpoint (10.1% vs. 11.7%; p=0.02; RR=0.86; 95% CI=0.77-0.97).
<p>| TIMI IIIb | TIMI III focused on UA and NQMI. Determine by coronary arteriography the incidence of coronary thrombi in these conditions and response of these thrombi to 0.8 mg/kg dose (max 80 mg) of TPA. Determine effects of thrombolytic therapy and early invasive strategy on clinical outcome (TIMI IIIb). Provide further understanding of natural Hx of UA and NQMI. | Randomized using 2×2 factorial design N=1473 Pts | Compare TPA vs. PC as initial therapy and an early invasive strategy (early coronary arteriography followed by revasc when anatomy was suitable) vs. early conservative strategy (coronary arteriography followed by revasc if initial medical therapy failed). | Pts seen within 24 h of ischemic chest discomfort at rest, considered to represent UA or NQMI. | Treatable cause of UA, experienced MI within preceding 21 d, undergone coronary arteriography within 30 d, PTCA within 6 mo, CABG anytime, or if, at enrollment, were in pulmonary edema, had SBP &gt;180 mm Hg or DBP &gt;100 mm Hg, contraindication to thrombolytic therapy or heparin, LBBB, a coexistent severe illness, woman of child-bearing potential, receiving oral anticoagulants. | TPA versus PC Early invasive strategy vs. early conservative strategy. | TPA-PC comparison (death, MI, or failure of initial therapy at 6 wk) occurred in 54.2% of the TPA-treated pts and 55.5% of PC-treated pts (p=NS). Fatal and nonfatal MI after randomization (reinfarction in NQMI pts) occurred more frequently in TPA-treated pts (7.4%) than in PC-treated pts (4.9%, p=0.04, Kaplan-Meier estimate). | N/A | Endpoint for comparison of the two strategies (death, MI, or unsatisfactory Sx-limited exercise stress test at 6 wk) occurred in 18.1% of pts assigned to the early invasive strategy and 16.2% of pts assigned to the early conservative strategy (p=NS). | p=NS | N/A | 4 intracranial hemorrhages occurred in TPA-treated group vs. none in PC treated group (p=.06). | N/A |
| Eikelboom 2000 (147) | Systematic overview of randomized | Meta-analysis 12 trials, n=17,157 pts | UFH or LMWH or PC | Trials had to be randomized; include pts with UA or NQMI; and | Studies were excluded: Randomized | UFH or LMWH or PC | Composite of death or MI at 7 d (OR: 0.53 95% CI: 0.38–0.73); 1º safety outcome major bleeding | 2º outcomes of interest were recurrent angina | N/A | N/A | Large numbers of pts randomized to receive short- |</p>
<table>
<thead>
<tr>
<th>Trials to assess effect of UFH and LMWH on death, MI, and major bleeding.</th>
<th>Include ASA-treated pts randomly assigned to UFH or LMWH or to PC or untreated control</th>
<th>Comparison heparin vs. ASA, heparin plus ASA vs. combined antiplatelet therapy, or heparin vs. non-ASA control; nonrandomized comparison reported; dose-ranging uncontrolled study; pts alternately allocated to LMWH or UFH therapy; lack of clarity as to whether study was properly randomized.</th>
<th>&amp;p=0.0001) Short term LMWH vs UFH (OR: 0.88; 95% CI: 0.69–1.12; p=0.34). Long-term LMWH (up to 3 mo) vs PC or untreated control (OR: 0.98; 95% CI: 0.81–1.17; p=0.80).</th>
<th>&amp;p=0.0001 and need for revasc.</th>
<th>Long-term therapy who did not continue therapy long term may have reduced power of studies to detect significant difference. Pts who did not receive long-term LMWH were those at highest risk for recurrent events.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCF/ACG/AHA report Bhatt 2008 (158) 19017521</td>
<td>ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Karjalainen 2008 (156) 18346963</td>
<td>Determine safety and efficacy of various periprocedural antithrombotic strategies in pts on long-term OAC with warfarin undergoing PCI. Assess safety of Retrospective analysis n=523 pts IAC and UAC group</td>
<td>All consecutive pts on warfarin therapy referred for PCI in four centers with a main policy to IAC before PCI and in three centers with a long experience on UAC during PCI.</td>
<td>N/A</td>
<td>IAC vs. UAC</td>
<td>Major bleeding, access-site complications, and major adverse cardiac events (death, MI, target vessel revasc, and stent thrombosis) Major bleeding 5.0% vs. 1.2%, p=0.02 and after adjusting for propensity score (OR:3.9, 95% CI: 1.0–15.3, p=0.05)</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oldgren 2001</strong>&lt;sup&gt;(157) 11319192&lt;/sup&gt;</td>
<td>Study intensity and duration of anticoagulation as predictors of thrombotic and bleeding events</td>
<td>N=530 pts</td>
<td>ASA plus coumarins (sts who were prospectively randomized to use of coumarins as part of BAAS study)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>RE-DEEM Oliden 2011</strong>&lt;sup&gt;(177) 21551462&lt;/sup&gt;</td>
<td>Evaluate the safety and indicators of efficacy of four dose regimens of dabigatran etexilate compared with PC when given in addition to dual antiplatelet therapy</td>
<td>Double-blind, PC-controlled, dose-escalation trial N=1861 pts</td>
<td>Dabigatran vs. PC</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Access-site complications (11.3% vs. 5.0%, p<0.01)** After adjusting for propensity score (OR=2.8, 95% CI: 1.3–6.1, p=0.008)

**Small but clinically significant differences in bleeding and thrombotic complications**
<table>
<thead>
<tr>
<th>Treatment in pts with recent STEMI or NSTEMI at high risk of new ischaemic CV events.</th>
<th>Congestive HF requiring treatment or LVEF 40%, PAD, moderate renal insufficiency (CRI ≥30–60 mL/min), or no revasc for the index event.</th>
<th>Surgery in previous mo, Hx of severe bleeding, gastrointestinal haemorrhage with in past y, gastroduodenal ulcer in previous 30 d, fibrinolytic agents within 48 h of study entry, uncontrolled hypertension, haemoglobin &lt;10 g/dL or platelet count, &lt;100 × 10^9/L, normal coronary arteries at angiogram for index event, congestive HF New York Heart Association Class IV, and severe renal impairment (CrCl &lt;30 mL/min).</th>
<th>In the PC group, p&lt;0.001 for linear trend. 96 1º outcome events, compared with PC a dose dependent increase with dabigatran, HR 1.77 (95% CI: 0.70–4.50) for 50 mg; HR=2.17 (95% CI: 0.88–5.31) for 75 mg; HR=3.92 (95% CI: 1.72–8.95) for 110 mg; and HR=4.27 (95% CI: 1.86–9.81) for 150 mg. Compared with PC, D-dimer concentrations reduced in all dabigatran dose groups by average of 37 and 45% at wk 1 and 4, respectively (p=0.001).</th>
</tr>
</thead>
</table>

**Uchino 2012 (178) 22231617**  
Systematically evaluated risk of MI or ACS with use of dabigatran.  
Meta-analysis  
Seven trials were selected N=30,514  
N/A  
Searched PubMed, Scopus, and Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as 2º outcomes.  
N/A  
Fixed-effects M-H used to evaluate the effect of dabigatran on MI or ACS. Expressed associations as OR and 95% CIs.  
Dabigatran was significantly associated with higher risk of MI or ACS than seen with agents used in control group (dabigatran, 237 of 20 000 [1.19%] vs. control, 83 of 10 514 [0.79%]; OR=1.33; 95% CI: 1.03-1.71; p=0.03).  
N/A  
N/A  
N/A  
N/A  
P=0.03  
OR=1.33  
CI=1.03-1.71  
N/A  
Dominant effect of RE-LY trial on results of meta-analysis. Other 6 trials had cohort sizes of 515-3451 with durations of ≤6mo. In RE-LY, 18,113 participants monitored for median of 2 y. Owing to sample size and duration of study, RE-LY comprised 59% of the cohort and...
<table>
<thead>
<tr>
<th>Alexander 2011 (179)</th>
<th>Determine whether in high-risk pts with ACS benefit of apixaban in reducing ischemic events outweigh increased risk of bleeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, PC-controlled N=7392</td>
<td>n=3705 apixaban, 5 mg bid vs. n=3687 PC</td>
</tr>
<tr>
<td>ACS (MI, NSTEMI, STEMI, or UA) within previous 7 d, Sx of MI lasting 10 mo or more with pt at rest plus either elevated levels of cardiac biomarkers or dynamic ST-segment depression or elevation of ≥0.1 mV. 2 or more of the following high-risk characteristics: age ≥65 y, DM, MI within previous 5 y, cerebrovascular disease, peripheral vascular disease, clinical HF or LVEF of &lt;40% in association with index event, impaired renal function with calculated creatinine clearance &lt;60 ml/min and no revasc after index event.</td>
<td>N/A</td>
</tr>
<tr>
<td>Apixaban 5 mg bid PC, in addition to standard antiplatelet therapy</td>
<td>CV death, MI, or ischemic stroke</td>
</tr>
<tr>
<td>Median follow-up of 241 d</td>
<td>7.5% pts assigned to apixaban 7.9% assigned to PC</td>
</tr>
<tr>
<td>HR=0.95; 95% CI: 0.80-1.11; p=0.51</td>
<td>Major bleeding according to TIMI definition occurred in 1.3% pts who received apixaban and in 0.5% pts who received PC</td>
</tr>
<tr>
<td>HR=2.59; CI, 1.50-4.46; p=0.001. Greater number of intracranial and fatal bleeding events occurred with apixaban than PC.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mega 2012 (180)</th>
<th>Double-blind, PC-controlled trial N=15,526 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>bidbid doses of either 2.5 mg or 5 mg of rivaroxaban or PC</td>
<td>Within 7 d after hospital admission for ACS. Condition of pts needed to be stabilized before enrollment with initial management strategies (e.g., revasc) completed</td>
</tr>
<tr>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>bid doses of either 2.5 mg or 5 mg of rivaroxaban or PC</td>
<td>Composite of death from CV causes, MI, or stroke. Rivaroxaban compared with PC, 8.9% and 10.7% (HR in rivaroxaban group, 0.84; 95% CI: 0.74-0.96; p=0.008), significant improvement for both bid 2.5-mg dose (9.1% vs. 10.7%, p=0.02) and bid 5 mg dose (8.8% vs. 10.7%, p=0.03). Compared with PC, rivaroxaban increased rates of major bleeding not related to CABG (2.1% vs. 0.6%, p&lt;0.001) and intracranial hemorrhage (0.6% vs. 0.2%, p=0.009), without bid 2.5-mg dose of rivaroxaban reduced rates of death from CV causes (2.7% vs. 4.1%, p=0.002) and from any cause (2.9% vs. 4.5%, p=0.002),</td>
</tr>
<tr>
<td>P=0.008 HR=0.84 CI=0.74-0.96</td>
<td>Rates of adverse events that were not related to bleeding similar in rivaroxaban and PC groups</td>
</tr>
</tbody>
</table>

Mega 2012 (180) 22077192

2014 NSTE-ACS Guideline Data Supplements | 2014 NSTE-ACS Guideline Data Supplements

© American Heart Association, Inc and American College of Cardiology Foundation
significant increase in fatal bleeding (0.3% vs. 0.2%, \( p = 0.66 \)) or other adverse events: bid 2.5-mg dose resulted in fewer fatal bleeding events than bid 5-mg dose (0.1% vs. 0.4%, \( p = 0.04 \)).

Warkentin 2012 (181)

| Report timeline of bleeding, hemostatic parameters, and dabigatran plasma levels (by HPLC) in response to emergency management with rFVIIa and hemodialysis. | Single patient case | N/A | N/A | N/A | N/A | Pts developed massive postoperative bleeding resulting from elective cardiac surgery performed with therapeutic dabigatran levels. This illustrates importance of adjusting the number of d off dabigatran before surgery according to current renal function. | N/A | N/A | N/A | N/A | N/A |

Eerenberg 2011 (182)

| Evaluated potential of PCC to reverse anticoagulant effect of rivaroxaban and dabigatran | Randomized, double-blind, PC-controlled N=12 | Twelve healthy male subjects | N/A | Rivaroxaban 20 mg bid (n=6) or dabigatran 150 mg bid (n=6) | Rivaroxaban induced significant prolongation of prothrombin time (15.6±1.3 vs. 12.3±0.7 s at baseline; \( p < 0.001 \)) that was immediately and completely reversed by PCC (12.5±1.0). | N/A | N/A | N/A | N/A | No major or clinically relevant bleeding complications occurred during treatment, no serious adverse events. Small size of study population accounting for variation in results of a few coagulation tests. No measurements performed between 6-24 h after infusion of... |
repeated with another anticoagulant treatment.

p<0.001).

Endogenous thrombin potential inhibited by rivaroxaban (51±22%; baseline, 92±22%; p<0.002) normalized with PCC (114±26%; p<0.001), salmine had no effect. Dabigatran increased activated partial thromboplastin time, ECT, and thrombin time. Administration of PCC did not restore these coagulation tests.

1º indicates primary; 2º, secondary; ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; ACT, activated clotting time; ACUTY, Acute Catheterization and Urgent Intervention Triage strategy; ACUTE II, Assessment of Cardioversion Using Transesophageal Echocardiography; ADP, adenosine diphosphate; AGC, AHA, American Heart Association; AIMS, APSAC Intervention Mortality Study; aPTT, Activated Partial Thromboplastin Time; ASA, aspirin; ASSET, Anglo-Scandinavian Study of Early Thrombolysis; BID, twice daily; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiography; ECT, ecarin clotting time; EMERAS, Estudio Multicentrico Estreptoquinasas Republicas de America del Sur; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events; FUTURA, The Fondaparinux Trial With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes; GISSI-1, Grupo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico acute-1; GP, glycoprotein; HF, heart failure; HR, hazard ratio; Hx, history; IAC, Interrupt anticoagulant; IgE, Immunoglobin E; ISAM, Intravenous Streptokinase in Acute Myocardial Infarction; ISIS, International Study of Infarct Survival; INTERACT, Intensive blood pressure reduction in acute cerebral haemorrhage trial; ISAM, Intravenous Streptokinase in Acute Myocardial Infarction; IV, intravenous; LATE, Late Assessment of Thrombolytic Efficacy Study; LBBB, left bundle-branch block; LD, loading dose; LMWH, low molecular weight heparins; LVEF, left ventricular ejection fraction; MH, Mantel-Haenszel test; MI, myocardial infarction; NQMI, non-Q-wave myocardial infarction; NS, not significant; NSAID, nonsteroidal anti-inflammatory drugs; NSTE, non-ST elevation; NSTEMI, non-ST-elevation myocardial infarction; OAC, Oral anticoagulation; OASIS, Organization for the Assessment of Strategies for Ischemic Syndromes; OD, once daily; OR, odds ratio; PAD, peripheral arterial disease; PC, placebo; PCC, prothrombin complex concentrate, PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes trial; pts, patients; RCT, randomized clinical trials; Revasc, revascularization; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy Trial; ROW, rest of the world; RR, relative risk; SBP, systolic blood pressure; STE, ST elevation; STEMI, ST-elevation myocardial infarction; Sx, symptoms; TIMI, thrombolysis in MI; Tnl, troponin I; TnT, troponin T; TPA, UA, unstable angina; UAC, Uninterrupted anticoagulation; UFH, unfractionated heparin; US, United States; and USIM, Urochinasi per via Sistemica nell'Infarto Miocardico.

Data Supplement 18. Comparison of Early Invasive and Initial Conservative Strategy (Section 4.4.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type / Size (n)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95 CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI IIIb, 1994 8149520 (176)</td>
<td>To determine the effects of an early invasive strategy on clinical course</td>
<td>RCT 1.473</td>
<td>Intervention: 740; Comparator: 733</td>
<td>Chest discomfort at rest caused by ischemia that lasted &gt;5 min but &lt;6 h. The discomfort must have occurred within 21 d, had undergone PCI</td>
<td>The protocol called for pts assigned to the early invasive strategy to have cardiac catheterization, LVA, and coronary angiography</td>
<td>Pts randomized to the early conservative strategy were to have angiography</td>
<td>Death, postrandomization MI, or an unsatisfactory ETT performed at the time of the 6-</td>
<td>None</td>
<td>Analyses for differences and interactions in the results of invasive vs. conservative strategies for death</td>
</tr>
</tbody>
</table>
### MATE, 1998

**McCullough et al, (183)**

To determine if early revasc favorably affects clinical outcomes in pts with suspected AMI

**RCT 201**

**Intervention:** 201; **Comparator:** 90

**Pts 18 y and older who presented to the ED with an acute chest pain syndrome consistent with AMI**

**Exclusion criteria**
- Subjects randomized to triage angiography were taken as soon as possible directly to the catheterization laboratory from the ED. All triage angiography pts underwent catheterization within 24 h of arrival to the hospital
- Subjects randomized to the conservative arm were admitted to a monitored bed and received continued medical therapy and noninvasive evaluation encouraged by the protocol

**Composite endpoint of all recurrent ischemic events or death**

**None**

**2º endpoints including LOS and hospital costs**

**The composite endpoint of all recurrent ischemic events or death occurred in 14 (13%) and 31 (34%), yielding a 45% risk reduction (95% CI 27-59%, p=0.0002)**

**High crossover rate (60%). No long-term benefit in cardiac outcomes compared with conservative medical therapy with revasc prompted by recurrent ischemia**

### VANQWISH, Boden et al 1998

**Mccullough et al, (184)**

To compare an invasive with a conservative strategy in pts with acute NQMI

**RCT 920**

**Intervention:** 462; **Comparator:** 458

**Eligible pts had to have evolving AMI, a level of (CK-MB) isoenzymes that was more than 1.5× the ULN for the hospital, and no new abnormal Q waves**

**Pts were excluded if they had serious coexisting conditions, ischemic complications that placed them at very high risk while in the CCU (persistent or**

**Pts assigned to the early invasive strategy underwent coronary angiography as the initial diagnostic test soon after randomization. Thereafter, the**

**Pts assigned to the early conservative strategy underwent RNV to assess LV function as the initial noninvasive**

**Death or nonfatal MI**

**Major procedural complications after coronary angiography or myocardial revasc**

**Overall mortality**

**A total of 152 1º endpoint events occurred in the invasive-strategy group, as did 139 cardiac events in the**

**The trial was conducted before coronary stents or platelet GP IIb/IIIa receptor antagonists were widely available**

---

© American Heart Association, Inc and American College of Cardiology Foundation 2014 NSTE-ACS Guideline Data Supplements
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRISC II</td>
<td>Prospective, randomized, multicenter trial</td>
<td>1,222</td>
<td>1,235</td>
<td>Pts were eligible for inclusion if they had Sx of ischemia that were increasing or occurring at rest, or that warranted the suspicion of AMI, with the last episode within 48 h</td>
<td>Persistent STE, 2º angina, a Hx of PCI or CAB grafting within the preceding 6 mo, factors associated with an increased risk of</td>
<td>Composite endpoint of death and MI after 6 mo</td>
<td>Bleeding</td>
</tr>
<tr>
<td>TACTICSS</td>
<td>Prospective, randomized, multicenter trial</td>
<td>1,114</td>
<td>1,106</td>
<td>Pts ≥18 y if they had had an episode of angina (with an accelerating pattern or prolonged ≥20 min) or recurrent episodes at rest or Persistent STE, 2º angina, a Hx of PCI or CAB grafting within the preceding 6 mo, factors associated with an increased risk of</td>
<td>Pts assigned to the early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when Pts assigned to the early conservative strategy were treated medically and, if their condition was Combined incidence of death, nonfatal MI, and rehospitalization for an ACS at 6 mo</td>
<td>Combined endpoint of death and MI after 6 mo</td>
<td>Bleeding</td>
</tr>
</tbody>
</table>

| Summary | | | | | | | |
with minimal effort) within the preceding 24 h, were candidates for coronary revasc, and had at least 1 of the following: a new finding of ST-segment depression of at least 0.05 mV, transient (<20 min) STE of at least 0.1 mV, or T-wave inversion of at least 0.3 mV in at least 2 leads; elevated levels of cardiac markers; or coronary disease, as documented by a Hx of catheterization, revasc, or M

bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of <2.5 mg/dL (221 μmol/L), or current participation in another study of an investigational drug or device

appropriate on the basis of coronary anatomical findings

stable, underwent an exercise-tolerance test (83% of such tests included nuclear perfusion imaging or echocardiography performed according to the protocol of the institution) before being discharged

19.4% with use of the conservative strategy (OR: 0.78; 95% CI: 0.62–0.97; p=0.025).

VINO, Spacek et al 2002

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Interventions</th>
<th>Comparator</th>
<th>Primary endpoint</th>
<th>CONSORT</th>
<th>Other endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT 131</td>
<td>Intervention: 64 vs. Comparator: 67</td>
<td>Rest ischaemic chest pain, lasting &lt;20 min, within the last 24 h before randomization; ECG evidence of AMI without STE (ST-segment depressions minimally 0.1 mm in at least 2 contiguous leads and/or negative T waves or documented old LBBB/RBBB; CK-MB higher than 1.5× X ULN and/or positive TnI assay</td>
<td>Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; cardiogenic shock; acute LBBB or RBBB or STE 2 mm in 2 leads; OMl or IV thrombolysis &gt;1 mo; coronary angioplasty or bypass surgery &gt;6 mo; any concomitant disease which may have possible influence on 1-y Px; lack of pt cooperation</td>
<td>1st d angiography/angioplasty treatment strategy guidelines were characterized by a coronary angiogram as soon as possible after randomization followed by immediate coronary angioplasty of the culprit coronary lesion + stent implantation whenever suitable</td>
<td>Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischaemia</td>
<td>Composite of death or nonfatal RMI 6 mo after the randomization</td>
</tr>
</tbody>
</table>

Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischaemia |

None |

Length of the initial hospitalization and the number of subsequent hospitalizations for UAP |

The primary endpoint (death/ reinfarction) at 6 mo occurred in 6.2% vs. 22.3% (p<0.001). 6 mo mortality in the 1st d angiography/angioplasty group was 3.1% vs. 13.4% in the conservative group (p=0.03). |

Small sample size, interventions were done in only one high volume tertiary center |

RITA-2, Fox et al, 2002

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Interventions</th>
<th>Comparator</th>
<th>Primary endpoint</th>
<th>CONSORT</th>
<th>Other endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT 1,810</td>
<td>Intervention: 895 vs.</td>
<td>Pts were eligible for inclusion if they had All those with probable evolving</td>
<td>Pts assigned to the interventional treatment</td>
<td>Pts assigned to the conservative</td>
<td>The coprimary trial endpoints</td>
<td>Bleeding</td>
</tr>
</tbody>
</table>

Death, MI, refractory angina |

At 4 mo, 86 (9.6%) of 895 Primary endpoint driven by reduction |

© American Heart Association, Inc and American College of Cardiology Foundation
| Statistic | Comparator: 915 | Intervention: 604 vs. Comparator: 596 | Eligible pts had to have all 3 of the following: Sx of ischemia that were increasing or occurred at rest, with the last episode occurring no more than 24 h before randomization; an elevated cTnT level (≥0.03 μg/L); and either ischemic changes as assessed by ECG (defined as ST-segment depression or transient STE exceeding 0.05 mV, or T-wave inversion of ≥0.2 mV in ≥2 contiguous leads) or exclusion criteria were an age >18 y or <80 y, STEMI in the past 48 h, an indication for primary PCI or fibrinolytic therapy, hemodynamic instability or overt CHF, the use of oral anticoagulant drugs in the past 7 d, fibrinolytic treatment within the past 96 h, PCI within the past 14 d, a contraindication to treatment with PCI or GP IIb/IIIa inhibitors, recent trauma or risk of bleeding, hypertension despite PTs assigned to the early invasive strategy were scheduled to undergo angiography within 24-48 h after randomization and PCI when appropriate on the basis of the coronary anatomy. PTs assigned to the selectively invasive strategy were treated medically. These pts were scheduled to undergo angiography and subsequent revasorasy if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischarge ECG. The primary endpoint was a composite of death, RMI, or rehospitalization for angina within 1 y after randomization. | Revasc rates were high in the 2 groups in our study (76% in the early-invasive-strategy group and 40% in the selectively-invasive-strategy group during the initial hospitalization, and 79% and 54%, respectively, within 1 y after randomization. | Percentage of pts free from anginal Sx. | The estimated cumulative rate of the primary endpoint was 22.7% in the group assigned to early invasive management and 21.2% in the group assigned to selectively invasive management (RR: 1.07; 95% CI: 0.87-1.33; \( p=0.33 \)). |
| Italian Trial J Am Coll Cardiol Intv 2012;5:906-16 | To determine the risk vs. bebefut ratio of an EA approach in elderly pts with NSTE-ACS  
RCT 313 | Intervention: 154 vs. Comparator: 159  
Excluded were pts with NSTE-ACS and an age of ≥75 y, with cardiac ischemic Sx at rest within 48 h before randomization, together with ischemic ECG changes and/or elevated levels of either Tn or CK-MB  
Pts enrolled in the trial were randomly assigned to either: 1) an EA strategy of coronary angiography within 72 h and, when indicated, coronary revasc by either PCI or CABG according to coronary anatomy, pt preference, and local skills; or 2) IC therapy  
IC therapy, in which case pts had to be managed with medical therapy, and coronary angiography during index hospital stay was allowed in the case of refractory ischemia, myocardial (re)infarction, HR of ischemic origin, or malignant ventricular arrhythmias  
The primary endpoint was the composite of death, MI, disabling stroke, and severe bleeding within 1 y  
Bleeding Individual components of the primary endpoint  
The outcome occurred in 43 pts (27.9%) in the EA group and 55 (34.6%) in the IC group (HR: 0.80; 95% CI: 0.5–1.19; p=0.26)  
The main limitation of this study is its relative lack of power, because our original sample size was amended due to slow enrollment  
| Pts enrolled in the trial were randomly assigned to either: 1) an EA strategy of coronary angiography within 72 h and, when indicated, coronary revasc by either PCI or CABG according to coronary anatomy, pt preference, and local skills; or 2) IC therapy  
IC therapy, in which case pts had to be managed with medical therapy, and coronary angiography during index hospital stay was allowed in the case of refractory ischemia, myocardial (re)infarction, HR of ischemic origin, or malignant ventricular arrhythmias  
The primary endpoint was the composite of death, MI, disabling stroke, and severe bleeding within 1 y  
Bleeding Individual components of the primary endpoint  
The outcome occurred in 43 pts (27.9%) in the EA group and 55 (34.6%) in the IC group (HR: 0.80; 95% CI: 0.5–1.19; p=0.26)  
The main limitation of this study is its relative lack of power, because our original sample size was amended due to slow enrollment  

1º indicates primary; 2º, secondary; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAB, coronary artery bypass; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCU, cardiac care unit; CD, cardiac disease; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase-MB; cTnT, cardiac troponin T; CV, cardiovascular; EA, early invasive; ECG, electrocardiograph; ETT, exercise treadmill test; GP, glycoprotein; HD, heart disease; HF, heart failure; Hx, history; IC, initially conservative; IV, intravenous; LBBB, left bundle branch block; LOS, length of stay; LV, left ventricular; LVA, left ventricular angiography; MI, myocardial infarction; NQMI, Non Q-wave myocardial infarction; NS, no(t) significant; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; pts, patients; Px, prognosis; QMI, Q-wave myocardial infarction; RBBB, right bundle branch block; RCT, randomized controlled trial; revasc, revascularization; RMI; recurrent MI; RNV, radionuclide ventriculogram; STE, ST-segment elevation; Sx, symptom(s); TIMI, thrombolysis in MI; Tnl, troponin I; UA, unstable angina; UAP, unstable angina pectoris; UCAD, unstable coronary artery disease; and ULN, upper limits of normal.
## Data Supplement 19. Comparison of Early Versus Delayed Angiography (Section 4.4.4.1)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>Safety Endpoint &amp; Results</th>
<th>Secondary Endpoint &amp; Results</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-COOL, Neumann et al 2003 <a href="190">14506118</a></td>
<td>To test the hypothesis that prolonged antithrombotic pretreatment improves the outcome of catheter intervention in pts with acute unstable coronary syndromes compared with early intervention</td>
<td>RCT 410</td>
<td>Intervention: 207 vs. Comparator: 203</td>
<td>Pts with AP at rest or with minimal exertion, with the last episode occurring ≥24 h before study entry</td>
<td>With the early intervention strategy investigators performed coronary angiography as soon as possible, at least within 6 h, during which time antithrombotic pretreatment was instituted</td>
<td>With the prolonged antithrombotic pretreatment strategy, investigators continued pretreatment for at least 3 d, to a max of 5 d, after which all pts underwent coronary angiography</td>
<td>Composite 30-d incidence of large nonfatal MI or death from any cause</td>
<td>Bleeding, thrombocytopenia</td>
<td>Death, nonfatal MI</td>
<td>1º endpoint was reached in 11.6% (3 deaths, 21 infarctions) of the group receiving prolonged antithrombotic pretreatment and in 5.9% (no deaths, 12 infarctions) of the group receiving early intervention (RR: 1.96; 95% CI: 1.01–3.82; p=0.04)</td>
</tr>
<tr>
<td>TIMACS, Mehta et al. 2009 (191) [19458363]</td>
<td>To study efficacy of an early invasive strategy (within 24 h of presentation) compared with delayed invasive strategy (anytime 36 h after presentation)</td>
<td>RCT 3,031</td>
<td>Intervention: 1,593 vs. Comparator: 1,438</td>
<td>Pt who is not a suitable candidate for revasc</td>
<td>Among pts who were randomly assigned to the early-intervention group, coronary angiography was to be performed as rapidly as possible and within 24 h after randomization</td>
<td>Pts who were assigned to the delayed-intervention group underwent coronary angiography after a min delay of 36 h after randomization</td>
<td>Composite of death, MI, or stroke at 6 mo</td>
<td>Bleeding</td>
<td>1º occurrence of the composite of death, MI, or refractory ischemia and the composite of MI, stroke, refractory ischemia, or repeat intervention at 6 mo</td>
<td>At 6 mo, 1º outcome (death, new MI, or stroke) occurred in 9.6% of pts in the early-intervention group, as compared with 11.3% in the delayed-intervention group (HR: 0.85; 95% CI: 0.68-1.06; p=0.15)</td>
</tr>
</tbody>
</table>
Table 20. Risk Stratification Before Discharge for Patients With Conservatively Treated NSTE-ACS (Section 4.5)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Aim</th>
<th>Study Type/ Size (n)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint &amp; Results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety Endpoint &amp; Results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Endpoint &amp; Results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STABOARD, Montalescot et al 2004 (192)</strong></td>
<td>To determine if immediate intervention on admission can result in reduction of MI vs. delayed intervention</td>
<td>RCT 352</td>
<td>Intervention: 175 vs. Comparator: 177</td>
<td>Presence of at least 2 of the following: ischemic Sx, ECG abnormalities in at least 2 contiguous leads, or positive Tn, TIMI risk score 3</td>
<td>Hemodynamic or arrhythmic instability requiring urgent catheterization, chronic oral anticoagulation, or thrombolytic therapy in the preceding 24 h</td>
<td>An immediate invasive strategy</td>
<td>Primary endpoint was peak Tn value during hospitalization</td>
<td>Bleeding</td>
<td>2º endpoints were composite of death, MI, or urgent revasc at 1-mo follow-up</td>
</tr>
<tr>
<td><strong>DANAMI, Valouev et al 2004 (193)</strong></td>
<td>To test the prognostic importance of predischarge maximal 5x-limit ET following AMI in the era of aggressive reperfusion</td>
<td>Post hoc subgroup analysis of A: RCT 1,164</td>
<td>In the DANAMI-2 study, pts with STEMI were randomized to 1º angioplasty (PCI) or fibrinolysis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1º endpoint was a composite of death and re-infarction</td>
<td>N/A</td>
<td>ST-depression was predictive of the clinical outcome (RR: 1.57 [1.00-2.48]; p&lt;0.05) in multivariable analysis, there was a significant association between ST-depression and outcome in the fibrinolysis group (RR: 1.95 [1.11-3.44]; p&lt;0.05), but not in the 1º PCI group (RR: 1.06 [0.47-2.36]; p=NS). However, the p-value for interaction was 0.15.</td>
</tr>
</tbody>
</table>
| **INSPIRE, Mahmarian et al 2006** | To test whether gated ADSPECT could accurately | Cohort study 728 pts | The study cohort consisted of 728 stabilized pts 18 y of age | Event rates were assessed within prospectively | Pt risk and subsequent therapeutic | Composite of death, MI, or stroke at 6 mo | N/A | N/A | Total cardiac events/death and reinfarction significantly increased within each INSPIRE | Investigators did not track the percentage of eligible pts who were
<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Risk Stratification</th>
<th>Clinical Events</th>
<th>Complications</th>
<th>Cost Comparison</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>COSTAMI II</td>
<td>1º</td>
<td>RCT 262</td>
<td>1º endpoint was cost effectiveness of the diagnostic strategies. The 2º endpoint was quality of life evaluation.</td>
<td>Pharmacological stress echocardiography (n=132) or conventional predischARGE (d 7-9) maximum Sx limited exercise ECG (n =130)</td>
<td>26 events (1 death, 5 nonfatal reinfarctions, 20 pts with UA requiring hospitalization) in pts randomly assigned to early stress echocardiography and 18 events (2 reinfarctions, 16 UA requiring hospitalization) in the group randomly assigned to exercise ECG (NS). The negative predictive value was 92% for stress echocardiography and 88% for exercise ECG (NS).</td>
<td>No complication occurred during either stress echocardiography or exercise ECG. At 1-y follow-up there were 26 events (1 death, 5 nonfatal reinfarctions, 20 pts with UA requiring hospitalization) in pts randomly assigned to early stress echocardiography and 18 events (2 reinfarctions, 16 UA requiring hospitalization) in the group randomly assigned to exercise ECG (NS). The negative predictive value was 92% for stress echocardiography and 88% for exercise ECG (NS). Total costs of the two strategies were similar (NS).</td>
<td>Early pharmacological stress echocardiography and conventional predischARGE Sx limited exercise ECG have similar clinical outcome and costs after uncomplicated infarction. Early stress echocardiography may be considered a valid alternative even for pts with interpretable baseline ECG who can exercise.</td>
<td></td>
</tr>
<tr>
<td>INSPIRE</td>
<td>Comparator: 132;</td>
<td>262 pts from 6 participating centers with a recent uncomplicated MI were randomly assigned to early (d 3-5) pharmacological stress echocardiography (n=132) or conventional predischARGE (d 7-9) maximum Sx limited exercise ECG (n =130)</td>
<td>Exclusion criteria were age &gt;75 y, serious arrhythmias (VF, SVT, or fixed 2º or 3º degree AV blocks), LBBB, pericarditis, insufficient acoustic window, and poor short-term Px because of concomitant disease</td>
<td>1º indicates primary; 2º, secondary; ADSPECT, adenosine Tc-99m sestamibi single-photon emission computed tomography; AMI, acute myocardial infarction; AV, atrioventricular; DANAMI-2, Danish Multicenter Study of Acute Myocardial Infarction 2; ECG, electrocardiograph; EF, ejection fraction; ET, exercise test; INSPIRE, Investigating New Standards for Prophylaxis in Reduction of Exacerbations; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NS, non/significant; NQAMI, non-Q-wave myocardial infarction; PCI, percutaneous coronary intervention; PDS, perfusion defect size; pts, patients; Px, prognosis; QAMI, Q-wave myocardial infarction; RCT, randomized controlled trial; revasc, revascularization; STEMI, ST-elevation myocardial infarction; SVT, sustained ventricular tachycardia; Sx, symptom(s); UA, unstable angina; and VF, ventricular fibrillation.</td>
<td>92% for stress echocardiography and 88% for exercise ECG (NS). Total costs of the two strategies were similar (NS).</td>
<td>No complication occurred during either stress echocardiography or exercise ECG. At 1-y follow-up there were 26 events (1 death, 5 nonfatal reinfarctions, 20 pts with UA requiring hospitalization) in pts randomly assigned to early stress echocardiography and 18 events (2 reinfarctions, 16 UA requiring hospitalization) in the group randomly assigned to exercise ECG (NS). The negative predictive value was 92% for stress echocardiography and 88% for exercise ECG (NS). Total costs of the two strategies were similar (NS).</td>
<td>Early pharmacological stress echocardiography and conventional predischARGE Sx limited exercise ECG have similar clinical outcome and costs after uncomplicated infarction. Early stress echocardiography may be considered a valid alternative even for pts with interpretable baseline ECG who can exercise.</td>
<td></td>
</tr>
</tbody>
</table>
### Data Supplement 21. RCTs and Relevant Meta-Analyses of GP IIb/IIIa Inhibitors in Trials of Patients With NSTE-ACS Undergoing PCI (Section 5)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Drug / Comparator</th>
<th>Population</th>
<th>Primary Endpoint</th>
<th>Results</th>
<th>Statistics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPILOG (196)</td>
<td>Abciximab vs. PC</td>
<td>2,792 pts with stable ischemia or UA</td>
<td>Death, MI or UTVR at 30 d</td>
<td>5.2% vs. 11.7% HR: 0.43</td>
<td>95% CI: (0.30-0.60); p&lt;0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>CAPTURE (197)</td>
<td>Abciximab (administered for 18-24 h before PCI) vs. PC</td>
<td>1,265 pts with “refractory UA” undergoing PCI 18-24 h after diagnostic catheterization</td>
<td>Death, MI or UTVR at 30 d</td>
<td>11.3% vs. 15.9%</td>
<td>p=0.012</td>
<td>Significant reduction in MI rate before and during PCI with abciximab therapy. No diff in 6-mo composite endpoint</td>
</tr>
<tr>
<td>EPIC (198)</td>
<td>Abciximab vs. PC</td>
<td>2,139 pts with ACS undergoing PTCA or DCA</td>
<td>Death, NFMI, UTVR, or stent placement at 30 d</td>
<td>10.3% vs. 12.2%</td>
<td>p=0.180</td>
<td>Composite endpoint was statistically lower at 2 and 7 d follow-up (but not at the 30-d 1º endpoint)</td>
</tr>
<tr>
<td>ISAR-REACT 2 (142)</td>
<td>Abciximab vs. PC</td>
<td>2,022 “high-risk” ACS pts undergoing PCI</td>
<td>Death, MI or UTVR at 30 d</td>
<td>8.9% vs. 11.9% RR: 0.75</td>
<td>p=0.03</td>
<td>95% CI: 0.58–0.97; RR: 0.71 in +Tn pts; RR: 0.99 in -Tn pts</td>
</tr>
<tr>
<td>ADVANCE (200)</td>
<td>Tirofiban (high-dose) vs. PC</td>
<td>202 pts undergoing elective or urgent PCI (1/3 with stable angina; 1/2 with ACS)</td>
<td>Death, NFMI, UTVR or bailout GPI therapy at median of 185 d</td>
<td>20% vs. 35% HR: 0.51</td>
<td>p=0.01</td>
<td>95% CI: 0.29–0.88; Pts pretreated with either ticlopidine or clopidogrel Death/Mi/TVR at 6-mo lower (HR: 0.57; 95% CI: 0.99-0.33; p=0.48)</td>
</tr>
</tbody>
</table>

1º indicates primary; ACS, acute coronary syndrome; DCA, directional coronary atherectomy; diff, difference; GP, glycoprotein; GPI, glycoprotein IIb/IIIa inhibitors; IABP, intracoronary balloon pump; MI, myocardial infarction; NFMI, nonfatal myocardial infarction; PC, placebo; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; pts, patients; RR, relative risk; std, standard; Tn, troponin; +Tn, positive troponin; -Tn, negative troponin; TVR, target vessel revascularization; UA, unstable angina; and UTVR, urgent target vessel revascularization.

### Data Supplement 22. Studies of Culprit Lesion Versus Multivessel (Culprit and Nonculprit) PCI in Patients with NSTE-ACS (Section 5)

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of Study</th>
<th>Type of Study</th>
<th>Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brener SJ, 2008 (202)</td>
<td>To compare outcomes of culprit only PCI to multivessel PCI in NSTE-ACS pts</td>
<td>Post hoc database analysis</td>
<td>105,866 pts</td>
<td>NCDR database</td>
<td>Multiple endpoints analyzed</td>
<td>Procedural success: 91% culprit PCI vs. 88% multivessel PCI (p=0.001) ln-hospital mortality: 1.3% culprit PCI vs. 1.2% multivessel PCI (p=0.09; adjusted OR: 1.11; 95% CI: 0.97-1.27)</td>
</tr>
<tr>
<td>Shishehbor MH, 2007 (203)</td>
<td>Examination of the safety and efficacy of nonculprit multivessel</td>
<td>Post hoc database analysis</td>
<td>1,240 pts</td>
<td>NSTE-ACS pts in institutional</td>
<td>Death, MI or TVR</td>
<td>Median follow-up 2.3 y Multivessel PCI associated with lower death/Mi/TVR rate; adjusted HR: 0.80 (95% CI: 0.64-0.99; p=0.04); propensity matched analysis HR: 0.67 (95% CI: 0.51-0.88; p=0.004)</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
PCI with culprit-only PCI in pts with NSTE-ACS

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Type</th>
<th>Study Size (n)</th>
<th>Study Intervention Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR; RR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zapata GO, 2009 (204) 19515083</td>
<td>To investigate MACE at 1-y follow-up in pts with NSTE-ACS and multivessel CAD who underwent either culprit vessel PCI or multivessel PCI</td>
<td>Post hoc database analysis</td>
<td>609 pts</td>
<td>NSTE-ACS pts in institutional database</td>
<td>MACE at 1 y</td>
<td>Lower revasc rate with multivessel PCI drove endpoint differences</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmer ND, 2004 (205) 15152143</td>
<td>Retrospective database review with additional pt follow-up</td>
<td>151 pts</td>
<td>NSTE-ACS pts treated at a tertiary care institute</td>
<td>Multiple endpoints analyzed</td>
<td>Compared to multivessel PCI, culprit lesion only PCI resulted in: More pts with residual angina (22.8% vs. 9.9%; p=0.041; no OR given) More pts required further PCI (17.5% vs. 7.0%; p=0.045; no OR given) Trend towards more readmissions for UA Greater use of long-term antianginal medications (52.6% vs. 38.0%; p=0.043; no OR given)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brener, 2002 (206) 22231091</td>
<td>Post hoc trial analysis</td>
<td>427 pts</td>
<td>NSTE-ACS pts in TACTICS-TIMI 18</td>
<td>In-hospital and 6-mo MACE</td>
<td>NS diff between the 3 groups at either 30-d or 6-mo follow-up for any of the endpoints: death; MI; and MACE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CAD, coronary artery disease; diff, difference(s); MACE, major adverse coronary events; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; NS, no(t) significance; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; pts, patients; revasc, revascularization; TACTICS, Treat Angina with Tirofiban and Determine Cost of Therapy with an Invasive or Conservative Strategy; TACTICS-TIMI, Treat Angina with Tirofiban and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; VD, vascular disease; and TVR, target vessel revascularization.

6.3.1 Physical activity

Munk, 2009 (207) 19853690 | To evaluate high intensity interval training on in-stent restenosis following PCI for stable or UA | RCT | 40 | 20 | Had PCI with implantation of a stent | History of MI or CAGB, significant valvular heart disease, >80 y, inability to give informed consent, inability to participate in High-intensity interval training program | Usual care, no exercise intervention | Restenosis was smaller in the treatment group (0.10 mm) compared to the control group (0.39) p-value (0.01) | N/A | Peak oxygen uptake increased by 16.6% (T) and 7.8% (C) (p<0.01). Flow-mediated dilation improved by 5.2% (T) and -0.1% (C) (p=0.01). | Unknown |

Limitations: small sample size and large interquartile ranges; heterogeneity of stents implanted. There were no serious training-related adverse events.
### Depression and other psychological conditions

| Tisminetzky 2011 (208) | To ID Sx profiles of depression and anxiety in pts with ACS and examine changes over time | Randomized trial | 79 | 45 | Age 35+, hospitalized with ACS, mild/medium anxiety and/or depression | Mental healthcare in prior 3 mo, psychotropic drug use in past y, Dx substance abuse in past y | 4-6 30 min cognitive behavioral therapy sessions | Booklet on coping with cardiac illness, and told to contact PCP if depressed | 26% of treatment Sx improved vs. 10% in control group | N/A | N/A | N/A | Limitations: findings do not apply to high-risk individuals because they were excluded from study, short duration of follow-up and small sample size. |

### 6.3.4 Nonsteroidal anti-inflammatory drugs

| Lee, 2007 (209) | To compare the use of celecoxib and rofecoxib on CV risk | Adjusted indirect comparison of 2 published RCTs (APPROVe and APC trials) | APPROVe=1287 APC=685 (200 mg group) | 671 (400 mg group) | History of colorectal neoplasia/adenomas | None mentioned | APPROVe: 25 mg rofecoxib for 3 y APC: Either 200mg or 400mg of celecoxib for 3 y | PC | N/A | There were NS differences in CV events | N/A | RR (95% CI) p-value | Celecoxib vs. 200mg rofecoxib 0.74-1.38 (0.96) Celecoxib vs. 400mg rofecoxib 1.09-1.81 — 1.45 (0.57) | Limitations: interpretation of adjusted indirect comparison should be done with caution |

### 6.3.6 Antioxidant vitamins and folic acid

| Galan, 2010 (210) | To determine if vitamin B & omega 3 fatty acids can prevent CV events in pts with Hx of heart disease or stroke. | Double blind RCT | 2,501 | G1=622 (Vitamin B + PC) | G2 = 633 (omega 3 + PC) | G3 = 620 (vitamin B + omega 3) | Personal Hx of MI, UA, or ischaemic stroke | <45 or >60 y; ill defined Dx of CV disease; inability or unwillingness to comply with study treatment | Vitamin B: 560 mg 5-methyltetrahydrofolate, 3 g B-6, 20 mcg B-12 Omega 3: 600 mg of eicosapentaenoic acid and docosahexaenoic acid at a ratio of 2:1 | Double PC | 1st major CV event, NS for Vitamin B or Omega 3 | N/A | Significant 2nd endpoints: Vitamin B use associated with fewer strokes (HR: 0.57; 95% CI: 0.33-0.97; p=0.04); and a higher risk of death from any cause (HR: 1.55; 95% CI: 1.07–2.25; p=0.02) | Vitamin B: HR: 0.9 95% CI: 0.66–1.23 (0.5) Omega 3: HR: 1.08 95% CI: 0.79–1.47 (0.6) | Limitations: number of participants, short duration (4.7 y) to provide statistical power to detect effects on major vascular events. |
To determine the effect of folic acid supplementation on prevention of ACS

- **RCT**
  - 240
  - 116
  - 124
- UA or NSTEMI in previous 2 wk
- Hemodynamic instability, liver disease, renal disease, <18 y, pregnant, Hemoglobin <10 g/dL, high-output failure, inability to provide adequate self-care, malignancy or any terminal illness, and geographic location
- 1 mg folic acid, 400mcg B12, 10 mg B6 daily
- PC
  - Re-hospitalization and composite of death, nonfatal ACS, and re-hospitalization were significantly increased in the treatment group
  - N/A
  - N/A
  - RR (95% CI), p value
  - all-cause mortality 1.18 (0.68-2.04), 0.54
  - Nonfatal ACS 1.28 (0.64-2.54), 0.5
  - Re-hospitalization 5.11 (1.14-23.0), 0.016
  - Composite endpoint 1.20 (1.00-1.44), 0.04
- **Limitations:** small sample size; compliance rate=60%; adverse events in treatment group: skin irritation, dyspnea, dizziness

ACS indicates acute coronary syndrome; APC, Adenoma Prevention with Celecoxib trial; APPROVe, Adenomatous Polyposis Prevention on Vioxx trial; CABS, coronary artery bypass graft; CV, cardiovascular; Dx, diagnosis; ID, identification; MI, myocardial infarction; N/A, not applicable; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PCP, primary care physician; Pts, patients; RCT, randomized controlled trials; and UA, unstable angina.

### Table: Data Supplement 24. Older Patients (Section 7.1)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Interventio n Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Interventio n</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander 2007 (212)</td>
<td>Summarize evidence on pt heterogeneity, clinical presentation, and treatment of NSTEMACS in relation to age (65-74, 75-84, and 85 y)</td>
<td>Summary or 5 pooled NSTEMACS clinical trials and 3 large NSTEMACS registries to assess and grade evidence and provide descriptive finding and compare pts in clinical trials vs those not</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>2014 NSTE-ACS Guideline Data Supplements</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
| Gale 2012 | Assess difference in risk factors, presentation, managemen t and outcomes across age groups and trends over 7 y in MI pts in United Kingdom | Mixed-effects regression analysis using data from MINAP registry in United Kingdom. Comparison across older age groups and over 7 y | N=616 011 ACS pts: age <55 y=23%; 55 - 64y=20%; 65-74 y=40%; 75-84 y=39%; ≥85 y=29% | N/A | ACS pts in National Audit registry with outcomes linked to national database.Pts included if met ACS definition on admission (diagnosis was adjudicated but did not exclude pt if not ACS). | Missing data or follow-up | N/A | Compared to younger NSTE-ACS pts, older pts had sig higher in-patient mortality rates, longer rates of stay and were prescribed less GDMT (med and procedures) despite same or better efficacy vs. young. These age discrepancies have decreased over time. | N/A | Too numerous to list include effect of age on presenting symptoms, comorbidities, use of GDMT, PCI, outcome, and trends over time. | N/A | Inpatient mortality from 2003-2010 across all age groups including pts ≥85 y age: OR, 95% CI: 2004: 0.94, 0.88–1.01; 2010: 0.52, 0.44–0.61; 75–84 y age: 2004: 0.98, 0.93–1.03; 2010: 0.52, 0.45–0.60, and pts ≥85 y age: 2004: 0.94, 0.79–1.13; 2010: 0.64, 0.44–0.93. | Diverse sample of hospital in United Kingdom but less in Wales- not all pts entered into MINAP. Approx. 4% missing data. |
| Devlin 2008 | Determine whether increasing age impacts in-hosp and 6-mo outcome of revasc therapy in high-risk NSTE-ACS pts | Retrospectiv e multiplev logistic regression analyses on NSTE-ACS pts in GRACE registry by age groups | N=18468 NSTE-ACS pts (27% 70-80 y ‘elderly’; 16% >80 y ‘very elderly’) | Data assessed by use of GDMT and early invasive treatment (cath with approp revasc) by 3 age groups | In-hospital and 6-mo outcomes compared for age group and by intervention | GRACE registry pts meeting criteria for NSTE-ACS who had data during hospitalization and 6 mo after discharge. (STEMI data also reported but omitted here) | Pts who underwent revasc during initial hospitalizatio n classified under revasc included high-risk pts with dynamic ECG changes or recurrent ischemia -regardless of timing of revasc strategy | Medical therapy types were specifically recorded for comparison. Age and intervention strategy were compared. | In NSTE-ACS pts, revasc vs. medical therapy sig lowered 6-mo MACE (stroke, death, MI) and 6-mo mortality. Older NSTE-ACS pts were sig less likely to undergo revasc (and GDMT) than younger pts. | N/A | Elderly and very elderly pts less likely than younger pts to receive GDMT | N/A | Revasc vs. no revasc 6-mo MACE <70 yo OR=0.69, 95% CI 0.56–0.84; 70-80 y OR=0.60, 95% CI 0.47–0.76; >80 y OR=0.72,95 % CI 0.54–0.95 | Although study reports benefit of early invasive therapy, pts who underwent PCI/CABG during admission were included including those who underwent revasc >24 h after admission and high-risk pts were also included (including dynamic ST changes, recurrent ischemia) |
Dammann 2012
(215) 21930723
To assess the impact of early invasive vs. early conservative strategy on long term outcomes (5 y) in older NSTE-ACS pts
Meta-analyses of FRISC II, ICTUS and RITA-3 studies
N=5467 NSTE-ACS pts (51.3% <65 y, 33.3% 65-74 y, 15.3% ≥75 y)
Early invasive: <65 y=1383 65-75 y=901 ≥75 y=437
Selective invasive (EC): <65 y=1424 65-75 y=920 ≥75 y=402
Pts enrolled in FRISC II, ICTUS and RITA-3 with follow-up data were included.
Those with missing data for specific analyses
Routine invasive strategy defined as card cath within 24-48 h in ICTUS trial, within 72 h in RITA-3 trial and within 7 d with subsequent revasc when appropriate.
Initial medical treatment with card angio and revasc only if refractory angina despite OMT, hemodynamic instability or positive stress (ICTUS and FRISC II)
Routine invasive strategy sig reduced 5-y MACE (death/MI) in 65-74 and ≥76 y but not in those <65 y.
In-hosp bleeding rates sig higher in older pts: <65 y=1.7%, 65-74 y=2.2%, ≥75 y=6.1% (p<0.001 for trend).
Bleeding rates higher in each age group with Routine invasive vs. Selective Invasive strategy but all p<0.1
The benefits were smaller for women than for men but sample size small (esp ≥75 y) underpowere d for gender and age analyses.
Routine invasive vs. Selective Invasive on 5- y death/MI in older pts (HR 1.11, 95% CI 0.90 to 1.38), 65-74 y (HR 0.72, 95% CI 0.58-0.90); ≥75 y (HR 0.71, 95% CI 0.55-0.91)
Trials had different time windows for routine invasive strategy (up to 7 d in FRISC II) and other between trial heterogeneity exists

Bach 2004
(216) 15289215
To assess impact of age and early invasive vs. initial conservative strategy on outcomes in NSTE-ACS pts
Prespecified subgroup analyses by age strata of TACTICS TIMI 18, a RCT evaluating Early Invasive vs. Initial Conservativ e strategy in NSTE-ACS pts
N=2220 NSTE-ACS pts: <65 y=1258 ≥65 y=962
Early invasive: <65 y=623 ≥65 y=491
Early Conservative: <65 y=635 ≥65 y=471
Pts with NSTE-ACS eligible for card cath/revasc
Persistent STE: 2nd angina; PCI or CABG within previous 6 mo; contain to AP and GP meds. Stroke/TIA; LBBB or paced rhythm, CHF or cardiogenic shock; clinically important systemic disease; SCR >2.5 mg/dL
Coronary angiography 4-48 h after randomization and have revasc when appropriate All pts received ASA 325 mg, UFH and tirofiban.
PT received ASA 325 mg, UFH and tirofiban,
treated medically and, if stable underwent ETT before discharge. Card angio in pts w failure of OMT or stress-induced ischemia
Among pts ≥75 y, Early Invasive vs. Initial Conservative strategy con terred an absolute reduction (10.8% vs. 21.6%, p=0.016) and relative reduction of 56% in death or MI at 6 mo. RR=0.61 in death/MI at 6 mo for Early
Major bleeding rates higher with Early Invasive vs. Initial Conservative strategy in pts ≥75y (16.6% vs. 6.5%, p=0.003). Sig higher minor bleeding rates and trasfusions w Early Invasive vs. Initial Conservative
Sig reduction in 30-d outcomes of MI, death/MI, ACS Rehosp and MACE for NSTE-ACS pts ≥75 y (none were sig for pts <65 y)
NSTE-ACS pts ≥75 y Early Invasive vs. Initial Conservative
Death/MI: RR=0.61 (0.41-0.92) ACS Rehosp: RR=0.49 (0.29-0.81) Death: RR=0.88 (0.51-1.53)
TACTICS-TIMI 18 excluded pts with multiple co-morbidities and marked renal dysfunction (included older pts with mild renal dysfunction by CrCl). Underpowered for many comparisons in older pts. Additional age group beyond single 65-y stratification were not prespecified and done post hoc
### Yourman (217) 22235089

**Assess quality and limitations of prognostic indices for mortality in older adults through systematic review.**

| N=21,593 titles reviewer | N/A | N/A | Prognostic index studies included if they validated and predicted absolute risk of mortality in pts whose average age ≥60 y | Studies were excluded if prognostic index estimated intensive care unit, disease-specific, or in-hospital mortality. | N/A | N/A | 16 prognostic indices identified predicting overall mortality (6 m-5 y) in diff pt groups/ settings including community, nursing home and hospital. 2 were validated. | N/A | Reports potential sources of bias for each measure | Identified mortality predictors for older adults need additional external validation but may be useful in comparing efficacy of treatment/intervention recommendation (time to benefit) vs. life expectancy in older pts. | N/A |

### Fenning 2012 (218) 22530044

**Compare utility of palliative care prognostic tool GSF and GRACE score, to help identify patients approaching EoL.**

| N=172 NSTE-ACS pts, of these compared n=40 pts identified by GSF with n=32 by GRACE score | N/A | N/A | 172 consecutive, unselected pts admitted for NSTE-ACS to urban hosp over 8 wk | Pts admitted with ACS who died in hospital were excluded from analysis. | N/A | N/A | GSF identified 40 pts (23%) meeting criteria for approaching EoL (GSF+ older, more comorb vs. GSF-). 1-y mortality: GSF+ vs. GSF- (20% vs. 7%; p=0.03). GRACE identified 32 (19%) pts with ≥10% risk of N/A | GSF and GRACE positive score both independently associated with increased number of comorbidities, readmissions, older age. GRACE score 12-mo mortality prediction (C-statistic 0.75) + prev hosp adm and stroke (C-statistic 0.88). GRACE (upper tertile)+GSF Sens=78%, Spec=89%, NPV= 97%. | Single-center study, additional validation studies needed. |
death within 6 mo. GRACE score at discharge highly predictive of 12-mo mortality and associated with readmission during subseq y. Improved by adding prev hosp adm and prev stroke hx.

| Death within 6 mo. | PPV=44% |

| Tinetti 2004 (219) | This is a very relevant expert/consensus opinion paper, but is not a study which can be put into a data supplement table. |
| Corsonello 2010 (220) | This reference is an extensive review and summary of major PD/PK changes with aging and their relevance to CV drugs. However, it is not amenable to list in data supplement format. |
| Triffio 2011 (221) | This reference is an extensive review and summary of major PD/PK changes with aging and their relevance to CV drugs. However, it is not amenable to list in data supplement format. |

| Alexander 2005 (222) | Investigation of relationship between UFH, LMWH and GPI excess dosing and major outcomes |
| Retrospective exploratory analysis of CRUSADE registry | N=50,136 NSTE-ACS pts who had received AT agents | N/A | N/A | N=50,136 NSTE-ACS pts in CRUSADE registry who had received AT agents | Pts with missing weight (n=826) or missing creatinine clearance (n=1120) data excluded from dosing calculations that required these variables. Pt who were transferred or underwent CABG excluded from bleeding anal. | N/A | N/A | 42% of NSTE-ACS pts who received ≥1 initial dose of AT agent outside rec range. Excess doses per agent: UFH=32.8%, LMWH=13.8% and GPI=26.8%. Excess dose assoc with older age, female, low body wt, DM and CHF. Pt who received excess AT dose had higher | 15% of major bleeding in NSTE-ACS pts attributable to excess AT dosing | Higher adjust mortality in those receiving excess vs. recomm dose of GPI (OR=1.50, 95% CI 1.01-2.17). LOS sig longer in pts given excess vs. rec doses of UFH, LMWH and GPI. | Adjusted OR for major bleeding with excess dosing (vs. no excess dosing): UFH: OR=1.08 (0.94-1.26) LMWH: OR=1.39 (1.11-1.74) GPI: OR=1.36 (1.10-1.68) | Dosing categories based on weight and renal function dosing (dependent on recorded data) studied population may vary from those with missing data in addition to limited generalizability to general NSTE-ACS pts in real world, esp older. |
| Lincoff 2003  
(223)  
12588269 | Determine efficacy of bivalrudin +GPI vs. GPI+UFH for PCI on periprocedural ischemia and bleeding  
Pre-specified analysis of 30-d and 1-y outcomes in 4 age groups, overall and among those undergoing PCI | N=6010 | Bival+GPI=2999 | UFH+GPI=30 11 | Pts ≥21 y undergo PCI with approved device | PCI performed as reperfusion therapy for AMI, poorly controlled HTN, unprotected LM, PCI w/ past mo., risk for bleeding, serum Cr >4 mg/dL, prior heparin tx. | Bivalrudin 0.75 mg/kg bolus + 1.75 mg/kg/hr inf during PCI with provisional GPI Pts received ASA and thienopyridine for ≥30 d post PCI | UFH 65 U/kg bolus+ GPI (abximab or epifibatide) Pts received ASA and thienopyridine for ≥30 d post PCI | Provisional GPI given to 7.2% Bival pts. Noninferiority statistically achieved in 30 d endpoint. M/Death/ revasc/ in-hosp major bleeding between Bival+GPI vs. UFH+GPI | In Hosp major bleeding rates sig lower in Bival vs. UFH+GPI (2.4% v 4.1%, p<0.001) | 30 d death/MI/revasc/ in-hosp major bleeding:no diff in MACE in Bival+GPI v UFH+GPI (OR=0.99, p=0.4) | 30 d death/MI/revasc/ in-hosp major bleeding:no diff in MACE in Bival+GPI v UFH+GPI (OR=0.92, p=0.32). | Included elective PCI – NSTE-ACS pts approx. 42% each arm + 30% each arm. | N/A |
| Lopes RD,  
2009  
(224)  
19298914 | Evaluate impact of age on antithrombotic strategy and outcomes in moderate and high-risk NSTE-ACS pts | Of 13,819 ACUTY pts, 3,655 (26.4%) were <55 y, 3,940 (28.5%) were 55-64 y, 3,783 (27.4%) were 65-74 y, and 2,441 (17.7%) were ≥75 y. | Of the pts in each age group (prev column), 1/3 were randomized to receive Hep+GPI | Of the pts in each age group (4th column), 1/3 were randomized to receive Hep+GPI | Pts excluded for any of following: STEMI, recent bleeding, CRCI <30 mg/mL, thrombocytopenia, shock, recent use of abciximab, warfarin, fondaparinux, bival, LMWH, fibrinolitics | Bivalrudin alone All pts- ASA+ mtn Clopidogrel post PCI × 1 y Clopidogrel load per invest | Bivalrudin+ GPI- randomized (2×2 factorial) to upstream or cath lab GPI admin Heparin +GPI randomized (2×2 factorial) to upstream or cath lab GPI admin All pts- ASA+ mtn Clopidogrelpost PCI × 1 y Clopidogrel load per invest | Mortality and composite ischemic outcomes at ≥30 d and 1 y were not statistically different in pts randomized to bivalrudin alone or randomized to heparin with GPI/llla inhibitors across all age categories. | Major bleeding increased in each age group regardless. Major bleeding rates were higher in PCI pts in the age groups: 3.4%, 5.1%, 5.5%, and 11.8%, for ages <55, 55-64, 65-74, and ≥75 y, respectively. Rates were signif lower in those treated w Bivalrudin alone in each age group | Older pts had more comorb, were more often female, weighed less, and had more hypertension, prior cerebral vascular disease, renal insufficiency (creatinine clearance ≤50 mL/min), and prior CABG | Number needed to treat with bivalrudin alone to avoid 1 major bleeding event was lower in pts ≥75 y (23 overall and 16 for PCI- treated pts) than in any other age group. | N/A |
Lernesle G., 2008
Analyze impact of replacing heparin with bivalirudin in octogenarians undergoing PCI on post-procedure hemorrhage and 6-mo mortality.

N=2766
N=1,107 (43.6%) received bivalirudin
Consecutive pts ≥80 y at single center who underwent PCI/stent from 2000-2007
None

Bivalirudin (dose not reported) at operator’s discretion. GPI given at operator’s discretion. ACT target >250 s
All pts received ASA >325 mg, clopidogrel >300 mg load then 75 mg qd xtn advised for 1 y
UFH (dose not reported) at operator’s discretion. GPI given at operator’s discretion. ACT target >250 s
All pts received ASA >325 mg, clopidogrel >300 mg load then 75 mg qd xtn advised for 1 y

Overall in-hospital bleeding and 6-mo mortality rates were 4.6% and 11.8%, respectively. Bival vs UFH reduced 6 mo mortal (8.8% vs 13.4%, p<0.003). Bival was associated with less in-hosp bleeding rate (2.2% vs. 6.8%, p<0.001).

After propensity score matching, bival sign reduced periprocedural bleeding vs. UFH (HR=0.38, 95% CI=0.22–0.65, p=0.001). Bival vs. heparin reduced 6 mo MACE (10.1% vs. 20.2%, p<0.001)

In-hospital major bleeding assoc with 6-mo mortality HR=2.5, 95%CI=1.6–3.9, p=0.001

Non-randomized observational study. Does not reported. Differences in baseline characteristics—propensity analyses used.

Summana F, 2012
To explore feasibility and safety of PCI via transradial approach and intraprocedural bivalirudin in >70 y MI pts

N=64 pts (22 male; 52 pts >80 y)
STEMI=53, NSTEMI=31
All pts were treated with bivalirudin and via transradial approach
Consecutive pt >70 y with ACS treated with EI strategy using transradial approach and bivalirudin as AT regimen.
None

Bivalirudin bolus dose of 0.75 mg/kg immediately followed by continuous infusion of 1.75 mg/kg/h. All pts received ASA >325 mg, clopidogrel >300 mg load 600 mg, UFH bolus and infusion in emer dept – stopped 6 h prior to PCI

Transradial approach successful in 100%, manual thrombus aspir in 52% of NSTEMI pts. Transfusions=0, sign bleeding event=1 (GI bleed). in-hosp. mort=0.30 d MACE=5 (6%, 1 death, 2 Ml, 2 TLR)

In-hospital major bleeding associ with 6-mo mortality HR=0.6, 95% CI=0.4–0.9, p=0.01) In-hosp bleeding Bival vs. UFH: HR=0.41, (95% CI: 0.23–0.73, p>0.003) by MRL and by multivar COX (HR=0.6, 95% CI: 0.4–0.9, p=0.01)

McKellar SH, 2008
To assess pt characteristics, procedural success, Systematic review and meta-analyses of 68 studies of CABG studies
N=66 studies (65,376 pts, 56% male) 35 CABG studies 32 PCI studies

Studies which included baseline characteristic and outcomes Studies that reported combined CABG and valve operations or CABG without additional procedure (i.e. valve
PCI with last enrollment 1997
30-d mortal CABG vs. PCI (7.2% vs 5.4%), 1-y survival: CABG=86%
3 y survival CABG 78% (74%–82%) v PCI 78% (68%–87%), 5
Greater number of reintervention post PCI vs. CABG.
Univariate analysis showed that CABG, male gender,
Clinical trials comparing PCI vs. CABG enrolled younger pts of lower risk with less
| Kimura T, 2008 (228) | Assess long-term outcomes between PCI vs. CABG in younger and older pts (≥75 y) | Retrospective analyses of multicenter registries (CREDO-Kyoto) of consecutive pts undergoing PCI or CABG and excluding those pts with AMI within wk before index procedure. | Consecutive pts undergoing 1st PCI or CABG and excluding those pts with multivessel disease without left main. | N/A | N/A | ≥75 y of age: 3-y survival adjusted for baseline char favored CABG (HR for death PCI vs. CABG HR=1.23 (0.99–1.53, p=0.06), but not for younger pts | Stroke rate higher in 4 y follow-up in CABG vs PCI | ≥75 y: Adj HR for death PCI vs. CABG prespecified subgroups: DM HR= 1.85 (1.1–3.12) p=0.02 All-cause death cum 75 y of age: 3-y survival adjusted for baseline char favored CABG HR for death PCI vs. CABG HR=1.23 (0.99–1.53, p=0.06), but nonrandomized observational study. Meta-analyses performed in BMS era, non-urgent cases only |
Dacey LJ, 2007  
18036905  
Compare long-term survival after PCI vs. CABG in ≥80 y  
Retrospectiv e observation al analyses of regional (New England) registries of consecutive 80-89 y pts (1992-2001) who underwent PCI or CABG but eligible for both  
N=1693 (  
57% 2V CAD, 42.3% 3V CAD without LM disease.  
CABG=991 (2V/4CAD=443, 3V/5CAD=548)  
80-84 y=83% 85-89=17%  
PCI=702 (2VCAD=532, 3VCAD=170)  
80-84 y=72% 85-89=27%  
Pts included were 80-89 y with 2 or 3 VCAD (>70% stenosis), eligible for 1st PCI or CABG. (BARI criteria)  
Pts undergoing emergent procedure or <24 h of MI, those with left main disease, or sig valve disease.  
N/A  
BMS era  
In-hospital mortality:  
PCI=3.0% vs. CABG= 5.3% (p=0.005). 6-mo survival: CABG vs. PCI (HR, 0.68; p=0.005) and for pts with 2VCAD (HR, 0.72; p=0.005) and for pts with 3VCAD (HR, 0.72; p=0.005) and for pts with 2VCAD (HR, 0.68; p=0.016).  
3VCAD (HR=0.75, p=0.17)  
N/A  
CABG pts were more freq male; had more PVD and less renal failure and prior MI.  
In-hospital mortality:  
PCI=3.0% vs. CABG= 5.9% (p=0.005). 6-mo to 8-y survival: all pts: CABG vs. PCI (HR, 0.72; p=0.005)  
Nonrandomized observational study. Analyses performed in BMS era. Regional data. Limited data in older half of cohort and those with 3VCAD. Various revasc indications.
ST-elevation myocardial infarction; OA, osteoarthritis; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PET, positron emission tomography; PPV, positive predictive value; pts, patients; PVD, peripheral vascular disease; RITA, Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina; RBC, red blood cell; revasc, revascularization; RR, relative risk; Rx, prescription; SCR, serum creatinine; Sx, symptom(s); TACTICS, Treat Angina With Tirofiban and Determine Cost of Therapy With an Invasive or Conservative Strategy; TIA, transient ischemic attack, TIMI, Thrombolysis In Myocardial Infarction; UFH, unfractionated heparin; U.S., United States; and VIGOUR, Virtual Coordinating Center for Global Collaborative Cardiovascular Research.

### Data Supplement 25. Heart Failure (Section 7.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (n)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boersma 2000 (2) 10840005</td>
<td>Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE-ACS</td>
<td>Retrospective analysis of pts with NSTE-ACS enrolled in PURSUIT trial (n=9,461; 3.6% with 1º outcome)</td>
<td>N/A</td>
<td>Pts enrolled in PURSUIT trial</td>
<td>Pts not enrolled in PURSUIT trial; pts with STE on initial ECG</td>
<td>N/A</td>
<td>1º outcome: 30-d death; 2º outcome: composite of 30-d death and myocardial (re)infarction; More than 20 variables were found to be predictive of 1º and 2º outcomes</td>
<td>N/A</td>
<td>N/A</td>
<td>There were 7 factors most predictive of death: age (adjusted $[X]^2=95$), heart rate ($[X]^2=32$), SBP ($[X]^2=20$), ST-segment depression ($[X]^2=20$), signs of HF ($[X]^2=18$), and cardiac markers ($[X]^2=15$); The C-index for the mortality model was 0.814</td>
<td>N/A</td>
</tr>
<tr>
<td>Granger 2003 (3)</td>
<td>Develop a regression</td>
<td>Retrospective</td>
<td>N/A</td>
<td>Inclusion in GRACE or Not included in these trials</td>
<td>N/A</td>
<td>Adverse event defined as in-</td>
<td>N/A</td>
<td>N/A</td>
<td>The discrimination ability of the</td>
<td>N/A</td>
<td>Regression model</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation 2014 NSTE-ACS Guideline Data Supplements 95
<p>| Pollack 2006 | Validation in an ED population with chest pain | Conveniencesample N=3,326 without new STE | N/A | Chest Sx and ECG obtained | New STE | N/A | Death/MI/revasc over 30 d | N/A | In-hospital and 14-d events | Graded relationship between score and events | N/A | Used parts of score to define management | Validation in an ED population with chest pain | Convenience sample N=3,326 without new STE |
| Go 2011 | Attempt to add creatinine to TIMI risk score | Single center N=798 | N/A | Ischemic Sx within 48 h | STEMI | N/A | CV death, MI, urgent revasc or Sx and elevated biomarkers | N/A | N/A | Renal dysfunction increased risk but not enough to add variable to system | N/A | Small and only 9% with eGFR, 30 | Attempt to add creatinine to TIMI risk score | Single center N=798 |
| Huynh 2009 | Across all ACS spectrum | Multicenter RCT with N=1,491 | N/A | NSTE, ACS and STEMI | N/A | N/A | 6-mo death and MI | N/A | N/A | 2 mm ST deviation increased risk and risk was less | N/A | All high-risk pts | Across all ACS spectrum | Multicenter RCT with N=1,491 from angiographic arm |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Objective</th>
<th>Study Details</th>
<th>Statistical Analysis</th>
<th>Registry Data</th>
<th>Study Excluded</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eagle 2004 (16)</td>
<td>2004</td>
<td>Original GRACE validation</td>
<td>From angiographic arm</td>
<td>N/A</td>
<td>All ACS</td>
<td>N/A</td>
<td>6-mo all-cause mortality</td>
<td>P&lt;0.25 into multivariate model</td>
</tr>
<tr>
<td>Eggers 2010 (17)</td>
<td>2010</td>
<td>Incremental prognostic value of multiple biomarkers in NSTE-ACS</td>
<td>Single center trial of 453 chest pain pts</td>
<td>NT-proBNP, cystatin GDF-15</td>
<td>Possible ACS</td>
<td>N/A</td>
<td>Biomarkers at presentation</td>
<td>All-cause mortality at 6 mo</td>
</tr>
<tr>
<td>Cannon 2001 (186)</td>
<td>2001</td>
<td>To compare an early invasive strategy to a more conservative approach</td>
<td>Prospective, randomized, multicenter trial 2,220</td>
<td>Intervention: 1,114 vs. Comparator: 1,106</td>
<td>Persistent STE, 2º angina, Hx of PCI or CAB grafting within preceding 6 mo, factors associated with increased risk of bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of &lt;2.5 mg/dL (221 μmol/L), or current participation in another study of an investigational drug or device</td>
<td>Pts assigned to early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when appropriate on the basis of coronary anatomical findings</td>
<td>Combined incidence of death, nonfatal MI, and rehospitalization for MI at 6 mo</td>
<td>Bleeding</td>
</tr>
</tbody>
</table>

**Note:** ROC analysis not shown for Cannon study due to small sample size.
To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level

<table>
<thead>
<tr>
<th>de Winter 2005 (188)</th>
<th>RCT 1,200</th>
<th>Intervention:</th>
<th>Comparator: 596</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible pts have all 3 of the following:</td>
<td></td>
<td>604 vs.</td>
<td></td>
</tr>
<tr>
<td>1. Sx of ischemia that</td>
<td></td>
<td>Compara</td>
<td></td>
</tr>
<tr>
<td>were increasing or</td>
<td></td>
<td>tor:</td>
<td></td>
</tr>
<tr>
<td>occurred at rest, with</td>
<td></td>
<td>596</td>
<td></td>
</tr>
<tr>
<td>the last episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>occurring no more than 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h before randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Elevated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTnT level (≥0.03 μg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and either ischemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>changes as assessed by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG (defined as ST-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>segment depression or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>transient STE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exceeding 0.05 mV, or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-wave inversion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exclusion criteria were an age >18 y or <80 y, STEMI in past 48 h, indication for 1º PCI or fibrinolytic therapy, hemodynamic instability or overt CHF, the use of oral anticoagulant drugs in past 7 d, fibrinolytic therapy within past 24-48 h after randomization and PCI when appropriate on the basis of the coronary anatomy.

Pts assigned to early invasive strategy were scheduled to undergo angiography within 24-48 h after randomization and PCI when appropriate on the basis of the coronary anatomy.

Pts assigned to the selectively invasive strategy were treated medically. Pts were scheduled to undergo angiography and subsequent revascularization only if they had refractory angina despite optimal medical treatment, hemodynamic or rhythm instability, or clinically significant ischemia on the predischARGE exercise test.

1º endpoint was composite of death, RMI, or rehospitalization for angina within 1 y after randomization.

Bleeding

Percentage of pts free from anginal Sx

Estimated cumulative rate of 1º endpoint was 22.7% in the group assigned to early invasive management and 21.2% in the group assigned to selectively invasive management (RR: 1.07; [0.87-1.33]; p=0.33).

Revascularization rates were high in the 2 groups in our study (76% in the early-invasive strategy group and 40% in the selectively-invasive strategy group during the initial hospitalization, and 79% and 54%, respectively, within 1 y after randomization.

To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level
≥0.2 mV in 2 contiguous leads) or documented Hx of CAD as evidenced by previous MI, findings on previous coronary angiography, or a positive exercise test despite treatment (i.e., systolic pressure >180 mmHg or diastolic pressure >100 mmHg), weight <120 kg, or inability to give informed consent.

### Fox KA 2002. (187) 12241831

To compare interventional strategy and conservative strategy in pts with unstable CAD

<table>
<thead>
<tr>
<th>RCT 1,810</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervent</td>
<td>on: 895 vs. Compara</td>
</tr>
<tr>
<td>Pts eligible for inclusion if they had suspected cardiac chest pain at rest and had documented evidence of CAD with at least 1 of the following: evidence of ischaemia on ECG (ST-segment depression, transient STE, LBBB [documented previously], or T-wave inversion); pathological Q waves suggesting previous MI; or arteriographic</td>
<td></td>
</tr>
<tr>
<td>All those with probable evolving MI, including those for whom reperfusion therapy was indicated, were ineligible. Those in whom new pathological Q waves developed, or those with CK or CK-MB concentration &gt;2× the ULN before randomization were excluded. Also excluded were those with MI within the previous mo, PCI in the</td>
<td></td>
</tr>
<tr>
<td>Pts assigned to interventional treatment strategy were managed with optimum antianginal and antiplatelet treatment (as for the conservative group), and enoxaparin 1 mg/kg subcutaneously 2× for 2-8 d. Protocol specified that coronary arteriography should be done as soon as possible after randomization and ideally within 72 h</td>
<td></td>
</tr>
<tr>
<td>Pts assigned to the conservative strategy were managed with antianginal and antithrombotic medication</td>
<td></td>
</tr>
<tr>
<td>Coprimary endpoints were: a combined rate of death, nonfatal MI, or refractory angina at 4 mo; and a combined rate of death or nonfatal MI at 1 y</td>
<td></td>
</tr>
</tbody>
</table>

### Bleeding

At 4 mo, 66 (9.6%) of 895 pts in intervention group had died or had a MI or refractory angina, compared with 133 (14.5%) of 915 pts in the conservative group (RR: 0.66, [0.51-0.85], p=0.001). 1<sup>st</sup> endpoint driven by reduction of refractory angina with no difference in hard clinical endpoints.

To compare interventional strategy and conservative strategy in pts with unstable CAD

© American Heart Association, Inc and American College of Cardiology Foundation
| Spacek 2002 | To compare 1-d angiography/angioplasty vs. early conservative therapy of evolving MI without persistent STE | RCT 131 | Intervention: 64 vs. Comparator: 67 | Rest ischemic chest pain, lasting >20 min, within last 24 h before randomization; ECG evidence of AMI without STE (ST-segment depressions minimally 0.1 mm in at least 2 contiguous leads and/or negative T waves or documented old LBBB/RBBB; CK-MB higher than 1.5× X ULN and/or positive TnI assay | 1-d angiography/angioplasty treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischemia | Composite of death or nonfatal RMI 6 mo after the randomization | None | Length of the initial hospitalization and the number of subsequent hospitalizations for UAP | 1º endpoint (death/infarction) at 6 mo occurred in 6.2% vs. 22.3% (p<0.001). 6-mo mortality in 1-d angiography/angioplasty group was 3.1% vs. 13.4% in the conservative group (p<0.03). | To compare 1-d angiography/angioplasty vs. early conservative therapy of evolving MI without persistent STE | RCT 131 |

| Hochman 1999 | Evaluate early revascularization in pts with cardiogenic shock | Multicenter RCT | 302 pts | 152 pts randomized to emergency revasc | STEMI, new LBBB, posterior infarction, anterior ST segment depression and cardiogenic | N/A | N/A | N/A | Mortality from all causes at 30 d At 30-d mortality p=0.11 Revasc 46.7% Medical therapy 56.0% | N/A | 6-mo survival 6-mo mortality p=0.027 Revasc 50.3% Medical therapy 63.1% | N/A | Emergency revasc did not significantly reduce overall mortality at 30 d. However, at 6 mo significant survival benefit |
Data Supplement 26. Cardiogenic Shock (Section 7.2.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Interventio n Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study group</th>
<th>Comparator group</th>
<th>Endpoints</th>
<th>Conclusions</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
</table>
| Bhatt 2004 (231) (15523070) | Determine use and predictors of early invasive management strategies in high-risk pts with NSTEMI | Registry-observation al study trial | 17,926 with NSTEMI 6,037 (44.8%) underwent early cardiac cath <48 h | 8,037 (44%) underwent early cardiac cath <48 h | N/A | NSTEMI pts presenting to 248 US hospitals with cardiac cath facilities and PCI or CABG availability | N/A | N/A | Use of early invasive management within 48 h of presentation Predictors of early invasive management In-hospital mortality | N/A | N/A | N/A | Predictors of early invasive management: lower-risk pts with lack of prior or current CHF, renal insufficiency, positive biomarkers Pts treated with early invasive strategy had lower in-hospital mortality 2.5% vs 3.7%, p<0.001

1ª indicates primary; 2ª indicates primary; ACS, acute coronary syndromes; AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CAB, coronary artery bypass; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CK-MB, creatine kinase MB; cTnT, cardiac troponin T; CV, cardiovascular; ECG, electrocardiography; ED, emergency department; eGFR, estimated glomerular filtration rate; GDF, growth differentiation factor; GP, glycoprotein; GRACE; Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HF, heart failure; Hx, history; LBBB, left bundle-branch block; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; NST-ACS, non–ST-elevation acute coronary syndrome; NSTEMI, non–ST-elevation myocardial infarction; NT-pro, N-terminal pro; PCI, percutaneous coronary intervention; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrillen Therapy; Pt, patient; Px, prognosis; QMI, q-wave myocardial infarction; RBBB, right bundle-branch block; RCT, randomized clinical trial; RMI, recognized myocardial infarction; ROC, receiver operating characteristic; RR, relative risk; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; Sx, symptom; TIMI, Thrombolysis In Myocardial Infarction trial; Tnl, troponin I; ULN, upper limit normal; US, United States.
Determine the outcomes of pts with cardiogenic shock complicating NSTEMI

Jacobs A. et al., 2000

102 pts with NSTEMI and cardiogenic shock
159 pts with STEMI and cardiogenic shock
881 pts with NSTEMI

729 pts with STEMI

Cardiogenic shock due to LV failure
Excluded pts with missing ECG + cardiogenic shock due to mechanical complications, tamponade, cardiac catheter laboratory complication, isolated RV dysfunction, severe valvular heart disease

NSTEMI + cardiogenic shock
STEMI + cardiogenic shock
In-hospital mortality similar in the 2 groups (62.5% for NSTEMI vs. 60.4% STEMI). After adjustment, STEMI did not independently predict in-hospital mortality (OR: 1.30; 95% CI: 0.83 - 2.02; p=0.252)

Compared with shock pts who had STEMI, pts with NSTEMI were older and more likely to have comorbid disease, prior infarctions and MVD
Left circumflex artery was the culprit vessel in 34.6% of non-ST-elevation vs. 13.4% of ST-elevation MI pts (p<0.001)
Similar LVEF in-hospital, and similar revascularization
Pts with cardiogenic shock and NSTEMI have a higher-risk profile than shock pts with ST-segment elevation, but similar in-hospital mortality.

No hemodynamic or LV function data
Registry data – subject to confounding

Assess the incidence and outcomes of cardiogenic shock developing among pts with and without ST-segment elevation

Holmes DR et al., 1999

Pre-specified sub-study from the GUSTO-IIb trial
12,084 (of those 4,092 or 34% had NSTEMI)
200 pts developed cardiogenic shock (out of 7,986 NSTEMI pts) 2.5%
173 pts developed cardiogenic shock (out of 4,087 STEMI pts) 4.2%

Pts who developed shock after enrollment in GUSTO-IIb eligibility criteria: chest pain of myocardial ischemia within 12 h + STE or ST-depression, or persistent T-wave inversion
Pts who had shock on presentation (n=58) + 11 pts with missing data Also excluded pts with STEMI who were not candidates for thrombolytic therapy

NSTEMI (incidence/outcome of cardiogenic shock)
STEMI (incidence/outcome of cardiogenic shock)
Lower OR of developing cardiogenic shock in NSTEMI compared with STEMI Incidence: 4.2% vs. 2.5% (OR: 0.58; 95% CI: 0.47-0.72; p<0.001)
High-30-d mortality in both: 63% among pts with STEMI with shock vs. 73% in NSTEMI with shock (p NS)

No STE was significant predictor of 30-d mortality (p=0.048)
Pts without ST-segment elevation were older, more frequently had DM and 3-vessel disease, but had less TIMI grade 0 flow at angiography Shock developed significantly later among pts without ST-segment elevation No STE was significant predictor of 30-d mortality (p=0.048)
Pts without STE developed shock much later than those with STEMI suggesting a window of opportunity to prevent shock Shock pts without STE had more high-risk clinical characteristics, more extensive CAD, and more frequent recurrent ischemia and MI before the development of shock
Regardless of the initial ECG findings, Shock was associated with a marked increase in mortality.

No hemodynamic or LV function data
Registry data – subject to confounding

GUSTO-IIb is a thrombolytic trial (excluded pts ineligible for thrombolytics)
Subgroup analysis Different baseline risk
**Data Supplement 27. Diabetes Mellitus (Section 7.3)**

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Patient Population</th>
<th>Study Comparator Group (n)</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon 2001 (186)</td>
<td>To compare an early invasive strategy to a more conservative approach</td>
<td>Prospective, randomized, multicenter trial 2,220</td>
<td>1,114 vs. Comparator: 1,106</td>
<td>Persistent STE, 2º angina, a Hx of PCI or CABG within the preceding 6 mo, factors associated with an increased risk of bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of &lt;2.5 mg/dL (221 μmol/L), or current participation in another study of an investigational drug or device</td>
<td>Pls assigned to the early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when appropriate on the basis of coronary anatomical findings</td>
<td>Pls assigned to the early conservative strategy were treated medically and, if their condition was stable, underwent an exercise-tolerance test (83% of such tests included nuclear perfusion imaging or echo performed according to the protocol of the institution) before being discharged</td>
<td>Bleeding</td>
<td>Combined incidence of death, nonfatal MI, and nonfatal MI, rehospitalization for MI</td>
<td>At 6 mo, the rate of the 1º endpoint was 15.5% with use of the early invasive strategy and 19.4% with use of the conservative strategy (OR: 0.78; 95% CI: 0.62-0.97; p=0.025). Study excluded pts with severe comorbid conditions or other serious systemic illness</td>
<td>To compare an early invasive strategy to a more conservative approach</td>
<td>Prospective, randomized, multicenter trial 2,220</td>
</tr>
<tr>
<td>Study/Citation</td>
<td>Type/Design</td>
<td>N/Total</td>
<td>N/DM</td>
<td>N/No DM</td>
<td>Inclusion/Notes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Angina at 6 mo</td>
<td>ITT</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>FRISC II (185) 10475181</td>
<td>Multicenter, RCT of 2,457 pts</td>
<td>2,457 pts, 21.4% diabetics</td>
<td>N/A</td>
<td>N/A</td>
<td>Early invasive strategy N=1,222</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>6-mo composite of death or MI. 9.4% in invasive vs. 12.1% in noninvasive group (RR: 0.78, 95% CI: 0.62–0.98, p=0.031). Decrease in MI alone 7.8% in invasive vs. 10.1% in conservative group (RR: 0.77 95% CI: 0.60–0.99; p=0.045). Nonsignificant decrease in death 1.9% vs. 2.5% (HR: 0.65, 95% CI: 0.39–1.09; p=0.10).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early invasive strategy N=1,222</td>
<td>Noninvasive strategy n=1,235</td>
<td>Inclusion: UA, NSTEMI Pts with DM- 21.4% of total but not analyzed separately</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1º composite of death or MI. ITT. DM remained a strong independent predictor of death and MI in multivariable analyses. Invasive strategy reduced composite of death or MI in pts with DM from 29.9% to 20.6% (OR 0.61; CI 0.36–1.04, p=0.068).</td>
</tr>
<tr>
<td>Norhammar 2004 (234) 14975468</td>
<td>Randomized clinical trial</td>
<td>299 pts with diabetes mellitus and 2,158 without Randomization to early invasive or a noninvasive strategy</td>
<td>299 pts with DM</td>
<td>2,158 patients without DM</td>
<td>UA, NSTEMI Pts with DM defined as treated with diet, oral agents, or insulin. Pts with DM were at higher baseline risk – more prior MI, CHF, PAD, HBP, more 3VD</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>6-mo composite of death or MI 9.4% in invasive vs. 12.1% in noninvasive group (RR: 0.78, 95% CI: 0.62–0.98, p=0.031). Decrease in MI alone 7.8% in invasive vs. 10.1% in conservative group (RR: 0.77 95% CI: 0.60–0.99; p=0.045). Nonsignificant decrease in death 1.9% vs. 2.5% (HR: 0.65, 95% CI: 0.39–1.09; p=0.10).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Evaluate influence of DM in outcome of unstable CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Early invasive strategy** preferred in most pts with unstable CAD who have signs of ischemia or have NSTEMI. Benefit is greatest in pts at higher risk at entry.
| Parkouh 2012 (235)  
| 23121323 | Compare strategy of aggressive medical therapy and DES vs. CABG for pts with DM and multivessel CAD | Multicenter randomized clinical trial | 1,900 pts | Aggressive medical therapy plus DES, n=953 | CABG, n=947 | Plts with DM with angiographic ally confirmed MVD of ≥2 major epicardial vessels | LMCA lesions excluded Minimum follow-up 2 y | N/A | N/A | Composite of death from any cause, nonfatal MI or nonfatal stroke 
Composite 5-y rate 26.6% in PCI vs. 18.7% in CABG; p=0.005 
5-y rate death from any cause 16.3% vs. 10.9%; p=0.049 PCI vs. CABG 
5-y rate MI 13.0 vs. 6.0%; p<0.001 PCI vs. CABG 
Rate stroke increased with CABG 5.2% vs. 2.4% PCI; p=0.03  
No subgroup analysis of pts with ACS | N/A | MACE at 30 d and 12 mo | N/A | For pts with DM and severe CAD undergoing revascularization,  
CABG was associated with significant reduction in death and MI,  
but with a significant increase in stroke compared with PCI. 
Limitations: Trial not blinded 
Some prespecified subgroups had very low prevalence |
### Data Supplement 28. Post-CABG (Section 7.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>Primary Endpoint (efficacy) and Results</th>
<th>Safety Endpoint and Results</th>
<th>Secondary Endpoint and Results</th>
<th>P Values, OR: HR: RR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kavsak 2006</td>
<td>Impact of new classification of MI</td>
<td>Retrospective analysis using CK-MB vs. Tnl analysis for MI def. 258 pts with ACS</td>
<td>Tri vs. CK-MB Dx based on MONICA or AHA def of MI</td>
<td>2 SPSS CK-MB, Tnl ≥20% change using 99% Tnl cutoff</td>
<td>N/A</td>
<td>2 specimens CK-MB, Tnl drawn at least 6 h apart</td>
<td>AMI prevalence&quot; MONICA CK-MB 19.4% AHA 19.6%, Tnl increase. to 35.7%</td>
<td>N/A</td>
<td>Tri vs. CK-MB p&lt;0.001 for increase MI def using Tnl</td>
<td>cTnI 35.7% (30.1- 41.7) Relative inc 84%</td>
<td>N/A</td>
<td>Exclusion of nonischemic diseases causing Tnl elevation</td>
<td>Impact of new classification of MI</td>
<td>Retrospective analysis using CK-MB vs. Tnl analysis for MI def. 258 pts with ACS</td>
</tr>
<tr>
<td>Goodman 2006</td>
<td>Diagnostic and prognostic impact of new UDMI</td>
<td>Multicenter observational prospective Registry (GRACE) 26,267 ACS pts</td>
<td>Use of CK and -Tn 16,797 vs. CK-MB and Tn 10,719 for hospital. Fatality, 14,083 vs. 8,785 for 6-mo mortality</td>
<td>&gt;16 y with possible ACS with ECG abnormal or CAD history, CK, CK-MB, Tn</td>
<td>NS comorbidty, trauma, surgery, lack of 1 biomarker</td>
<td>CK CK-MB Tn Follow-up for 6 mo</td>
<td>Tn+ levels demonstrated higher in hospital and 6-mo mortality than higher CK levels</td>
<td>N/A</td>
<td>In entire population, Tn+ status vs. CK status 6-mo mortality:1.6 (1.4-1.9)</td>
<td>Hospital fatality rates higher with Tn+ vs. CK+: 2.2 (1.8- 2.9) with Tn+/CK-MB+: 2.1 (1.4-3.2)</td>
<td>N/A</td>
<td>34% in GRACE registry excluded because of use of 1 biomarker only</td>
<td>Diagnostic and prognostic impact of new UDMI</td>
<td>Multicenter observational prospective Registry (GRACE) 26,267 ACS pts</td>
</tr>
<tr>
<td>Eggers 2011</td>
<td>Clinical implications of relative change in cTnl levels with chest pain</td>
<td>Retrospective study of 454 ACS pts within 24 h of admission with 5.8 y follow-up</td>
<td>UDMI with presp cTnl changes from ≥20%, 50%, 100%</td>
<td>N/A</td>
<td>cTnl &lt;99th percentile</td>
<td>cTnl levels</td>
<td>Peak cTnl level ≥99th percentile + change ≥20% in 160.25 had no AMI by ESC/ACC criteria</td>
<td>N/A</td>
<td>N/A</td>
<td>All 160 had significant raised mortality HR: 2.9 (1.7- 3.8) Higher Tnl deltas were not associated with higher mortalities</td>
<td>N/A</td>
<td>Analysis of assay could not be validated by hs Tnl assay. No review of pts records for type I or 2 AMI No long-term risk assessment</td>
<td>Clinical implications of relative change in cTnl levels with chest pain</td>
<td>Retrospective study of 454 ACS pts within 24 h of admission with 5.8 y follow-up</td>
</tr>
<tr>
<td>Giannitsis 2010</td>
<td>Dx, perf. of hs-cTnlT for detection of NSTEMI in ACS</td>
<td>Retrospective cohort analysis 57 with UA</td>
<td>Baseline vs. and serial conc. at 3 h and 6 h</td>
<td>UA or NSTEMI with initial -cTnlT</td>
<td>Immed PCI or kidney dysfunction</td>
<td>Hs-cTnlTx baseline,3.6 h delta change</td>
<td>Hs-cTnlT Dx 61% at baseline to 100% at 6 h.</td>
<td>N/A</td>
<td>Doubling of hs-TnT with initial 99% + pos</td>
<td>Delta changes and ROC opt. values spec 100% with</td>
<td>N/A</td>
<td>Admission to chest pain unit more selective than typical ED</td>
<td>Dx, perf. of hs-cTnlT for detection of NSTEMI in ACS</td>
<td>Retrospective cohort analysis 57 with UA and evolving NSTEMI</td>
</tr>
<tr>
<td>Le 2004 (236) 15528943</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Lindahl 2010 (32) 20691825</td>
<td>Hs-cTnT comparison with std cTnT for risk assessment</td>
<td>Prospective cohort 1,452</td>
<td>Effect of pos. by both assays vs. only 1 assay</td>
<td>ACS pts</td>
<td>No coronary angiography within 12 h</td>
<td>Both cTnT collected 48 h after randomization</td>
<td>+hs-TnT same 1-y mortality. Whether + or – with st-TnT</td>
<td>N/A</td>
<td>For death or AMI at 30 d + only for hs-TnT had interim risk</td>
<td>+hs-TnT 1-y mortality 9.2% vs. 1.6% p=0.001</td>
<td>For – by both assays</td>
<td>N/A</td>
<td>Pts with higher pretest risk than typical chest pain pts in ED</td>
<td>Hs-cTnT comparison with std cTnT for risk assessment</td>
</tr>
<tr>
<td>Cannon 2001 (186) 11419424</td>
<td>To compare an early invasive strategy to a more conservative approach</td>
<td>Prospective, randomized multicenter trial 2,220</td>
<td>Intervention: 1,114 vs. Comparator: 1,106</td>
<td>Pts ≥18 y if they had had an episode of angina (with an accelerating pattern or prolonged [&gt;20 min] or recurrent episodes at rest or with minimal effort) within the preceding 24 h, were candidates for coronary revasc, and had at least 1 of the following: a new finding of ST-segment depression of at least 0.05 Persistent STE, 2° angina, a Hx of PCI or CABG within the preceding 6 mo, factors associated with an increased risk of bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of &gt;2.5 mg/dL (221 Pts assigned to the early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when appropriate on the basis of coronary anatomical findings Pts assigned to the early conservative strategy were treated medically and, if their condition was stable, underwent an exercise-tolerance test (83% of such tests included nuclear perfusion imaging or echocardiography performed according to the protocol of the institution) before being discharged Combined incidence of death, nonfatal MI, and rehospitalization for ACS at 6 mo Bleeding Death, death or MI, fatal or nonfatal MI, rehospitalization for MI At 6 mo, the rate of the 1° endpoint was 15.9% with use of the early invasive strategy and 19.4% with use of the conservative strategy (OR: 0.78; 95% CI: 0.62-0.97; p=0.025). Study excluded pts with severe comorbid conditions or other serious systemic illness To compare an early invasive strategy to a more conservative approach</td>
<td>Prospective, randomized, multicenter trial 2,220</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fox 2002 (187)</td>
<td>To compare interventional strategy and conservative strategy in pts with unstable CAD</td>
<td>RCT 1,810</td>
<td>Intervention: 895 vs. Comparator: 915</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
<td>----------</td>
<td>--------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PtS were eligible for inclusion if they had suspected cardiac chest pain at rest and had documented evidence of CAD with at least 1 of the following: evidence of ischaemia on ECG (ST-segment depression, transient STE, LBBB [documented previously])</td>
<td>All those with probable evolving MI, including those for whom reperfusion therapy was indicated, were ineligible. Those in whom new pathological Q waves developed, or those with CK or CK-MB concentration s 2× the ULN before</td>
<td>Pts assigned to the interventional treatment strategy were managed with optimum antianginal and antithrombotic treatment (as for the conservative group), and enoxaparin 1 mg/kg subcutaneously 2× for 2–8 d. The protocol specified that coronary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts assigned to the conservative strategy were managed with antianginal and antithrombotic medication</td>
<td>The coprimary trial endpoints were: a combined rate of death, nonfatal MI, or refractory angina at 4 mo; and a combined rate of death or nonfatal MI at 1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>Death, MI, refractory angina as individual endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 mo, 86 (9.6%) of 895 pts in the intervention group had died or had a MI or refractory angina, compared with 133 (14.5%) of 915 pts in the conservative group (RR: 0.66, [0.51–0.85], p=0.001).</td>
<td>1º endpoint driven by reduction of refractory angina with no difference in hard clinical endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To compare interventional strategy and conservative strategy in pts with unstable CAD</td>
<td>RCT 1,810</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Criteria</td>
<td>Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>------------</td>
<td>----------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spacek 2002 (120) 1176138</td>
<td>To compare 1st d angiography/angioplasty vs. early conservative therapy of evolving MI without persistent STE</td>
<td></td>
<td>Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; cardiogenic shock; acute LBBB or STE 2 mm in 2 leads; QMI or IV thrombolysis &gt;1 mo; coronary angioplasty or bypass surgery &gt;6 mo; any concomitant disease which may have possible influence on randomized strategy</td>
<td></td>
<td>Contrast with conservative treatment and death or nonfatal RMI 6 mo after the randomization. Length of initial hospitalization and the number of subsequent hospitalizations for UAP. 1st endpoint (death/reinfarction) at 6 mo occurred in 6.2% vs. 22.3% (p&lt;0.001). 6 mo mortality in the 1st d angiography/angioplasty group was 3.1% vs. 13.4% in the conservative group (p=0.03).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Name, Author, Year</td>
<td>Aim of study</td>
<td>Study Type</td>
<td>Study Size (N)</td>
<td>Study Intervention Group (n)</td>
<td>Study Comparator Group (n)</td>
<td>Patient Population</td>
<td>Endpoints</td>
<td>P Values, OR: HR: RR &amp; 95% CI:</td>
<td>Study Limitations &amp; Adverse Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>--------------------</td>
<td>-----------</td>
<td>---------------------------------</td>
<td>-----------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wright 2002 12353943 (237)</td>
<td>Compare outcomes after AMI in pts with varying degrees of renal function</td>
<td>Retrospectiv e cohort study</td>
<td>4,426</td>
<td>n=3,106 with: endstage renal disease, severe renal insufficiency CrCl &lt;35 mL/min, moderate renal insufficiency CrCl ≥35, ≤50 mL/min, mild renal insufficiency CrCl &gt; 50 mL/min</td>
<td>n=1,320 with normal renal function</td>
<td>Consecutive pts with acute infarction between 1988 and 2000. Renal function estimated according to the Cockcroft-Gault.</td>
<td>N/A</td>
<td>Short- and long-term survival compared after pts were stratified by CrCl. In-hospital mortality: 2% in pts with normal renal function, 6% in pts with mild renal failure, 14% in pts with moderate renal failure, 21% in pts with severe renal failure, and 30% in pts with endstage renal disease; p&lt;0.001 Post-discharge mortality in abnormal renal function vs. normal renal function Mild renal failure HR: 2.4 (CI 1.7–3.3; p&lt;0.001) Moderate renal failure HR: 2.2 (CI: 1.5–3.3; p&lt;0.001) Pts with renal failure received reperfusion therapy less frequently than pts with normal renal function; p&lt;0.001. Post-discharge death less likely in pts who received acute reperfusion therapy. OR: 0.7 (CI: 0.6–0.9) ASA OR: 0.7 (CI: 0.5–0.8) BB OR: 0.7 (CI: 0.6–0.9)</td>
<td>N/A</td>
<td>N/A</td>
<td>Retrospective Analysis Potential referral bias Single center study</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table: Association of Renal Insufficiency on Survival After MI

| Shlipak 2002 [12353942](238) | Determine how pts with renal insufficiency are treated during MI Determine association of renal insufficiency on survival after MI | All nongovernmenal U.S. hospitals cohort study | 130,099 older pts with MI 1994-1995 | Mild renal insufficiency: Cr: 1.5-2.4 mg/dL n=36,756 Moderate renal insufficiency: Cr: 2.5-3.9 mg/dL n=10,888 | No renal insufficiency: Cr <1.5 mg/dL n=82,455 | All older (age ≥65 y) Medicare beneficiaries with AMI 1994-1995 | 6,790 pts with severe renal insufficiency Cr ≥4.0 mgm/dL 10,570 pts with no information on estimating CrCl | Primary: pts with moderate renal insufficiency less likely to receive aspirin, BB, thrombolytic therapy, angiography or PCI | N/A | 1 y-mortality 24% with no renal insufficiency 46% with mild renal insufficiency 66% with moderate renal insufficiency Secondary: after adjustment for pt and treatment characteristic renal insufficiency was associated with elevated risk of death after MI Mild renal insufficiency: HR: 1.68 (95% CI: 1.68–1.73) Moderate renal insufficiency: HR: 2.35 (95% CI: 2.26–2.45) | N/A | No measurement of true GFR Size of data collected from 1994-1995 Focus on patients ≥65 y |

Severe renal failure HR: 1.9 (CI: 1.2–3.0; p=0.006) End-stage renal disease HR: 5.4 (CI: 3.0–9.7; p<0.001)
| Solomon 1994 | 1994280 | (239) | Evaluate effect of saline, mannitol on renal function in pts undergoing coronary angiography | RCT | 78 | n=28, 45% saline alone for 12 h before and 12 h after n=25 1) 45% saline plus mannitol n=25 2) 45% saline plus furosemide | 78 pts with chronic renal insufficiency undergoing coronary angiography Serum Cr measure prior to and 48 h after angiography | N/A | An increase in baseline serum Cr of ≥0.5 mgm/dL within 48 h of angiography 11% with saline 28% with saline + mannitol 40% with saline + furosemide p=0.05 | N/A | N/A | N/A | Hydration with 0.45% saline provides better protection against CIN than hydration plus either mannitol or furosemide Limitations: Small sample size |
| Charytan 2009 | 19423566 | (240) | Evaluate effectiveness of an early invasive strategy or conservative strategy in pts with CKD admitted with UA/NSTEMI | Collaborative meta-analysis of RCT | 5 randomized studies of 1,453 pts with CKD | Early invasive strategy of routine coronary angiography Conservative strategy of selective coronary angiography | Total 1,453 pts with CKD in 5 RCT stages 3a, 3b, and 4-5 GFR calculated using modification of diet in renal disease Serum Cr measure prior to and 48 h after angiography | N/A | 1-y mortality Invasive strategy associated with: Nonsignificant reduction in all-cause mortality RR: 0.76; 95% CI: 0.49–1.17; p=0.21 Nontotal MI RR: 0.78; 95% Cl: 0.52–1.16; p=0.22 Death or nonfatal MI RR: 0.79; 95% CI: 0.53–1.18; p=0.24 Significant reduction in rehospitalization RR: 0.76; 95% CI: 0.66–0.87; p<0.0001 | N/A | In-hospital death, MI, death/MI, 1-y MI, rehospitalization, combined death/MI | N/A | Routine coronary angiography should be considered for pts with CKD who are admitted with NSTEMI Limitations: Publication bias Small number trials Small number of stage 4-5 CKD |
| Szummer 2009 | 19704097 | (241) | Evaluate influence of renal function on effects of early revascularization in NSTEMI | Nationwide registry | 23,262 consecutive NSTEMI pts ≤80 y old treated from 2003-2006 | Pts revascularized within 14 d of admission, N=12,030 23,262 consecutive pts ≤80 y with NSTEMI Subdivision in 5 groups eGFR ≥90 n=6,064 eGFR 60-89 n=11,509 eGFR 30-59 n=4,839 eGFR 15-29 n=572 eGFR <15/dialysis N=278 | After adjustment overall 1-y mortality was 36% lower (HR: 0.64; 95% CI: 0.56–0.73; p<0.001) with invasive strategy Magnitude of survival difference similar in normal to moderate renal function groups Lower mortality observed with invasive therapy declined with lower renal function No difference in mortality in pts with | N/A | N/A | N/A | Early invasive therapy is associated with greater 1-y survival in pts with NSTEMI and mild-moderate renal insufficiency. Benefit declines with lower renal function. Limitations: Registry study Selection bias Arbitrary cut point 14 d Pts ≤80 y |
Cox regression model with adjustment for propensity score and discharge medication to assess association between early revascularization and 1-y mortality. Kidney failure or in those dialysis p=0.15, HR: 1.61; 95% CI: 0.84–3.09

AMI indicates acute myocardial infarction; BB, beta blocker; CKD, chronic kidney disease; CIN, contrast induced nephropathy; Cr, creatinine; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MI, myocardial infarction; N/A, nonapplicable; NSTEMI, Non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; pts, patients; RCT, randomized controlled trial; RR, relative risk; UA, unstable angina; and U.S., United States.

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson-Jaffe AB, Goodman SG, Yan RT, et al.</td>
<td>Characterize differences in clinical characteristics and clinical management between pts with NSTE-ACS in clinical trials and not in clinical trials</td>
<td>Retrospective case-control of several large NSTE-ACS registries</td>
<td>N=13,556 pts with NSTE-ACS (8.3% in clinical trials)</td>
<td>None</td>
<td>Pts with NSTE-ACS in 4 large prospectively collected registries: Canadian ACS I (1999 to 2001), ACS II (2002-2003), GRACE (2004-2007), and CANRACE (2008) over 10 y, ≥18 y age, within 24 h of NSTE-ACS presentation</td>
<td>Pts with NSTE-ACS with ACS precipitated or accompanied by a serious concurrent illness, such as trauma or GI bleeding</td>
<td>N/A</td>
<td>N/A</td>
<td>Pts enrolled in clinical trials were younger, more likely to be men, and had fewer comorbidities. Clinical trial pts were more likely to be on several GDMT, undergo invasive procedures (all p&lt;0.001). Unadjusted in-hospital mortality nonclinical vs. clinical trials (2.1% vs. 0.7%, p&lt;0.001) and 1-y (8.9% vs. 6.3%, p=0.037) In</td>
<td>N/A</td>
<td>Results too numerous to list</td>
</tr>
<tr>
<td>Study</td>
<td>Design/Method</td>
<td>Population</td>
<td>Outcomes</td>
<td>Limitations</td>
<td>Extrapolation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>------------</td>
<td>----------</td>
<td>-------------</td>
<td>---------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akhter N, Milford-Beland S, Roe MT, et al.</td>
<td>Retrospective case-control of registry data</td>
<td>N=199,690 pts, 55,691 women presented with NSTE-UA vs. 101,961 men</td>
<td>Men and women with NSTE-ACS who underwent PCI in ACC-NCDR Registry 1/104-3/30/06; index PCI only</td>
<td>Women presented more often with NSTE-ACS than men (82% vs. 77% of men, &lt;0.0001). Women with NSTE-ACS had more comorbidities, but fewer high-risk angiographic features than men. Women were less likely to receive ASA, GPI, and less often discharged on ASA or statin. In-hospital mortality was similar for women and men (OR: 0.97, p=0.5). Women had higher rates of cardiogenic shock, CHF, any bleeding (7.6 vs. 3.6%, p&lt;0.01), and any vascular complications, but subacute stent</td>
<td>Limited extrapolation – all subjects are registry NSTE-ACS pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To assess clinical and angiographic characteristics, procedural and treatment patterns, and in-hospital outcomes between men and women.
| Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the Dx and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol. 2005;45:832-7. | To examine differences of gender in treatment and outcomes among pts with NSTE ACS | Retrospective case-control of registry data | N=35,875 pts (41% women) | None | None | 35,875 pts with NSTE-ACS (14,552 women) at 391 U.S. hospitals participating in the CRUSADE initiative between March 31, 2000, and December 31, 2002 | Pts excluded from this analysis included those who were transferred to another hospital, (3,210 men and 1,827 women), and pts with missing gender status (n=66) | N/A | N/A | Women were older (median age 73 vs. 65 y) and more often had DM and HTN. Women were less likely to receive acute heparin, ACE-I, and GPI and ASA, ACE-I, and statins at discharge. Men underwent more angiography/revascularization than women, but among pts with significant CAD, PCI was performed similarly in men and women. NS gender difference was seen in adjusted rates of in-hospital death, reinfarction, HF, and stroke. RBC transfusion rates were higher in women (OR: 1.17; CI: 1.09-1.25) | N/A | Too numerous to list | Too numerous to list | Limited generalizability from registry data |
| Lansky AJ, Mehran R, Cristea E, et al. Impact of gender on antithrombotic therapy for NSTE-ACS. Retrospective analysis of ACUITY trial (prespecified) | 4,157 women with NSTE-ACS (31% of total) | Overall women =4,157 | Overall men =9,662 | Men and women enrolled in ACUITY trial, randomized to open-label AT | Missing data/follow-up | AT Strategy: GPI + heparin Bivalirudin + GPI | 1) Men vs. women ± PCI – bleeding, net | No gender difference in 30 d composite ischemia; women significantly less in women: bivalirudin alone significantly less | Same as 1º endpoint findings at 1 y and ± PCI | 30-d composite ischemia: women=7%, men=8%; p=NS; 30-d bleeding: Although prespecified gender analysis, study was underpowered to detect difference so |
| antithrombin strategy on early and late clinical outcomes in patients with non-ST-elevation acute coronary syndromes (from the ACUITY trial). Am J Cardiol. 2009;103:1196-203. 19406258 (245) |
|---|---|---|---|---|---|---|---|---|
| ischemia vs. bleeding in pts with NSTE-ACS in ACUITY trial | d but not powered | enrolled | UFH or enoxaparin) n=1,354 women vs. bivalirudin + GPI n=1,386 women vs. bivalirudin =1,417 women PCI=1,190 women No PCI =2,967 women | enoxaparin) vs. bivalirudin + GPI vs. bivalirudin PCI=3,838 men No PCI=5,824 men | treatment | Bivalirudin Intervention: PCI Non-PCI ischemia, and overall clinical benefit at 30-d 2) AT strategy on outcome in women ± PCI at 30 d higher 30-d bleeding; net clinical outcome 30 d worse in women due to bleeding bleeding than GPI + heparin (5% vs. 10%; p<0.0001) with no difference in composite ischemia (7% vs. 10% no difference in bivalirudin + GPI and GPI + heparin | Alexander KP, Chen AY, Neubly LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE initiative. Circulation. 2006;114:1380-7. 16982940 (246) |
| To examine gender impact on GPI use, dose, bleeding in pts with NSTE-ACS in CRUSADE registry | Retrospective analysis of CRUSADE registry | N=32,601 total; GPI Rx=18,436 (6,084 women, 12,352 men) | Use of GPI-dose was evaluated based on pts' CrCl Rate of dosing, excessive dosing, bleeding and outcome were compared by gender | All enrolled CRUSADE pts Jan.-Dec. 2004 Contraindicated to GPI; those without complete data including GPI dose, CrCl, follow-up Those treated with GPI vs. not; women vs. men Those treated with GPI vs. not; women vs. men | For GPI Rx: Rate of bleeding significantly higher in women vs. men (15.7% vs. 7.3%; p<0.0001); For those NOT GPI Rx’d: women had significantly higher bleeding rates than men (8.5 vs. 5.4%; p<0.0001) | Despite NS difference in serum Cr, women had mean CrCl significantly lower (20 mg/min) vs. men; excess GPI dose given to women significantly more than men (46.4 vs. 17.2%; p<0.0001) | Excess GPI dose associated with increased bleeding. Women (OR: 1.72; 95% CI: 1.30-2.28) Men (OR: 1.27; 95% CI: 0.97-1.66) GPI bleeding attributed risk=25% women, 4.4% men; Excess GPI dose for women vs. N/A |
| N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

© American Heart Association, Inc and American College of Cardiology Foundation

15523070 (231)

Determine use and predictors of early invasive management strategies in high-risk pts with NSTEMI

Registry-observation al study trial

17,926 with NSTEMI in CRUSADE (women =7,353)

8,037 (44.8%) underwent early cardiac cath <48 h (women =2,642)

Pts with NSTEMI presenting to 248 US hospitals with cardiac cath facilities and PCI or CABG availability

N/A

Pts with NSTEMI in 8 RCTs evaluate early invasive vs. selective invasive (if recurrent Sx) or positive stress test after initial pharmacological test

N/A

Pts with missing biomarker data excluded from high-risk analyses

N/A

Use of early invasive management within 48 h of presentation; predictors of early invasive management; in-hospital mortality

Propensity matched analyses revealed OR: 0.8 significantly favors early invasive over selective invasive in women

N/A

Female sex as predictor of early invasive

OR: 0.86 (95% CI: 0.80-0.92);

Registry data estimating “real world” practice’ with usual limitations of generalizability

Predictors of early invasive management: lower-risk pts with lack of prior or current CHF, renal insufficiency, positive biomarkers

Pts treated with early invasive strategy had lower in-hospital mortality 2.5% vs. 3.7%; p<0.001

O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-

To compare the effects of an invasive vs. conservative strategy in women and men with NSTE ACS


Data combined from 8 trials (3,075 women and 7,075 men).

Women: Early invasive =1,571 Initial conservative =1,581

Men: Early invasive: 3,641 Initial conservative: 3,619

Pts with MACE early invasive vs. initial conservative for death/MI/ACS

Women: OR: 0.81 (95% CI: 0.65-1.01)

Men: OR: 0.73 (95% CI: 0.55-0.98)

Registry data

Predictors of early invasive management: lower-risk pts with lack of prior or current CHF, renal insufficiency, positive biomarkers

Pts treated with early invasive strategy had lower in-hospital mortality 2.5% vs. 3.7%; p<0.001

O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-

To compare the effects of an invasive vs. conservative strategy in women and men with NSTE ACS


Data combined from 8 trials (3,075 women and 7,075 men).

Women: Early invasive =1,571 Initial conservative =1,581

Men: Early invasive: 3,641 Initial conservative: 3,619

Pts with MACE early invasive vs. initial conservative for death/MI/ACS

Women: OR: 0.81 (95% CI: 0.65-1.01)

Men: OR: 0.73 (95% CI: 0.55-0.98)

Results persisted for 12-m follow-up. Heterogeneity between trials; trials not individually powered for sex-specific analyses

© American Heart Association, Inc and American College of Cardiology Foundation 2014 NSTE-ACS Guideline Data Supplements
To determine efficacy and safety of early invasive vs. initial conservative strategy in women with NSTE-ACS

- Analyses of RCTs and systematic reviews of observational studies
- 7 studies: early invasive vs. initial conservative for women with NSTE-ACS
- N=17,930 pts, of which 6,084 (34%) were women

Analyses run separately for different time points (6 mg, 1 y, 5 y); n=4,030 (36% women) for risk modifier studies; n=2,220 (34% women) for safety studies

Pts with NSTE-ACS in RCT of early invasive vs. initial conservative studies including FRISC-II, TACTICS-TIMI-18, GUSTO-IIb-ACS, ICTUS, RITA-3, TIMI-IIIB:

- Those with missing data
- Early invasive vs. initial conservative

Women showed trend toward benefit from early invasive vs. initial conservative at 6 mo and 1 y (death/MI): OR: 0.78; 95% CI: 0.56; CI: 0.32 – 0.97

Increased bleeding in women vs. men in NSTE-ACS pts undergoing PCI (adjusted OR: 3.6; 95% CI: 1.6-8.3)

Increased bleeding in women vs. men in NSTE-ACS pts undergoing PCI (adjusted OR: 3.6; 95% CI: 1.6-8.3)

Women showed trend toward benefit from early invasive vs. initial conservative at 5 y favoring initial conservative (1.05; CI: 0.81-1.35); Troponin-positive women benefited from early invasive vs. initial conservative at 6 mo (OR: 0.91; CI: 0.64-1.20); 5 y (OR: 0.91; CI: 0.53-1.56)

Meta-analyses of RCTs and systematic reviews of observational studies

- 7 studies: early invasive vs. initial conservative for women with NSTE-ACS
- N=17,930 pts, of which 6,084 (34%) were women

Analyses run separately for different time points (6 mg, 1 y, 5 y); n=4,030 (36% women) for risk modifier studies; n=2,220 (34% women) for safety studies

Pts with NSTE-ACS in RCT of early invasive vs. initial conservative studies including FRISC-II, TACTICS-TIMI-18, GUSTO-IIb-ACS, ICTUS, RITA-3, TIMI-IIIB:

- Those with missing data
- Early invasive vs. initial conservative

Women showed trend toward benefit from early invasive vs. initial conservative at 6 mo and 1 y (death/MI): OR: 0.78; 95% CI: 0.56; CI: 0.32 – 0.97

Increased bleeding in women vs. men in NSTE-ACS pts undergoing PCI (adjusted OR: 3.6; 95% CI: 1.6-8.3)

Increased bleeding in women vs. men in NSTE-ACS pts undergoing PCI (adjusted OR: 3.6; 95% CI: 1.6-8.3)

Women showed trend toward benefit from early invasive vs. initial conservative at 5 y favoring initial conservative (1.05; CI: 0.81-1.35); Troponin-positive women benefited from early invasive vs. initial conservative at 6 mo (OR: 0.91; CI: 0.64-1.20); 5 y (OR: 0.91; CI: 0.53-1.56)

To determine sex differences in baseline characteristics and outcome in ACS and if women benefit from early invasive strategy

- Analyses of data from TACTIC TIMI-18 by gender (multivariable logistic regression with PCI/revasc as predictor of outcome–prospective

N=2,220 (women =757):

Early invasive =1,114 – Angiography 4-48 h after randomization with PCI/revasc as indicated

Initial conservative =1,106 – medical therapy – angiography/PCI if recurrent Sx or positive stress test

Pts with NSTE-ACS without contraindications to angiography: pt received ASA (325 mg), UFH, tirofiban

Missing data, lack of follow-up (6 mo and 1 y)

Early invasive =angio graph y 4-48 h after randomization with PCI/revasc as indicated

Initial conserv ativ e =medical therapy – angiograph y/PCI if recurrent Sx or positive stress test

Pts were older, had more HTN, less Hx CAD, and less positive biomarkers, no difference in TIMI risk score. Women had less severe CAD. Women benefit from early invasive PCI had higher bleeding rate vs. men (8.3% vs. 2.9%; OR: 3.6, 1.6-8.3)

Women who underwent PCI had higher bleeding rate vs. men (8.3% vs. 2.9%; OR: 3.6, 1.6-8.3). Rates of

For women with NSTE-ACS troponin negative OR: 1.46 (CI: 0.78-2.72); TIMI Risk 0-2: OR: 1.59 (CI: 0.69-3.67), no

Early invasive vs. initial conservative for MACE

Women: OR: 0.45 (95% CI: 0.24-0.88) adjusted for baseline difference Men: OR: 0.6 (95% CI: 0.47-0.88) (p=0.6 for gender interaction)

This subanalysis may not be adequately powered to detect differences among women.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Exposure</th>
<th>End Points</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen J, Einstein AJ, Fazel R, et al.</td>
<td>2010</td>
<td>Retrospective, observational study</td>
<td>Adults undergoing cardiac imaging</td>
<td>Cumulative radiation dose</td>
<td>Radiation outcomes linked to all cardiac imaging procedures</td>
<td>Multiple outcomes identified potential to reduce radiation exposure with age.</td>
</tr>
<tr>
<td>Einstein AJ, Weiner SD, Bernheim A, et al.</td>
<td>2010</td>
<td>Retrospective cohort study</td>
<td>Adults undergoing myocardial perfusion imaging</td>
<td>Cumulative radiation dose</td>
<td>Radiation outcomes</td>
<td>Likely underestimation of longitudinal radiation exposure if scans could not be assessed (other institutions, not known); changes in technology over time, some date imputed, single center experience.</td>
</tr>
</tbody>
</table>

To determine the LAR of cancer incidence associated with 64-slice CTCA radiation exposure and determine influence of age, sex, and scan protocol.

| Monte Carlo simulation estimation of organ doses from 64 slice CTCA: age and sex-specific LAR of cancer using BEIR VII | N/A | N/A | N/A | N/A | N/A | N/A | Doses of 8 CTCA protocols given for organs; younger women had a significantly higher LAR of cancer, especially breast and lung, from single CTCA | N/A | N/A | Title of paper: To determine the LAR of cancer incidence associated with 64-slice CTCA radiation exposure and determine influence of age, sex, and scan protocol. | Data Supplement 31. Anemia, Bleeding, and Transfusion-Relationship Between Transfusion and Mortality (Section 7.8)

<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Aim of Study</strong></th>
<th><strong>Type of Study</strong></th>
<th><strong>Study Size</strong></th>
<th><strong>Patient Population</strong></th>
<th><strong>Primary Endpoint</strong></th>
<th><strong>Outcome</strong></th>
<th><strong>Comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander KP 2008 18513518 (253)</td>
<td>To describe the association between transfusion nadir HCT and outcome</td>
<td>Post hoc registry analysis</td>
<td>44,242</td>
<td>CRUSADE registry of NSTE-ACS pts</td>
<td>Numerous endpoints. Most relevant: adjusted OR for mortality with transfusion for</td>
<td>Adjusted OR: HCT ≤24%: 0.67 (0.45-1.02)</td>
<td>Transfusion only beneficial at HCT ≤24%</td>
</tr>
</tbody>
</table>
Yang 2007 1711710 (254)  
To assess transfusion patterns and in-hospital outcomes in pts receiving transfusions  
Post hoc registry analysis  
74,271  
CRUSADE registry of NSTE-ACS pts  
Relevant endpoints: Death and death or MI  
Adjusted OR: 1.67 (1.48-1.88)  
Death or MI: 1.44 (1.30-1.60)  
N/A

Rao 2004 15467057 (255)  
To determine the association between blood transfusion and mortality in pts with ACS  
Post hoc analysis of data from 3 randomized trials  
24,112  
GUSTO-llb, PURSUITS, and PARAGON pts with ACS  
30-d mortality rates in transfused and nontransfused pts  
Adjusted HR: 3.94 (3.26-4.75)  
Transfusion associated with increased mortality for Hct >25%

Carson 2012 22751760 (256)  
Clinical guideline from the AABB on RBC transfusion  
Analysis of all randomized trials of restrictive vs. liberal transfusion strategies  
19 trials; 30-d mortality available in 11 trials  
Published randomized trials; various pt populations  
Numerous endpoints assessed. Most relevant: 30-d mortality  
RestRICTIVE transfusion strategy; 6.9%  
Liberal transfusion strategy; 8.0%  
RR: 0.85 (0.7-1.03)  
N/A

Carson 2012 22513904 (257)  
Cochrane Database Systematic Review  
Analysis of randomized trials of restrictive vs. liberal transfusion strategies  
19 trials  
Various trials in context of surgery, acute blood loss/trama, coronary care unit pts, or leukemia pts  
Numerous endpoints assessed. Restrictive transfusion strategy compared to liberal transfusion strategy  
Hospital mortality OR: 0.77 (0.62-0.95)  
30-d mortality OR: 0.85 (0.70-1.03)  
MI OR: 0.88 (0.38-2.04)  
N/A

## Data Supplement 32. Anemia, Bleeding, and Transfusion Studies for Weight-Based and Renally-Adjusted Dosing of Anticoagulants (Section 7.8)

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of Study</th>
<th>Type of Study</th>
<th>Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Alexander 2005 16380591 (258) | Investigation of relationship between UFH, LMWH and GPI excess dosing and major outcomes | Exploratory registry analysis | 3,354 | NSTE-ACS pts in CRUSADE registry | Major clinical outcomes and bleeding | Adjusted OR for major bleeding with excess dosing (vs. no excess dosing):  
- UFH: OR: 1.08 (0.94 — 1.26)  
- LMWH: OR: 1.39 (1.11 — 1.74)  
- GPI: OR: 1.36 (1.10 — 1.68) |
| Melloni 2008 18657648 (259) | Exploratory analysis of CRUSADE registry examining relation between UFH dosing and bleeding | Post hoc analysis of registry | 31,445 | NSTE-ACS pts in CRUSADE registry | Excess dosing percent; factors associated with excess dosing; major bleeding | Dosing of UFH above recommended weight-based dosing associated with increased major bleeding  
- Excess bolus OR: 1.03 (1.00 — 1.06)  
- Excess infusion dosing OR: 1.16 (1.05 — 1.28) |
| LaPonte 2007 17646609 (260) | Exploratory analysis of CRUSADE registry examining relation between enoxaparin dosing and bleeding | Post hoc analysis of registry | 10,887 | NSTE-ACS pts in CRUSADE registry | Inappropriate dosing percent; major bleeding and death | Excess dosing associated significantly associated with increased risk of major bleeding (adjusted OR: 1.43; CI: 1.18 — 1.75) |
| Taylor LA 2012 22170973 (261) | Chart review assessing incidence of bleeding in CKD pts with incorrectly dosed bivalirudin or GPI | Chart review | 199 | Pts undergoing PCI | Incidence and extent of bleeding (TIMI or GUSTO) | Eritilatabile:  
- Incorrectly dosed in 64%  
- Incorrectly dosed pts experienced more overall bleeding (64% vs. 35%; p=0.04), numerically more TIMI major bleeding (19% vs. 5%; p value given), and a greater extent of bleeding (p=0.03 for TIMI bleeding and p=0.009 for GUSTO bleeding) |
Bivalirudin:
- Incorrectly dosed in 28%
- Bleeding rates (incorrect vs. correct) 37% vs. 21% (p=0.055)
- Extent of bleeding greater with incorrect bleeding (p=0.013 for GUSTO bleeding; p=0.058 for TIMI bleeding)

Becker 2002 12040334 (262)
Pharmacokinetic/dynamic study of enoxaparin and anti-Xa activity and factors that affect anti-Xa levels
Pharmacokinetic/pharm acodynamic substudy
TIMI 11A study of ACS pts
Relationship of pt factors and anti-Xa levels
Pts with creatinine clearance <40 mL/min had sig higher trough and peak anti-Xa levels (numerous statistically significant p values for multiple comparisons)

ACS indicates acute coronary syndrome; CRUDE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines Registry; GPI, glycoprotein; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; LMWH, low molecular weight heparin; N/A, not applicable; NSTE-ACS, non-ST-elevation-acute coronary syndrome; PCI, percutaneous coronary intervention; Pts, patients; TIMI, Thrombolysis In Myocardial Infarction; and UFH, unfractionated heparin.

Data Supplement 33. Cocaine and Methamphetamine Users (Section 7.10)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR; HR: RR: &amp; 95 CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentiation of cocaine-induced vasoconstriction by beta-blockade Lange RA et al. 1990 1971166 (263)</td>
<td>To determine whether beta-blockade augments cocaine-induced coronary vasoconstriction</td>
<td>Prospective; N=30</td>
<td>Intracoronary propranolol (n=15) vs. saline (n=15)</td>
<td>Pts referred for coronary arteriogram for chest pain</td>
<td>HTN, recent MI</td>
<td>Quantitative angiography performed before and 15 min after intranasal saline or cocaine; repeat measurements obtained following intracoronary propranolol</td>
<td>Heart rate, arterial BP, coronary sinus blood flow, epicardial left coronary arterial dimensions; Intracoronary propranolol caused no change in BP or heart rate, but decreased coronary sinus blood flow and increased coronary vascular resistance</td>
<td>N/A None</td>
<td>Decrease in coronary blood flow (p&lt;0.05); increase in coronary vascular resistance (p&lt;0.05)</td>
</tr>
<tr>
<td>BB associated with reduced risk of MI after cocaine use Dattilo PB et al. 2008 17883376 (264)</td>
<td>Determine if rates of MI increased with BB treatment after recent cocaine use</td>
<td>Retrospective N=348 (60 with recent cocaine use)</td>
<td>BB treatment vs. no BB treatment</td>
<td>Admitted pts with positive urine drug screen for cocaine who received BB</td>
<td>Cardiac markers not obtained; pt on oral BB</td>
<td>In-hospital MI after BB use; lower incidence of MI after administration of BB</td>
<td>In-hospital mortality; trend for lower mortality in pts receiving BB</td>
<td>N/A</td>
<td>Incidence MI in BB vs. no BB 6.1% vs. 26.0% (95% CI: 10.3% — 30.0%); Mortality 1.7% vs.4.5% (95% CI: -)</td>
</tr>
<tr>
<td>BB for chest pain associated with recent cocaine use</td>
<td>Determine if rates of adverse events associated with BB treatment in chest pain pts with recent cocaine use</td>
<td>Retrospective 331 (151 received BB)</td>
<td>BB treatment vs. no BB treatment</td>
<td>Chest pain pts with urine drug screen positive for cocaine</td>
<td>No chest pain; urine drug screen not performed or urine drug screen negative for cocaine</td>
<td>Death on long-term follow-up of National Death Registry (median 972 d)</td>
<td>N/A</td>
<td>ED BP; Peak Tn levels, ventricular fibrillation/tachycardia, intubation, or vasopressor agents</td>
<td>Pts receiving BB had larger decrease in SBP in ED even after adjusting for other anti-HTN agents administered; there were no differences in any of the secondary outcome measures</td>
</tr>
<tr>
<td>Benzodiazepines and Nitroglycerine in treatment of cocaine chest pain</td>
<td>To compare the use of lorazepam and nitroglycerine in treatment of cocaine chest pain</td>
<td>Prospective, randomized, single-blind controlled trial; N=27</td>
<td>NTG (n=15) vs. NTG + lorazepam (n=12)</td>
<td>Chest pain and self-reported cocaine use in the preceding 72 h</td>
<td>Age &gt;45 y, chest pain duration &gt;72 h, documented CAD, pretreatment with NTG</td>
<td>NTG vs. NTG + lorazepam</td>
<td>Chest pain relief as assessed on a 0-10 ordinal scale was greatest in the pts treated with the combination of NTG and lorazepam.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### ACS in chest pain pts after amphetamine use

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>ACS diagnosis</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnipseed SD et al. 2003</td>
<td>Retrospective</td>
<td>36</td>
<td>9 pt visits (25%; 95% CI: 11% - 48%)</td>
<td>ACS defined as MI, ischemia on cardiac stress testing, or ≥70% stenosis on cardiac cath</td>
<td>ACS diagnosed in 9 pt visits (25%; 95% CI: 11% - 48%)</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td>3 pt visits with arrhythmias (8%; 95% CI: 2% - 24%)</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; BB, beta blocker(s); BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CXR, chest x-ray; Dx, diagnosis; ED, emergency department; HBP, high blood pressure; HTN, hypertension; Hx, history; MI, myocardial infarction; N/A, not applicable; NTG, nitroglycerin; pt(s), patient(s); SBP, systolic blood pressure; SVT, supraventricular tachycardia; Sx, symptoms; Tn, troponin; UA, unstable angina; V-fib, ventricular fibrillation; and V-tach, ventricular tachycardia.
### Additional Data Supplement Tables

(These tables were created during the evidence review process but do not support a specific section of recommendations in the guideline. They are provided for transparency and completeness.)

#### Data Supplement A. Other (Newer) Biomarkers

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95 CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRISC-II Wollert 2007 (269) 17848615</td>
<td>Effect of PGF-15 on ACS outcomes in invasive vs. conservative strategy</td>
<td>Multicenter prospective study (FRISC –II) 2,079</td>
<td>PGF-15 in intervention vs. conservative treatment outcomes</td>
<td>ACS with criteria for PCI or conservative strategy with PGF-15 levels</td>
<td>Previous heart surgery, PCI within 6 mo, bleeding tendency, high creatinine</td>
<td>PGF-15 with PCI or conservative strategy</td>
<td>2-y MACE. PGF independently predicted outcomes in conservative strategy only</td>
<td>Occurrence of MACE reduced with PCI with highest PGF-15 levels: 0.49 (0.33-0.73) p=0.001</td>
</tr>
<tr>
<td>C-NET Viswanathan 2010 (270) 20513600</td>
<td>Px value of H-FABP in low-int. risk ACS pts</td>
<td>Prospective observational cohort 955</td>
<td>H-FABP vs. Tn</td>
<td>Chest pain</td>
<td>Non-cardiac Chest pain. Age &lt;18 y</td>
<td>H-FABP/Tn 12-24 h from Sx onset</td>
<td>Death/MI 12 mo H-FABP predicted outcome after multivariate adjustment</td>
<td>Among Tr-pts, (79% of cohort) high FH-FA bp identify pts at high risk</td>
</tr>
<tr>
<td>Charpentier 2010 (271) 20078436</td>
<td>Detection of AMI by H-FABP and IMA</td>
<td>Prospective observational cohort 677</td>
<td>H-FABP vs. IMA</td>
<td>Chest pain and suspected NSTEMI</td>
<td>Age &lt;18 y Skeletal muscle injury, trauma, renal impairment.</td>
<td>H-FABP and IMA on admission</td>
<td>Dx NSTEMI IMA not predictor of ACS Dx H-FABP predictor</td>
<td>H-FABP did not add info to std predicted model</td>
</tr>
<tr>
<td>Haaf 2011 (272) 21531234</td>
<td>BNP in Dx and risk in chest pain pts</td>
<td>Prospective multicenter 1,075</td>
<td>BNP vs. TnT</td>
<td>Possible ACS</td>
<td>ESRD with dialysis</td>
<td>BNP and TnT at admission and 1 h, 2 h, 3 h, 6 h</td>
<td>Dx accuracy of BNP for MI lower than Tn</td>
<td>BNP predicted 24 mo outcome more accurate than TnT AUC 0.81 vs. 0.76 p=0.001</td>
</tr>
<tr>
<td>Keller 2010 (273) 20447532</td>
<td>Copeptin in Dx of AMI</td>
<td>Prospective multicenter 1,386</td>
<td>Copeptin vs. TnI</td>
<td>Possible ACS</td>
<td>Trauma, major surgery, IV drug abuse, anemia</td>
<td>Copeptin and TnT on admission</td>
<td>TnT vs. combined C-statistic vs. TnT alone: 0.93 vs. 0.84</td>
<td>C-statistic within 3 h chest pain combined 0.90 T alone 0.77</td>
</tr>
<tr>
<td>Reference</td>
<td>Methods</td>
<td>Patients</td>
<td>Endpoints</td>
<td>Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>----------</td>
<td>-----------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peacock 2011</td>
<td>MPO for Dx of AMI</td>
<td>Prospective multicenter cohort 1,018</td>
<td>MPO vs. TnI</td>
<td>Possible ACS &lt;8 h Sx, &lt;18-y non-cardiac chest pain</td>
<td>MPO and TnT on admission, Using 90% spec. cutpoint MPO had insufficient accuracy, MPO C-statistic: ACS vs. NCCP 0.623 AMI vs. NCCP 0.666</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iversen 2009</td>
<td>PAPP-A as risk marker in ACS</td>
<td>Prospective cohort 123 NSTEMI</td>
<td>PAPP-A vs. std Dx (TnT)</td>
<td>Possible ACS NSTE</td>
<td>STE-ACS (evaluated separately), PAPP-A on admission and every 6 h to 8 h, Risk for MI and death 2.66 y to 3.47 y, PAPP-A related to risk for both in NSTEMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RISCA Bogaty 2008</td>
<td>CRP in pred 1-y outcome in ACS</td>
<td>Prospective cohort 1,210</td>
<td>CRP</td>
<td>Transfer from other hospital</td>
<td>CRP on admission, NS pred of UA, MI, or death individually, MACE at 1-y multivariate analysis: NS predictability, NS pred of UA, MI, or death individually, Adjusted OR for MACE admission:1.04 (0.91-1.14), Discharge: 0.90 (0.77-1.06), 1 m. 1.12 (0.93-1.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuch 2008</td>
<td>CRP and TnI in short termPx in NSTEMI</td>
<td>Prospective cohort 697 NSTEMI (612 with STEMI)</td>
<td>CRP vs. Tn in 28-d mortality event</td>
<td>Dx of NSTEMI</td>
<td>Cardiac Sx of NSTEMI, STEMI separately evaluated, CRP and TnI on admission, Multivariate analysis: Both CRP+ and TnI+ showed pred of 28 d mortality, In NSTEMI CRP+ but not Tn+ pred mortality: 4.59 (1.68 — 12.5) vs. 1.75 (0.55 — 5.54), Tr+ OR 1.99 (1.15-3.44), CRP+ OR 2.05 (1.09-3.84) For 28-d mortality prediction: Possible CRP influenced by larger myocardial necrosis or longer prehospital delay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schaub 2012</td>
<td>GDF-15 in early Dx and risk in AMI</td>
<td>Prospective multicenter 646</td>
<td>GDF-15 vs. TnI and BNP</td>
<td>ACS Sx</td>
<td>ESRD, Assays on admission to ED, ROC for MIAUC GDF-15 0.69 Hs-TnI 0.96 BNP 0.74, GDF-15 pred 26-mo mortality &gt;TnT and BNP 0.91, 26-mo mortality AUC GDF-15: 0.85 TnI: 0.77 p=0.002 BNP: 0.75 p=0.007, Clinical benefit of imp. risk strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mega 2008</td>
<td>Px of Tp in ACS</td>
<td>Prospective multicenter 2,349 with ACS</td>
<td>Tp+ vs. Tp– in predicated. Compared with Tn</td>
<td>NSTEMI UA</td>
<td>STEMI evaluated separately, Assay at median 40 h from presentation, 10-mo MACE, TpP significant pred risk for comparative events as well as death or MI, Weak correlation of TpP with TnI, BNP, and Hs-CRP R&lt;0.15 for each, HR for MACE: 1.45 (1.20-1.95)&lt;0.001 adjusted for Cl. characteristic and other biomarkers: 1.51 (1.19-1.91) &lt;0.001, TpP not measured at presentation Possible that study median inflated TpP levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saraf 2010</td>
<td>Px significant of ETA in ACS</td>
<td>Prospective cohort 300 with ACS on dual</td>
<td>Use of GTT</td>
<td>ACS</td>
<td>Sepsis, malignancy blood, Dyscrasia, antiocoagulant, Assay time not stated, Evaluation OT and LT, 12-mo death, MI, or stroke by LT pred MACE and CV death, No correlation between OT and MACE, LT predicted MACE: 2.52 (1.34-4.71)&lt;0.004, Antiplatelet effects of ASA and Clopidogrel, Heparin effects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Body 2010
(281) 21167522

Effect of P-selectin on Dx of AMI and risk
Prospective cohort 713
P-selectin vs. TnT with 5 other novel biomarkers
Suspected ACS
Chest trauma, ESRD, pregnancy, prisoners
Assay time at present. Only P-selectin and PAPP-A Dx AMI
30-d MACE prediction: only P-selectin 1.84 (1.1-3.1) <0.001
C-statistic for MI P-selectin: 0.68 (0.63-0.73) PAPP: 0.57 (0.51-0.63)
No serial evaluation

Wang 2007
(282) 16887214

Presence of PMAs and other novel biomarkers in ACS
Prospective cohort 132
74 ACS 58 SAP
PMAs and other novel biomarkers
ACS SAP
Renal, hepatic, hematologic, immunologic disorders
Assay at presentation included IL-6, IL-8, MCP-1, sCD40L
Pts with ACS have higher levels of PMAs compared with SA
PMA, CRP, IL-6 Each confer risk for ACS
Regression analysis ACS and biomarkers PMA 1.33 (1.05-1.68) CRP 2.64 (1.01-6.89) IL-6 1.03 (1.001-1.06) Small observational study

ACS indicates acute coronary syndrome, ACS NSTE, acute coronary syndrome non-ST elevation; AMI, acute myocardial infarction; ASA, aspirin; AUC, area under the curve; BNP, B-type natriuretic peptide; BP, blood pressure; CK-MB, creatine kinase-MB; CRP, C-reactive protein; CV, cardiovascular; Dx, diagnosis; ED, emergency department; ESRD, end stage renal disease; ETA, End Thrombosis Act; FRISC, Fragmin During Instability in Coronary Artery Disease; GDF-15, growth differentiation factor-15; GGT, global thrombosis test; H-FABP, heart fatty acid-binding protein; hs-CRP, high sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; IL, interleukin; iMA, ischemia-modified albumin; IV, intravenous; LT, lysis time; MACE, major adverse cardiac events; MCP, monocyte chemoattractant protein; MI, myocardial infarction; MPO, myeloperoxidase; N/A, not applicable; NS, not significant; NSTEMI, non-ST elevation MI; NCCP, non-cardiac chest pain; OT, occluded time; PAPP-A, pregnancy-associated plasma protein A; PCI, percutaneous coronary intervention; PMAs, platelet-monocyte aggregates; Pts, patients; Px, prognosis; ROC, receiver operator curve; SA, stable angina pectoris; sCD40L, soluble CD40 ligand; Sens, sensitivities; Spec, specificities; Std, standard; STE-ACS, ST-elevation acute coronary syndrome; Sx, symptoms; Tn, troponin; TnI, troponin I; TnT, troponin T; TP5, thrombus precursor protein; and UA, unstable angina.

Data Supplement B. Other Anticoagulants

<table>
<thead>
<tr>
<th>Study, Author, Year</th>
<th>Study Type</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
</table>
| Oldgren 2011
(283) 21551462
RE-DEEM | Safety and efficacy of dabigatran in ACS | Mullicr Prosp. Dose Escalation trial | 1,861 on dual platelet therapy Dabigatran bid. 50 mg 369 75 110 406 150 347 | PC 371 Both groups ASA and clopidogrel AMI <14 d Dual antplatelet therapy at least 1 risk factor for CV complication s | Severe bleeding Stroke bleeding diathesis Recent Gl ulcer Uncontrolled HTN Anemia Recent fibrinolytic agents 4 doses of dabigatran for 6 mo | PC | 6-mo bleeding Dose dependent Increase with Dabigatran Sig with 110 mg and 150 mg dose 3.8% PC pts had stroke, MI or death vs. 3.0%- 4.9% Dabigatran (not dose related) | Dabigatran reduced D-dimer in all dose groups | Bleeding Dabigatran vs. Warfarin Significant: Dabigatran 110 mg; 3.92 (1.71,8.95) Dabigatran 150 mg 4.27 (1.86,9.81) | Dose-dependent increase in bleeding significant at 110 and 150 mg qd Dabigatran. |
| Uchino 2012
(178) 2231617 | AMI risk with dabigatran | Meta-analysis of 7 trials | 30,514 Dabigatran 20,001 | Warfarin 7,357 Enoxaparin RCTs including stroke, AFIB, Not stated | Dabigatran 6-10 d 28-35 d Warfarin, enoxaparin, o r PC Risk of ACS with Dabigatran higher than control | Not analyzed Dabigatran risk with exclusion of Dabigatran risk: 1.33 (1.03,1.71) | p=0.03 | Dominant effect of RE-LY trial on results of |
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Follow-Up</th>
<th>Endpoint</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPRAISE 2009 (284)</td>
<td>Safety and efficacy of apixaban in ACS</td>
<td>Multicenter prospective trial</td>
<td>1,715</td>
<td>Apixaban 2.5 bid 317 10 qd 318 10 bid 248 20 qd 221 (611 total)</td>
<td>PC 611</td>
<td>MI within 7 d with at least 1 additional risk factor for recurrent events</td>
<td>Planned PCI ASA allergy Significant, HTN Bleeding diathesis Recent stroke Pericardial effusion</td>
<td>1 of 4 doses of apixaban 28-wk follow-up on ASA</td>
</tr>
<tr>
<td>Alexander 2011 (179)</td>
<td>Risk of events with apixaban in ACS</td>
<td>Multicenter prospective trial</td>
<td>7,392</td>
<td>Apixaban 3705</td>
<td>PC 3687</td>
<td>Median 6 d after ACS with significant risk factors: prior MI, DM, HF</td>
<td>Planned PCI, ASA allergy, Significant HTN Bleeding diathesis Recent stroke Pericardial effusion</td>
<td>Apixaban 5 mg bid Median follow-up 241 d ASA</td>
</tr>
<tr>
<td>RUBY-1 Steg 2011 (285)</td>
<td>Safety and tolerability of darexaban</td>
<td>Multicenter prospective trial</td>
<td>1,258</td>
<td>Darexaban Multiregimen 939 5 mg bid 10 mg qd 15 mg bid 30 mg qd 30 mg bid 60 mg qd</td>
<td>PC 319</td>
<td>ACS &lt;7 d from event</td>
<td>Bleeding diathesis Planned PCI Recent stroke Renal or hepatic insufficiency Allergy to study drug</td>
<td>One of 6 regimens Darexaban 26 wk follow-up</td>
</tr>
<tr>
<td>ATLAS ACS-2 TIMI-51Mega 2012 (180)</td>
<td>CV outcomes with Rivaroxaban in ACS</td>
<td>Multicenter prospective trial</td>
<td>15,526</td>
<td>Rivaroxaban 2.5 mg bid (5,174) Rivaroxaban 5 mg bid (5,176)</td>
<td>PC (5,176)</td>
<td>ACS &lt;7 d from event</td>
<td>Low platelet count Low hematocrit Renal dysfunction Recent GI bleed Hx of intracranial bleed</td>
<td>1 of 2 rivaroxaban regimens Mean 13 mo follow-up</td>
</tr>
</tbody>
</table>

**Meta-analysis.** MI events few and infrequent in other studies.
### Meta-analysis

**2012 (7)**

**Bleeding, outcomes in ACS**

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Bleeding outcomes in ACS</th>
<th>31,286</th>
<th>Apixaban Dabigatran Darenxaban Rivaroxaban Ximelagatran</th>
<th>PC or warfarin</th>
<th>ACS (4-71%) &lt;6 to &lt;14 d from event</th>
<th>Trials of parental AC, VKA</th>
<th>OAC with antplatelet 6-31 mo</th>
<th>Antiplatlet with PC or warfarin</th>
<th>Increase major bleeding: Reduce stent thrombosis, ischemic events, no difference in overall death, net clinical benefit</th>
<th>Major Bleeding 3.03 (2.20-4.16) &lt;0.01</th>
<th>Net clinical benefit 0.96 (0.90-1.06)</th>
<th>Ischemic events 0.73 (0.63-0.84)&lt;0.001</th>
<th>Mortality 0.90 (0.76-1.06)</th>
<th>Stent thrombosis 0.73 (0.54-0.98)</th>
</tr>
</thead>
</table>


**Study Limitations & Adverse Events**

- **Mixed clinical conditions** Only 38% (avg) ACS <post PC but also warfarin control Ximelagatran no longer active Newer antiplatlet drugs not adjuncts

---

### Data Supplement C. Lipid Management

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon 2006 (286) 15687136</td>
<td>Efficacy of high dose vs. standard dosing for CV</td>
<td>Meta-analysis 4 trials</td>
<td>27,548</td>
<td>High-dose statin 13,798</td>
<td>Standard-dose statin 13,750</td>
<td>Stable CAD or ACS Intensive vs. standard statin &gt;1000 pts each</td>
<td>Not stated</td>
<td>High-dose statin</td>
<td>Standard-dose statin</td>
<td>High-dose produced a significant 16% reduction in coronary death or MI Significant 16% reduction in</td>
<td>Coronary death or MI 0.84 (0.77-0.91) p&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>Design</td>
<td>Duration</td>
<td>Treatment</td>
<td>Comparator</td>
<td>Number</td>
<td>Sample Size</td>
<td>Outcome</td>
<td>Effect</td>
<td>Notes</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>--------</td>
<td>----------</td>
<td>-----------</td>
<td>------------</td>
<td>--------</td>
<td>-------------</td>
<td>---------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Spencer 2007</td>
<td>2007</td>
<td>Use of statin at hospital discharge with ACS</td>
<td>Retrospective analysis</td>
<td>8,492</td>
<td>Statin use with LDL-C &lt;100 mg/dL or ≥100 mg/dL at discharge 5,710</td>
<td>No statin at discharge 2,762</td>
<td>ACS</td>
<td>ACS not precipitated by non-CV comorbidities</td>
<td>Statin use with LDL-C &lt;100 or ≥100 mg/dL</td>
<td>Control</td>
<td>LDL levels &lt;100 55% receiving statin at discharge LDL levels &gt;100 72% receiving statin at discharge</td>
</tr>
<tr>
<td>Robinson 2009</td>
<td>2009</td>
<td>Non-HDL-C reduction and CV risk</td>
<td>Meta-analysis of 30 trials</td>
<td>11,254</td>
<td>Non-HDL-C change 14 statin 100,827 7 fibrate 21,667 6 niacin 4,445 3 others 5,102</td>
<td>Change in risk Randomized PC or active control trials</td>
<td>&lt;2 y trial No serious non-CV disease</td>
<td>Change in lipid level</td>
<td>Change in risk Statins, each 1% Decrease in non-HDL-C decreased 4.5-y RR by 1% (0.98-1.00)</td>
<td>N/A</td>
<td>Fibrate trials vs. statin trials no different results Bayes factor K=0.49 Moderate different effect on non-HDL-C niacin vs. statin Bayes factor K=7.43</td>
</tr>
<tr>
<td>Hulten 2008</td>
<td>2008</td>
<td>Effect of statin therapy in ACS</td>
<td>Meta-analysis of 13 trials</td>
<td>17,963</td>
<td>Early statin in ACS Approximatively 50%</td>
<td>No statin, PC or usual care Approximately 50%</td>
<td>Statin&lt;14 d of hospitalization for ACS</td>
<td>Standard attain dose</td>
<td>Intensive statin</td>
<td>PC or standard statin</td>
<td>2-y rate of death and CV events reduced with intensive statin therapy</td>
</tr>
<tr>
<td>Sattar 2007</td>
<td>2007</td>
<td>Risk of DM with statins</td>
<td>Meta-analysis of 13 statin trials</td>
<td>4,278</td>
<td>Statin use 2,226</td>
<td>No statin 2,052</td>
<td>Statin Trials with &gt;1 y follow-up in both treatment groups</td>
<td>Mean follow-up ≤1 y</td>
<td>Statin</td>
<td>No statin</td>
<td>Statin therapy was associated with a 9% increased risk of incident DM with little</td>
</tr>
<tr>
<td>Javed 2010 (291)</td>
<td>Discharge intensiv e LTT in ACS</td>
<td>Retrospective data on base analysis</td>
<td>65,396</td>
<td>Intensive LTT regimen likely to cause &gt;50% LDL reduction</td>
<td>25,036</td>
<td>Less intensive LTT regimen</td>
<td>40,360</td>
<td>ACS related hospitalization with LTT</td>
<td>Left against medical advice discontinued care</td>
<td>Discharged to nonparticipating facility</td>
<td>Intensive LTT regimen</td>
</tr>
<tr>
<td>Baigent 2010 (292)</td>
<td>Efficacy and safety of intensive LDL–C decrease</td>
<td>Meta-analysis 26 trials</td>
<td>165,13 8</td>
<td>More intensive 19,829 5 trials</td>
<td>64,744 21 trials</td>
<td>Less intensive 19,783 Control 64,782</td>
<td>Main effect of trial to lower LDL–C 1000+ pts &gt;2 y follow-up treatment</td>
<td>Lack of trial eligibility criteria</td>
<td>Intensive LTT regimen</td>
<td>Less intensive LTT regimen</td>
<td>MACE reduction in 4.8 y by intensive LTT 15%</td>
</tr>
<tr>
<td>Boekholt 2012 (293)</td>
<td>RRs of lipid values in statin treatment</td>
<td>Meta-analysis 8 trials</td>
<td>38,153</td>
<td>Statin therapy</td>
<td>Risk with 1 SD increase in LDL–C non–HDLC apoB</td>
<td>Trials with serial evaluation of TC, LDL–C, HDL–C, TG &gt;2 y follow-up 1000+ participants</td>
<td>Lack of trial eligibility criteria</td>
<td>LDL–C HDL–C Apo B during statin Rx</td>
<td>RRs for values</td>
<td>Adjusted HR for major CV events Per 1-SD increase 1.16 non-HDL–C 1.14 apoB 1.13 LDL–C</td>
<td>RRs higher for non-HDL–C than LDL–C p=0.002 and apo B p=0.02</td>
</tr>
<tr>
<td>Mora 2012 (294)</td>
<td>CV risk in statin treated pts</td>
<td>Retrospective evaluation of a mul tivariate analysis</td>
<td>9251</td>
<td>High-dose statin 80 mg Atorvastatin Approximately</td>
<td>Low-dose statin 10 mg Atorvastatin Approximately</td>
<td>CAD</td>
<td>TG&gt;600 mg/dL Unstable CAD</td>
<td>High-dose atorvastatin</td>
<td>Low-dose atorvastatin</td>
<td>Multivariate detection of increased residual risk</td>
<td>Older age</td>
</tr>
</tbody>
</table>

**RAW TEXT END**
<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR, HR, RR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nissen 2004 (295) 15536108 CAMELOT</td>
<td>Antihypertensive agents on CV events in CAD and normal BP</td>
<td>Multicenter prospective study</td>
<td>1991 274 IVUS</td>
<td>Amlodipine 663 Enalapril 673 IVUS substudy: Amlodipine 91 Enalapril 86 PC 655 IVUS substudy: 95</td>
<td>Angiog.Doc. CAD Age 30-79 DBP&lt;100 BB, α1 blockers, Diuretics permitted</td>
<td>Amlodipine 10 mg or Enalapril 20 mg + IVUS Substudy 24-mo follow-up</td>
<td>PC CV events in 24 mo/CV events in fewer Amlodipine vs. PC Substudy: No athero. Px in amlodipine Trend toward Px in Enalapril, progression in PC p&lt;0.001</td>
<td>BP baseline 129/78 Decreased by 4.8/2.5 mm in Amlodipine, 4.9/2.4 in Enalapril increased in PC p&lt;0.001 vs. Amlodipine and Enalapril Individual components of primary and 2º endpoints showed trend toward fewer events with enalapril</td>
<td>CV events: Amlodipine: 16.6% 0.69 (0.54 — 0.88)=.003 Enalapril:20.2% 0.85 (0.67 — 1.07)=.16 NS diff between Enalapril and Amlodipine 0.81 (0.63 — 1.04)=.10</td>
<td>Amlodipine Dosed for edema in 5.0%. Enalapril D/C for cough in 3.9% HTN in 3.2% PC, 2.2% amiodpine, 9.5% enalapril. Limitations: extended composite endpoint, modest sample size, CIs around point estimates relatively large.</td>
<td></td>
</tr>
</tbody>
</table>
Messerli 2006
(296) 16785477

Low BP with adverse events in CAD 22576
BP reduction Sustained Rel. verapamil or atenolol Outcome Stable pts with CAD and hypertension MI within 3 mo and Class IV or V CHF

Verapamil Purpose was to evaluate BP with outcomes, not compare agents Atenolol

All-cause death and total MI 2.7 yrs J-shaped curve Nadir at 119/84

Lowest outcome 120-140 systolic 70-90 diastolic

DBP Nadir for MI: 70-90 mmHg Nadir for stroke 70-90 mmHg

Primary outcome 18% vs. 9% SBP 110 vs. 120-130 32% vs. 8% DBP 60 vs. 80-90 No p values provided

PROVE-IT TIMI 22 Bangalore 2010
(297) 21060068

BP control and adverse events in ACS Multicenter prospective study Ad hoc analysis 4162
BP level reached Outcome MACE ACS within 0 d Randomly assigned to Pravastatin or atorvastatin Not stated Pravastatin 40 mg Purpose was to evaluate BP with outcome, not to compare agents Atorvastatin 80 mg Composite MACE SBP followed a J- or U-shaped curve Risk Nadir: 136 mmHg systolic 85 mmHg diastolic HR 49% vs. 13% SBP<130 vs. 130-140 HR 46% vs. 15% DBP<80 vs. 80-90 Significant increased risk for outcomes As SBP decrease below 110 systol. or 70 diastolic CAD death, nonfatal MI or revasc Similar J- or U-shaped curve. For SBP/SBP X=37,<0.0001 X=47,<0.0001 respectively

Risk for 1º outcome increased 4.9 fold with SBP<100 vs. 130-140 mmHg 136 mmHg had lowest event rate by Cox model on a continuous scale X²=49, p<0.0001

Ad hoc analysis limited to pts studies for lipid evaluation. Not adjusted for many confounders nor dosages of antihypertensive agents received. Cannot determine whether SBP, DBP, or mean BP is main risk

Cooper-DeHoff 2010
(298) 20606150 INVEST Study

Effect of tight BP control in CAD and diabetes Observational study of multicenter clinical trial 6400
Tight BP control BP 130/85 Usual BP control Stable CAD and hypertension with diabetes Not stated Tight BP control Verapamil/tra ndolapril 16,893 patienty of follow-up Usual BP control Composite MACE Usual control vs. uncontrolled 12.8% vs. 19.6% Tight vs. usual Control : NS diff. 12.8% vs. 12.7%

Extended analysis follow-up indicated increased risk with tight BP control Mortality: 11.0% vs. 10.2% Tight vs. usual Control 1.20 (0.99-1.45) p=0.06 Extended follow-up 1.15 (1.01-1.32) p=0.04 Tight vs. usual control MACE Usual control: 1.11(0.93-1.32)= 24

Post hoc analysis. No randomization for different BP groups. Data only applied to CAD pts with diabetes.

1º indicated primary; 2º, secondary; ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; DBP, diastolic blood pressure; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; PC, placebo; Pts, patients; Px, prognosis; and SBP, systolic blood pressure.

Data Supplement E. Diabetes Mellitus

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Study Type</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Primary Endpoint (efficacy) and Results</th>
<th>Safety Endpoint and Results</th>
<th>Secondary Endpoint and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGAMI (Malmberg 1999)</td>
<td>Glyco- metabolic state in DM</td>
<td>Multicenter prospective study</td>
<td>620 Intensive Insulin 306 34 Routine diabetic therapy DM with AMI &lt;24 h</td>
<td>Not stated Intensive insulin-glucone infusion, then sc insulin 3.4-y follow-up</td>
<td>Regular DM coverage Mortality 33% died in intensive group, 44% in regular group Admission body weight, HbA1C, pulmonary rates, heart rate were all independently linked to hyperglycemia at p&lt;0.001.0.0001</td>
<td>Admission blood glucose HbA1C were independent predictors of mortality Long-term mortality reduction Intensive vs. regular 28% (8-45%) p=0.011 No prior insulin and low CV risk; reduction 51% (19-70%) =0.004</td>
<td>No indication whether increased use of insulin or decreased use of sulfonylureas decreased risk.</td>
</tr>
<tr>
<td>Diabetes Prevention Program Research Group (Knowler 2002)</td>
<td>Effects of treating elevated glucose on development of DM</td>
<td>Multicenter prospective study</td>
<td>3234 Metformin 1,073 Or lifestyle modification 1,079 PC 1,082 25 y or older BMI ≥24 FBS 95-125 Or 140-199 2-h global throrisis test Glucose tolerance affects medications Short life expectancy Metformin 850 mg bid Or lifestyle Int. to reduce weight and inc exercise PC or lack of lifestyle intervention Incidence of DM 2.8-y follow-up Cases/100 pat-y PC 11.0 Metformin 7.8 Lifestyle 4.8 Hospitalizations and deaths NS different among groups Gl sx p=0.0167 metformin vs. PC Average weight loss PC 0.1 kg Metformin 2.1 kg Life 5.6 kg p=0.001 v. Metformin and PC Reduced incidence vs. PC Lifestyle: 58% (48 — 66) Metformin 31 (17 — 43) Lifestyle vs. metformin 39% (24- 51%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suleiman 2005 (301)</td>
<td>Fasting glucose and 30-d mortality in AMI</td>
<td>Prospective cohort observational study</td>
<td>735 Fasting glucose Admission glucose Non-DM AMI &lt;24 h &gt;24 h from Sx onset, inflammatory disease, surgery or trauma preceding mo Fasting blood glucose Admission blood glucose 30-d mortality compared with FBG &lt;110, adjusted 30-d mortality increased with increasing tertile of FBG 30-d death and heart failure vs. normal FBG: Impaired FBG: 2.8 (1.3-5.0)=0.004 FBS ≥126: 5.8 (2.2 — 10.3) p=0.0001 30-d mortality compared with normal AG and FG Elevated FG and AG: 9.6 Elevated AG and Normal FG 3.4 30-d mortality vs. tertile of normal FBG 1st: 4.6 (1.7 — 12.7) P=0.003 2nd: 6.4 (2.5 — 16.6) P=0.0001 3rd: 11.5 (4.7 — 20.0) P=0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinnaeve 2009 (302)</td>
<td>Elevate FBS in ACS and Multicenter retrospective</td>
<td>13,526 Range of FBS In-hospital and 6-mo mortality ACS Noncardiac chest pain Admission and FBS 6-mo follow-up Mortality in-hospital 6 mo Higher FBS associated with graded in-hospital and 6-mo Major bleeding complications increased with 6-mo death: FBS &gt;100 vs. 100-125 6 mo-mortality: FBS 126 — 199 mg/dL 1.71(1.25 — Retrospective analysis, unmeasured variables not accounted for; hospital glucose levels may not</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation

134
ACS indicates acute coronary syndrome; AG, admission glucose; AMI, acute myocardial infarction; bid, twice daily; CV, cardiovascular; DM, diabetes mellitus; FBG, fasting blood glucose; FBS, fasting blood sugar; FG, fasting glucose; GI, gastrointestinal; GP, glycoprotein; HbA1c, Hemoglobin A1c; NS, nonsignificant; NSTEMI, non-ST-elevation myocardial infarction; PC, placebo; Sig, significant; Sx, symptom; and UA, unstable angina.

Data Supplement F. Smoking Cessation

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Aim of study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Primary Endpoint (efficacy) and Results</th>
<th>Safety Endpoint and Results</th>
<th>Secondary Endpoint and Results</th>
<th>P Values, OR: HR: RR &amp; 95% CI:</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daly 1983 (303) 6409291</td>
<td>Persistence of smoking cessation after ACS</td>
<td>Prospective cohort study</td>
<td>498</td>
<td>Smoking cessation 217 Nonsmokers at entry and follow-up 147</td>
<td>Continued smoking 157</td>
<td>Survived 1st attack of ACS by at least 26 d</td>
<td>Nonsmokers at entry who started to smoke died within 2 y of entry. Follow up by life tables for 13 y beyond 2 y survival stopped smoking</td>
<td>Continued smoking</td>
<td>Mortality 13-y life tables beyond 1st 2 y from ACS Stopped smoking vs. continued smoking was 2.8× lower</td>
<td>Vascular causes of death: 68% 24% MI 35% sudden death NS diff among 3 groups</td>
<td>Mortality of previous nonsmoker 62.1% n=124 Average annual RR of death: 2.4× for smokers vs. stopped p&lt;0.01</td>
<td>Mortality 2-15 y beyond ACS: stopped vs. continued 36.9% vs. 82.1% p&lt;0.01</td>
<td>Average annual mortality: stopped vs. continued smoking Initial ACS St Cont RR UA 1.9 10.0 5.4; p&lt;0.01 MI uncomp 3.9 8.6 2.2 p&lt;0.05 MI comp 4.7 12.4 2.7 p&lt;0.01</td>
</tr>
<tr>
<td>Jorenby 2006 (304) 18820547</td>
<td>Efficacy and safety of varencline</td>
<td>Multicenter Prospective Study</td>
<td>1,027</td>
<td>Varenclined 344 Bupropion 342</td>
<td>PC 341</td>
<td>18-75 y. 10+ cigarettes/d during previous y No abstinence longer than 3 mo</td>
<td>Previous use of bupropion. Contraindication s to medications. Sig CV disease; HTN; pulmonary disease; depression</td>
<td>Varenclined 1 mg bid Bupropion SR 150 mg bid 12 wk + brief counseling 12 wk with 40-wk follow-</td>
<td>PC+brief smoking cessation counseling</td>
<td>Continuous abstinence: wk 9-12 Varenclined vs. PC: 43.9% vs. 17.6% Bupropion vs. PC: 29.8% vs. 17.6%</td>
<td>&gt;10% side effects: Bupropion Insomnia 21% Varenclined Nausea 29% Abnormal dreams 13.1%</td>
<td>Wk 9-52 Abstinence Varenclined vs. PC 23% vs. 10.3% 2.66 (1.72-4.11) p&lt;0.001</td>
<td>Abstinence 9-12 vs. PC 3.85 (2.69,5.50) p&lt;0.001 9-12 Bupropion vs. PC: 1.90 (1.38-2.62) p&lt;0.001</td>
</tr>
<tr>
<td>Study</td>
<td>Effect of varenclilne on smoking cessation</td>
<td>Multicenter Prospective Study</td>
<td>1,210</td>
<td>18-75 y, 10 cigarettes/day + smoking cessation Alion after 12 wk of varenclilne</td>
<td>Unstable disease, depression, COPD, CV disease within 6 mo, uncontrolled HTN, smoking cessation aid</td>
<td>12-wk open label vs. if stopped smoking Randomized for 40 wk</td>
<td>PC</td>
<td>Continued abstinence Wk 13-24 Varenclilne vs. PC 70.5% vs. 49.6% Wk 13-52 43.8% vs. 36.9% Major adverse Effects: Varenclilne Nasopharyngi tis 4.8% Headache 2.8% Psych disorders 6.4% N/A</td>
<td>Abstinence vs. PC Wk 13-24 2.48 (1.95-3.16)&lt;0.001 Wk 13-52 1.34 (1.06,1.69)&lt;0.02 Generally healthy group. No depression. CO may not evaluate complete check on self-report of nonsmoking. Those lost to follow-up differed between groups.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------</td>
<td>-------------------------------</td>
<td>-------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>-------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>-------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Dawood 2008 (307) 18852396</td>
<td>Effect of varenclilne on smoking cessation</td>
<td>Multicenter Prospective Study</td>
<td>607</td>
<td>18-75 y, 10 cigarettes/day + smoking cessation Alion after 12 wk of varenclilne</td>
<td>Unstable disease, depression, COPD, CV disease within 6 mo, uncontrolled HTN, smoking cessation aid</td>
<td>12-wk open label vs. if stopped smoking Randomized for 40 wk</td>
<td>PC</td>
<td>Continued abstinence Wk 13-24 Varenclilne vs. PC 70.5% vs. 49.6% Wk 13-52 43.8% vs. 36.9% Major adverse Effects: Varenclilne Nasopharyngi tis 4.8% Headache 2.8% Psych disorders 6.4% N/A</td>
<td>Abstinence vs. PC Wk 13-24 2.48 (1.95-3.16)&lt;0.001 Wk 13-52 1.34 (1.06,1.69)&lt;0.02 Generally healthy group. No depression. CO may not evaluate complete check on self-report of nonsmoking. Those lost to follow-up differed between groups.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREMIER Registry</td>
<td>Predictors of smoking cessation after AMI</td>
<td>Multicenter Prospective Study</td>
<td>297</td>
<td>Nonsmokers at 6 mo</td>
<td>Smoking behavior by self-report During hospital and 6 mo in pt smoking cessation program Continued smoking</td>
<td>Same but stopped smoking at 6 mo</td>
<td>PC</td>
<td>Smoking cessation counseling for cardiac rehab or smoking cessation facility</td>
<td>Hospital smoking cessation counseling did not predict cessation: 0.90 (0.51,1.25) Depressive pts during MI less likely to quit.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© American Heart Association, Inc and American College of Cardiology Foundation
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Setting</th>
<th>Design</th>
<th>Follow-up</th>
<th>Sample Size</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohuiddin 2007</td>
<td>Intensive smoking cessation intervention in acute CV disease</td>
<td>Prospective randomized cohort</td>
<td>209</td>
<td>Usual care 100, 2-y follow-up</td>
<td>30-75 y daily smokers with &gt;5 y in CCU with AMI or heart failure</td>
<td>Alcohol or illicit drug use Unfamiliar with English Smokers stopped after quitting relapse rate of smoking Hospitalized CABG mortality: 33% intensive vs. 9% UC p=0.0001 Small sample size lacking multivariate analysis to adjust for other factors on outcome. Pharmacotherapy at no cost. Question of whether results would have been achieved if smokers purchased their own medications.</td>
</tr>
<tr>
<td>Smith 2009</td>
<td>Hospital smoking cessation in CAD with long-term effects</td>
<td>Multi-institutional Prospective Study</td>
<td>275</td>
<td>Intensive smoking cessation intervention 139</td>
<td>18 or older Smokers in previous mo AMI or CABG admission Pregnant Medically unstable Lived in an institution No English Psychiatric disorder Substance abuse</td>
<td>Smoking cessation rates 6-12 mo decreased with smoking counseling. Adding NRT produced a trend toward efficacy vs. counseling alone. Smoking cessation 6-12 mo with counseling: 1.65 (CI: 1.44-1.90) Smoking cessation 6-12 mo without counseling: 2.8% intensive vs. 4.6% minimal GP Confirmed: 54% intensive GP vs. 35% minimal group 1-y abstinence self-reported: 62% intensive GP vs. 46% minimal GP Confirmed: 54% intensive GP vs. 35% minimal group 1-y abstinence self-reported: 2.0 (95% CI: 1.2-3.1) Confirmed: 2.0 (CI: 1.3-3.6) Not evaluated</td>
</tr>
<tr>
<td>Rigotti 2008</td>
<td>Hospital smoking cessation intervention with 6-mo follow-up</td>
<td>Meta-analysis s of 33 trials (Figure 1 and 2)</td>
<td>6,252 (using numbers in pharmacotherapy 332)</td>
<td>Usual care or control counseling 2,935</td>
<td>Trials not recruiting on basis of smoking, Hx, Hospitalization with psychiatric disorder, or substance abuse</td>
<td>Smoking cessation rates 6-12 mo decreased with smoking counseling. No benefit with less postdischarge contact. Usual care with minimal smoking counseling Smoking cessation rates 6-12 mo decreased with smoking counseling. No benefit with less postdischarge contact. Usual care with minimal smoking counseling</td>
</tr>
<tr>
<td>Colivicchi 2011</td>
<td>Smoking relapse rate after quitting following ACS</td>
<td>Prospective cohort study</td>
<td>813</td>
<td>12-mo relapse 813 (of 1,294 not relapsing)</td>
<td>Previous smokers who stopped after ACS following hospital</td>
<td>Major concurrent illness, depression, alcohol and drug abuse. Several in-hospital counseling sessions. 12-mo follow-up</td>
</tr>
</tbody>
</table>
Planer 2011 (303) 21403011

Efficacy of bupropion in smoking cessation after AMI

2 center prospective study

149 Smokers hospitalized for ACS Smoking >10 cigarettes/d Intention to quit smoking

Prior use of bupropion in past y or NRT in past 6 mo Prior head trauma, depression, bulimia liver or kidney disease, pregnancy

Bupropion 150 mg bid for 2 mo 1-y abstinence evaluation

PC Same abstinence evaluation Abstinence rates at 3 mo, 6 mo and 1 y were not increased by bupropion

Bupropion safe. NS diff vs. PC in:

diabetes mellitus more likely to remain abstinent

(1.09,1.42)

0.79 (CI: 0.68-0.94)=0.03

0.23 (95% CI: 0.07-0.78)

Recruitment stopped early after interim analysis limiting sample size. Self-reports of quitting, no biochemical confirmation. High self-reports of quitting in PC group. Dizziness more common than PC 14% vs. 1.4% p=0.005

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; bid, twice daily; CAD, coronary artery disease; CABG, coronary artery bypass graft; CCU, coronary care unit; CO, COPD, chronic obstructive pulmonary disease; CV, cardiovascular; Diff, difference(s); DM, diabetes mellitus; GP, glycoprotein; HTN, hypertension; Hx, history; MI, myocardial infarction; N/A, not available; NRT, nicotine replacement therapy; NS, nonsignificant; PC, placebo; Pt, patient; RR, relative risk; Sens, sensitivity; Sig, significance; SR, sustained release; UA, unstable angina; and UC, usual care.

Data Supplement G. Weight Management

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Study Intervention Group (n)</th>
<th>Study Comparator Group (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Study Comparator</th>
<th>Endpoints</th>
<th>Safety Endpoint and Results</th>
<th>P Values, OR: HR: RR &amp; 95% CI</th>
<th>Study Limitations &amp; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordmann 2006 (312) 18478688</td>
<td>Low-carb vs. low-fat diets on weight loss and CV risk</td>
<td>Meta-analysi s</td>
<td>447 5 trials</td>
<td>Low carb 222</td>
<td>Randomized controlled low carb vs. low fat, BMI≥25, Follow-up 6 mo + Age 16+</td>
<td>Trials with cross-over or sequential design</td>
<td>Low-carb weight loss at 6 and 12 mo</td>
<td>Low fat same</td>
<td>Weight loss to 6 and 12 mo. 6 mo: low carb&gt;weight loss. 12 mo: NS difference</td>
<td>Trend toward lower BP in low carb group at 6 mo only. TG and HDL changed more favorably in high-carb diets, LDL-C in low-fat diets</td>
<td>HbA1c dec. In low carb gp. vs. low fat -12 mo -0.7% vs.-0.1% p=0.02 Weighted mean difference 6 mo Low carb vs. low fat -3.3 kg (-5.3,-1.4) 12 mo. -1.0 kg (-3.5,1.5)</td>
</tr>
</tbody>
</table>
Chow 2010
(313)
20124123

Adherence to behavior recommendations in CV risk

Multicenter Observational study

18,809

Adherence to diet, exercise, smoking cessation

Nonadherence to individual components

UA, NSTEMI Age 60+ y

Contraindication to LMW heparin, recent hemorrhagic stroke AC for other than ACS, high creatinine

Survey at 30, 90, 180 d on 3 lifestyle values adherence

No diet, exercise, No smoking cessation

CV events at 6 mo decreased with exercise only and diet + exercise and ex-smoker vs. persistent smoker

Side effects not addressed

Increased independent risk of stroke/MI/death
All 3 with diet/exercise Death with ex-smoker vs. continued smoker

Risk of CV events
Exercise vs. no 0.69
(0.54,0.89)<0.003

Exercise/diet vs. no
0.46 (0.38-0.57) <0.001

Ex-smoker vs. smoker
0.68 (0.51-0.90) 0.007

No active study intervention program. Self-report of outcomes. No details of actual diet and exercise quantification. Adherers/nonadherers categorized only at 30-d follow-up.

Gaddis 2011
(314)
21481449

Efficacy and safety of Qnexa

Multicenter prospective trial

2,448

Phenteramine/Topiramate 7.5mg/46mg

488

P/T 15/92mg

981

PC 979

Age: 18-70

BMI: 27-45

Or diabetes 2 or more CV risk factors

BP >160/100

FBS >13.32

mmol/L

TG >4.52

mmol/L

Type 1 diabetes or Type 2 managed with antidiabetic drugs except for metformin

Phenteramin/Topiramate 1 of 2 dosages for 56 wk

PC for same period

Proportion of pts achieving at least 5% weight loss:
Low-dose Qnexa: 62%
High-dose Qnexa: 70%
PC: 21%  
Adverse effects vs. PC
10% or more with sig diff:
Dry mouth 21%
Paresthesia 21%
Constipation 17%
Dysgeusia 10%
Headache 10%
Attention disturbance (sig)
Cognitive (sig)
Dysgeusia 10%
Dry mouth

<10% weight loss
Low-dose Qnexa 37%
P=0.0001
High-dose Qnexa 48%
P=0.0001
PC 7%

>10% weight loss
Low-dose Qnexa OR: 6.3 (4.9-8.0) p<0.0001
High-dose Qnexa OR: 9.0 (7.3-11.1) p<0.0001

5% weight loss: Low-dose Qnexa 0.68 (0.51-0.90) 0.007

56 vs. 56 wk period

Risk of CV events
Low-dose: 79.3%
High-dose: 75.2%

Dyslipidemia and HTN on AC

Impact of Rx of secondary cardiometabolic variables. Type of adverse events similar to 1st 56-wk period but incidence rates lower.

Garvey 2012
(315)
22158731

Long-term efficacy and safety of Qnexa

Multicenter prospective trial

676

Out of original 2,448

Phenteramine/Topiramate 7.5mg/46mg

173

P/T 15/92mg

285

PC 227

See above agreed to extension

See above

See above 52-wk extension

PC for same period

Percentages achieving >5%, >10%, >15% and >20% weight loss in 108-wk period, in all 4 categories, Qnexa low and high dose + PC

Change in percentages Adverse effects were 0-56 vs. 56-108 High-dose Q constipation 21% to 4% Paresthesia 21% to 2.4% Dry mouth

Percentage changes in BP, lipid, DM meds:
High-dose Q BP: -9.8% Lipid: +11.7% DM: 0%
Low-dose Q 
BP: -3.9% Lipid: +11.7% DM: 0%

>5% weight loss
Low-dose: 79.3%
High-dose: 75.2%

PC: 30.0%
P<0.0001

>10% weight loss
Low-dose: 53.9%
High-dose: 50.3%

PC: 11.5%
P<0.0001

>15% weight loss
Low-dose: 31.9%

Discontinuation rates similar to 1st 56-wk period above. Higher rate lost to follow-up in the 15/92 arm. Impact of Rx of dyslipidemia and HTN on secondary cardiometabolic variables. Type of adverse events similar to 1st 56-wk period but incidence rates lower.

End of table
20% to 1.4% upper respiratory infection
18.6% to 15.3% Nasopharyngitis
13.2% to 8.8% Depression

From PC Lipid: +5.2%
DM: +1.9%
PC BP: +3.5%
Lipid: +17.2%
DM: +7.1%

High dose: 24.2%
PC: 6.6%
p<0.0001
>20% weight loss
Low dose: 9.2%
High dose: 15.3%
p<0.001 for low dose <0.0001 for high dose.

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR &amp; 95 CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goel, K et al Circulation. 2011; 123: 2344-2352 (316)</td>
<td>Assess CR participation and impact on mortality</td>
<td>2,395</td>
<td>CR (1431) vs. non-CR (964) participants</td>
<td>PCI registry, Olmstead County</td>
<td>No prior pt authorization</td>
<td>All-cause mortality HR</td>
<td>Subsequent MI, PCI-NS</td>
<td>Death, PCI, MI</td>
<td>CABG p=0.28</td>
</tr>
<tr>
<td>Hammil, Circulation. 2010;121:63-70 (317)</td>
<td>Characterize dose-response for # CR sessions</td>
<td>30,161</td>
<td>6,181 with AMI as qualifying reason for CR</td>
<td>Internal: cumulative comparison with # of CR sessions (&quot;dose&quot;)</td>
<td>Medicare 5% sample 2001-2005</td>
<td>None identified</td>
<td>At least 1 CR outpatient session billed to Medicare</td>
<td>Death</td>
<td>Subsequent hospitalization</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; CR, cardiac rehabilitation; HR, hazard ratio; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention; Pt, patient; and RR, relative risk.

AC indicates anticoagulant; ACS, acute coronary syndrome; BMI, body mass index; BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; FBS, fasting blood sugar (glucose); HbA1c, Hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LMW, low molecular weight; MI, myocardial infarction; NS, no(n) significance; NSTEMI, non-ST-elevation myocardial infarction; PC, placebo; Pl, patient; Rx, prescription; TG, triglycerides; and UA, unstable agina.
References


© American Heart Association, Inc and American College of Cardiology Foundation


© American Heart Association, Inc and American College of Cardiology Foundation


Lee YH, Ji JD, Song GG. Adjusted indirect comparison of celecoxib versus rofecoxib on cardiovascular risk. Rheumatol Int. 2007;27:477-82.


309. Smith PM, Burgess E. Smoking cessation initiated during hospital stay for patients with coronary artery disease: a randomized controlled trial. CMAJ. 2009;180:1297-303.


