

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 of Thoracic Surgeons

Endorsed by the American Association for Clinical Chemistry

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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.

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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.000000000000134/-/DC1>.

The online-only Data Supplement files are available with this article at
<http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.000000000000134/-/DC2>.

The American Heart Association requests that this document be cited as follows: Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 2014 ACC/AHA 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. *Circulation*. 2014;000:000–000.

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



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(*Circulation*. 2014;000:000–000.)

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DOI:10.1161/CIR.000000000000134

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Preamble

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

In response to published reports from the Institute of Medicine (1, 2) and the ACC/AHA's mandate to evaluate new knowledge and maintain relevance at the point of care, the ACC/AHA Task Force on Practice Guidelines (Task Force) began modifying its methodology. This modernization effort is published in the 2012 Methodology Summit Report (3) and 2014 perspective article (4). The latter recounts the history of the collaboration, changes over time, current policies, and planned initiatives to meet the needs of an evolving healthcare environment. Recommendations on value in proportion to resource utilization will be incorporated as high-quality comparative-effectiveness data become available (5). The relationships between CPGs and data standards, appropriate use criteria, and performance measures are addressed elsewhere (4).

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

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

Guideline-Directed Medical Therapy—Recognizing advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force designated the term “guideline-directed medical therapy” (GDMT) to

represent recommended medical therapy as defined mainly by Class I measures, generally a combination of lifestyle modification and drug- and device-based therapeutics. As medical science advances, GDMT evolves, and hence GDMT is preferred to “optimal medical therapy.” For GDMT and all other recommended drug treatment regimens, the reader should confirm the dosage with product insert material and carefully evaluate for contraindications and possible drug interactions. Recommendations are limited to treatments, drugs, and devices approved for clinical use in the United States.

Class of Recommendation and Level of Evidence—Once recommendations are written, the Class of Recommendation (COR; i.e., the strength the GWC assigns to the recommendation, which encompasses the anticipated magnitude and judged certainty of benefit in proportion to risk) is assigned by the GWC. Concurrently, the Level of Evidence (LOE) rates the scientific evidence supporting the effect of the intervention on the basis on the type, quality, quantity, and consistency of data from clinical trials and other reports (Table 1) (4). Unless otherwise stated, recommendations are presented in order by the COR and then the LOE. Where comparative data exist, preferred strategies take precedence. When more than 1 drug, strategy, or therapy exists within the same COR and LOE and there are no comparative data, options are listed alphabetically.

Relationships With Industry and Other Entities—The ACC and AHA exclusively sponsor the work of GWCs without commercial support, and members volunteer their time for this activity. The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities (RWI). All GWC members and reviewers are required to fully disclose current industry relationships or personal interests from 12 months before initiation of the writing effort. Management of RWI involves selecting a balanced GWC and requires that both the chair and a majority of GWC members have no relevant RWI (see Appendix 1 for the definition of relevance). GWC members are restricted with regard to writing or voting on sections to which their RWI apply. In addition, for transparency, GWC members’ comprehensive disclosure information is available as an online supplement (<http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.000000000000134/-/DC1>). Comprehensive disclosure information for the Task Force is also available at <http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx>. 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

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illnesses are discordant or interacting (7). CPGs attempt to define practices that meet the needs of patients in most, but not all, circumstances and do not replace clinical judgment.

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

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

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



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Table 1. Applying Classification of Recommendations and Level of Evidence

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

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

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated

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

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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 Data Supplement available online at

(<http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.000000000000134/-/DC2>). 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 Cardiovascular Angiography and Interventions (SCAI), and Society of Thoracic Surgeons (STS).

1.3. Document Review and Approval

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

This document was approved for publication by the governing bodies of the ACC and the AHA and endorsed by the American Association for Clinical Chemistry and the Society of Thoracic Surgeons.

1.4. Scope of the CPG

The 2014 NSTE-ACS CPG is a full revision of the 2007 ACCF/AHA CPG for the management of patients with unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) and the 2012 focused update (8).

The new title, “Non–ST-Elevation Acute Coronary Syndromes,” emphasizes the continuum between UA and NSTEMI. At presentation, patients with UA and NSTEMI can be indistinguishable and are therefore considered together in this CPG.

In the United States, NSTEMI-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 NSTEMI-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 NSTEMI-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.

Table 2. Associated CPGs and Statements

Title	Organization	Publication Year (Reference)
CPGs		
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/SCAI/STS	2014 (10)* 2012 (11)
Atrial fibrillation	AHA/ACC/HRS	2014 (12)
Assessment of cardiovascular risk	ACC/AHA	2013 (13)
Heart failure	ACC/AHA	2013 (14)
Lifestyle management to reduce cardiovascular risk	AHA/ACC	2013 (15)
Management of overweight and obesity in adults	AHA/ACC/TOS	2013 (16)
ST-elevation myocardial infarction	ACC/AHA	2013 (17)
Treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults	ACC/AHA	2013 (18)
Acute myocardial infarction in patients presenting with ST-segment elevation	ESC	2012 (19)
Device-based therapy	ACC/AHA/HRS	2013 (20)
Third universal definition of myocardial infarction	ESC/ACC/AHA/WHF	2012 (21)
Acute coronary syndromes in patients presenting without persistent ST-segment elevation	ESC	2011 (22)
Coronary artery bypass graft surgery	ACC/AHA	2011 (23)

*Estimate includes secondary discharge diagnoses.

Hypertrophic cardiomyopathy	ACC/AHA	2011 (24)
Effectiveness-based guidelines for the prevention of cardiovascular disease in women	AHA/ACC	2011 (25)
Percutaneous coronary intervention	ACC/AHA/SCAI	2011 (26)
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011 (27)
Assessment of cardiovascular risk in asymptomatic adults	ACC/AHA	2010 (28)
Myocardial revascularization	ESC	2010 (29)
Unstable angina and non-ST-elevation myocardial infarction	NICE	2010† (30)
Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care—Part 9: postcardiac arrest care	AHA	2010 (31)
Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure	NHLBI	2003 (32)
Statements		
Key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease	ACC/AHA	2013 (33)
Practical clinical considerations in the interpretation of troponin elevations	ACC	2012 (34)
Testing of low-risk patients presenting to the emergency department with chest pain	AHA	2010 (35)
Primary prevention of cardiovascular diseases in people with diabetes mellitus	AHA/ADA	2007 (36)
Prevention and control of influenza	CDC	2005 (37)

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

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

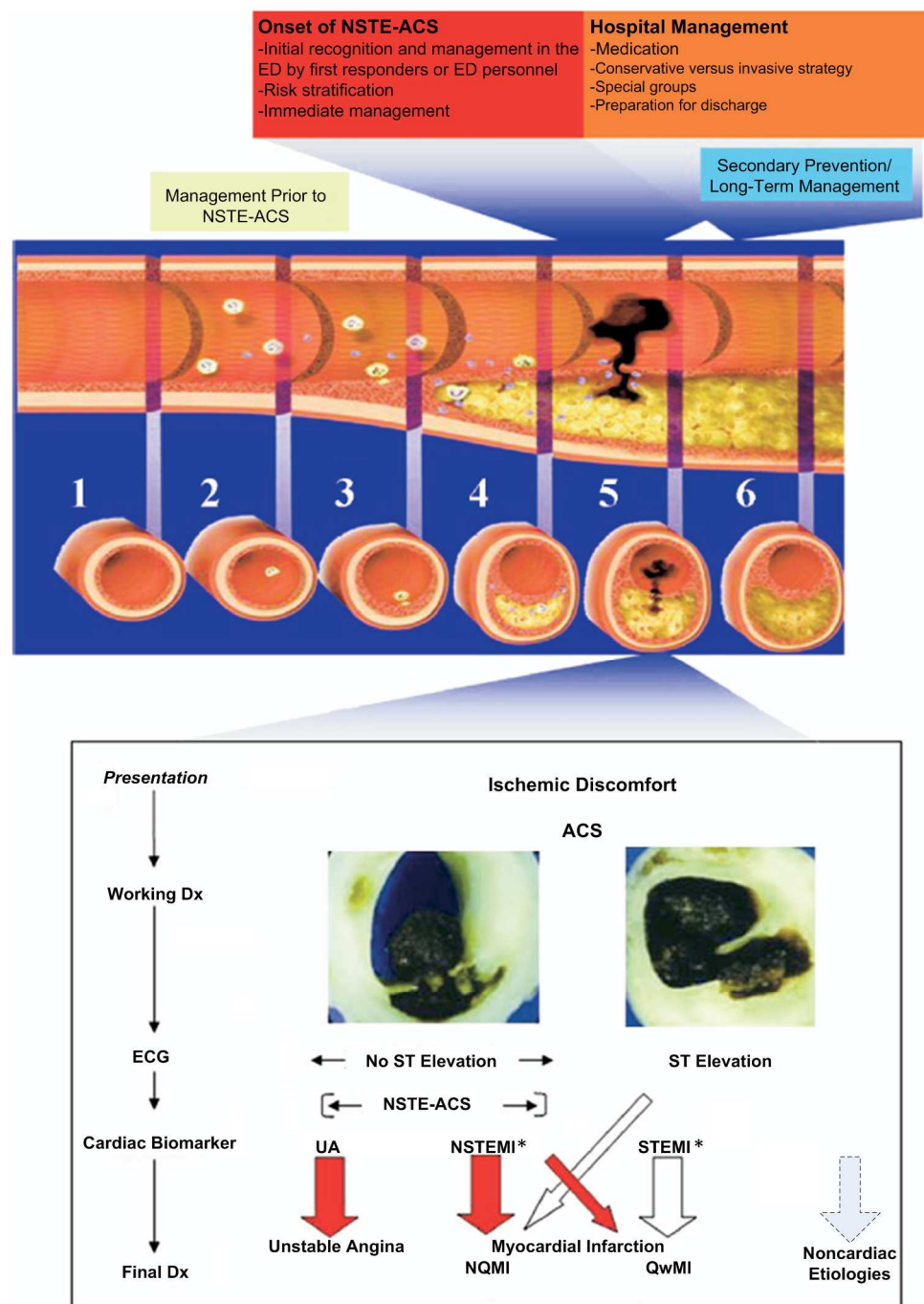
AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; CDC, Centers for Disease Control and Prevention; CPG, clinical practice guideline; ESC, European Society of Cardiology; HRS, Heart Rhythm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

2. Overview of ACS

2.1. Definition of Terms

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

Figure 1. Acute Coronary Syndromes



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The top half of the figure illustrates the progression of plaque formation and onset and complications of NSTEMI-ACS, with management at each stage. The numbered section of an artery depicts the process of atherosclerosis 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 NSTEMI-ACS CPG includes sections on initial management before NSTEMI-ACS, at the onset of NSTEMI-ACS, and during the hospital phase. Secondary prevention and plans for long-term management begin early during the hospital phase. Patients with noncardiac etiologies make up the largest group presenting to the ED with chest pain (dashed arrow).

*Elevated cardiac biomarker (e.g., troponin), Section 3.4.

ACS indicates acute coronary syndrome; CPG, clinical practice guideline; Dx, diagnosis; ECG, electrocardiogram; ED, emergency department; MI, myocardial infarction; NQMI, non-Q-wave myocardial infarction; NSTEMI-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).

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

2.2. Epidemiology and Pathogenesis

2.2.1. Epidemiology

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

2.2.2. Pathogenesis

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

3. Initial Evaluation and Management

3.1. Clinical Assessment and Initial Evaluation: Recommendation



Class I

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

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

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

Risk assessment scores and clinical prediction algorithms using clinical history, physical examination, ECG, and cardiac troponins have been developed to help identify patients with ACS at increased risk of adverse outcome(s). Common risk assessment tools include the TIMI (Thrombolysis In Myocardial Infarction) risk score (42), the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk score (43), the GRACE (Global Registry of Acute Coronary Events) risk score (44), and the NCDR-ACTION (National Cardiovascular Data Registry-Acute Coronary Treatment and Intervention Outcomes Network) registry (<https://www.ncdr.com/webncdr/action/>). These assessment tools have been applied with variable efficacy to predict outcomes in patients presenting to the emergency department (ED) with undifferentiated chest pain ("pain" encompasses not only pain, but also symptoms such as discomfort, pressure, and squeezing) (45-48). The Sanchis score (49), Vancouver rule (50), Heart (History, ECG, Age, Risk Factors, and Troponin) score (51), HEARTS₃ score (52), and Hess prediction rule (53) were developed specifically for patients in the ED with chest pain. Although no definitive study has demonstrated the superiority of risk assessment scores or clinical prediction rules over clinician judgment, determination of the level of risk on

initial evaluation is imperative to guide patient management, including the need for additional diagnostic testing and treatment. See Section 3.2.2 for a discussion of risk stratification variables.

See [Online Data Supplement 1](#) for additional information on clinical assessment and initial evaluation.

3.1.1. ED or Outpatient Facility Presentation: Recommendations

Class I

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

Class IIb

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

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

3.2. Diagnosis of NSTEMI-ACS

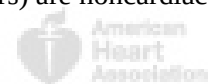
Differential diagnosis of NSTEMI-ACS includes (41):

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

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

3.2.1. History

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



3.2.2. Physical Examination

The physical examination in NSTEMI-ACS can be normal, but signs of HF should expedite the diagnosis and treatment of this condition. Acute myocardial ischemia may cause a S_4 , a paradoxical splitting of S_2 , or a new murmur of mitral regurgitation due to papillary muscle dysfunction. However, these signs may also exist without NSTEMI-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 NSTEMI-ACS. The physical examination can indicate alternative diagnoses in patients with chest pain, several of which are life threatening. Aortic dissection is suggested by back pain, unequal palpated pulse volume, a difference of ≥ 15 mm Hg between both arms in systolic blood pressure (BP), or a murmur of aortic regurgitation. Acute pericarditis is suggested by a pericardial friction rub. Cardiac tamponade can be reflected by pulsus paradoxus. Pneumothorax is suspected when acute dyspnea, pleuritic chest pain, and differential breath sounds are present. A pleural friction rub may indicate pneumonitis or pleuritis.

3.2.3. Electrocardiogram

A 12-lead ECG should be performed and interpreted within 10 minutes of the patient's arrival at an emergency facility to assess for cardiac ischemia or injury (21). Changes on ECG in patients with NSTEMI-ACS include ST depression, transient ST elevation, or new T-wave inversion (21, 58). Persistent ST elevation or anterior ST depression indicative of true posterior MI should be treated according to the STEMI CPG (17). The ECG can be relatively normal or initially nondiagnostic; if this is the case, the ECG should be repeated (e.g., at 15- to 30-minute intervals during the first hour), especially if symptoms recur (21). A normal ECG does not exclude ACS and occurs in 1% to 6% of such patients (59-61). A normal ECG may also be associated with left circumflex or

right coronary artery occlusions, which can be electrically silent (in which case posterior electrocardiographic leads [V₇ to V₉] may be helpful). Right-sided leads (V_{3R} to V_{4R}) are typically performed in the case of inferior STEMI to detect evidence of right ventricular infarction. Left ventricular (LV) hypertrophy, bundle-branch blocks with repolarization abnormalities, and ventricular pacing may mask signs of ischemia/injury (62).

3.2.4. Biomarkers of Myocardial Necrosis

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

3.2.5. Imaging

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



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3.3. Prognosis—Early Risk Stratification: Recommendations

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

Class I

1. In patients with chest pain or other symptoms suggestive of ACS, a 12-lead ECG should be performed and evaluated for ischemic changes within 10 minutes of the patient's arrival at an emergency facility (21). (*Level of Evidence: C*)
2. If the initial ECG is not diagnostic but the patient remains symptomatic and there is a high clinical suspicion for ACS, serial ECGs (e.g., 15- to 30-minute intervals during the first hour) should be performed to detect ischemic changes. (*Level of Evidence: C*)
3. Serial cardiac troponin I or T levels (when a contemporary assay is used) should be obtained at presentation and 3 to 6 hours after symptom onset (see Section 3.4, Class I, #3 recommendation if time of symptom onset is unclear) in all patients who present with symptoms consistent with ACS to identify a rising and/or falling pattern of values (21, 64, 67-71). (*Level of Evidence: A*)
4. Additional troponin levels should be obtained beyond 6 hours after symptom onset (see Section 3.4, Class I, #3 recommendation if time of symptom onset is unclear) in patients with normal troponin levels on serial examination when changes on ECG and/or clinical presentation confer an intermediate or high index of suspicion for ACS (21, 72-74). (*Level of Evidence: A*)

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

Class IIa

1. Risk-stratification models can be useful in management (42-44, 75-81). (*Level of Evidence: B*)
2. It is reasonable to obtain supplemental electrocardiographic leads V₇ to V₉ in patients whose initial ECG is nondiagnostic and who are at intermediate/high risk of ACS (82-84). (*Level of Evidence: B*)

Class IIb

1. Continuous monitoring with 12-lead ECG may be a reasonable alternative in patients whose initial ECG is nondiagnostic and who are at intermediate/high risk of ACS (85, 86). (*Level of Evidence: B*)
2. Measurement of B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide may be considered to assess risk in patients with suspected ACS (87-91). (*Level of Evidence: B*)

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

Assessment of prognosis guides initial clinical evaluation and treatment and is useful for selecting the site of care (coronary care unit, monitored step-down unit, or outpatient monitored unit), antithrombotic therapies (e.g., P2Y₁₂ inhibitors, platelet glycoprotein [GP] IIb/IIIa inhibitors [Sections 4.3.1.2 and 5.1.2.2]), and invasive management (Sections 4.4.2.1, 4.3.1, 4.4, 4.4.4, 4.4.5). There is a strong relationship between indicators of ischemia due to CAD and prognosis (Table 3 and Figure 2). Patients with a high likelihood of ischemia due to CAD are at greater risk of a major adverse cardiac event (MACE) than patients with a lower likelihood of ischemia due to CAD. Risk is highest at the time of presentation but remains elevated past the acute phase. By 6 months, NSTE-ACS mortality rates may equal or exceed those of STEMI (58). By 12 months, rates of death, MI, and recurrent instability in contemporary registries are >10%. Early events are related to the ruptured coronary plaque and thrombosis, and later events are more closely associated with the pathophysiology of chronic atherosclerosis and LV systolic function (92-98).

3.3.2. Estimation of Level of Risk

At initial presentation, the clinical history, anginal symptoms and equivalents, physical examination, ECG, renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events (Table 3 and Figure 2) (42, 78).

3.3.2.1. History: Angina Symptoms and Angina Equivalents

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

The characteristics of angina include deep, poorly localized chest or arm pain that is reproducibly associated with exertion or emotional stress (106). Angina is relieved promptly (i.e., in <5 minutes) with rest

and/or short-acting nitroglycerin. Patients with NSTEMI-ACS may have typical or atypical anginal symptoms, but episodes are more severe and prolonged, may occur at rest, or may be precipitated by less exertion than the patient previously experienced. Some patients have no chest pain but present solely with dyspnea or with arm, shoulder, back, jaw, neck, epigastric, or ear discomfort (107-109).

Features not characteristic of myocardial ischemia include:

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

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

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

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

3.3.2.2. Demographics and History in Diagnosis and Risk Stratification

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

A family history of premature CAD is associated with increased coronary artery calcium scores (119) and increased risk of 30-day cardiac events in patients with ACS (120, 121). Diabetes mellitus, extracardiac

(carotid, aortic, or peripheral) arterial disease, and hypertension are major risk factors for poor outcomes in patients with ACS (Section 6.2) with both STEMI (122) and NSTEMI-ACS (92).

The current or prior use of aspirin at presentation is associated with increased cardiovascular risk (42), likely reflecting the greater probability that patients who have been prescribed aspirin have an increased cardiovascular risk profile and/or prior vascular disease. Smoking is associated with a lower risk of death in ACS (42, 123, 124), primarily because of the younger age of smokers with ACS and less severe CAD. Overweight and/or obesity at ACS presentation are associated with lower short-term risk of death. The “obesity paradox” may be a function of younger age at presentation, referral for angiography at an earlier stage of disease, and more aggressive management of ACS (123). These individuals, especially those with severe obesity (body mass index >35), have a higher long-term total mortality risk (124-129).

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

3.3.2.3. Early Estimation of Risk

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

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

Among patients with a higher TIMI risk score (e.g., ≥ 3), there is a greater benefit from therapies such as low-molecular-weight heparin (LMWH) (133, 136), platelet GP IIb/IIIa inhibitors (137), and an invasive strategy (138). Similarly, the GRACE risk model can identify patients who would benefit from an early invasive strategy (139). Patients with elevated cardiac troponin benefit from more aggressive therapy, whereas those without elevated cardiac troponins may not (140). This is especially true for women in whom some data suggest

adverse effects from invasive therapies in the absence of an elevated cardiac troponin value (141). Although B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide are not useful for the diagnosis of ACS per se (but rather HF, which has many etiologies), they add prognostic value (87-91).

Table 3. TIMI Risk Score* for NSTE-ACS

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

*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 $\geq 50\%$; ST deviation on ECG; ≥ 2 anginal events in prior 24 h; use of aspirin in prior 7 d; and elevated cardiac biomarkers.

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

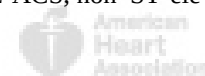


Figure 2. Global Registry of Acute Coronary Events Risk Calculator for In-Hospital Mortality for Acute Coronary Syndrome

A. GRACE Risk Model Nomogram

1. Find Points for Each Predictive Factor:

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

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

2. Sum Points for All Predictive Factors:



3. Look Up Risk Corresponding to Total Points:

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

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.

His score would be: $20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196$

This person would have about a 16% risk of having an in-hospital death.

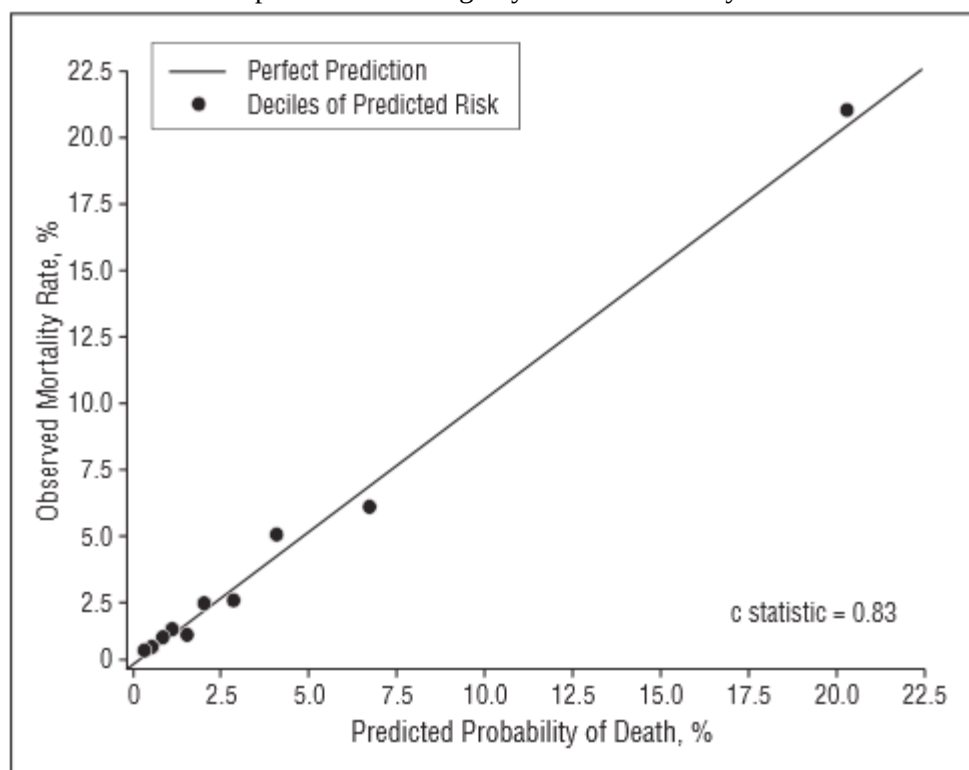
Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4, and no risk factors would have the following score:

$0 + 58 + 3 + 41 + 1 = 103$, which gives approximately a 0.9% risk of having an in-hospital death.

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

SBP indicates systolic blood pressure.
Reprinted with permission from Granger et al. (142).

B. Calibration of Simplified Global Registry of ACS Mortality Model



ACS indicates acute coronary syndrome.
Reprinted with permission from Granger et al. (142).

3.3.2.4. Electrocardiogram

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

Nonspecific ST-T changes (usually defined as ST deviation of < 0.5 mm [0.05 mV] or T-wave inversion of < 2 mm [0.2 mV]) are less helpful diagnostically. Significant Q waves are less helpful, although by suggesting prior MI, they indicate a high likelihood of significant CAD. Isolated Q waves in lead 3 are a normal finding. A completely normal ECG in a patient with chest pain does not exclude ACS, because 1% to 6% of such patients will have a MI, and at least 4% will have UA (59-61). Fibrinolytic therapy is contraindicated for patients with

ACS without ST elevation, except for those with electrocardiographic evidence of true posterior MI (i.e., ST elevation in posterior chest leads [V₇ to V₉]). This can be evaluated when acute myocardial infarction (AMI) is suspected but electrocardiographic changes are modest or not present (82-84); a transthoracic echocardiogram to evaluate for posterior wall motion abnormalities may also be helpful in this setting.

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

3.3.2.5. Physical Examination

The physical examination is helpful in assessing the hemodynamic impact of an ischemic event. Patients with suspected ACS should have vital signs measured (BP in both arms if dissection is suspected) and should undergo a thorough cardiovascular examination. Patients with evidence of LV dysfunction on examination (e.g., rales, 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 (92, 151). The physical examination may also help identify comorbid conditions (e.g., occult GI bleeding) that could impact therapeutic risk and decision making.

Table 4. Summary of Recommendations for Prognosis: Early Risk Stratification

Recommendations	COR	LOE	References
Perform rapid determination of likelihood of ACS, including a 12-lead ECG within 10 min of arrival at an emergency facility, in patients whose symptoms suggest ACS	I	C	(21)
Perform serial ECGs at 15- to 30-min intervals during the first hour in symptomatic patients with initial nondiagnostic ECG	I	C	N/A
Measure cardiac troponin (cTnI or cTnT) in all patients with symptoms consistent with ACS*	I	A	(21, 64, 67-71)
Measure serial cardiac troponin I or T at presentation and 3–6 h after symptom onset* in all patients with symptoms consistent with ACS	I	A	(21, 72-74)
Use risk scores to assess prognosis in patients with NSTE-ACS	I	A	(42-44, 75-80)
Risk-stratification models can be useful in management	IIa	B	(42-44, 75-81)
Obtain supplemental electrocardiographic leads V ₇ to V ₉ in patients with initial nondiagnostic ECG at intermediate/high risk for ACS	IIa	B	(82-84)
Continuous monitoring with 12-lead ECG may be a reasonable alternative with initial nondiagnostic ECG in patients at intermediate/high risk for ACS	IIb	B	(85, 86)
BNP or NT-pro-BNP may be considered to assess risk in patients with suspected ACS	IIb	B	(87-91)

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

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

See [Online Data Supplement 2](#) for additional information on risk stratification.

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

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

3.4.1. Biomarkers: Diagnosis

Class I

1. Cardiac-specific troponin (troponin I or T when a contemporary assay is used) levels should be measured at presentation and 3 to 6 hours after symptom onset in all patients who present with symptoms consistent with ACS to identify a rising and/or falling pattern (21, 64, 67-71, 152-156). (*Level of Evidence: A*)
2. Additional troponin levels should be obtained beyond 6 hours after symptom onset in patients with normal troponins on serial examination when electrocardiographic changes and/or clinical presentation confer an intermediate or high index of suspicion for ACS (21, 72-74, 157). (*Level of Evidence: A*)
3. If the time of symptom onset is ambiguous, the time of presentation should be considered the time of onset for assessing troponin values (67, 68, 72). (*Level of Evidence: A*)

Class III: No Benefit

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

3.4.2. Biomarkers: Prognosis

Class I

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

Class IIb

1. It may be reasonable to remeasure troponin once on day 3 or day 4 in patients with MI as an index of infarct size and dynamics of necrosis (164, 165). (*Level of Evidence: B*)
2. Use of selected newer biomarkers, especially B-type natriuretic peptide, may be reasonable to provide additional prognostic information (87, 88, 167-171). (*Level of Evidence: B*)

Cardiac troponins are the mainstay for diagnosis of ACS and for risk stratification in patients with ACS. The primary diagnostic biomarkers of myocardial necrosis are cardiac troponin I and cardiac troponin T. Features that favor troponins for detection of ACS include high concentrations of troponins in the myocardium; virtual absence of troponins in nonmyocardial tissue; high-release ratio into the systemic circulation (amount found in blood relative to amount depleted from myocardium); rapid release into the blood in proportion to the extent of myocardial injury; and the ability to quantify values with reproducible, inexpensive, rapid, and easily applied assays. The 2012 Third Universal Definition of MI provides criteria that classify 5 clinical presentations of MI based on pathological, clinical, and prognostic factors (21). In the appropriate clinical context, MI is indicated by a rising and/or falling pattern of troponin with ≥ 1 value above the 99th percentile of the upper reference level

and evidence for serial increases or decreases in the levels of troponins (67, 68, 156). The potential consequences of emerging high-sensitivity troponin assays include increases in the diagnosis of NSTEMI (152, 172, 173) influenced by the definition of an abnormal troponin (67, 153, 174, 175). The recommendations in this section are formulated from studies predicated on both the new European Society of Cardiology/ACC/AHA/World Health Organization criteria (21) and previous criteria/redefinitions of MI based on earlier-generation troponin assays (Appendix 4, Table A).

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

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

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

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3.4.3. Cardiac Troponins

See [Online Data Supplement 4](#) for additional information on cardiac troponins.

Of the 3 troponin subunits, 2 subunits (troponin I and troponin T) are derived from genes specifically expressed in the myocardium. Cardiac troponin measurements provide highly sensitive results specific for detecting cardiomyocyte necrosis (34, 173). Highly sensitive assays can identify cardiac troponin not only in the blood of patients with acute cardiac injury but also in the blood of most healthy people (64, 68, 70, 166, 176, 177). As assay sensitivity increases, a greater proportion of patients will have detectable long-term elevations in troponin, thus requiring consideration of serial changes for the diagnosis of MI. Clinicians should be aware of the sensitivity of the tests used for troponin evaluation in their hospitals and cutpoint concentrations for clinical decisions. Markedly elevated values are usually related to MI, myocarditis, rare analytical factors, or chronic elevations in patients with renal failure and in some patients with HF.

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

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

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

Solitary elevations of troponin cannot be assumed to be due to MI, because troponin elevations can be due to tachyarrhythmia, hypotension or hypertension, cardiac trauma, acute HF, myocarditis and pericarditis, acute pulmonary thromboembolic disease, and severe noncardiac conditions such as sepsis, burns, respiratory failure, acute neurological diseases, and drug toxicity (including cancer chemotherapy). Chronic elevations can result from structural cardiac abnormalities such as LV hypertrophy or ventricular dilatation and are also common in patients with renal insufficiency (34). Patients with end-stage renal disease and no clinical evidence of ACS frequently have elevations of cardiac troponin (180-182). With conventional assays, this is more common with cardiac troponin T than with cardiac troponin I (180). In the diagnosis of NSTEMI, cardiac troponin values must manifest an acute pattern consistent with the clinical events, including ischemic symptoms and electrocardiographic changes. Troponin elevations may persist for up to 14 days or occasionally longer. There is a paucity of guidelines for establishment of reinfarction during the acute infarct period on the basis of troponin measurements. References suggest that an increase of $>20\%$ of previous troponin levels or an absolute increase of high-sensitivity cardiac troponin T values (e.g., >7 ng/L over 2 hours) may indicate reinfarction (183-185).

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

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

3.4.3.1. Prognosis

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

3.4.4. CK-MB and Myoglobin Compared With Troponin

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

See [Online Data Supplements 5, 6, and 7](#) for additional information on cardiac injury markers.

3.5. Immediate Management

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

Class IIa

1. It is reasonable to observe patients with symptoms consistent with ACS without objective evidence of myocardial ischemia (nonischemic initial ECG and normal cardiac troponin) in a chest pain unit or telemetry unit with serial ECGs and cardiac troponin at 3- to 6-hour intervals (196, 197, 199-201). (*Level of Evidence: B*)
2. It is reasonable for patients with possible ACS who have normal serial ECGs and cardiac troponins to have a treadmill ECG (200-202) (*Level of Evidence: A*), stress myocardial perfusion imaging (200), or stress echocardiography (203, 204) before discharge or within 72 hours after discharge. (*Level of Evidence: B*)
3. In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary CT angiography to assess coronary artery anatomy (205-207) (*Level of Evidence: A*) or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia (208, 209). (*Level of Evidence: B*)

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

The majority of patients presenting to the ED with chest pain do not have ACS (Figure 1), and most are at low risk for major morbidity and mortality (35). Low-risk patients are usually identified by an absence of history of cardiovascular disease, normal or near-normal initial ECG, normal initial troponin, and clinical stability (35, 202). The utility of an accelerated diagnostic protocol for detecting patients with benign conditions versus those who require admission for serious disease has been established (35). At minimum, these protocols involve serial ECGs and troponin measurements, both of which can be performed in the ED, a separate chest pain unit, or a telemetry unit. A 30-day negative predictive value >99% for ACS has been reported for patients presenting to the ED with chest pain who undergo a 2-hour accelerated diagnostic protocol composed of a TIMI risk score of 0, normal ECG, and normal high-sensitivity troponin at 0 hours and 2 hours (assuming appropriate follow-up care) (65, 210). Some protocols also call for a functional or anatomic test (e.g., treadmill test, rest scintigraphy, coronary CT angiography, stress imaging). Coronary CT angiography is associated with rapid assessment, high negative predictive value, decreased length of stay, and reduced costs (205-207); however, in the latter studies, it increased the rate of invasive coronary angiography and revascularization with uncertain long-term benefits in low-risk patients without ECG or troponin alterations (211). Accelerated diagnostic protocols are also potentially applicable in intermediate-risk patients, whose presentation includes a history of cardiovascular disease, diabetes mellitus, chronic kidney disease (CKD), and/or advanced age (202).

See [Online Data Supplement 8](#) for additional information on discharge from the ED or chest pain unit.

4. Early Hospital Care

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

Patients with continuing angina, hemodynamic instability, uncontrolled arrhythmias, or a large MI should be admitted to a coronary care unit. The nurse-to-patient ratio should be sufficient to provide 1) continuous electrocardiographic rhythm monitoring, 2) frequent assessment of vital signs and mental status, and 3) ability to perform rapid cardioversion and defibrillation. These patients are usually observed in the coronary

care unit for at least 24 hours. Those without recurrent ischemia, significant arrhythmias, pulmonary edema, or hemodynamic instability can be considered for admission or transfer to an intermediate care or telemetry unit.

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

4.1. Standard Medical Therapies

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

4.1.1. Oxygen: Recommendation

Class I

1. Supplemental oxygen should be administered to patients with NSTEMI-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 NSTEMI-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 NSTEMI-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 NSTEMI-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 mg to 0.4 mg) every 5 minutes for up to 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin if not contraindicated (216-218). (*Level of Evidence: C*)
2. Intravenous nitroglycerin is indicated for patients with NSTEMI-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 NSTEMI-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 MVO₂. This may be partially offset by reflex increases in heart rate and contractility, which counteract the reduction in MVO₂ unless a beta blocker is concurrently administered. Nitrates also dilate normal and atherosclerotic coronary arteries and increase coronary collateral flow. Nitrates may also inhibit platelet aggregation (228).

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

Intravenous nitroglycerin is beneficial in patients with HF, hypertension, or symptoms that are not relieved with sublingual nitroglycerin and administration of a beta blocker (219, 221-224). Patients who require intravenous nitroglycerin for >24 hours may require periodic increases in the infusion rate and use of nontolerance-producing regimens (e.g., intermittent dosing) to maintain efficacy. In current practice, most patients who require continued intravenous nitroglycerin for the relief of angina undergo prompt coronary angiography and revascularization. Topical or oral nitrates are acceptable alternatives to intravenous nitroglycerin for patients who do not have refractory or recurrent ischemia (229, 230). Side effects of nitrates include headache and hypotension. Nitrates should not be administered to patients with hypotension or to those who received a phosphodiesterase inhibitor and 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 NSTEMI-ACS. To our knowledge, no RCTs have assessed the use of morphine in patients with NSTEMI-ACS or defined its optimal administration schedule. Observational studies have demonstrated increased adverse events associated with the use of morphine sulfate in patients with ACS and acute decompensated HF (232, 233, 236). Although these reports were observational, uncontrolled studies limited by selection bias, they raised important safety concerns.

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

Traditional NSAIDs and selective cyclooxygenase (COX)-2 inhibitors markedly block endothelial prostacyclin production, which leads to unopposed platelet aggregation by platelet-derived thromboxane A₂. Both types of NSAIDs prevent the beneficial actions of aspirin and interfere with the inhibition of COX-1, thromboxane A₂ production, and platelet aggregation. Because of their inhibitory activity on the ubiquitous COXs, NSAIDs have an extensive adverse side effect profile, particularly renal and gastrointestinal. The increased cardiovascular hazards associated with NSAIDs have been observed in several studies of patients without ACS (234, 235, 237, 238). The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen Or Naproxen) trial, in progress at the time of publication, is the first study of patients with high cardiovascular risk who are receiving long-term treatment with a selective COX-2 inhibitor or traditional NSAIDs. PRECISION will examine the relative cardiovascular safety profiles of celecoxib, ibuprofen, and naproxen in patients without ACS (239).

See [Online Data Supplement 10](#) for additional information on analgesic therapy.

4.1.2.3. Beta-Adrenergic Blockers: Recommendations

Class I

1. Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) (240-242). (*Level of Evidence: A*)
2. In patients with concomitant NSTEMI-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 NSTEMI-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 NSTEMI-ACS (241, 243). (Level of Evidence: C)**

Class III: Harm

1. **Administration of intravenous beta blockers is potentially harmful in patients with NSTEMI-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 mm Hg, and late presentation (244). In patients with LV dysfunction (LVEF <0.40) with or without pulmonary congestion, beta blockers are strongly recommended before discharge. Beta blockers should be used prudently with ACE inhibitors or angiotensin-receptor blockers (ARBs) in patients with HF. Renin-angiotensin-aldosterone system blocking agents should be cautiously added in patients with decompensated HF (246). Beta blockers without intrinsic sympathomimetic activity should be used, especially beta-1 blockers such as sustained-release metoprolol succinate, bisoprolol, or carvedilol, a beta-1 and alpha-1 blocker. This is because of their mortality benefit in patients with HF and systolic dysfunction (246, 247). In patients with chronic obstructive lung disease or a history of asthma, beta blockers are not contraindicated in the absence of active bronchospasm. Beta-1 selective beta blockers are preferred and should be initiated at a low dosage.

See [Online Data Supplement 11](#) for additional information on beta blockers, including risk factors for shock.

4.1.2.4. Calcium Channel Blockers: Recommendations

Class I

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

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

Class III: Harm

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

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

See [Online Data Supplement 12](#) for additional information on CCBs.

4.1.2.5. Other Anti-Ischemic Interventions

Ranolazine

Ranolazine is an antianginal medication with minimal effects on heart rate and BP (260, 261). It inhibits the late inward sodium current and reduces the deleterious effects of intracellular sodium and calcium overload that accompany myocardial ischemia (262). Ranolazine is currently indicated for treatment of chronic angina. The MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombosis In Myocardial Infarction) 36 trial examined the efficacy and safety of ranolazine in 6,560 patients with NSTE-ACS who presented within 48 hours of ischemic symptoms (263). In a post hoc analysis in women, ranolazine was associated with a reduced incidence of the primary endpoint (cardiovascular death, MI, or recurrent ischemia), principally due to a 29% reduction in recurrent ischemia (116). In the subgroup with prior chronic angina (n=3,565), ranolazine was associated with a lower primary composite endpoint, a significant reduction of worsening angina, and increased exercise duration (264). Because the primary endpoint of the original MERLIN-TIMI 36 trial was not met, all additional analyses should be interpreted with caution. The recommended initial dose is 500 mg orally twice daily, which can be uptitrated to a maximum of 1,000 mg orally twice daily. Ranolazine is usually well tolerated; its major adverse effects are constipation, nausea, dizziness, and headache. Ranolazine prolongs the QTc interval in a dose-related manner,

but QTc prolongation requiring dose reduction was comparable with ranolazine and placebo in the MERLIN-TIMI 36 trial (263).

See [Online Data Supplement 13](#) for additional information on ranolazine.

Intra-Aortic Balloon Pump (IABP) Counterpulsation

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



4.1.2.6. Cholesterol Management

Class I

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

Class IIa

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

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

Table 6. Summary of Recommendations for Early Hospital Care

Recommendations	COR	LOE	References
Oxygen			
Administer supplemental oxygen only with oxygen saturation $< 90\%$, respiratory distress, or other high-risk features for hypoxemia	I	C	N/A
Nitrates			
Administer sublingual NTG every 5 min $\times$ 3 for continuing ischemic pain and then assess need for IV NTG	I	C	(216-218)
Administer IV NTG for persistent ischemia, HF, or hypertension	I	B	(219-224)
Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor	III: Harm	B	(225-227)

Analgesic therapy			
IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications	IIb	B	(232, 233)
NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTEMI-ACS because of the increased risk of MACE associated with their use	III: Harm	B	(234, 235)
Beta-adrenergic blockers			
Initiate oral beta blockers within the first 24 h in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade	I	A	(240-242)
Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant NSTEMI-ACS, stabilized HF, and reduced systolic function	I	C	N/A
Re-evaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers	I	C	N/A
It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTEMI-ACS	IIa	C	(241, 243)
IV beta blockers are potentially harmful when risk factors for shock are present	III: Harm	B	(244)
CCBs			
Administer initial therapy with nondihydropyridine CCBs with recurrent ischemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 s, or second- or third-degree atrioventricular block without a cardiac pacemaker	I	B	(248-250)
Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications	I	C	N/A
CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects*	I	C	N/A
Long-acting CCBs and nitrates are recommended for patients with coronary artery spasm	I	C	N/A
Immediate-release nifedipine is contraindicated in the absence of a beta blocker	III: Harm	B	(251, 252)
Cholesterol management			
Initiate or continue high-intensity statin therapy in patients with no contraindications	I	A	(269-273)
Obtain a fasting lipid profile, preferably within 24 h	IIa	C	N/A

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

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

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

Class I

1. ACE inhibitors should be started and continued indefinitely in all patients with LVEF less than 0.40 and in those with hypertension, diabetes mellitus, or stable CKD (Section 7.6), unless contraindicated (275, 276). (Level of Evidence: A)
2. ARBs are recommended in patients with HF or MI with LVEF less than 0.40 who are ACE inhibitor intolerant (277, 278). (Level of Evidence: A)
3. Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who

are receiving therapeutic doses of ACE inhibitor and beta blocker and have a LVEF 0.40 or less, diabetes mellitus, or HF (279). (*Level of Evidence: A*)

Class IIa

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

Class IIb

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

ACE inhibitors reduce mortality in patients with recent MI, primarily those with LV dysfunction (LVEF <0.40) with or without pulmonary congestion (283-285). In patients with normal LV function (including patients with diabetes mellitus), total mortality and MACE (including HF) are reduced. It has been found that approximately 15% of patients with NSTEMI develop HF during hospitalization, with the rate increasing to 24% of patients 1 year later (286). A meta-analysis demonstrated a small but significant (0.48%) absolute benefit of early initiation of an ACE inhibitor on survival at 30 days, with benefit seen as early as 24 hours after admission for AMI (283). An ACE inhibitor should be used cautiously in the first 24 hours of AMI, because it may result in hypotension or renal dysfunction (283). It may be prudent to initially use a short-acting ACE inhibitor, such as captopril or enalapril, in patients at increased risk of these adverse events. In patients with significant renal dysfunction, it is sensible to stabilize renal function before initiating an ACE inhibitor or an ARB, with re-evaluation of creatinine levels after drug initiation. An ARB may be substituted for an ACE inhibitor with similar benefits on survival (277, 278). Combining an ACE inhibitor and an ARB may result in an increase in adverse events (277, 278). In a study in which patients with AMI with LV dysfunction (LVEF <0.40) with or without HF were randomized 3 to 14 days after AMI to receive eplerenone (a selective aldosterone blocker), eplerenone was efficacious as an adjunct to ACE inhibitors and beta blockers in decreasing long-term mortality (279, 287). In a study of patients with HF, >50% of whom had an ischemic etiology, spironolactone (a nonselective aldosterone inhibitor) was beneficial (279); however, RCT data on MI are not available.

See [Online Data Supplement 14](#) for additional information on inhibitors of renin-angiotensin-aldosterone system.

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

4.3.1. Initial Oral and Intravenous Antiplatelet Therapy in Patients With Definite or Likely NSTEMI-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 NSTEMI-ACS treated with an early invasive or an ischemia-guided strategy.

Class I[‡]

1. **Non-enteric-coated, chewable aspirin (162 mg to 325 mg) should be given to *all* patients with NSTEMI-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 mg/d to 162 mg/d) should be continued indefinitely (288-290). (Level of Evidence: A)**
2. **In patients with NSTEMI-ACS who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered (291). (Level of Evidence: B)**
3. **A P2Y₁₂ inhibitor (either clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTEMI-ACS without contraindications who are treated with either an early invasive[§] or ischemia-guided strategy. Options include:**
 - **Clopidogrel: 300-mg or 600-mg loading dose, then 75 mg daily (289, 292) (Level of Evidence: B)**
 - **Ticagrelor^{||}: 180-mg loading dose, then 90 mg twice daily (293, 294) (Level of Evidence: B)**

Class IIa

1. **It is reasonable to use ticagrelor in preference to clopidogrel for P2Y₁₂ treatment in patients with NSTEMI-ACS who undergo an early invasive or ischemia-guided strategy (293, 294). (Level of Evidence: B)**

Class IIb

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

Despite the large number of new antiplatelet and antithrombotic agents, aspirin, which targets COX and subsequent thromboxane 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 thienopyridine prodrug 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, eptifibatide, and tirofiban, target the final common pathway of platelet aggregation. In the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome) trial, patients were randomly assigned to either early, pre-PCI double-bolus eptifibatide or delayed, provisional eptifibatide. Seventy-five percent of the patients received upstream, preprocedure clopidogrel. The risk of TIMI major bleeding in the early eptifibatide group was 2.6% compared with 1.8% (p=0.02) in the delayed provisional group (295). In the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV-Acute Coronary Syndromes) trial, there was no clinical benefit of abciximab in this population; in troponin-negative patients, mortality was 8.5% compared with 5.8 % in controls (p=0.002) (288, 289, 296, 297).

[‡]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).

4.3.1.1. 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; patients treated with ticagrelor should receive only 81 mg per day (290). High-dose (≥ 160 mg) versus low-dose (< 160 mg) aspirin is associated with increased bleeding risk in the absence of improved outcomes (298). Most NSAIDs reversibly bind to COX-1, preventing inhibition by aspirin and by COX-2 and may cause prothrombotic effects. Enteric-coated aspirin should be avoided initially because of its delayed and reduced absorption (299).

4.3.1.2. P2Y₁₂ Receptor Inhibitors

Three P2Y₁₂ receptor inhibitors are approved in the United States for treatment of ischemic myocardial disorders, including NSTE-ACS. For discontinuation before surgery, see Section 5.

Clopidogrel

Administration of clopidogrel with aspirin was superior to administration of aspirin alone in reducing the incidence of cardiovascular death and nonfatal MI or stroke both acutely and over the following 11 months (289, 296). There was a slight increase in major bleeding events with clopidogrel, including a nonsignificant increase in life-threatening bleeding and fatal bleeding (289). An initial loading dose of 300 mg to 600 mg is recommended (289, 296, 300). A 600-mg loading dose results in a greater, more rapid, and more reliable platelet inhibition compared with a 300-mg loading dose (301). Use of clopidogrel for patients with NSTE-ACS who are aspirin intolerant is based on a study in patients with stable ischemic heart disease (291). When possible, discontinue clopidogrel at least 5 days before surgery (301).

Prasugrel

The metabolic conversion pathways of prasugrel produce more rapid and consistent platelet inhibition than clopidogrel (300). In patients with NSTE-ACS and defined coronary anatomy undergoing planned PCI, a 60-mg loading dose of prasugrel followed by 10 mg daily was compared with a 300-mg loading dose and 75 mg daily of clopidogrel. The composite primary endpoint (cardiovascular death, nonfatal MI, and stroke) was reduced in patients treated with prasugrel (hazard ratio [HR]: 0.81; $p=0.001$). This was driven by a risk reduction for MI and stent thrombosis with no difference in mortality (302). Counterbalancing the salutary effects of prasugrel was a significant increase in spontaneous bleeding, life-threatening bleeding, and fatal bleeding in the patients treated with prasugrel compared with patients treated with clopidogrel. There was net harm in patients with a history of cerebrovascular events and no clinical benefit in patients > 75 years of age or those with low body weight (< 60 kg) (302). In patients with NSTE-ACS treated with an ischemia-guided strategy, 1 RCT comparing aspirin and either clopidogrel or prasugrel evaluated the primary endpoint of death from cardiovascular causes, MI, or stroke for up to 30 months; there were similar bleeding rates and no benefit of treatment with prasugrel when compared with treatment with clopidogrel (303). The ACCOAST (A Comparison of Prasugrel at the Time

of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non-ST-Elevation Myocardial Infarction) RCT of high-risk patients with NSTEMI-ACS scheduled to undergo early coronary angiography found that a strategy of administration of prasugrel at the time of randomization before angiography did not lead to a reduction in the composite primary endpoint when compared with a strategy of administration of prasugrel only at the time of PCI; however, it did lead to an increase in bleeding complications (304). On the basis of TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study design and the results of TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) and ACCOAST, prasugrel is not recommended for “upfront” therapy in patients with NSTEMI-ACS. The use of prasugrel in patients undergoing PCI is addressed in Section 5.

Ticagrelor

Ticagrelor is an oral, reversibly binding P2Y₁₂ inhibitor with a relatively short plasma half-life (12 hours). Compared with clopidogrel, ticagrelor has a more rapid and consistent onset of action and, because it is reversible, it has a faster recovery of platelet function. The loading dose of ticagrelor for patients treated either invasively or with an ischemia-guided strategy is 180 mg followed by a maintenance dose of 90 mg twice daily (293, 294). In patients with NSTEMI-ACS treated with ticagrelor compared with clopidogrel, there was a reduction in the composite outcome of death from vascular causes, MI, or stroke (reduction: 11.7% to 9.8%; HR: 0.84; $p < 0.001$) (293). The mortality rate was also lower in those patients treated with ticagrelor. Although overall major bleeding was not increased with ticagrelor, a modest increase in major bleeding and non-procedure-related bleeding occurred in the subgroup of patients who did not undergo CABG (major bleeding: 4.5% versus 3.8%; $p = 0.02$; nonprocedure major bleeding: 3.1% versus 2.3%; $p = 0.05$); however, there was no difference in blood transfusion or fatal bleeding (305). Side effects unique to ticagrelor include dyspnea (which occurs in up to 15% of patients within the first week of treatment but is rarely severe enough to cause discontinuation of treatment) (293) and bradycardia. The benefit of ticagrelor over clopidogrel was limited to patients taking 75 mg to 100 mg of aspirin (290). The short half-life requires twice-daily administration, which could potentially result in adverse events in noncompliant patients, particularly after stent implantation. When possible, ticagrelor should be discontinued at least 5 days before surgery (306). Although ticagrelor has not been studied in the absence of aspirin, its use in aspirin-intolerant patients is a reasonable alternative.

Intravenous GP IIb/IIIa Receptor Inhibitors

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

Several large RCTs evaluated the impact of GP IIb/IIIa receptor inhibitors in patients with NSTEMI-ACS who were committed to an invasive strategy (295, 296, 306). The ACUTY (Acute Catheterization and Urgent

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

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

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

Class I[‡]

1. In patients with NSTEMI-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 is 30 mg (133, 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 4,000 IU) with initial infusion of 12 IU/kg per hour (maximum 1,000 IU/h) adjusted per activated partial thromboplastin time to

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

maintain therapeutic anticoagulation according to the specific hospital protocol, continued for 48 hours or until PCI is performed (316-322). (Level of Evidence: B)

4.3.2.1. Low-Molecular-Weight Heparin

LMWHs have a molecular weight approximately one third that of UFH and have balanced anti-Xa and anti-IIa activity. LMWHs are readily absorbed after subcutaneous administration and have less platelet activation (323). The anticoagulant activity of LMWH does not require routine monitoring. The dose of enoxaparin is 1 mg/kg SC every 12 hours for NSTEMI-ACS; an initial intravenous loading dose is 30 mg. In the presence of impaired renal function ($\text{CrCl} < 30$ 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 NSTEMI-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 ACUTY trial, a randomized open-label trial, in 13,819 moderate- to high-risk patients with NSTEMI-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 NSTEMI-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 NSTEMI-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 NSTEMI-ACS were performed primarily on patients with a diagnosis of “unstable angina” in the era before DAPT and early catheterization and revascularization. In general, those studies found a strong trend for reduction in composite adverse events with the addition of parenteral UFH to aspirin therapy (316-322).

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

4.3.2.5. Argatroban

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

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

Class III: Harm

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

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

See [Online Data Supplement 17](#) for additional information on parenteral anticoagulant and fibrinolytic therapy in patients with definite NSTEMI-ACS.

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

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.

Recommendations	Dosing and Special Considerations	COR	LOE	References
Aspirin				
• Non-enteric-coated aspirin to <i>all</i> patients promptly after presentation	162 mg–325 mg	I	A	(288–290)
• Aspirin maintenance dose continued indefinitely	81 mg/d–162 mg/d	I	A	(288–290)
P2Y₁₂ inhibitors				
• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B	(291)
• P2Y ₁₂ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: – Clopidogrel – Ticagrelor*	300-mg or 600-mg loading dose, then 75 mg/d	I	B	(289, 292)
	180-mg loading dose, then 90 mg BID			(293, 294)
• P2Y ₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	N/A	I	B	(293, 296, 302, 330, 331)
• Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B	(293, 294)
GP IIb/IIIa inhibitors				
• GP IIb/IIIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin)	• Preferred options are eptifibatide or tirofiban	IIb	B	(43, 94, 295)
Parenteral anticoagulant and fibrinolytic therapy				
• SC enoxaparin for duration of hospitalization or until PCI is performed	• 1 mg/kg SC every 12 h (reduce dose to 1 mg/kg/d SC in patients with CrCl <30 mL/min) • Initial IV loading dose 30 mg	I	A	(133, 136, 309)
• Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only	• Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h	I	B	(292, 293, 310, 311)

	• Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT			
• SC fondaparinux for the duration of hospitalization or until PCI is performed	• 2.5 mg SC daily	I	B	(312-314)
• Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux	N/A	I	B	(313-315)
• IV UFH for 48 h or until PCI is performed	• Initial loading dose 60 IU/kg (max 4,000 IU) with initial infusion 12 IU/kg/h (max 1,000 IU/h) • Adjusted to therapeutic aPTT range	I	B	(316-322)
• IV fibrinolytic treatment not recommended in patients with NSTEMI-ACS	N/A	III: Harm	A	(93, 329)

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

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

4.4. Ischemia-Guided Strategy Versus Early Invasive Strategies

See Figure 3 for the management algorithm for ischemia-guided versus early invasive strategy.

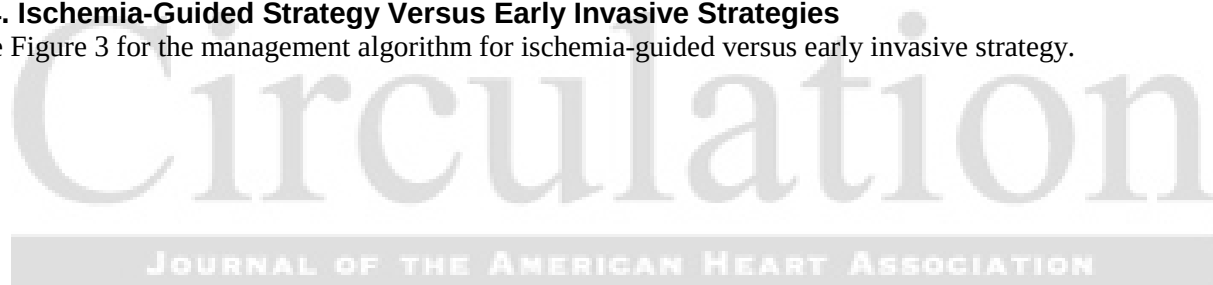
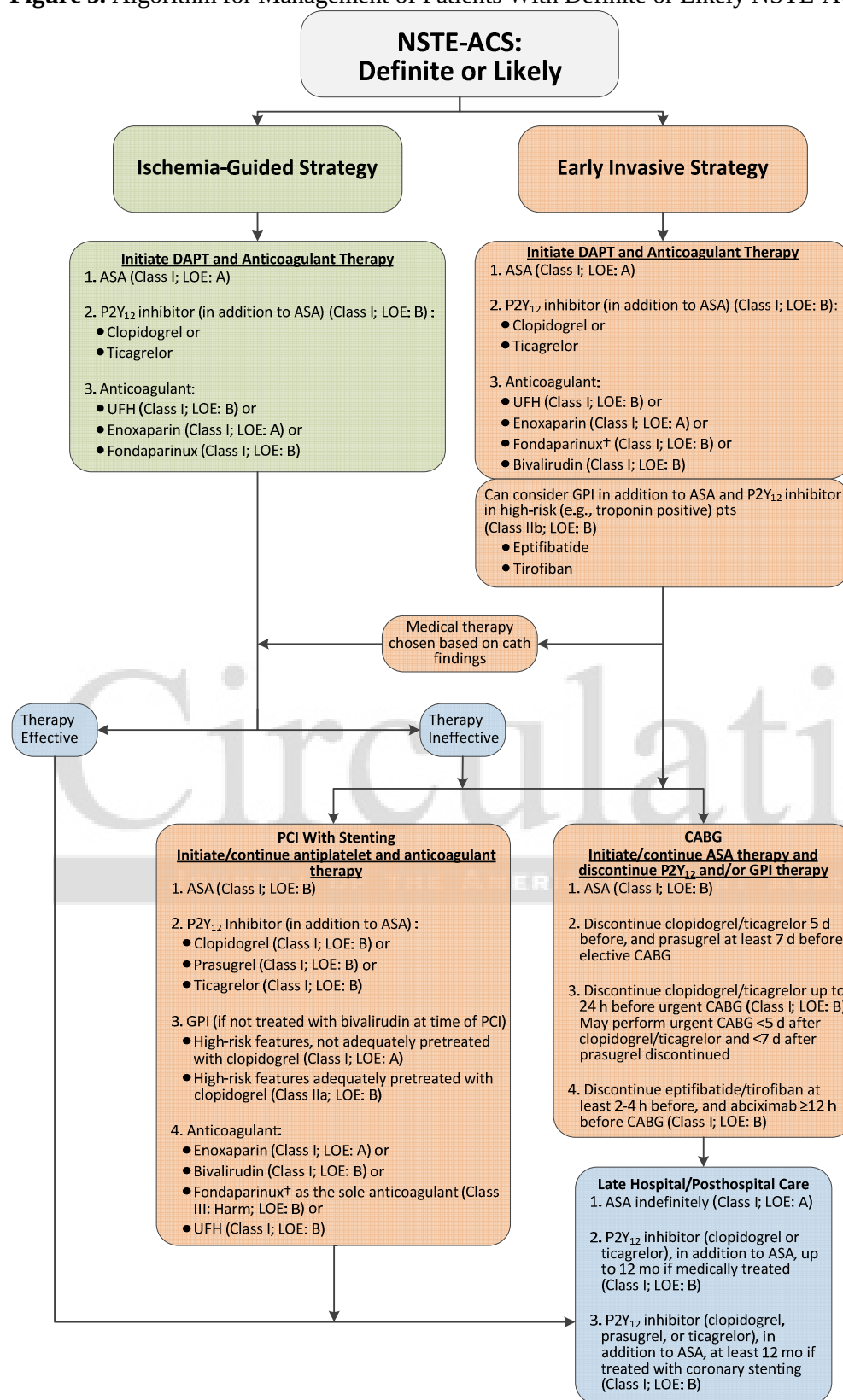


Figure 3. Algorithm for Management of Patients With Definite or Likely NSTE-ACS*



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

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

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

4.4.1. General Principles

Two treatment pathways have emerged for all patients with NSTE-ACS. The invasive strategy triages patients to an invasive diagnostic evaluation (i.e., coronary angiography). In contrast, the initial ischemia-guided strategy calls for an invasive evaluation for those patients who 1) fail medical therapy (refractory angina or angina at rest or with minimal activity despite vigorous medical therapy), 2) have objective evidence of ischemia (dynamic electrocardiographic changes, myocardial perfusion defect) as identified on a noninvasive stress test, or 3) have clinical indicators of very high prognostic risk (e.g., high TIMI or GRACE scores). In both strategies, patients should receive optimal anti-ischemic and antithrombotic medical therapy as outlined in Section 4.1. A subgroup of patients with refractory ischemic symptoms or hemodynamic or rhythm instability are candidates for urgent coronary angiography and revascularization.



4.4.2. Rationale and Timing for Early Invasive Strategy

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

4.4.2.1. Routine Invasive Strategy Timing

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

4.4.3. Rationale for Ischemia-Guided Strategy

The ischemia-guided strategy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability. When the ischemia-guided strategy is chosen, a plan for noninvasive evaluation is required to detect severe ischemia that occurs at a low threshold of stress and to promptly refer these patients for coronary angiography and revascularization as indicated. The major advantage offered by the ischemia-guided strategy is that some patients' conditions

stabilize during medical therapy and will not require coronary angiography and revascularization. Consequently, the ischemia-guided strategy may potentially avoid costly and possibly unnecessary invasive procedures.

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

Class IIa

1. It is reasonable to choose an early invasive strategy (within 24 hours of admission) over a delayed invasive strategy (within 25 to 72 hours) for initially stabilized high-risk patients with NSTEMI-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 NSTEMI-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events (333, 334, 338). (*Level of Evidence: B*)
2. The decision to implement an ischemia-guided strategy in initially stabilized patients (without serious comorbidities or contraindications to this approach) may be reasonable after considering clinician and patient preference. (*Level of Evidence: C*)

Class III: No Benefit

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

Several studies (93, 138, 334-337) and meta-analyses (141, 340) have concluded that a strategy of routine invasive therapy is generally superior to an ischemia-guided strategy or selectively invasive approach. One study reported that the routine invasive strategy resulted in an 18% relative reduction in death or MI, including a significant reduction in MI alone (341). The routine invasive arm was associated with higher in-hospital mortality (1.8% versus 1.1%), but this disadvantage was more than compensated for by a significant reduction in mortality between discharge and the end of follow-up (3.8% versus 4.9%). The invasive strategy was also associated with less angina and fewer rehospitalizations. Patients undergoing routine invasive treatment also had

[†]See Section 7.7 for additional information on women.

improved quality of life. In an analysis of individual patient data (340) that reported 5-year outcomes from the FRISC (Framingham and Fast Revascularization During Instability in Coronary Artery Disease)-II trial (339), ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial (338), and RITA (Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina)-3 trial (334), 14.7% of patients (389 of 2,721) randomized to a routine invasive strategy experienced cardiovascular death or nonfatal MI versus 17.9% of patients (475 of 2,746) in the selective invasive strategy (HR: 0.81; 95% CI: 0.71 to 0.93; $p=0.002$). The most marked treatment effect was on MI (10.0% routine invasive strategy versus 12.9% selective invasive strategy), and there were consistent trends for fewer cardiovascular deaths (HR: 0.83; 95% CI: 0.68 to 1.01; $p=0.068$) and all-cause mortality (HR: 0.90; 95% CI: 0.77 to 1.05). There were absolute reductions of 2.0% to 3.8% in cardiovascular death or MI in the low- and intermediate-risk groups and an 11.1% absolute risk reduction in the highest-risk patients. The invasive strategy demonstrated its greatest advantage in the highest-risk stratum of patients with no significant benefit on mortality over the noninvasive approach in moderate- and low-risk patients (342). An ischemia-guided strategy has been used with favorable results in initially stabilized patients with NSTEMI-ACS at elevated risk for clinical events, including those with positive troponin levels (338). One limitation of these studies is the absence of adherence to optimal medical therapy in noninvasively treated patients during long-term management. In addition, in FRISC-II, invasive management was delayed and patients with markedly positive stress tests (up to 2.9-mm exercise-induced ST depression) were randomized to noninvasive or invasive therapy (338).

Table 8. Factors Associated With Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients With NSTEMI-ACS

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

CABG indicates coronary artery bypass graft; EF, ejection fraction; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; NSTEMI-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.

See [Online Data Supplement 18](#) for additional information on comparison of early invasive strategy and ischemia-guided strategy.

4.4.4.1. Comparison of Early Versus Delayed Angiography

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

See [Online Data Supplement 19](#) for additional information on comparison of early versus delayed angiography.

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

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

4.4.6. Care Objectives

Coronary angiography is designed to provide detailed information about the size and distribution of coronary vessels, the location and extent of atherosclerotic obstruction, and the suitability for revascularization. The LV angiogram, usually performed with coronary angiography, provides an assessment of the extent of focal and global LV dysfunction and of the presence and severity of coexisting disorders (e.g., valvular or other associated

lesions). Patients with NSTE-ACS can be divided into risk groups on the basis of their initial clinical presentation. The TIMI, PURSUIT, and GRACE scores are useful tools for assigning risk to patients with NSTE-ACS.

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

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

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

Class I

1. **Noninvasive stress testing is recommended in low- and intermediate-risk patients who have been free of ischemia at rest or with low-level activity for a minimum of 12 to 24 hours (349-353). (Level of Evidence: B)**
2. **Treadmill exercise testing is useful in patients able to exercise in whom the ECG is free of resting ST changes that may interfere with interpretation (349-352). (Level of Evidence: C)**
3. **Stress testing with an imaging modality should be used in patients who are able to exercise but have ST changes on resting ECG that may interfere with interpretation. In patients undergoing a low-level exercise test, an imaging modality can add prognostic information (349-352). (Level of Evidence: B)**
4. **Pharmacological stress testing with imaging is recommended when physical limitations preclude adequate exercise stress. (Level of Evidence: C)**
5. **A noninvasive imaging test is recommended to evaluate LV function in patients with definite ACS (349-352). (Level of Evidence: C)**

The management of patients with NSTE-ACS requires continuous risk stratification. Important prognostic information is derived from initial assessment, the patient's course during the early days of management, and the response to anti-ischemic and antithrombotic therapy. The choice of stress test is based on the patient's resting ECG and ability to exercise, local expertise, and available technologies. The exercise intensity of the treadmill test (low level or symptom-limited) is used at the discretion of the attending clinician based on individual patient

assessment. For invasively managed patients with residual nonculprit lesions, additional evaluation may be indicated to ascertain the significance of such lesions. Refer to the PCI CPG for additional details (26).

4.5.1. Noninvasive Test Selection

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

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

4.5.2. Selection for Coronary Angiography

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

The general indications for coronary angiography and revascularization should be tempered by individual patient characteristics and preferences (a patient-centered approach). Patient and clinician judgments about risks and benefits are important for patients who might not be candidates for coronary revascularization, such as very frail older adults and those with serious comorbid conditions (e.g., severe hepatic, pulmonary, or renal failure; active or inoperable cancer).

See [Online Data Supplement 20](#) for additional information on risk stratification.

5. Myocardial Revascularization

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

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

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

See [Online Data Supplements 21 and 22](#) for additional information on myocardial revascularization.

5.1. Percutaneous Coronary Intervention

5.1.1. PCI—General Considerations: Recommendation

Class IIb

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

Approximately half of all PCI procedures are performed in patients with UA or NSTEMI, and approximately 32% to 40% of patients with NSTEMI-ACS will undergo PCI (365). As discussed previously, in patients with NSTEMI-ACS, a strategy of early angiography and revascularization (primarily with PCI) results in lower rates of recurrent UA, recurrent rehospitalization, MI, and death (366, 367). Although PCI of a nonculprit lesion is not advocated in patients with STEMI (26), there is less agreement on whether nonculprit lesions should undergo intervention at the time of culprit-lesion PCI for NSTEMI-ACS. Most reports (359-364), but not all (330),

comparing culprit lesion-only PCI with multivessel PCI (e.g., PCI of multiple vessels performed at the same time) in patients with NSTE-ACS did not find an increased risk of MACE with multivessel PCI and found a reduction in the need for repeat revascularization. However, the data consist predominantly of post hoc analysis of nonrandomized data with variable duration of follow-up. This question has not been resolved and is an area of current investigation.

5.1.2. PCI—Antiplatelet and Anticoagulant Therapy

5.1.2.1. Oral and Intravenous Antiplatelet Agents: Recommendations

Class I

1. Patients already taking daily aspirin before PCI should take 81 mg to 325 mg non-enteric-coated aspirin before PCI (26, 368-370). (*Level of Evidence: B*)
2. Patients not on aspirin therapy should be given non-enteric-coated aspirin 325 mg as soon as possible before PCI (26, 368-370). (*Level of Evidence: B*)
3. After PCI, aspirin should be continued indefinitely at a dose of 81 mg to 325 mg daily (27, 288, 371). (*Level of Evidence: B*)
4. A loading dose of a P2Y₁₂ receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting (26, 293, 302, 331, 372-375). (*Level of Evidence: A*) Options include:
 - a. Clopidogrel: 600 mg (331, 372-374, 376-378) (*Level of Evidence: B*) or
 - b. Prasugrel[#]: 60 mg (302) (*Level of Evidence: B*) or
 - c. Ticagrelor^{||}: 180 mg (293) (*Level of Evidence: B*)
5. In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI (379-382). (*Level of Evidence: A*)
6. In patients receiving a stent (bare-metal stent or drug-eluting stent [DES]) during PCI for NSTE-ACS, P2Y₁₂ inhibitor therapy should be given for at least 12 months (330). Options include:
 - a. Clopidogrel: 75 mg daily (296, 331) (*Level of Evidence: B*) or
 - b. Prasugrel[#]: 10 mg daily (302) (*Level of Evidence: B*) or
 - c. Ticagrelor^{||}: 90 mg twice daily (293) (*Level of Evidence: B*)

Class IIa

1. It is reasonable to choose ticagrelor over clopidogrel for P2Y₁₂ inhibition treatment in patients with NSTE-ACS treated with an early invasive strategy and/or coronary stenting (293, 294). (*Level of Evidence: B*)
2. It is reasonable to choose prasugrel over clopidogrel for P2Y₁₂ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications (302, 303). (*Level of Evidence: B*)
3. In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI (195, 383, 384). (*Level of Evidence: B*)
4. After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses (331, 368, 385-388). (*Level of Evidence: B*)

[#]Patients should receive a loading dose of prasugrel, provided that they were not pretreated with another P2Y₁₂ receptor inhibitor.

^{||}The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

5. **If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of P2Y₁₂ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <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)**

Class III: Harm

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

Comprehensive recommendations on the use of antiplatelet and anticoagulant therapy in patients with NSTE-ACS undergoing PCI are given in the 2011 PCI CPG (26). Aspirin reduces the frequency of ischemic complications after PCI and is ideally administered at least 2 hours, and preferably 24 hours, before PCI (26, 368, 369). DAPT, consisting of aspirin and a P2Y₁₂ inhibitor, in patients treated with coronary stents reduces the risk of stent thrombosis and composite ischemic events (296, 331, 372-375, 389, 390). Compared with a loading dose of 300 mg of clopidogrel, a loading dose of 600 mg of clopidogrel in patients undergoing PCI achieves greater platelet inhibition with fewer low responders and decreases the incidence of MACE (376-378). In patients with ACS who have undergone coronary stenting, treatment with prasugrel or ticagrelor, compared with treatment with clopidogrel, results in a greater reduction in composite ischemic events and the incidence of stent thrombosis, although at a risk of increased non-CABG bleeding (293, 302). The optimal duration of DAPT therapy in patients treated with DES is not well established (26). However, aspirin is continued indefinitely in all patients managed with a bare-metal stent or DES, and DAPT is an option for >12 months in patients who have received a DES. This determination should balance the risks of stent thrombosis and ischemic complications versus bleeding and should be jointly made by the clinician and the patient.

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

Patients undergoing PCI who have previously received a loading dose of 300 mg of clopidogrel and are on a 75-mg daily maintenance dose should receive another 300-mg loading dose (315). There are no data

appropriate for prasugrel because this drug is administered before PCI. For ticagrelor, there are no data on additional loading.

5.1.2.2. GP IIb/IIIa Inhibitors: Recommendations

Class I

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

Class IIa

1. In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately 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 (195, 383). (*Level of Evidence: B*)

GP IIb/IIIa receptor antagonist therapy in patients with NSTE-ACS undergoing PCI reduced the incidence of composite ischemic events, primarily through a decrease in documented MI, although in some trials this is counterbalanced by an increased rate of bleeding (193, 195, 310, 379-382, 392). Most, but not all, randomized trials of the use of GP IIb/IIIa inhibitor were conducted in the era before clopidogrel therapy (193, 195, 310, 379-383, 392). Abciximab, double-bolus eptifibatide, and high-bolus dose tirofiban result in a high degree of platelet inhibition, reduce ischemic complications in patients undergoing PCI, and appear to afford comparable angiographic and clinical outcomes (26). As trials of the GP IIb/IIIa inhibitors generally excluded patients at high risk of bleeding, recommendations for the use of GP IIb/IIIa inhibitors are best understood as applying to patients not at high risk of bleeding complications. Although GP IIb/IIIa inhibitors were used in 27% and 55% of patients, respectively, in the PLATO (Platelet Inhibition and Patient Outcomes) and TRITON studies of ticagrelor and prasugrel, there are insufficient data (293, 302, 393) (and no RCT data) from which to make specific recommendations about GP IIb/IIIa inhibitor use in patients treated with either of these 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, 394-398). (*Level of Evidence: B*)
4. An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than 2 therapeutic subcutaneous doses (e.g., 1 mg/kg SC) or received the last subcutaneous enoxaparin dose 8 to 12 hours before PCI (309, 399-403). (*Level of Evidence: B*)
5. If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60)

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

6. In patients with NSTEMI-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 NSTEMI-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 NSTEMI-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 NSTEMI-ACS due to an increased risk of catheter thrombosis (26, 313-315). (*Level of Evidence: B*)

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

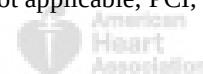
Table 9. Dosing of Parenteral Anticoagulants During PCI

Drug*	In Patients Who Have Received Prior Anticoagulant Therapy	In Patients Who Have Not Received Prior Anticoagulant Therapy
Enoxaparin	- For prior treatment with enoxaparin, if last SC dose was administered 8–12 h earlier or if <2 therapeutic SC doses of enoxaparin have been administered, an IV dose of enoxaparin 0.3 mg/kg should be given - If the last SC dose was administered within prior 8 h, no additional enoxaparin should be given	0.5 mg/kg–0.75 mg/kg IV loading dose

Bivalirudin	- For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV loading dose, then 1.75 mg/kg/h IV infusion - For patients already receiving bivalirudin infusion, give additional loading dose 0.5 mg/kg and increase infusion to 1.75 mg/kg/h during PCI	0.75 mg/kg loading dose, 1.75 mg/kg/h IV infusion
Fondaparinux	For prior treatment with fondaparinux, administer additional IV treatment with anticoagulant possessing anti-IIa activity, considering whether GPI receptor antagonists have been administered	N/A
UFH	- IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve ACT of 200–250 s - No IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve ACT of 250–300 s for HemoTec, 300–350 s for Hemochron	- IV GPI planned: 50–70 U/kg loading dose to achieve ACT of 200–250 s - No IV GPI planned: 70–100 U/kg loading dose to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron

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

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



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

Class I

1. Non-enteric-coated aspirin (81 mg to 325 mg daily) should be administered preoperatively to patients undergoing CABG (408–410). (*Level of Evidence: B*)
2. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (23, 411–413) (*Level of Evidence: B*) and prasugrel for at least 7 days before surgery (8, 414). (*Level of Evidence: C*)
3. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding (8, 412, 415–417). (*Level of Evidence: B*)
4. In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery (418, 419) and abciximab for at least 12 hours before to limit blood loss and transfusion (389). (*Level of Evidence: B*)

Class IIb

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

In-hospital CABG is performed in 7% to 13% of patients hospitalized with NSTEMI-ACS (420–422).

Approximately one third of patients with NSTEMI undergo CABG within 48 hours of hospital admission (421). In these patients, CABG was performed at a median time of 73 hours after admission (interquartile range: 42 to 122) (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 NSTEMI-ACS is associated with an increase in post-CABG bleeding and the need for transfusion (293, 302, 411, 413, 423-425). Although it is recommended that clopidogrel and ticagrelor be discontinued at least 5 days before surgery and prasugrel at least 7 days before surgery in patients referred for elective CABG (23, 411-413), the timing of CABG in patients with NSTEMI-ACS treated with a P2Y₁₂ inhibitor (330) should reflect a balance of the potential increase in bleeding against the potential benefits of not delaying surgery 5 to 7 days. The risk of major bleeding complications is increased when CABG is performed <24 hours after discontinuation of clopidogrel (23, 416, 417). In patients who undergo CABG 1 to 4 days after discontinuation of clopidogrel, it appears that the incidence of life-threatening bleeding is not significantly increased, but an increase in blood transfusions is likely (23, 415, 416, 425, 426). In the TRITON-TIMI 38 trial (302), the incidence of CABG-related major bleeding was higher in patients treated with prasugrel than in patients treated with clopidogrel (23, 386). In the PLATO trial, the rates of major bleeding and transfusion requirements were similar between patients treated with ticagrelor and patients treated with clopidogrel (294). The more rapid recovery of platelet function in pharmacokinetic studies of ticagrelor did not translate to a lower risk of bleeding or lessen the need for transfusion compared with clopidogrel when CABG was performed early (i.e., <5 days) after drug discontinuation (23, 293, 412).

See [Online Data Supplements 21 and 22](#) for more information on myocardial revascularization.

6. Late Hospital Care, Hospital Discharge, and Posthospital Discharge Care

6.1. General Principles (Cardioprotective Therapy and Symptom Management)

The goals of therapy after NSTEMI-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 NSTEMI-ACS represent a high-risk cohort in whom secondary cardiovascular disease prevention is likely to be particularly effective (Table 10). Clinicians have an opportunity to provide evidence-based care to this high-risk cohort and to aggressively treat the underlying atherosclerotic process through lifestyle modification and effective pharmacological therapies (427). In most cases, the inpatient anti-ischemic medical regimen should be continued after discharge, and the antiplatelet/anticoagulant medications should be changed to an outpatient regimen. The goals for continued medical therapy after discharge relate to potential prognostic benefits (primarily shown for antiplatelet agents, beta blockers, statins, and inhibitors of the renin-angiotensin aldosterone system, especially for LVEF <0.40). Added benefits are control of ischemic symptoms (nitrates, beta blockers, CCBs, and ranolazine) and treatment of major risk factors such as smoking, hypertension, dyslipidemia, physical inactivity, obesity, and diabetes mellitus (427). Selection

of a medical regimen should be individualized to each patient based on in-hospital findings, risk factors for CAD, drug tolerability, and recent procedural interventions. The mnemonic “ABCDE” (Aspirin, Antianginals, and ACE Inhibitors; Beta Blockers and BP; Cholesterol and Cigarettes; Diet and Diabetes Mellitus; Education and Exercise) is useful in guiding treatment (428).

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

Class I

1. Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTEMI-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required (427, 428). (*Level of Evidence: C*)
2. All patients who are post-NSTEMI-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use (429). (*Level of Evidence: C*)
3. Before hospital discharge, patients with NSTEMI-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms (429). (*Level of Evidence: C*)
4. Before hospital discharge, patients who are post-NSTEMI-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use (429). (*Level of Evidence: C*)
5. For patients who are post-NSTEMI-ACS and have initial angina lasting more than 1 minute, nitroglycerin (1 dose sublingual or spray) is recommended if angina does not subside within 3 to 5 minutes; call 9-1-1 immediately to access emergency medical services (429). (*Level of Evidence: C*)
6. If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing (429). (*Level of Evidence: C*)
7. Before discharge, patients should be educated about modification of cardiovascular risk factors (428). (*Level of Evidence: C*)

6.2.1. Late Hospital and Posthospital Oral Antiplatelet Therapy: Recommendations

Class I

1. Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients (288-290). (*Level of Evidence: A*)
2. In addition to aspirin, a P2Y₁₂ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTEMI-ACS without contraindications who are treated with an ischemia-guided strategy. Options include:
 - Clopidogrel: 75 mg daily (289, 296) (*Level of Evidence: B*) or
 - Ticagrelor^{||}: 90 mg twice daily (293, 294) (*Level of Evidence: B*)
3. In patients receiving a stent (bare-metal stent or DES) during PCI for NSTEMI-ACS, P2Y₁₂ inhibitor therapy should be given for at least 12 months (330). Options include:
 - Clopidogrel: 75 mg daily (296, 331) (*Level of Evidence: B*) or
 - Prasugrel[#]: 10 mg daily (302) (*Level of Evidence: B*) or

^{||}The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

[#]Patients should receive a loading dose of prasugrel, provided they were not pretreated with another P2Y₁₂ receptor inhibitor.

^{||}The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (290).

- Ticagrelor[®]: 90 mg twice daily (293) (*Level of Evidence: B*)

Class IIa

1. It is reasonable to use an aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients with NSTEMI-ACS treated either invasively or with coronary stent implantation (26, 331, 368, 385-388). (*Level of Evidence: B*)
2. It is reasonable to choose ticagrelor over clopidogrel for maintenance P2Y₁₂ treatment in patients with NSTEMI-ACS treated with an early invasive strategy and/or PCI (293, 294). (*Level of Evidence: B*)
3. It is reasonable to choose prasugrel over clopidogrel for maintenance P2Y₁₂ treatment in patients with NSTEMI-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 (e.g., <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 NSTEMI-ACS

Class I

1. The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y₁₂ receptor inhibitor in patients with NSTEMI-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 NSTEMI-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 NSTEMI-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) (e.g., 2.0 to 2.5) may be reasonable in patients with NSTEMI-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 an approximate range of 2% to 3% to 4% to 6%, whereas the addition of DAPT to oral anticoagulant therapy ("triple therapy") increased the risk of bleeding from an approximate range of 4% to 6% to 10% to 14% (432-435). This risk was also related to the duration of triple therapy.

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

Recommendations about the management of patients treated with triple therapy have been published in ACC/AHA CPGs and by other organizations (17, 26, 430, 433, 436). Although some organizations have recommended a target INR of 2.0 to 2.5 in patients with atrial fibrillation (AF) who require triple therapy (437), others continue to recommend a target INR of 2.0 to 3.0 (436, 438). The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score has relevance in these deliberations (439). No prospective study to date has demonstrated that a target INR of 2.0 to 2.5 reduces bleeding complications.

Whenever possible, shorter durations of triple therapy are favored in preference to longer durations of triple therapy. In patients with NSTEMI-ACS who require oral anticoagulation for AF, mechanical heart valve, deep venous thrombosis, or other conditions, a bare-metal stent may offer the advantages of lower bleeding risk over a DES because of the potentially shorter duration of triple antithrombotic therapy. The WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial is the first published study to address the question of optimal antiplatelet therapy in patients taking oral anticoagulant medication (440). WOEST was a randomized, open-label trial of 563 patients (approximately 25% of whom had NSTEMI-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 NSTEMI-ACS. One such study that has been initiated is PIONEER AF-PCI (an Open-Label, Randomized, Controlled, Multicenter Study Exploring two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation who Undergo Percutaneous Coronary Intervention).

Although there are some data on therapy with aspirin, clopidogrel, and warfarin, there is sparse information on the use of newer P2Y₁₂ inhibitors (prasugrel, ticagrelor), direct thrombin inhibitor (dabigatran), or factor-Xa inhibitors (rivaroxaban, apixaban) in patients receiving triple therapy. Prasugrel (302) and ticagrelor (412) produce a greater degree of platelet inhibition than clopidogrel and are associated with greater rates of bleeding (300, 302, 412, 441). These are important potential disadvantages in patients requiring triple therapy, a group in which the inherent risks of bleeding are significantly increased. (Overall bleeding risk was not increased with ticagrelor, although there was increased bleeding in certain subgroups on this drug (412)). Because there are no well-established therapies to reverse the anticoagulant effects of the newer oral antiplatelet

agents, caution is required when considering the use of these agents in patients who require triple therapy and are at significantly increased risk of bleeding. This admonition is especially important in elderly patients, a group in which bleeding risk is inherently increased (Section 7.1).

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

6.2.3. Platelet Function and Genetic Phenotype Testing

Although higher platelet reactivity has been associated with a greater incidence of adverse events in patients undergoing stent implantation, a strategy of adjusting antiplatelet therapy based on routine platelet function testing has not been beneficial in reducing ischemic complications (26, 443-445). Similarly, a strategy of routine genetic phenotype testing has also not been beneficial and thus is not recommended (26, 446-448). A more detailed discussion of these issues and current recommendations about platelet function testing and genetic testing are in the 2011 PCI CPG (26).

6.3. Risk Reduction Strategies for Secondary Prevention

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

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

See [Online Data Supplement 23](#) for additional information on risk reduction strategies.

6.3.1. Cardiac Rehabilitation and Physical Activity: Recommendation

Class I

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

The U.S. Public Health Service emphasizes comprehensive cardiac rehabilitation programs (449), and the 2011 secondary prevention CPG underscores referral to cardiac rehabilitation for survivors of ACS (27). Since 2007, referral to these programs has been designated a quality performance measure (453-455). Barriers to referral can be obviated by discussion with the patient and referral by the patient's primary care clinician and/or cardiovascular caregiver. These comprehensive programs provide patient education, enhance regular exercise, monitor risk factors, and address lifestyle modification (456). Aerobic exercise training can generally begin 1 to 2 weeks after discharge in patients treated with PCI or CABG (457). Mild-to-moderate resistance training can be considered and started 2 to 4 weeks after aerobic training (458). Unsupervised exercise may target a heart rate range of 60% to 75% of maximum age-predicted heart rate based on the patient's exercise stress test. Supervised training may target a higher heart rate (70% to 85% of age-predicted maximum) (457). Additional restrictions apply when residual ischemia is present. Daily walking can be encouraged soon after discharge for most patients. Resource publications on exercise prescription in cardiovascular patients are available (456, 457). Regular physical activity reduces symptoms in patients with cardiovascular disease, enhances functional capacity, improves other risk factors such as insulin resistance and glucose control, and is important in weight control (456). Questionnaires and nomograms for cardiac patients have been developed to guide exercise prescription if an exercise test is unavailable (459-462). See Section 6.4 and Table 10 for more information.

6.3.2. Patient Education: Recommendations

Class I

- 1. Patients should be educated about appropriate cholesterol management, BP, smoking cessation, and lifestyle management (15, 16, 18). (Level of Evidence: C)**
- 2. Patients who have undergone PCI or CABG derive benefit from risk factor modification and should receive counseling that revascularization does not obviate the need for lifestyle changes (463). (Level of Evidence: C)**

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

6.3.3. Pneumococcal Pneumonia: Recommendation

Class I

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

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

6.3.4. NSAIDs: Recommendations

Class I

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

Class IIa

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

Class IIb

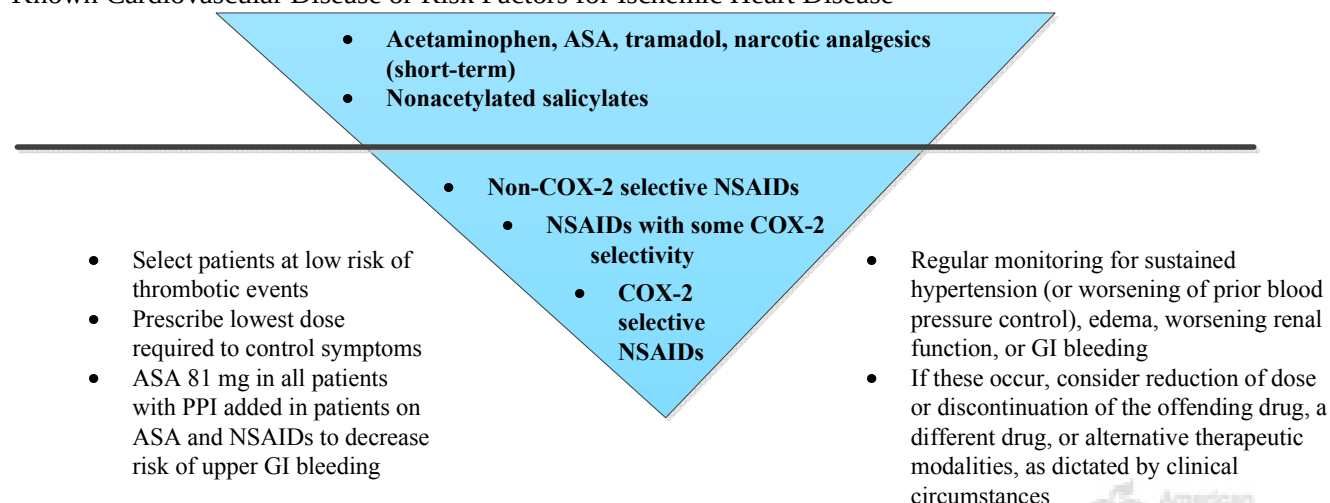
1. NSAIDs with increasing degrees of relative COX-2 selectivity may be considered for pain relief only for situations in which intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, nonacetylated salicylates, tramadol, small doses of narcotics, or nonselective NSAIDs.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

Class III: Harm

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

Selective COX-2 inhibitors and other nonselective NSAIDs have been associated with increased cardiovascular risk, and the risk appears to be amplified in patients with established cardiovascular disease (234, 235, 467-469). In a large Danish observational study of patients with first MI (n=58,432), the HR and 95% CI for death were 2.80 (2.41 to 3.25) for rofecoxib, 2.57 (2.15 to 3.08) for celecoxib, 1.50 (1.36 to 1.67) for ibuprofen, 2.40 (2.09 to 2.80) for diclofenac, and 1.29 (1.16 to 1.43) for other NSAIDs (234). There were dose-related increases in risk of death and non-dose-dependent trends for rehospitalization for MI for all drugs (234, 467). An AHA scientific statement on the use of NSAIDs concluded that the risk of cardiovascular events is proportional to COX-2 selectivity and the underlying risk in the patient (237). Nonpharmacological approaches were recommended as the first line of treatment, followed by the stepped-care approach to pharmacological therapy, as shown in Figure 4.

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



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

6.3.5. Hormone Therapy: Recommendation

Class III: Harm

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

Although prior observational data suggested a protective effect of hormone therapy for coronary events, a randomized trial of hormone therapy for secondary prevention of death and MI (the HERS [Heart and Estrogen/Progestin Replacement] study) failed to demonstrate a beneficial effect (473). There was an excess risk for death and MI early after initiation of hormone therapy. The Women's Health Initiative included randomized primary prevention trials of estrogen plus progestin and estrogen alone (472). Both trials were stopped early owing to an increased risk related to hormone therapy that was believed to outweigh the potential benefits of further study (470-472). It is recommended that postmenopausal 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 (e.g., treatment of perimenopausal symptoms such as flushing or prevention of osteoporosis) if the benefits are believed to outweigh the increased cardiovascular risk. Postmenopausal women who are >1 to 2 years past the initiation of hormone therapy who wish to continue such therapy for

another compelling indication should weigh the risks and benefits, recognizing the greater risk of cardiovascular events and breast cancer (combination therapy) or stroke (estrogen) (473).

6.3.6. Antioxidant Vitamins and Folic Acid: Recommendations

Class III: No Benefit

1. **Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) should not be used for secondary prevention in patients with NSTE-ACS (474, 475). (Level of Evidence: A)**
2. **Folic acid, with or without vitamins B₆ and B₁₂, should not be used for secondary prevention in patients with NSTE-ACS (476, 477). (Level of Evidence: A)**

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

See [Online Data Supplement 23](#) for additional information on antioxidant vitamins and folic acid.

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

Class I

1. **Posthospital systems of care designed to prevent hospital readmissions should be used to facilitate the transition to effective, coordinated outpatient care for all patients with NSTE-ACS (481-485). (Level of Evidence: B)**
2. **An evidence-based plan of care (e.g., GDMT) that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with NSTE-ACS. (Level of Evidence: C)**
3. **In addition to detailed instructions for daily exercise, patients should be given specific instruction on activities (e.g., lifting, climbing stairs, yard work, and household activities) that are permissible and those to avoid. Specific mention should be made of resumption of driving, return to work, and sexual activity (452, 486, 487). (Level of Evidence: B)**
4. **An annual influenza vaccination is recommended for patients with cardiovascular disease (27, 488). (Level of Evidence: C)**

Education of patients with NSTEMI and their families is critical and often challenging, especially during transitions of care. Failure to understand and comply with a plan of care may account for the high rate of AMI rehospitalization rates in the United States (489, 490). An important intervention to promote coordination is to provide patients and caregivers with a comprehensive plan of care and educational materials during the hospital stay that support compliance with evidence-based therapies (491-493). The posthospitalization plan of care for patients with NSTE-ACS (Table 10) should address in detail several complex issues, including medication

adherence and titration, timely follow-up, dietary interventions, physical and sexual activities, cardiac rehabilitation, compliance with interventions for secondary prevention, and reassessment of arrhythmic and HF risks. In addition, clinicians should pay close attention to psychosocial and socioeconomic issues, including access to care, risk of depression, social isolation, and healthcare disparities (494-496).

6.4.1. Systems to Promote Care Coordination

There has been improved understanding of the system changes necessary to achieve safer care (497). This includes adoption by all U.S. hospitals of a standardized set of “Safe Practices” endorsed by the National Quality Forum (498), which overlap with the National Patient Safety Goals espoused by The Joint Commission (499). Examples of patient safety standards for all patients after AMI include improved communication among clinicians, nurses, and pharmacists; medication reconciliation; careful transitions between care settings; and consistent documentation. The National Quality Forum has also endorsed a set of patient-centered “Preferred Practices for Care Coordination” (500), which detail comprehensive specifications that are necessary to achieve successful care coordination for patients and their families. Systems of care designed to support patients with NSTE-ACS, STEMI, and other cardiac diseases can result in significant improvement in patient outcomes. Table 10 provides reference documents for multiple risk-reduction strategies for secondary prevention in the posthospital phase of NSTE-ACS. These include the 2013 ACC/AHA CPGs on management of blood cholesterol (18), obesity (16), and lifestyle (15) and the 2014 recommendations for management of hypertension (501), which were published during the development of this CPG. To provide the interventions and services listed in Table 10, appropriate resources must be used so that patients with MI have full access to evidence-based therapies and follow-up care. There is a growing emphasis on penalizing hospitals for avoidable hospital readmissions. It is imperative for health systems to work with clinicians, nurses, pharmacists, communities, payers, and public agencies to support the interventions that achieve comprehensive care. Several patient characteristics have been predictors of readmission after AMI (502, 503).

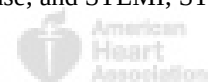
Table 10. Plan of Care for Patients With NSTE-ACS

Plan of Care	Resources/References
Medications	
Antithrombotic therapies	• Section 6.1.2 and 6.2.2 • Sections 4.1.2.3 • Sections 4.2 • Section 4.1.2.4 • 2013 Blood cholesterol CPG (18) • 2014 SIHD focused update (10) • 2012 SIHD CPG (11) • 2012 Management of AMI in patients with persistent STEMI CPG (19) • 2011 Secondary prevention CPG (27)
Beta blockers	
ACE inhibitors/ARBs/aldosterone antagonists	
CCBs	
Statins	
Discontinuation of antithrombotic therapies for elective surgical and medical procedures with increased risk of bleeding	

	2007 Science Advisory on the prevention of premature discontinuation of DAPT in patients with coronary artery stents (504)
Inappropriate use of analgesics (NSAIDs)	2010 Expert consensus document on PPIs and thienopyridines (430)
Use of PPIs	2011 PCI CPG (26)
Risk factor modification/lifestyle interventions and physical activity/cardiac rehabilitation	
Smoking cessation	Tobacco cessation toolkit (505)
Diet nutrition	2013 Lifestyle CPG (15)
Physical activity	2013 Lifestyle CPG (15) 2011 Secondary prevention CPG (27)
Cardiorespiratory fitness (MET capacity)	2011 Secondary prevention CPG (27) 2010 Performance measures on cardiac rehabilitation (454) 2012 Scientific statement on sexual activity and cardiovascular disease (231)
Management of comorbidities	
Overweight/obesity	2013 Obesity CPG (16) 2011 Secondary prevention CPG (27)
Statins	2013 Lifestyle CPG (15) 2013 Blood cholesterol CPG (18)
Hypertension	2014 Report on high BP (501) 2013 Science advisory on high BP control (506)
Diabetes mellitus	2013 Position statement on standards of medical care in diabetes (507)
HF	2013 HF CPG (14)
Arrhythmia/arrhythmia risk	2012 Focused update incorporated into the 2008 DBT CPG (20) 2014 AF CPG (12)
Psychosocial factors	
Sexual activity	2012 Scientific statement on sexual activity and cardiovascular disease (231) 2013 Consensus document on sexual counseling for individuals with cardiovascular disease and their partners (508)
Gender-specific issues	2007 Cardiovascular disease prevention in women CPG (475)
Depression, stress, and anxiety	2008 Science advisory on depression and coronary heart disease (509)
Alcohol use	2011 Secondary prevention CPG (27)
Culturally sensitive issues	2009 Consensus report on a comprehensive framework and preferred practices for measuring and reporting cultural competency (510)
Return to work schedule	
Clinician follow-up	
Cardiologist	2011 Secondary prevention CPG (27) 2013 Hospital to Home Quality Initiative (511)
Primary care clinician	
Advanced practice nurse/physician assistant	
Pharmacists	2013 Discharge counseling for patients with HF or MI (512)
Other relevant medical specialists	
Electronic personal health records	
Influenza vaccination	2005 Recommendations for prevention and control of influenza (37)
Patient/family education	
Plan of care for AMI	2010 CPG for cardiopulmonary resuscitation and emergency cardiovascular care—Part 9: postcardiac arrest care (31)

	2013 STEMI CPG (17)
Recognizing symptoms of MI	
Activating EMS, signs and symptoms for urgent vs. emergency evaluations	
CPR training for family members	
Risk assessment and prognosis	
Advanced directives	
Social networks/social isolation	
Socioeconomic factors	
Access to health insurance coverage	
Access to clinicians	Effective communication and care coordination (513)
Disability	Cardiovascular disability: updating Social Security listings (514)
Social services	
Community services	

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



7. Special Patient Groups

See Table 11 for summary of recommendations for this section.

7.1. NSTEMI-ACS in Older Patients: Recommendations

Class I

1. Older patients** with NSTEMI-ACS should be treated with GDMT, an early invasive strategy, and revascularization as appropriate (515-519). (*Level of Evidence: A*)
2. Pharmacotherapy in older patients with NSTEMI-ACS should be individualized and dose adjusted by weight and/or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity (515, 520-522). (*Level of Evidence: A*)
3. Management decisions for older patients with NSTEMI-ACS should be patient centered, and consider patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy (515, 523-525). (*Level of Evidence: B*)

Class IIa

1. Bivalirudin, rather than a GP IIb/IIIa inhibitor plus UFH, is reasonable in older patients with NSTEMI-ACS, both initially and at PCI, given similar efficacy but less bleeding risk (396, 526-528). (*Level of Evidence: B*)
2. It is reasonable to choose CABG over PCI in older patients** with NSTEMI-ACS who are appropriate candidates, particularly those with diabetes mellitus or complex 3-vessel CAD (e.g., SYNTAX score >22), with or without involvement of the proximal LAD artery, to reduce cardiovascular disease events and readmission and to improve survival (529-534). (*Level of Evidence: B*)

In this CPG, “older adults” refers to patients ≥ 75 years of age (515). Older adults have the highest incidence, prevalence, and adverse outcomes of NSTEMI-ACS (9, 515-517, 535, 536). Older age is accompanied by

**Those ≥ 75 years of age (see text).

comorbidities, polypharmacy, and age- and disease-related physiological changes that adversely impact NSTEMI-ACS presentation, management, and outcome. As older patients are under-represented in clinical trials, the recommendations in this CPG are largely supported by registry data and meta-analyses (516, 537).

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

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

In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) study, excessive doses of UFH, LMWH, and GP IIb/IIIa inhibitors accounted for 15% of major bleeding, longer lengths of stay, and increased mortality (522, 548). Aspirin should be maintained at 81 mg per day (after initial stent implantation). Due to excess bleeding without clinical benefit, the U.S. Food and Drug Administration lists a Black Box warning that does not recommend administration of prasugrel to patients with NSTEMI-ACS who are ≥ 75 years of age or weigh < 60 kg except in those at very high risk. A meta-analysis of 6 RCTs about the use of GP IIb/IIIa inhibitors in patients with NSTEMI-ACS reported no significant age-treatment interaction, although older women had significantly more adverse events (549). Bivalirudin appears safer for older patients with NSTEMI-ACS $\pm$ PCI compared with GP IIb/IIIa inhibitors plus UFH with less bleeding and similar efficacy (526, 550). AF is more common in older patients with NSTEMI-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 (440). Nonetheless, practice should not be changed on the basis of this limited study alone.

Older patients with NSTEMI-ACS benefit as much or more than younger patients from an early invasive strategy compared with an ischemia-guided strategy (340, 341, 515, 518, 519). In a 5-year follow-up meta-

analysis of FRISC-II and RITA-3, an early invasive strategy versus an ischemia-guided strategy was associated with a significant reduction in death/MI and MI in patients ≥ 75 years of age but not in patients < 65 years of age (518). Although the highest risk reduction in death/MI with an early invasive strategy occurred in those ≥ 75 years of age, this strategy was associated with a 3-fold bleeding risk (552). However, despite the overall favorable evidence for an early invasive strategy in older patients, age is the strongest risk factor for this group not undergoing an early invasive strategy (553).

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

Operative mortality rates for CABG in patients ≥ 80 years of age with NSTEMI-ACS range from 5% to 8% (11% for urgent cases) and increase to approximately 13% at ≥ 90 years of age. Complications occur more frequently in older patients with CABG (557, 558). Length of stay averages 6 days longer in older patients than in patients < 50 years of age, and discharge (to home [52%]) is less frequent than in younger patients (557). In a meta-analysis, off-pump CABG appeared to offer a potentially safer and more effective revascularization technique compared with on-pump CABG in older patients with NSTEMI-ACS (559). Older patients with NSTEMI-ACS with diabetes mellitus had a greater survival advantage with CABG (529). Evaluation tools can help identify older patients with NSTEMI-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 NSTEMI-ACS should be treated according to the same risk stratification guidelines and recommendations for patients without HF (14, 42-44, 75-81). (Level of Evidence: B)**
2. **Selection of a specific revascularization strategy should be based on the degree, severity, and extent of CAD; associated cardiac lesions; the extent of LV dysfunction; and the history of prior revascularization procedures (14, 138, 141, 333, 334, 337, 341, 560, 561). (Level of Evidence: B)**

In patients with HF and NSTEMI-ACS, the plan of care should be implemented as in patients without HF using medical therapy and an early invasive approach, because patients with abnormal LV function are at increased risk of mortality and morbidity (562). HF itself may be associated with elevated serum troponin in the presence or absence of obstructive CAD. After angiography, risk stratification can be used to select revascularization strategies. The effect of surgical revascularization on improving survival has been most clearly demonstrated in

patients with both extensive CAD and LV dysfunction (356, 357, 563-567). Such patients should undergo testing to identify the severity and extent of ischemia and should in general be referred for coronary angiography. In selected patients with appropriate anatomy, PCI has been used (23, 568). In patients who have already undergone CABG or in whom the anatomy is not favorable for CABG, PCI has been performed using CPG-based PCI performance strategies if specific targeted areas that are amenable to PCI can be identified (26). If there is a large amount of ischemic territory and very poor LV function, percutaneous ventricular assist devices or, in less severe cases, an IABP can be used for support during the procedure (266, 569-573).

See [Online Data Supplement 25](#) for additional information on HF.

7.2.1. Arrhythmias

Ventricular arrhythmias are common early after onset of NSTE-ACS, and not all require intervention. The mechanisms for these arrhythmias include continuing ischemia, hemodynamic and electrolyte abnormalities, reentry, and enhanced automaticity. Approximately 5% to 10% of hospitalized patients may develop ventricular tachycardia (VT)/ventricular fibrillation (VF), usually within 48 hours of presentation (574). The incidence of VF in otherwise uncomplicated AMI appears to have decreased within the past few years from >4% to <2%, of which 59% of patients had non-Q-wave MI (574). A study of 277 consecutive patients with NSTE-ACS who underwent cardiac catheterization within 48 hours found VT/VF occurring in 7.6% of patients, 60% of which developed within 48 hours after admission (575). Risk factors for VT/VF include HF, hypotension, tachycardia, shock, and low TIMI flow grade. Treatment consists of immediate defibrillation or cardioversion for VF or pulseless sustained VT. Early administration of beta blockers has been associated with reduction in incidence of VF (576). The prophylactic use of lidocaine is not recommended. Although VT/VF is associated with higher 90-day mortality risk, premature ventricular contractions not associated with hemodynamic compromise and accelerated ventricular rhythms do not confer higher mortality risks and do not require specific therapy other than maintaining electrolyte balance. NSTE-ACS nonsustained VT occurring >48 hours after admission indicates an increased risk of cardiac and sudden death, especially when associated with accompanying myocardial ischemia (577). Life-threatening ventricular arrhythmias that occur >48 hours after NSTE-ACS are usually associated with LV dysfunction and signify poor prognosis. RCTs in patients with ACS have shown consistent benefit of implantable cardioverter-defibrillator therapy for survivors of VT or VF arrest (578-582). For other at-risk patients, especially those with significantly reduced LVEF, candidacy for primary prevention of sudden cardiac death with an implantable cardioverter-defibrillator should be readdressed ≥ 40 days after discharge (583). A life vest may be considered in the interim.

AF, atrial flutter, and other supraventricular arrhythmias may be triggered by excessive sympathetic stimulation, atrial stress due to volume overload, atrial infarction, pericarditis, electrolyte abnormalities, hypoxia, or pulmonary disease. AF is the most common of these arrhythmias and may develop in >20% of patients. AF is associated with shock, HF, stroke, and increased 90-day mortality (584). Management of AF

requires rate control and adequate anticoagulation according to the 2014 AF CPG (12). For hemodynamically unstable patients and those with continuing ischemia, treatment should be implemented according to the 2010 advanced cardiac life support CPGs (585).

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

First-degree atrioventricular block does not require treatment. High-grade atrioventricular block after inferior NSTEMI usually is transient, with a narrow QRS complex and a junctional escape rhythm that can be managed with an ischemia-guided strategy. Prophylactic placement of a temporary pacemaker is recommended for high-grade atrioventricular block, new bundle-branch block, or bifascicular block with anterior infarction. Indications for permanent pacing are reviewed in the 2012 device-based therapy CPGs (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 NSTEMI-ACS (560, 588, 589). (Level of Evidence: B)**

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

In-hospital mortality of all patients with shock was 59% (594). Patients with NSTEMI developed cardiogenic shock later than patients with STEMI, and had higher-risk clinical characteristics, more extensive CAD, and more recurrent ischemia and infarction before developing shock compared with patients with STEMI,

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

See [Online Data Supplement 26](#) for additional information on cardiogenic shock.

7.3. Diabetes Mellitus: Recommendation

Class I

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

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

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

Although patients with diabetes mellitus and NSTE-ACS are at higher risk for in-hospital and longer-term events, they undergo less frequent revascularization procedures. In a multinational study of 6,385 patients with ACS, 25% of whom had diabetes mellitus, those with diabetes mellitus had more adverse risk profiles,



more atypical presentations, longer treatment delays, more HF, and renal insufficiency but underwent less angiography and revascularization (607). In the GRACE Registry (593) and other studies (606), patients with diabetes mellitus and NSTE-ACS in the United Kingdom (603) and Finland (612) had higher baseline risk profiles but received effective medical cardiac therapies and revascularization less frequently.

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

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

7.3.1. Adjunctive Therapy

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

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

See [Online Data Supplement 27](#) for additional information on diabetes mellitus.

7.4. Post-CABG: Recommendation

Class I

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

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

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

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

See [Online Data Supplement 28](#) for additional information on post-CABG.

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

Class I

- 1. Patients who develop NSTEMI-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 NSTEMI-ACS (626, 627). (Level of Evidence: C)**
- 2. In patients who develop NSTEMI-ACS after noncardiac surgery, management should be directed at the underlying cause (21, 626-634). (Level of Evidence: C)**

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

The definition of ACS has a substantial effect on reported incidence (178, 184, 635-644). Some patients may not be able to give a history of ischemic symptoms because of the noncardiac surgery. The criteria in the 2012 Third Universal Definition of MI should be applied (21). In patients at risk of ACS following noncardiac surgery, routine monitoring of troponins and ECGs may be performed. As the sensitivity of troponin assays improves, the frequency of identifying perioperative MI will increase. In the POISE (Perioperative Ischemic

Study Evaluation) trial (645), of 8,351 patients randomized to extended-release metoprolol versus placebo, 5.7% of patients in the control group had a perioperative MI typically occurring within 48 hours and often not associated with ischemic symptoms.

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



7.6. CKD: Recommendations

Class I

1. **CrCl should be estimated in patients with NSTE-ACS, and doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications (649, 650). (Level of Evidence: B)**
2. **Patients undergoing coronary and LV angiography should receive adequate hydration. (Level of Evidence: C)**

Class IIa

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

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

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

The strength and consistency of relationships between specific isosmolar or low-osmolar agents and contrast-induced nephropathy or renal failure are insufficient for selection of low-osmolar and isosmolar media. Limitation of the risk of contrast-induced nephropathy is based on reduced contrast volume (660) and adequate hydration (661).

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

See [Online Data Supplement 29](#) for additional information on CKD.

7.6.1. Antiplatelet Therapy

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

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

bleeding, and non-CABG-related major bleeding events demonstrating its utility in patients with renal insufficiency.

7.7. Women: Recommendations

Class I

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

Women of all ages have higher rates of in-hospital and long-term complications of NSTEMI-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 NSTEMI-ACS and have higher rates of inappropriate discharges from the ED (671, 677, 678). Women more commonly report atypical symptoms than men (675, 679). Women presenting with chest pain are more likely than men to have either a noncardiac cause or cardiac causes other than obstructive epicardial coronary disease (108, 677, 680, 681). Women with NSTEMI-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 NSTEMI-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 NSTEMI-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 NSTEMI-ACS incur a higher rate of bleeding complications (672, 673) (Section 7.8) and renal failure. A risk score has been developed to attempt to reduce the bleeding risk in women with NSTEMI-ACS (688).

The decision for an early invasive versus an ischemia-guided strategy in women with NSTEMI-ACS is based on a meta-analysis (366) and post hoc gender analyses of clinical trials, including FRISC II, RITA-3, and

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

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

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

An Agency for Healthcare Research and Quality meta-analysis of 10 RCTs through December 2011 reported no efficacy or safety difference between PCI and CABG for NSTE-ACS in men or women in 30-day or 1-year MACE (death/MI/stroke). At 2 years, the procedural success remained equal in women but favored CABG in men ($p=0.002$) (345, 564). The Agency for Healthcare Research and Quality reported similar outcomes in women with diabetes mellitus with PCI and CABG for NSTE-ACS at 7 years, but men with diabetes mellitus had fewer events with CABG. A prespecified gender analysis of the FREEDOM trial favored CABG over PCI for women with diabetes mellitus, although the difference was not as significant as it was for men (616).

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

See [Online Data Supplement 30](#) for more information on women.

7.8. Anemia, Bleeding, and Transfusion: Recommendations

Class I

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

Class III: No Benefit

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

Anemia in patients with ACS is associated with an increased risk for Holter monitor-detected recurrent ischemia and for MACE, with greater anemia correlating with greater risk (704-708). In 1 large analysis of multiple studies, the risk of adverse outcome was higher in patients with NSTEMI-ACS with hemoglobin levels <11 g/dL (704). The potentially detrimental effects of severe anemia include decreased myocardial oxygen delivery and increased MVO₂ 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 ACUTY 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) due to differing definitions of major bleeding, patient populations, anticoagulation regimens, and PCI or CABG. Factors in patients with ACS related to an increased bleeding risk include older age, female sex, lower body weight, history of prior bleeding and/or invasive procedures, anemia, use of GP IIb/IIIa inhibitors or thrombolytics, and CKD (522, 711, 713-715, 722, 723). Non-weight-based dosing of anticoagulants and dosing of antithrombin and antiplatelet medications that are not adjusted for CKD are associated with an increased risk of bleeding (522, 697, 698). Bleeding is related to adverse outcomes because it may be a marker of underlying disease, such as occult malignancy; leads to cessation of antithrombin and antiplatelet therapy; may prompt transfusion, which itself may have adverse effects; can cause hypotension; and, if intracranial, can be fatal (724). Proton pump inhibitors decrease the risk of upper GI bleeding, including in patients treated with DAPT. Proton pump inhibitors are used in patients with a history of prior GI bleeding who require DAPT and are an option in patients at increased risk of GI bleeding (26, 430).

Evaluation of the risk of bleeding includes a focused history of bleeding symptoms, predisposing comorbidities, evaluation of laboratory data, and calculation of a bleeding risk score (688, 716, 725). Approximately 15% of all patients with NSTEMI-ACS and 3% to 12% of those not undergoing CABG receive blood transfusion (702). Rates vary widely and are closer to the lower figure but increase in association with factors such as coronary intervention, anticoagulant/antithrombotic therapy, older age, female sex, anemia, renal

insufficiency, and frailty. Tissue oxygenation does not change or may actually decrease with transfusion (722). Blood transfusion in patients with ACS is associated with an increased risk of adverse outcome, including death (702-704). A restrictive transfusion strategy leads to an outcome that is at least as good, if not better, than a liberal transfusion strategy (699, 700). An analysis of a large ACS registry found no benefit from blood transfusion in patients with a nadir hematocrit >24% (702). In a meta-analysis of 10 studies of patients with AMI, transfusion versus no transfusion was associated with an increase in all-cause mortality (18.2% versus 10.2%; $p < 0.001$) and subsequent MI rate (RR: 2.0; 95% CI: 1.06 to 3.93; $p = 0.03$) (726). A restrictive approach to transfusion generally consists of no routine transfusion for a hemoglobin level >7 g/dL to 8 g/dL (699, 700, 727). A restrictive approach to blood transfusion is advocated by the American Association of Blood Banks (700) and the European Society of Cardiology (727). On the basis of data available at the time of publication, a strategy of routine liberal blood transfusion in hemodynamically stable patients with NSTE-ACS and mild to moderate anemia is not recommended.

See [Online Data Supplement 31](#) for more information on anemia, bleeding, and transfusion.



7.9. Thrombocytopenia

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

Thrombocytopenia on presentation or related to antithrombotic therapy is associated with significantly increased risk of thrombotic events, MI, major bleeding, and in-hospital mortality in patients with and without ACS (728-731, 735-739). The OR for development of these endpoints with thrombocytopenia (compared to without thrombocytopenia) is 2 to 8. Data from the CATCH (Complications After Thrombocytopenia Caused by Heparin) registry identified a platelet count nadir of $125 \times 10^9/L$ 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 (e.g., euphoria, tachycardia, and/or hypertension) and beta-blocker use, unless patients are receiving coronary vasodilator therapy. (Level of Evidence: C)**

Class IIa

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

Class III: Harm

1. **Beta blockers should not be administered to patients with ACS with a recent history of cocaine or methamphetamine use who demonstrate signs of acute intoxication due to the risk of potentiating coronary spasm. (Level of Evidence: C)**

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

ACS in patients with a history of cocaine use should be treated in the same manner as patients without cocaine use (744). The exception is in patients with ACS in the presence of acute cocaine intoxication. Because cocaine stimulates both alpha- and beta-adrenergic receptors, administration of intravenous beta blockers may result in unopposed alpha stimulation with worsening coronary spasm (48, 132, 744-746). Evidence suggests it is safe to administer intravenous beta blockers in patients with chest pain and recent cocaine ingestion, although information is lacking about the effects of beta-blocker administration during the acute stages of cocaine intoxication (747, 748). Intravenous beta blockers should be avoided in patients with NSTE-ACS with signs of acute cocaine intoxication (euphoria, tachycardia, and/or hypertension). In these patients, benzodiazepines alone or in combination with nitroglycerin have been useful for management of hypertension and tachycardia due 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 due to the ease of manufacturing and the lower cost of methamphetamines compared with cocaine (131, 749, 750). Methamphetamines may be ingested orally, inhaled, or used intravenously. Methamphetamine affects the central nervous system by simultaneously stimulating the release and blocking the reuptake of dopamine and norepinephrine (751). Like cocaine, methamphetamine exerts multiple effects on the cardiovascular system, all of which may precipitate ACS (131, 750-752). The acute effects of methamphetamine are euphoria, tachycardia, hypertension, and arrhythmias. MI may result from coronary spasm or plaque rupture in the presence of enhanced platelet aggregation. Long-term use of methamphetamine has been associated with myocarditis, necrotizing vasculitis, pulmonary hypertension, and cardiomyopathy (750-752). Because methamphetamine and cocaine have similar pathophysiological effects, treatment of patients with ACS associated with methamphetamine and cocaine use should theoretically be similar.

See [Online Data Supplement 33](#) for additional information about cocaine and methamphetamine users.

7.11. Vasospastic (Prinzmetal) Angina: Recommendations

Class I

1. CCBs alone (753-757) or in combination with long-acting nitrates (755, 758) are useful to treat and reduce the frequency of vasospastic angina. (*Level of Evidence: B*)
2. Treatment with HMG-CoA reductase inhibitor (759, 760), cessation of tobacco use (761, 762), and additional atherosclerosis risk factor modification (762, 763) are useful in patients with vasospastic angina. (*Level of Evidence: B*)
3. Coronary angiography (invasive or noninvasive) is recommended in patients with episodic chest pain accompanied by transient ST elevation to rule out severe obstructive CAD. (*Level of Evidence: C*)

Class IIb

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

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

Nonpharmacological provocative tests, such as cold pressor and hyperventilation, have been used diagnostically; potent vasoconstrictors (e.g., acetylcholine) may be useful when noninvasive assessment is uninformative (764-767). Smoking, which exacerbates coronary vasospasm, should be proscribed, and CCBs are first-line therapies (642); long-acting nitrates are also effective and when combined with CCBs (755, 758). Statins improve endothelium-dependent vasodilation and can be useful in vasospastic angina (759, 760). Magnesium supplementation and alpha-receptor blockers may be effective and can be added (755, 758).

7.12. ACS With Angiographically Normal Coronary Arteries: Recommendation

^{††}Provocative testing during invasive coronary angiography (e.g., using ergonovine, acetylcholine, methylegonovine) 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.

Class IIb

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

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

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

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

7.13. Stress (Takotsubo) Cardiomyopathy: Recommendations

Class I

1. **Stress (Takotsubo) cardiomyopathy should be considered in patients who present with apparent ACS and nonobstructive CAD at angiography. (Level of Evidence: C)**
2. **Imaging with ventriculography, echocardiography, or magnetic resonance imaging should be performed to confirm or exclude the diagnosis of stress (Takotsubo) cardiomyopathy (795-798). (Level of Evidence: B)**
3. **Patients should be treated with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) as otherwise indicated if hemodynamically stable. (Level of Evidence: C)**

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

Class IIa

1. **It is reasonable to use catecholamines for patients with symptomatic hypotension if outflow tract obstruction is not present. (Level of Evidence: C)**
2. **The use of IABP is reasonable for patients with refractory shock. (Level of Evidence: C)**
3. **It is reasonable to use beta blockers and alpha-adrenergic agents in patients with outflow tract obstruction. (Level of Evidence: C)**

Class IIb

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

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

Care is predominantly supportive and includes beta blockers, vasodilators, and catecholamines. The latter 2 interventions must be used cautiously, because they may induce outflow tract obstruction (800). If shock is present, IABP can be used. Prophylactic anticoagulation should be considered to prevent or treat LV thrombus (798).

7.14. Obesity

Obesity is associated with conditions such as dyslipidemia, diabetes mellitus, hypertension, arrhythmias, and HF that adversely affect ACS outcomes. In the MADIT (Multicenter Automatic Defibrillator Implantation)-II trial, there was an inverse relation between body mass index and both all-cause mortality and sudden cardiac death in patients with LV dysfunction after MI (807). In the SYNERGY trial of 9,837 patients with NSTEMI, mortality was lower in morbidly obese patients, consistent with the “obesity paradox” (808). The “obesity paradox” has not been clarified and is under continuing investigation. Standard approaches to weight reduction in obese patients are usually unsuccessful in producing large decreases in weight. A weight reduction study of obese and morbidly obese patients following AMI resulted in weight loss of only 0.5% in obese patients and 3.5% in morbidly obese patients after 1 year (809). Two drugs, controlled-release phentermine/topiramate (810) and

lorcaserin (811), are available for weight reduction but have not been studied in patients following NSTEMI-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 NSTEMI-ACS. For example, antineoplastic agents such as gemcitabine, sorafenib, sunitinib, and 5-fluorouracil have been associated with coronary artery spasm or stenosis (813, 814). Trastuzumab and possibly other anticancer drugs may alter biomarker levels (815). Antineoplastic agents can induce changes in the arterial wall (813), and modulators of inflammation may promote atherogenesis (816). In patients receiving these agents, it is prudent to communicate with the prescribing clinician about the necessity of their continuation during NSTEMI-ACS and future resumption.



Table 11. Summary of Recommendations for Special Patient Groups

Recommendations	COR	LOE	References
NSTEMI-ACS in older patients			
Treat older patients (≥ 75 y of age) with GDMT, early invasive strategy, and revascularization as appropriate	I	A	(515-519)
Individualize pharmacotherapy in older patients, with dose adjusted by weight and/or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics, volume of distribution, comorbidity, drug interactions, and increased drug sensitivity	I	A	(515, 520-522)
Undertake patient-centered management for older patients, considering patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy	I	B	(515, 523-525)
Bivalirudin rather than GP IIb/IIIa inhibitor plus UFH is reasonable for older patients (≥ 75 y of age), given similar efficacy but less bleeding risk	IIa	B	(396, 526-528)
It is reasonable to choose CABG over PCI in older patients, particularly those with DM or multivessel disease, because of the potential for improved survival and reduced CVD events	IIa	B	(529-534)
HF			
Treat patients with a history of HF according to the same risk stratification guidelines and recommendations for patients without HF	I	B	(14, 42-44, 75-81)
Select a revascularization strategy based on the extent of CAD, associated cardiac lesions, LV dysfunction, and prior revascularization	I	B	(14, 138, 141, 333, 334, 337, 341, 560, 561)
Cardiogenic shock			
Recommend early revascularization for cardiogenic shock due to cardiac pump failure	I	B	(560, 588, 589)
DM			
Recommend medical treatment and decisions for testing and revascularization similar to those for patients without DM	I	A	(138, 339, 601)
Post-CABG			
Recommend GDMT antiplatelet and anticoagulant therapy and early invasive strategy because of increased risk with prior CABG	I	B	(67, 68, 141, 340-342)

Perioperative NSTEMI-ACS			
Administer GDMT to perioperative patients with limitations imposed by noncardiac surgery	I	C	(626, 627)
Direct management at underlying cause of perioperative NSTEMI-ACS	I	C	(21, 626-634)
CKD			
Estimate CrCl and adjust doses of renally cleared medications according to pharmacokinetic data	I	B	(649, 650)
Administer adequate hydration to patients undergoing coronary and LV angiography	I	C	N/A
Invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD	IIa	B	(649-652)
Women			
Manage women with the same pharmacological therapy as that for men for acute care and secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk	I	B	(669-673)
Early invasive strategy is recommended in women with NSTEMI-ACS and high-risk features (troponin positive)	I	A	(141, 345, 346, 561)
Myocardial revascularization is reasonable for pregnant women if ischemia-guided strategy is ineffective for management of life-threatening complications	IIa	C	(674)
Women with low-risk features (Section 3.3.1) should not undergo early invasive treatment because of lack of benefit and the possibility of harm	III: No Benefit	B	(141, 345, 346)
Anemia, bleeding, and transfusion			
Evaluate all patients for risk of bleeding	I	C	N/A
Recommend that anticoagulant and antiplatelet therapy be weight-based where appropriate and adjusted for CKD to decrease the risk of bleeding	I	B	(522, 697, 698)
There is no benefit of routine blood transfusion in hemodynamically stable patients with hemoglobin levels >8 g/dL	III: No Benefit	B	(699-703)
Cocaine and methamphetamine users			
Manage patients with recent cocaine or methamphetamine use similarly to those without cocaine- or methamphetamine-related NSTEMI-ACS. The exception is in patients with signs of acute intoxication (e.g., euphoria, tachycardia, and hypertension) and beta-blocker use unless patients are receiving coronary vasodilator therapy.	I	C	N/A
It is reasonable to use benzodiazepines alone or in combination with NTG to manage hypertension and tachycardia and signs of acute cocaine or methamphetamine intoxication.	IIa	C	(741-744)
Do not administer beta blockers to patients with recent cocaine or methamphetamine use who have signs of acute intoxication due to risk of potentiating coronary spasm	III: Harm	C	N/A
Vasospastic (Prinzmetal) angina			
Recommend CCBs alone or in combination with nitrates	I	B	(753-758)
Recommend HMG-CoA reductase inhibitor, cessation of tobacco use, and atherosclerosis risk factor modification	I	B	(759-763)
Recommend coronary angiography (invasive or noninvasive) for episodic chest pain with transient ST elevation to detect severe CAD	I	C	N/A
Provocative testing during invasive coronary angiography* may be considered for suspected vasospastic angina when clinical criteria and noninvasive assessment fail to determine diagnosis	IIb	B	(764-767)
ACS with angiographically normal coronary arteries			
Invasive physiological assessment (coronary flow reserve measurement) may be considered with normal coronary arteries if endothelial dysfunction is suspected	IIb	B	(629, 773-776)
Stress (Takotsubo) cardiomyopathy			

Consider stress-induced cardiomyopathy in patients with apparent ACS and nonobstructive CAD	I	C	N/A
Perform ventriculography, echocardiography, or MRI to confirm or exclude diagnosis	I	B	(795-798)
Treat with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) if hemodynamically stable	I	C	N/A
Administer anticoagulant therapy for LV thrombi	I	C	N/A
It is reasonable to administer catecholamines for symptomatic hypotension in the absence of LV outflow tract obstruction	IIa	C	N/A
It is reasonable to use IABP for refractory shock	IIa	C	N/A
It is reasonable to use beta blockers and alpha-adrenergic agents for LV outflow tract obstruction	IIa	C	N/A
Prophylactic anticoagulation may be considered to prevent LV thrombi	IIb	C	N/A

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

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

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

- 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 NSTEMI-ACS care (817-825). (Level of Evidence: B)**

The development of national systems for ACS is crucial and includes the participation of key stakeholders to evaluate care using standardized performance and quality-improvement measures for ACS (819, 821).

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

9. Summary and Evidence Gaps

Despite landmark advances in the care of patients with NSTEMI-ACS since the publication of the 2007 UA/NSTEMI CPG (212), many emerging diagnostic and therapeutic strategies have posed new challenges. There is general acceptance of an early invasive strategy for patients with NSTEMI-ACS in whom significant coronary vascular obstruction has been precisely quantified. Low-risk patients with NSTEMI-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 NSTEMI-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 NSTEMI-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 NSTEMI-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 NSTEMI-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 NSTEMI-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

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application of this evidence to the individual patient. This CPG has adhered to these principles for optimal management of patients with NSTEMI-ACS.

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

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Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

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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 makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

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

†Significant relationship.

‡No financial benefit.

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.

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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

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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 $\geq 5\%$ 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. 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.

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*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

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
AF = atrial fibrillation
AMI = acute myocardial infarction
BP = blood pressure
CABG = coronary artery bypass graft
CAD = coronary artery disease
CKD = chronic kidney disease
CK-MB = creatine kinase myocardial isoenzyme
COX = cyclooxygenase
CPG = clinical practice guideline
CrCl = creatinine clearance
CT = computed tomography
DAPT = dual antiplatelet therapy
DES = drug-eluting stent
ECG = electrocardiogram
ED = emergency department
GDMT = guideline-directed medical therapy
GP = glycoprotein
GFR = glomerular filtration rate
GWC = guideline writing committee
HF = heart failure
IABP = intra-aortic balloon pump
IV = intravenous
LMWH = low-molecular-weight heparin
LV = left ventricular
LVEF = left ventricular ejection fraction
MACE = major adverse cardiac event
MI = myocardial infarction
MVO₂ = myocardial oxygen consumption
NSAID = nonsteroidal anti-inflammatory drug
NSTEMI-ACS = non-ST-elevation acute coronary syndromes
NSTEMI = non-ST-elevation myocardial infarction
PCI = percutaneous coronary intervention



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RCT = randomized controlled trial

SC = subcutaneous

STEMI = ST-elevation myocardial infarction

UA = unstable angina

UFH = unfractionated heparin

VF = ventricular fibrillation

VT = ventricular tachycardia



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Appendix 4. Additional Tables

Table A. Universal Classification of MI

Type 1: Spontaneous MI
Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in ≥ 1 of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD, but on occasion nonobstructive or no CAD.
Type 2: MI secondary to ischemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between MVO_2 , e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: MI resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiographic changes or new LBBB, but death occurred before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases where blood was not collected for cardiac biomarker testing.
Type 4a: MI related to PCI
MI associated with PCI is arbitrarily defined by elevation of cTn values $>5 \times$ 99th percentile URL in patients with normal baseline values (<99 th percentile URL) or a rise of cTn values $>20\%$ if baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic electrocardiographic changes or new LBBB, (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.
Type 4b: MI related to stent thrombosis
MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with ≥ 1 value above the 99th percentile URL.
Type 5: MI related to CABG
MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values $>10 \times$ 99th percentile URL in patients with normal baseline cTn values (<99 th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographically documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

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

Modified from Thygesen et al. (21).

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

	Age-Related Pharmacological Change	Clinical Effect	Dose-Adjustment Recommendations	Additional Precautions
General principles	• $\downarrow$In renal function (CrCl*): drug clearance, water/electrolyte balance • SCr unreliable measure of renal function in older adults • Change in body composition	• $\uparrow$Levels renally cleared drug • Risk high/low electrolyte levels • $\uparrow$Levels hydrophilic agents • $\downarrow$Levels lipophilic agents • Longer time to reach steady-state lipophilic agents	• Calculate CrCl in all pts—renal-dose accordingly • Start at lowest recommended dose, titrate up slowly	• Caution fall risk with $\downarrow$BP agents and diuretics • Monitor for ADR, especially delirium • Frequent monitoring of renal function/electrolytes

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	• ↑Fat, ↓lean body mass/total water • ↓GI absorption		• Avoid interacting drugs • Consider ↓doses in women, malnourished, hypovolemic	• Minimize polypharmacy—watch for drug-drug interactions
ASA	Hydrophilic; levels ↑with ↓total body water; age-related ↑plasma concentration for similar dose	↑Bleeding risk with ↑age, dehydration, frailty, diuretics	• Maintenance=81 mg/d (lowest possible dose)	↑Bleeding with NSAIDs, other AP, AC, AT; ↑risk peptic ulcer with NSAIDs
Nitrates	↑Sensitivity	↑Hypotensive response with ↓baroreceptor response	Lowest dose possible, especially if hypovolemic	↑Risk OH, syncope, falls
ACE inhibitors	↓First-pass metabolism (some) with ↓effect; enalapril ↑effect	May have ↓effect	May need ↑dose	↑Risk AKI and ↑K ⁺ and ↓effect with NSAIDs; avoid K-sparing diuretics
ARBs	No significant age-related changes	No age-related clinical changes	None	↑Risk AKI and ↑K ⁺ and ↓effect with NSAIDs; avoid K-sparing diuretics
Alpha blockers	↑Sensitivity; ↓BP with ↓baroreceptor response	↓BP; OH	Avoid when possible	↑Risk OH, falls, syncope, especially with loop diuretics
Beta blockers	↓Myocardial sensitivity (↓postreceptor signaling), ↑conduction system sensitivity	Bradycardia/heart block; ↓BP effect vs. younger pts	May need ↑dose with age	Caution conduction system blocks
CCBs				
• DHPs (amlodipine; nifedipine)	Lipophilic; ↓hepatic and overall clearance; ↑fat storage; ↑sinus node sensitivity; ↓baroreceptor response to ↓BP	↓BP more than non-DHP and with ↑age; edema hypotension, bradycardia	Initiate low dose, titrate cautiously	Inhibits clopidogrel; ↑risk OH, falls, syncope; most potent ↓BP first 3 mo, then less
• Non-DHP (verapamil; diltiazem)	↓Hepatic and overall clearance; less PR prolongation than DHP and with ↑age; negative inotropy; ↑SA node sensitivity and ↓HR than DHP and with ↑age; ↓AV conduction with ↑age; ↓baroreceptor response to ↓BP	↓BP more with ↑age; edema; ↑heart block; hypotension; ↑bradycardia and bradyarrhythmias with ↑age	Initiate low dose, titrate cautiously	↑Risk OH, falls, syncope; consider rhythm monitoring
Diuretics	↓Diuretic/natriuretic response, ↓EC space, ↑drug concentration if ↓GFR; ↓baroreceptor response to volume shifts	↑Sensitivity; ↑hypotension; risk hypokalemia/hypomagnesemia/hyponatremia; ↓diuretic effect with ↓GFR; risk hypovolemia-↓thirst	May need ↑doses if ↓GFR; may need ↑dose if cotreating with NSAIDs	• Monitor Na⁺, K⁺, Mg²⁺ levels; ↑risk OH/falls; • With NSAIDs: ↓natriuretic and diuretic effect, ↑K⁺, ↓Mg²⁺
Heparins				

*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 NSTEMI-ACS but are included for management of pts with nonvalvular chronic atrial fibrillation.

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• UFH	Hydrophilic; ↑concentration, especially if ↓lean body mass or ↓plasma proteins; ↑levels with ↑age	↑Bleeding risk with age; more potent anticoagulation per dose with ↑age; weight-based dosing but with precautions for shift in body composition	Weight-based 60 U/kg loading dose + 12 U/kg/h INF. Suggested max loading dose: 400 U and 900 U/h INF or 5,000 U loading dose/1,000 U/h if pt weight >100 kg <u>Enoxaparin:</u> Weight-based 1 mg/kg SC q 12 h; CrCl* <30 mL/min—avoid or 1 mg/kg SC q 24 h; CrCl 30–60 mL/min: ↓75%; <u>Dalteparin:</u> Use caution in older pts with low body weight or renal insufficiency	↑Bleeding with ASA; ↑bleeding risk with other AP, AT, and GP IIb/IIIa; vigilantly monitor aPTT • ↑Bleed with ASA • Monitor anti-Xa; ↑bleeding with GP IIb/IIIa with ↑age 
Direct Thrombin Inhibitors • Bivalirudin • Fondaparinux	Cleared renally; more predictable dose response; not dependent on plasma protein levels Cleared renally	Significantly less bleeding in older pts, even with renal dysfunction vs. UFH + GP IIb/IIIa with similar efficacy Renal/weight adjust; less bleeding but similar efficacy vs. enoxaparin in older pts with NSTEMI-ACS, even with mild to moderate renal dysfunction	CrCl <30 mL/min: 1 mg/kg/h; CrCl: 30 to 60 mL/min—less bleeding than UFH Renal adjustment: CrCl <30—contraindicated; CrCl 30 to 60—preferred over enoxaparin	Less bleeding than GP IIb/IIIa inhibitor + heparin ↓Bleeding vs. enoxaparin; good safety profile vs. UFH/LMWH
P2Y₁₂ Inhibitors • Clopidogrel • Prasugrel • Ticagrelor	Lipophilic; ↑HPR; ↑metabolism; ↑fat distribution; ↑to steady state (↑fat distribution/T _{1/2}) ↑19% Active metabolite >75 y of age None known	↓Antiplatelet effect in some older pts ↑Bleeding risk N/A	Maintenance: 75 mg (no ↑response to higher dose) Avoid in pts ≥75 y of age or if weight ≤60 kg; 10 mg in very high-risk pts None	↓Effect with proton pump inhibitors; if HPR—may respond to prasugrel or ticagrelor N/A Reversible
GP IIb/IIIa Inhibitors • Abciximab	N/A	• ↑Bleeding with ↑age • ↑Bleeding risk without clinical benefit	Not recommended	N/A

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

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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; NSTEMI-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; T_{1/2}, half-life; and UFH, unfractionated heparin.

Table C. Age-Related Physiological Changes: Clinical Impact in Older Patients With NSTEMI-ACS

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

AF indicates atrial fibrillation; AKI, acute kidney injury; AV, atrioventricular; BP, blood pressure; CKD, chronic kidney disease; CO, cardiac output; CrCl, creatinine clearance; DBP, diastolic blood pressure; DOE, dyspnea on exertion; DVT, deep vein thrombosis; EDP, end-diastolic pressure; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HR, heart rate; K, potassium; LA, left atrium; LBBB, left bundle-branch block; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; NA, sodium; Na/K sodium and potassium clearance; NSTEMI-ACS, non-ST-elevation acute coronary syndrome; PA, pulmonary artery;

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PE, pulmonary embolism; RBBB, right bundle-branch block; SBP, systolic blood pressure; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; and $VO_{2\text{ max}}$, maximum oxygen consumption.



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

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

*P values were calculated with the log-rank test on the basis of all available follow-up data (i.e., >5 y).

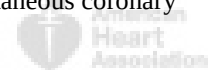
†The primary composite outcome was rate of death from any cause, MI, or stroke.

‡p=0.006 in the as-treated (non-intention-to-treat) analysis.

§p=0.16 by the Wald test of the Cox regression estimate for study-group assignment in 1,712 patients after adjustment for average glucose level after procedure.

CABG indicates coronary artery bypass graft; FREEDOM, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Modified with permission from Farkouh et al. (616).



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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

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Circulation. published online September 23, 2014;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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2014 NSTE-ACS Guideline Data Supplements

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Data Supplement 1. Clinical Assessment and Initial Evaluation (Section 3.1)

Title, Author, Year	Study Aim	Study Type/Size (N)	Patient Population		Endpoints		P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
			Inclusion Criteria	Exclusion Criteria	Primary Endpoint & Results	Safety Endpoint & Results			
Antman EM et al. 2000 10938172 (1)	Develop a simple scoring system to predict the risk of death and ischemic events for pts with UA/NSTEMI	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	Inclusion in TIMI 11B trial or ESSENCE trial	Not included in these trials	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: ≥65 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: 0/1: 4.7%; 2: 8.3%; 3:13.2%; 4: 19.9%; 5:26.2%; 6/7: 40.9%	N/A	Event rates <significantly as TIMI risk score <in test cohort in TIMI 11B (p=001 by ×2 for trend). Pattern of <event rates with <TIMI risk score confirmed in all 3 validation groups (p=001). Slope of <in event rates with <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)	N/A	Regression model developed in pts with diagnosed ACS and was not designed to be applied indiscriminately to undifferentiated chest pain pts
Boersma E et al. 2000 10840005 (2)	Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE-ACS	Retrospective analysis of pts with NSTEMI-ACS enrolled in PURSUIT trial (N=9,461; 3.6% with 1° outcome)	Pts enrolled in PURSUIT trial	Pts not enrolled in PURSUIT trial; pts with STE on initial ECG	1° outcome: 30-d death; 2° outcome: composite of 30-d death and myocardial (re)infarction; More than 20 variables were found to be predictive of 1° and 2° outcomes	N/A	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); C-index for the mortality model was 0.814	N/A	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
Granger CB et al. 2003 14581255 (3)	Develop a regression model in pts with diagnosed ACS (including pts with	Retrospective observational study utilizing pts from GRACE (N=11,389; 509 deaths); validation set	Inclusion in GRACE or GUSTO-IIb trial	Not included in these trials	Adverse event defined as in-hospital mortality; Regression model identified following 8 independent risk factors: accounted age, Killip class, SBP,	N/A	The discrimination ability of the simplified model was excellent with C-statistics of 0.83 in the derived database, 0.84 in the confirmation	N/A	Regression model developed in pts with diagnosed ACS (including STEMI pts) and was not designed to be applied indiscriminately to

	STEMI) for in-hospital 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 pre-existing 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 1° outcome)	Pts with chest pain who had an ECG obtained	Pts <30; cocaine use within 7 d	1° outcome composite of death, MI, PCI, CABG within 30 d of initial presentation	Increasing TIMI score associated with increased rates of adverse outcome	N/A	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 1° 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	N/A	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 1° endpoint (N=1,017)	Pts presenting to ED with chest pain in whom a	Pts with STE-AMI, hemodynamic instability, cocaine	1° outcome defined as MI, PCI, CABG, or cardiac death within 30 d of initial presentation	Increasing sens of modified TIMI score seen with increasing	N/A	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

	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 21988945 (7)	Compared GRACE, PURSUIT, and TIMI scores in risk stratification of chest pain pts	Prospective data collection for TIMI score; retrospective determination of PURSUIT and GRACE score (N=4,743; 319 pts with 1° outcome)	Chest pain pts>30 y who had ECG obtained and were enrolled in previous study utilizing TIMI score in risk stratification of chest pain pts	Pts in which scores were unable to be calculated due to incomplete data (e.g., no creatinine obtained)	1° outcome composite of death, MI, PCI, or CABG within 30 d of presentation	The TIMI and GRACE score outperformed the PURSUIT score in risk stratification of ED chest pain pts	N/A	The AUC for TIMI was 0.757 (95% CI: 0.728-0.785); GRACE, 0.728 (95% CI: 0.701-0.755); and PURSUIT, 0.691 (95% CI: 0.662-0.720)	Retrospective nature of comparison of TIMI score to GRACE and PURSUIT
Sanchis J et al. 2005 16053956 (8)	Develop a risk score for ED pts with chest pain	Retrospective (N=646; 6.7% with 1° endpoint)	Chest pain pts presenting to ED undergoing evaluation for ACS who subsequently were admitted to chest pain unit	Significant STE or depression on initial ECG; abnormal Tn; not admitted to chest pain unit	N/A	1° endpoint: 1-y mortality or MI; point); 4 factors were found to be predictive of 1° endpoint and were assigned following score: chest pain score ≥10 points: 1 point, ≥2 pain episodes in last 24 h: 1 point; age≥67 y: 1 point; IDDM: 2 points, and prior PCI: 1 point; Pts were classified in 5 categories of risk (0, 1, 2, 3, 4, >4) with direct correlation of increasing rates of 1° outcome with risk score	N/A	Accuracy of score was greater than that of the TIMI risk score for the 1° (C-index of 0.78 vs. 0.66; p=0.0002) and 2° (C-index of 0.70 vs. 0.66; p=0.1) endpoints	Small study size; selection bias towards more healthy pts as study population limited to pts admitted to chest pain unit; chest pain component of score is not easily calculated

Christenson J et al. 2006 16387209 (9)	Develop a scoring system for discharge of pts from the ED that would miss <2% of ACS	Prospective cohort with retrospective creation of decision rule (N=769; 165 with 1° outcome)	Pts presenting to ED with chest pain between 7 am-10 pm h	<25, traumatic or radiologically evident cause of CP, enrolled in study in previous 30 d, or had terminal noncardiac illness	1° outcome MI or definite UA	Prediction rule: if pt had normal initial ECG, no Hx CAD, age<40 y, and normal baseline CK-MB<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	CI for prediction rule not supplied	N/A	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
Backus BE et al. 2010 20802272 (10)	Validation of the HEART Score which utilizes elements of patient History, ECG, Age, Risk factors, and Troponin to risk stratify ED chest pain pts	Retrospective analysis of prospective database (N=880; 158 with 1° outcome)	Pts admitted to “cardiology” ED	STE on initial ECG	1° outcome was a composite of AMI, PCI, CABG, and death within 6 wk of initial presentation	Rates of 1° outcome seen with increasing score: 0–3: 0.1%; 4–6: 11.6%; 7–10: 65.2%	N/A	Hx, ECG, and Tn were independent predictors of the combined endpoint (p<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±0.0001). C–stat 0.897	Retrospective; weighting of the elements of HEART Score arbitrarily assigned and not based on likelihood ratio analysis or regression analysis
Fesmire et al. 2012 22626816 (11)	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	Retrospective analysis of prospective database (N=2,148; 315 with 1° outcome)	Pts presenting to ED with chest pain undergoing evaluation for ACS	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)	1° outcome was 30-d ACS defined as MI, PCI, CABG, life-threatening cardiac complications, or death within 30 d of initial presentation	Increasing HEARTS ₃ 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 ₃ score	N/A	HEARTS ₃ 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)	Retrospective; utilized older-generation Tn
Hess EP et al. 2012 21885156 (12)	Develop a prediction rule for pts at low risk of 30-d adverse cardiac events	Retrospective analysis of prospective database (N=2,718 pts; 336 with adverse events)	Pts presenting to ED with chest pain in whom Tn value was obtained	Pts with STE-AMI, hemodynamic instability, cocaine use, terminal illness, or pregnancy	1° outcome defined as MI, PCI, CABG, or cardiac death within 30 d of initial presentation	Prediction rule consisted of the absence of 5 predictors: ischemic ECG changes, Hx of CAD, pain typical for ACS, initial or 6-h Tn	N/A	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	Rule developed retrospectively; only 82% of eligible pts enrolled

						level > 99 th percentile, and age <50 y. Pts aged ≤40 y required only a single Tn evaluation			

1° indicates primary; ACS, acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; AUC, area under the curve; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CK-MB, creatine kinase-MB; CP, chest pain; ECG, electrocardiograph; ED, emergency department; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HEART, Healing and Early Afterload Reducing Therapy Trial; HF, heart failure; Hx, history; MI, myocardial infarction; N/A, not applicable; NSTEMI, non-ST-elevation; NSTEMI-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non–ST-elevation myocardial infarction; Pts, patients; PCI, percutaneous coronary intervention; revasc, revascularization; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina:Receptor Suppression Using Integrilin Therapy; ROC, receiver operator curve; SBP, systolic blood pressure; Sens, sensitivity/sensitivities; Spec, specificity/specificities; STE, ST-elevation; STE-AMI, ST-elevation acute myocardial infarction; STEMI, ST-elevation myocardial infarction; TAAR, tachyarrhythmia; TIMI, Thrombolysis In Myocardial Infarction; Tn, troponin; UA, unstable angina; and UFH, unfractionated heparin.

Data Supplement 2. Risk Stratification (Section 3.3)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Secondary Endpoint & Results		
Antman 2000 10938172 (1)	Development of original score to risk stratify pts presenting with ACS	Multisite RCTs, TIMI-11 B and ESSENCE	N/A	Clinical ACS, ECG changes, and elevated biomarkers	Planned revasc, bleeding risks, and correctable cause for angina	N/A	All-cause mortality, new or recurrent MI, severe ischemia leading to revasc	N/A	p<2 selected for multivariate modeling, then variables scored	Biomarkers all elevated; 65 y pg age cutoff
Pollack 2006 16365321 (13)	Validation in ED population with chest pain	Convenience sample N=3,326 without new STE	N/A	Chest Sx and ECG obtained	New STE	N/A	Death/MI/revasc over 30 d	In-hospital and 14-d events	Graded relationship between score and events	Used parts of score to define management
Go 2011 21691204 (14)	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	Renal dysfunction increased risk, but not enough to add variable to system	Small and only 9% with eGFR, 30
Huynh 2008 19960136 (15)	Across all ACS spectrum	Multicenter RCT with N=1,491 from angiographic arm	N/A	NSTEMI-ACS and STEMI	N/A	N/A	6-mo death and MI	N/A	2 mm ST deviation increased risk and risk was less regardless of score with less	All high-risk pts
Boersma 2000 10840005 (2)	N/A	Multicenter RCT-Pursuit	N/A	NSTEMI-ACS	STE	N/A	Death and MI	N/A	Similar risk prediction to TIMI over groups with many similar variables	No biomarkers
Eagle 2004 15187054 (16)	Original GRACE validation	Registry N=17,141	N/A	All ACS	N/A	N/A	6-mo all-cause mortality	N/A	p<0.25 into multivariate model	Registry data, 200 pts without 6-mo follow-up

Granger 2003 14581255 (3)	Validation in NSTE-ACS as training set and then test set in registry with validation in RCT	11,389 from registry and then testing in 3,872 from GRACE and 12,142 from GUSTO IIb	N/A	NSTE-ACS	N/A	N/A	All-cause mortality during hospitalization	N/A	p<0.25 into multivariate model	Only high-risk pts
Eggers 2010 20598977 (17)	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Single center trial of 453 chest pain pts	NT-proBNP, cystatin GDF-15	Possible ACS	N/A	Biomarkers at presentation	All-cause mortality at 6 mo	NT-pro BNP not additive, cystatin minimally and GDF-15 helpful	ROC analysis	Small, but 92 deaths
Abu-Assi 2010 21095268 (18)	Does GRACE score still work with modern management	MASCARA national registry N=5,985	N/A	Confirmed ACS	N/A	LVEF included	In-hospital and 6-mo mortality	LVEF did not add to GRACE score	N/A	Registry data, but contemporary management
Meune 2011 21444339 (19)	Question as to whether hs-cTn or NT-proBNP influence prediction	370 pts from APACE trial with 192 MIs	Hs-cTnT and NT-pro added to GRACE score	Non-STE-ACS	N/A	N/A	Hospital and 1-y mortality	No additive benefit	N/A	All pts likely had elevated hs-cTnT

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 national 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.

Data Supplement 3. Cardiac Injury Markers and the Universal Definition of AMI (Section 3.4)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Secondary Endpoint & Results		
Thygesen 2012 22958960 (20)	Definition of MI	Guideline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Roger 2006 16908764 (21)	Prospective Evaluation of new criteria for Dx of MI	Prospective community based epidemiologic study	Identification of MI using TrT vs. CK-MB and CK compared with WHO and ARIC criteria	County residents with TrT ≤0.03 ng/mL identifying MI	Lower TrT values	N/A	Identification of MI 538 MI with TrT; 327 with CK; 427 with CK-MB	Clinician Dx mentioned MI in only 42% of TrT-based criteria (diagnosing UA in many) vs. 74% using previous criteria p<0.001	74% increase TrT vs. CK (95% CI: 69%–79%) 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
Hamm 2000 10880424 (22)	Classification of UA	Reclassification based on Tr levels	N/A	Angina at rest within 48-h Class IIIB into Tr+ and Tr-	N/A	N/A	30-d risk of death 20% in IIIB Tr+, <2% in IIIB Tr +	N/A	N/A	N/A

Kavsak 2006 16824840 (23)	Impact of new classification of MI	Retrospective analysis using CK-MB vs. TnI analysis for MI defined by 258 pts with ACS	TrI vs. CK-MB Dx based on MONICA or AHA definition of MI	2 SPSS CK-MB, TrI $\geq 20\%$ change using 99% TrT cutoff	N/A	2 specimens CK-MB, TrI drawn at least 6 h apart	AMI prevalence MONICA CK-MB 19.4% AHA 19.8%. TnI to 35.7%	TrI-vs. CK-MB $p < 0.001$ for increase MI definition using TnI	cTnI 35.7% (30.1–41.7) Relative increase 84%	Exclusion of nonischemic diseases causing Tr elevation
Eggers 2009 19231317 (24)	Effects of new UDMI on misdiagnosis with single evaluation of Tr	Retrospective evaluation of stable community sample (995) and post-AMI pts (1380) with TrI $\geq 99^{\text{th}}$ percentile	Evaluation of single Tr in stable population	Stable community population. Stable 3-mo post-MI pts	Evidence of clinical instability	1 cTnI	Community Sample; 0.6% MI by UDMI Stable post-MI; 6.7% MI by UDMI	N/A	N/A	N/A
Goodman 2006 16504627 (25)	Diagnostic and prognostic impact of new UDMI	Multicenter observational prospective Registry (GRACE) 26,267 pts with ACS	Use of CK and Tn neg 16,797 vs. CK-MB and Tn 10,719 for hospital. fatality, 14,063 vs. 8,785 for 6-mo mortality	>18 y with possible ACS with ECG abnormal or CAD history. CK, CK-MB. Tn.	NS comorbity, trauma, surgery, lack of 1 biomarker	CK CK-MB Tn Follow up for 6 mo	Tn+ levels demonstrate higher in-hospital and 6-mo mortality rates than higher CK levels	In entire population, Tn+ status vs. CK status 6-mo. mortality: 1.6 (1.4–1.9)	Hospital fatality rates higher with Tn+ vs. CK+: 2.2 (95% CI: 1.6–2.9) with Tn+/CK-MB-: 2.1 (95% CI: 1.4-3.2)	34% in GRACE registry excluded because of use of 1 biomarker only
Eggers 2011 20869357 (26)	Clinical implications of relative change in cTnI levels with chest pain	Retrospective study of 454 pts with ACS within 24 h of admission with 5.8-y follow-up	UDMI with prespecified cTnI changes from $\geq 20\%$, 50%, 100%	N/A	cTnI $< 99^{\text{th}}$ percentile	cTnI levels	Peak cTnI level $\geq 99^{\text{th}}$ percentile positive change $\geq 20\%$ in 160 pts. 25 pts had no AMI by ESC/ACC criteria	N/A	All 160 pts had significant raised mortality HR 2.5 (95% CI: 1.7–3.8) Higher TnI deltas were not associated with higher mortalities	Analysis of assay could not be validated by hs-Tr assay. No review of pts records for type I or 2 AMI No long-term risk assessment
Mills 2012 22422871 (27)	Evaluation of ACS pts by using cTnI diagnostic threshold and $\leq 99^{\text{th}}$ percentile on Dx and risk for future events	Retrospective cohort study with 1-y follow-up of 2,092 consecutive pts with suspected ACS	Study groups: cTnI < 0.012 , 0.012–0.049, and ≥ 0.50 (99 th percentile) with C of V $\geq 20\%$ vs. previous diagnostic criteria	cTnI ACS	Noncardiac chest pain, tachyarrhythmia, anemia. Severe Valve HD, HOCM, pericarditis, cocaine use	cTnI values	1-y outcomes based on cTnI subgroups: 0.012–0.049 had higher mortality and re-MI than < 0.012 (13% vs. 3%) Increase in Dx of MI based on new criteria by 47%	Compared with ≥ 0.050 , Tr 0.012–0.049 had a higher risk profile, but less likely to be investing for AMI	$p < 0.001$ for 1-y outcome of 0.012–0.049 vs. < 0.012	Not a prospective study. Tn levels of 0.012-0.049 were considered “normal” and not repeated. Possible myocardial ischemia due to noncardiac illness.
TRITON-TIMI 38 Bonaca 2012 22199016 (28)	Association between new and recurrent MI using new UDMI classification system and risk of death	Prospective cohort analysis of 13,608 pts with ACS undergoing PCI TRITON-TIMI 38 study	Follow-up of recurrent MI vs. no follow-up MI and risk of death at 6 mo	Types 1, 2, 3, 4, 5 MI	Cardiogenic shock or any condition that was associated with decreased survival over 15 mo	Tn used preferentially for recurrent MI and CK-MB for peri-PCI MI	Risk of death at 6 mo after follow-up MI: MI at follow-up 6.5% vs. 1.3% and by subtypes	N/A	$p < 0.001$ for death after recurrent MI vs. no recurrent MI $p < 0.001$ for difference with each of 5 subtypes	Association of MI with death not necessarily related to causality. Confounders could explain relationship. Standard Cox regression may bias

									results
ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; AMI, acute myocardial infarction; ARIC, Atherosclerosis Risk in Communities; CAD, coronary artery disease; C of V, coefficient of variation; CK, Creatine Kinase; CK-MB, Creatine kinase-MB; cTnI, Cardiac troponin I; Dx, diagnosis; ECG, electrocardiograph; Elev, elevation; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; HD, heart disease; Hs-Tn, high-sensitivity Troponin; HOCM, Hypertrophic Obstructive Cardiomyopathy; MB, myocardial band; MI, myocardial infarction; MONICA, Multinational MONItoring of trends and determinants in CArdiovascular disease; N/A, not applicable; NSTEMI, non-ST segment elevation myocardial infarction; pt, patient; PCI, percutaneous coronary intervention; SPSS; STEMI, ST elevation MI; TIMI, thrombolysis in myocardial infarction; Tn, Troponin; Tn+, positive troponin, Tn-, negative troponin; Tr, Troponin; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel; TrT, Troponin T; TrI, Troponin I; UA, Unstable angina; UDMI, Universal Definition of MI; and WHO, World Health Organization.									

Data Supplement 4. Cardiac Troponins (Section 3.4.3)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Secondary Endpoint & Results		
Apple 2009 19299542 (29)	Dx, accuracy of cTnI for early detection of AMI and risk prediction for adverse events	Prospective cohort study 381 with possible ACS	VITROS TnI-ES assay 2× vs. clinical Dx of AMI	Sx suggestive of ACS in ED	No 2 nd Tn level	Tn assay at admission and 6 h later for delta change	Sens and spec for MI from admission and delta change (see p values) Sens increased from admission to 6-h cTnI and ROC from 0.82–0.96 (p<0.001)	Risk stratification improved by 30^ Delta to initial cTnI >99 th percentile. Risk of death/follow-up MI within 60 d	Sens admission cTnI for AMI 69% (95% CI: 55%–81%) Spec 78% (95% CI: 73%–82%) 6-h cTnI Sens 94% (95% CI: 84–99) Spec 81% (95% CI: 77%–85%) Deltas >30% Sens 75% (95% CI: 6%–86%) Spec 91% (95% CI: 87%–94%) Delta cTnI added to initial or follow-up cTnI improved risk stratification p<0.001	Difficulty in ascertaining time of initial Sx. Problems with getting 2 nd sample at 6 h Question of false +cTnI Initial rather than discharge sampling may have biased evaluation of risk at 60 d
Bonaca 2010 20447535 (30)	Px implication of low-level inclusion in Hs-cTnI in possible ACS	Prospective multi study 4,513 with NST-ACS	+ or – hs-cTnI 99 th percentile for death/MI in 30 d	NST-ACS	Shock ,ST-elevation, revasc before random	Baseline cTnI with cutpoint at 99 th percentile	+cTnI higher risk of death/MI at 30 d than - cTnI 6.1% vs. 2.0% p<0.001	Pts with low-level increases 0.04-1.0 at <risk than cutpoint of 0.04 (5.0% vs. 2.0%); p=0.001	Risk of death 12 mo vs. <0.04 ug/L 6.4% vs. 2.4%; p=0.005	Does not address all pts with nontraumatic chest pain
Kontos 2010 21095267 (31)	NSTEMI with +Tn but -CK-MB in treatment and outcomes	Post hoc data base analysis 16,064 with NSTEMI	Tr+ MB- vs. Tr+ MB+	Present within 24 h of Sx with NSTEMI	No STEMI	Biomarkers on admission, Tr and CK-MB	Treatment and in-hospital outcomes. In-hospital mortality lower in MB pts	MB- were older and had more comorbidities. p<0.01 and fewer intervals	In-hospital mortality: MB+ 4.9 vs. 3.8 MB– p<0.02	No central core lab in multi-institutional study

		Tr+ and MBCK -								
Lindahl 2010 20691825 (32)	Hs-cTnT comparison with std cTnT for risk assessment	Prospective cohort 1,452	Effect of + by both assays vs. only 1 assay	Pts with ACS	No coronary angiography within 12 h	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 1-y 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
Giannitsis 2010 20167697 (33)	Dx, performance of Hs-cTnT for detection of NSTEMI in ACS	Retrospective cohort analysis 57 with UA and evolving NSTEMI	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
Giannitsis 2008 18206741 (34)	Serial TnT measurements vs. MRI infarct mass	Retrospective cohort analysis 31 STEMI and 30 NSTEMI	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	cTnT at d 4 showed highest correlation and performed as well as peak cTnT and AUC r=0.66 vs. r=0.65 vs. r=0.69	Possible poor timing of sampling with NSTEMI and visualization problems with MRI in NSTEMI vs. STEMI
Keller 2011 22203537 (35)	Diagnostic performance of hs-cTnI with continued. cTnI for serial changes	Prospective multicenter analysis 1,818 with suspected ACS, 413 with AMI	Hs-TnI and St-TnI	Suspected ACS	Major surgery or trauma within 4 wk, pregnancy, drug abuse	Hs-TnI and St-TnI at baseline and 3 h serial changes	Both Hs-TnI and St-TnI at 99 th 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
Younger 2007 17540686 (36)	72-h TnI estimate with MRI for infarct size	Prospective cohort analysis 93 MI 19 NSTEMI	TnI correlation with MRI	STEMI, NSTEMI, LBBB 1 st MI TnI CK MRI	Prior AMI contraindication to MRI previous revasc, PCI before MRI	Admission and 12-h TnI and CK MRI average 3.7 d from admission	72h Tn similar to CK for infarct size estimate and superior to 12-h TnI	Correlation of 12-h TnI with microvascular obstruction was NS p=0.16 Compared with peak CK r=0.44 72-h TnI 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.
Apple 2012 22465126 (37)	Diagnostic accuracy and risk stratification of cTnI-ultra assay	Prospective cohort study 371	cTnI at admission and up to 24 h for optimum deltas using ROC analysis	Possible ACS with follow-up for 60 d	N/A	cTnI at 0-, 6-, 24-h for optimum % change, absolute % change, change, absolute value of change	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

Reichlin 2011 21709058 (38)	Diagnostic accuracy of absolute value relative changes in cTn	Prospective multicenter 836 with ACS	Absolute value relative changes in cTn	Sx suggesting AMI	STEMI, terminal kidney failure	Hs-TnT and cTnI ultra at admission and 1 h and 2 h	ROC at 2-h higher for absolute than relative changes	ROC absolute cutoff 2 h 0.007 ug/L hs and 0.020 ug/L for ultra	ROC absolute change Hs-TnT 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
Aldous 2012 22291171 (39)	Early means of hs-TnT vs. conventional cTnT in NSTE-ACS	Prospective cohort 909, and 205 with AMI	NSTE-ACS with conventional and hs-TnT assays	NSTE-ACS	STEMI <18 y, unable to follow-up	Hs-TnT and conservative TnT at admission, 2 h and 6-12 h	Dx of MI on admission at 2 h Hs-sens 92.2% and spec of 79.7%	Mortality at 1 y 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 2 h Sens (95% CI: 88.1%–95.0%) spec (95% CI: 78.6–80.5)	Blood samples not taken beyond 2 h. Used cTnI as gold standard for Dx of MI
Mueller 2012 22134520 (40)	Kinetic changes on hs-cTnT in ACS and non-ACS	Prospective cohort 784 NSTEMI 165	Pts with ACS with hs TnT vs. non-ACS with hs-TnT above 99 th percentile	ACS with 2 nd blood draw within 6-h Non-ACS with 2 blood draws	STEMI or LBBB	Hs-TnT-ACS and non-ACS with elevated hs-TnT2 blood draw within 6 h	Absolute delta vs. relative delta ROC-optimized value 6.9 ng/L was sup to rel change ≥20%	+Predicted value of absolute change 82.8% -predicted 93.0%	ROC for absolute change added value for entire ACS cohort vs. relative change. p<0.0001	Relative changes confined to 6 h, not 24 h. Not all pts received angiography

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; AUC, area under the curve; CK, Creatine Kinase; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; cTnT, cardiac troponin T; cTn, cardiac troponin; cTnI, cardiac troponin I; Dx, diagnosis; ED, emergency department; Hs, high sensitivity; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity troponin T; hs-TnT, high-sensitivity troponin T; LBBB, left bundle-branch block; MBCK, MB Isoenzyme of Creatine Kinase; MI, myocardial infarction; MRI, magnetic resonance imaging; N/A, not applicable; NST-ACS, non-ST acute coronary syndrome; NSTE, Non-ST-elevation; NSTEMI, Non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; Pts, patients; Px, prognosis; ROC, Receiver Operating Curves; Sens, sensitivity/sensitivities; Spec, specificity/specificities; Std TnI, standard troponin I; Std cTnT, standard cardiac troponin T; STEMI, ST-elevation myocardial infarction; Sx, symptom; Tn, troponin; TnT, troponin T; TnI, troponin I; and UA, unstable angina.

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

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Secondary Endpoint & Results		
Apple 1999 9931041 (41)	Use of triage panel of TrT, CK-MB, and myoglobin for AMI detection	Multicenter prospective study 192	Comparison of myoglobin, TnI and CK-MB for sens and spec	Pts in ED with ACS	N/A	Triage panel biomarkers to evaluate ROC for AMI pred	Concordance for detection or rule-out of MI TnI >89% CK-MB >81% Myoglobin >69%	Sens/Spec TnI: 98/100 CK-MB: 95/91 Myoglobin: 81/92	ROC values TnI: 0.97 CK-MB: 0.905 Myoglobin: 0.818 diff p<0.05	Does not address reinfarction or AMI presenting after 72 h
TACTICS-TIMI 18 Kleiman 2002 12354426 (42)	CK-MB vs. TnT to predicted cardiac risk and benefit in AMI invasive strategy	Multicenter prospective study 2,220	CK-MB elevated in 826. With CK-MB-, TnT elevated in 361	1 st 24 h of chest pain	N/A	Invasive or conservative strategy with CK-MB and TrT for 30-d and 180-d risk.	CV events 30 d/180 d Event rates 2× as high with CK-MB+ value –. benefit in invasive with Tr+, but CK-	No evidence of interaction between CK-MB elevation and strategy on 30-d and 180-d endpoints	OR benefit of invasive strategy CK-Tr+ 30 d: 0.13 (95% CI: 0.04–0.39) 180 d: 0.29 (95% CI: 0.16–0.52)	Small group analysis–hypothesis generating

Aviles 2002 12372578 (43)	Long term Px in UA with elevated Tnl and normal CK-MB and CK	Retrospective cohort 724	All CK-MB- and Tnl+	Clinical UA including Class IIIa	N/A	Using Trl with normal CK and CK-MB for 2-y risk evaluation	2-y all-cause mortality 20% with Tn>0.5 ug/L, 8% with <0.5 ug/L	N/A	2-y mortality Tr >0.5 vs. <0.5 HR 2.59 (95% CI: 1.66–4.05); p<0.001	Study did not evaluate serial ECGs for dynamic changes
Sallach 2004 15464666 (4)	Sens of myoglobin with normal Tnl in AMI	Prospective multicenter 817	Myoglobin and Tnl	Possible AMI with normal Trl (27)	Incomplete biomarker panel or noncardiac	Myoglobin Dx of MI with normal Tnl	Increase myoglobin of 20 ng/mL from 0-90 min max diagnostic utility with –myoglobin and-Tnl at admission	Combination sens change myoglobin+ Tnl at 90 min 97.3%	Change Myoglobin >20 90 min Sens: 83.3%, 88.6% spec: 99.5% – Predicted value for AMI	Relatively small number of AMIs. Predetermined values of myoglobin not evaluated
Eggers 2004 15459585 (44)	Value of adding myoglobin to Tnl to exclude AMI	Prospective cohort 197	Tnl and CK-MB	Chest pain >15 min in past 24 h	STE	Tnl and Myoglobin for exclusion of MI	Tnl highest sens of all markers at all-time pts.	Tnl 0.07 ug/L cutoff sens: 30 min=93%, 2 h=98%, 3 h=100%	Tnl sens 93% spec 81% at 2-h CK-MB 79% Myoglobin 67%	Relatively small group. Relatively long delay time from pain to admission
Storrow 2006 17112930 (45)	Associated among discordant Tn, CK, and CK-MB chest pain evaluation	Multicenter prospective registry 1,614	Discordant CK-MB/Tn 113 includes MB with normal CK 239	Possible ACS	Transfer or ECG for routine purposes	CK-MB and Tr with evaluation of significance. of discordant values	OR for AMI vs. Tr-/CK-MB-both positive: 26.6 Tn+ 4.8 CK-MB+ 2.2	CK-MB+/CK- 5.7 (95% CI: 4.4–7.4) CKMN+/CK+ 4.36 (95% CI: 3.6–5.2) Ref: vs. CK-MB-	CK-MB/Tn+: 26.6 (95% CI: 18.0–39.3) Tn+/CK-MB-: 4.8 (95% CI: 3.4–6.8) Tn-/CK-MB+: 2.2 (95% CI: 1.7–2.8)	N/A
CRUSADE Newby 2006 16412853 (46)	Frequency and implications of discordant CK-MB and Tn in ACS	Multicenter prospective 29,357	22,687 Tn+ 20,506 CK-MB+ 3,502 both – 2,988 only CK+ 5,349 only Tn +	High-risk NSTE-ACS	N/A	CK-MB and Tr during 1 st 36 h of ACS to evaluate discordance	Adjusted OR for hospital mortality CK-MB+/Tn +: 1.53 CK-MB-/Tn+: 1.15 CK-MB+/Tn- 1.02	In-hospital mortality both–: 2.7% both+: 5.9% Only CK-MB+: 3.0% Only Tn: 4.5%	CK-MB+/Tn+: 1.53 (95% CI: 1.18–1.98) CK-MB-tn+: 1.15 (95% CI: 0.86–1.54) NS CK-MB+/Tn-: 1.02 (95% CI: 0.75–1.38) NS	Used individual labs for ULN. No account for timing of positive markers
Kavsak 2007 17306781 (47)	Effect of Tn on myoglobin and CK-MB isoforms in ACS	Retrospective cohort 228	CK-MB isoforms, myoglobin and Accu Tnl	Possible ACS	N/A	CK-MB , myoglobin and Trl to compare utility in R/O MI <6 h assays	Clinical sens for AMI: For both myoglobin and CK-MB Dec. in ESC/ACC MI def	N/A	WHO MI def: sen >90% ESC/ACC def: Both sen<70% Using Tnl assay	Insufficient time elapse before remeasuring Tnl
Jaffery 2008 19061710 (9)	Myoglobin and Tnl pred of long-term mortality in ACS	Retrospective cohort 951	Tnl, myoglobin, and CK-MB	Possible ACS	N/A	Tnl, Myoglobin, and CK-MB at presentation with ACS	+Tnl and +Myoglobin, but not +CK-MB Pred. 5-y all-cause mortality	N/A	+Tnl: 1.7 (95% CI: 1.3–2.3) +Myoglobin: 1.6 (95% CI: 1.2–2.1) +MB: NS	Single center. Tnl assay no longer in use. No peak levels of markers recorded
Di Chiara 2010	Pred value of Tnl vs.	Prospective	55 STEMI and 5	AMI + reperfusion	No pacemakers,	Tnl and CK-MB at	Tn at 72 h most accurate	N/A	Tnl:	Blood samples every

20588136 (10)	CK-MB for infarct size with CMR	cohort 60	NSTEMI TnI, CK-MB	with CMR within 7 d	clips, peak markers on admission	admission and serially up to 96 h from Sx onset	estimate of predischage infarct volume		0.84 (95% CI: 0.75–0.91) CK-MB: 0.42 (0.19–0.62) p<0.02	6 h could be too sparse. Could miss biomarker peak
ACTION-GWTG Registry Chin 2012 22434769 (48)	Prognostic value of CK-MB vs. Tn in AMI	Retrospective registry 26,854	Peak CK-MB and TnI	AMI in data registry with biomarkers	Peak values below lab ULN	Peak CK-MB and TnI for in-hospital mortality	Both peak CK-MB and TnI are independently associated with hospital mortality CK-MB >TnI	N/A	Peak CK-MB C-statistic 0.831 Peak TnI C-statistic 0.824 p=0.001	Registry only collects in-hospital outcomes. Participation in registry voluntary
Ilva 2005 15667582 (12)	Novel TnI in early risk stratification in ACS	Prospective cohort 531	Standard TnI novel TnI myoglobin	Biomarkers at 0 h, 1-12 h and 24 h after admission	Absence of 1 or more biomarkers	Comparison of 3 biomarkers at times indicated	Positivity of novel TnI assay for AMI in higher percent than other biomarkers	MI within 3 h of presentation: 50% by novel TnI and only 11.5% by reference TnI assay, (p<0.001) 44% by myoglobin (p=NS)	Novel TnI+ in 27.5%, standard TnI in 17.5%, (p<0.010) and myoglobin+ in 24.1% (p=0.067) ROC: novel TnI 0.937, ref TnI 0.775, myoglobin 0.762 (p<0.001)	Use a 1 st generation TnI assay with low analytic limits
Volz 20012 21129891 (13)	Can Tn alone be used for initial AMI screening with elimination of CK-MB	Retrospective cohort 11,092	TrT and CK-MB	All pts with TrT in ED with correspond CK-MB	Initial nonnegative Tn	CK-MB+ with TnT- to determine value on AMI screening	None with Tn- but CK-MB+ Judged to have AMI	N/A	Rate of true +CK MB with Tn- : 0% (95% CI: 0–0.04%)	No evaluation of CK-MB in pts with intermed or Tn+. No follow-up with - CK-MB or Tn.
Lim 2011 21292125 (49)	CK-MB vs. Tn in Dx of AMI after PCI	Prospective cohort 32	TnI and CK-MB	PCI and CMR imaging baseline and 7 d	N/A	CK-MB and TnI after PCI to determine Dx of AMI	Only small min of +Tn had CMR abnormal CK-MB+ closely approximate CMR injury	Percent changes in inflamed markers corresponded with CK-MB, but not TnI levels for CRP and SAA	ROC for detection of new MI CK-MB: 0.97 TnI: 0.985 NS, but poor TnI specific 22% TnI 93% CK-MB	Small sample size. No evaluation of inflamed markers after 24 for TNF alpha

ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase MB; CK-Tr+, 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; TnI, troponin I; TnT, troponin T; TrT, troponin T; UA, unstable angina; ULN, upper limit normal; and WHO, World Health Organization.

Data Supplement 6. Bedside Testing for Cardiac Biomarkers (Section 3.4.4)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population	Study Intervention	Endpoints	P Values, OR: HR: RR: & 95 CI:	Study Limitations

				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results		
Hamm 1997 9385123 (50)	Bedside evaluation of TnT and TnI in acute chest pain	Prospective cohort 773	TnT vs. TnI for Dx of MI and 30-d events +TnT 123 +TnI 171	Acute chest pain <12 h without STE	STE or AMI within 2 wk	Bedside tests of TrT and TrI 2×, arrival and >4 h	AMI TrI sens: 100% TrT sens: 94%	N/A	Event rates for – tests: 1.1% TnT 0.3% TnI	30-d event TrT 26 (10–49) TrI 61 (15–512)	All pts with +TnT admitted so event rate may be lower than that with conventional decision making
Van Domburg 2000 10980212 (51)	Long-term prognostic significance of bedside TnT	Prospective cohort 163	TnT, CK-MB, myoglobin 98 TnT + <12 h 48 + baseline 50 positive 3-12 h 2 positive 12-96 h	Suspected ACS	MI within previous wk	Blood specimen at 0 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h Bedside assay TROPT and quantitative assay sample up to 12-h effect on mortality prediction	29%+ on admission 60%+ in 12 h	N/A	Early myoglobin predict 3-y mortality 3.7 (95% CI: 1.0–12.0)	+TROPT risk for 3-y mortality: 4.3 (95% CI: 1.3–14.0) Quantitative assay 2.9 (95% CI: 1.0–8.6)	Detection limit of TnT higher than 2 nd generation Tn
Amodio 2007 17429291 (52)	POC TnI at 99 th percentile cutoff for diagnostic accuracy of MI	Retrospective cohort 516	Higher vs. lower TnI cutoffs and Dx of AMI 70 TnI+	Suspected angina or AMI	STE-ACS or LBBB	Bedside TrI Stratus CS for AMI Dx using different cutoffs 0.03–0.07 ug/L	Best clinical cutoff at 99 th percentile 0.03	N/A	Sens of myoglobin at 2 cutoffs 36.4% and 49%	Tn Sens at 99 th percentile 77.3% (68.3–84.7) 0.03>0.07 p<0.005	No info on outcomes Long median delay time from pain onset to admission No consideration of muscle trauma or renal insufficiency
DISPO-ACS Ryan 2009 18691791 (53)	POC length of stay in ED	Multi-institute prospective study 2,000	Bedside Tn testing + central lab Central lab only 1,000 in each arm	Suspected ACS with biomarkers	Tachyarrhythmia or ECG AMI	POC markers vs. lab markers	POC discharge Home 4.5 h Lab discharge Home 4.6 h	N/A	Transfer to inpt POC 5.4 h Lab 5.5 h	Turnaround at baseline POC 0.30 h Lab 1.07 h	Possible Hawthorne effect bias in testing areas. Different interinstitute sampling times.
CRUSADE Takakuwa 2009 19743496 (54)	Use patterns of POC testing for Tn in NSTE-ACS	Retrospective multi-institutional 12,604	POC with Tn+ vs. Tn- 6,185 +POC result 6,419 negative POC result	POC Tn in NSTE-ACS	Death within 24 h Hospital with 30 pts. Infrequent percentage use of bedside Tn	Hospital and pt characteristics In-hospital events and care variables Hospital using POC testing >50% vs. <50% testing	Higher POC had shorter ED stay, less likely to use drug IV	N/A	ED length of stay (h) No POC 4.2 (2.9–6.5) High POC 3.9 (2.6–6.0) p<0.0001	+POC results associated with expedited and higher use of anti-ischemic therapy. p<0.0001	Sample size relatively limited. No record of type of bedside marker test. No std. for + or – test
Birkhahn 2011 20825823 (55)	POC vs. core lab testing for time saving and cost/benefit	Prospective cohort 151	POC and core lab testing of TnT TnT+ in 12 pts	Suspected ACS with 2 TnT 6 h apart	STE, ECG, or lack of serial biomarkers	POC (TnT) CK-MB, myoglobin vs. central lab testing (TnI) baseline +2h vs. baseline +6 h	6.5 h saved using POC and relative sens of 100%. p<.00001	N/A	POC pathway had 32% false positives POC sens 100%, spec 65% Accuracy 68%	POC benefited 60% (95% CI: 52–68) of pts with cost of \$7.40 (95% CI: \$6.40–\$8.70) per direct pt care h saved.	Time of 2 nd blood test varied widely

Scharnhorst 2011 21350097 (56)	Sens and spec of bedside Tn compared with CK-MB and myoglobin	Prospective cohort 137	POC evaluation Tn, CK-MB, myoglobin, for rapid detection of +test 37+ ACS: 7 UA 26 NSTEMI 4 STEMI	Suspected NSTEMI	STE on AD ambulance to hospital	POC Tn values T0–T12 h and sens/spec for MI at 99% cutoff	At T2 Sens: 87% Spec: 100% +PV: 100% –PV: 96%	N/A	Use of 30% Diff T2-T0 without absolute included above 99 th percentile Sens: 100% Spec: 87%	2-h sens and spec of myoglobin and CK-MB lower than Tn Myoglobin: 50/92 CK-MB: 48/96	Low number of pts. No subgroup analysis. Broad 95% CI.
ASPECT Than 2011 21435709 (57)	Validate safety of predefine 2 h protocol (ADP) for ACS	Multicenter prospective observation study 3,582	POC evaluation Tn, CK-MB, Myoglobin 3260 ADP+ 270 ADP– 3,582 30-d follow-up	Suspected ACS	STE ACS, Noncoronary chest pain	ADP use of POC Tn, CK-MB, and myoglobin with 30-d follow-up	Major CV events at 30 d ADP Sens 99.3%	ADP class. 9.8% low risk. Major adverse event in only 0.9%	For 30-d events TIMI + ECG Sens: 98.1% Spec: 14.6% –PV: 98.3%	For 30-d events ADP Sens: 99.3% (95% CI: 07.9–99.8) Spec: 11% (10–12.2) –PV: 99.1% (97.3–99.8)	Low specificity. Atypical Sx not included
GUSTO-IV Venge 2010 21095269 (58)	Comparison of POC vs. laboratory assays of Tn	Prospective cohort 1,069	2 POC vs. 2 central laboratory assays cTnI	All pts in ED with Tn assays	N/A	Tn assays with 99 th percentile URL cutoffs	99 th percentile cutoffs: central lab cutoffs identified more pts with high cTnI and predicted higher % deaths	N/A	Central lab identified more who died of CV disease up to 3 mo: 88% vs. 50% 1: 81% vs. 54% 2	99 th percentile POC 1 vs. central lab 1: 20% vs. 39% POC 2 vs. central lab: 2:27% vs. 74% p<0.001 for each	No attempts to relate results to Dx of MI, only outcome predictions
[RATPAC] Bradburn 2012 21617159 (10)	Variation in outcomes and costs in different hospitals using POC	Multicenter prospective analysis 2,243	POC vs. central lab assays at 6 hospitals	Suspected, but not proven AMI at 6 hospitals.	Proven MI by ECG, high-risk ACS, known CAD, serious noncoronary pathology, recurrent chest pain	POC or std care with CK-MB, myoglobin, and Tn biomarkers	Difference in proportion of pts successfully discharged. POC led to higher proportion in 4, lower in 1 and equivocal in 1.	N/A	The cost per pt varied from £214.49 <control group to £646.57 more expensive with weak evidence of heterogeneity among centers p=0.08	OR varied from 0.12 (95% CI: 0.01–1.03) to 11.07 (05% CI: 6.23–19.66) with significant heterogeneity between hospitals	1° outcome based upon 1° effectiveness outcome rather than economic measures. Response rate was only 70% so possible responder bias
[RATPAC] Fitzgerald 2011 21569168 (59)	Cost effectiveness of POC biomaker assay	Multicenter prospective analysis 2,243	Std care 1,118 POC 1,125	Suspected, but not proven AMI at 6 hospitals	Proven MI by ECG, high-risk ACS, known CAD, serious noncoronary pathology, recurrent chest pain	POC or std care with CK-MB, myoglobin, and Tn biomarkers	POC associated with higher ED costs, coronary care costs, and cardiac intervention costs, but lower general pts costs	N/A	Probability of std care being dominant 0.888 POC dominant 0.004	Mean costs per pt \$1,987.14 with POC vs. \$1,568.64 with std care p=0.056	1° outcome based on 1° effectiveness outcome rather than economic measures. Response rate 70% so possible responder bias.

1° indicates primary; ACS, acute coronary syndrome; ADP, adenosine diphosphate; AMI, acute myocardial infarction; CAD, coronary artery disease; CK-MB, creatine kinase MB; cTnl, cardiac troponin I; CV, cardiovascular; Dx, diagnosis; ECG, electrocardiograph; ED, emergency department; IV, intravenous; Lab, laboratory; LBBB, left bundle-branch block; MI, myocardial infarction; Myo, myoglobin; NSTEMI, Non-ST-elevation MI; POC, point of care; pts, patients; +PV, positive predictive value; -PV, negative predictive value; Sens, sensitivities; Spec, specificities; Std, standard; STE, ST-elevation; STE ACS, ST-elevation acute coronary syndrome; STEMI, ST-elevation MI; Sx, symptom; TIMI, thrombolysis in MI; Tnl, Troponin I; TnT, troponin T; TrI, troponin I; TROPT, Troponin T rapid test; TrT, troponin T; and UA, unstable angina.

Data Supplement 7. Summary Comparison of Injury Markers (Section 3.4.4)

Study Name, Author, Year	Study Aim	Study Type / Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Secondary Endpoint & Results		
FRISC Lindahl 2000 11036119 (60)	Multiple biomarkers as long-term risk predictors for CV death	Multi-institution prospective 917	TnT CRP Fibrinogen	UA or possible MI within 72 h	Increased risk of bleeding (dalteparin trial)	Biomarker samples at 0 h, 12 h, 24 h	Cardiac death at 37 mo Multivariate analysis TnT and CRP independently predicted of mortality	Highest tertile of CRP significant for mortality. Lowest 2 tertiles NS difference p=0.001 3 rd vs. 2 nd tertile	Multivariate analysis: High TnT: 10.8 (95% CI: 2.6–44.6) High CRP 2.3 (95% CI: 1.3–4.0) Fibrinogen NS	No evaluation of LV function. Use of death certificates may misclassify.
TACTICS-TIMI18 Sabatine 2002 11956114 (61)	Use of multiple biomarkers to predict MACE in NSTEMI-ACS	Multi-institution prospective 450 (OPUS-TIMI 16) 1,635 (TACTICS-18)	Tnl, CRP, BNP in combination vs. each alone	Possible ACS within 72 h	Age <18 y pregnancy, significant comorbidities, bleeding tendency	3 biomarkers at enrollment	Death/MI/HF at 6 mo Number of elevated biomarkers include prediction of outcome	30-d mortality RR 0 Biomarker+: 1 1 Biomarker+: 1.8 2 Biomarker+: 3.5 3 Biomarker+: 6 p=0.014	1 Biomarker+:2.1 p=0.006 2 Biomarker+:3.1 p<0.001 3 Biomarker+: 3.7 p=0.001 (6 mo)	Using binary cutpoints of biomarkers rather than higher levels. Very insensitive cTn assay
HOPE Blankenberg 2006 16831981 (62)	9 Biomarkers to evaluate improved CV risk in a 2 nd d prevention population	Multicenter prospective 3,199	Evaluation of CRP fibrinogen, IL-6, TNF 1, 2, sIAM-1, s-IAM-1, BNP, IL-1 RA microalbuminuria, individually for MACE	Hx of CAD, stroke, PAD, diabetes	HF, low LVEF, nephropathy MI, or stroke 4 wk before enrollment	9 biomarkers on enrollment	Combined events 4.5 y Significant relations: BNP, sIAM, Microalbuminuria, s- IRA-1, fibrongen	Only inclusion of BNP provided info above that from traditional risk factors	HR: BNP 1.721<0.001 sIAM 1.46=0.0003 Microalbuminuria 1.55=0.0004 sIAM1.46=0.0003 Fibriogenen 1.31=0.02	Only baseline measurements; later analysis on frozen specimens; for our purposes, not an ACS study
McCann 2008 18682444 (63)	Role of novel biomarkers in AMI Dx	Multicenter prospective 664	Multiple biomarker comparisons including cTnT, H-FABP, BNP, hs-CRP, D-dimer, MPO, MMP-9, PAPP- A, sCD40L	Chest pain <24 h to 2 CCUs	Transfer from other hospital thrombolytics or anticoagulant	Biomarkers on entry	Dx of AMI only H-FABP challenged cTnT and combined approach improved -PV	-PV H-FABP 75% cTnT–90% Either–97% (95% CI: 91%–99%)	Sens H-FABP: 73% Sens cTnT: 55% On admission p=0.043. Combined improved sens: 85%; p≤0.04 vs. individual values	Only single measure of biomarker.
FRISC Eggers 2009 (64) 19608034 (64)	Risk predicted by multiple biomarkers in NST-ACS	Multicenter retrospective analysis 877	Evaluated: cTnl, BNP, CRP, estimated GFR	NSTEMI-ACS	Bleeding risk, high creatinine, PCI in previous 6 mo, decision for PCI before randomization	Biomarkers at enrollment, 6 wk, and 6 mo	5-y follow-up BNP strongest predictor for mortality	BNP: 6 wk: 1.5 p<0.001 6 mo: 1.4 p=0.001	BNP 1.7 (95% CI: 1.3–2.1); p<0.001 5 y only 6 wk BNP showed significant increments to established risk factors C- statistic 0.69; p=0.03	Outcomes before more advanced 2° previous measures. Preselected population
ARCHIPELAGO	Multiple biomarkers	Multicenter	Evaluated 9	NSTEMI-ACS	STE-ACS,	Biomarkers at	Biomarkers for	IL-6 AUC significant	IL-6: 1.69 (95% CI: 1.2–2.3)	Post-hoc analysis;

Beygui 2010 20723640 (65)	for risk in NSTE-ACS	prospective trial Post hoc analysis 440	biomarkers: CRP, IL-6, MPO, PL- 22, MMP-9, IMA, sCD40L, BNP, aldosterone, cTnI		planned corresponding interval, CHF, hypotension, low creatinine Cl	randomization	Ischemia/HF at 2 mo IL-6 corresponding with Ischemia BNP, aldosterone MMP-9 for HF	improved model for ischemia, 3 biomarkers + for HF improved performance models for HF	BNP :3.2 (95% CI: 2.0–5.0) Aldo: 1.57 (95% CI: 1.1–2.6) MMP-9: 0.64 (95% CI: 0.46– 0.88)	Only 2-mo follow-up Select group of pts. No indication of severity of HF.
Manhenke 2011 22197217 (66)	Elucidating complex interactions between circulated biomarkers following AMI	Multicenter prospective trial 236	37 biomarkers	AMI complicated by HF	Not Stated	Biomarkers median 3 d after AMI Dx	2 sets of biomarkers corresponded with risk for death and combined death/reinfarction	Natriuretic peptides among others provided significant contribution to risk assessment	Of 5 sets of biomarkers only 2 sets showed significant prediction	Limited number pts Relatively small number events. Blood Time frame 1 d–10 d post- MI
Bhardwaj 2011 21835288 (67)	Assess role of 5 biomarkers in Dx in ACS	Prospective cohort 318	Evaluated: BNP, IMA, H-FABP, hs-TnI, FFAu vs. cTnT	Possible ACS	Multiple including ESRD, thrombolytic agents, noncardiac chest pain	Biomarkers at presentation	Compared with cTnT, diagnostic information increased with BNP, FFAu, hs-TnI, but not IMA and H-FABP	+PV cTnT: 65% hs-TnI: 50% FFAu: 40% BNP: 28% IMA: 17% H-FABP: 26%	Sens and –PV: BNP: 73%, 90% Hs-TnI: 57%, 89% FFAu: 75%, 92% (Highest) Increased C-statistic for cTnT : BNP 0.09 Hs-TnI 0.13 FFAu 0.15 All p≤0.001	Small sample size Incomplete biomarker Data. Dichotomous cutpoints rather than multiple cutpoints
MERLIN-TIMI Scirica 2011 21183500 (68)	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Multicenter prospective 4,352	cTnI BNP CRP MPO	Possible ACS	STE-ACS ESRD CV Shock Short life expectancy	Biomarkers at presentation	Including all biomarkers only BNP and cTnI associated with 12-mo CV death Only TnI with reinfarction	Addition of biomarkers to reference for CV death/HF: cTnI: 0.776 BNP: 0.790Ref: 0.749	Addition of biomarkers to reference for CV Death: cTnI: 0.805 BNP: 0.809 p<0.001 Ref: 0.784	LV function incomplete. No serial evaluations of biomarkers, not generalizable to overall population.
CAPTURE Oemrawsingh 2011 21558475 (69)	Predictive value of 7 Biomarkers in NSTE- ACS	Multicenter prospective 1,090	Hs-CRP MPO sCD40L IL-10 TnT PIGF PAPP-A	Possible NSTE-ACS	Ischemia >48 h from enrollment	Biomarkers after last episode of angina	4-y MI/death A multimarker model of TnT, IL-10, MPO, and PIGF predicted 4-y rates: 6.0% (all normal) 35.8% (3+ abnormal)	TnT: 1.8 (95% CI: 1.2– 2.6) IL10: 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	Admission levels of +TnT: HR 1.8 +IL-10:HR: 1.7 +PIGF:HR: 1.9 +Myoglobin:HR: 1.5 Significant prediction for outcomes in multivariate analysis	Not adjudicated data for MI Dx No info on long-term medications
FAST II FASTER I Eggers 2011 22456003 (70)	Predictive of MI with multiple biomarkers Combines with hs- TnT	Retrospective cohort 360	Hs-TnT + h-FABP copeptin	NSTEMI (retrospective Classification)	STEMI	Biomarkers at enrollment	Hs-TnT greater accuracy in Dx of AMI than H-FABP and copeptin	No increase in C-statistic for hs-TnT by combining with H-FABP 0.85 or copeptin 0.84	C-statistics Hs-Tnt: 0.84 H-FABP: 0.80 p=0.04	Retrospective, small sample, from 2 different studies. No serial biomarkers

									Copeptin: 0.62 p<0.001	
Meune 2012 22507551 (71)	Multimarker evaluation in suspected AMI with undetectable cTn levels	Retrospective multi-institution 325 with undetectable cTnT	cTnT-15 biomarkers Including CK-MB and MPO	ACS with undetectable cTnT at 0 h and 6 h.	Detectable cTnT	Biomarkers >6 h from enrollment ESRD	At mean follow-up 668 d for death/MI hs-TnT, MR-Pro ADM and PDF-15 showed increased risk	Sens/spec for death/MI (%) Hs-TnT: 43,86 MR-Pro ADM: 43,76 GDF-15: 95,55	ROC AUC for death/MI: Hs-TnT: 0.73 (95% CI: 0.6–0.8) MR-Pro ADM: 0.71 (95% CI: 0.6–0.8) GDF-15: 0.78 (95% CI: 0.71–0.86)	Subgroup analysis Relatively low cardiac events in follow-up
Schaub 2012 22057876 (72)	Markers of plaque instability use in AMI Dx and risk	Prospective multicenter 398	Multimarkers: Hs-cTnT cTnT MPO PAPP-A CRP MRP 8/14	Possible ACS	ESRD	Biomarkers at presentation	Diagnostic accuracy for all non-TnT biomarkers was low using ROC AUC	AUC for combination with hs-TnT: MPO: 0.95 MRP-8/14: 0.95 PAPP-A: 0.95 CRP: 0.95 (NS change)	ROC (AUC): MPO: 0.63 MRP8/14: 0.65 PAPP-A: 0.62 CRP: 0.59 cTnT: 0.88 hs-TnT: 0.96	Biomarkers linked to factors related to morbidity: potentially confusing. No info on avoiding adverse outcomes
Weber 2008 18355657 (73)	Prognosis. value of BNP with normal TnT in ACS	Retrospective multicenter 2,614 From 2 center registries 1,131 and 1,483	BNP vs. TnT	Cohorts 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	Biomarkers at entry	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	Mortality rate TnT+ vs. TnT-: Registry 1: 8.2 vs. 3.8% p=0.009 Registry 2: 8.6 vs. 2.8% p=0.009	Kaplan-Meier analysis of risk for death by BNP: Registry 1: Log-rank: 19.01 p<0.001 Adjusted HR: 9.56 (95% CI: 2.42–37.7) p=0.001 Registry 2: Log rank: 23.16 p<0.001 HR: 5.02 (95% CI: 2.04–12.33) p<0.001	Retrospective study. No serial measurements
Wiviott 2004 14769678 (74)	Gender and biomarkers in ACS	Multicenter prospective trial off 1,865 pts in TACTICS-TIMI 18, 34% were women	Multiple biomarker analysis Men vs. women	Women with ACS with criteria for PCI. Randomized to invasive vs. conservative strategies	No criteria for PCI	Biomarkers at entry: TnT TnI CK-MB CRP BNP	Women more likely had elevated CRP and BNP. Men more likely had elevated CK-MB and Tn	Women with +Tn were more likely to have recurrent 6-mo MI whether TnI or TnT	Women more likely to have elevated hs-CRP 1.49 (95% CI: 1.16-1.92) and elevated BNP 1.33 (95% CI: 1.02-1.75)	Cutpoints rather than continuum. N/A to atypical chest pain. Not designed to answer pathophysiological questions

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; cTnI, cardiac troponin I; 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, glycogen 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-cTnT, 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; MRP 8/14, myeloid related protein 8/14; 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, orbofiban in

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; Sens, sensitivities; sIAM, 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)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Interventi on Group (n)	Study Comparat or Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
CHEER, Farkouh, 1998 9862943 (75)	Evaluate utility of CPU management of low-risk pts with CP	Single-center, prospective RCT	424	212	212	Intermediate risk, UA	MI, instability marked ST changes	6-h CPU observation followed by pre-D/C ETT or Ex-MPI with early D/C if negative	Routine hospital admission	No significant diff in early (30 d) and late (6 mo) MI, death, CHF, CVA, card arrest in-hospital admission vs. CPU pts	Same as 1° endpoint	CPU pts: Fewer follow-up ED visits, cardiac tests (p<0.003). (Also, median LOS in CPU 9.2 h)	No significant diff in early 30-d/late 6-mo cardiac events. Fewer repeat ED visits, cardiac tests (p<0.003)	Relatively small single-center, tertiary care with extensive expertise/resource s; Pts 95% white. No. ETT/Nuc pts not given. Study not blinded
ROMIO Gomez, 1996 8752791 (76)	Test rapid R/O MI to ↓time/\$	Single-center, prospective RCT	100	50	N/A	CP low-risk for MI (Goldman), stable, nonischemic ECG; injury marker data not required	<30 y, >7% MI prob (Goldman), ECG, ischemia, VT, AV BI, new BBB, BP >220/120, unstable	Rapid rule-out MI protocol in ED: Serial ECGs and CK-MB q 3-h x 4. If negative, PD-ETT	Routine hospital adm	No diff in low 30-d cardiac events. ITT analysis: LOS shorter, \$ less in ED rule-out pts with MI	No MI missed	Echo substudy: low incremental value in rapid rule-out patients with MI	Admission vs. rapid rule-out: LOS 14 h vs. 27 h; p<0.0001; Initial cost: \$2,089 vs. \$1,108; p>0.0001; 30-d cost: \$2,253 vs. \$1,237	Small single center study, not blinded, shorter follow-up, hospital charges, and costs not equivalent
Amsterdam, 2002 12106928 (77)	Utility of immediate ETT in triage of ED CP pts	Observation al, single-center	1,000	1,000	N/A	Nontraumatic CP, negative ECG, marker, no arrhythmia, stable, Hx CVD not excluded	Abnormal ECG, positive marker, clinically unstable	Immediate ETT, Max/Sx/ Sign limited	N/A	Negative ETT in 64% pts enabled direct discharge from ED, 30-d follow-up: NPV 98.3%. Non-Dx: 23% pts, 7 revasc predischARGE; positive: 13%, 4 NSTEMI at	No adverse effects of ETT. No deaths at 30 d.	No MACE at 6 mo in pts who did not have ACS at index visit. Approx 40 min total time for scan and interpret.	N/A	ETT performed by specially trained MDs (Noncardiologist), 7 d/12 h function. Limitation: Includes only pts able to do ETT

										30 d				
Udelson, 2002 12460092 (78)	Does addition of rest MPI improve ED triage of low-risk CP pts to admission or D/C from ED	Prospective Multicenter (n=7) RCT	2,475	1,215	N/A	Suspected acute ischemia (CP or equivalent) present within ≤3 h, nonischemic ECG, ≥30 y	Hx of MI, non-Dx ECG	Rest SPECT Tc 99m sestamibi, results to ED for use in clinical decision-making	Usual ED strategy in each institution's ED	MPI: Admission rate <UC (RR: 0.87; 95% CI: 0.81-0.93; p<0.001)	No adverse effects of MPI except radiation and longer time to discharge from ED in negative scan pts.	MPI: ↓unnecessary admission rate to 42% (10% absolute ↓); RR: 0.84; 95% CI: 0.77–0.92; p<0.001. 30-d cardiac event rate was related to MPI data; p<0.001	See 1°/2° endpoint columns	May not be generalizable to small hospitals; performed during daytime. LOS MPI>UC (5.3 vs. 4.7 h; p<0.001)
Trippi, 1997 9283518 (79)	Evaluate utility of DSE telemedicine triage of low-risk pts with CP in ED	Prospective, single-center, DSE by nurse and sonographer	173 screened, 139 eligible and received DSE (24 no DSE d/t LV wall motion abnormal)	139	N/A	ROMI, negative markers, NL ECG, No Hx CVD. Initially: pts obs'v'd 12 h; later. neg DSE: direct D/C from ED	No Hx CAD, screened for exclusions by nurse (not specified) (LV wall motion abnormal = exclusion)	DSE by nurse & sonographer Card present; later cardiologist available by phone, ED MDs present. DSE telemetry to Card, Dx to ED. Follow-up confirm, ECG	N/A	3-mo follow-up: NPV for ACS 98.5%, PPV 51.5%. Agreement TeleEcho/conv ential Echo kappa 0.78; 95% CI: 0.65–0.90	54.7% Sx with DSE: test terminated for PVCs=6.3%; CP, nausea, SOB common Sx	72.0% pts 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.	See 1°/2° endpoints	No control group. Method not generalizable, highly developed/specialized personnel
Bholasingh, 2003 12598071 (80)	Study prognostic value of DSE in low-risk CP pts	Prospective single-center, blinded. ED MDs blinded to DSE results.	377 of 557 eligible pts received DSE. No DSE: 119 ACS, 34 other serious Dis., 24 rest LV abn.	377	N/A	≥18 y, non-Dx ECG, present within 6 h of CP, neg cTt.	Arrhythmias, HF, severe HTN, serious noncard disease	DSE after 12-h observation, 6.9% (26/377) pts had Pos DSE	N/A	6-mo follow-up: 1° endpoints: Neg DSE 4% (1 death), Pos DSE 30.8% (1 death); OR 10.7; 95% CI: 4.0–28.8; p<0.0001)	All DSE completed within 24 h of admission; follow-up 100%; 19.9% protocol terminated d/t ECG changes, CP, arrhythmia, severe HTN, hypotension.	Revasc: Pos DSE 3/26 pts, Neg DSE 7/351 pts ~5X greater in neg DSE	See 1°/2° endpoints Pts discharged	No control group. DSE not performed d/t poor window in 5.7% pts.
ROMICAT, Hoffman, 2009 19406338 (81)	Utility of CCTA in acute CP pts	Observational cohort study	368	368	N/A	CP, neg initial Tn, nonischemic ECG	Hx CAD: stent or CABG, renal discharge	CCTA before admission, results not	N/A	Pts without CAD: NPV for ACS at 6	1 ACS in absence of + CCTA showing	No MACE at 6 mo in pts who did not have	See 1° endpoint column	Single center, wk'd h, underrepresent of elderly d/t

		(blinded)						disclosed, sig stenosis: >50%		mo=98% (95% CI: 98%–100%; PPV=35% (95% CI: 24%– 48%)	coronary plaque	ACS at index visit. ~40 min total time for scan & interpret		exclusion of CAD, renal dis. May not be generalizable to smaller hospitals, radiation
Litt, 2012 22449295 (82)	CCTA vs UC to assess low- risk CP pts in ED	Prospective multictr (n=5) RT	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 1 st test in CTA group. In traditional care pts clinicians decided 1 st 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 1°/2° endpoint columns	All exclusions to CCTA not noted, young study group (age 50 y), radiation
ROMICAT II, Hoffman, 2012 22830462 (83)	CCTA vs UC to assess low- risk CP pts in ED	Prospective multictr (9) RCT	1000	501	499	CP, 40-74 y, NSR	CAD, ischemic ECG, +Tn, Cr >1.5, instability, allergy to contrast, BMI >40, asthma	CTA	Traditional care	LOS: CCTA 23 h vs. UC 31 h (p<0.001)	28-d follow-up: no missed ACS; no difference in MACE at 28 d	Direct D/C from ED: CTA 47% vs. 12%, p<0.001; no difference in downstream care	See 1° and 2° endpoint columns	Wkd, daytime, radiation. May not be generalizable to smaller hospitals

1°indicates primary; 2°, secondary; ACS, acute coronary syndrome; BBB, bundle branch block; BMI, body-mass index; BP, blood pressure; CAD, coronary artery disease; CABG, coronary artery bypass graft; CCTA, coronary computed tomographic angiography; CTA, computed tomographic angiography; CHF, congestive heart failure; CK, creatine kinase; CP, chest pain; CPU, chest pain unit; Cr, creatinine; CrCl, creatinine clearance; CTA, computed tomography angiography; CVA, cardiovascular accident; CVD, cardiovascular disease; D/C, discharge; diff, difference; DSE, dobutamine stress echocardiography; Dx, diagnosis; ECG, echocardiograph; ED, emergency department; pts, patients; ETT, exercise treadmill testing; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ITT, intention to treat; LOS, length of stay; MACE, major adverse cardiac events; MI, myocardial infarction; MPI, myocardial perfusion imaging; NPV, net present value; NSR, normal sinus rhythm; PPV, positive predictive value; PVC, premature ventricular contractions; R/O, rule out; RCT, randomized controlled trial; ROMI, rule out myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; and UA, unstable angina.

Data Supplement 9. Nitrates (Section 4.1.2.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparat or	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>			<i>Primary Endpoint (efficacy) and Results</i>	<i>Safety Endpoint and Results</i>	<i>Secondary Endpoint and Results</i>		
Ambrosio G., 2010	Investigate whether	Multicenter registry	52,693	10,555 (20%) pts on	42,138 (80%) (nitrate-naïve)	Clinical history of ACS,	Pts with non-CV causes for the	Chronic nitrates on	Nitrate-naïve	Chronic nitrate use was	N/A	Antecedent nitrate use was	Chronic nitrate use remained	Registry data– No data on dose

19903682 (84)	antecedent nitrate therapy affords protection toward acute ischemic events	(GRACE)		chronic nitrates on admission	pts)	accompanied by at least 1: ECG complete with ischemia, serial increases in cardiac markers, documented CAD	clinical presentation were excluded, as were pts in whom initial Dx of ACS was not confirmed at discharge	admission		associated with a shift away from STEMI in favor of NSTE-ACS. Chronic nitrate use remained independent predictor of NSTE-ACS: (OR: 1.36; 95% CI: 1.26–1.46; p<0.0001)		associated with significantly lower levels of peak CK-MB and Tn (p<0.0001 for all) (in both STEMI and NSTEMI)	independent predictor of NSTE-ACS: (OR: 1.36; 95% CI: 1.26–1.46; p<0.0001)	or duration of antecedent Rx
Mahmorian, 1998 9610531 (85)	Investigate the long-term (6 mo) efficacy of NTG patches on LV remodeling in pts surviving a AMI	Multicenter RCT	291	214	77	Pts surviving a A-QMI	Exclusion criteria: severe CHF, persistent hypotension, sustained VT, or high-degree AVB, UA, significant noncardiac illness, or either a requirement for or known intolerances	Intermittent NTG patch therapy initiated within 1 wk after AMI and continued for 6 mo (0.4, 0.8, and 1.6 mg/h)	PC	1° endpoint: Change in ESVI was significantly reduced with 0.4 mg/h NTG patches	Cardiac event rates were not significantly different between PC and active treatment groups	The beneficial effects seen primarily in pts with baseline LVEF ≤40% (delta ESVI, -31 mL/m ² ; delta EDVI, -33 mL/m ² ; both p<0.05) and only at the 0.4 mg/h dose	Both ESVI and EDVI were significantly reduced with 0.4 mg/h NTG patches (-11.4 mL/m ² and -11.6 mL/m ² , p<0.03)	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).
ISIS-4, 1995 7661937 (86)	Examine the effect of oral controlled-release	RCT	58,050	29,018	28,539	Within 24 h of Sx onset of suspected AMI with no clear	Contraindications at the clinician's discretion (e.g., conditions	1 mo of oral controlled-release mononitrate	PC	NS difference in 5-wk mortality (mononitrate vs. PC):	Greater effect early after starting treatment	No effect on any subgroup studied (age, sex, previous MI, ECG on	5-wk mortality: (mononitrate vs. PC) 7.34% vs.	Hypotension 17.4% vs. 14.4%, p<0.0005 (mononitrate vs.

	mononitrate on early mortality (4 wk)					indications 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).	presentation, HF at entry, early after Sx onset, etc) No difference in 12-mo mortality	7.54%, p=NS	PC) 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 1 st 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	Nitrate	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 1 st wk of follow-up	Both NTG and nitroprusside reduced mortality, the reduction being NS greater with NTG than with nitroprusside	NS reduction after the 1 st wk of follow-up	Publication bias Baseline risk heterogeneity Different definitions of clinical endpoints across the various studies

1° indicates primary; 2D, two-dimensional; ACS, acute coronary syndrome; AMI, acute myocardial infarction; A-QMI, acute Q-myocardial infarction; AVB, auriculoventricular block; CAD, coronary artery disease; CHF, congestive heart failure; CK-MB, creatine kinase-MB; CV, cardiovascular; Dx, diagnosis; ECG, electrocardiogram; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; GTN, glyceryl trinitrate; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; IV, intravenous; LV, left ventricular;

LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, nonsignificant; NTG, intermittent transdermal nitroglycerin; NSTE-ACS, non-STE-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)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (Efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Iakobishvili, 2011 21627393 (89)	Determine the impact of IVM on outcomes of pts with ADHF with and without ACSs	Observational registry	2,336	218 (9.3%)	2,118 (90.7%)	Consecutive pts with ADHF participating in a national HF survey	N/A	IVM	No IVM	IM associated with higher unadjusted (11.5% vs. 5.0%) and adjusted in-hospital mortality using logistic regression adjustment	IVM increased in-hospital mortality	Using adjustment with propensity matched analysis, IVM was not associated with increased in-hospital death (OR: 1.2; 95% CI: 0.6–2.4; p=0.55)	IVM had higher adjusted OR for in-hospital death: 2.0; 95% CI: 1.1-3.5; p=0.02) using logistic regression analysis	Pts with IVM were more likely to have ACSs
Iakobishvili, 2010 20346305 (90)	Assess the 30-d outcomes stratified by IVNs use among pts enrolled in a national survey of pts with STEMI and NSTE-ACS	Multicenter retrospective analysis from the ACSIS 2008 database	993 pts with NSTE-ACS	97 (9.8%)	896 (90.2%)	Consecutive pts presenting with ACS to any of 26 CCU and cardiology wards in Israel	Pts transferred to another institution	IVM	No IVN	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)	N/A	Using propensity analysis, of 249 matched STEMI pairs, 30-d death was lower in pts receiving IVN; this trend persisted after logistic regression analysis (OR: 0.40; 95% CI: 0.14-1.14; p=0.09)	Using logistic regression analysis, there were no diff in 30-d mortality among NSTE-ACS (OR: 0.56; 95% CI: 0.14-2.33; p=0.43)	Retrospective On-site catheterization and bypass surgery facilities were available in 22 and 10 of the centers only. Relatively small cohort. No data regarding the exact timing of IVN use or the cumulative dose administered. Did not specify the types of IVN used.

														Only a minority of pts were treated with IVN
Meine, 2005 15976786 (91)	Compare outcomes in pts who received IVM vs. those who did not receive IVM	Observational registry, GRACE	57,039	17,003 (30%)	40,036 (70%)	Pts presenting with NSTE-ACS at 443 hospitals across the US from 01/2003–06/2003 Pts included in the CRUSADE initiative have ischemic Sx at rest within 24 h prior to presentation and high-risk features including ST-segment depression, transient ST-segment elevation, and/or positive cardiac markers.	Pts who were transferred out to another institution were excluded, because data could not be collected	Morphine within 24 h of presentation	No morphine at presentation	Higher adjusted risk of in-hospital death in pts treated with morphine compared with no morphine (OR: 1.48; 95% CI: 1.33-1.64)	Increased adjusted OR of in-hospital death in all subgroups (including pts with CHF, ST depression, <75 y, positive biomarkers, nonhypotensive pts) Also, increased adjusted OR of in-hospital adverse outcomes (death/MI; CHF; postadmission MI; cardiac shock)	Relative to those receiving NTG, pts treated with morphine had a higher adjusted OR of death: 1.50; 95% CI: 1.26-1.78	In-hospital death: morphine vs. no morphine: adjusted (OR: 1.48; 95% CI: 1.33-1.64) Using propensity score matching, morphine use was associated with increased in-hospital mortality (OR: 1.41; 95% CI: 1.26-1.57)	Nonrandomized, retrospective, observational data Only a minority of pts were treated with IVM

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)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results			
TIMI-IIB Roberts,	Immediate vs. deferred BB	Prospective multicenter	Immediate IV group	AMI treated with invasive	Implanted pacemaker; resting	IV metoprolol as soon as rt-PA	Global LVEF at time of discharge using	No diff in mortality in both	Lower incidence of reinfarction	Resting EF: immediate 51.0% vs. 50.1%	NS diff in deaths at 6 wk or 1 y	Complexity of interventions other

1991 1671346 (92)	therapy	1,434	720 Deferred group 714	vs. conservative strategy. Susceptible to BB therapy.	HR <55; SBP <100 mm Hg; pulmonary edema; advanced 1 st degree or higher heart block; asthma or COPD.	was started followed by oral metoprolol or oral metoprolol beginning on d 6	radionuclide ventriculography. LVEF 50.5% at discharge was virtually the same in both groups	groups. In low- risk group there were 7 deaths in 6 wk in deferred group vs. none in immediate group	(2.7% vs. 5.1%; p=0.02) at 6 d in the immediate group and less recurrent chest pain (18.8% vs. 24.2%; p<0.02)	delayed p=0.22 NS diff invasive or conservatives strategy in EF comparisons	with immediate vs. delayed BB treatment. More intracranial hemorrhage in the delayed group	than BB administration may have affected results.
Ryden, 1983 6828092 (93)	Occurrence of ventricular tachyarrhythm ias in suspected AMI with BB.	Prospective multicenter 2,395	Metoprolol 698 PC 697	Sx suggestive of AMI	Contraindications for beta-blockade; need for beta-blockade's “administrative considerations.”	Metoprolol IV than po or PC with admission to CCU	Significant ventricular tachyarrhythmias: More cases of VF in the PC group	No increase in significant heart block with BB	BB did not influence PVCs or short bursts of VT in 1 st 24 h. 3-mo mortality lower in BB group (5.7% vs. 8.9%) p<0.03	VF: 6 in BB group, 17 in PC group (0.9% vs. 2.4%) p<0.01 Requirement for lidocaine less in BB group 16 vs. 38 p<0.01	NS adverse events with BB vs. PC	Use of a beta-1- blocker precludes assessment with other type BB. No indication of whether deferred BB would have affected results.
Al Reesi, 2008 19019272 (94)	Effect of BB use within 72 h of MI on 6- wk mortality vs. PC	Meta-analysis 18 studies 74 643 1966–2007	BB vs. PC or no control group Roughly 50% each	RCT of MI with BB vs. PC within 72 h of AMI	No information on 6- wk mortality. Treatment started after 72 h. Non- English speakers	Beta-1 or nonselective BB or PC within 72 h of MI. Follow- up for 6 wk	6-wk mortality: Adding a BB had no effect compared with control	N/A	Subgroup analysis that excluded high- risk pts showed mortality benefit of BB: 0.93 [0.88– 0.99]	6-wk mortality Reduction BB vs. control: 0.95 (95% CI: 0.90–1.01) NS With high quality studies only: 0.96 (95% CI: 0.91–1.02) NS	N/A	Publication bias as with all meta- analyses. No evaluation of other outcomes or adverse events. Mixed beta-1 and nonselective BB.
Janosi, 2003 14564329 (95)	BB effects in post-MI with CHF	Multi-institute prospective trial 1,926	950 metoprolol 976 PC	MI >0.28 d before.	AMI or UA <28 d Contraindicated to BB.	Metoprolol or PC for 1 y.	BB reduced total mortality by 40%, combined MACE by 31%.	Withdrawal of BB vs. PC NS.	Reduced CV death, MI by 45%, SCD by 50%	Total mortality p=0.0004, MACE p<0.0001	Death from worsening HF educed 49% vs. PC	Only 68% of post- MI pts ideal candidates for BB
Hjalmarson 1997 9375948 (96)	Meta-analysis of early BB trials in MI	>55 RCT of over 73,000 pts	Over 38,000 BB Over 35,000 PC	AMI	Contraindicate to BB, sever HF, heart block.	BB vs. PC	Total deaths 13% reduction. Short-term SCD 34% reduction.	Lipophilic BBs prevent vs. fibrillation after MI	N/A	Total mortality p<0.0001 SCD reduction <0.0001	N/A	N/A
Emery, 2006 17161045 (97)	Use of early BBs in NSTEMI	Registry of 96 hospital pts admitted for ACS retrospective 7,106	5,422 early BB 1,684 None	NSTEMI	STEMI Contraindications to BB therapy Transfer pts with Hx of CHF Cardiac arrest on admission	Early BB therapy or none beginning <24 h	BB therapy showed lower hospital mortality 6-mo mortality also lower	N/A	Hospital Mortality Killip II/III 0.39 (95% CI: 0.23–0.68)	Hospital mortality 0.58 (95% CI: 0.42–0.81) 6-mo mortality 0.75 (95% CI: 0.56–0.997)	N/A	Observational No adjustment for confounders. No indication of dose or brand
Freemantle , 1999 10381708 (98)	BBs in short- term Rx in MI and in longer term	Meta - regression analysis of trials with	82 randomized trials Short-term: 29,260	BB in MI in PC or alternative Rx in controlled trials	N/A	BB/PC or alternative Rx begun at any stage of AMI	Short-term: small and NS reduction of risk for death Long-term:	N/A	N/A	Short-term risk for death 0.96 (95% CI: 0.85– 0.98)	Usually bradycardia or hypotension	Multiple BB brands, varied follow-up, diff times of initiation

	secondary preview	acute or past AMI 54,234	Long-term: 24,974 pts				significant reduction			Long-term: 0.77 (95% CI: 0.69–0.85)		and withdrawal.
Dargie, 2001 11356434 (99)	Outcomes of carvedilol in AMI with LV dysfunction	Multicenter randomized PC controlled 1,959	Carvedilol 975 PC 984	AMI with LVEF≤40%, use of ACE inhibitors	<18 y, use of diuretics or inotropes	6.25 mg BB to 25 mg bid or PC followed until requisite number of endpoints	Death or hospital admission for CV problem no difference	N/A	All-cause mortality alone Lower in BB group 0.77 (0.60–0.98) p=0.03	1° endpoint 0.92 (95% CI: 0.80–1.07)	N/A	Insignificant power to detect a diff in all-cause mortality
Chen, 2005 16271643 (100)	Effect of adding BB to current std therapies in AMI	Multicenter randomized PC controlled 45,852	Metoprolol 22,929 PC 22,923	<24 h of ACS with STEMI, NSTEMI, or LBBB	Scheduled for PCI, hypotension, bradycardia, heart block, shock	IV then po, BB, or PC for up to 4 wk	Death/reinfarction/ cardiacarrest NS	11/1,000 more with BB having cardiac shock during d 0–1 of admission	Less vs. fibrillation with BB p=0.001 Less reinfarct p=0.001	MACE for BB: 0.96 (95% CI: 0.90–1.01); p=0.1 NS	More cardiac shock with BB (d 0–1)	Different population groups at centers
Ellis, 2003 14562669 (101)	BB therapy in ACS PCI ± abciximab	Pooled data from 5 RCTs 2,894	1,939 BB 955 No BB	MI or UA within 48 h	Pts presenting within 24 h with ECG change /UA	BB vs. control through hospital stay PCI	30-d, 6-mo MACE BB decreased death during both periods	N/A	NS diff recurrent MI Death or MI	Death 30-d BB vs. no BB 0.6% vs. 2.0% p=0.017 Death 6 mo 1.7% vs. 3.7% p=0.01	NA	1° comparison not randomized. Diff pt populations. No uniform definition of ACS
McMurray, 2005 15708698 (102)	Effect of BB in reducing arrhythmias added to ACEI	Multicenter PC controlled 1,959 Post hoc analysis of arrhythmias	975 carvedilol 984 PC	3–21 d after MI follow-up 1.3 y	Not stated	Carvedilol of PC for duration of study (average 1.3 y)	Arrhythmias over 2 y, atrial and ventricular arrhythmias lower in BB group	N/A	Malignant vs. arrhythmias: 0.9% BB 3.9% PC 0.24 (95% CI: 0.11–0.49) p<0.0001	Atrial arrhythmias: 0.41 (95% CI: 0.25–0.68); p=0.0003 vs. arrhythmias 0.34 (95% CI: 0.11–0.49); p<0.0001	AT, atrial flutter, atrial fibrillation, vs. tachm, vs. fibrillation	Not prespecified analysis. ECG confirmation not available
Miller, 2007 17679127 (103)	Impact of early use of BB in ACS	Multi-institutional retrospective analysis 72,054 at 509 hospitals	82.5% received acute BB vs. no BB	Acute ischemia <24 h, NSTE, contrary to BB	Hospital transfer, no +cardiac markers, no acute medications recorded	BB vs. no BB	Lower in-hospital mortality, reinfarction, shock with BB. No diff in CHF	N/A	Acute BB associated with more invasive procedures and other acute therapy	Hospital mortality: 0.66 (95% CI: 0.60–0.72) Reinfarction 0.80 (95% CI: 0.72–0.89) Shock 0.76 (95% CI: 0.67–0.87)	N/A	Undocumented contraindicated to BB use, hospital actively seeking to improve performance
Brandler, 2010 20078433 (104)	Literature review to determine BB effects on outcome in ACS	Meta-analysis of RCTs 72,249 18 articles	Early BB 36,173 pts with/without PC 36,076	18+ y, ACE within 24-h pain onset, BB within 8 h of presentation	Contraindications to BB	Early BB vs. no BB ± PC	No diff in in-hospital mortality	N/A	In largest study (45,852) higher cardio shock in BB 5.0% vs. control 3.9% p<0.0001	In-hospital mortality 0.95 (95% CI: 0.90–1.01)	N/A	Single outcome variable. No long-term evaluation. Heterogeneous pt population

Kontos, 2011 21570515 (105)	Registry of BB use in ACS	NCDR ACTION-GWTG registry 34,661 pts with NSTEMI 21 822	291 hospitals 2007–2008 21 822 BB	BB within 24 h of ACS	Contraindications to BB Missing data	BB only: early vs. late use	Very early BB use increased cardiogenic shock and death or shock	Evidence of increased cardiogenic shock with early use (<24 h) of BB	NS diff between early or late use in death alone	Early vs. late use cardiogenic shock: 1.54 (95% CI: 1.26–1.88); p<0.001 Death or shock: 1.23 (95 % CI: 1.08–1.40); p=0.0016	Cardiogenic shock with use of BB in ED	Oral or IV? No information on type of BB or dose. No information on arrhythmias.

1° indicates primary; ACS, acute coronary syndrome; ACE, angiotensin- converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ACTION, Acute Coronary Treatment and Intervention Outcomes Network Registry; AMI, acute myocardial infarction; AT, atrial tachycardia; BB, beta blocker; CCU, cardiac care unit; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; diff, difference; ECG, electrocardiograph; ED, emergency department; EF, ejection fraction; GWTG, Get With the Guidelines; HF, heart failure; Hx, history; IV, intravenous; LBBB, left bundle-branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NCDR- National Cardiovascular Data Registry; NCDR ACTION-GWTG, National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry- Get With the Guidelines; NS, no/t significant; NSTEMI, non-ST-elevation MI; PC, PC; PCI, percutaneous coronary intervention; pt, patient; PVCs, premature ventricular contractions; RCT, randomized controlled trial; Rt-PA, recombinant tissue plasminogen activator; Rx, prescription; SBP, systolic blood pressure; SCD, sudden cardiac death; std, standard; STEMI, ST-elevation MI; UA, unstable angina; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 12. Calcium Channel Blockers (Section 4.1.2.4)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (Efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Gibson, 1986 3526151 (106)	Effect of diltiazem on NQMI.	Multicenter double-blind randomized	576	Diltiazem 287	PC 289	NQMI >30 m Ischemic pain or ST changes	Q waves or conduction disturbances AV block Bradycardia Cardio shock	Diltiazem 24–72 h from admission Up to 14 d	PC	14-d reinfarction 9.3% in PC 5.2% in Diltiazem Reduced by diltiazem	No increased mortality with CCB Tolerated well with BB	Refractory angina reduced by diltiazem	Reinfarction: 51.2%(90% CI: 7%–67%); p=0.0297 Refractory angina 49.7% (90% CI: 6%–73%); p=0.0345	Only 4.8% withdrawn because of adverse effects. No diff vs. PC in LV failure, shock, AV block, severe bradycardia, or hypotension
Lubsen, 1987 2887097 (107)	Efficacy of BB and CCB in UA in a CCU	Multicenter PC control	338	Combination of nifedipine and metoprolol	PC	UA not previously on BB	AMI	Nifediipine, metoprolol, or combination	PC	Ischemia or progression to MI in 48 h. Only pretreatment with BB showed favorable effects with nifedipine.	No increased mortality with CCB.	Starting a BB plus nifedipine showed no benefit from BB initiation alone vs. PC.	Rate ratio for CCB: pretreated with BB: 0.68 (0.47, 0.97) Not on BB: 1.51 (0.87, 2.74) vs. PC	Equal numbers on BB alone or combination developed AMI or reversible ischemia.
Gibson, 1987 3303886	Px effect of dilriazem on recurrent	Multicenter double-blind	576	Diltiazem 287	PC 289	Confirmed NQMI	Q waves or conduction disturbances	Diltiazem 24-72 h from	PC	Incidence of early recurrent ischemia	N/A	N/A	CCB red of ischemia: 28% (95% CI:	N/A

(108)	ischemia						AV block Bradycardia Cardio shock	admission Up to 14 d		decreased by CCB 15.7% vs. 24.2%			9.3%–53.8%); p=0.0103	
Held, 1989 2513047 (109)	CCB effect on events	Meta-analysis of 28 trials	19,000	8,870 CCB	8,889 control	MI 22 trials UA 6 trials	CHF Hypotension AV block (most common)	CCB usually early in ACS	Control	Risk of death, infarct size, or reinfarction. No effect by CCB vs. PC in MI trials.	No increase in reinfarction or infarct size vs. PC by CCB	Results similar in UA trials	Mortality: CCB vs. PC 1.06 (95% CI: 0.96–1.18) in MI trials	Usual limitation of meta-analysis heterogeneity of populations and various agents. Adverse effects not addressed per se
Moss, 1991 1872266 (110)	Diltiazem and long-term outcome	Multicenter PC control	2,464	No HTN Diltiazem: 760 PC: 762	Hypertension Diltiazem: 471 PC: 471	MI treated with diltiazem with or without hypertension	CHF Hypotension AV block	Diltiazem at ACS for 12- 52 mo	PC for same time period	1 st recurrent cardiac event: CCB benefit only in hypertensives with no pulmonary congestion.	+pulmonary congestion; CCB increased Risk: Hypertension/ No hypertension 1.32 (95% CI: 0.83-2.10) 1.63 (0.99, 2.69) vs. PC	Significant reduction in BP and HR with CCB though small.	CCB benefit hyperension without pulmonary congestion 0.67 (95% CI: 0.47–0.96)	Retrospective analysis. Post-hoc analysis of HTN effect. Adverse effect of pulmonary congestion on diltiazem outcome
Furberg, 1995 7648682 (111)	Meta-analysis of nifedipine trials on outcome	Meta-analysis of 16 studies	8,350	Nifedipine 4,171	Control 4,183	Nifedipine 2° prevention trials with mortality data	No randomization	Nifedipine 12 AMI 3 UA 1 SA Short-acting	PC	Effect on mortality Nifedipine increased mortality by 16% Dose related	Increased sympathy stim and active of RAAS	Total mortality Low dose 1.06 (95% CI: 0.89-1.27) High dose 2.83 (95% CI: 1.35–5.93)	Total mortality 1.16 (95% CI: 1.01-1.33); p=0.01	Heterogeneity of clinical trial populations
Rengo, 1996 8602564 (112)	Effect of verapamil on mortality after AMI	Multicenter prospective trial	1,073	Verapamil 531	PC 542	Dx of AMI	Contraindication to verapamil Hx of severe HF	Long acting Verapamil 7-21 d after AMI 360 mg qd for 24 mo	PC For 24 mo	Total mortality and CV deaths. No diff between groups	No safety issues	Verapamil group had lower reinfarction rates (NS) 39 vs. 49 Significantly less angina OR: 0.8 (95% CI: 0.5-0.9)	Total mortality verapamil vs. PC 30 vs. 29 NS Cardiac deaths 21 vs. 22 NS	No diff in discontinuation of therapy due to adverse reactions. Death rate and number of pts recruited were lower than expected and pts were relatively young decreasing the power of study

Smith, 1998 9809940 (113)	Long-term outcome BB + CCB in UA	Retrospective cohort	247	Diltiazem 188	BB 59	At discharge with UA Dx	MI or stroke during hospitalization	Monotherapy CCB for 1- 7 y	Monotherapy BB for 1-7 y	Deaths in 51 mo No diff between BB and CCB	N/A	Adjusted: for CCB NS increase in CAD rehospitalization/ death 1.4 (95% CI: 0.8–2.4)	Deaths: CCB vs. BB 1.1 (95% CI: 0.49-2.4)	Compliance issues. No information on follow-up treatment. Relatively small number of BB users
Pepine, 1998 9755379 (114)	Safety of CCB in CV disease	Meta-analysis 14 randomized parallel group studies	4,000 person y	Verapamil	PC	Randomized studies of verapamil and PC from AMI	No randomization or control group	Verapamil	PC	Outcomes with CCBs after MI: vs. PC No diff in deaths Decreased nonfatal MI Decreased death/reinfarction	Data too limited for pts with hypertension No evidence for increased harm with verapamil	No diff verapamil vs. PC in angina pts	Combined death/reinfarction: 0.82 (95% CI: 0.70–0.97); p=0.016 Death: 0.93 (95% CI: 0.78– 1.1) Reinfarction: 0.79 (95% CI: 0.65–0.97); p=0.024	No evidence of harm with CCB in angina.
DAVIT Danish study, 1984 6383832 (115)	6 mo and 12 mo mortality after AMI with verapamil	Multicenter prospective study	3,498	Verapamil roughly 50%	PC roughly 50%	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.	6-mo reinfarctions: verapamil 7% PC 8.3 % NS	6-mo mortality: 12.8% verapamil 13.9% PC NS 12-mo mortality: 15.2% verapamil 16/4% PC NS	Dosage of verapamil caused significantly increased AV block in 1 st wk More HF in verapamil group p<0.005
DAVIT II Danish study, 1990 2220572 (116)	18 mo mortality rates and major CV events with verapamil after AMI	Multicenter prospective trial	1,775	Verapamil 878	PC 897	AMI	HF, AV block, severely disabling diseases, treatment with BB or CCB	Verapamil 360 mg qd from 2 nd wk of AMI and up to 18 mo	PC for same period	Long-term treatment with verapamil decreased major CV events without significant effect on mortality	Significant diff in reasons for permanently stopping verapamil vs. PC: 2 nd or 3 rd 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

											abdominal pain, constipation	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)	assumption, not the case for the Tarone-Ware test

2° 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; CCU, 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.

Data Supplement 13. Other Anti-Ischemic Interventions (Ranolazine) (Section 4.1.2.5)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (Efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Wilson SR, 2009 19389561 (117)	Evaluate the efficacy and safety of ranolazine in pts with prior chronic SA	Substudy from a multinational RCT	3,565	1,789	1,776	Pts with NSTE-ACS within 48 h of ischemic Sx (between Oct 2004–Feb 2007) Eligibility criteria: ≥18 y; Sx of myocardial ischemia; at least 1 moderate-high-risk indicator	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 <12 mo	Ranolazine	PC	1° endpoint (CV death, MI, recurrent ischemia) was less frequent with ranolazine (HR: 0.86; 95% CI: 0.75–0.97; p=0.017) (Follow-up was a median of 350 d)	Symptomatic documented arrhythmias (2.9% vs. 2.9%; p=0.92) and total mortality (6.2% vs. 6.4%; p=0.96) were similar with ranolazine or PC. CV death or MI did not differ between treatment groups (HR: 0.97; 95% CI: 0.80–1.16; p=0.71)	Composite endpoint driven by significant reduction in recurrent ischemia (HR: 0.78; 95% CI: 0.67–0.91; p=0.002). Ranolazine reduced worsening angina (p=0.048) and intensification of antianginal therapy (p=0.005) Exercise duration at 8 mo greater with ranolazine (p=0.002)	1° endpoint: ranolazine vs. PC HR: 0.86; 95% CI: 0.75-0.97; p=0.017	Substudy of a RCT that did not meet its 1° endpoint (exploratory) Randomization was not stratified by Hx of prior angina, small diffs in clinical characteristics between those randomized to ranolazine or PC exist.
Scirica, 2007 17804441	Assess the potential	Sub-study from a	6,351	3,162	3,189	Pts with NSTE-ACS	Cardiogenic shock,	Ranolazine	PC	Ranolazine was associated	(numerically, but not statistically,	Lower incidence of pauses ≥3 s	VT ≥8 beats (5.3% vs. 8.3%;	Substudy of a RCT that did not

(118)	antiarrhythmic actions of ranolazine after ACS	multinational RCT				within 48 h of ischemic Sx (between Oct 2004–Feb 2007) Eligibility criteria: ≥18 y; Sx of myocardial ischemia; at least 1 moderate-high-risk indicator	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 <12 mo			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 1 st 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 1 ^o endpoint (exploratory)
Morrow, 2007 17456819 (119)	Determine the efficacy and safety of ranolazine during long-term treatment of pts with NSTE-ACS	Multinational RCT	6,560	3,279	3,281	Pts with NSTE-ACS within 48 h of ischemic Sx (between Oct 2004 and Feb 2007) Eligibility criteria: ≥18 y; Sx of myocardial ischemia; at least 1 mod-high-risk indicator	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 <12 mo	Ranolazine (initiated IV followed by oral ranolazine extended-release 1000 mg 2× daily)	PC	1 ^o efficacy endpoint (composite of CV death/MI/recurrent ischemia): 21.8% in the ranolazine group vs. 23.5%, p=0.11 Follow-up was a median of 350 d	No diff in total mortality with ranolazine vs. PC (HR: 0.99; 95% CI: 0.80–1.22) No diff in QTc prolongation requiring dose reduction: 0.9% in pts receiving ranolazine vs. 0.3% in PC, p NS No difference in symptomatic arrhythmias (ranolazine: 3.0% vs. PC: 3.1%; p=0.84)	No diff in the major 2 ^o endpoint (CV death/MI/severe recurrent ischemia), or in the composite of CV death/MI. Ranolazine was associated with reduced recurrent ischemia: 13.9% vs. 16.1%; HR: 0.87; 95% CI: 0.76–0.99; p=0.03).	1 ^o efficacy endpoint (ranolazine vs. PC): HR: 0.92; 95% CI: 0.83–1.02	Given the statistically NS result for the 1 ^o endpoint, all additional efficacy analyses, although prespecified, should be considered as de facto exploratory 915 and 736 pts discontinued the study Rx in the ranolazine and PC arms, respectively.

1^o indicates primary; 2^o, 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, no/t 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)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparato r Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (Efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
SAVE Pfeffer, 1992 1386652 (120)	Captopril on events in AMI with LV dysfunction	Multi-institute prospective	2,231	Captopril 1,115	PC 1,116	3 d after AMI LVEF≤4% 21–79 y.	Contraind. to ACEI Creatinine >2.5 mg/dL	Captopril for 42 mo	PC	All-cause mortality reduced in captopril group vs. PC (20% vs. 25%) Reduction of MACE by 21%	No prospective safety evaluators	Reduction of CV death by ACEI 37% Reduction of severe HF by 22% Reduction of recurrent MI by 25%	All-cause mortality reduction by ACEI 19% (95% CI: 3%–32%); p=0.019 MACE: 21% (95% CI: 5–35); p=0.014 CV deaths 37% (95% CI: 20–50); p<0.001 Recurrent MI: 25%:(95% CI: 5–40); p=0.015	Adverse: dizziness, dysgeusia, cough, diarrhea. Exclusion of pts with symptomatic HF
Ambrosioni, 1995 7990904 (121)	ACEI for short-term events	Multi-institute prospective	1,556	Zofenopril 772	PC 784	CCU with AMI	Contraindication to ACEI	ACEI for 6 wk	PC	6-wk death or severe HF reduced by 34% with ACEI	N/A	1-y death rate reduced by ACEI 29%; p=0.011	6-wk death reduction: 34% (95% CI: 8%–54%); p=0.018 MACE: 46% (95% CI: 11–71); p=0.018	Side effects: 6.8% PC, 8.6% ACEI No use of initial IV ACI to see beneficial or adverse effects.
CONSENSUS II Swedberg, 1992 1495520 (122)	Long-term reduction in mortality with ACEI	Multi-institute prospective	6,090	Enalapril 3,044	PC 3,046	<24 h after onset of chest pain with ECG/ enzyme changes	BP <100/60; need for vasopressors, severe heart block, valvular disease, contraindication to ACEI, TIA	Enalapril for 6 mo	PC	1- and 6-mo mortality unchanged with enalapril vs. PC 7.2% vs. 6.3% 1 mo 11.0% vs. 10.2% 6 mo	Death due to HF 4.3% ACEI 3.2% PC p=0.06	Change in therapy due to HF increased in PC group. p<0.006 NS diff in reinfarctions or rehospitalization due to HF	Mortality; p=0.26	Early hypotension 12% ACEI and 3% PC p<0.001 Lack of ACEI benefit possibly due to low dose of ACEI
ACEI MI Coll. Group 1998 9631869 (123)	Use of ACEI in early AMI	Meta-analysis of 4 clinical trials	98,496	ACEI roughly 1/2	PC roughly 1/2	AMI-early short-term trials>1,000 pts	Smaller trials, no control group	ACEI from 28–42 d	PC	30-d mortality reduction 7% by ACEI	Hypotension less common in ACEI vs. controls 9.3 vs. 17.6%	Absolute benefit highest in Killip 2, 3 anterior MI	30-d mortality reduction 7% (95% CI: 2%–11%); p<0.004 HF reduction 14.6% vs. 15.2%	Significant increase in cardiac shock and renal dysfunction with ACEI Higher 2 nd -3 d AV block.

													2p=0.01	
AIREX Hall, 1997 9167457 (124)	Cumulative Mortality 3 y after end of AIRE trial of MI with HF	Multi- institute prospective-	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 reduced 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 1 st 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 al cohort study retrospective	1,725	ACEI in all or ARB in some cases	Various levels of BNP	ACS in CCU 44% NSTE- ACS	Resident pts outside health authority area.	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: 0.613 (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 or 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

						diuretics				PC	p<0.001 Increase in K+ greater in EP		CV Death or Hospital: 0.87 (95% CI: 0.79– 0.95); p=0.02	5.5% vs. 3.9%; p=0.002
Gheorghiade, 2009 19699868 (128)	Effect of epplerenone on readmission hospital stay after MI with LV dysfunction	Retrospectiv e analysis of prospective multicenter trial	6,632; 827 with subseque nt hospital readmissi on	Eplerenone 3,319	PC 3,313	Rehospitali zation for HF 827	No rehospitalization from original group 5,805	Eplerenone 16-mo follow-up	PC	Reduction of d of rehospitalization by eplerenone	In rehospitalization pts: K+>6.0 in 10.1% EP vs. 5.8% PC p=0.02	NS effect of geographic region on results	Total d in hospital for HF; (reduction) 3.6 (13.3–16.9) p=0.0006 vs. PC	In subset rehospitalized: No deaths from hyperkalemia, 2-fold reduction of hypokalemia, impotence was rare
Weir, 2009 19464421 (129)	MRI study to evaluate eplerenone effects on LV after MI	Prospective cohort study	100	Eplerenone 50	PC 50	AMI 1-14 d LVEF <0.40	Clinical HF, DM, preexisting, LV dysfunction, elevated creatinine, K+> mmol/L	Eplerenone 24 wk	PC	Change in LV systolic volume after covariate adjusted volume fell by 6.1± 2.7 mL/m ² vs. PC	NS diff between eplerenone and PC in HR, BP changes 2/50 EP pts developed K+ bet, 5.6 and 5.9	Diastolic volume fell EP vs. PC 7.5±3.4 mL/m ² p=0.031 Increased MMP -9 and decreased MMP-2	Systolic volume decreased with EP vs. PC: p=0.027	3 eplerenone pts died, vs. fibrillation, stroke, recurrent AMI, NS change in creatinine or eGFR. Need for covariate adjustment; LVEF changes between screening TTE and MRI.
Rossignol 2011, 22032706 (130)	Mechanism of eplerenone benefit in AMI	Retrospectiv e analysis of multicenter study	6,080	Eplerenone 3,055	PC 3,025	3-14 d after overall AMI; LVEF ≤0.40 CHF on ACEI, BB, diuretics	K+ sparing diuretic Creatinine >2.5 K+>5 meq/L	Eplerenone 1-mo evaluation	PC	Interaction between diuretic effects and K+ sparing effects of eplerenone and benefit of CV outcome	Decreased rate of CV death due to K+ sparing effect of EP vs. PC	EP vs. PC Reduced weight <0.0001 Plasma volume p=0.047 Increased K+ p<0.0001	EP decreased total mortality, CV death/ hospitalization and hospitalization for HF independent of K+ and diuretic effects	Post-hoc analysis Short-term evaluation of K+ and diuretic effects only
Rossignol, 2012 22128223 (131)	Eplerenone effects on renal function after AMI	Retrospectiv e analysis of multicenter study	5,792	Eplerenone 2,918	PC 2,874	3-14 d after AMI; LVEF ≤0.40 CHF, on ACEI, BB, diuretics	K+ sparing diuretic Creatinine>2.5 K+>5 meq/L	Eplerenone 24 mo follow-up	PC	Serial changes in eGFR EP had a decline in eGFR from 1 st mo and persisted throughout study	Most salient: early decline in eGFR by EP vs. PC	Early decline in eGFR by>20% associated with worse CV outcomes independent of baseline eGFR and use of eplerenone	Decline >20% eGFR 1 st mo: 16.9% EP vs. 14.7% PC OR: 1.15 (95% CI: 1.02–1.30); p=0.017	Post-hoc analysis and included nonprespecified subgroups Changes focused only on a 1-mo timepoint At this timepoint, deaths in eplerenone were already lower than PC
GISSI-3, 1994 7910229 (87)	Effect of ACEI on mortality and LV function	Multicenter prospective trial	18,895	Lisinopril, 9,435	Open control 9,460	In CCU within 24 h of chest pain, ECG	Severe HF requiring study treatment, hemodynamic	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	Relatively low dosage of lisinopril, many elderly and women excluded

	after MI					changes and no contraindications to study med	deterioration, bilateral renal artery stenosis, other life threatening disorders			Lisinopril reduced mortality and combined outcome	higher with ACEI	stroke did not differ	death plus decreased. LV dysfunction: 0.90 (0.84-0.98)	Concern about slightly increased creatinine and hypotension with ACEI
ISIS-4, 1995 7661937 (86)	Effect of ACEI on 5-wk mortality after AMI	Multicenter prospec trial	58,050	Captopril 29,028	PC 29,022	In CCU within 24 h of chest pain	Hypotension, cardiogenic shock, fluid depletion	Captopril 50 mg bid for 28 d	PC	5-wk mortality lower with ACE inhibitor	Rates of hypotension increased with ACEI, renal dysfunction No excess of deaths with lower BPs on ACEI	Somewhat fewer deaths 1 st 2 d of treatment with ACEI vs. PC	5-wk mortality:7.19% ACI vs. 7.69% PC 2p=0.02	Possible contending effects of magnesium and nitrates in regard to results

ACS indicates acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitor; AIRE Trial, Acute Infarction Ramipril Efficacy Trial; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; AV,block, atrioventricular block; BB, beta blocker; bid, twice a day; BNP, B-type Natriuretic Peptide; BP, blood pressure; CCU, cardiac care unit; CHF, congestive heart failure; CV, cardiovascular; diff, difference(s); D/C, discharge; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; EP, eplerenone; HD, heart disease; HF, heart failure; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; MRI, magnetic resonance imaging; NS, no(t) significance; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation-acute coronary syndrome; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PC, placebo; pts, patients; RN, radionuclide; and TTE, transthoracic echocardiography.

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)

Study Name, Author, Year	Study Aim	Study Type / Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results			
Baigent 2009 19482214 (132)	Low-dose ASA is of definite and substantial net benefit for people who already have occlusive vascular disease. Assessed the benefits and risks in 1° prevention.	Meta-analysis N=95,000 pts at low avg risk	ASA vs. no ASA	1° or 2° prevention trials eligible only if they involved randomized comparison of ASA vs. no ASA (with no other antiplatelet drug in either group).	1° prevention trials excluded individuals with any Hx of occlusive disease at entry	ASA or no ASA	Serious vascular events (MI, stroke, or vascular death) 0.51% vs 0.57%	Major bleeds 0.10% vs. 0.07% per y; p<0.0001	2° 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 a 1/5 in total stroke (2.08% vs. 2.54% per y;	p=0.0001	N/A	N/A

									p=0.002) and in coronary events (4.3% vs 5.3% per y; p<0.0001).			
CURE Yusuf 2001 11519503 (133)	Compare efficacy and safety of the early and long-term use of clopidogrel plus ASA with those of ASA alone in pts with ACS and no STE	Randomized, double-blind, PC trial N=12,562 pts	Clopidogrel vs. PC in addition to ASA	Pts were eligible for study if they had been hospitalized within 24 h after onset of Sx and no STE	Contraindications to 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	Clopidogrel (300 mg immed followed by 75 mg od) vs. PC in addition to ASA	Death from CV causes, nonfatal MI, or stroke 9.3% vs 11.4%	Pts with major bleeding 3.7% vs. 2.7%; p=0.001 RR: 1.38	1 st outcome or refractory ischemia 16.5% vs 18.8% RR: 0.86; CI: 0.79–0.94; p<0.001 Percentage of pts with in-hospital refractory or severe ischemia, HF, and revasc procedures were significantly lower with clopidogrel.	p<0.001 RR: 0.80 CI: 0.72–0.90	Clopidogrel was not associated with excess rate of any other type of adverse event that necessitated discontinuation of study drug	N/A
PLATO Mahaffey 2011 21709065 (134)	Prespecified subgroup analysis showed significant interaction between treatment and region (p=0.045), with less effect of ticagrelor in NA than in ROW. Exploratory analyses performed to identify potential explanations for observed region-by-treatment interaction.	Observed regional interaction driven by interaction of treatment with 78% of NA pts in US compared with ROW pts (p=0.01 vs. p=0.045 for interaction using NA). Analyses focus on comparison of US and ROW, with Canadian pts included in ROW group.	Reasons for the interaction were explored independently by 2 statistical groups.	N/A	N/A	2 independently performed analyses identified 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 is associated with low-maintenance dose of concomitant ASA	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 qd. Of 37 baseline and postrandomization factors explored, only ASA dose explained substantial fraction of the regional interaction.	N/A	Pts taking low-dose maintenance ASA, ticagrelor associated with better outcomes compared with clopidogrel, with statistical superiority in the rest of the world and similar outcomes in US cohort.	N/A	N/A	N/A
Gremmel 2010	Investigate age dependency of	Prospective observational	Clopidogrel and age	Pts on dual antiplatelet therapy	Known acetylsalicylic acid or	LD of 300 mg (n=116; 60.7%)	ADP-inducible platelet reactivity increased	N/A	N/A	p=0.003 for LTA and p<0.001 for	N/A	Lack of clinical outcome data,

19818001 (135)	clopidogrel mediated platelet inhibition	study N=191 pts		after angioplasty and stenting for CVD	clopidogrel intolerance (allergic reactions and gastrointestinal bleeding), therapy with VKA (warfarin, phenprocoumon and acenocoumarol), treatment with ticlopidine, dipyridamol or NSAID, a family or personal Hx of bleeding disorders, malignant paraproteinemias, myeloproliferative disorders or heparininduced thrombocytopenia, severe hepatic failure, known qualitative defects in thrombocyte function, a major surgical procedure within 1 wk before enrollment, a platelet count <100, 000 or >450, 000 IL-1 and hematocrit <30%.	or 600 mg (n=50; 26.2%) of clopidogrel prior intervention followed by 75 mg of clopidogrel od Pts received daily acetylsalicylic acid therapy (100 mg qd).	linearly with age after adjustment for CV risk factors, type of intervention, medication, CRP and renal function [using LTA 0.36% of maximal aggregation per y, 95% CI: 0.08–0.64%; p=0.013; using the VerifyNow P2Y ₁₂ assay 3.2 P2Y ₁₂ reaction units (PRU) per y, 95% CI: 1.98–4.41 PRU; p<0.001. ADP-inducible platelet reactivity significantly higher in pts 75 y or older compared with younger pts (p=0.003 for LTA and p<0.001 for VerifyNow P2Y ₁₂ assay). High on-treatment residual ADP-inducible platelet reactivity significantly more common among pts 75 y or older (p=0.02 for LTA and p<0.001 for VerifyNow P2Y ₁₂ assay).			the VerifyNow P2Y ₁₂ assay		the relatively small number of patients on chronic clopidogrel therapy and pts were not studied again under maintenance therapy with clopidogrel.
CAPRIE 1996 8918275 (136)	Assess potential benefit of clopidogrel compared with ASA in reducing risk of ischaemic stroke, MI, or vascular death in pts with	Randomized N=19,185 pts	N=9577 clopidogrel (75 mg od) plus PC n=9,566 ASA (325 mg od) plus PC	Ischaemic 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 ischaemic 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%), diarrhoea (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%.				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. 1° mechanism of sensitivity less often related to drug-specific IgE antibody production leading to	N/A	N/A	N/A	N/A	N/A

							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 1 ^o 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 HR: 0.81 CI: 0.73 - 0.90	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

								nonfatal bleeding 1.1% vs. 0.9%; HR: 1.25; p=0.23 fatal bleeding 0.4% vs. 0.1%; p=0.002				
PLATO Wallentin 2009 19717846 (139)	Determine whether ticagrelor is superior to clopidogrel for the 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 thereafter) or clopidogrel (n=9291) (300-600 mg LD, 75 mg daily thereafter)	Hospitalized for ACS with or without STE; with an onset of Sx during the previous 24 h. Pts who had ACS NSTEMI 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 revascularization; DM; PAD; chronic renal dysfunction, defined as a creatinine clearance of <60 ml/min per 1.73 m ² of body surface area with STE the following 2 inclusion	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	Ticagrelor or clopidogrel	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<0.001).	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	MI alone 5.8% vs. 6.9%, p=0.005 Death from vascular causes 4.0% vs. 5.1%, p=0.001 Stroke alone 1.5% vs. 1.3%, p=0.22 The rate of death from any cause 4.5% vs. 5.9%, p<0.001	p<0.001 HR: 0.84 CI: 0.77-0.92	Discontinuation of the study drug due to adverse events 7.4% ticagrelor vs 6.0% clopidogrel p<0.001 Dyspnea 13.8% vs. 7.8%; Higher incidence of ventricular pauses in 1 wk but not at 30 d in ticagrelor group than clopidogrel group	Geographic differences between populations of pts or practice patterns influenced the effects of the randomized treatments

				criteria had to be met: persistent STE of at least 0.1 mV in at least 2 contiguous leads or a new left bundle-branch block, and the intention to perform 1° PCI.								
Mehta 2010 20818903 (140)	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.	N=25,086 pts	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 y and presented with a NSTEMI, 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	Increased risk of bleeding or active bleeding and known allergy to clopidogrel or ASA	2×2 factorial design. Pts were randomly assigned in double blind fashion to double-dose regimen of clopidogrel or standard-dose regimen. In the 2 nd 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 1 st , 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 1° 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).	Composite of death from CV causes, MI, stroke, or recurrent ischemia; the individual components of 1° outcome; death from any cause; Definite or probable stent thrombosis. Double-dose clopidogrel associated with significant reduction in 2° 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).	p=0.30 HR=0.94 CI=0.83-1.06	N/A	Nominally significant reduction in 1° 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

			randomly assigned to higher-dose ASA received 300 to 325 mg daily d 2-30.									result could have been due to the play of chance.
Plato James 2011 21685437 (141)	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.	Randomized N=5216 pts	Ticagrelor n=2601 vs. clopidogrel n=2615	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 >60 y, previous MI or CABG, CAD, previous ischaemic stroke. TIA, carotid stenosis, cerebral revasc, DM, PAD, or chronic renal dysfunction	Contraindication to clopidogrel, fibrinolytic treatment within 24 h, need for oral anticoagulation treatment, need for dialysis, and clinically important anaemia or thrombocytopenia	ticagrelor or clopidogrel	CV death, MI, and stroke; their individual components; and PLATO defined major bleeding during 1 y 12.0% (n=295) ticagrelor vs. 14.3% (n=346) clopidogrel HR 0.85, 95% CI 0.73 to 1.00; p=0.04).	Incidence of total major bleeding 11.9% vs. 10.3%, HR: 1.17; 95% CI: 0.98–1.39; p=0.08 non-CABG related major bleeding 4.0% vs. 3.1%; HR: 1.30; 95% CI: 0.95–1.77; p=0.10	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	N/A	N/A
ISAR- REACT 2 Kastrati 16533938 (142)	Assess whether abciximab is associated with clinical benefit in high-risk pts with ACS undergoing PCI after	Randomized N=2,022 pts	Abciximab n=1012 vs PCn=1010	High-risk ACS pts undergoing PCI	STE-AMI	Abciximab (0.25 mg/kg bolus, followed by a 0.125-microg/kg/min max, 10 mcg/min) infusion for 12 h plus	Death, MI or UTVR at 30 d 8.9% vs. 11.9%	NS differences between 2 groups regarding risk of major and minor bleeding as	N/A	p=0.03 RR: 0.75 95% CI: 0.58–0.97	N/A	Cannot exclude possibility that greater benefit from abciximab might have been present had therapy been initiated

	pretreatment with 600 mg of clopidogrel					heparin, 70 U/kg or PC (PC bolus and infusion of 12 h, plus heparin bolus, 140 U/kg). All pts received clopidogrel 600 mg at least 2 h prior to procedure as well as 500 mg oral or IV ASA		well as need for transfusion.				earlier prior to the cath lab
PURSUIT Trial 2010 9705684 (143)	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.	Double blind N=10,948 pts	Bolus and infusion of eptifibatide or PC n=1487 low-dose eptifibatide group n=4722 high-dose eptifibatide group n=4739 PC group	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	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	Eptifibatide 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	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 1° 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	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	Mortality from all causes within 30 d after the index event, a 1 st for recurrent MI within 30 d, composite endpoint (death or nonfatal MI) at 96 h and 7 d	p=0.04	Bleeding was more common in eptifibatide group, although there was no increase in the incidence of hemorrhagic stroke.	N/A

					thrombolytic therapy within previous 24 h			randomly assigned to treatment groups, committee recommended dropping to lower dose				
PRISM-PLUS 1998 9599103 (144)	Evaluate tirofiban, a specific inhibitor of platelet GP IIb/IIIa receptor, in treatment of UA and non-Q-wave MI	Double-blind N=1915 pts	Tirofiban, heparin, or tirofiban plus heparin	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	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	Tirofiban, heparin, or tirofiban 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	Death, MI, or refractory ischemia within 7 d lower among pts who received tirofiban 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).	Study was stopped prematurely for group receiving tirofiban alone because of excess mortality at 7 d (4.6%, compared with 1.1% for pts treated with heparin alone	Death, MI, or refractory ischemia within 48 h and 30 d after randomization, the three components of this end point as separate measures, and composite of death and MI.	Tirofiban plus heparin vs. heparin alone p=0.004 RR=0.68 CI=0.53–0.88	Major bleeding occurred in 3.0% of pts receiving heparin alone and 4.0% of pts receiving combination therapy p=0.34	N/A
EARLY ACS Giugliano 2009 19332455 (145)	Determine optimal timing for initiation of treatment with GP IIb/IIIa inhibitors in pts who have ACS without STE and undergoing invasive procedures	Randomized N=9492 pts	Early, routine administration of Eptifibatide n=4722 vs. delayed Eptifibatide n=4684	Pts ACS NSTEMI undergoing invasive strategy	N/A	Early, routine administration of Eptifibatide or delayed Eptifibatide after angiography but before the pts underwent PCI	Composite of death, MI, recurrent ischemia requiring urgent revasc or occurrence of thrombotic complication during PCI at 96 h 9.3% vs. 10.0%	Major bleeding Pts in early eptifibatide group had significantly higher rates of bleeding. There was NS difference between 2 groups in	Rate of death or MI at 30 d 11.2% vs. 12.3%; OR=0.89; 95% CI: 0.79–1.01; p=0.08	p=0.23 OR=0.92 95% CI=0.80–1.06	N/A	Convergence of use of eptifibatide during PCI in 2 study groups probably reduced the difference in efficacy. Could not assign pts to strict PC group since guidelines

								rates of severe bleeding or nonhemorrhagic serious adverse events.				at time of planning trial strongly endorsed use of GP IIb/IIIa inhibitors during PCI
ACUITY subgroup analysis Stone 2007 17368152 (146)	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 isozyme; 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	Composite ischemia p=0.16; major bleeding p=0.32; net clinical outcomes p=0.1	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
BRILINTA TM (ticagrelor) tablets AstraZeneca LP (147)	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	Daily maintenance dose of ASA, coadministered with BRILINTA, should not exceed 100 mg Increased risk of bleeding Decreased efficacy with BRILINTA (ticagrelor) in	N/A	N/A	N/A	N/A

								combination with ASA doses exceeding 100 mg				
GUSTO IV-ACS Ottervanger 2003 12551868 (148)	Investigate long term effects of GP IIb/IIIa inhibitor abciximab in pts with ACS without STE who were not scheduled for coronary intervention	Randomized N=7800 pts	n=2590 abciximab for 24 h n=2612 abciximab for 48 h n=2598 PC	Pts with ACS without persistent STE including NSTEMI and UA. ≤ 21 y and should have had $1 \geq$ episodes of angina lasting at least 5 min within 24 h before admission. Either abnormal cardiac TnT or TnI test or at least 0.5 mm of transient or persistent ST-segment depression.	N/A	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)	Death (of any cause) or MI within 30 d Follow-up data obtained up to 1 y for 7746 pts (99.3%). Overall 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	N/A	N/A	24-hour abciximab HR: 1.1; 95% CI: 0.86–1.29), and 48-h abciximab HR: 1.2; 95% CI: 0.95–1.41	N/A	N/A
PCI-CURE Mehta 2001 11520521 (149)	Find out whether in addition to ASA pretreatment with clopidogrel followed by long-term therapy after PCI is superior to strategy of no pretreatment and short-term therapy for only 4 wk after PCI	Randomized N=2658 pts	clopidogrel (n=1313) or PC (n=1345)	N/A	N/A	Clopidogrel vs. PC	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 associated with a lower rate of CV death, MI, or any revasc (p=0.03), and of CV death or MI (p=0.047). Overall (including events before and after PCI) there was 31% reduction CV death or MI (p=0.002). Less use of GP IIb/IIIa inhibitor in clopidogrel group (p=0.001)	At follow-up, there was NS difference in major bleeding between groups p=0.64	N/A	p=0.03 RR: 0.70 95% CI: 0.50–0.97	N/A	N/A

Petersen 2004 18056526 (150)	Systematically evaluate end points 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	Systematic overview N=21946 pts ESSENCE, A to Z, and SYNERGY, TIMI 11B, ACUTE II, and INTERACT Performed using a random-effects empirical Bayes model	N/A	All 6 RCTs comparing enoxaparin and UFH in NSTE ACS were selected for analysis	N/A	N/A	Enoxaparin is 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 observed for enoxaparin in populations receiving no prerandomization antithrombin therapy (8.0% vs 9.4%; OR: 0.81; 95% CI: 0.70–0.94).	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

												statistical analyses.
PRINCIPL E-TIMI 44 Wiviott 2007 18056526 (150)	Compare prasugrel with higher than currently approved 300-mg LD and 75-mg/d 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	1° 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 qd with a 1° 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 (46.1±21.3%; p<0.0001). Results were consistent across all key 2° endpoints; significant differences emerged by 30 min and persisted across all time points	p<0.0001 CI: 38.0–48.4	N/A	LTA requires very precise sample conditions and processing. Significant proportion of samples did not meet prespecified conditions and were excluded from analyses. Absence of a washout period between MD treatments also could be considered limiting.
TRILOGY ACS Roe 2012 22920930 (151)	Evaluate whether ASA plus prasugrel is superior to ASA plus clopidogrel for long term therapy in pts with UA or MI without STE who were <75 y	Double-blind, randomized trial N=7243 pts <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 <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	Prespecified analysis of multiple recurrent ischemic events (all components of 1° endpoint) suggested lower risk for prasugrel among pts <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	Higher frequency of HF in clopidogrel group	N/A

				with either PCI or CABG.				events.				
PLATO Trial Becker 2011 22090660 (152)	Determine the rate, clinical impact, and predictors of major and fatal bleeding complications in the PLATO study	Randomized, double-blind, active control N=18,624 pts	Ticagrelor n=9235 or clopidogrel n=9186 in addition to ASA	Pts admitted to hospital with either STE or NSTE-ACS	N/A	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	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)	Fatal bleeding and transfusion rates did not differ between groups	Procedure related bleeding rates were also similar. Non-CABG major bleeding (4.5 vs. 3.8%, p=0.02) and nonprocedure related major bleeding (3.1 vs. 2.3%, p=0.05) were more common in ticagrelor treated pts, primarily after 30 d on treatment.	PLATO major bleeding p=0.43 TIMI major bleeding p=0.56) GUSTO severe bleeding p=0.22	N/A	N//A
Valgimigli 2010 19755402 (153)	To perform a thorough and updated systematic review of randomized clinical trials comparing tirofiban vs. PC or vs. abciximab.	Meta analysis 31 studies involving 20,006 pts	12,874 comparing tirofiban vs. heparin plus PC or bivalirudin alone, and 7132 vs. abciximab	Pts undergoing treatment for various CAD conditions	N/A	N/A	Tirofiban associated at 30 d with significant reduction in mortality compared with PC (OR: 0.68; 95% CI: 0.54–0.86; p=0.001) and death or MI (OR: 0.69; 95% CI: 0.58–0.81; p<0.001) Compared with abciximab, mortality at 30 d did not differ (OR: 0.90; 95% CI: 0.53–1.54; p=0.70) In overall group tirofiban tended to increase the composite of death or MI (OR=1.18; 95% CI: 0.96–1.45; p=0.11)	N/A	N/A	N/A	N/A	Heterogeneity in pt populations, different study drug regimens, and variable endpoint definitions across studies
ACUITY Stone 2007 17299194 (154)	To determine optimal strategy for use of GP IIb/IIIa inhibitors in pts with moderate and	Randomized N=9207 pts	Routine upstream (n=4605) deferred selective (n=4602) GP	Moderate- and high-risk ACS pts undergoing invasive-treatment strategy	Included STE AMI or shock; bleeding diathesis or major bleeding within 2 wk; thrombocytopenia; CrCl <30 mL/min	Routine upstream or deferred selective GP IIb/IIIa inhibitor administration	Composite ischemic events (death, MI, or unplanned revasc for ischemia) at 30 d 7.1% vs. 7.9%	N/A	Noninferiority or superiority of major bleeding and net clinical outcomes (composite ischemia or major bleeding).	p=0.044 for noninferiority; p=0.13 for superiority RR: 1.12 95% CI: 0.97–	N/A	Open label design of the trial, a result of the logistic complexities of the study

	high-risk ACS undergoing an early invasive treatment strategy		IIb/IIIa inhibitor administration						30-d rates of major bleeding 6.1% vs. 4.9% p<.001 for noninferiority; p=009 for superiority Net clinical outcomes (11.7% vs. 11.7%; p<.001 for noninferiority; p=0.93 for superiority).	1.29		design, introducing the potential for bias.

1° indicates primary; 2°, secondary; A to Z, AGGRASTAT to ZOCOR; ACS, acute coronary syndrome; ACUTEAcute Catheterization and Urgent Intervention Triage strategy; ADP, adenosine diphosphate; ASA, aspirin; 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; ;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, Immunoglobulin E; INTERACT, Intensive blood pressure reduction in acute cerebral haemorrhage trial; IPA; IV, 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)

Study Name, Author, Year	Study Aim	Study Type/ Size (n)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results			
CURE Yusuf 2001 (133) 11519503	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	Randomized , double-blind, PC-controlled trial 12,562 pts	Clopidogrel vs. PC in addition to ASA	Pts were eligible for the study hospitalized within 24 h after the onset of Sx and did not have STE	Contraindications to antithrombotic or antiplatelet therapy, high risk for bleeding or severe HF, taking OACs, had undergone coronary revasc in the previous 3 mo or had received IV GP IIb/IIIa receptor inhibitors in the previous 3 d	Clopidogrel (300 mg immediately followed by 75 mg once daily) vs. PC in addition to ASA	Death from CV causes, nonfatal MI, or stroke 9.3% vs. 11.4%	Pts with major bleeding 3.7% vs. 2.7% p=0.001 RR: 1.38	1° outcome or refractory ischemia 16.5% vs. 18.8% RR: 0.86; 95% CI: 0.79–0.94; p<0.001 % of pts with in-hospital refractory or severe ischemia, HF, and revasc procedures were also significantly lower with clopidogrel	p<0.001 RR: 0.80 95% CI: 0.72 — 0.90	Clopidogrel not associated with excess rate of any other type of adverse event that necessitated discontinuation of study drug	N/A
ASPECT-2 van Es 2002	Investigate whether ASA or OACs is more	Randomized N=999 pts	LDASA n=336, Coumadin-high intensity OAC	Men or non-pregnant women admitted with	Established indications for treatment with OAC,	LDASA, high intensity OAC, or combined LDASA	1 st occurrence of MI, stroke, or death 9% vs. 5% vs. 5%	Major bleeding 1% ASA, 1% on OAC	N/A	ASA vs. coumadin HR: 0.55; 95% CI:	N/A	N/A

(155) 12126819	effective in the long term after ACS, and whether the combination of ASA and OAC offers greater benefit than either of these agents alone, without excessive risk of bleeding		n=325, combined LDASA and coumadin-moderate intensity OAC n=332	AMIMI or UA within preceding 8 wk	contraindications for the study drug, planned revasc procedure, serious comorbidity, increased risk of bleeding, abnormal blood platelets or erythrocytes, anemia, Hx of stroke, and inability to adhere to the protocol	and moderate intensity OAC	ASA vs. coumadin HR: 0.55; 95% CI=0.30-1.00; p=0.0479 ASA vs. combined HR=: 0.50; CI: 0.27-0.92; p=0.03	(HR: 1.03; 95% CI: 0.21-5.08; p=1.0), and 2% on combination therapy HR: 2.35; 95% CI: 0.61-9.10; p=0.2		0.30-1.00; p=0.0479 ASA vs. combined HR: 0.50; 95% CI: 0.27-0.92; p=0.03		
Karjalainen 2008 (156) 18346963	Determine the safety and efficacy of various periprocedural antithrombotic strategies in pts on long-term OAC with warfarin undergoing PCI to assess the safety of the simplistic UAC strategy	Retrospective analysis n=523 pts	IAC group; UAC group	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	N/A	IAC vs. UAC	Major bleeding, access-site complications, and MACE (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) 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	N/A	N/A	N/A	Major bleeding, stroke, access-site complications	Inherent limitations of a retrospective study including individual risk-based decision making in the treatment choices; outcome assessment was not blinded; sample size may not be sufficient to cover small, but clinically significant diff in bleeding and thrombotic complications
BAAS ten Berg 2001 (157) 11319192	Study the intensity and the duration of AC as predictors of thrombotic and bleeding events	N=530 pts	ASA plus coumarins	Pts who were prospectively randomized to the use of coumarins as part of the BAAS study	N/A	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	Thrombotic events - death, MI, target lesion revasc, and thrombotic stroke 17 early thrombotic events (3.2%), 7 early bleeding	Bleeding complications - hemorrhagic stroke, major extracranial bleeding, and false aneurysm	N/A	N/A	N/A	N/A

						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	episodes (1.3%), and 10 false aneurysms (1.9%) 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				
ACCF/ACG /AHA report Bhatt 2008 (158) 19017521	Not a study but a report with recommendations	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ruiz-Nodar 2009 (159) 19246502	Evaluate the safety and efficacy of use of DES vs. BMS in a cohort of pts with AF	Retrospectiv e cohort study N=604 pts	DES (n=207) vs. BMS (n=207)	Pts with AF who had undergone PCI with stent	N/A	DES or BMS	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)	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)	N/A	N/A	N/A	Limited by its registry design and as well as being the experience of only 2 European centers; study may not be adequately powered enough to detect diff in clinical outcomes; the retrospective design of the study could explain an underreporting of minor

												bleeding; the exact length of triple treatment in BMS and DES groups
Lip 2010 (160) 20447945	Not a study but a summary report 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	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
WARSS Mohr 2001 (161) 11794192	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	Multicenter, double-blind, randomized	Warfarin (dose adjusted INR of 1.4-2.8) n=1,103 vs. ASA (325 mg qd) n=1,103	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	Baseline INR above normal range (>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	Warfarin (dose adjusted INR 1.4-2.8) vs. ASA (325 mg qd)	Combined recurrent ischemic stroke or death from any cause within 2 y Death or recurrent ischemic stroke 17.8% vs. 16.0% p=0.25; HR: 1.13; 95% CI: 0.92-1.38	Major hemorrhage 2.22 per 100 pt-y vs. 1.49 per 100 pt-y	N/A	p=0.25 HR:1.13 95% CI: 0.92-1.38	N/A	N/A
CARS Peverill 1997 (162) 15687136	N/A	Commentary	Fixed low-dose warfarin (1-3 mg) combined ASA (80 mg)	N/A	N/A	Fixed low-dose warfarin (1-3 mg) combined ASA (80 mg)	Reinfarction, stroke, or CV death. Provides no reduction in reinfarction beyond	N/A	N/A	N/A	N/A	N/A

							that achievable with 160 mg ASA					
Rossini 2008 (163) 19064015	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	N=102	Triple antiplatelet therapy ASA and clopidogrel and OAC n=102 Control group: dual antiplatelet therapy ASA and clopidogrel n=102	Pts undergoing coronary stenting treated with dual antiplatelet therapy also requiring OAC	Pts requiring OAC therapy because of mechanical valve prosthesis	Triple antiplatelet therapy ASA and clopidogrel and OAC or control group: dual antiplatelet therapy ASA and clopidogrel INR targeted to lower therapeutic range (2.0-2.5)	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%)	N/A	MACE 5.8% vs. 4.9%, p=0.7	N/A	N/A	N/A
Sarafoff 2008 (164) 18624903	Investigate the efficacy and safety of 2 regimens of antithrombotic AC therapy in pts who present for DES implantation whilst on OAC	N=515 pts	n=306 pts continued OAC (triple therapy) and n=209 pts discontinued OAC (dual therapy) they received antiplatelet therapy with clopidogrel and ASA	Pts on chronic OAC who underwent DES implantation	N/A	Clopidogrel and ASA	Composite of death, MI, stent thrombosis or stroke During SRAT 13 pts in group with triple therapy vs. 15 pts in the group with dual therapy Kaplan–Meier estimates 4.2% and 7.2%, OR: 0.61, 95% CI: 0.29-1.28; p=0.19. 2 y follow-up, 35 pts triple therapy vs. 36 pts dual therapy (Kaplan–Meier estimates 14.1% and 18.0%, OR: 0.76, 95% CI: 0.48-1.21; p=0.25).	Major bleeding 2 y 1.4% (n=4, triple therapy) vs. 3.1% (n=6, dual therapy, p=0.34)	N/A	N/A	N/A	Lack of randomization; diff regarding indication for OAC amongst both groups; study may be underpowered

^{1°} indicates primary; AC, anticoagulants; ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ASA, aspirin; BAAS, 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, internationalized normalized ratio; IV, intravenous; LDASA, low-dose aspirin; MACE, major adverse cardiac events; MI, myocardial

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)

Study Name, Author, Year	Study Aim	Study Type / Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results			
PLATO Mahaffey 2011 (134) 21709065	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.	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.	Reasons for interaction explored independently by 2 statistical groups.	N/A	N/A	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.	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%)	N/A	Both Cox regression with median 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.	N/A	N/A	N/A

							took median ASA dose ≥ 300 mg qd. Only ASA dose explained substantial fraction of regional interaction in 37 baseline and postrandomization factors explored.					
PLATO Wallentin 2009 (139) 19717846	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 NSTEMI, 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 $\geq 50\%$ at least 2 vessels; prev ischemic stroke, TIA, carotid stenosis $\geq 50\%$, or cerebral revasc; DM; PAD; chronic renal dysfunction, defined as CrCl of < 60 mL/min per 1.73 m^2 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 1 ^o 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; $p < 0.001$).	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	MI alone 5.8% vs. 6.9%, $p = 0.005$ Death from vascular causes 4.0% vs. 5.1%, $p = 0.001$ Stroke alone 1.5% vs. 1.3%, $p = 0.22$ Rate of death from any cause 4.5% vs. 5.9%, $p < 0.001$	$p < 0.001$ HR=0.84 95% CI=0.77-0.92	Discontinuation of study drug due to adverse events 7.4% ticagrelor vs. 6.0% clopidogrel $p < 0.001$ 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

Mehta 2010 (140) 20818903	Clopidogrel and ASA widely used for pts with ACS and those undergoing PCI. Evidence-based guideline for dosing not been established for either agent.	25,086 pts	Pts randomly assigned to double-dose clopidogrel received LD of 600 mg 1 d followed by 150 mg od on 2-7 d. Pts assigned to standard-dose clopidogrel received 300 mg LD 1 d before angiography followed by 75 mg od 2-7 d. 8-30 d both double-dose and standard-dose groups received 75 mg of clopidogrel od. 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.	≥18 y and presented with NSTE ACS or STEMI. ECG changes compatible with ischemia or elevated levels of cardiac biomarkers; coronary angiographic assessment, with plan to perform PCI early as possible but no later than 72 h after randomization	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. 2 nd 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 1 st , 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 1° 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 1° outcome; death from any cause; Definite or probable stent thrombosis. Double-dose clopidogrel associated with significant reduction in 2° 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).	p=0.30 HR: 0.94 CI: 0.83–1.06	N/A	Nominally significant reduction in 1° outcome 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 since 13 prespecified subgroup analyses were performed for clopidogrel dose comparison, result could have been due to play of chance.
ACUITY subgroup analysis Stone 2007 (146) 17368152	Assess anticoagulation with direct thrombin inhibitor bivalirudin during PCI in	Randomized n=7789 pts	n=2561 Heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors n=2609	Pts undergoing PCI after angiography, ST depression; raised Tnl, TnT, or CK-MB isozyme; known CAD; or all 4 other UA risk criteria as defined by TIMI study	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	30-d endpoints of composite ischemia (death, MI, or unplanned revasc for ischemia), major bleeding, and net clinical outcomes	N/A	N/A	Composite ischemia p=0.16; major bleeding p=0.32; net clinical outcomes p=0.1	N/A	Randomization occurred before angiography, study drugs were administered at median of 4 h before PCI. PCI

	individuals with moderate- and high-risk ACS.		Bivalirudin plus GP IIb/IIIa inhibitors, or n=2619 bivalirudin alone.	group		inhibitors, or bivalirudin alone	(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%					subgroup represents subset of 56% of all pts enrolled in ACUITY, randomization not stratified by treatment assignment.
Petersen 2004 (165) 15238596	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	Systematic overview N=21946 pts ESSENCE, A to Z, and SYNERGY, TIMI 11B, ACUTE II, and INTERACT performed using random effects empirical Bayes model	N/A	All 6 RCT comparing enoxaparin and unfractionated heparin in NSTEMI ACS selected for analysis	N/A	N/A	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	NS difference was 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) at 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 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 revascularization 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

							(8.0% vs. 9.4%; OR: 0.81; 95% CI: 0.70–0.94)					studies. Not having individual pt data from trials precluded more sophisticated statistical analyses.
Hochman 1999 (166) 10426845	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 Group 1 n=23 Group 2 n=19 Group 3 n=38	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/h pts <70 kg and a fixed 5000-U IV bolus/1000 U/hr for pts who weighed ≥70 kg) (group 3) 60 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 1 st 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 1 st 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<0.001).	Significantly higher proportion of pts above target range in groups 1 (95%) and 2 (84%) versus group 3 (47%) (p<0.0005)	No major complications in any group	Pts not randomly assigned, and the 2 weight adjusted regimens were not concurrently tested. At initiation of 2 nd weight-adjusted nomogram the target aPTT changed to 45-70 s from 50-75 s
Garcia 2012 (167) 22315264	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

	thrombin inhibitors hirudin, bivalirudin, and argatroban.											
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	Randomized N=3910 pts	UFH n=1957 vs. enoxaparin n=1953	Pts with UA/NQMI ischemic discomfort of >5 min duration at rest; Hx of CAD (abnormal coronary angiogram, prior MI, CABG surgery, or PTCA), ST deviation, or elevated serum cardiac markers	Planned revasc 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 >24 h before enrollment, Hx of heparin-associated thrombocytopenia with or without thrombosis, and contraindications to anticoagulation	UFH >3 d followed by subcutaneous PC injections or enoxaparin (30 mg IV bolus followed by injections of 1.0 mg/kg every 12 h) Outpatient phase (injections every 12 h of 40 mg pts <65 kg, 60 mg >65 kg)	Composite of all-cause mortality, recurrent MI, or urgent revasc 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	Major hemorrhage, bleed in retroperitoneal, intracranial, or intraocular location; hemoglobin drop of >3 g/dL; requirement of transfusion of >2 U blood 72 h no difference	Individual elements of 1° endpoint and composite of death or nonfatal MI	8 d p=0.048 OR=0.83 95% CI: 0.69–1.00 at 43 d p=.048 OR= 0.85 95% CI= 0.72–1.00	Stroke (1.0% vs. 1.2%), TIA (0.3% vs. 0.3%), or thrombocytopenia (2.1% vs. 1.9%)	N/A
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	Double-blind, randomized 20,078 pts	n=1,414 subcutaneous fondaparinux 2.5 mg od or n=1,420 subcutaneous enoxaparin 1 mg/kg bid	Pts with UA or NSTEMI; at least 2 of following criteria: age >60 y, positive cardiac biomarkers, or ECG changes compatible with ischemia.	Contraindication to low molecular weight heparin, hemorrhagic stroke within last 12 mo, indication for anticoagulation other than ACS, revasc procedure already performed for qualifying event, and severe renal insufficiency	Fondaparinux or enoxaparin total of 12,715 pts underwent heart catheterization during the initial hospitalization, and 6,238 pts underwent PCI.	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 >0.5 (2.4% vs. 5.1%; HR: 0.46, p<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	N/A	p<0.00001 HR: 0.46	N/A	Randomized treatments may have influenced which pts underwent PCI. Types of pts undergoing PCI and number and timing of PCI procedures similar in 2 randomized treatment groups. Number of pts who received open-label UFH before PCI in OASIS-5 trial

							10.4%; HR: 0.78, p=0.004). Fondaparinux reduced major bleeding 48 h after PCI irrespective of whether PCI was performed <6 h of the last enoxaparin dose (1.6% vs. 3.8%; HR: 0.42, p<0.0001) or >6 h when UFH was given (1.3% vs. 3.4%; HR: 0.39, p<0.0001).					modest.
OASIS-5 Yusuf (170) 16537663	Compare the efficacy and safety of fondaparinux and enoxaparin in high-risk pts with UA or NSTEMI	Randomized, double-blind, double-dummy trial N=20,078 pts	n=10,057 fondaparinux vs. n=10,021 enoxaparin	Pts with UA or NSTEMI; ≥60 y, elevated level of troponin or CK-MB isoenzyme, or ECG changes indicative of ischemia.	Contraindications to low molecular weight heparin, recent hemorrhagic stroke, indications for anticoagulation other than ACS or serum creatinine level of ≥3 mg/dL (265 μmol/L)	Fondaparinux (2.5 mg d) or enoxaparin (1 mg/kg od) for mean of 6 d	Death, MI, or refractory ischemia at 9 d 1° outcome events similar in 2 groups (5.8% (579 events) with fondaparinux vs. 5.7% (573 events) enoxaparin HR=1.01; 95% CI, 0.90-1.13); composite of 1° outcome and major bleeding at 9 d favored fondaparinux (737 events) 7.3% vs. (905 events) 9.0%; HR=0.81; p<0.001.	Rate of major bleeding at 9 d markedly lower with fondaparinux than with enoxaparin (217 events) 2.2% vs. 4.1%; HR: 0.52; p<0.001	Death, MI, or refractory ischemia; and individual components of composite outcomes at 30 d and at end of study NS trend toward lower value in fondaparinux group at 30 d (805 vs. 864, p=0.13) and at end of study (1222 vs. 1308, p=0.06). Fondaparinux associated with significantly reduced number of deaths at 30 d (295 vs. 352; p=0.02) and at 180 d (574 vs. 638; p=0.05).	HR: 1.01 CI: 0.90-1.13	N/A	N/A
FUTURA/OASIS-8 Steg 2010 (171) 20805623	Compare safety of 2 UFH regimens during PCI in high-risk pts with NSTEMI	Double-blind randomized parallel group N=2,026 pts	Low-dose UFH n=1024 vs. standard-dose UFH n=1002	Pts undergoing PCI within 72 h Hx consistent with new or worsening ischemia, occurring at rest or with minimal activity;	<21 y; contraindications to UFH or fondaparinux; contraindications for angiography; pts	IV low-dose UFH, 50 U/kg, regardless of use of GpIIb-IIIa inhibitors or standard-dose	Composite of major bleeding, minor bleeding, or major vascular access-site complications up to 48 h after PCI	Major bleeding or minor bleeding Major bleeding no difference minor bleeding	Composite of major bleeding at 48 h 5.8% vs. 3.9%; OR: 1.51; 95% CI: 1.00–2.28; p=0.05 death, MI, or target	p=0.27 OR: 0.80 95% CI: 0.54-1.19	Catheter thrombus 0.5% vs. 0.1% p=0.15	FUTURA still underpowered to conclusively rule out moderate, but important, reductions in

	acss 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 acss; women pregnant, breastfeeding, or of childbearing potential not using contraception; life expectancy <6 mo; receiving experimental pharmacological 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)	vessel revasc within 30 d 4.5% vs. 2.9%; OR: 1.58; 95% CI: 0.98–2.53; p=0.06			bleeding from use of low-dose UFH. Based on observed 5.8% event rate of 1° 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 mechanistically 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

	true pharmacologic al resistance to ASA—such as might be explained by genetic causes		received enteric coated ASA response was measured 8 h after dosing. Group 3 (n=150) received enteric coated ASA, response was assessed at 4 h				resistance to single dose of 325 mg enteric coated ASA (up to 49%) but not to immediate release ASA (0%).					
FUTURA/OASIS 8 Steg (173) 21146654	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 TnI 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	Major and minor bleeding; major vascular access site complications	Composite of peri-PCI major bleeding with death, MI, or target vessel revasc at 30 d.	N/A	N/A	N/A

					within last 12 mo; indication for anticoagulation other than ACS; pregnancy, women who are breastfeeding or childbearing potential who are not using effective method of contraception; comorbid conditions with life expectancy <6 mo; currently receiving an experimental pharmacologic agent; revasc procedure for qualifying event already performed; and severe renal insufficiency							
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 TnI, 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).					be considered wide
Fibrinolytic Therapy Trialists' (FTT) Collaborative Group 1994 (175) 7905143	Systematic overview of effects of treatment on mortality and on major morbidity in various pt categories in 9 trials designed to randomize >1000 pts with AMI between fibrinolytic	Collaborative overview	N=58600 pts	All trials of fibrinolytic therapy vs. control that randomized >1000 pts with suspected AMI GISSI-1, ISAM, AIMS, ISIS-2, ASSET, USIM, ISIS-3, EMERAS, LATE	N/A	Streptokinase, anistreplase, tPA, urokinase	Deaths during 1 st 5 wk and major adverse events occurring during hospitalization 10.5% deaths 1.0% strokes 0.7% major non-cerebral bleeds Fibrinolytic therapy excess of deaths during 0-1 d (especially among pts presenting >12 h after Sx and in the elderly)	N/A	Benefit in 45,000 pts presenting with STE or BBB irrespective of age, sex, blood pressure, HR, or previous MI or D greater earlier treatment began Relation between benefit and delay from Sx onset indicated highly significant absolute	N/A	Fibrinolytic therapy associated with 4 extra strokes per 1000 during 0-1 d	N/A

	therapy and control – GISSI-1, ISAM, AIMS, ISIS-2, ASSET, USIM, ISIS-3, EMERAS, LATE						Much larger benefit during 2-35 d		mortality reductions – 30 per 1000 within 0-6 h; 20 per 1000 presenting 7-12 h; statistically uncertain benefit 10 per 1000 within 13-18 h			
TIMI IIIB 1994 (176) 8149520	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 >180 mm Hg or DBP >100mm 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 early conservative strategy and 16.2% of pts assigned to the early invasive strategy (p=NS).	p=NS	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;	1° safety outcome major bleeding	2° outcomes of interest were recurrent angina	N/A	N/A	Large numbers of pts randomized to receive short-

	trials to assess effect of UFH and LMWH on death, MI, and major bleeding.			include ASA-treated pts randomly assigned to UFH or LMWH or to PC or untreated control	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.		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	Long-term LMWH OR=2.26, 95% CI=1.63–3.14, p<0.0001	and need for revasc.			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.
ACCF/ACG/AHA report Bhatt 2008 (158) 19017521	ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Karjalainen 2008 (156) 18346963	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	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.	N/A	IAC vs. UAC	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)	N/A	N/A	N/A	Major bleeding, stroke, access-site complications	Inherent limitations of retrospective study including individual risk-based decision making in treatment choices; outcome assessment not blinded; sample size may not be sufficient to cover

	simplistic UAC strategy.						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
BAAS ten Berg 2001 (157) 11319192	Study intensity and duration of anticoagulation as predictors of thrombotic and bleeding events	N=530 pts	ASA plus coumarins	Pts who were prospectively randomized to use of coumarins as part of BAAS study	N/A	ASA (LD, 300 mg; then 100 mg qd) and coumarins (acenocoumarol or Sintrom at 6 mg 1 d, 4 mg on 2 d, 2 mg on 3 d and after until intervention) started 1 wk before intervention Target INR was 2.1-4.8 during angioplasty and 6-mo follow-up INR measured on morning before PTCA and daily after until discharge	Thrombotic events - Death, MI, target lesion, revasc, and thrombotic stroke 17 early thrombotic events (3.2%), 7 early bleeding episodes (1.3%), and 10 false aneurysms (1.9%). 61 late thrombotic events occurred (11.6%). Optimal anticoagulation an independent predictor of late thrombotic events (RR: 0.33; 95% CI: 0.19-0.57) and associated with 0.21 mm (95% CI: 0.17-0.42) larger vessel lumen at 6 mo	Bleeding Complications, hemorrhagic stroke, major extracranial bleeding, and false aneurysm Late bleeding episodes (1.4%) lowest in pts in target range.	N/A	N/A	N/A	N/A
RE-DEEM Oldgren 2011 (177) 21551462	Evaluate the safety and indicators of efficacy of four dose regimens of dabigatran etexilate compared with PC when given in addition to dual antiplatelet	Double-blind, PC-controlled, dose-escalation trial N=1861 pts	Dabigatran vs. PC	Pts age ≥18 y, hospitalized with NSTEMI or STEMI within last 14 d, and receiving treatment with dual antiplatelet therapy (ASA and clopidogrel or another thienopyridine). ≥1 risk factor for subsequent CV complications: age ≥65 y, DM on treatment, previous MI, LBBB,	Ongoing or planned treatment with VKAs, severe disabling stroke within previous 6 mo or any stroke within previous 14 d, conditions associated with increased risk of bleeding such as major surgery (including bypass	Dabigatran initially one of two lower doses (50 mg bid n=369 and 75 mg bid) n=368 vs. PC n=371 N=406 110 mg dose in 2 nd stage n=347 150 mg dose group in third stage	Composite of major or clinically relevant minor bleeding during 6 mo treatment period. Composite of major or clinically relevant minor bleeding events 3.5, 4.3, 7.9, and 7.8% in respective 50, 75, 110, and 150 mg dabigatran groups, compared with 2.2%	N/A	Indicators of efficacy such as reduction in D-dimer levels and incidences of CV ischaemic events. D-dimer concentrations reduced in all dabigatran dose groups by an average of 37 and 45% at wk 1 and 4,	p<0.001 for linear trend 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)	14(3.8%) pts died, had a MI or stroke in PC group compared with 17 (4.6%) in 50 mg, 18 (4.9%) in 75 mg, 12 (3.0%) in 110 mg, and 12 (3.5%) in the 150 mg	N/A

	treatment in pts with recent STEMI or NSTEMI at high risk of new ischaemic CV events.			congestive HF requiring treatment or LVEF 40%, PAD, moderate renal insufficiency (CrCl $\geq$ 30–60 mL/min), or no revasc for the index event.	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 ,10 g/dL or platelet count ,100 $\times$ 10 ⁹ /L, normal coronary arteries at angiogram for index event, congestive HF New York Heart Association Class IV, and severe renal impairment (CrCl ,30 mL/min).		in the PC group, $p<0.001$ for linear trend. 96 1 ^o 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 ($p=0.001$).		respectively ($p<0.001$).	for 150 mg.	dabigatran groups	
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 2 ^o 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 _{M-H} , 1.33; 95% CI: 1.03-1.71; $p=.03$).	N/A	N/A	$p=.03$ OR _{M-H} , 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 $\leq$ 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

												74% of the events.
Alexander 2011 (179) 21780946	Determine whether in high-risk pts with ACS benefit of apixaban in reducing ischemic events outweigh increased risk of bleeding.	Randomized, double-blind, PC-controlled N=7392	n=3705 apixaban, 5 mg bid vs. n=3687 PC	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 $<40\%$ in association with index event, impaired renal function with calculated creatinine clearance <60 ml/min and no revasc after index event.	N/A	Apixaban 5 mg bid PC, in addition to standard antiplatelet therapy	CV death, MI, or ischemic stroke Median follow-up of 241 d 7.5% pts assigned to apixaban 7.9% assigned to PC HR=0.95; 95% CI: 0.80-1.11; p=0.51	Major bleeding according to TIMI definition occurred in 1.3% pts who received apixaban and in 0.5% pts who received PC HR=2.59; CI, 1.50-4.46; p=0.001. Greater number of intracranial and fatal bleeding events occurred with apixaban than PC.	N/A	P=0.51 HR=0.95 CI=0.80-1.11	N/A	N/A
Mega 2012 (180) 22077192	N/A	Double-blind, PC-controlled trial N=15,526 pts	bidbid doses of either 2.5 mg or 5 mg of rivaroxaban or PC	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	N/A	bid doses of either 2.5 mg or 5 mg of rivaroxaban or PC	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<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),	p=0.008 HR=0.84 CI=0.74-0.96	Rates of adverse events that were not related to bleeding similar in rivaroxaban and PC groups	N/A

								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) 22383791	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) 21900088	Evaluated potential of PCC to reverse anticoagulant effect of rivaroxaban and dabigatran	Randomized, double-blind, PC-controlled N=12	Rivaroxaban 20 mg bid (n=6) or dabigatran 150 mg bid(n=6)	Twelve healthy male subjects	N/A	Rivaroxaban 20 mg bid (n=6) or dabigatran 150 mg bid. (n=6) for 2.5 d followed by either single bolus 50 IU/kg PCC or similar volume of saline. After washout period procedure	Rivaroxaban induced significant prolongation of prothrombin time (15.8±1.3 vs. 12.3±0.7 s at baseline; p<0.001) that was immediately and completely reversed by PCC (12.8±1.0;	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 other 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), saline had no effect. Dabigatran increased activated partial thromboplastin time, ECT, and thrombin time. Administration of PCC did not restore these coagulation tests.					PCC or PC. If PCC had any effect of reversal for dabigatran it may have been missed; any rebound effect on anticoagulant activity of rivaroxaban in that same period could not be observed.

1° indicates primary; 2°, secondary; ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; ACT, activated clotting time; ACUITY, 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 Estreptoquinasa 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, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico acuto-1; GP, glycoprotein; HF, heart failure; HR, hazard ratio; Hx, history; IAC, Interrupt anticoagulation; IgE, Immunoglobulin 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, Urochinas per via Sistemica nell'Infarto Miocardico.

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

Study Name, Author, Year	Study Aim	Study Type / Size (n)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR: & 95 CI:	Study Limitations & Adverse Events
				Inclusion Criteria	Exclusion Criteria			Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results		
TIMI IIIB, 1994 8149520 (176)	To determine the effects of an early invasive strategy on clinical	RCT 1,473	Intervention: 740; Comparator: 733	Chest discomfort at rest caused by ischemia that lasted >5 min but <6 h. The discomfort must have occurred within	Pts were excluded if they had a treatable cause of UA, had experienced a MI within the preceding 21 d, had undergone	The protocol called for pts assigned to the early invasive strategy to have cardiac catheterization, LVA, and coronary	Pts randomized to the early conservative strategy were to have angiography	Death, postrandomization MI, or an unsatisfactory ETT performed at the time of the 6-	None	Analyses for differences and interactions in the results of invasive vs. conservative strategies for death	1° endpoint occurred in 16.2% of the pts randomized to the early invasive	Significant crossover with 64% in the conservative arm undergoing angiography by 42

	outcome			24 h of enrollment and accompanied by objective evidence of ischemic HD, i.e., either new or presumably new ECG evidence of ischemia in at least 2 contiguous leads or documented CAD	coronary arteriography within 30 d, PTCA within 6 mo, CABG at any time, or if, at enrollment, they were in pulmonary edema, had a systolic arterial pressure >180 mmHg or a diastolic pressure >100 mmHg, a contraindication to thrombolytic therapy or heparin. LBBB, a coexistent severe illness, were a woman of child-bearing potential, or were receiving OAC.	arteriography 18-48 h after randomization	carried out only after failure of initial therapy	wk visit		or MI were carried out on several prespecified subgroups	strategy vs. 18.1% of those assigned to the early conservative strategy (p=NS)	d
MATE, 1998 Mccullogh et al, (183) 9741499	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 were Sx lasting for more than 24 h or an absolute indication or contraindication to cardiac catheterization	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	2° 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 (184) 9632444	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 1° 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

				(or R waves) on serial electrocardiograms	recurrent ischemia at rest despite intensive medical therapy or severe HF that persisted despite treatment with IV diuretics, vasodilators, or both	management guidelines of the TIMI IIIB for revasc were followed	test; this was followed before discharge by a Sx-limited treadmill exercise test with thallium scintigraphy				conservative-strategy group (p=0.35) during an average of 23 mo of follow-up	
FRISC II, 1999 (185) 10475181	To compare an early invasive with a non-invasive treatment strategy in UCAD	Prospective, randomized, multicenter trial 2,457	Intervention: 1,222; Comparator: 1,235	Pts were eligible for inclusion if they had Sx of ischaemia that were increasing or occurring at rest, or that warranted the suspicion of AMI, with the last episode within 48 h	Exclusion criteria were raised risk of bleeding episodes, anaemia, or indication for or treatment in the past 24 h with thrombolysis, angioplasty in the past 6 mo, being on a waiting list for coronary revasc, other acute or severe CD, renal or hepatic insufficiency, known clinically relevant osteoporosis, other severe illness, hypersensitivity to randomized drugs, anticipated difficulties with cooperation or participation in this or another clinical trial	The direct invasive treatments were coronary angiography within a few d of enrollment, aiming for revasc within 7 d of the start of open-label treatment	Non-invasive treatment included coronary pts with refractory or recurrent Sx, despite max medical treatment, or severe ischaemia on a Sx-limited exercise test before discharge	Composite endpoint of death and MI after 6 mo	Bleeding	Total death, MI, Sx of angina, need for late coronary angiography and revasc, bleeding episodes, and stroke	There was a significant 22.0% relative and 2.7% absolute decrease in death and MI in the invasive compared with the non-invasive group after 6-mo RR: 0.78 (95% CI: 0.62–0.98), p=0.031	Revasc window of 7 d longer than actual contemporary practice
TACTICS - TIMI 18, Cannon et al 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220	Intervention: 1,114 vs. Comparator: 1,106	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, 2° angina, a Hx of PCI or CAB grafting within the preceding 6 mo, factors associated with an increased risk of	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	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	Study excluded pts with severe comorbid conditions or other serious systemic illness

				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 (120) 11792138	To compare 1 st d angiography/angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131	Intervention: 64 vs. Comparator: 67	Rest ischaemic chest pain, lasting <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 Tnl assay	Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; cardiogenic shock; acute LBBB or RBBB or STE 2 mm in 2 leads; QMI or IV thrombolysis >1 mo; coronary angioplasty or bypass surgery >6 mo; any concomitant disease which may have possible influence on 1-y Px; lack of pt cooperation	1 st 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	Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischaemia	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	The primary endpoint (death/reinfarction) at 6 mo occurred in 6.2% vs. 22.3% (p<0.001). 6 mo mortality in the 1 st 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	To compare interventional	RCT 1,810	Intervention: 895 vs.	Pts were eligible for inclusion if they had	All those with probable evolving	Pts assigned to the interventional treatment	Pts assigned to the conservative	The coprimary trial endpoints	Bleeding	Death, MI, refractory angina	At 4 mo, 86 (9.6%) of 895	Primary endpoint driven by reduction

(187) 12241831	strategy and conservative strategy in pts with unstable CAD		Comparator: 915	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 arteriographically proven CAD on a previous arteriogram	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 concentrations 2× the ULN before randomization, were excluded. Also excluded were those with MI within the previous mo, PCI in the preceding 12 mo, or CABG at any time.	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. The protocol specified that coronary arteriography should be done as soon as possible after randomization and ideally within 72 h	strategy were managed with antianginal and antithrombotic medication	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		as individual endpoints	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; 95% CI: 0.51–0.85; p=0.001).	of refractory angina with no difference in hard clinical endpoints
ICTUS, de Winter et al, 2005 (188) 16162880	To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level	RCT 1,200	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 revasconly if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischARGE	The primary endpoint was a composite of death, RMI, or rehospitalization for angina within 1 y after randomization	Bleeding	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).	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

				a documented Hx of CAD as evidenced by previous MI, findings on previous coronary angiography, or a positive exercise test	treatment (i.e., systolic pressure >180 mmHg or diastolic pressure >100 mmHg), weight <120 kg, or inability to give informed consent		exercise test.					
Italian Trial J Am Coll Cardiol Intv 2012;5:906-16) (189) 22995877	To determine the risk vs. bebefut ratio of an EA approach in elderly pts with NSTE-ACS	RCT 313	Intervention: 154 vs. Comparator : 159	Eligible 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	Excluded were pts with 2° causes of myocardial ischemia, ongoing myocardial ischemia or HF despite optimized therapy, PCI or CABG within 30 d before randomization, serum creatinine >2.5 mg/dL, a cerebrovascular accident within the previous mo, recent transfusions, gastrointestinal or genitourinary bleeding within 6 wk before randomization, platelet count 90,000 cells/ l, ongoing oral anticoagulation, severe obstructive lung disease, malignancy, or neurological deficit limiting follow-up	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 repeat hospital stay for CV causes or severe bleeding within 1 y	Bleeding	Individual components of the primary endpoint	The 1outcome 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

1° indicates primary; 2°, 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)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR: & 95 CI:	Study Limitations & Adverse Events
				Inclusion Criteria	Exclusion Criteria			Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results		
ISAR-COOL, Neumann et al 2003 14506118 (190)	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	RCT 410	Intervention: 207 vs. Comparator: 203	Pts with AP at rest or with minimal exertion, with the last episode occurring ≥24 h before study entry	Pts with evidence of large MI, including STE of at least 1 mV in 2 or more contiguous leads or elevation of the catalytic activity of creatine kinase and its MB isoenzyme to ≤3× the ULN; those with hemodynamic instability; those with contraindications to study medication; or those unable to provide written informed consent for participation	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	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	Composite 30-d incidence of large nonfatal MI or death from any cause	Bleeding, thrombocytopenia	Death, nonfatal MI	1° 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)	Small sample size
TIMACS, Mehta et al, 2009 (191) 19458363	To study efficacy of an early invasive strategy (within 24 h of presentation) compared with delayed invasive strategy (anytime 36 h after presentation)	RCT 3,031	Intervention: 1,593 vs. Comparator: 1,438	Presentation to a hospital with UA or MI without STE within 24 h after onset of Sx and if 2 of the following 3 criteria for increased risk are present: age ≥60 y, cardiac biomarkers above ULN, or results on ECG compatible with ischemia (i.e., ST-segment depression ≥1 mm or transient	Pt who is not a suitable candidate for revasc	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	Pts who were assigned to the delayed-intervention group underwent coronary angiography after a min delay of 36 h after randomization	Composite of death, MI, or stroke at 6 mo	Bleeding	1 st occurrence of the composite of death, MI, or refractory ischemia and the composite of death, MI, stroke, refractory ischemia, or repeat intervention at 6 mo	At 6 mo, 1° 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)	The trial may have been relatively underpowered. Heterogeneity was observed in the 1° endpoint, with pts in the highest tertile experiencing a sizeable risk reduction and suggesting a potential advantage of

				STE or T-wave inversion >3 mm)								early revasc in this high-risk subgroup
ABOARD, Montalescot et al (192) 19724041	To determine if immediate intervention on admission can result in reduction of MI vs. delayed intervention	RCT 352	Intervention: 175 vs. Comparator: 177	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	Hemodynamic or arrhythmic instability requiring urgent catheterization, chronic oral anticoagulation, or thrombolytic therapy in the preceding 24 h	An immediate invasive strategy	An invasive strategy scheduled on the next working d	Primary endpoint was peak Tn value during hospitalization	Bleeding	2° endpoints were composite of death, MI, or urgent revasc at 1-mo follow-up	The primary endpoint did not differ between the 2 strategies (median [IQR] TnI value, 2.1 [0.3-7.1] ng/mL vs. 1.7 [0.3-7.2] ng/mL in the immediate and delayed intervention groups, respectively; p=0.70)	Immediate (at a median of 70 min) vs. delayed (at a median of 21 h) angiography and revasc in UA/ NSTEMI pts conferred no advantage with regard to the primary endpoint

1° indicates primary; 2°, secondary AP, angina pectoris; ECG, electrocardiograph; IQR, interquartile range; MB, myocardial band; MI, myocardial infarction; non-ST-elevation myocardial infarction; pts, patients; RCT, randomized controlled trial; revasc, revascularization; RR, relative risk; STE, ST- segment elevation; Sx, symptom(s); TIMI; thrombolysis in myocardial infarction; Tn, troponin; TnI, troponin I; UA, unstable angina; and UA/NSTEMI, unstable angina/ non-ST-elevation MI.

Data Supplement 20. Risk Stratification Before Discharge for Patients With Conservatively Treated NSTEMI-ACS (Section 4.5)

Study Name, Author, Year	Study Aim	Study Type/ Size (n)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR: & 95 CI:	Study Limitations & Adverse Events
				Inclusion Criteria	Exclusion Criteria			Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results		
DANAMI, Valeur et al 2004 (193) 15618067	To test the prognostic importance of predischage maximal Sx-limited ET following AMI in the era of aggressive reperfusion	Post hoc subgroup analysis of a RCT 1,164	N/A	In the DANAMI-2 study, pts with STEMI were randomized to 1° angioplasty (PCI) or fibrinolysis	N/A	N/A	N/A	1° endpoint was a composite of death and re-infarction	N/A	N/A	ST-depression was predictive of the clinical outcome (RR: 1.57 [1.00- 2.48]; p<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<0.05), but not in the 1° PCI group (RR: 1.06 [0.47-2.36]; p=NS). However, the p-value for interaction was 0.15.	Post hoc analysis. Exercise capacity was a strong prognostic predictor of death and re-infarction irrespective of treatment strategy, whereas the prognostic significance of ST-depression seems to be strongest in the fibrinolysis-treated pts.
INSPIRE, Mahmarian et al 2006	To test whether gated ADSPECT could accurately	Cohort study 728 pts	N/A	The study cohort consisted of 728 stabilized pts 18 y of	N/A	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

(194) 17174181	define risk and thereby guide therapeutic decision making in stable survivors of AMI			age who had either QAMI or NQAMI and were prospectively enrolled		defined INSPIRE risk groups based on the adenosine-induced LV perfusion defect size, extent of ischemia, and EF	decision making were prospectively defined by specific ADSPECT variables. Pts with a small (<20%) ischemic PDS were classified as low risk and most had a LVEF of 35% (96%) and an ischemic PDS of <10% (97%).				risk group from low (5.4%, 1.8%), to intermediate (14%, 9.2%), to high (18.6%, 11.6%) (p<0.01). Event rates at 1 y were lowest in pts with the smallest perfusion defects but progressively increased when defect size exceeded 20% (p<0.0001).	enrolled in the INSPIRE trial so there may be selection bias. The perfusion results significantly improved risk stratification beyond that provided by clinical and EF variables. The low-risk INSPIRE group, comprising 1/3 all enrolled pts, had a shorter hospital stay with lower associated costs compared with the higher-risk groups (p<0.001).
COSTAMI -II, Decidari et al (195) 15657220	To compare in a prospective, randomized, multicenter trial the relative merits of predischage exercise ECG and early pharmacological stress echocardiography concerning risk stratification and costs of treating pts with uncomplicated AMI	RCT 262	Intervention: 132; Comparator: 130	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 predischage (d 7-9) maximum Sx limited exercise ECG (n =130)	Exclusion criteria were age >75 y, serious arrhythmias (VF, SVT, or fixed 2 nd or 3 rd degree AV blocks), LBBB, pericarditis, insufficient acoustic window, and poor short-term Px because of concomitant disease	Pharmacological stress echocardiography	Maximum Sx limited exercise ECG	1 ^o endpoint was cost effectiveness of the diagnostic strategies. The 2 ^o endpoint was quality of life evaluation. Pts were seen at 1 and 6 mo and 1 y after discharge. Cardiac events, use of resources, costing, and quality of life were recorded.	N/A	2 ^o endpoints were composite of death, MI, or urgent revasc at 1-mo follow-up	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).	Early pharmacological stress echocardiography and conventional predischage 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.

1^o indicates primary; 2^o, 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/t 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.

Data Supplement 21. RCTs and Relevant Meta-Analyses of GP IIb/IIIa Inhibitors in Trials of Patients With NSTE-ACS Undergoing PCI (Section 5)

Trial	Study Drug / Comparator	Population	Primary Endpoint	Results	Statistics	Comments
Elective (stable) and urgent (ACS) patients enrolled (without routine clopidogrel pretreatment)						
EPILOG (196) 9182212	Abciximab vs. PC	2,792 pts with stable ischemia or UA	Death, MI or UTVR at 30 d	5.2% vs. 11.7% HR: 0.43	95% CI: (0.30-0.60); p<0.001	N/A
ACS/high risk (without routine clopidogrel pretreatment)						
CAPTURE (197) 10341274	Abciximab (administered for 18-24 h before PCI) vs. PC	1,265 pts with “refractory UA” undergoing PCI 18-24 h after diagnostic catheterization	Death, MI or UTVR at 30 d	11.3% vs. 15.9%	p=0.012	Significant reduction in MI rate both before and during PCI with abciximab therapy. No diff in 6-mo composite endpoint
EPIC (198) 8121459	Abciximab vs. PC	Pts at high risk for abrupt vessel closure	Death, MI, UTVR, IABP, or unplanned stent placement at 30 d	Bolus only: 11.4% Bolus + infusion: 8.3% PC: 12.8%	p=0.009 overall; p=0.008 for bolus + infusion vs. PC	N/A
RESTORE (199) 9315530	Tirofiban (std dose) vs. PC	2,139 pts with ACS undergoing PTCA or DCA	Death, NFMI, UTVR, or stent placement at 30 d	10.3% vs. 12.2%	p=0.160	Composite endpoint was statistically lower at 2 and 7 d follow-up (but not at the 30-d 1° endpoint)
ACS/high risk or mixed study population (with routine clopidogrel pretreatment)						
ISAR-REACT 2 (142) 16533938	Abciximab vs. PC	2,022 “high-risk” ACS pts undergoing PCI	Death, MI or UTVR at 30 d	8.9% vs. 11.9% RR: 0.75	p=0.03 95% CI: 0.58–0.97	RR: 0.71 in +Tn pts; RR: 0.99 in -Tn pts
ADVANCE (200) 15234398	Tirofiban (high-dose) vs. PC	202 pts undergoing elective or urgent PCI (1/3 with stable angina; 1/2 with ACS)	Death, NFMI, UTVR or bailout GPI therapy at median of 185 d	20% vs. 35% HR: 0.51	p=0.01 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)
Pannu Meta-analysis (201) 18458661	GP IIb/IIIa vs. PC	5,303 pts undergoing PCI	Death, MI or TVR	OR: 0.84	95% CI: 0.58–1.22; p=0.35	N/A

1° indicates primary; ACS, acute coronary syndrome; DCA, directional coronary atherectomy; diff, difference; GP, glycoprotein; GPI, glycoprotein IIb/IIIa inhibitors; IABP, intraaortic 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)

Study	Aim of Study	Type of Study	Study Size	Patient Population	Primary Endpoint	Outcome
Brener SJ, 2008 (202) 18082505	To compare outcomes of culprit only PCI to multivessel PCI in NSTE-ACS pts	Post hoc database analysis	105,866 pts	NCDR database	Multiple endpoints analyzed	Procedural success: 91% culprit PCI vs. 88% multivessel PCI (p<0.001) In-hospital mortality: 1.3% culprit PCI vs. 1.2% multivessel PCI (p=0.09; adjusted OR: 1.11; 95% CI: 0.97–1.27)
Shishehbor MH, 2007 (203)	Examination of the safety and efficacy of nonculprit multivessel	Post hoc database analysis	1,240 pts	NSTE-ACS pts in institutional	Death, MI or TVR 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)

17320742	PCI with culprit-only PCI in pts with NSTE-ACS			database		Lower revasc rate with multivessel PCI drove endpoint differences
Zapata GO, 2009 (204) 19515083	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	Post hoc database analysis	609 pts	NSTE-ACS pts in institutional database	MACE at 1 y	MACE lower with multivessel PCI than culprit vessel PCI (9.45% vs.16.34%; p=0.02; no OR given) Revasc lower with multivessel PCI than culprit vessel PCI (7.46 vs. 13.86%; p=0.04; no OR given) No diff in death or death/MI between groups
Palmer ND, 2004 (205) 15152143	Compare short and medium-term outcomes of complete revasc PCI vs. culprit revasc in NSTE-ACS pts	Retrospective database review with additional pt follow-up	151 pts	NSTE-ACS pts treated at a tertiary care institute	Multiple endpoints analyzed	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)
Brener, 2002 (206) 12231091	To compare 30-d and 6-m outcome in NSTE-ACS pts undergoing PCI with (1) 1 VD and culprit PCI; (2) multivessel disease and culprit PCI; and (3) multivessel disease and multivessel PCI	Post hoc trial analysis	427 pts	NSTE-ACS pts in TACTICS-TIMI 18	In-hospital and 6-mo MACE	NS diff between the 3 groups at either 30-d or 6-mo follow-up for any of the endpoints: death; MI; and MACE

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.

Data Supplement 23. Risk Reduction Strategies for Secondary Prevention (Sections 6.3.)

Study Name, Author, Year	Aim of study	Study Type	Study Size (n)	Study Intervention Group (n)	Study Comparator or Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
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	20	Had PCI with implantation of a stent	History of MI or CABG, 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 16.8% (T) and 7.8% (C) (p<0.01). Flowmediated 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.

							regular training, any known chronic inflammatory disease other than atherosclerosis, or planned surgery in next 6 mo.					Levels of high-sens C-reactive protein decreased by -0.4 mg/L (T) and increased by 0.1 mg/L (C) (p=0.03 for trend)		
Depression and other psychological conditions														
Tisminetzky 2011 (208) 22409097	To ID Sx profiles of depression and anxiety in pts with ACS and examine changes over time	Randomized trial	79	45	34	Age 35+, hospitalized with ACS, mild/medium anxiety and/or depression	Mental healthcare in prior 3 mo, psychoactive 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) 17051359	To compare the use of celecoxib and rofecoxib on CV risk	Adjusted indirect comparison of 2 published RCTs (APPROVe and APC trials)	APPROVe=2,586 APC=2,035	APPROVe=1287 APC=685 (200 mg group) 671 (400 mg group)	APPROVe=1299 APC=679	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 0.81 — 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) 21115589	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)	626	Personal Hx of MI, UA, or ischaemic stroke	<45 or >80 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	1 st major CV event, NS for Vitamin B or Omega 3	N/A	Significant 2 ^o 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.

Imasa, 2009 (211) 19515873	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 Polyp Prevention on Vioxx trial; CABG, 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.

Data Supplement 24. Older Patients (Section 7.1)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Interventio n Group (n)	Study Comparator Group (n)	Patient Population		Study Interventio n	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Alexander 2007 (212) 17502590	Summarize evidence on pt heterogeneit y, clinical presentation , and treatment of NSTE-ACS in relation to age (65-74, 75-84, and 85 y)	Summary or 5 pooled NSTE-ACS clinical trials and 3 large NSTE-ACS registries to assess and grade evidence and provide descriptive finding and compare pts in clinical trials vs those not	Clinical Trials n=34266 (18.1% ≥75 y); Registries n=114572 7 (38.3% ≥75 y)	N/A	N/A	Clinical trial and registry specific- pooled (VIGOUR) included GUSTO IIb, PARAGON A and B, PURSUIT, GUSTO IV-ACS Registries=NR MI 2-4, CRUSADE, GRACE	Clinical trial and registry specific	Clinical trial specific	Clinical trial specific	Too numerous to list	Serum creatinine inadequately assesses age-related renal function decline- CrCl should be calculated in all older NSTE- ACS pts. Excess bleeding related to excess AP/AT dose	Summarizes available evidence of presentation, treatment and outcomes of OA in RCTs and registries.	Too numerous to list	Not a trial but an important paper on understanding mgt of older pts. Older NSTE-ACS are underrepresented in clinical trials and are younger and have less comorbidities vs. older pts in registries (and likely ‘real world’) warranting cautious extrapolation of results.

		included												
Gale 2012 (213) 22009446	Assess difference in risk factors, presentation, management 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	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	N/A	Compared to younger NSTEMI-ACS pts, older pts had sig higher in-pt 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.	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 ≥55 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 (214) 18387940	Determine whether increasing age impacts in-hosp and 6-mo outcome of revascularization in high-risk NSTEMI-ACS pts	Retrospective multiple logistic regression analyses on NSTEMI-ACS pts in GRACE registry by age groups	N=18466 NSTEMI-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 revascularization) by 3 age groups	In-hospital and 6-mo outcomes compared for age group and by intervention	GRACE registry pts meeting criteria for NSTEMI-ACS who had data during hospitalization and 6 mo after discharge. (STEMI data also reported but omitted here)	Pts with non-CV causes for the clinical presentation such as trauma, surgery, or aortic aneurysm, were excluded.	Pts who underwent revascularization during initial hospitalization classified under revascularization included high-risk pts with dynamic ECG changes or recurrent ischemia-regardless of timing of revascularization strategy	Medical therapy types were specifically recorded for comparison. Age and intervention strategy were compared.	In NSTEMI-ACS pts, revascularization vs. medical therapy sig lowered 6-mo MACE (stroke, death, MI) and 6-mo mortality. Older NSTEMI-ACS pts were sig less likely to undergo revascularization (and GDMT) than younger pts.	N/A	Elderly and very elderly pts less likely than younger pts to receive GDMT	Revascularization vs. no revascularization 6-mo MACE <70 yo OR=0.69, 95% CI 0.56–0.86; 70-80 y OR=0.60, 95% CI 0.47–0.76; >80 y OR=0.72, 95% CI 0.54–0.95 Revascularization vs. no revascularization 6-mo mortality: <70 y OR=0.52,	Although study reports benefit of early invasive therapy, pts who underwent PCI/CABG during admission were included including those who underwent revascularization >24 h after admission and high-risk pts were also included (including dynamic ST changes, recurrent ischemia)

													95% CI 0.37–0.72; 70-80 OR=0.38,95 %CI 0.26–0.54; >80 y OR=0.68,9% CI 0.49–0.95	
Damman 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 ≥75 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) underpowered for gender and age analyses	Routine Invasive vs. Selective Invasive on 5-y death/MI: <65 y (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 Conservative 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; 2° 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 conferred 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=0.009); Sig higher minor bleeding rates and transfusions 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 6-mo outcomes: Death/MI: RR=0.61 (0.41–0.92) MI: 0.49 (0.29–0.81) Death: RR=0.88 (0.51–1.53) ACS Rehosp: RR=0.75	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

										Invasive vs. Initial Conservative in NSTE-ACS pts ≥65 y but no sig diff in 6-mo outcome seen in pts <65 y	in ≥75 y		(0.50–1.11) MACE RR=0.75 (0.54–1.03) None of 6 mo outcomes sig in NSTE-ACS pt <65 y	
Yourman (217) 22235089	Assess quality and limitations of prognostic indices for mortality in older adults through systematic review.	Extensive literature review of prognostic indices for mortality (6 m-5 y) in pts age ≥60 y	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 (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	Single site study of consecutive pts admitted with NSTE-ACS pts- compared 12-mo outcome vs. prog tool estimate of EoL care.	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.			PPV=44%	
Tinetti 2004 (219) 15625341	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) 20015034	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.													
Trifiro 2011 (221) 21495972	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) 16380591	Investigation of relationship between UFH, LMWH and GPI excess dosing and major outcomes	Retrospective exploratory analysis of CRUSADE registry	N=30,136 NSTE-ACS pts who received AT agents	N/A	N/A	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 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.

										bleeding rate, mortality and length of stay vs. those given rec dose.				
Lincoff 2003 (223) 12588269	Determine efficacy of bivalirudin +GPI vs. GPI+UFH for PCI on periprocedural ischemia and bleeding	RCT, double-blind trial in pt undergoing urgent or elective PCI-prespecified for non-inferiority	N=6010	Bival+GPI-2999	UFH+GPI=3011	Pts ≥21 y undergo PCI with approved device	PCI performed as reperfusion therapy for AMI, poorly controlled Htn, unprotected LM, PCI w/l past mo., risk for bleeding, serum Cr >4 mg/dL, prior heparin tx.	Bivalirudin 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 (abciximab or eptifibatide) Pts received ASA and thienopyridine for ≥ 30 d post PCI	Provisional GPI given to 7.2% Bil pts. Noninferiority statistically achieved in 30 d endpoint: MI/death/ revascularization/ in-hospital major bleeding between BiV+GPI vs. UFH+GPI	In Hospital major bleeding rates significantly lower in Biv+GPI vs. UFH+GPI (2.4% v 4.1%, p<0.001)	30 d death/MI/revascularization: no difference in MACE BiV+GPI vs. UFH+GPI (OR=0.90, p=0.4)	30 d death/MI/revascularization/in-hospital major bleeding: no difference in MACE in BiV+GPI v UFH+GPI (OR=0.92, p=0.32).	Included elective PCI – NSTEMI-ACS pts approx. 42% each arm + 30% positive stress test; 13% ≥75 y
Lopes RD, 2009 (224) 19298914	Evaluate impact of age on antithrombotic strategy and outcomes in moderate and high-risk NSTEMI-ACS pts	Pre-specified analysis of 30-d and 1-y outcomes in 4 age groups, overall and among those undergoing PCI	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 (previous column), 1/3 were randomized to receive bivalirudin alone	Of the pts in each age group (4 th column), 1/3 were randomized to receive Hep+GPI	NSTEMI-ACS pts at moderate or high risk for adverse clinical outcomes at 30 d. All pts underwent cath w/l 72 h of admission	Pts excluded for any of following: STEMI, recent bleeding, CrCl <30 mg/mL, thrombocytopenia, shock, recent use of abciximab, warfarin, fondaparinux, bivalirudin, LMWH, fibrinolytics	Bivalirudin alone All pts- ASA+mtn Clopidogrel post PCI × 1 y Clopidogrel load per invest	Bivalirudin+GPI-randomized (2×2 factorial) to upstream or cath lab GPI administration Heparin +GPI randomized (2×2 factorial) to upstream or cath lab GPI administration All pts- ASA+mtn Clopidogrel post 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 bivalirudin alone or randomized to heparin with GP IIb/IIIa 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 significantly lower in those treated with Bivalirudin alone in each age group	Older pts had more comorbidities, 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 bivalirudin 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

Lemesle G., 2009 (225) 19360860	Analyze impact of replacing heparin with bivalirudin in octogenarians undergoing PCI on post-procedure hemorrhage and 6-mo mortality.	Single center retrospective analyses of consecutive pts ≥80 y who underwent PCI	N=2766	N=1,207 (43.6%) received bivalirudin	N=1,559 (56.4%).received UFH	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 mtn 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 mtn 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 mort (8.8% vs. 13.4%, p=0.003). Bival was assoc with sig less in-hosp bleeding rate (2.2% vs. 6.8%, p< 0.001).)	After propensity score matching, bival sign reduced periproced bleeding vs. UFH (HR=0.38, 95% CI=0.22–0.65, p=0.001). Bival vs. hep 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)	Bival vs. UFH reduced 6-m 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 anal. and by multivar COX (HR=0.6, 95% CI= 0.4–0.9, p=0.01)	Non-randomized observational study. Doses not reported. Differences in baseline characteristics-propensity analyses used.
Summaria F, 2012 (226) 22476002	To explore feasibility and safety of PCI via transradial approach and intraprocedural bivalirudin in >70 y MI pts	Retrospective analyses of data from consecutive ACS pts >70 y with Early Invasive strategy via transradial approach with bivalirudin as AT.	N=84 pts (22 male; 52 pts >80 y) STEMI=53, NSTEMI=31	All pts were treated with bivalirudin and via transradial approach	N/A	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 300 mg, clopidogrel 600 mg, UFH bolus and infusion in emerg dept – stopped 6 h prior to PCI	N/A	Transradial approach successful in 100%, manual thrombus aspir in 52% of NSTEMI pts. Transfusions=0, sign bleeding events=1 (GI bleed), in-pt mort=0,30 d MACE=5 (6%, 1 death, 2 MI, 2 TLR)	N/A	N/A	N/A	Pilot feasibility study in very elderly cohort. Single center, no comparison group.
McKellar SH, 2008 (227) 18825133	To assess pt characteristics, procedural success,	Systematic review and meta-analyses of 66 studies of	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 mort CABG vs. PCI (7.2% v 5.4%). 1-y survival: CABG=86%	3 y survival CABG 78% (74%–82%) v PCI 78% (68%–87%), 5	Greater number of reintervention s 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

	complications and outcomes of ≥80 y who undergo PCI vs. CABG	coronary revascularization in ≥80 y (subgroup analysis by revascularization type)				in ≥80 y undergoing revascularization (PCI vs. CABG) with 30-day survival (English language)	studies where baseline clinical data or outcomes were not reported separately were excluded.	replacement), last enrolled 1996		(83%–88%) vs. PCI 87% (84%–91%)	1-year survival CABG 68% (62%–73%) vs. PCI 62% (46%–77%),		multivessel disease, and abnormal LVEF predicted 30-day mortality. Being treated more recently, having nonelective status, and having DM were protective. The only univariate predictor of decreased survival at 1 year was CABG (p=0.005); a more recent date of enrollment (p=0.003) and diabetes (p<0.001) were protective factors.	comorbidities, 65 of 66 studies observational, Older studies w/o DES
Kimura T, 2008 (228) 18824755	Assess long-term outcomes between PCI vs. CABG in younger and older patients (≥75 years)	Retrospective analyses of multicenter registry (CREDO-Kyoto) of consecutive patients undergoing first PCI or	N=9,877 enrolled, 5420 (PCI: 3712, CABG: 1708) had multivessel disease without left main	CABG=1,708 ≥75 years, (21%) ≥80 years (6%)	PCI=3,712 ≥75 years (27%) ≥80 years (12%)	Consecutive patients undergoing first PCI or CABG and excluding those patients with AMI within week before index procedure.	Patients undergoing concomitant valvular, left ventricular, or major vascular operation were excluded from the current analysis. Patients with disease of the left main	N/A	N/A	≥75 years of age: 3-year survival adjusted for baseline characteristics favored CABG (HR for death PCI vs. CABG HR=1.23 (0.99-1.53, p=0.06), but not for younger patients	Stroke rate higher in 4 years follow-up in CABG vs. PCI	≥75 years: Adjusted HR for death PCI vs. CABG prespecified subgroups: DM HR= 1.85 (1.1–3.12) p=0.02 All-cause death cumulative	75 years of age: 3-year survival adjusted for baseline characteristics 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

		CABG-stratified by age <75 vs. ≥75 y	involvement.				coronary artery and with single-vessel disease were excluded.			(HR=1.09, p=0.55); 3VCAD Cox survival favors CABG vs. PCI (p=0.004)		incidence: 1 y: PCI 9% vs. CABG 8.8% 2 y: PC 15.4% vs. CABG 12.2% 3 y: PCI 20.7% vs. CABG 13.3% 4y: PCI 22.7% vs. 15.5%	not for younger pts (HR=1.09, p=0.55)	
Dacey LJ, 2007 (229) 18036905	Compare long-term survival after PCI vs. CABG in ≥80 y	Retrospective observational 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 (2VCAD=443, 3VCAD=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 1 st 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= 5.9% (p=0.005). 6-mo survival: CABG vs. PCI (HR,1.32; p=0.135). 6-mo to 8-y survival- all pts: CABG vs. PCI (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 CHF 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.

2° indicates secondary; 2VCAD, double-vessel coronary artery disease ; 3VCAD, triple-vessel coronary artery disease; ACC-NCDR indicates American College of Cardiology National Cardiovascular Data Registry; ACE, angiotensin-converting enzyme; ACS, acute coronary syndromes; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; AMI, acute myocardial infarction; AP, antiplatelet; ASA, aspirin; AT, antithrombins; BARI, Bypass Angioplasty Revascularization Investigation; BEIR, Biological Effects of Ionizing Radiation; BMS, bare metal stent; CHF, congestive heart failure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CANRACE, Canadian Registry of Acute Coronary Events; cath, catheterization; CHF, congestive heart failure; CR, creatinine; CrCl, creatinine clearance; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; 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; CT, computed tomography; CTCA, Cancer Treatment Centers of America; DES, drug-eluting stent; DM, diabetes mellitus; EoL, end of life; EPR, electronic patient record; EPS, electrophysiology study; ETT, Exercise tolerance testing; FRISC, Framingham and Fast Revascularization During Instability in Coronary Artery Disease; GDMT, guideline-directed medical therapy; GI, gastrointestinal; GP, glycoprotein; GPI, glycoprotein IIb/IIIa inhibitors; GRACE; Global Registry of Acute Coronary Events; GSF, Gold Standards Framework; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HF, heart failure; HTN, hypertension; Hx, history; ICTUS, Invasive versus Conservative Treatment in Unstable Coronary Syndromes; LAR, life attributable risk; LBBB, left bundle branch block; LOS; length of stay; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MI, myocardial infarction; MINAP, Myocardial Ischaemia National Audit Project; MPI, myocardial perfusion imaging; MUGA, Multigated Wall Motion Study; N/A, not applicable; NPV, negative predictive value; NS, not significant; NRMI, National Registry of Myocardial Infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-

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 count; 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)

Study Name, Author, Year	Aim of study	Study Type	Study Size (n)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Interventi on	Study Comparat or	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Boersma 2000 (2) 10840005	Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE-ACS	Retrospecti ve analysis of pts with NSTEMI-ACS enrolled in PURSUIT trial (n=9,461; 3.6% with 1° outcome)	N/A	Pts enrolled in PURSUIT trial	Pts not enrolled in PURSUIT trial; pts with STEMI on initial ECG	N/A	1° outcome: 30- d death; 2° outcome: composite of 30- d death and myocardial (re)infarction; More than 20 variables were found to be predictive of 1° and 2° outcomes	N/A	N/A	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	N/A	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	Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE- ACS	Retrospective analysis of pts with NSTEMI-ACS enrolled in PURSUIT trial (n=9,461; 3.6% with 1° outcome)
Granger 2003 (3)	Develop a regression	Retrospecti ve	N/A	Inclusion in GRACE or	Not included in these trials	N/A	Adverse event defined as in-	N/A	N/A	The discrimination ability of the	N/A	Regression model	Develop a regression model	Retrospective observational study

14581255	model in pts with diagnosed ACS (including pts with STEMI) for in-hospital mortality	observational study utilizing pts from GRACE (n=11,389; 509 deaths); validation set included a subsequent cohort of 3,972 pts enrolled in GRACES and 12,142 pts enrolled in GUSTO-IIb trial		GUSTO-IIb trial			hospital mortality; Regression model identified the following 8 independent risk factors: accounted age, Killip class, SBP, ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac enzyme findings, and heart rate			simplified model was excellent with C-statistics of 0.83 in the derived database, 0.84 in the confirmation 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)		developed in patients with diagnosed ACS (including STEMI pts) and was not designed to be applied indiscriminately to undifferentiated chest pain pts; difficult to calculate; original model requires pre-existing programmed calculator; simplified version requires print-out of scoring system for each variable with corresponding nomogram	in pts with diagnosed ACS (including pts with STEMI) for in-hospital mortality	utilizing pts from GRACE (n=11,389; 509 deaths); validation set included a subsequent cohort of 3,972 pts enrolled in GRACES and 12,142 pts enrolled in GUSTO-IIb trial
Pollack 2006 (13) 16365321	Validation in an ED population with chest pain	Convenience sample 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 (14) 21691204	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 (15) 19960136	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

		from angiographic arm								regardless of score with less				
Eagle 2004 (16) 15187054	Original GRACE validation	Registry N=17,141	N/A	All ACS	N/A	N/A	6-mo all-cause mortality	N/A	N/A	p<0.25 into multivariate model	N/A	Registry data, 200 pts without 6 mo follow-up	Original GRACE validation	Registry N=17,141
Eggers 2010 (17) 20598977	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Single center trial of 453 chest pain pts	NT-proBNP, cystatin GDF-15	Possible ACS	N/A	Biomarkers at presentation	All-cause mortality at 6 mo	N/A	NT-proBNP not additive, cystatin minimally and GDF-15 helpful	ROC analysis	N/A	Small but 92 deaths.	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Single center trial of 453 chest pain pts
Cannon 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220	Intervention: 1,114 vs. Comparator: 1,106	Pts ≥18 y if they had episode of angina (with accelerating pattern or prolonged [≥20 min] or recurrent episodes at rest or with minimal effort) within preceding 24 h, candidates for coronary revascularization, and at least 1 of the following: 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	Persistent STE, 2° 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 <2.5 mg/dL (221 μmol/L), or current participation in another study of an investigational drug or device	Pts assigned to early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revascularization when appropriate on the basis of coronary anatomical findings	Pts assigned to 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 an 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	Prospective, randomized, multicenter trial 2,220

				at least 0.3 mV in at least 2 leads; elevated levels of cardiac markers; or coronary disease, as documented by Hx of cath, revasc, or M										
de Winter 2005 (188) 16162880	To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level	RCT 1,200	Intervention: 604 vs. Comparator: 596	Eligible pts 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; elevated cTnT level (≥ 0.03 $\mu\text{g/L}$); 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	Exclusion criteria were an age >18 y or <80 y, STEMI in past 48 h, indication for 1° PCI or fibrinolytic therapy, hemodynamic instability or overt CHF, the use of oral anticoagulant drugs in past 7 d, fibrinolytic treatment within past 96 h, PCI within the past 14 d, contraindication to treatment with PCI or GP IIb/IIIa inhibitors, recent trauma or risk of bleeding, hypertension	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 revasc only if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischARGE exercise test.	1° 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 1° 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]; $p=0.33$).	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	To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level	RCT 1,200

				≥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	RCT 1,810	Intervention: 895 vs. Comparator: 915	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	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 concentrations 2× the ULN before randomization, were excluded. Also excluded were those with MI within the previous mo, PCI in the	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	Pts assigned to the conservative strategy were managed with antianginal and antithrombotic medication	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	Bleeding	Death, MI, refractory angina as individual endpoints	At 4 mo, 86 (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° 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	RCT 1,810

				ally proven CAD on a previous arteriogram	preceding 12 mo, or CABG at any time.									
Spacek 2002 (120) 11792138	To compare 1-d angiography /angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131	Intervention: 64 vs. Comparator: 67	Rest ischaemic 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 Tnl assay	Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; cardiogenic shock; acute LBBB or RBBB or STE 2 mm in 2 leads; QMI or IV thrombolysis >1 mo; coronary angioplasty or bypass surgery >6 mo; any concomitant disease which may have possible influence on 1 y Px; lack of pt cooperation	1-d angiography /angioplasty treatment strategy guidelines characterized by coronary angiogram as soon as possible after randomization followed by immediate coronary angioplasty of the culprit coronary lesion + stent implantation whenever suitable	Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischaemia	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	1° endpoint (death/reinfarction) 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).	Small sample size, interventions were done in only one high volume tertiary center	To compare 1-d angiography/angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131
Hochman 1999 (230) 10460813	Evaluate early revascularization in pts with cardiogenic shock	Multicenter RCT	302 pts	152 pts randomized to emergency revasc	150 pt-initial medical stabilization	STEMI, new LBBB, posterior infarction with 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

						shock 2° to LV dysfunction								
Bhatt 2004 (231) 15523070	Determine use and predictors of early invasive management strategies in high-risk pts with NSTEMI	Registry-observational study trial	17,926 with NSTEMI 8,037 (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	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

1° indicates primary; 2° 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; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTE, non–ST-elevation; 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 Integrilin 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; TnI, troponin I; ULN, upper limit normal; US, United States.

Data Supplement 26. Cardiogenic Shock (Section 7.2.2)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study group	Comparator group	Endpoints		Conclusions	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Major Study Findings	Additional Findings		

Jacobs A. et al, 2000 (232) 10985710	Determine the outcomes of pts with cardiogenic shock complicating NSTEMI	Registry Sub-study of the SHOCK trial	881	152 pts with NSTEMI and cardiogenic shock	729 pts with STEMI and cardiogenic shock	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<5 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
Holmes DR et al., 1999 (233) 10562262	Assess the incidence and outcomes of cardiogenic shock developing among pts with and without ST-segment elevation	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 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)	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.	GUSTO-IIb is a thrombolytic trial (excluded pts ineligible for thrombolytics). Subgroup analysis. Different baseline risk.

1° indicates primary; CAD, coronary artery disease; DM, diabetes mellitus; ECG, electrocardiogram; GUSTO, Global Use of Strategies To Open Occluded Coronary Arteries; LV, left ventricular; LVEF, left ventricular ejection fraction; MVD, multi-vessel disease; NS, nonsignificant; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; Pts, patients; RV, right ventricular; SHOCK, Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock; STE, ST-elevation; STEMI, ST-elevation myocardial infarction; and TIMI, Thrombolysis In Myocardial Infarction.

Data Supplement 27. Diabetes Mellitus (Section 7.3)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Cannon 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial	Intervention: 1,114 vs. Comparator: 1,106	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 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	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 <2.5 mg/dL (221 μmol/L), or current participation in another study of an investigational drug or device	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 echo performed according to the protocol of the institution) before being discharged	Combined incidence of death, nonfatal MI, and rehospitalization for an 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	Prospective, randomized, multicenter trial 2,220

FRISC II (185) 10475181	Compare early invasive with a noninvasive treatment strategy in unstable CAD	Multicenter RCT of 2,457 pts	2,457 pts, 21.4% diabetic	Early invasive strategy N=1,222	Study comparator group: noninvasive strategy n=1,235	Inclusion: UA, NSTEMI Pts with DM—21.4% of total but not analyzed separately	N/A	N/A	N/A	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)	N/A	Angina at 6 mo In pts with DM invasive strategy improved anginal Sx – 24% for invasive vs. 41% for noninvasive RR: 0.59 (0.41–0.84)	N/A	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
Norhammar 2004 (234) 14975468	Evaluate influence of DM in outcome of unstable CAD	Randomized clinical trial	299 pts with diabetes mellitus and 2,158 without Randomization to early invasive or a noninvasive strategy	299 pts with DM	2,158 patients without DM	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	N/A	N/A	N/A	1° 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=0.066) Invasive strategy	N/A	N/A	N/A	An invasive strategy improved outcomes for both patients with and without DM with unstable CAD DM is an independent risk factor for death and MI in both invasive and noninvasive groups

										reduced composite of death or MI in nondiabetic patients without DM from 12.0% to 8.9% (OR 0.72; CI 0.54–0.95 p=0.019)				
Farkouh 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	Pts with DM with angiographically 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% - CABG 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

1° indicates primary; 2°, secondary; 3VD, three-vessel disease; ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; DES, drug-eluting stents; DM, diabetes mellitus; HBP, high blood pressure; Hx, history; ITT, intention to treat; LBBB, left bundle-branch block; LMCA, left main coronary artery disease; MACE, major adverse cardiac events; MI, myocardial infarction; MVD, multi-vessel disease; N/A, not applicable; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Pts, patients; RCT, randomized controlled trial; RR, relative risk; Sx, symptom(s); UA, unstable angina.

Data Supplement 28. Post-CABG (Section 7.4)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Kavsak 2006 16824840 (23)	Impact of new classification of MI	Retrospective analysis using CK-MB vs. TrI analysis for MI def. 258 pts with ACS	TrI vs. CK-MB Dx based on MONICA or AHA def of MI	2 SPSS CK-MB, TrI $\geq 20\%$ change using 99% TrT cutoff	N/A	2 specimens CK-MB, TrI drawn at least 6 h apart	AMI prevalence” MONICA CK-MB 19.4% AHA 19.8%. TnI increase. to 35.7%	N/A	TrI vs. CK-MB p<0.001 for increase MI def using TnI	cTnI 35.7% (30.1-41.7) Relative inc 84%	N/A	Exclusion of nonischemic diseases causing Tr elevation	Impact of new classification of MI	Retrospective analysis using CK-MB vs. TrI analysis for MI def. 258 pts with ACS
Goodman 2006 16504627 (25)	Diagnostic and prognostic impact of new UDMI	Multicenter observational prospective Registry (GRACE) 26,267 ACS pts	Use of CK and -Tn 16,797 vs. CK-MB and Tn 10,719 for hospital. fatality, 14,063 vs. 8,785 for 6-mo mortality	>18 y with possible ACS with ECG abnormal or CAD history. CK, CK-MB. Tn	NS comorbidity, trauma, surgery, lack of 1 biomarker	CK CK-MB Tn Follow-up for 6 mo	Tn+ levels demonstrated higher in hospital and 6-mo mortality rates than higher CK levels	N/A	In entire population, Tn+ status vs. CK status 6-mo mortality:1.6 (1.4-1.9)	Hospital fatality rates higher with Tn+ vs. CK+: 2.2 (1.6-2.9) with Tn+/CK-MB-: 2.1 (1.4-3.2)	N/A	34% in GRACE registry excluded because of use of 1 biomarker only	Diagnostic and prognostic impact of new UDMI	Multicenter observational prospective Registry (GRACE) 26,267 ACS pts
Eggers 2011 20869357 (26)	Clinical implications of relative change in cTnI levels with chest pain	Retrospective study of 454 ACS pts within 24 h of admission with 5.8 y follow-up	UDMI with presp cTnI changes from $\geq 20\%$, 50%, 100%	N/A	cTnI <99 th percentile	cTnI levels	Peak cTnI level $\geq 99^{\text{th}}$ percentile + change $\geq 20\%$ in 160. 25 had no AMI by ESC/ACC criteria	N/A	N/A	All 160 had significant raised mortality HR: 2.5 (1.7-3.8) Higher TnI deltas were not associated with higher mortalities	NA	Analysis of assay could not be validated by hs Tr assay. No review of pts records for type I or 2 AMI No long-term risk assessment	Clinical implications of relative change in cTnI levels with chest pain	Retrospective study of 454 ACS pts within 24 h of admission with 5.8 y follow-up
Giannitsis 2010 (33) 20167697	Dx, perf. of hs-cTnT for detection. of NSTEMI in ACS	Retrospective cohort analysis 57 with UA	Baseline vs. and serial conc. at 3 h and 6 h	UA or NSTEMI with initial -cTnT	Immed PCI or kidney dysfunction	Hs-cTnT baseline,3,6 h delta change	Hs -cTnT Dx 61% at baseline to 100% at 6 h.	N/A	Doubling of hs-Tnt with initial 99% + pos	Delta changes and ROC opt. values spec 100% with	N/A	Admission to chest pain unit more selective than typical ED	Dx, perf. of hs-cTnT for detection. of NSTEMI in ACS	Retrospective cohort analysis 57 with UA and evolving NSTEMI

		and evolving NSTEMI				>20%,or ROC optimized value >117% 3 h, or 246% 6 h	Dx inc by 34% above std cTnT		predicted value 100% neg predicted value 88%	sens 69% and 76%		admissions		
le 2004 (236) 15528943	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
Lindahl 2010 (32) 20691825	Hs-cTnT comparison with std cTnT for risk assessment	Prospective cohort 1,452	Effect of pos. by both assays vs. only 1 assay	ACS pts	No coronary angiography within 12 h	Both cTnT collected 48 h after randomization	+hs-TnT same 1-y mortality. Whether + or – with st-TnT	N/A	For death or AMI at 30 d + only for hs-TnT had interim risk	+hs-TnT 1-y mortality 9,2% vs. 1.6% p=0.001 For – by both assays	N/A	Pts with higher pretest risk than typical chest pain pts in ED	Hs-cTnT comparison with std cTnT for risk assessment	Prospective cohort 1,452
Cannon 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective , randomized , multicenter trial 2,220	Intervention: 1,114 vs. Comparator: 1,106	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 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 <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	Prospective, randomized, multicenter trial 2,220

				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, revascularization, or MI	μmol/L), or current participation in another study of an investigational drug or device									
Fox 2002 (187) 12241831	To compare interventional strategy and conservative strategy in pts with unstable CAD	RCT 1,810	Intervention: 895 vs. Comparator: 915	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]),	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	Pts assigned to the 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. The protocol specified that coronary	Pts assigned to the conservative strategy were managed with antianginal and antithrombotic medication	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	Bleeding	Death, MI, refractory angina as individual endpoints	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).	1° 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	RCT 1,810

				or T-wave inversion); pathological Q waves suggesting previous MI; or arteriographically proven CAD on a previous arteriogram	randomization, were excluded. Also excluded were those with MI within the previous month, PCI in the preceding 12 months, or CABG at any time.	arteriography should be done as soon as possible after randomization and ideally within 72 hours								
Spacek 2002 (120) 11792138	To compare 1 st day angiography/angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131	Intervention: 64 vs. Comparator: 67	Rest ischaemic chest pain, lasting <20 minutes, within the last 24 hours 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 × ULN and/or positive Tnl assay	Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; cardiogenic shock; acute LBBB or RBBB or STE 2 mm in 2 leads; QMI or IV thrombolysis >1 month; coronary angioplasty or bypass surgery >6 months; any concomitant disease which may have possible influence on	1 st day 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	Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revascularization only in the presence of recurrent myocardial ischaemia	Composite of death or nonfatal RMI 6 months after the randomization	None	Length of the initial hospitalization and the number of subsequent hospitalizations for UAP	1 ^o endpoint (death/reinfarction) at 6 months occurred in 6.2% vs. 22.3% (p<0.001). 6 months mortality in the 1 st day 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	To compare 1 st day angiography/angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131

					1-y Px; lack of pt cooperation									

1° indicates primary; 2°, secondary; 3VD, three-vessel disease; ACS indicates acute coronary syndrome; AMI acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CK, creatine kinase;; CK-MB, creatine kinase MB; Dx, diagnosis; ECG, electrocardiograph; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; HBP, high blood pressure; Hs-cTnT, high-sensitivity cardiac troponin I; Hx, history; IV, intravenous; LBBB, left bundle-branch block; MI, myocardial infarction; MONICA, Multinational MONItoring of trends and determinants in CArdiovascular disease; NS, no(n) significance; PCI, percutaneous coronary intervention; Pt, patient; Px, prognosis; QMI, Q-wave myocardial infarction; RBBB, right bundle-branch block; RCT, randomized controlled trials; revasc, revascularization; ROC, receiver operating characteristic;RMI; RR, relative risk; cTnT, cardiac troponin T; SSPS; STE, ST-elevation; Tn, troponin; TnI, troponin I; UAP; UDMI, Universal Definition of Myocardial Infarction; and ULN, upper limit of normal.

Data Supplement 29. Chronic Kidney Disease (Section 7.6)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria	Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Wright 2002 12353943 (237)	Compare outcomes after AMI in pts with varying degrees of renal function	Retrospectiv e cohort study	4,426	n=3,106 with: endstage renal disease, severe renal insufficiency CrCl <35 mL/min, moderate renal insufficiency CrCl ≥35, ≤50 mL/min, mild renal insufficiency CrCl > 50 mL/min	n=1,320 with normal renal function	Consecutive pts with acute infarction between 1988 and 2000. Renal function estimated according to the Cockcroft-Gault.	N/A	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<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<0.001) Moderate renal failure HR: 2.2 (CI: 1.5–3.3; p<0.001)	Pts with renal failure received reperfusion therapy less frequently than pts with normal renal function; p<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)	N/A	N/A	Retrospective Analysis Potential referral bias Single center study

								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)				
Shlipak 2002 12353942 (238)	Determine how pts with renal insufficiency are treated during MI Determine association of renal insufficiency on survival after MI	All nongovernmental 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 mg/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 characteristics, 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

Solomon 1994 7969280 (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 Nonfatal MI RR: 0.78; 95% CI: 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
Szumner 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	Patients not revascularized within 14 d of admission, n=11,232	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	N/A	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.

Data Supplement 30. Women (Section 7.7)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparato r	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Hutchinson-Jaffe AB, Goodman SG, Yan RT, et al. Comparison of baseline characteristics , management and outcome of patients with non-ST-segment elevation acute coronary syndrome in versus not in clinical trials. Am J Cardiol. 2010;106:138 9-96.	Characterize differences in clinical characteristics and clinical management between pts with NSTEMI-ACS in clinical trials and not in clinical trials	Retrospecti ve case-control of several large NSTEMI-ACS registries	N=13,556 pts with NSTEMI-ACS (8.3% in clinical trials)	None	None	Pts with NSTEMI-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 NSTEMI-ACS presentation	Pts with NSTEMI-ACS with ACS precipitated or accompanied by a serious concurrent illness, such as trauma or GI bleeding	N/A	N/A	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<0.001). Unadjusted in-hospital mortality nonclinical vs. clinical trials (2.1% vs. 0.7%, p<0.001) and 1-y (8.9% vs. 6.3%, p=0.037) In	N/A	N/A	Results too numerous to list	N/A

21059426 (242)										multivariable analysis, pts who were older, women, had Hx of CHF failure, and increased CrCr levels on presentation were less likely to be enrolled in clinical trials.				
Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J. 2009;157:141-8. 19081410 (243)	To assess clinical and angiographic characteristics, procedural and treatment patterns, and in-hospital outcomes between men and women	Retrospective case-control of registry data	N=199,690 pts, 55,691 women presented with NSTE-UA vs. 101,961 men	All pts underwent PCI (index)	None	Men and women with NSTE-ACS who underwent PCI in ACC-NCDR Registry 1/104-3/30/06; index PCI only	Not fitting predefined NSTE-ACS definition or not undergoing PCI	N/A	N/A	Women presented more often with NSTE-ACS than men (82% vs. 77% of men, <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<0.01), and any vascular complications, but subacute stent	N/A	Too numerous to list	Too numerous to list	Limited extrapolation – all subjects are registry NSTE-ACS pts

										thrombosis rates were less in women compared to men (0.43% vs. 0.57%, p=0003).				
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. 15766815 (244)	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/revere then 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 and	To examine gender impact on antithrombotic therapy for	Retrospective analysis of ACUITY trial (prespecified	4,157 women with NSTE-ACS (31% of total	Overall women =4,157 GPI + heparin	Overall men =9,662 GPI + heparin (UFH or	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	In women: bivalirudin alone significantly less	Same as 1° 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;103:119 6-203. 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=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. 6%); no difference in bivalirudin + GPI and GPI + herparin		women=8% vs. men=3%; p<0.0001; 30-d net clinical outcome women=13% vs. men=10%; p<0.0001	regression analysis performed to account for baseline difference
Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE initiative. Circulation. 2006;114:138 0-7. 16982940 (246)	To examine gender impact on GPI use, dose, bleeding in pts with NSTE-ACS in CRUSADE	Retrospecti ve 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

												men=3.81 (95% CI: 3.39- 4.27)		
Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA. 2004;292:2096-104. 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 =2,842)	8,037 (44%) underwent early cardiac cath <48 h	N/A	Pts with NSTEMI presenting to 248 US hospitals with cardiac cath facilities and PCI or CABG availability	N/A	N/A	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 NSTEMI ACS	Meta-analysis of RCTs (1970-4/2008) with gender-specific analyses	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 NSTEMI-ACS in 8 RCTs evaluate early invasive vs. selective invasive (if recurrent Sx) or positive stress test after initial pharmacological test	Pts with missing biomarker data excluded from high-risk analyses	N/A	N/A	Women had lower MACE with early invasive vs. initial conservative as did men without significant gender interaction. Biomarker-positive women. Early invasive vs. initial conservative for death/MI/ACS (OR: 0.67; 95%	N/A	In men: early invasive vs. initial conservative for MACE. Biomarker positive: OR: 0.56 (95% CI: 0.46-0.67) Biomarker	MACE early invasive vs. initial conservative: Women: OR: 0.81 (95% CI: 0.65-1.01) Men: OR: 0.73 (95% CI: 0.550.98)	Results persisted for 12-m follow-up. Heterogeneity between trials; trials not individually powered for sex-specific analyses

segment elevation myocardial infarction: a meta-analysis. JAMA. 2008;300:71-80. 18594042 (247)										CI: 0.50-0.88), but not in biomarker negative women and 35% higher risk of death/MI (OR: 1.35; 95% CI: 0.78-2.35)		Negative OR: 0.72 (95% CI: 0.51-1.01)		
Dolor RJ, Melloni C, Chatterjee R, et al. Treatment Strategies for Women With Coronary Artery Disease [Internet].2012 23016160 (248)	To determine efficacy and safety of early invasive vs. initial conservative strategy in women with NSTE-ACS	Meta-analyses of RCTs and systematic reviews of observational studies	7 studies early invasive vs. initial conservative for women with NSTE-ACSMI 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	N/A	Pts with NSTE-ACS in RCT of early invasive vs. initial conservative studies including FRISC-II, TACTICS-TIMI-18, GUSTO-IV-ACS, ICTUS, RITA-3, TIMI-IIIb	Those with missing data	Early invasive vs. initial conservative	N/A	Women showed trend toward benefit from early invasive vs. initial conservative at 6 mo and 1 y (death/MI) OR: 0.78; OR: 0.77, respectively), but at 5 y the trend favored initial conservative (1.05; CI: 0.81-1.35); Troponin-positive women benefit from early invasive vs. initial conservative (OR: 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)	Early invasive showed benefit (death/MI) over initial conservative in men at 6 m (OR: 0.65; CI: 0.52-0.82; p=0.0002). Results for these at 1y (OR: 0.88; CI: 0.64-1.20); 5 y (OR: 0.91; CI: 0.53-1.56)	N/A	N/A
Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes.	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 of sex as predictor of outcome—prospective	N=2,220 (women =757)	Early invasive =1,114 – Angiography 4-48 h after randomization with PCI/revascularization 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 =angiography 4-48 h after randomization with PCI/revascularization as indicated	Initial conservative =medical therapy – angiography/PCI if recurrent Sx or positive stress test	Women 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	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.

JAMA. 2002;288(24): 3124-9. 12495392 (249)		RCT of early invasive vs. initial conservative strategy)								invasive vs. initial conservative in MACE (OR: 0.72; 95% CI: 0.47-1.11) overall but OR: 0.47 (95% CI: 0.26-0.83) for elevated troponin	bleeding and stroke showed in women undergoing CABG no different from men	ST segment changes OR: 1.00 (CI: 0.61-1.65)		
Chen J, Einstein AJ, Fazel R, et al. Cumulative exposure to ionizing radiation from diagnostic and therapeutic cardiac imaging procedures: a population-based analysis. J Am Coll Cardiol. 2010;56:702-11. 20619569 (250)	To determine the cumulative dose of ionizing radiation exposure of cardiac imaging over 3 y	Retrospective, observational. Administrative claims used to identify insured adults undergoing cardiac imaging	N=952,420 enrollees, n=90,121 ≥1 cardiac imaging procedure	Determine cumulative dose-cardiac procedure= myocardial perfusion imaging (CT or PET), cardiac CT, diagnostic cath/PCI, cardiac PET, MUGA, EPS/ablation 2005-7 vs. background radiation level	3 categories were 3 mSv/y background level of naturally absorbed radiation in the U.S; 3-20 mSv/y, and 20 mSv/y (upper annual limit for occupational exposure for at-risk workers/ 5 y)	Insured adults (18-65) with 3 y data – member 1 of 5 health care markets having ≥1 cardiac imaging procedure	N/A	N/A	N/A	9.5% underwent having ≥1 cardiac imaging procedure within 3 y. Mean cumulative dose=23.1 mSv (range 1.5 mSv-544 mSv). MPI accounted for 74%; 80/100 rec >3-20 mSv; 3.3/1,000 rec >20 mSv	Myocardial imaging studies account for most of radiation-identifies potential to reduce radiation with alternate imaging	Radiation levels for comparable procedure higher in doctors' office vs. hospital. Higher in men and increasing exposure with age.	N/A	Radiation estimates, insured younger adult population studied, not specific to those with NSTEMI-ACS
Einstein AJ, Weiner SD, Bernheim A, et al. Multiple testing, cumulative radiation dose, and clinical indications in patients undergoing myocardial perfusion imaging.	To characterize procedure counts, cumulative estimated effective radiation doses, and clinical indications for pts undergoing MPI	Retrospective cohort study of consecutive pts undergoing MPI –single center-index exam linked to all radiation studies pre (18 y)/post (2 y) follow-	N=1,097 pts with index exam in 2006; (51.5% women)	MPI	N/A	Consecutive inpts and outpts in single center undergoing single-photon emission CT MPI (index procedure) in 2006- EPR linked records 1988-2008	Radiotherapy procedures excluded	N/A	N/A	Median procedures=15 (IQR 6-32), 4 were high-dose ionizing radiation; 31% received cumulative dose >100 mSv. Multiple MPIs performed on 39% pts, MPI accounted for majority of radiation	N/A	Women underwent more ionizing radiation procedures than men, even excluding mammogram, but cumulative effective-dose higher	Multiple outcomes-doses/types of testing. Multiple MPI performed on individual pats with highest radiation dose associated	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.

JAMA. 2010;304:213 7-44. 21078807 (251)		up								exposure.		in men. More procedure/d ose in White>Blac ks and Hispanics		
Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007 Jul 18;298(3):317-23. 17635892 (252)	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	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	RR of attributable cancer vs. 80 y Male: 20 y Female RR: 23, 40 y Female OR: 11.5, 60 y Female OR: 7.0 for heart scan (slightly higher for heart/aorta scan)	Models for single CTCA scans without shielding

ACC-NCDR indicates American College of Cardiology National Cardiovascular Data Registry; ACE, angiotensin-converting enzyme; ACS, acute coronary syndromes; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy trial; ASA, aspirin; AT, antithrombins; BEIR, Biological Effects of Ionizing Radiation VII; CHF, congestive heart failure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CANRACE, Canadian Registry of Acute Coronary Events; cath, catheterization; Cr, creatinine; CrCl, creatinine clearance; 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; CT, computed tomography; CTCA, Cancer Treatment Centers of America; DM, diabetes mellitus; EPR, electronic patient record; EPS, electrophysiology study; FRISC, Framingham and Fast Revascularization During Instability in Coronary Artery Disease trial; GDMT, guideline-directed medical therapy; GI, gastrointestinal; GPI, glycoprotein IIb/IIIa inhibitors; GRACE; Global Registry of Acute Coronary Events; GUSTO-IV-ACS, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries –IV-acute coronary syndrome trial; HF, heart failure; HTN, hypertension; Hx, history; ICTUS, Invasive Versus Conservative Treatment in Unstable Coronary Syndromes trial ; IQR, interquartile range; LAR, life attributable risk; MACE, major adverse cardiac event; MI, myocardial infarction; MPI, myocardial perfusion imagin; MUGA, Multigated Wall Motion Study; N/A, not applicable; NS, not significant; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PET, positron emission tomography; pts, patients; RCTs, randomized controlled trials; RITA, Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina-3 trial; RBC, red blood count; revasc, revascularization; RR, relative risk; Rx, prescription; Sx, symptom(s); TACTICS, Treat Angina With Tirofiban and Determine Cost of Therapy With an Invasive or Conservative Strategy; TIMI, Thrombolysis In Myocardial Infarction; UFH, unfractionated heparin; and U.S., United States.

Data Supplement 31. Anemia, Bleeding, and Transfusion-Relationship Between Transfusion and Mortality (Section 7.8)

Study	Aim of Study	Type of Study	Study Size	Patient Population	Primary Endpoint	Outcome	Comments
Alexander KP 2008 18513518 (253)	To describe the association between transfusion nadir HCT and outcome	Post hoc registry analysis	44,242	CRUSADE registry of NSTE-ACS pts	Numerous endpoints. Most relevant: adjusted OR for mortality with transfusion for	Adjusted OR: ●HCT ≤24%: 0.67 (0.45-1.02) ●HCT 24.1%-27%: 1.01 (0.79-1.30)	Transfusion only beneficial at HCT ≤24%

					HCT range	•HCT 27.1%-30%: 1.18 (0.92-1.50) •HCT >30%: 3.47 (2.30-5.23)	
Yang 2007 17711710 (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: •Death: 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-IIb, PURSUIT, 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/trauma, 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

AABB indicates American Association of Blood Banks; ACS, coronary artery syndrome; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines Registry; GUSTO IIb, GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HCT, hematocrit; MI, myocardial infarction; N/A, nonapplicable; NSTE-ACS, non-ST-elevation-acute coronary syndrome; PARAGON, Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network trial; Pts, patients; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; and RBC, red blood cell.

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

Study	Aim of Study	Type of Study	Study Size	Patient Population	Primary Endpoint	Outcome
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)
LaPointe 2007 17646609 (260)	Exploratory analysis of CRUSADE registry examining relation between enoxaparin dosing and bleeding	Post hoc analysis of registry	10,687	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)	<u>Eptifibatide:</u> •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%; no p value given), and a greater extent of bleeding (p=0.03 for TIMI bleeding and p=0.009 for GUSTO bleeding)

						<u>Bivalirudin:</u> •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; CKD, chronic kidney disease; CRUSADE, 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; NSTEMI-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)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results			
Potential of cocaine-induced vasoconstriction by beta-blockade Lange RA et al. 1990 1971166 (263)	To determine whether beta-blockade augments cocaine-induced coronary vasoconstriction	Prospective; N=30	Intracoronary propranolol (n=15) vs. saline (n=15)	Pts referred for coronary arteriogram for chest pain	HTN, recent MI	Quantitative angiography performed before and 15 min after intranasal saline or cocaine; repeat measurements obtained following intracoronary propranolol	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	N/A	None	Decrease in coronary blood flow (p<0.05); increase in coronary vascular resistance (p<0.05)	N/A	Small n; not randomized; intranasal cocaine during catheterization does not apply to real world pts presenting with cocaine induced chest pain; intracoronary propranolol does not pertain to intravenous BB
BB associated with reduced risk of MI after cocaine use Dattilo PB et al. 2008 17583376 (264)	Determine if rates of MI increased with BB treatment after recent cocaine use	Retrospective N=348 (60 with recent cocaine use)	BB treatment vs. no BB treatment	Admitted pts with positive urine drug screen for cocaine who received BB	Cardiac markers not obtained; pt on oral BB	N/A	In-hospital MI after BB use; lower incidence of MI after administration of BB	N/A	In-hospital mortality; trend for lower mortality in pts receiving BB	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: -	N/A	Included pts without ACS Sx (56% with chest pain); retrospective; did not take into consideration time of cocaine use;

				during current hospitalization						1.2% — 6.7%		did not check serum cocaine levels; urine drug screen only detects pts with cocaine use within 48-72 h. Selection bias as pts receiving BB were older, more frequent Hx of HBP and CHF, higher SBP, and higher glucose levels; mortality mainly due to non-ACS causes
BB for chest pain associated with recent cocaine use Rangel C et al 2010 20498415 (265)	Determine if rates of adverse adverts associated with BB treatment in chest pain pts with recent cocaine use	Retrospective 331 (151 received BB)	BB treatment vs. no BB treatment	Chest pain pts with urine drug screen positive for cocaine	No chest pain; urine drug screen not performed or urine drug screen negative for cocaine	N/A	Death on long-term follow-up of National Death Registry (median 972 d)	N/A	ED BP; Peak Tn levels, ventricular fibrillation/tachycardia, intubation, or vasopressor agents 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	BB use associated with 70% reduction in risk of CV death (HR: 0.29; 95% CI: 0.09 — 0.98)	N/A	Retrospective; unknown how recent was time of cocaine use; patients treated with BB more likely to be given nitrates in ED which may have ameliorated any cocaine induces spasm; unknown what factors may have influenced clinician to treat or not treat with BB (note: clinicians most commonly were treating pt without knowledge of cocaine use as results of drug screen pending)
Benzodiazepines and Nitroglycerine in treatment of cocaine chest pain Honderick T et al 2003 12563578 (266)	To compare the use of lorazepam and nitroglycerine in treatment of cocaine chest pain	Prospective, randomized, single-blinded controlled trial; N=27	NTG (n=15) vs. NTG + lorazepam (n=12)	Chest pain and self-reported cocaine use in the preceding 72 h	Age >45 y, chest pain duration >72 h, documented CAD, pretreatment with NTG	NTG vs. NTG + lorazepam	Chest pain relief as assessed on a 0- 10 ordinal scale was greatest in the pts treated with the combination of NTG and lorazepam.	N/A	N/A	Kruskal-Wallis testing showed a sig difference in pain relief between the 2 study groups (p=0.003) with greater pain relief noted at 5 and 10 min in the NTG + lorazepam group	None	Small n; none of the pts diagnosed with MI; lorazepam only subgroup not investigated

										(p=0.02 and 0.005 respectively)		
Diazepam, Nitroglycerin, or both for treatment of cocaine ACS Baumann BM et al 2010 10958127 (267)	To compare diazepam, nitroglycerin, or both in treatment of pts with potential cocaine-associated ACS	Randomized double-blinded trial; N=40.	Diazepam (n=12) vs. NTG (n=13) vs. both (n=15)	Chest pain and cocaine use within the preceding 24 h	<18 y age; >60 y age	Diazepam vs. NTG vs. both	Chest pain resolution as measured by a visual analog scale	Chest pain resolution equivalent in all 3 groups	Changes in BP, pulse rate, cardiac output, cardiac index, stroke volume, and stroke index	Hemodynamic parameters equivalent in all subgroups. Outcomes: though not statistically sig, changes in mean arterial pressure for diazepam, diazepam + NTG, and NTG respectively were 2.1, -12.1, and -8.4 mm Hg respectively (p=0.08)	None	Small n; only 3 pts had MI and 5 pts Dx of UA
ACS in chest pain pts after amphetamine use 2003 Turnipseed SD et al. 12745036 (268)	Determine frequency of ACS in pts presenting with methamphetamine induced chest pain	Retrospective N=36 visits in 33 pts (3 with CV events)	N/A	Nontraumatic chest pain, positive amphetamine on urine drug screen	Not admitted for MI rule out; abnormal CXR	N/A	ACS defined as MI, ischemia on cardiac stress testing, or $\geq 70\%$ stenosis on cardiac cath	N/A	Cardiac arrhythmias (V-tach, V-fib, SVT)	ACS diagnosed in 9 pt visits (25%; 95% CI: 11%- 48%) 3 pt visits with arrhythmias (8%; 95% CI: 2%- 24%)	N/A	Retrospective; small n; only investigated results in admitted pts and thus ACS rate over-estimated; urine drug testing in admitted pts not done routinely

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

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Secondary Endpoint & Results		
FRISC-II Wollert 2007 (269) 17848615	Effect of PGF-15 on ACS outcomes in invasive vs. conservative strategy	Multicenter prospective study (FRISC –II) 2,079	PGF-15 in intervention vs. conservative treatment outcomes	ACS with criteria for PCI or conservative strategy with PGF-15 levels	Previous heart surgery, PCI within 6 mo, bleeding tendency, high creatinine	PGF-15 with PCI or conservative strategy	2-y MACE. PGF independently predicted outcomes in conservative strategy only	Occurrence of MACE reduced with PCI with highest PGF-15 levels: 0.49 (0.33-0.73) p=0.001	2-y MACE prediction with PGF-15 levels p=0.016	PGF-15 not independently related to ST depression or Tn levels
C-NET Viswanathan 2010 (270) 20513600	Px value of H-FABP in low-int. risk ACS pts	Prospective observational cohort 955	H-FABP vs. Tn	Chest pain	Non-cardiac Chest pain. Age <18 y	H-FABP/Tn 12-24 h from Sx onset	Death/MI 12 mo H-FABP predicted outcome after multivariate adjustment	Among Tr-pts, (79% of cohort) high FH-FA bp identify pts at high risk	HR:2.62 (1.30- 5.28) p=0.0007 H-FABP for adverse events ROC 0.79 (0.74- 0.84) ROC Tnl 0.77 (0.72- 0.82)	Only 53% of eligible pts enrolled because of timing. Statistical modeling/ adjustment
Charpentier 2010 (271) 20078436	Detection of AMI by H-FABP and IMA	Prospective. observational cohort 677	H-FABP vs. IMA	Chest pain and suspected NSTEMI	Age <18 y Skeletal muscle injury, trauma, renal impairment.	H-FABP and IMA on admission	Dx NSTEMI IMA not predictor of ACS Dx H-FABP predictor	H-FABP did not add info to std predicted model	IMA OR 1.23 (0.87-1.81) H-GFABP OR 4.65 (2.39-9.04) Sens 96.8% Spec 98.1%	Relatively low enrollment. Some lack of agreement on Dx by 2 physicians. Possible misclassification of UA pts. No serial testing.
Haaf 2011 (272) 21531234	BNP in Dx and risk in chest pain pts	Prospective multicenter 1,075	BNP vs. TnT	Possible ACS	ESRD with dialysis	BNP and TnT at admission and 1 h, 2 h, 3 h, 6 h	Dx accuracy of BNP for MI lower than Tn	BNP predicted 24 mo outcome more accurate than TnT AUC 0.81 vs. 0.76 p<0.001	BnP Dx: AUC: 0.74 (0.70-0.78) TnT: 0.88 (0.84-0.92) p<0.001	Clinical benefit of risk stratification BNP levels linked to factors related to outcome confusing.
Keller 2010 (273) 20447532	Copeptin in Dx of AMI	Prospective multicenter 1,386	Copeptin vs. Tnl	Possible ACS	Trauma, major surgery, IV drug abuse, anemia	Copeptin and TnT on admission	TnT vs. combined C-statistic vs. TnT alone: 0.93 vs.0.84	C-statistic within 3 h chest pain combined 0.90 T alone 0.77	Combination of copeptin and TnT superior to all single or other marker detm.	Using Tn for Dx might favor tested Tr compared with copeptin

								p<0.001	(myocardial, CK-MB, BNP)	
Peacock 2011 (274) 22093206	MPO for Dx of AMI	Prospective multicenter 1,018	MPO vs. TnI	Possible ACS <8 h Sx	<18-y non-cardiac chest pain	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	MPO sens 18% -PV 69%, +PV 0.47 to diff ACS from non-cardiac chest pain.	Spectrum bias Physician Dx bias Differing local Tn platforms
Iversen 2009 (275) 19932776	PAPP-A as risk marker in ACS	Prospective cohort 123 NSTEMI	PAPP-A vs. std Dx (TnT)	Possible ACS NSTEMI	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	N/A	PAPP-A risk MI p=0.02 Death p=0.03 Multivariable: combined risk 2.65 (1.40-5.03) in NSTEMI	Long time between sample collection (6 h to 8 h)
RISCA Bogaty 2008 (276) 18549920	CRP in pred 1-y outcome in ACS	Prospective cohort 1,210	CRP No comparator	Dx of UA or AMI	Transfer from other hospital	CRP on admission discharge and 1 mo later	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)	Not stated
Kuch 2008 (277) 18940277 MONICA/KORA	CRP and TnT in short term Px in NSTEMI	Prospective cohort 697 NSTEMI (612 with STEMI)	CRP vs. Tn in 28-d mortality event	Dx of NSTEMI	STEMI separately evaluated	CRP and TnT on admission	Multivariate analysis Both CRP+ and TnT+ showed pred of 28 d mortality	In NSTEMI CRP+ but not Tr+ 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
Schaub 2012 (278) 22205695	GDF-15 in early Dx and risk in AMI	Prospective multicenter 646	GDF-15 vs. TnT and BNP	ACS Sx	ESRD	Assays on admission to ED	ROC for MIAUC GDF-15 0.69 Hs-TnT 0.96 BNP 0.74	GDF-15 pred 26-mo mortality >TnT and BNP	26-mo mortality AUC GDF-15: 0.85 TnT: 0.77 p=0.002 BNP: 0.75 p=0.007	Clinical benefit of imp. risk strategy
Mega 2008 (279) 18565400	Px of TpP in ACS	Prospective multicenter 2,349 with ACS	TpP+ vs. TpP– in predicted. Compared with Tn	NSTEMI UA	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<0.15 for each	HR for MACE: 1.45 (1.20-1.95)<0.001 adjusted for Cl. characteristic and other biomarkers: 1.51 (1.19-1.91) <0.001	TpP not measured at presentation Possible that study median inflated TpP levels
Saraf 2010 (280) 20447533	Px significant of ETA in ACS	Prospective cohort 300 with ACS on dual	Use of GTT	ACS	Sepsis, malignancy blood, Dyscrasia, anticoagulant	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)=0.004	Antiplatelet effects of ASA and Clopidogrel. Heparin effects.

		antiplatelet therapy							CV Death: 4.2 (1.13-15.62)=0.033	Diurnal variation of TpP
Body 2010 (281) 21167826	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. for P-selectin	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; GTT, 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 chemaattractive 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; PMA, platelet-monocyte aggregates; Pts, patients; Px, prognosis; ROC, receiver operator curve; SA, stable angina; SAP, stable agina pectoris; sCD40L, soluble CD40 ligand; Sens, sensitivities; Spec, specificities; Std, standard; STE-ACS, ST-elevation acute coronary syndrome; Sx, symptoms; Tn, troponin; Tnl, troponin I; TnT, troponin T; TpP, thrombus precursor protein; and UA, unstable angina.

Data Supplement B. Other Anticoagulants

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparato r Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Oldgren 2011 (283) 21551462 RE-DEEM	Safety and efficacy of dabigatr in ACS	Multictr Prosp. Dose Escalation trial	1,861 on dual platelet therapy	Dabigatran bid. 50 mg 369 75 368 110 406 150 347	PC 371 Both groups ASA and clopidogrel	AMI <14 d Dual antiplatelet therapy at least 1 risk factor for CV complications	Severe stroke Bleeding diathesis Recent GI 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 m: 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) 22231617	AMI risk with dabigatrn	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

					2,851 Or PC 371	ACS, DVT, acute embolus		12 wk 6 mo		group. Risk similar when eliminating short-term trials.		short-term trials: 1.33 (1.03 — 1.72) p=0.03		meta-analysis. MI events few and infrequent in other studies.
APPRAISE 2009 (284) 19470889	Safety and efficacy of apixaban in ACS	Multicenter prospective trial	1,715	Apixaban 2.5 bid 317 10 qd 318 10 bid 248 20 qd 221 (611 total)	PC 611	MI within 7 d with at least 1 additional risk factor for recurrent events	Planned PCI ASA allergy Significant. HTN Bleeding diathesis Recent stroke Pericardial effusion	1 of 4 doses of apixaban 26-wk follow-up on ASA	PC On ASA	Clinically relevant bleeding: Apixaban increased bleeding at 10 mg qd	Similar liver enzyme elevations Apixaban and PC	Apixaban 2.5 mg bid and 10 mg qd trend toward decreased ischemic events	Bleeding with 10 mg 2.45 (1.31 — 4.61) p=0.005 Reduced ischemia 0.61 (0.35 — 1.04) p=0.07	One intracranial hemorrhage with apixaban. 2 higher-dose Apixaban arms discontinued because of excess bleeding.
Alexander 2011 (179) 21780946	Risk of events with Apixaban in ACS	Multicenter prospective trial	7,392	Apixaban 3705	PC 3687	Median 6 d after ACS with significant risk factors: prior MI, DM, HF	Planned PCI, ASA allergy, Significant HTN Bleeding diathesis Recent stroke Pericardial effusion	Apixaban 5 mg bid Median follow-up 241 d ASA	PC ASA	MACE: NS difference between apixaban and PC	Trial stopped because of major bleeding with apixaban	Bleeding Apixaban vs. PC 1.3% vs. 0.5% 2.59 (1.5,4.46) p=0.001	MACE: Apixaban vs. PC. 0.95 (0.80- 1.11) p=0.051	Only high-risk pts. No pts undergoing revascularization.
RUBY-1 Steg 2011 (285) 21878434	Safety and tolerability of darexaban	Multicenter prospective trial	1,258	Darexaban Multiregimen 939 5 mg bid 10 mg qd 15 mg bid 30 mg qd 30 mg bid 60 mg qd	PC 319	ACS <7 d from event	Bleeding diathesis Planned PCI Recent stroke Renal or hepatic Insufficiency Allergy to study drug	One of 6 regimens Darexaban 26-wk follow-up	PC 26 wk	Bleeding numerically higher in all darexaban arms than PC. Dose response effect	Safety was primary outcome	SI Increase in efficacy outcomes Darexaban 5.6% PC 4.4%	Pooled bleeding rate for darexaban: 2.275 (1.13- 4.60) p=0.022 Dose response: 6.2,6.2,9.3% Sig for 30 bid p=0.002	Limited power for efficacy. Only relevant with dual platelet treatment
ATLAS ACS-2 TIMI-51Mega 2012 (180) 22077192	CV outcomes with Rivaroxaban in ACS	Multicenter prospective trial	15,526	Rivaroxaban 2.5 mg bid (5,174) Rivaroxaban 5 mg bid (5,176)	PC (5,176)	ACS <7 d from event	Low platelet count Low hematocrit Renal dysfunction Recent GI bleed Hx of intracranial bleed	1 of 2 rivaroxaban regimens Mean 13 mo follow-up	PC Mean 13mo follow-up	MACE Rivaroxaban lower than PC	Increased major bleeding 2.1% vs. 0.6% p<0.01	Decreased total mortality 9.2% vs. 11.0% HR:0.84 (0.74-0.95)p=0.006	Primary endpoint 8.9% vs. 10.7% 0.84 (0.74, 0.96) 9=0.008 2.5 mg dose CV death 2.7% vs. 4.1% p=0.002 Total mortality:	Increased major bleeding unrelated to CABG Large missing data

							Stroke/TIA with antiplatelets					Reduced stent-throm 0.69 (0.51, 0.93) p=0.002	2.9% vs. 4.5% p=0.002	
Meta-analysis 2012 (7)	Bleeding, outcomes in ACS	Meta-anlysis	31,286	Apixaban Dabigatran Darexaban Rivaroxaban Ximelagatran	PC or warfarin	ACS (4-71%) <6 to <14 d from event	Trials of parental AC, VKA	OAC with antiplatelet 6-31 mo	Antiplatelet with PC or warfarin	Increase major bleeding: Decrease stent thrombosis, ischemic events, no difference in overall death, net clinical benefit	Major Bleeding 3.03 (2.20-4.16) <0.01	Net clinical benefit 0.98 (0.90-1.06) Ischemic events 0.73 (0.63-0.84)<0.001 Mortality 0.90 (0.76-1.06) Stent thrombosis 0.73 (0.54-0.98)	Mixed clinical conditions Only 58% (avg) ACS <pst;y PC but also warafarin control Ximelagatran no longer active Newer antiplatelet drugs not adjuncts	

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; AFIB, atrial fibrillation; bid, twice daily; CABG, coronary artery bypass graft; CV, cardiovascular; DM, diabetes mellitus; DVT, deep vein thrombosis; GI, gastrointestinal; HF, heart failure; HTN, hypertension; Hx, history; MACE, major adverse cardiovascular events; MI, myocardial infarction; NS, nonsignificant; OAC, oral anticoagulant; PC, placebo; PCI, percutaneous coronary intervention; Pts, patients; qd, daily; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; RCT, randomized controlled trial; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

Data Supplement C. Lipid Management

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Cannon 2006 (286) 15687136	Efficacy of high dose vs. standard dosing for CV	Meta-analyses 4 trials	27,548	High-dose statin 13,798	Standard-dose statin 13,750	Stable CAD or ACS Intensive vs. standard statin >1000 pts each	Not stated	High-dose statin	Standard-dose statin	High dose produced a significant 16% reduction in coronary death or MI Significant 16% reduction in	High-dose: Rhabdomyolysis 0.13% A to Z trial CK>10× ULN 0.15% PROVE-IT AST or ALT	Trend toward decreased CV mortality with high dose p=0.054	Coronary death or MI 0.84 (0.77- 0.91) p<0.00001 Coronary death or CV events 0.84 (0.80- 0.89) p<0.0000001	Underpowered for CV death and total death. Different duration and treatments. No individual pt data. No evaluation of benefit from statin or LDL–C level.

	outcome									coronary death or any CV event	3× ULN: 3.3% PROVE-IT			
Spencer 2007 (287) 17826369 GRACE	Use of statin at hospital discharge with ACS	Registry Retrospective analysis	8,492	Statin use with LDL-C <100 mg/dL or ≥100 mg/dL at discharge 5,710	No statin at discharge 2,782	ACS	ACS not precipitated by non-CV comorbidities	Statin use with LDL-C <100 or ≥100 mg/dL	Control	LDL levels <100 55% receiving statin at discharge LDL levels >100 72% receiving statin at discharge	N/A	Statin at time of discharge associated with MACE reduction 0.76 (0.63,0.93)	Statin at time of discharge associated with 6-mo total mortality 0.66 (0.51- 0.85)	6-mo statin use by pt self-report No info on statin types or dosages
Robinson 2009 (288) 19161879	Non-HDL-C reduction and CV risk	Meta-analysis 30 trials	11,254	Non-HDL-C change 14 statin 100,827 7 fibrate 21,667 6 niacin 4,445 3 others 5,102	Change in risk	Randomized PC or active control trials	<2-y trial No serious non-CV disease	Change in lipid level	Change in risk	Statins: each 1% Decrease in non-HDL-C decreased 4.5-y RR by 1% (0.98-1.00)	N/A	Fibrate and niacin models also had a 1:1 relation between non-HDL-C reduction and risk reduction	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	Lack of access to pt data Unknown method of endpoint adjudication. No info on fibrates=statins.
Hulten 2008 (289) 17000936	Effect of statin therapy in ACS	Meta-analysis 13 trials	17,963	Early statin in ACS Approximately 50%	No statin, PC or usual care Approximately 50%	Statin <14 d of hospitalization for ACS	Standard attain dose	Intensive statin	PC or standard statin	2-y rate of death and CV events reduced with intensive statin therapy	Comparable tolerability for intensive statins and control. Only 3 cases of rhabdomyolysis. PROVE-IT: 3.3% hepatitis in high-dose GP.	Pooled 2-y HR For intensive statin therapy MI 0.89 (0.60,1.33) Ischemia 0.68 (0.50-0.92) CV death 0.76 (0.66=0.87)	Rate of death and CV events reduction: 0.81 (0.77 — 0.87) p<0.001	Sig. statistical heterogeneity. Limited trials available. Not a pooled analysis. Adverse effects under safety box.
Sattar 2007 (290) 20167359	Risk of DM with statins	Meta-analysis 13 statin trials	4,278	Statin use 2,226	No statin 2,052	Statin Trials with >1 y follow-up in both treatment groups	Mean follow-up ≤1 y	Statin	No statin	Statin therapy was associated with a 9% increased risk of incident DM with little	Aside from DM risk, not available	Lipophilic Statins risk: 1.10 (0.99=1.22) Hydrophilic Statins risk:	DM risk: 1.09 (1.02 — 1.17) PC controlled trials: 1.10 (1.01 —	Varied methods of dx of DM. HRs not available in all trials. In 2 trials Dx based on physician reporting rather than biochemical analysis.

										heterogeneity (11%) between trials		1.08 (0.98-1.20)	1.20)	Nonstandard criteria for Dx of DM in some studies.
Javed 2010 (291) 21146668 GWTG	Discharge intensive LLT in ACS	Retrospective database analysis	65,396	Intensive LLT regimen likely to cause >50% LDL reduction 25,036	Less intensive LLT regimen 40,360	ACS related hospitalization with LLT	Left against medical advice discontinued care Discharged to nonparticipating facility	Intensive LLT regimen	Less intensive LLT regimen	Mostly AMI pts at discharge 38% received intensive LLT and 62% less intensive LLT	N/A	Factors associated with lack of LLT Female sex Increased age Dialysis (Multivariate 95% CI<1.00)	Factors associated with intensive LLT: LLT prior to admission PCI with stent Known CAD on admission PVD Prior MI (Multivariate 95% CI>1.00)	Discharge LLT dosing data not available on 50% of pts. Performance feedback in GWTG hospitals may influence pt care giving higher rates of LLT than general hospitals. Change in LLT dosing after not available.
Baigent 2010 (292) 21067804 CTT	Efficacy and safety of intensive LDL-C decrease	Meta-analysis 26 trials	165,138	More intensive 19,829 5 trials Statin 64,744 21 trials	Less intensive 19,783 Control 64,782	Main effect of trial to lower LDL-C 1000+ pts >2 y follow-up treatment	Lack of trial eligibility criteria	Intensive LLT regimen	Less intensive LLT regimen	MACE reduction in 4.8 y by intensive LLT 15%	No further adverse effects from lowering cholesterol including cancer risk	Reduction in revasc 19% (15-24) p<0.0001 Ischemic stroke 16% (5-26] p=0.005	MACE reduction by intensive LLT 15% (11-18) <0.0001 Major vascular events 13% 97-19) <0.0001 Total mortality 10%/1 mmol/L LDL-C Reduction 0.90 (0.87 — 0.93)	Nonsignificant excess of hemorrhagic stroke with lowering cholesterol p=0.2
Boekholdt 2012 (293) 22453571	RRs of lipid values in statin treatment	Meta-analysis 8 trials	38,153	Statin therapy	Risk with 1 SD increase in LDL-C non-HDL-C apoB	Trials with serial evaluation of TC, LDL-C, HDL-C, TG >2 y followup 1000+ participants	Lack of trial eligibility criteria	LDL-C HDL-C Apo B during statin Rx	RRs for values	Adjusted HR for major CV events Per 1-SD increase 1.16 non-HDL-C 1.14 apoB 1.13 LDL-C	N/A	HRs higher for non-HDL-C than LDL-C p=0.002 and apo B p=0.02	Adjusted HR per 1-SD increase non-HDL-C :1.16 (1.12,1.19) apo B 1.14 (1.11 — 1.18) LDL-C 1.13 (1.10 — 1.17)	Fatal CV events occurring in the 1 st y of therapy not accounted for. Participating trials had different inclusion criteria.
Mora 2012 (294) 22461416	CV risk in statin treated pts	Retrospective evaluation of a multicenter	9251	High-dose statin 80 mg Atorvastatin Approximately	Low-dose statin 10 mg Atorvastatin Approximately	CAD	TG>600 mg/dL Unstable CAD	High-dose atorvastatin	Low-dose atorvastatin	Multivariable detection of increased residual risk Older age	Decreased residual risk: High-dose statin Aspirin use	Known baseline variables performed moderately	Residual increased risk: HTN 1.38 (1.17,1.63) DM 1.33	Excluded patients >130 mg/dL on Atorvastatin 10 mg, study was observational, novel risk factor data not available for

		nter trial		y 50%	50%					Increased BMI Male sex HTN DM Apo B BUN	Apo A1	well in discriminatin g future cases Harrell c index=0.679	(1.11,1.60) Male 1.33 (1.07,1.65) Age 1.13 (1.04,1.23) Apo B 1.19 (1.11,1.28) BUN 1.10 (1.03,1.17) BMI 1.09 (1.02,1.17)	the entire study group

A to Z indicates Aggrastat to Zocor; ACS, acute coronary syndrome; ALT, alanine aminotransferase; AMI, acute myocardial infarction; Apo A, Apolipoprotein A; Apo B, Apolipoprotein B; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen test; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; Dx, diagnosis; GP, glycoprotein; GWTG, Get With the Guidelines; HDL–C, high density lipoprotein cholesterol; HR, hazard ratio; HTN, hypertension; LDL–C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; MACE, major adverse cardiovascular events; N/A, not available; PC, placebo; PCI, percutaneous coronary intervention; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; Pts, patients; PVD, peripheral vascular disease; Revasc, revascularization; Rx, prescription; Sig, significant; TC, total cholesterol; TG, triglyceride; and ULN, upper limit of normal.

Data Supplement D. Blood Pressure Control

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparat or	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Nissen 2004 (295) 15536108 CAMELOT	Antihypert ensive agents on CV events in CAD and normal BP	Multicente r prospectiv e study	1991 274 IVUS	Amlodipine 663 Enalapril 673 IVUS substudy: Amlodipine 91 Enalapril 86	PC 655 IVUS substdy: 95	Angiog.Doc. CAD Age 30- 79 DBP<100 BB, a1 blockers, Diuretics permitted	Left main CAD LVEF<40% Moderate or severe CHF >79 y	Amlodipine 10 mg or Enalapril 20 mg + IVUS Substudy 24-mo follow-up	PC	CV events in 24 mo/CV events in fewer Amlodipine vs. PC Substdy: No athero. Px in amlodipine Trend toward Px in Enalapril, progression in PC p<0.001	BP baseline 129/78 Decreased by 4.8/2.5 mm in Amlodipine, 4.9'2.4 in Enalapril increased in PC p<0.001 vs. Amlodipine and Enalapril	Individual components of primary and 2° endpoints showed trend toward fewer events with enalapril	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	Amlodipine D/ced for edema in 5.0%. Enalapril D/C for cough in 3.9% HTN in 3.2% PC, 2.2% amlodipine, 9.5% enalapril. Limitations: extended composite endpoint, modest sample size, CIs around point estimates relatively large.

Messerli 2006 (296) 16785477	Low BP with adverse events in CAD	Multictr Ad hoc analysis	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 y/pts 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	2° analysis, limited to hypertensive pts with stable CAD.
PROVE-IT TIMI 22 Bangalore 2010 (297) 21060068	BP control and adverse events in ACS	Multicente r prospectiv e study Ad hoc analysis	4162	BP level reached	Outcome MACE	ACS within 10 d Randomly assigned to Pravastatin or atorvastatin	Not stated	Pravastatin 40 mg Purpose was to evaluate BP with outcome, not to compare agents	Atorvastati n 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<100 vs. 130-140 HR 46% vs. 15% DBP<60 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/DBP X²=37,<0.0001 X²=47,<0.0001 respectively	Risk for 1° 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	Effect of tight BP control in CAD and diabetes	Observati onal substudy of multicente r clinical trial	6400	Tight BP control BP 130/85	Usual BP control	Stable CAD and hypertension with diabetes	Not stated	Tight BP control Verapami/trandolapril 16,893 patient/y of follow-up	Usual BP control	Composite MACE Usual control vs. uncontrolled 12.8% vs. 19.8% Tight vs. usual Control : NS diff. 12.6% vs. 12.7%	Extended analysis follow-up indicated increased risk with tight BP control	Mortality: 11.0% vs. 10.2% Tight vs. Usual 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.

1° indicated primary; 2°, 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

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population	Study Intervention	Study Comparator	Endpoints	P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events

						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
DIGAMI Malmberg 1999 (299) 10338454	Glyco- metabo- lic state in DM in ACS and mortalit- y risk	Multice- nter prospe- ctive study	620	Intensive Insulin 306	314 Routine diabetic therapy	DM with AMI <24 h	Not stated	Intensive insulin- glucose infusion, then sc insulin 3.4-y follow-up	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 hyperglycemi- a p<0.001-0.00 01	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	No indication whether increased use of insulin or decreased use of sulfonylureas decreased risk.
Diabetes Prevention Program Research Group Knowler 2002 (300) 11832527	Effects of treating elevate- d glucos- e on develo- pment of DM	Multice- nter prospe- ctive study	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 thrombosis test	Glucose tolerance affects medications Short life expentancy	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	Hospitalizatio- ns and deaths NS different among groups GI 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%]	GI Sx highest in metformin group and musculoskeletal highest in lifestyle GP Incidence of DM in PC group higher than anticipated
Suleiman 2005 (301) 15699267	Fasting glucos- e and 30-d mortalit- y in AMI	Prospe- ctive cohort observ- ational study	735	Fasting glucose	Admission glucose	Non-DM AMI <24 h	>24 h from Sx onset, inflammatory disease, surgery or trauma preceding mo	Fasting blood glucose	Admission blood glucose	30-d mortality compared with FBG <110, adjusted 30 d-mortality increased with increasing tertile of FBG	30-d death and heart failure vs. normal FBG: Impaired FBS: 2.6 (1.3- 5.0)=0.004 FBS ≥126: 5.8 (2.2 — 10.3) <0.0001	30 d- mortality co- mpared with normal AG and FG Elevated FG and AG: 9.6 Elevated AG and Normal FG 3.4	30-d mortality by tertile vs. normal FBS 1 st : 4.6 (1.7 — 12.7) P=0.003 2 nd : 6.4 (2.5 — 16.6) P<0.0001 3 rd : 11.5 (4.7 — 20.0) P<0.0001	Did not attempt to evaluate for undiagnosed DM Significant overlap in HbA1c levels in AMI in known or newly diagnosed DM and no DM
Sinnaeve 2009 (302) 19237725 GRACE	Elevate- d FBS in ACS and	Multice- nter retrosp- ective	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 <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

	mortality	study								mortality. 6 mo sig higher with FBS above 125 mg/dL vs. <100 mg/sL	higher FBS. Stroke level unrelated to glucose level.	NSTEMI: 4.66 vs. 7.14% UA: 2.56 vs.2.28	2.34) FBS≥300: 2.93 (1.33 — 6.33) But not 200 — 299: 1.08 (0.60 — 1.95)	reflect “true” glucose levels. Because of glucose infusions, some FBS levels might not have been truly fasting levels.

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

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Daly 1983 (303) 6409291	Persistence of smoking cessation after ACS	Prospective cohort study	498	Smoking cessation 217 Nonsmokers at entry and follow-up 147	Continued smoking 157	Survived 1 st attack of ACS by at least 28 d	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	Continued smoking	Mortality 13-y life tables beyond 1 st 2 y from ACS Stopped smoking vs. continued smoking was 2.8× lower	Vascular causes of death: 68% 24% MI 35% sudden death NS diff among 3 groups	Mortality of previous nonsmoker 62.1% n=124 Average annual RR of death: 2.4× for smokers vs. stopped p<0.01	Mortality 2-15 y beyond ACS: stopped vs. continued 36.9% vs. 82.1% p<0.01	Average annual mortality: stopped vs. continued smoking Initial ACS St Cont RR UA 1.9 10.0 5.4; p<0.01 MI uncomp 3.9 8.6 2.2 p<0.05 MI comp 4.7 12.4 2.7 p<0.01
Jorenby 2006 (304) 16820547	Efficacy and safety of varencline	Multicenter Prospective Study	1,027	Varencline 344 Bupropion 342	PC 341	18-75 y. 10+ cigarettes/d during previous y No abstinence longer than 3 mo	Previous use of bupropion. Contraindications to medications. Sig CV disease; HTN; pulmonary disease; depression	Varencline 1 mg bid Bupropion SR 150 mg bid 12 wk + brief counseling 12 wk with 40-wk follow-	PC+brief smoking cessation counseling	Continuous abstinence: wk 9-12 Varencline vs. PC: 43.9% vs. 17.6% Bupropion vs. PC: 29.8% vs. 17.6%	>10% side effects: Bupropion Insomnia 21% Varencline Nausea 29% Abnormal dreams 13.1%	Wk 9-52 Abstinence Varencline vs. PC 23% vs. 10.3% 2.66 (1.72,4.11) p<0.001	Abstinence 9-12 vs. PC 3.85 (2.69,5.50) p<0.001 9-12 Bupropion vs. PC: 1.90 (1.38- 2.62) p<0.001	Volunteers. Minimal counseling may confound results. Exclusion of depression. 35% did not complete follow-up period. Dropout rate for adverse events higher in PC group.

								up			Headache 12.8%	Bupropion vs. PC 1.77 (1.19,2.63) p=0.004		
Tonstad 2006 (305) 16820548	Effect of varenicline on smoking cessation	Multice nter Prospe ctive Study	1,210	Varencline 603	PC 607	18-75 y. 10 cigarettes/ d + smoking cessation Ation after 12 wk of varenicline	Unstable disease, depression, COPD, CV disease within 6 mo, uncontrolled HTN, smoking cessation aid	12-wk open label vs. if stopped smoking Randomized for 40 wk	PC	Continued abstinence Wk 13-24 Varenicline vs. PC 70.5% vs. 49.6% Wk 13- 52 43.6% vs. 36.9%	Major adverse Effects: Varenclin Nasopharyngi tis 4.8% Headache 2.8% Psych disorders 6.4%	N/A	Abstinence vs. PC Wk 13-24 2.48 (1.95- 3.16)<0.001 Wk 13-52 1.34 (1.06,1.69)=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.
Rigoitti 2006 (306) 17145253	Bupropion in smokers with ACS	Multice nter Prospe ctive Study	248	Bupropion 124	PC 124	Smoked >1 Cigarette in previous mo CAD admissions	Not willing to stop Smoking. Risk of seizure, sig. HTN, heavy alcohol use, depression, liver or renal disease, illegal drug use	Smoking counseling to 12-wk postdischarg e Bupropion SR 1-y follow-up	Same smoking counseling PC	Abstinence and CV events 3 m and 1 y Borderline Sig abstinence at 3 mo only. NS diff in outcome events	Noncardiac serious adverse events: NS 3 mo: 1.31 (0.62,2.77) 1 y: 1.34 (0.64,2.84)	CV mortality 1 y Bupropion vs. PC 0% vs. 2% CV events 1 y: 26% vs. 18% 1.56 (0.91,2.69) NS	Abstinence vs. PC 3 mo: 37.1% vs. 26.8% 1.61 (0.94,2.76)=0.08 1 y: 25.0% vs. 21.3% 1.23 (0.68,2.23) NS	1/3 lost at 1 y. Study not powered to detect less than a 1.8-fold increase in cessation rates with bupropion. Many eligible declined to enroll. Reluctance to be randomized to PC.
PREMIER Registry Dawood 2008 (307) 18852396	Predictors of smoking cessation after AMI	Retros pective from registry	639	342 smokers at 6 m	297 Nonsmokers at 6 mo	AMI Smoker >18 y age	Transfer to hospital >24 h from AMI Did not speak English or Spanish. Could not consent	Smoking behavior by self-report During hospital and 6 mo in pt smoking cessation program Continued smoking	Same but stopped smoking at 6 mo	6-mo post MI: 46% had stopped Odds greater for those receiving discharge recommendations for cardiac rehab or smoking cessation facility	Not evaluated	Hospital smoking cessation counseling did not predict cessation: 0.80 (0.51,1.25) Depressive pts during MI less likely to quit:	Smoking cessation with rehab: 1.80 (1.17-2.75) Treated at smoking cessation facility: 1.71 (1.03=2,83)	Limited insights on smoking cessation programs available at different hospitals. Loss to follow-up. Self-reporting assessment without biochemical evaluation. Unmeasured confounding.

												0.57 (0.36-0.90) p<0.05		
Mohiuddin 2007 (308) 17296646	Intensive smoking cessation intervention in acute CV disease	Prospective randomized cohort	209	Intensive intervention 109 2 y follow-up	Usual care 100 2-y follow-up	30-75 y Daily smokers >5 y in CCU with AMI or heart failure	Alcohol or illicit drug use Unfamiliar with English	30-min counseling before discharge. Intensive counseling for 3 mo + pharmacotherapy in 75%	Same counseling before discharge only.	At each follow-up interval, point prevalence and continued abstinence greater in the intensive treatment group	Over 2-y period more in UC group Hospitalized RR reduction:44% (16,63)=0.007	2-y all-cause mortality: 2.8% intensive vs. 12.0% UC RR reduction: 77% (27, 93%) p=0.014	2-y abstinence: 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.
Smith 2009 (309) 19546455	Hospital smoking cessation in CAD with long-term effects	Multi-institutional Prospective Study	275	Intensive smoking cessation intervention 136	Minimal intervention 139	18 or older Smoked in previous mo AMI or CABG admission	Pregnant Medically unstable Lived in an institution No English Psychiatric disorder Substance abuse	Minimal intervention + 45-60 min bedside counseling 7 telephone counseling sessions after discharge	Minimal intervention 2 pamphlets No smoking message by physician	1-y abstinence self-reported 62% intensive GP vs. 46% minimal GP Confirmed: 54% intensive GP vs. 35% minimal group	Not evaluated	Abstinence lower in those using pharmacotherapy p<0.01 Abstinence higher in CABG vs. MI pts p<0.05	1-y abstinence self-reported: 2.0 (95% CI: 1.2-3.1) Confirmed: 2.0 (CI: 1.3-3.6)	Pharmacotherapy used by 34% of pts in both groups. Slightly less than 1/2 smokers did not want to quit or refused to participate. Exclusion of pts with substance abuse or psychiatric comorbidities, many of whom are smokers, limits generalizability of results.
Rigotti 2008 (310) 18852395	Hospital smoking cessation intervention with 6-mo follow-up	Meta-analysis of 33 trials	6,252 (using numbers in Figure 1 and 2)	Intensive intervention counseling 2,673 Pharmacotherapy 332	Usual care or control counseling 2,935 No pharmacotherapy 312	Hospitalized and current smokers	Trials not recruiting on basis of smoking, Hx, Hospitalization with psychiatric disorder, or substance abuse	Intensive intervention with or without pharmacotherapy	Usual care with minimal smoking counseling	Smoking cessation rates 6-12 mo decreased with smoking counseling. No benefit with less postdischarge contact.	Not evaluated	Adding NRT produced a trend toward efficacy vs. counseling alone: 1.47 (CI: 0.92- 2.35)	Smoking cessation 6-12 mo with counseling: 1.65 (CI: 1.44-1.90)	Benefit of adding bupropion limited to 1 study. Counseling intervention not delivered by staff responsible for patient care. Only 1/2 studies used sustained abstinence to assess outcome, the rest point prevalence
Colivicchi 2011 (311) 21741609	Smoking relapse rate after quitting following ACS	Prospective cohort study	813	12-mo relapse 813 (of 1,294 not relapsing)	Predictors of relapse	Previous smokers who stopped after ACS following hospital	Major concurrent illness, depression, alcohol and drug abuse,	Several in-hospital counseling sessions. 12-mo follow-up	Predictors of relapse	Age and female sex were predictors of relapse. Pts in cardiac rehab and pts	Resumption of smoking predicted 1-y mortality: 3.1 (CI: 1.3-5.7) p=0.004	Age and resumption: 1.034 (1.03,1.04) p=0.001 Female:	Cardiac rehab and abstinence: 0.74 (CI: 0.51-0.91)=0.02 DM and abstinence:	Sig diff in age and CV risk factors in cohort. Questions about sens of troponin assay for Dx of AMI

						discharge	renal, lung, liver disease, stroke, malignancy			with DM more likely to remain abstinent		1.23 (1.09,1.42)	0.79 (CI: 0.68-0.94)=0.03	
Planer 2011 (303) 21403011	Efficacy of bupropion in smoking cessation after AMI	2 center prospective study	149	Bupropion 74	PC 75	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: death, any hospitalizations, MI, ACS, Chest pain	Adverse effects attributed to treatment was a negative predictor of smoking cessation: 0.23 (95% CI: 0.07-0.78)	3-mo abstinence: Bupropion vs. PC: 45% b 44% p=0.99 6 mo. Abstinence: Bupopion vs. PC: 37% vs. 42% p=0.61 1-y abstinence: 31% vs. 33% p=0.86	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

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Nordmann 2006 (312) 16476868	Low-carb vs. low-fat diets on weight loss and CV risk	Meta-analyses	4475 trials	Low carb 222	Low fat 225	Randomized controlled low carb vs. low fat, BMI≥25, Follow-up 6 mo + Age 16+	Trials with cross-over or sequential design	Low-carb weight loss at 6 and 12 mo	Low fat same	Weight loss to 6 and 12 mo. 6 mo: low carb>weight loss. 12 mo: NS difference	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	In diabetics, HbA1cdec. 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)	Substantial losses to follow-up. No blinded outcome assessment. Had to use ITT analysis because of dropouts. Heterogeneity concerning main outcome.

Chow 2010 (313) 20124123	Adherence to behavioral recommendation 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	Decreased 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)]=.0037 Exercise/diet vs. no 0.46 (0.38- 0.57) <0001 Ex-smoker vs. smoker 0.68 (0.51-.90).0067	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.
Gadde 2011 (314) 21481449	Efficacy and safety of Qnexa	Multicenter prospective trial Phase 3	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	Phenteramine/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 dif: Dry mouth 21% Paresthesia 21% Constipation 17% Dysgeusia 10% Headache 10% Cognitive (sig Attention dist 4%	>10% weight loss Low-dose Qnexa 37% p<0.0001 High-dose Qnexa 48% p<0.0001 PC 7%	5% 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	Endpoint assessment not available for 31% of sample. Restriction of upper limit to BMI: 45. Lack of ethnic diversity (86% white), few men (30%). No active comparator group such as orlistat or lorcaserin
Garvey 2012 (315) 22158731	Long-term efficacy and safety of Qnexa	Multicenter prospective trial Extension of previous trial (4)	676 Out of original 2,448	Phenteramine/Topiramate 7.5mg/46mg 173 P/T15/92mg 295	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: +4.7% DM: 0% Low-dose Q BP: -3.9%	>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 1 st 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 1 st 56-wk period but incidence rates lower.

											20% to 1.4% upper respiratory infection 18.6% to 15.3% Nasopharyngi tis 13.2% to 8.8% Depression NS 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% PC: 2.2% p=.0072 for low dose <0.0001 for high dose.	

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; Pt, patient; Rx, prescription; TG, triglycerides; and UA, unstable agina.

Data Supplement H. Cardiac Rehabilitation

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Safety Endpoint & Results	Secondary Endpoint & Results			
Goel, K et al Circulation. 2011; 123: 2344-2352 (316) 21576654	Assess CR participation and impact on mortality	2,395	CR (1431) vs. non- CR (964) participants	PCI registry, Olmstead County	No prior pt authorization	At least 1 CR outpatient session	All-cause mortality HR	Subsequent MI, PCI-NS	Death, PCI, MI, CABG p=0.28	HR 0.54 (0.41- 0.71) p<0.001	Events in CR=83; in non-CR=139	Observational, Cohort
Hammil, Circulation. 2010;121:63-70 (317) 20026778	Characterize dose-response for # CR sessions	30,161 (6,181 with AMI as qualifying reason for CR)	Internal: cumulative comparison with # of CR sessions ("dose")	Medicare 5% sample 2001-2005	None identified	At least 1 CR outpatient session billed to Medicare	Death	Subsequent hospitalization	MI	Death HR 0.86 (0.76-0.97) for those attending >6 sessions	Subsequent hospitalization	Observational, sample of Medicare claims

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.

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