

Part 10: Acute Coronary Syndromes

2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Robert E. O'Connor, Chair; William Brady; Steven C. Brooks; Deborah Diercks; Jonathan Egan; Chris Ghaemmaghami; Venu Menon; Brian J. O'Neil; Andrew H. Travers; Demetris Yannopoulos

The 2010 AHA Guidelines for CPR and ECC for the evaluation and management of acute coronary syndromes (ACS) are intended to define the scope of training for healthcare providers who treat patients with suspected or definite ACS within the first hours after onset of symptoms. These guidelines summarize key out-of-hospital, emergency department (ED), and related initial critical-care topics that are relevant to diagnosis and initial stabilization and are not intended to guide treatment beyond the ED. Emergency providers should use these contents to supplement other recommendations from the ACC/AHA Guidelines, which are used throughout the United States and Canada.¹⁻³ As with any guidelines, these general recommendations must be considered within the context of local resources and their application to individual patients by knowledgeable healthcare providers. The healthcare providers managing the individual patients are best suited to determine the most appropriate treatment strategy.

The primary goals of therapy for patients with ACS are to

- Reduce the amount of myocardial necrosis that occurs in patients with acute myocardial infarction (AMI), thus preserving left ventricular (LV) function, preventing heart failure, and limiting other cardiovascular complications
- Prevent major adverse cardiac events (MACE): death, nonfatal MI, and need for urgent revascularization
- Treat acute, life-threatening complications of ACS, such as ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), unstable tachycardias, symptomatic bradycardias (See Part 8: "Advanced Cardiovascular Life Support"), pulmonary edema, cardiogenic shock and mechanical complications of AMI
- An overview of recommended care for the ACS patient is illustrated in Figure 1, the Acute Coronary Syndromes Algorithm. Part 10 provides details of the care highlighted in the numbered algorithm boxes; box numbers in the text correspond to the numbered boxes in the algorithm. In this part, the abbreviation "AMI" refers to acute myocardial infarction, whether associated with ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial

infarction (NSTEMI). The diagnosis and treatment of AMI, however, will often differ for patients with STEMI versus NSTEMI. Please note carefully which AMI type is being discussed.

Prehospital Management

Patient and Healthcare Provider Recognition of ACS (Figure 1, Box 1)

Prompt diagnosis and treatment offers the greatest potential benefit for myocardial salvage in the first hours of STEMI; and early, focused management of unstable angina and NSTEMI reduces adverse events and improves outcome.⁴ Thus, it is imperative that healthcare providers recognize patients with potential ACS in order to initiate the evaluation, appropriate triage, and management as expeditiously as possible; in the case of STEMI, this recognition also allows for prompt notification of the receiving hospital and preparation for emergent reperfusion therapy. Potential delays to therapy occur during 3 intervals: from onset of symptoms to patient recognition, during prehospital transport, and during emergency department (ED) evaluation.

Patient-based delay in recognition of ACS and activation of the emergency medical services (EMS) system often constitutes the longest period of delay to treatment.⁵ With respect to the prehospital recognition of ACS, numerous issues have been identified as independent factors for prehospital treatment delay (ie, symptom-to-door time), including older age,⁶ racial and ethnic minorities,^{7,8} female gender,⁹ lower socioeconomic status,^{10,11} and solitary living arrangements.^{7,12}

Hospital-based delays in ACS recognition range from nonclassical patient presentations and other confounding diagnostic issues to provider misinterpretation of patient data and inefficient in-hospital system of care.^{9,13-16}

Symptoms of ACS may be used in combination with other important information (biomarkers, risk factors, ECG, and other diagnostic tests) in making triage and some treatment decisions in the out-of-hospital and ED settings. The symptoms of AMI may be more intense than angina and most often

The American Heart Association requests that this document be cited as follows: O'Connor RE, Brady W, Brooks SC, Diercks D, Egan J, Ghaemmaghami C, Menon V, O'Neil BJ, Travers AH, Yannopoulos D. Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(suppl 3):S787-S817.

(*Circulation*. 2010;122[suppl]:S787-S817.)

© 2010 American Heart Association, Inc.

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

DOI: 10.1161/CIRCULATIONAHA.110.971028

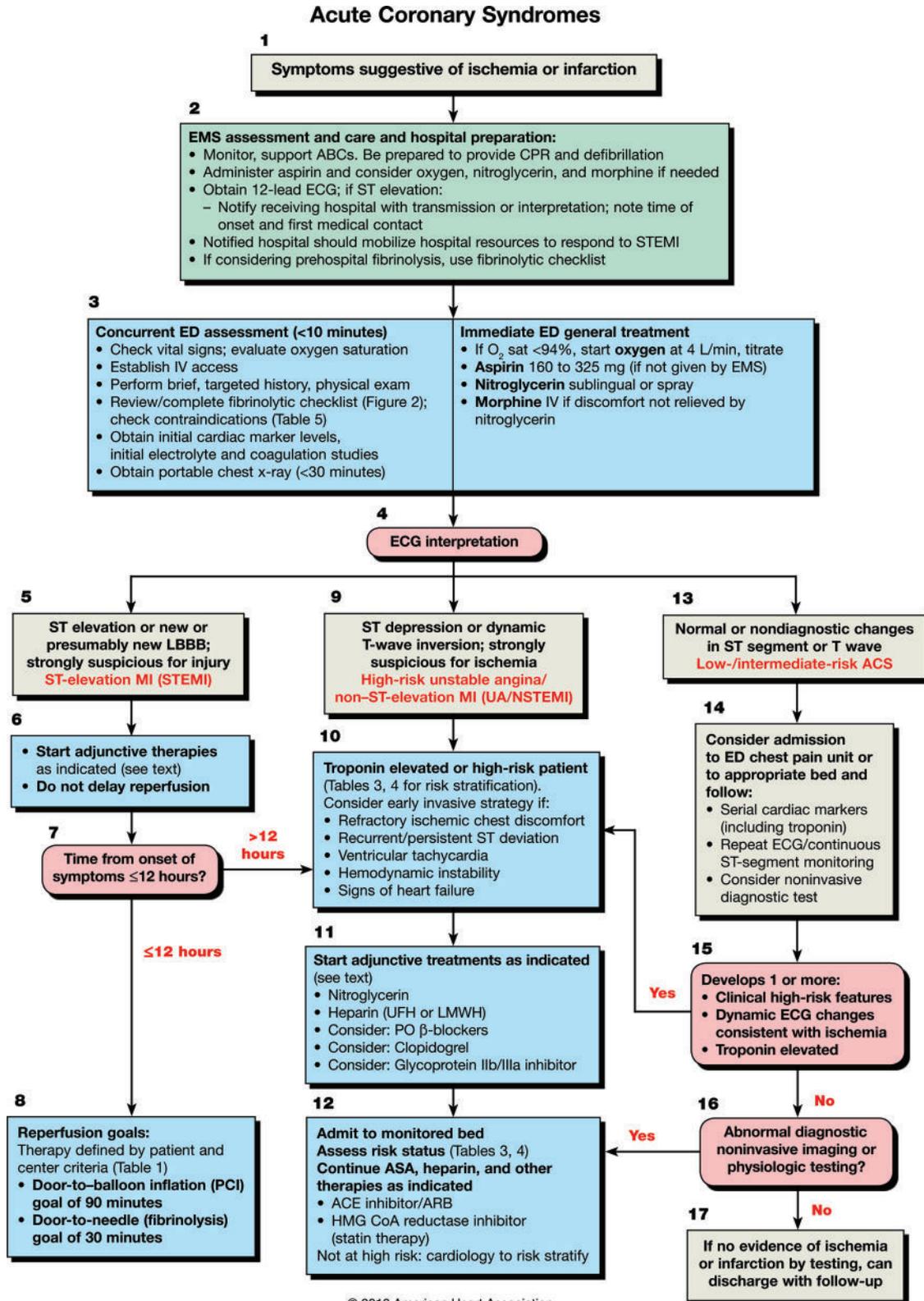


Figure 1. Acute Coronary Syndromes Algorithm.

persist for longer periods of time (eg, longer than 15–20 minutes). The classic symptom associated with ACS is chest discomfort, but symptoms may also include discomfort in other areas of the upper body, shortness of breath, sweating, nausea, vomiting, and dizziness. Most often the patient will

note chest or upper body discomfort and dyspnea as the predominant presenting symptoms accompanied by diaphoresis, nausea, vomiting, and dizziness.^{17–19} Isolated diaphoresis, nausea, vomiting, or dizziness are unusual predominant presenting symptoms.²⁰ Atypical or unusual symptoms are

Prehospital Fibrinolytic Checklist*

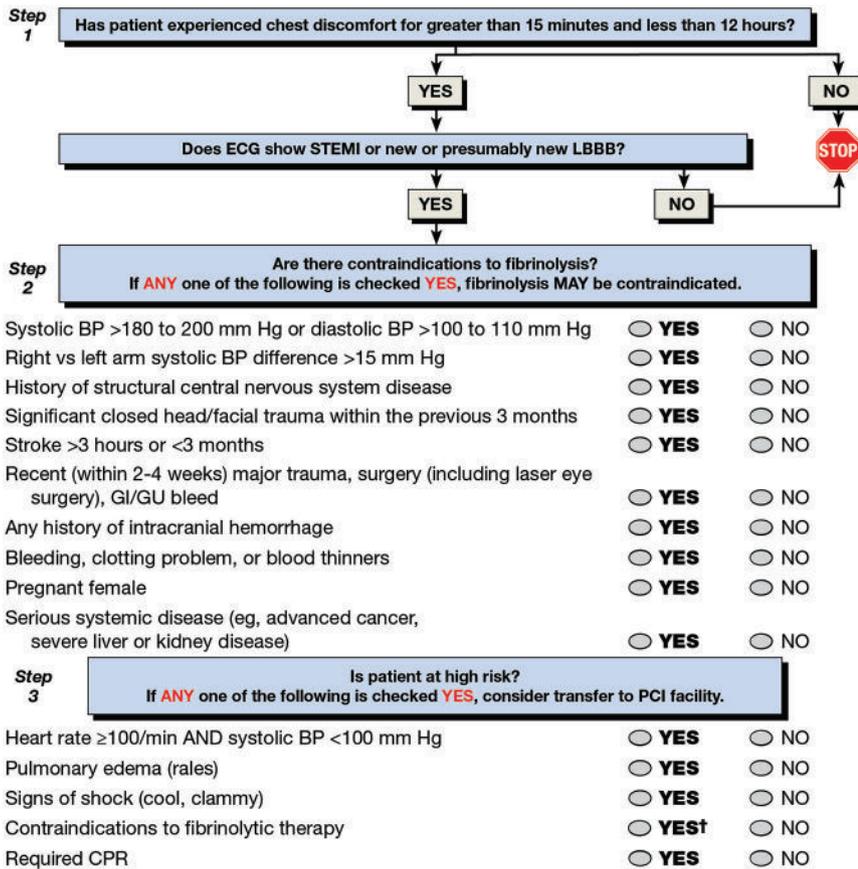


Figure 2. Prehospital fibrinolytic checklist. Adapted from Antman EM, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110:e82-e292, with permission from Lippincott Williams & Wilkins. Copyright 2004, American Heart Association.

more common in women, the elderly, and diabetic patients.²¹⁻²³ The physical examination of the patient with ACS is often normal.

Public education campaigns increase patient awareness and knowledge of the symptoms of ACS, yet have only transient effects on time to presentation.^{24,25} For patients at risk for ACS (and for their families), primary care physicians and other healthcare providers should consider discussing the appropriate use of aspirin and activation of EMS system. Furthermore, an awareness of the location of the nearest hospital that offers 24-hour emergency cardiovascular care can also be included in this discussion. Previous guidelines have recommended that the patient, family member, or companion activate the EMS system rather than call their physician or drive to the hospital if chest discomfort is unimproved or worsening 5 minutes after taking 1 nitroglycerin treatment.²

Initial EMS Care (Figure 1, Box 2)

Half the patients who die of ACS do so before reaching the hospital. VF or pulseless VT is the precipitating cardiac arrest rhythm in most of these deaths,^{26,27} and it is most likely to develop in the early phase of ACS evolution.²⁸ Communities should develop programs to respond to cardiac emergencies that include the prompt recognition of ACS symptoms by

patients and their companions as well as by healthcare and public safety providers and early activation of the EMS system. Additional features of such a program include high-quality CPR for patients in cardiac arrest (see Part 5: “Adult Basic Life Support”) and rapid access to and use of an automated external defibrillator (AED) through community AED programs (see Part 6: “Electrical Therapies”).²⁹ Emergency dispatch center personnel should be educated in the provision of CPR instructions for lay rescuers before the arrival of EMS. EMS providers should be trained to respond to cardiovascular emergencies, including ACS and its acute complications.

Emergency dispatch center personnel can provide instructions to the patient or caller before EMS arrival. Because aspirin should be administered as soon as possible after symptom onset to patients with suspected ACS, it is reasonable for EMS dispatchers to instruct patients with no history of aspirin allergy and without signs of active or recent gastrointestinal bleeding to chew an aspirin (160 to 325 mg) while awaiting the arrival of EMS providers (Class IIa, LOE C).³⁰⁻³⁵

EMS providers should be familiar with the presentation of ACS and trained to determine the time of symptom onset. EMS providers should monitor vital signs and cardiac rhythm and be prepared to provide CPR and defibrillation if needed.

EMS providers administer oxygen during the initial assessment of patients with suspected ACS. However, there is insufficient evidence to support its routine use in uncomplicated ACS. If the patient is dyspneic, hypoxemic, or has obvious signs of heart failure, providers should titrate therapy, based on monitoring of oxyhemoglobin saturation, to $\geq 94\%$ (Class I, LOE C).³⁶

EMS providers should administer nonenteric aspirin (160 [Class I, LOE B] to 325 mg [Class I, LOE C]). The patient should chew the aspirin tablet to hasten absorption.^{30,37–39} EMS providers should administer up to 3 nitroglycerin doses (tablets or spray) at intervals of 3 to 5 minutes. Nitrates in all forms are contraindicated in patients with initial systolic blood pressure < 90 mm Hg or ≥ 30 mm Hg below baseline and in patients with right ventricular infarction.^{40–42} Caution is advised in patients with known inferior wall STEMI, and a right-sided ECG should be performed to evaluate RV infarction. Administer nitrates with extreme caution, if at all, to patients with inferior STEMI and suspected right ventricular (RV) involvement because these patients require adequate RV preload. Nitrates are contraindicated when patients have taken a phosphodiesterase-5 (PDE-5) inhibitor within 24 hours (48 hours for tadalafil).⁴³ Morphine is indicated in STEMI when chest discomfort is unresponsive to nitrates (Class I, LOE C); morphine should be used with caution in unstable angina (UA)/NSTEMI due to an association with increased mortality in a large registry (Class IIa, LOE C).⁴⁴ The efficacy of other analgesics is unknown.

Prehospital ECGs (Figure 1, Box 2)

Prehospital 12-lead ECGs speed the diagnosis, shorten the time to reperfusion (fibrinolytics^{45–52} or primary percutaneous coronary intervention [PPCI]^{53–60}). EMS personnel should routinely acquire a 12-lead electrocardiogram (ECG) as soon as possible for all patients exhibiting signs and symptoms of ACS. The ECG may be transmitted for remote interpretation by a physician or screened for STEMI by properly trained paramedics, with or without the assistance of computer-interpretation. Advance notification should be provided to the receiving hospital for patients identified as having STEMI (Class I, LOE B).

Implementation of 12-lead ECG diagnostic programs with concurrent medically-directed quality assurance is recommended (Class I, LOE B). Prehospital personnel can accurately identify ST-segment elevation from the 12-lead ECG.^{47,50,61–74} If providers are not trained to interpret the 12-lead ECG, field transmission of the ECG or a computer report to the receiving hospital is recommended (Class I, LOE B).

Prehospital Fibrinolysis

Clinical trials have shown the benefit of initiating fibrinolysis as soon as possible after onset of ischemic-type chest discomfort in patients with confirmed STEMI or new or presumably new left bundle branch block (LBBB).^{75,76} Several prospective studies^{77–79} have documented reduced time to administration of fibrinolytics and decreased mortality rates when out-of-hospital fibrinolytics were administered to patients with STEMI. Physicians in the Grampian Region Early

Anistreplase Trial (GREAT) trial administered fibrinolytic therapy to patients at home 130 minutes earlier than to patients at the hospital with both a 50% reduction in hospital mortality and greater 1-year and 5-year survival in those treated earlier.^{79–81} Meta-analyses have demonstrated reduced mortality and improved outcomes with prehospital fibrinolysis regardless of the training and experience of the prehospital provider.^{75,77}

When fibrinolysis is the chosen reperfusion strategy the fibrinolytic agent should be initiated as soon as possible, preferably within 30 minutes of first medical contact (Class I, LOE A). It is strongly recommended that systems which administer fibrinolytics in the prehospital setting include the following features: protocols using fibrinolytic checklists, 12-lead ECG acquisition and interpretation, experience in advanced life support, communication with the receiving institution, medical director with training and experience in STEMI management, and continuous quality improvement (Class I, LOE C).

Triage and Transfer

Prehospital Triage and EMS Hospital Destination

In approximately 40% of patients with a myocardial infarction, the EMS provider establishes first medical contact.^{82,83} In these patients, the ability to identify STEMI in the prehospital setting allows for the consideration of specific hospital destination. Direct triage from the scene to a PCI-capable hospital may reduce the time to definitive therapy and improve outcome. In a large historically controlled clinical trial, the mortality rate was significantly reduced (8.9% versus 1.9%) when transport time was *less than 30 minutes*.⁸⁴ Increased out-of-hospital times with longer EMS-initiated diversion to a PCI-capable hospital may worsen outcomes. If PCI is the chosen method of reperfusion for the prehospital STEMI patient, it is reasonable to transport patients directly to the nearest PCI facility, bypassing closer EDs as necessary, in systems where time intervals between first medical contact and balloon times are < 90 minutes and transport times are relatively short (ie, < 30 minutes) (Class IIa, LOE B).

In patients presenting within 2 hours of symptom onset or when delays to PCI are anticipated, fibrinolytic therapy is recommended. In these circumstances fibrinolytic therapy has equivalent or improved outcomes compared to PCI, especially when the benefit to bleeding risk is favorable (eg, young age, anterior location of MI) (Class I, LOE B).^{85,86}

Interfacility Transfer

Hospital and ED protocols should clearly identify criteria for expeditious transfer of patients to PCI facilities. These include patients who are ineligible for fibrinolytic therapy or who are in cardiogenic shock (Class I, LOE C).¹ A door-to-departure time < 30 minutes is recommended by ACC/AHA Guidelines.² Transfer of high-risk patients who have received primary reperfusion with fibrinolytic therapy is reasonable (Class IIa, LOE B).^{87,88}

Systems of Care

A well-organized approach to STEMI care requires integration of community, EMS, physician, and hospital resources.

The most appropriate STEMI system of care starts “on the phone” with activation of EMS. Hospital-based issues include ED protocols, activation of the cardiac catheterization laboratory, and admission to the coronary intensive care unit.

In PCI-capable hospitals an established “STEMI Alert” activation plan is critical. Components include prehospital ECGs and notification of the receiving facility,^{45–60} and activation of the cardiac catheterization team to shorten reperfusion time^{54,59,82,89–92} and other hospital personnel important for treatment and resource allocation.

Continuous review and quality improvement involving EMS and prehospital care providers are important to achieve ongoing optimal reperfusion time. Quality assurance, real-time feedback, and healthcare provider education can also reduce the time to therapy in STEMI.^{89,93–97} Involvement of hospital leadership in the process and commitment to support rapid access to STEMI reperfusion therapy are critical factors associated with successful programs.

If the emergency physician activates the STEMI reperfusion protocol, including the cardiac catheterization team, significant reductions in time to reperfusion are seen, and the rate of “false-positive” activations are infrequent, ranging from 0% to 14%.^{89,93,95,96,98–107}

ED Evaluation and Risk Stratification (Figure 1, Boxes 3 and 4)

Focused Assessment and ECG Risk Stratification

ED providers should quickly assess patients with possible ACS. Ideally within 10 minutes of ED arrival providers should obtain a targeted history while a monitor is attached to the patient and a 12-lead ECG is obtained (if not done in the prehospital setting).¹⁰⁸ The evaluation should focus on chest discomfort, associated signs and symptoms, prior cardiac history, risk factors for ACS, and historical features that may preclude the use of fibrinolytics or other therapies. This initial evaluation must be efficient because if the patient has STEMI, the goals of reperfusion are to administer fibrinolytics within 30 minutes of arrival (30-minute interval “door-to-drug”) or to provide PCI within 90 minutes of arrival (90-minute interval “door-to-balloon”) (Class I, LOE A).

Potential delay during the in-hospital evaluation period may occur from door to data, from data (ECG) to decision, and from decision to drug (or PCI). These 4 major points of in-hospital therapy are commonly referred to as the “4 D’s.”¹⁰⁹ All providers must focus on minimizing delays at each of these points. Prehospital transport time constitutes only 5% of delay to treatment time; ED evaluation constitutes 25% to 33% of this delay.^{3,109–111}

The physical examination is performed to aid diagnosis, rule out other causes of the patient’s symptoms, and evaluate the patient for complications related to ACS. Although the presence of clinical signs and symptoms may increase suspicion of ACS, evidence does not support the use of any single sign or combination of clinical signs and symptoms alone to confirm the diagnosis.^{17–19,112}

When the patient presents with symptoms and signs of potential ACS, the clinician uses ECG findings (Figure 1, Box 4) to classify the patient into 1 of 3 groups:

1. ST-segment elevation or presumed new LBBB (Box 5) is characterized by ST-segment elevation in 2 or more contiguous leads and is classified as *ST-segment elevation MI (STEMI)*. Threshold values for ST-segment elevation consistent with STEMI are J-point elevation 0.2 mV (2 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men \geq 40 years old); J-point elevation 0.25 mV (2.5 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men <40 years old); J-point elevation 0.15 mV (1.5 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (women).¹¹³
2. Ischemic ST-segment depression >0.5 mm (0.05 mV) or dynamic T-wave inversion with pain or discomfort (Box 9) is classified as UA/NSTEMI. Nonpersistent or transient ST-segment elevation ≥ 0.5 mm for <20 minutes is also included in this category. Threshold values for ST-segment depression consistent with ischemia are J-point depression 0.05 mV (-.5 mm) in leads V2 and V3 and -0.1 mV (-1 mm) in all other leads (men and women).¹¹³
3. The nondiagnostic ECG with either normal or minimally abnormal (ie, nonspecific ST-segment or T-wave changes, Box 13). This ECG is nondiagnostic and inconclusive for ischemia, requiring further risk stratification. This classification includes patients with normal ECGs and those with ST-segment deviation of <0.5 mm (0.05 mV) or T-wave inversion of ≤ 0.2 mV. This category of ECG is termed *nondiagnostic*.

The interpretation of the 12-lead ECG is a key step in this process, allowing not only for this classification but also the selection of the most appropriate diagnostic and management strategies. Not all providers are skilled in the interpretation of the ECG; as a consequence, the use of computer-aided ECG interpretation has been studied. While expert ECG interpretation is ideal, computer-aided ECG interpretation may have a role, particularly in assisting inexperienced clinicians in achieving a diagnosis (Class IIa, LOE B).

Cardiac Biomarkers

Serial cardiac biomarkers are often obtained during evaluation of patients suspected of ACS. Cardiac troponin is the preferred biomarker and is more sensitive than creatine kinase isoenzyme (CK-MB). Cardiac troponins are useful in diagnosis, risk stratification, and determination of prognosis. An elevated level of *troponin* correlates with an increased risk of death, and greater elevations predict greater risk of adverse outcome.¹¹⁴

In the patients with STEMI reperfusion therapy should not be delayed pending results of biomarkers. Important limitations to these tests exist because they are insensitive during the first 4 to 6 hours of presentation unless continuous persistent pain has been present for 6 to 8 hours. For this reason cardiac biomarkers are not useful in the prehospital setting.^{115–120}

Clinicians should take into account the timing of symptom onset and the sensitivity, precision, and institutional norms of the assay, as well as the release kinetics and clearance of the measured biomarker. If biomarkers are initially negative within 6 hours of symptom onset, it is recommended that biomarkers should be remeasured between 6 to 12 hours after symptom onset (Class I, LOE A). A diagnosis of myocardial

infarction can be made when clinical symptoms or new ECG abnormalities are consistent with ischemia and one biomarker is elevated above the 99th percentile of the upper reference limit (URL) using a test with optimal precision defined as a CV \leq 10%.

There is insufficient evidence to support the use of troponin point-of-care testing (POCT) either in or out of hospital. There is also insufficient evidence to support the use of myoglobin, β -natriuretic peptide (BNP), NT-proBNP, D-dimer, C-reactive protein, ischemia-modified albumin pregnancy-associated plasma protein A (PAPP-A) or interleukin-6 in isolation.

STEMI (Figure 1, Boxes 5 Through 8)

Patients with STEMI usually have complete occlusion of an epicardial coronary artery. The primary goal of initial treatment is early reperfusion therapy through administration of fibrinolytics (pharmacological reperfusion) or PPCI (mechanical reperfusion). Providers should rapidly identify patients with STEMI and quickly screen them for indications and contraindications to fibrinolytic therapy and PCI. Patients who are ineligible for fibrinolytic therapy should be considered for transfer to a PCI facility regardless of delay.

Within a STEMI system of care, the first physician who encounters a patient with STEMI determines the need and strategy (fibrinolytic or PPCI) for reperfusion therapy (see Table 1). If the patient meets the criteria for fibrinolytic therapy, a door-to-needle time (initiation of fibrinolytic agent) $<$ 30 minutes is recommended—the earlier the better (Class I, LOE A). Routine consultation with a cardiologist or another physician is not recommended except in equivocal or uncertain cases.^{89,121} Consultation delays therapy and is associated with increased hospital mortality rates (Class III, LOE B).

UA and NSTEMI (Figure 1, Boxes 9 Through 12)

Unstable angina (UA) and NSTEMI are difficult to distinguish initially. These patients usually have a partially or intermittently occluding thrombus. Both ACS syndromes may present with similar symptoms and ECG. Clinical features can correlate with the dynamic nature of clot formation and degradation (eg, waxing and waning clinical symptoms). The ECG will demonstrate a range of findings short of diagnostic ST-segment deviation; these ECG presentations include normal, minimal nonspecific ST-segment/T-wave changes, and significant ST-segment depression and T-wave inversions.

An elevated biomarker separates NSTEMI from UA and has incremental value in addition to the ECG. Elevation of cardiac troponin indicates increased risk for major adverse cardiac events and benefit from an invasive strategy. Cardiac troponins indicate myocardial necrosis, although numerous conditions other than ACS may cause elevated biomarkers (eg, myocarditis, heart failure, and pulmonary embolism).

Management strategies for UA/NSTEMI include antiplatelet, antithrombin, and antianginal therapy and are based on risk stratification. Fibrinolysis is contraindicated in this het-

Table 1. ST-Segment Elevation or New or Presumably New LBBB: Evaluation for Reperfusion

Step 1: Assess time and risk	
Time since onset of symptoms	
Risk of STEMI	
Risk of fibrinolysis	
Time required to transport to skilled PCI catheterization suite	
Step 2: Select reperfusion (fibrinolysis or invasive) strategy	
<i>Note:</i> If presentation $<$ 3 hours and no delay for PCI, then no preference for either strategy.	
Fibrinolysis is generally preferred if:	An invasive strategy is generally preferred if:
<ul style="list-style-type: none"> ● Early presentation (\leq3 hours from symptom onset) ● Invasive strategy is not an option (eg, lack of access to skilled PCI facility or difficult vascular access) or would be delayed <ul style="list-style-type: none"> – Medical contact-to-balloon or door-to-balloon $>$90 minutes – (Door-to-balloon) minus (door-to-needle) is $>$1 hour ● No contraindications to fibrinolysis 	<ul style="list-style-type: none"> ● Late presentation (symptom onset $>$3 hours ago) ● Skilled PCI facility available with surgical backup <ul style="list-style-type: none"> ● Medical contact-to-balloon or door-to-balloon $<$90 minutes ● (Door-to-balloon) minus (door-to-needle) is $<$1 hour ● Contraindications to fibrinolysis, including increased risk of bleeding and ICH ● High risk from STEMI (CHF, Killip class is \geq3) ● Diagnosis of STEMI is in doubt

Modified from ACC/AHA 2004 Update Recommendations.²

erogenous group of patients and may be harmful; an invasive strategy is indicated in patients with positive biomarkers or unstable clinical features.

The Process of Risk Stratification

Diagnosis of ACS and risk stratification become an integrated process in patients presenting to an acute care setting with possible ACS and an initially nondiagnostic evaluation. This nondiagnostic evaluation includes a normal or nondiagnostic 12-lead ECG and normal serum cardiac biomarker concentrations. The majority of these patients will not be experiencing an ACS, but many may have underlying CAD or other clinical features putting them at subsequent risk for major adverse cardiac events over the course of a few days to several months.

A major goal of the risk stratification process is to identify those patients who do not appear to have high-risk features on initial assessment but are found, through the course of the diagnostic process, to have ACS and clinically significant CAD. This strategy allows physicians to target patients who would benefit from guidelines-based ACS therapies while avoiding unnecessary procedural and pharmacological risks (eg, anticoagulation therapy and invasive cardiac catheterization) in patients with low risk for major adverse cardiac events.

Although the diagnosis of ACS is important and will help to guide immediate therapy, the estimation of risk for major adverse cardiac events in the immediate, short-term, and long-term time frames helps the physician determine the urgency in completing the diagnostic workup not just for ACS but also for CAD. Many patients can be managed in the outpatient setting once it is determined that they are at very low risk for short-term (30 days) major adverse cardiac events.

Braunwald Risk Stratification

ACC/AHA Guidelines recommend that all patients be risk stratified for the selection of an initial management strategy and site of care.³ A well-recognized approach is the one initially proposed and later refined by Braunwald and colleagues and published in ACC/AHA Guidelines on the Management of Patients With Unstable Angina and Non-ST Segment Elevation MI.^{122–126} This approach is based on a combination of historical, clinical, laboratory, and ECG variables and answers two questions: what is the likelihood that signs and symptoms represent ACS secondary to obstructive CAD, and what is the likelihood of an adverse clinical outcome?

Table 2¹²⁷ is a modified version of Braunwald and colleagues' approach updated over several publications.^{124,126,128} Patients are initially risk-stratified according to the likelihood that symptoms are due to unstable CAD. Patients at intermediate or high risk for CAD are further classified by their risk of major adverse cardiac events. This second classification is useful for prospectively identifying patients at intermediate or high risk who can benefit from an invasive strategy and more aggressive pharmacology with antiplatelet and antithrombin agents. Other risk stratification schemes include the TIMI, GRACE, and PURSUIT risk scores developed for short- and longer-term risk assessment.^{129–133} Stratification tools cannot be used to determine discharge from the ED.

TIMI Risk Score

The risk of major adverse cardiac events has been further studied and refined. Researchers who derived the important Thrombolysis in Myocardial Ischemia (TIMI) risk score used data from the TIMI-11B and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events) trials for UA/NSTEMI^{134,135} and from the In-TIME trial for STEMI.¹³⁶

The TIMI risk score comprises 7 independent prognostic variables (Table 3). These 7 variables were significantly associated with the occurrence within 14 days of at least one of the primary end points: death, new or recurrent MI, or need for urgent revascularization. The score is derived from complex multivariate logistic regression. It is useful to note that traditional cardiac risk factors are only weakly associated with major adverse cardiac events. Aspirin use was found to be one of the most powerful predictors.¹³⁴ It is possible that aspirin use identified a subgroup of patients at higher risk or on active but failed therapy for CAD.

The TIMI risk score was validated with 3 groups of patients, and 4 clinical trials showed a significant interaction between the TIMI risk score and outcome (Table 3).^{136–139}

These findings confirm the value of the TIMI risk score as a guide to therapeutic decisions (Class IIa, LOE B).

Indicators for Early Invasive Strategies

Risk stratification (Figure 1, Boxes 9, 13, 14, 15) helps the clinician identify patients with non-ST-elevation ACS who should be managed with an early invasive strategy versus a selectively invasive one. Early coronary angiography may allow the clinician to determine whether patients are appropriate candidates for revascularization with PCI or coronary artery bypass grafting (CABG).

The 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention contains the following recommendations related to the selection of early invasive PCI versus conservative strategies.

1. An early invasive PCI strategy is indicated for patients with non-ST-elevation ACS who have no serious comorbidity and who have coronary lesions amenable to PCI and an elevated risk for clinical events (Class I, LOE A). (See Table 4 and Section 3.3 of the ACC/AHA 2007 UA/NSTEMI Guidelines).
2. An early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) is indicated in non-ST-elevation ACS patients who have refractory angina or hemodynamic or electric instability (without serious comorbidities or contraindications to such procedures) (Class I, LOE B).
3. In initially stabilized patients, an initially conservative (ie, a selectively invasive) strategy may be considered as a treatment strategy for non-ST-elevation ACS patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events including those with abnormal troponin elevations (Class IIb, LOE B).
4. The decision to implement an initial conservative (versus initial invasive) strategy in these patients may be made by considering physician and patient preference (Class IIb, LOE C).

Normal or Nondiagnostic ECG Changes (Figure 1, Boxes 13 Through 17)

The majority of patients with normal or nondiagnostic ECGs do not have ACS. Patients in this category with ACS are most often at low or intermediate risk. The physician's goal involves risk stratification (see above) to provide appropriate diagnostic or treatment strategies for an individual patient. These strategies then target patients at increased risk for benefit while avoiding risk (eg, anticoagulation therapy and invasive cardiac catheterization) in patients with low or minimal risk.

The Chest Pain Unit Model

Chest pain observation protocols may be employed in a dedicated space (ie, a physical chest pain unit [CPU]) or throughout an ED/hospital (ie, virtual CPU). These chest pain observation protocols are a rapid system of patient assessment that should generally include a history and physical examination, a period of observation, serial electrocardiography, and serial measurement of serum cardiac markers. In selected patients, an evaluation for inducible myocardial ischemia or anatomic coronary disease after AMI is excluded

Table 2. Likelihood That Signs and Symptoms Represent ACS Secondary to CAD

Feature	High Likelihood Any of the following:	Intermediate Likelihood Absence of high-likelihood features and presence of any of the following:	Low Likelihood Absence of high- or intermediate-likelihood features but may have the following:
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina; known history of CAD including MI	Chest or left arm pain or discomfort as chief symptom; age >70 years; male sex; diabetes mellitus	Probable ischemic symptoms in absence of any intermediate-likelihood characteristics; recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New or presumably new transient ST-segment deviation (≥ 1 mm) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.5 to 1 mm or T-wave inversion >1 mm	T-wave flattening or inversion <1 mm in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac Tnl, TnT, or CK-MB	Normal	Normal

CAD indicates coronary artery disease; CK-MB, MB fraction of creatine kinase; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; Tnl, troponin I; and TnT, troponin T.

Modified from Braunwald E, et al. *Unstable Angina: Diagnosis and Management*. 1994;3-1-AHCPR Publication No 94-0602:1-154. In the public domain.¹²⁷

when indicated. Eleven randomized trials^{140–150} suggest that these protocols may be used to improve accuracy in identifying patients requiring inpatient admission or further diagnostic testing and, thereby, reduce length of stay, rate of hospital admission, and health care costs while improving quality of life measures.

In patients with suspicion for ACS, normal initial biomarkers, and nonischemic ECG, chest pain observation protocols may be recommended as a safe and effective strategy for evaluating patients in the ED (Class I, LOE A). There is no direct evidence demonstrating that CPUs/observation protocols reduce adverse cardiovascular outcomes, including mortality for patients presenting with possible ACS, normal serum cardiac biomarkers, and a nondiagnostic ECG.

Advanced Testing to Detect Coronary Ischemia and CAD

For ED/CPU patients who are suspected of having ACS, have nonischemic ECG's and negative biomarkers, a noninvasive test for inducible myocardial ischemia or anatomic evaluation of the coronary arteries (eg, computed tomography [CT] angiography, cardiac magnetic resonance, myocardial perfusion imaging, stress echocardiography) can be useful in identifying patients suitable for discharge from the ED (Class IIa, LOE B). This strategy may be considered to increase diagnostic accuracy for ACS thereby decreasing costs, length of stay, time to diagnosis, and can provide valuable short-term and long-term prognostic information of future major cardiac events.

Myocardial perfusion scintigraphy (MPS) has a high negative predictive value (NPV) for ruling out ACS; 99% in patients presenting to the ED with acute chest pain, nondiagnostic ECG, and negative cardiac markers. MPS can also be used for risk stratification, especially in low- to intermediate-likelihood of cardiac events according to traditional cardiac markers (Class IIa, LOE B).^{151–154} MPS is best utilized in patients with an intermediate probability or LOE of risk stratification.

The use of multidetector computed tomography (MDCT) angiography (64-slice scanner) after presentation to the ED with chest discomfort, a nondiagnostic ECG, and negative cardiac biomarkers has also been demonstrated to have high sensitivity and specificity for CAD and ACS.^{155,156} The use of MDCT angiography for selected low-risk patients can be useful to allow for safe early discharge from the ED (Class IIa, LOE B).^{157–159}

It is reasonable to consider both the exposure to radiation and iodinated contrast agents when using MDCT angiography and myocardial perfusion imaging. Little evidence is available to support the use of MRI in this patient population.

Safety of Discharge and Risk of Major Adverse Cardiac Events After Discharge From the ED/CPU

The final step in the CPU risk-stratification process is the decision to discharge or admit the patient. No simple clinical decision rule is adequate and appropriate to identify ED chest discomfort patients with suspected ACS who can be safely discharged from the ED.¹⁶⁰ The use of inpatient-derived risk scoring systems are useful for prognosis (Class I, LOE A) but are not recommended to identify patients who may be safely discharged from the ED (Class III, LOE C).

The Bayesian process of serial assignment of pretest risk, diagnostic testing, and reclassification into post-test risk levels based on the test results is the most reliable method to identify patients at the lowest risk for short term major adverse cardiac events and those patients in need of further evaluation for underlying CAD.

Patients at low and intermediate clinical risk for ACS who have remained stable in the CPU and have negative serial ECGs, serial cardiac biomarker measurements, and noninvasive physiological or anatomic testing for ACS have very low rates of major adverse cardiac events at 30 days from ED discharge.^{161–165} Patients younger than 40 years-of-age with nonclassical presentations and no significant past medical history have very low short-term rates of major adverse cardiac events when serial biomarkers and 12-lead ECGs are

Table 3. TIMI Risk Score for Patients With Unstable Angina and Non-ST-Segment Elevation MI: Predictor Variables

Predictor Variable	Point Value of Variable	Definition
Age ≥65 years	1	
≥3 risk factors for CAD	1	Risk factors <ul style="list-style-type: none"> ● Family history of CAD ● Hypertension ● Hypercholesterolemia ● Diabetes ● Current smoker
Aspirin use in last 7 days	1	
Recent, severe symptoms of angina	1	≥2 anginal events in last 24 hours
Elevated cardiac markers	1	CK-MB or cardiac-specific troponin level
ST deviation ≥0.5 mm	1	ST depression >0.5 mm is significant; transient ST elevation ≥0.5 mm for <20 minutes is treated as ST-segment depression and is high risk; ST elevation ≥1 mm for more than 20 minutes places these patients in the STEMI treatment category
Prior coronary artery stenosis ≥50%	1	Risk predictor remains valid even if this information is unknown
Calculated TIMI Risk Score	Risk of ≥1 Primary End Point* in ≤14 Days	Risk Status
0 or 1	5%	Low
2	8%	Low
3	13%	Intermediate
4	20%	Intermediate
5	26%	High

*Primary end points: death, new or recurrent MI, or need for urgent revascularization.

normal. These patients may be discharged directly from the ED/CCU if appropriate outpatient testing can be arranged within 72 hours.^{3,161-163,165-167} Any system that attempts to facilitate outpatient testing should include mechanisms to ensure patient access to outpatient clinics and testing facilities and should consider nonmedical barriers to discharge from the ED that may require inpatient admission.

Initial General Therapy for ACS

Several initial therapeutic measures are appropriate for all patients with suspected ACS in the ED setting. These include continuous cardiac monitoring, establishment of intravenous (IV) access, and consideration of several medications discussed below.

Oxygen

Oxygen should be administered to patients with breathlessness, signs of heart failure, shock, or an arterial oxyhemoglobin saturation <94% (Class I, LOE C). Noninvasive moni-

Table 4. Selection of Initial Treatment Strategy for Patients With Non-ST-Elevation ACS: Invasive Versus Conservative Strategy*

Preferred Strategy	Patient Characteristics
Invasive	<ul style="list-style-type: none"> ● Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy ● Elevated cardiac biomarkers (TnT or TnI) ● New or presumably new ST-segment depression ● Signs or symptoms of HF or new or worsening mitral regurgitation ● High-risk findings from noninvasive testing ● Hemodynamic instability ● Sustained ventricular tachycardia ● PCI within 6 months ● Prior CABG ● High-risk score (eg, TIMI, GRACE) ● Reduced LV function (LVEF less than 40%)
Conservative	<ul style="list-style-type: none"> ● Low-risk score (eg, TIMI, GRACE) ● Patient or physician preference in absence of high-risk features

CABG indicates coronary artery bypass graft surgery; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; TnI, troponin I; and TnT, troponin T.

*Adapted from the ACC/AHA 2007 UA/NSTEMI Guidelines.

toring of blood oxygen saturation can be useful to decide on the need for oxygen administration.

In the absence of compelling evidence for established benefit in uncomplicated cases, ACC/AHA Guidelines have noted that there appeared to be little justification for continuing routine oxygen use beyond 6 hours.² There is insufficient evidence to recommend the routine usage of oxygen therapy in patients suffering from an uncomplicated AMI or an ACS without signs of hypoxemia or heart failure. Supplementary oxygen has been shown to limit ischemic myocardial injury in animals,¹⁶⁸⁻¹⁷¹ but evidence of benefit from supplementary oxygen from human trials is limited.¹⁶⁸ A case study found improvement in ST changes with the use of oxygen in humans.¹⁷² Others suggested harm with *high-flow* oxygen administration.^{173,174}

Aspirin and Nonsteroidal Anti-Inflammatory Drugs

Early administration of aspirin (acetylsalicylic acid [ASA]), has been associated with decreased mortality rates in several clinical trials.^{30,32,175,176} Multiple studies support the safety of aspirin administration. Therefore, unless the patient has a known aspirin allergy or active gastrointestinal hemorrhage, nonenteric aspirin should be given as soon as possible to all patients with suspected ACS (Class I, LOE A).

Aspirin produces a rapid clinical antiplatelet effect with near-total inhibition of thromboxane A2 production. It reduces coronary reocclusion and recurrent ischemic events after fibrinolytic therapy. Aspirin alone reduced death from AMI in the Second International Study of Infarct Survival (ISIS-2), and its effect was additive to that of streptokinase.³² Aspirin was found to substantially reduce vascular events in

all patients with AMI, and in high-risk patients it reduced nonfatal AMI and vascular death.¹⁷⁷ Aspirin is also effective in patients with NSTEMI. The recommended dose is 160 to 325 mg. Chewable or soluble aspirin is absorbed more quickly than swallowed tablets.^{178,179}

Aspirin suppositories (300 mg) are safe and can be considered for patients with severe nausea, vomiting, or disorders of the upper gastrointestinal tract.

Other nonsteroidal anti-inflammatory medications (NSAIDs) are contraindicated and should be discontinued in patients who are taking these medications. NSAIDs (except for aspirin), both nonselective as well as COX-2 selective agents, should not be administered during hospitalization for STEMI because of the increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use (Class III, LOE C).^{180–182}

Nitroglycerin (or Glyceryl Trinitrate)

Nitroglycerin has beneficial hemodynamic effects, including dilation of the coronary arteries (particularly in the region of plaque disruption), the peripheral arterial bed, and venous capacitance vessels. The treatment benefits of nitroglycerin are limited, however, and no conclusive evidence has been shown to support the routine use of IV, oral, or topical nitrate therapy in patients with AMI.¹⁸³ With this in mind, these agents should be carefully considered, especially in the patient with low blood pressure and when their use would preclude the use of other agents known to be beneficial, such as angiotensin-converting enzyme (ACE) inhibitors.

Patients with ischemic discomfort should receive up to 3 doses of sublingual or aerosol nitroglycerin at 3- to 5-minute intervals until pain is relieved or low blood pressure limits its use (Class I, LOE B). Topical nitrates are acceptable alternatives for patients who require anti-anginal therapy but who are hemodynamically stable and do not have ongoing refractory ischemic symptoms. Parenteral formulations, rather than long acting oral preparations, can be used acutely to enable titration in patients with obvious ACS, objective test abnormality, and ongoing discomfort. In patients with recurrent ischemia, nitrates are indicated in the first 24 to 48 hours.

The use of nitrates in patients with hypotension (SBP <90 mm Hg or ≥ 30 mm Hg below baseline), extreme bradycardia (<50 bpm), or tachycardia in the absence of heart failure (>100 bpm) and in patients with right ventricular infarction is contraindicated (Class III, LOE C). Caution is advised in patients with known inferior wall STEMI, and a right-sided ECG should be performed to evaluate RV infarction. Administer nitrates with extreme caution, if at all, to patients with inferior-wall MI and suspected right ventricular (RV) involvement because these patients require adequate RV preload. Nitroglycerin should not be administered to patients who had taken a phosphodiesterase inhibitor (eg, sildenafil) for erectile dysfunction within 24 hours (48 hours if tadalafil use).

Relief of chest discomfort with nitroglycerin is neither sensitive nor specific for ACS; gastrointestinal etiologies as well as other causes of chest discomfort can “respond” to nitroglycerin administration.^{18,184–186}

Analgesia

Providers should administer analgesics, such as intravenous morphine, for chest discomfort unresponsive to nitrates. Morphine is the preferred analgesic for patients with STEMI (Class I, LOE C). However, analysis of retrospective registry data raised a question about the potentially adverse effects of morphine in patients with UA/NSTEMI.⁴⁴ As a result, the ACC AHA UA/NSTEMI writing group reduced morphine use to a Class IIa recommendation for that patient population.³

Reperfusion Therapies (Figure 1, Box 7, 8)

Acute reperfusion therapy using PPCI or fibrinolytic therapy in patients with STEMI restores flow in the infarct-related artery, limits infarct size, and translates into early mortality benefit that is sustained over the next decade.^{187,188} While optimal fibrinolysis restores normal coronary flow (TIMI 3) in 50% to 60% of subjects, PPCI is able to achieve restored flow in >90% of subjects. The patency rates achieved with PPCI translates into reduced mortality and reinfarction rates as compared to fibrinolytic therapy.¹⁸⁹ This benefit is even greater in patients presenting with cardiogenic shock. PPCI also results in a decreased risk of intracranial hemorrhage and stroke, making it the reperfusion strategy of choice in the elderly and those at risk for bleeding complications.

Fibrinolytics

Early fibrinolytic therapy is a well-established treatment modality for patients with STEMI who present within 12 hours of the onset of symptoms and who lack contraindications to its use.^{188,190–193} Early reperfusion results in reduced mortality, and the shorter the time to reperfusion, the greater the benefit. A 47% reduction in mortality was noted when fibrinolytic therapy was provided within the first hour after onset of symptoms.^{188,193}

The major determinants of myocardial salvage and long-term prognosis are short time to reperfusion,^{190,193} complete and sustained patency of the infarct-related artery with normal (TIMI grade 3) flow,^{194,195} and normal microvascular perfusion.^{22,196–198}

In the absence of contraindications, fibrinolytic therapy is recommended for STEMI if symptom onset has been within 12 hours of presentation and PCI is not available within 90 minutes of first medical contact (Class I, LOE A). Patients are evaluated for risk and benefit; for absolute and relative contraindications to therapy (see Table 5).

If fibrinolysis is chosen for reperfusion, the ED physician should administer fibrinolytics to eligible patients as early as possible according to a predetermined process of care developed by the ED and cardiology staff (Class I, LOE A). The goal is a door-to-needle time of less than 30 minutes with effort focused on shortening the time to therapy. Patients treated within the first 70 minutes of onset of symptoms have >50% reduction in infarct size and 75% reduction in mortality rates.¹⁹⁹ For fibrinolytic therapy, it is estimated that 65 lives will be saved per 1000 patients treated if fibrinolytics are provided in the first hour, with a pooled total of 131 lives saved per 1000 patients treated if fibrinolytics are provided within the first 3 hours of onset of symptoms.²⁰⁰ Although fibrinolytics may be beneficial if given within 12 hours after

Table 5. Fibrinolytic Therapy

Contraindications and cautions for fibrinolytic use in STEMI from ACC/AHA 2004 Guideline Update*

Absolute Contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion (eg, AVM)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head trauma or facial trauma within 3 months

Relative Contraindications

- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)†
- History of prior ischemic stroke >3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase/anistreplase: prior exposure (>5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

CPR, cardiopulmonary resuscitation; AVM indicates arteriovenous malformation; SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, International Normalized Ratio.

*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive.

†Could be an absolute contraindication in low-risk patients with myocardial infarction.

onset of symptoms, the mortality benefit is time sensitive, with shorter intervals to administration being associated with better outcomes.^{201,202}

Patients with STEMI presenting at later times in the myocardial infarction evolution are much less likely to benefit from fibrinolysis. In fact, fibrinolytic therapy is generally not recommended for patients presenting between 12 and 24 hours after onset of symptoms based on the results of the LATE and EMERAS trials,^{201,204} unless continuing ischemic pain is present with continuing ST-segment elevation (Class IIb, LOE B). Fibrinolytic therapy should not be administered (Class III, LOE B) to patients who present greater than 24 hours after the onset of symptoms.

Risks of Fibrinolytic Therapy

Physicians who administer fibrinolytic agents must be aware of the indications, contraindications, benefits, and major risks of administration so that they are able to weigh the net clinical benefit for each patient (see Table 5).^{203,204} This net clinical benefit requires integration of relative and absolute contraindications versus overall potential clinical gain.

Patients who present early after symptom onset with extensive ECG changes (consistent with a large AMI) and a

low risk of intracranial bleeding receive the greatest benefit from fibrinolytic therapy.¹⁹⁰ Patients who have symptoms highly suggestive of ACS and ECG findings consistent with LBBB are also appropriate candidates for intervention because they have the highest mortality rate when LBBB is due to extensive AMI. Inferior wall STEMI also benefits from fibrinolysis, yet the magnitude of this outcome improvement is markedly less robust. More extensive inferior STEMI presentations, of course, demonstrate more robust benefit when undergoing fibrinolysis; inferior wall STEMI with RV involvement is such an example. Fibrinolytics have been shown to be beneficial across a spectrum of patient subgroups with comorbidities such as previous MI, diabetes, tachycardia, and hypotension.¹⁹⁰ Although superior to placebo, the lack of efficacy in the setting of cardiogenic shock makes referral for PPCI an optimal strategy in this setting.

Although older patients (>75 years) have a higher risk of death, their absolute benefit appears to be similar to that of younger patients. The incidence of stroke does increase with advancing age,^{205,206} reducing the relative benefit of fibrinolytic therapy. Older age is the most important baseline variable predicting nonhemorrhagic stroke.²⁰⁶ Although 1 large trial reported lower early and 1-year mortality rates with accelerated administration of tissue plasminogen activator (rtPA) in patients <85 years of age,²⁰⁷ a retrospective analysis found no specific survival advantage and possible risk for patients >75 years of age.²⁰⁸

Intracranial Hemorrhage

Fibrinolytic therapy is associated with a small but definite increase in the risk of hemorrhagic stroke, which contributes to increased mortality.¹⁹⁰ More intensive fibrinolytic regimens using rtPA (alteplase) and heparin pose a greater risk than streptokinase and aspirin.^{200,209} Clinical factors that may help risk-stratify patients at the time of presentation are age (≥ 65 years), low body weight (<70 kg), hypertension on presentation (>180/110 mm Hg), and use of rtPA. The number of risk factors can be used to estimate the frequency of stroke, which ranges from 0.25% with no risk factors to 2.5% with 3 risk factors.²⁰⁴ Several risk factor estimates are available for use by clinicians, including Simoons,²⁰⁴ the Co-Operative Cardiovascular Project,²¹⁰ and the In-Time 2 trial.²¹¹

Percutaneous Coronary Intervention (PCI)

Coronary angioplasty with or without stent placement is the treatment of choice for the management of STEMI when it can be performed effectively with a door-to-balloon time <90 minutes by a skilled provider (performing >75 PCIs per year) at a skilled PCI facility (performing >200 PCIs annually, of which at least 36 are primary PCI for STEMI) (Class I, LOE A).^{2,212,213} PPCI may also be offered to patients presenting to non-PCI centers when prompt transfer can result in an effective balloon time of <90 minutes from first medical contact as a systems goal.²¹⁴ The TRANSFER AMI trial supports the transfer of high-risk patients who receive fibrinolysis in a non-PCI center to a PCI center within 6 hours of presentation to receive routine early PCI.⁸⁷

PCI Following ROSC After Cardiac Arrest

Each year in the United States, 236 000 to 325 000 patients experience out-of-hospital cardiac arrest, and the prognosis is generally grim with a median survival to discharge rate of only 8.4%.²¹⁵ Large variations in outcome have been observed across EMS systems, and this has resulted in a call for regionalization of care with a goal to optimize the utilization of proven beneficial therapies and interventions.²¹⁶ Despite the lack of data from RCTs in this situation, the performance of PCI has been associated with favorable outcomes in this setting and is supported by the observation that following early angiography, half of the studied population is noted to have an acute coronary occlusion.²¹⁷ The data are strongest for patients with out-of-hospital cardiac arrest due to VF in the setting of STEMI (or new or presumably new LBBB), and emergent angiography with prompt recanalization of the infarct-related artery is recommended (Class I, LOE B). PPCI also appears applicable in the setting of NSTEMI subjects in whom emergent revascularization may result in hemodynamic and electric stability. PPCI after ROSC in subjects with arrest of presumed ischemic cardiac etiology may be reasonable, even in the absence of a clearly defined STEMI (Class IIb, LOE B).

There is concern that the poor prognosis for out-of-hospital cardiac arrest will prove detrimental to the public perception and reputation of interventional programs dedicated to treating patients following ROSC because of poorer outcome that could adversely affect mortality data for PCI programs. As a result, the AHA policy statement strongly supports a mechanism to report PCI outcomes for out-of-hospital cardiac arrest separate from PCI outcomes following STEMI, as this will remove potential barriers for interventional cardiologists to actively participate in the care of this population.²¹⁶ In contrast to PCI, randomized control trials of acute reperfusion therapy using fibrinolytic agents have been performed in subjects with out-of-hospital cardiac arrest without a favorable outcome.^{218,219}

A 12-lead ECG should be performed as soon as possible after ROSC. Clinical findings of coma in patients prior to PCI are commonly present in patients with out-of-hospital cardiac arrest, and should not be a contraindication to consider immediate angiography and PCI. It is reasonable to include cardiac catheterization and coronary angiography in standardized post-cardiac arrest protocols as part of an overall strategy to improve neurologically intact survival in this patient group (Class IIa, LOE B) and appropriate treatment of ACS or STEMI, including PCI or fibrinolysis, should be initiated regardless of coma (Class I, LOE B). Angiography and/or PCI need not preclude or delay other therapeutic strategies including therapeutic hypothermia (Class IIa, LOE B).

Cardiac angiography and PCI, when used as part of a standardized advanced post-cardiac arrest protocol, may result in improved survival to hospital discharge.²²⁰ Acute coronary artery occlusion is frequent in survivors of out-of-hospital cardiac arrest. PCI is feasible following ROSC, and almost 50% of cardiac arrest survivors have an acute thrombotic occlusion, or culprit lesion, that is amenable to reperfusion.^{217,221–235} In addition, successful PCI can result in

improved cardiac ejection fraction and survival.²¹⁷ Cardiac catheterization alone (without PCI) has been associated with improved neurologically intact survival.²³⁵ Although coronary artery occlusion after cardiac arrest is associated with ST elevation or LBBB, specific ECG findings may also be conspicuously absent.^{217,235}

Outcomes after angiography and PCI vary considerably depending on patient subsets. Survival in post-cardiac arrest patients with STEMI is as high as 70% to almost 100% with shorter durations of witnessed arrest due to VF.^{221,223} A significant number of eventual survivors may initially be comatose before PCI.²²¹

A 12-lead ECG should be performed as soon as possible after ROSC (Class I, LOE A). Appropriate treatment of ACS or STEMI, including PCI or fibrinolysis, should be initiated regardless of coma (Class I, LOE B). Coma and the use of induced hypothermia are not contraindications or reasons to delay PCI or fibrinolysis.

PCI Versus Fibrinolytic Therapy

For patients admitted to hospitals with PCI facilities, PPCI confers clinical benefit as compared to fibrinolysis (both in terms of death and reinfarction or stroke) for the majority of patients.^{189,236} There is scant evidence for incremental benefit of PCI over fibrinolysis for specific subgroups such as post-CABG patients²³⁵ or patients with renal failure.²³⁸

PCI is the preferred reperfusion strategy in the STEMI patient who can arrive in the catheterization laboratory with balloon inflation within 90 minutes of initial hospital arrival. As a system goal, PCI should ideally be performed within 90 minutes of first medical contact. PCI should be performed by an experienced provider (an individual who performs >75 PCI procedures per year) in a high-volume center (a laboratory that performs more than 200 PCI procedures per year, of which at least 36 are PCI for STEMI). High-risk STEMI patients, “late presenters” (ie, >3 hours since the onset of STEMI symptoms), and individuals with contraindication to fibrinolysis are all candidates for PCI as well. And, of course, if the diagnosis of STEMI is in doubt, regardless of the reason, initial coronary angiography followed by PCI is the most appropriate diagnostic and therapeutic strategy.

Although PCI may offer an improved outcome over fibrinolysis, catheter-based techniques must be applied early without prolonged delay. If applied without delay by experienced providers, PCI provides improved outcome in the STEMI patient. As noted in the DANAMI-2 study,²³⁹ PCI initiated within 3 hours of initial hospital arrival was superior to fibrinolysis. For patients admitted in hospital without PCI capabilities, there may be some benefit associated with transferring patients for PPCI versus on-site fibrinolytics in terms of reinfarction, stroke and a trend to a lower mortality in the PPCI group.^{214,240} For patients with cardiogenic shock, early revascularization was associated with improved survival at six months, especially in patients younger than 75 years-of-age.²⁴¹ Transfer for PCI instead of more immediate fibrinolysis has shown the combined rate of death, nonfatal MI, and stroke to be reduced by 42% if the mean transfer to PCI time could be less than 80 to 122 minutes.

If the time required to mobilize staff and arrange for PCI is prolonged or delays in transfer are anticipated, the treating physician must consider fibrinolysis, assuming that the patient is an appropriate candidate. Time delays to PCI range from 45 to 120 minutes and are associated with age, symptom duration, and location of infarction. These delays may negate the benefit of PCI over fibrinolytics.^{86,242} In addition, the benefit of PCI over fibrinolytics is offset when PCI is carried out in low-volume PCI centers.²¹² PCI has been shown to be superior to fibrinolysis on the combined end points of short-term death, nonfatal myocardial infarction, and stroke.

Pinto and colleagues⁸⁶ have performed a very important analysis of the “PCI versus fibrinolysis” consideration in the STEMI patient. Their analysis asked the following questions for the patient with STEMI: How long should the practitioner wait for PCI in a patient who is fibrinolytic eligible? And, in this waiting period for PCI, when is the benefit of the catheter-based therapy lost and fibrinolysis becomes the preferred option? Time recommendations—essentially the answer to the above questions—are provided with respect to patient age, infarct duration, and MI anatomic location. This paper provides the emergency physician with the total elapsed time that he or she should wait for PCI, at which point the survival benefit of the invasive strategy is lost and the patient should receive a fibrinolytic agent. These times include the following:

- For patients presenting within 2 hours of symptom onset: 94 minutes
- For patients presenting beyond 2 hours of symptom onset: 190 minutes
- For patients less than 65 years of age: 71 minutes
- For patients greater than 65 years of age: 155 minutes
- Anterior STEMI: 115 minutes
- Nonanterior STEMI: 112 minutes

Further analysis combined commonly encountered clinical variables in typical STEMI presentations:

- Patient presentation within 2 hours of symptom onset and
 - anterior STEMI with age <65 years: 40 minutes
 - anterior STEMI with age >65 years: 107 minutes
 - non-anterior STEMI with age <65 years: 58 minutes
 - non-anterior STEMI with age >65 years: 168 minutes
- Patient presentation beyond 2 hours of symptom onset and
 - anterior STEMI with age <65 years: 43 minutes
 - anterior STEMI with age >65 years: 148 minutes
 - nonanterior STEMI with age <65 years: 103 minutes
 - nonanterior STEMI with age >65 years: 179 minutes

Post hoc analysis and theoretical constructs have addressed the time delay that mitigates the benefit of PPCI as compared to fibrinolytic therapy in the absence of randomized trials. The time delay has been analyzed to be between 60 and 120 minutes.^{86,243–243b} Taking these into consideration, the recent European Society of Cardiology recommendation extended the time delay indicating that PPCI should be performed within 2 hours from first medical contact except in those

patients with a large amount of myocardium is at risk (maximum delay of 90 minutes).^{242c} The ACC AHA 2009 Focused STEMI Writing Group noted, “There has been discussion about whether the recommended door-to-balloon time (or first medical contact to balloon time) should be greater than 90 minutes. However, the writing group continues to believe that the focus should be on developing systems of care to increase the number of patients with timely access to PCI rather than extending the acceptable window for door-to-balloon time.”¹

Delays to reperfusion therapy are not without negative consequence as noted in a subset of patients in the GRACE (Global Registry of Acute Coronary Events) database. The authors of this registry examined the outcome impact of treatment delays on STEMI patients receiving reperfusion therapy. This study involved 3959 patients from 106 hospitals in 14 countries who presented within 6 hours of chest pain onset and underwent either PCI (55%) or fibrinolysis (45%). Delays in reperfusion were associated with increased mortality for both treatment strategies, yet were more pronounced in those patients receiving fibrinolysis.^{243d}

A cooperative and interdisciplinary effort between emergency medicine and cardiology, as well as among the EMS agencies, the catheterization laboratory, and the CCU, has the potential to reduce markedly the door-to-therapy time in STEMI patients and therefore limit delays in providing this time-sensitive treatment. Prior agreement between the ED and cardiovascular physicians at institutions with invasive capability must be obtained so that consideration of PCI does not introduce further delays in fibrinolytic drug administration; such cooperation can limit additional delays in the administration of fibrinolytic agents in patients who are considered for PCI in AMI.

A systems of care approach involving a reperfusion team or “STEMI alert” system mobilizes hospital-based resources, optimizing the approach to the patient. This system, whether activated by data gathered in the ED or prehospital-based information, has the potential to offer time-sensitive therapies in a rapid fashion to these ill patients.

In summary, for patients presenting within 12 hours of symptom onset and electrocardiographic findings consistent with STEMI, reperfusion should be initiated as soon as possible – independent of the method chosen (Class I, LOE A). Primary PCI performed at a high-volume center within 90 minutes of first medical contact by an experienced operator that maintains an appropriate expert status is reasonable, as it improves morbidity and mortality as compared with immediate fibrinolysis (<30 minutes door-to-needle) (Class I, LOE A). If PCI cannot be accomplished within 90 minutes of first medical contact, independent of the need for emergent transfer, then fibrinolysis is recommended, assuming the patient lacks contraindications to such therapy (Class I, LOE B). For those patients with a contraindication to fibrinolysis, PCI is recommended despite the delay, rather than foregoing reperfusion therapy (Class I, LOE A). For those STEMI patients presenting in shock, PCI (or CABG) is the preferred reperfusion treatment. Fibrinolysis should only be consid-

ered in consultation with the cardiologist if there is a substantial delay to PCI.

Complicated AMI

Cardiogenic Shock, LV Failure, and Congestive Heart Failure

Infarction of $\geq 40\%$ of the LV myocardium usually results in cardiogenic shock and carries a high mortality rate. Of those who developed shock,²⁴⁴ patients with ST-segment elevation developed shock significantly earlier than patients without ST-segment elevation. Cardiogenic shock and congestive heart failure are not contraindications to fibrinolysis, but PCI is preferred if the patient is at a facility with PCI capabilities. Based on the results of the SHOCK trial ACC/AHA guidelines note that PPCI is reasonable in those who develop shock within 36 hours of symptom onset and who are suitable candidates for revascularization that can be performed within 18 hours of the onset of shock.³ Although the benefits in the SHOCK trial were observed only in patients ≤ 75 years of age, selected elderly patients also appear to benefit from this strategy. The guidelines also support the use of hemodynamic support with intra-aortic balloon counterpulsation (IABP) in this setting as part of aggressive medical treatment. The IABP works synergistically with fibrinolytic agents in this setting, and the benefits observed with early revascularization strategy in the SHOCK trial were also obtained in the setting of IABP support. The use of PPCI for patients with cardiogenic shock has increased over time and contributes to the observed decrease in hospital mortality.^{245,246} The majority of survivors following cardiogenic shock experience a good quality of life, and the early mortality benefit with revascularization is sustained over time.^{247–249} In hospitals without PCI facilities, fibrinolytic administration needs to be considered with prompt transfer to a tertiary care facility where adjunct PCI can be performed if cardiogenic shock or ongoing ischemia ensues.²⁵⁰ The ACC/AHA STEMI guidelines recommend a door-to-departure time of ≤ 30 minutes for transfer to a PCI-capable center.³

RV Infarction

RV infarction or ischemia may occur in up to 50% of patients with inferior wall MI. The clinician should suspect RV infarction in patients with inferior wall infarction, hypotension, and clear lung fields. In patients with inferior wall infarction, obtain an ECG with right-sided leads. ST-segment elevation (>1 mm) in lead V4R is sensitive (sensitivity, 88%; specificity, 78%; diagnostic accuracy, 83%) for RV infarction and is a strong predictor of increased in-hospital complications and mortality.²⁵¹

The in-hospital mortality rate of patients with RV dysfunction is 25% to 30%, and these patients should be routinely considered for reperfusion therapy. Fibrinolytic therapy reduces the incidence of RV dysfunction.²⁵² Similarly PCI is an alternative for patients with RV infarction and is preferred for patients in shock. Patients with shock caused by RV failure have a mortality rate similar to that for patients with shock due to LV failure.

Patients with RV dysfunction and acute infarction are dependent on maintenance of RV “filling” pressure (RV

end-diastolic pressure) to maintain cardiac output.²⁵³ Thus, nitrates, diuretics, and other vasodilators (ACE inhibitors) should be avoided because severe hypotension may result. Hypotension is initially treated with an IV fluid bolus.

Adjunctive Therapies for ACS and AMI

Thienopyridines

Clopidogrel

Clopidogrel is an oral thienopyridine prodrug that irreversibly inhibits the adenosine diphosphate receptor on the platelet, resulting in a reduction in platelet aggregation through a different mechanism than aspirin. Since the publication of the 2005 AHA Guidelines, several important clopidogrel studies have been published that document its efficacy for patients with both NSTEMI and STEMI.

There is a reduction in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) and/or mortality; with a resultant small increase in major bleeding when clopidogrel is administered by providers in the ED or in hospital to patients with NSTEMI ACS.^{254–256} Patients with ACS and a rise in cardiac biomarkers or ECG changes consistent with ischemia had reduced stroke and major adverse cardiac events if clopidogrel was added to aspirin and heparin within 4 hours of hospital presentation.²⁵⁷ Clopidogrel given 6 hours or more before elective PCI for patients with ACS without ST elevation reduces adverse ischemic events at 28 days.²⁵⁸

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial documented an increased rate of bleeding (but not intracranial hemorrhage) in the 2072 patients undergoing CABG within 5 to 7 days of administration.²⁵⁹ Although a posthoc analysis of this trial reported a trend toward life-threatening bleeding²⁵⁷ and a prospective study failed to show increased bleeding in 1366 patients undergoing CABG,²⁶⁰ a subsequent risk-to-benefit ratio analysis concluded that the bleeding risk with clopidogrel in patients undergoing CABG was modest. The use of clopidogrel in ACS patients with a high likelihood of needing CABG requires weighing the risk of bleeding if given against the potential for perioperative ACS events if withheld. The current ACC/AHA guidelines recommend withholding clopidogrel for 5 to 7 days in patients for whom CABG is anticipated.

In patients up to 75 years of age with STEMI managed by fibrinolysis, a consistent improvement in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) and/or mortality, with a resultant small increase in major bleeding, is observed when clopidogrel, in a 300-mg loading dose, was administered in addition to aspirin and heparin (low-molecular-weight heparin [LMWH] or unfractionated heparin [UFH]), at the time of initial management (followed by a 75 mg daily dose for up to 8 days in hospital).^{260–265}

In patients with STEMI managed with PPCI, there is a reduction in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) and/or mortality with a resultant small increase in major bleeding

when clopidogrel is administered by ED, hospital, or prehospital providers.^{261,264–267}

On the basis of these findings, providers should administer a loading dose of clopidogrel in addition to standard care (aspirin, anticoagulants, and reperfusion) for patients determined to have moderate- to high-risk non-ST-segment elevation ACS and STEMI (Class I, LOE A).²⁵⁷ In patients <75 years of age a loading dose of clopidogrel 300 to 600 mg with non-STE ACS and STEMI, regardless of approach to management, is recommended. It is reasonable to administer a 300-mg oral dose of clopidogrel to ED patients with suspected ACS (without ECG or cardiac marker changes) who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (Class IIa, LOE B). Providers should administer a 300-mg oral dose of clopidogrel to ED patients up to 75 years of age with STEMI who receive aspirin, heparin, and fibrinolysis (Class I, LOE B). There is little evidence on the use of a loading dose of clopidogrel in patients aged ≥ 75 years of age with NSTEMI and STEMI treated by PPCI, and patients >75 years of age were excluded in the studies on STEMI treated by fibrinolysis, therefore the ideal dose of clopidogrel in patients over 75 years of age has yet to be delineated. In the ED the choice of immediate antiplatelet therapy (as well as protocols for STEMI and NSTEMI) should be guided by local interdisciplinary review of ongoing clinical trials, guidelines, and recommendations.

Prasugrel

Prasugrel is an oral thienopyridine prodrug that irreversibly binds to the ADP receptor to inhibit platelet aggregation. Prasugrel may be associated with a reduction in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) with no benefit in mortality compared to clopidogrel but with an overall resultant increase in major bleeding (as compared to clopidogrel) when administered after angiography to patients with NSTEMI undergoing PCI.^{268–272} Risk factors associated with a higher rate of bleeding with prasugrel use are age ≥ 75 years, previous stroke or TIA, and body weight less than 60 kg.

Small improvements in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) and/or mortality are observed when prasugrel (compared to clopidogrel) is administered before or after angiography to patients with NSTEMI and STEMI managed with PCI.^{268–271,273,274}

Prasugrel (60 mg oral loading dose) may be substituted for clopidogrel after angiography in patients determined to have non-ST-segment elevation ACS or STEMI who are more than 12 hours after symptom onset prior to planned PCI (Class IIa, LOE B). There is no direct evidence for the use of prasugrel in the ED or prehospital settings. In patients who are not at high risk for bleeding, administration of prasugrel (60-mg oral loading dose) prior to angiography in patients determined to have STEMI ≤ 12 hours after the initial symptoms may be substituted for administration of clopidogrel (Class IIa, LOE B). Prasugrel is not recommended in STEMI patients managed with fibrinolysis or NSTEMI patients before angiography.

Glycoprotein IIb/IIIa Inhibitors

The use and efficacy of glycoprotein IIb/IIIa receptor inhibitors for treatment of patients with UA/NSTEMI has been well established.^{274–279} These trials were conducted prior to contemporary conservative and invasive strategies, and ongoing questions have been investigated concerning their timing (eg, upsteam initiation) and use combined with other contemporary agents (eg, clopidogrel).

Two recent studies do not support the routine use of upstream GP IIb/IIIa inhibitors.^{280,281} Other studies have documented benefit largely in patients who have elevated cardiac troponin and a planned invasive strategy or specific subsets such as those patients with diabetes or significant ST-segment depression on the presenting ECG.^{282–286} The current evidence supports a selective strategy for the use of GP IIb/IIIa inhibitors in the use of dual platelet inhibitor treatment of patients with planned invasive strategy taking into consideration the ACS risk of the patient and weighing this against the potential bleeding risk. There is no current evidence supporting the routine use of GP IIb/IIIa inhibitor therapy prior to angiography in patients with STEMI and use of these agents upstream is uncertain. Use of GP IIb/IIIa inhibitors should be guided by local interdisciplinary review of ongoing clinical trials, guidelines, and recommendations.

β -Adrenergic Receptor Blockers

Controversy surrounds the administration of β -adrenergic receptor blockers in the setting of ACS. Several studies have shown reduced mortality^{287,288} and decreased infarct size^{289–291} with early IV β -blocker use. Early β -blocker administration may help prevent dangerous arrhythmias^{288,290,292,293} and reduce reinfarction, but there is an increased incidence of cardiogenic shock.

Recent evidence shows no particular benefit to the IV administration of β -blockers on either mortality, infarct size, prevention of arrhythmias, or reinfarction^{294–301} There may be, however, a statistically significant short-term benefit to 6-week mortality when IV β -blockers were given to low-risk (ie, Killip Class I) patients.²⁹⁶ IV β -blockers may also be beneficial for NSTEMI. One study³⁰² suggested that the earlier the IV β -blockers were administered, the greater the effect seen on infarct size and mortality. Of note, none of the papers reviewed showed that β -blockers caused irreversible harm when given early in the development of suspected ACS. Balancing the evidence overall for non-ST-segment elevation ACS patients, current ACC/AHA Guidelines recommend β -blockers be initiated orally within the first 24 hours after hospitalization.³

Contraindications to β -blockers are moderate to severe LV failure and pulmonary edema, bradycardia (<60 bpm), hypotension (SBP <100 mm Hg), signs of poor peripheral perfusion, second-degree or third-degree heart block, or reactive airway disease. Studies of β -blockers varied significantly in the treatment times used, with no high quality papers studying the administration of β -blockers in the prehospital setting or in the very early ED setting (ie, within the first hour of a suspected ACS).

For patients with ACS, there is no evidence to support the routine administration of IV β -blockers in the prehos-

pital setting or during initial assessment in the ED. IV β -blocker therapy may be considered as reasonable in specific situations such as severe hypertension or tachyarrhythmias in patients without contraindications (Class IIa, LOE B). In the absence of contraindications, PO β -blockers should be administered within the first 24 hours to patients with suspected ACS (Class I, LOE A). Patients with initial contraindications should be re-evaluated periodically. It is reasonable to start oral β -blockers with low doses after the patient is stabilized prior to discharge (Class IIa, LOE B).

Heparins

Heparin is an indirect inhibitor of thrombin that has been widely used in ACS as adjunctive therapy for fibrinolysis and in combination with aspirin and other platelet inhibitors for the treatment of non-ST-segment elevation ACS. UFH has several disadvantages, including (1) the need for IV administration; (2) the requirement for frequent monitoring of the activated partial thromboplastin time (aPTT); (3) an unpredictable anticoagulant response in individual patients; and (4) heparin can also stimulate platelet activation, causing thrombocytopenia. Because of the limitations of heparin, newer preparations of LMWH have been developed.

Unfractionated Heparin Versus Low-Molecular-Weight Heparin in UA/NSTEMI

Enoxaparin

Eleven in-hospital randomized clinical trials,^{303–313} and additional studies (including 7 meta-analyses)^{314–320} document similar or improved composite outcomes (death, MI, and/or recurrent angina or recurrent ischemia or revascularization) when enoxaparin was administered instead of UFH to patients with non-ST-segment elevation ACS with an increase in the proportion of patients with minor bleeding complications.

Fondaparinux

There was similar^{321–323} or improved^{324,325} outcomes of combined end points (death, MI, urgent revascularization) without increased bleeding when fondaparinux was administered in-hospital rather than UFH in patients with non-ST-segment elevation ACS. Fondaparinux was associated with increased risk of catheter thrombosis in PCI.³²⁴

Bivalirudin

No benefit in combined outcome was observed when bivalirudin was administered in hospital compared to UFH in patients with non-ST-segment elevation ACS, however less bleeding was observed with bivalirudin and no renal dosing is required.^{326–329}

Treatment Recommendations for UA/NSTEMI

For in-hospital patients with NSTEMI managed with a planned initial conservative approach, either fondaparinux (Class IIa, LOE B) or enoxaparin (Class IIa, LOE A) are reasonable alternatives to UFH or placebo. For in-hospital patients with NSTEMI managed with a planned invasive approach, either enoxaparin or UFH are reasonable choices

(Class IIa, LOE A). Fondaparinux may be used in the setting of PCI, but requires co-administration of UFH and does not appear to offer an advantage over UFH alone (Class IIb, LOE A). For in-hospital patients with NSTEMI and renal insufficiency, bivalirudin or UFH may be considered (Class IIb, LOE A). For in-hospital patients with NSTEMI and increased bleeding risk, where anticoagulant therapy is not contraindicated, fondaparinux (Class IIa, LOE B) or bivalirudin (Class IIa, LOE A) are reasonable and UFH may be considered (Class IIb, LOE C) There is no specific evidence for or against anticoagulant use in NSTEMI in the prehospital setting.

Unfractionated Heparin Versus Low-Molecular-Weight Heparin With Fibrinolysis in STEMI

Nine randomized clinical trials^{320,331–338} and additional studies (including one meta-analyses)³³⁹ document similar or improved composite outcomes (death, MI, and/or recurrent angina or recurrent ischemia or revascularization) when enoxaparin was administered instead of UFH to patients with STEMI undergoing fibrinolysis. This must be balanced against an increase in intracranial hemorrhage in patients >75 years of age who received enoxaparin documented in one of these randomized controlled trials.³³⁸

One randomized clinical trial³⁴⁰ demonstrated superiority in clinical outcomes when fondaparinux was compared to UFH in patients treated with fibrinolysis.

There is insufficient evidence to provide a recommendation on bivalirudin, nadroparin, reviparin, or parnaparin for use in STEMI patients undergoing fibrinolysis.

Enoxaparin

For patients with STEMI managed with fibrinolysis in the hospital, it is reasonable to administer enoxaparin instead of UFH (Class IIa, LOE A). In addition, for prehospital patients with STEMI managed with fibrinolysis, adjunctive enoxaparin instead of UFH may be considered (Class IIb, LOE A). Patients initially treated with enoxaparin should not be switched to UFH and vice versa because of increased risk of bleeding (Class III, LOE C).³⁴¹ In younger patients <75 years the initial dose of enoxaparin is 30 mg IV bolus followed by 1 mg/kg SC every 12 hours (first SC dose shortly after the IV bolus) (Class IIb, LOE A). Patients \geq 75 years may be treated with 0.75 mg/kg SC enoxaparin every 12 hours without an initial IV bolus (Class IIb, LOE B). Patients with impaired renal function (creatinine clearance <30 mL/min) may be given 1 mg/kg enoxaparin SC once daily (Class IIb, LOE B). Patients with known impaired renal function may alternatively be managed with UFH (Class IIb, LOE B).

Fondaparinux

Fondaparinux (initially 2.5 mg IV followed by 2.5 mg SC once daily) may be considered in the hospital for patients treated specifically with non-fibrin-specific thrombolytics (ie, streptokinase), provided the creatinine is <3 mg/dL (Class IIb, LOE B).

There are insufficient data to recommend other LMWH or bivalirudin over UFH in patients treated with fibrinolysis in STEMI.

Unfractionated Heparin Versus Low-Molecular-Weight Heparin With PPCI in STEMI

Two registry studies^{342,343} and other studies demonstrated similar or improved outcomes when enoxaparin was compared to UFH in patients undergoing PPCI combined with a GP IIb/IIIa antagonist and thienopyridine inhibitor.

One large clinical trial³⁴⁰ demonstrated better outcomes in terms of acute cardiac events and bleeding using fondaparinux and PPCI. Thrombus formation on catheter material in patients on fondaparinux, however, required the addition of UFH during PCI.³²⁴

Two large randomized clinical trials resulted in less bleeding and a short- and long-term reduction in cardiac events and overall mortality with bivalirudin compared to UFH plus a glycoprotein inhibitor in patients with STEMI and PPCI.^{344,345}

For patients with STEMI undergoing contemporary PCI (ie, additional broad use of glycoprotein IIb/IIIa inhibitors and a thienopyridine) enoxaparin may be considered a safe and effective alternative to UFH (Class IIb, LOE B). Patients initially treated with enoxaparin should not be switched to UFH and vice versa to avoid increased risk of bleeding. Fondaparinux may be considered as an alternative to UFH, however, there is an increased risk of catheter thrombi with fondaparinux alone. Additional UFH (50 to 100 U/kg bolus) may help to avoid this complication (Class IIb, LOE B), but using these two agents is not recommended over UFH alone. For fondaparinux and enoxaparin it is necessary to adjust the dose in patients with renal impairment. Bivalirudin may be considered as an alternative to UFH and GP IIb/IIIa inhibitors (Class IIb, LOE A).

Calcium Channel Blockers

There is little evidence that calcium channel blocking agents can be safely used as an alternative or additional therapy to β -blockers when the later are contraindicated or their maximum dose has been achieved.

Calcium channel blocking agents have not been shown to reduce mortality after acute MI, and in certain patients with cardiovascular disease there are data to suggest that they are harmful. β -blockers have been used much more broadly, have a much safer profile, and appear to be a more appropriate choice for patients presenting with myocardial infarction compared to calcium channel blockers.

ACE Inhibitor Therapy

ACE Inhibitors and ARBs in the Hospital

ACE inhibitor therapy has improved survival rates in patients with AMI, particularly when started early after the initial hospitalization.^{183,346–349} Evidence from 7 large clinical trials,^{183,346–351} 2 meta-analyses,^{352,353} and 10 minor trials^{348,351,354–362} documents consistent improvement in mortality when oral ACE inhibitors are administered in the hospital setting to patients with AMI with or without early reperfusion therapy. In these studies ACE inhibitors were not administered in the presence of hypotension (SBP <100 mm Hg or ≥ 30 mm Hg below baseline). *The beneficial effects are most pronounced in patients with anterior infarction, pulmonary congestion, or LV ejection fraction <40%.*

Administration of an oral ACE inhibitor is recommended within the first 24 hours after onset of symptoms in STEMI patients with pulmonary congestion or LV ejection fraction <40%, in the absence of hypotension (SBP <100 mm Hg or ≥ 30 mm Hg below baseline) (Class I, LOE A). Oral ACE inhibitor therapy can also be useful for all other patients with AMI with or without early reperfusion therapy (Class IIa, LOE B). IV administration of ACE inhibitors is contraindicated in the first 24 hours because of risk of hypotension (Class III, LOE C).

ACE Inhibitors in the Prehospital Setting

Despite multiple studies that have shown a benefit of ACE inhibitors and ARBs in patients with a myocardial infarction when therapy is started during the first 24 hours of the index hospitalization, no trial specifically evaluates patients in the ED or prehospital settings. An older randomized trial showed a reduction in mortality with an increased risk of hypotension in patients treated soon after presentation in the inpatient setting.¹⁸³ Several trials showed a reduction in the rate of heart failure and mortality in patients treated soon after fibrinolysis,^{363–365} and several others showed no benefit with the early or prehospital use of angiotensin converting enzyme.^{364,366,367}

In conclusion, although ACE inhibitors and ARBs have been shown to reduce long-term risk of mortality in patients suffering an AMI, there is insufficient evidence to support the routine initiation of ACE inhibitors and ARBs in the prehospital or ED setting (Class IIb, LOE C).

HMG Coenzyme A Reductase Inhibitors (Statins)

A variety of studies documented consistent reduction in indicators of inflammation and complications such as reinfarction, recurrent angina, and arrhythmias when statin treatment is administered within a few days after onset of an ACS.^{368–371} There is little data to suggest that this therapy should be initiated within the ED; however, early initiation (within 24 hours of presentation) of statin therapy is recommended in patients with an ACS or AMI (Class I, LOE C). If patients are already on statin therapy, continue the therapy (Class IIb, LOE C).

An increase in short-term mortality and incidence of major adverse cardiac events have been reported with discontinuation of statin treatment in ACS patients at hospital admission. Statins should not be discontinued during the index hospitalization unless contraindicated (Class III, LOE C).^{372–381}

Pretreatment with statins in patients undergoing elective percutaneous angioplasty for stable angina or hemodynamically stable ACS has been shown to significantly reduce biomarkers of myocardial necrosis or inflammation compared to placebo when given between 3 and 7 days prior to the procedure.^{382,383}

Furthermore, pretreatment with atorvastatin 80 mg 12 hours before and an additional 40 mg immediately before PCI for NSTEMI or documented ischemia has been shown to significantly decrease the 30 day composite of death, MI, and unplanned revascularization compared to placebo in a prospective randomized trial. There were no deaths in any of the two groups and the primary end point was driven by peripro-

cedural myocardial infarction in concordance to the previously published studies.³⁸⁴

In conclusion, intensive (target LDL values optimally <70 mg/dL) statin treatment should be initiated within the first 24 hours after onset of an ACS event (eg, immediately after hospital admission) in all patients presenting with any form of ACS unless strictly contraindicated (eg, by proven intolerance) (Class I, LOE A).

It is reasonable to use statin pretreatment for patients who will be undergoing elective or urgent angioplasty in order to decrease perioperative myocardial infarction. There are no reports on risk or safety considerations of early initiation of statin treatment in ACS.

Glucose-Insulin-Potassium

Although glucose-insulin-potassium (GIK) therapy was formerly thought to reduce the chance of mortality during AMI by several mechanisms, recent clinical trials found that GIK did not show any benefit in STEMI.^{385,386} At this time there is little evidence to suggest that this intervention is helpful (Class IIb, LOE C).

Management of Arrhythmias

This section discusses management of arrhythmias during acute ischemia and infarction.

Ventricular Rhythm Disturbances

Treatment of ventricular arrhythmias during and after AMI has been a controversial topic for three decades. Primary VF accounts for the majority of early deaths during AMI.^{387–389} The incidence of primary VF is highest during the first 4 hours after onset of symptoms^{28,390–392} but remains an important contributor to mortality during the first 24 hours. Secondary VF occurring in the setting of CHF or cardiogenic shock can also contribute to death from AMI. VF is a less common cause of death in the hospital setting with the use of fibrinolytics and percutaneous revascularization as early reperfusion strategies. Broad use of β -blockers also contributes significantly in the reduction of VF incidence in the after AMI.

Although prophylaxis with lidocaine reduces the incidence of VF, an analysis of data from ISIS-3 and a meta-analysis suggest that lidocaine increased all-cause mortality rates.³⁹³ Thus, the practice of prophylactic administration of lidocaine is not recommended (Class III, LOE A).

Sotalol has not been adequately studied (Class IIb, LOE C).

Amiodarone in a single RCT did not appear to improve survival in low doses and may increase mortality in high doses when used early in patients with suspected myocardial infarction (Class IIb, LOE C).³⁹⁴

Twenty published studies including 14 RCTs and 4 meta-analyses/reviews provide no good evidence that prophylactic antiarrhythmics improve outcomes (survival to discharge, 30/60 day mortality) and despite a documented decrease in the incidence of malignant ventricular arrhythmias, they may cause harm. Therefore prophylactic antiarrhythmics are not recommended for patients with suspected ACS or myocardial infarction in the prehospital or ED (Class III, LOE A).

Routine IV administration of β -blockers to patients without hemodynamic or electric contraindications is associated with a reduced incidence of primary VF (Class IIb, LOE C).

Low serum potassium, but not magnesium, has been associated with ventricular arrhythmias. It is prudent clinical practice to maintain serum potassium >4 mEq/L and magnesium >2 mEq/L (Class IIb, LOE A).

Routine administration of magnesium to patients with MI has no significant clinical mortality benefit, particularly in patients receiving fibrinolytic therapy.¹⁸³ ISIS-4 enrolled >58 000 patients and showed a trend toward increased mortality rates when magnesium was given in-hospital for primary prophylaxis to patients within the first 4 hours of known or suspected AMI.

Following an episode of VF, there is no conclusive data to support the use of lidocaine or any particular strategy for preventing VF recurrence. Further management of ventricular rhythm disturbances is discussed in Part 8.2: "Management of Cardiac Arrest" and Part 8.3: "Management of Symptomatic Bradycardia and Tachycardia."

Summary

There has been tremendous progress in reducing disability and death from ACS. But many patients still die before reaching the hospital because patients and family members fail to recognize the signs of ACS and fail to activate the EMS system. Once the patient with ACS contacts the healthcare system, providers must focus on support of cardiorespiratory function, rapid transport, and early classification of the patient based on ECG characteristics. Patients with STEMI require prompt reperfusion; the shorter the interval from symptom onset to reperfusion, the greater the benefit. In the STEMI population, mechanical reperfusion with percutaneous coronary intervention improves survival and decreases major cardiovascular events compared to fibrinolysis. Patients with UA/NSTEMI (non-STEMI ACS) or nonspecific or normal ECGs require risk stratification and appropriate monitoring and therapy. Healthcare providers can improve survival rates and myocardial function of patients with ACS by providing skilled, efficient, and coordinated out-of-hospital and in-hospital care.

Disclosures

Guidelines Part 10: ACS Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Robert E. O'Connor	University of Virginia Health System—Professor and Chair of Emergency Medicine	None	None	None	None	None	None
William Brady	University of Virginia	None	None	None	None	None	*Expert Witness: If contacted by attorneys, I will consider reviewing cases under litigation/potentially under litigation. I am not affiliated with any agency or business entity in this regard. When paid, the money is paid to my department at the University of Virginia—I can then use the money for professional issues and/or receive a certain amount in my personal pay check from the University.
Steven C. Brooks	University of Toronto—Clinician-Scientist	None	None	None	None	None	None
Deborah Diercks	University of California, Davis Medical Center—Professor of Emergency Medicine	*Collaborator on Research Grant Nanosphere and Heartscape with money going to the University	None	*Speakers Bureau for Sanofi-Aventis and Bristol Myer Squibb *Sanofi Aventis, Heartscape, Bristol Myers Squibb, and Schering Plough	None	*Scheuring Plough, Heartscape, Sanofi-Aventis	None
Jonathan Egan	Children's hospital at Westmead, Sydney—Paediatric Intensivist	None	None	None	None	None	None
Chris Ghaemmaghami	University of Virginia School of medicine Faculty Department of Emergency Medicine Associate Professor and Vice Chair	None	None	*Speaker and program chair for the 2010 national meeting of the Society of Chest Pain Centers	None	None	None
Venu Menon	Cleveland Clinic—Director CCU	None	None	None	None	None	None
Brian J. O'Neil	Wayne State, Associate Chair	†Medivance Corporation, Zoll Circulation, Heartscape Technologies	*Somanetics Corp	Speakers bureau †Sanofi- Aventis, Bristol Meyer Squibb *Glaxo-Smith Kline; Medivance Corp; Heartscape Technologies Honoraria* Heartscape Technologies	None	Advisory board- *Heartscape Technologies; *Zoll Circulation	Expert witness- *Seimien Huckabay law offices
Andrew H. Travers	Emergency Health Services—Provincial Medical Director; Dalhousie University—Associate Professor; QE-II Hospital—Attending Physician	None	None	None	None	None	None
Demetris Yannopoulos	University of Minnesota—Interventional cardiologist	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition

*Modest.

†Significant.

References

- Kushner FG, Hand M, Smith SC Jr, King SB III, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE Jr, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the Am College of Cardiology Foundation/Am Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;120:2271–2306.
- Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the Am College of Cardiology/Am Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation*. 2004;110:588–636.
- Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the Am College of Cardiology/Am Heart Association Task Force on Practice Guidelines

- (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the Am College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the Am Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation*. 2007;116:e148–e304.
4. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, Leizorovicz A, Touboul P. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation*. 2003;108:2851–2856.
 5. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRFMI)-3/4 analysis. *Circulation*. 2005;111:761–767.
 6. Saczynski JS, Yarzebski J, Lessard D, Spencer FA, Gurwitz JH, Gore JM, Goldberg RJ. Trends in prehospital delay in patients with acute myocardial infarction (from the Worcester Heart Attack Study). *Am J Cardiol*. 2008;102:1589–1594.
 7. Lefler LL, Bondy KN. Women's delay in seeking treatment with myocardial infarction: a meta-synthesis. *J Cardiovasc Nurs*. 2004;19:251–268.
 8. McGinn AP, Rosamond WD, Goff DC Jr, Taylor HA, Miles JS, Chambless L. Trends in prehospital delay time and use of emergency medical services for acute myocardial infarction: experience in 4 US communities from 1987–2000. *Am Heart J*. 2005;150:392–400.
 9. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118:2803–2810.
 10. Foraker RE, Rose KM, McGinn AP, Suchindran CM, Goff DC Jr, Whitsel EA, Wood JL, Rosamond WD. Neighborhood income, health insurance, and prehospital delay for myocardial infarction: the atherosclerosis risk in communities study. *Arch Intern Med*. 2008;168:1874–1879.
 11. Sari I, Acar Z, Ozer O, Erer B, Tekbas E, Ucer E, Genc A, Davutoglu V, Aksoy M. Factors associated with prolonged prehospital delay in patients with acute myocardial infarction. *Turk Kardiyol Dern Ars*. 2008;36:156–162.
 12. Gibler WB, Armstrong PW, Ohman EM, Weaver WD, Stebbins AL, Gore JM, Newby LK, Califf RM, Topol EJ. Persistence of delays in presentation and treatment for patients with acute myocardial infarction: The GUSTO-I and GUSTO-III experience. *Ann Emerg Med*. 2002;39:123–130.
 13. Mehta RH, Bufalino VJ, Pan W, Hernandez AF, Cannon CP, Fonarow GC, Peterson ED. Achieving rapid reperfusion with primary percutaneous coronary intervention remains a challenge: insights from Am Heart Association's Get With the Guidelines program. *Am Heart J*. 2008;155:1059–1067.
 14. Rathore SS, Curtis JP, Chen J, Wang Y, Nallamothu BK, Epstein AJ, Krumholz HM. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. *BMJ*. 2009;338:b1807.
 15. Song YB, Hahn JY, Gwon HC, Kim JH, Lee SH, Jeong MH. The impact of initial treatment delay using primary angioplasty on mortality among patients with acute myocardial infarction: from the Korea acute myocardial infarction registry. *J Korean Med Sci*. 2008;23:357–364.
 16. Moser DK, Kimble LP, Alberts MJ, Alonzo A, Croft JB, Dracup K, Evenson KR, Go AS, Hand MM, Kothari RU, Mensah GA, Morris DL, Pancioli AM, Riegel B, Zerwic JJ. Reducing delay in seeking treatment by patients with acute coronary syndrome and stroke: a scientific statement from the Am Heart Association Council on cardiovascular nursing and stroke council. *Circulation*. 2006;114:168–182.
 17. Goodacre SW, Angelini K, Arnold J, Revill S, Morris F. Clinical predictors of acute coronary syndromes in patients with undifferentiated chest pain. *QJM*. 2003;96:893–898.
 18. Goodacre S, Locker T, Morris F, Campbell S. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Acad Emerg Med*. 2002;9:203–208.
 19. Everts B, Karlson BW, Wahrborg P, Hedner T, Herlitz J. Localization of pain in suspected acute myocardial infarction in relation to final diagnosis, age and sex, and site and type of infarction. *Heart Lung*. 1996;25:430–437.
 20. Panju AA, B.R. Hemmelgarn, G.G. Guyatt, and DLSimel. Is this patient having a myocardial infarction? *JAMA*. 1998;280:1256–1263.
 21. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Engl J Med*. 1996;334:1311–1315.
 22. Solomon CG, Lee TH, Cook EF, Weisberg MC, Brand DA, Rouan GW, Goldman L. Comparison of clinical presentation of acute myocardial infarction in patients older than 65 years of age to younger patients: the Multicenter Chest Pain Study experience. *Am J Cardiol*. 1989;63:772–776.
 23. Peberdy MA, Ornato JP. Coronary artery disease in women. *Heart Dis Stroke*. 1992;1:315–319.
 24. Blohm M, Herlitz J, Schroder U, Hartford M, Karlson BW, Risenfors M, Larsson E, Luepker R, Wennerblom B, Holmberg S. Reaction to a media campaign focusing on delay in acute myocardial infarction. *Heart Lung*. 1991;20:661–666.
 25. Hedges JR, Feldman HA, Bittner V, Goldberg RJ, Zapka J, Osganian SK, Murray DM, Simons-Morton DG, Linares A, Williams J, Luepker RV, Eisenberg MS. Impact of community intervention to reduce patient delay time on use of reperfusion therapy for acute myocardial infarction: rapid early action for coronary treatment (REACT) trial. REACT Study Group. *Acad Emerg Med*. 2000;7:862–872.
 26. Antman EM, Berlin JA. Declining incidence of ventricular fibrillation in myocardial infarction: implications for the prophylactic use of lidocaine. *Circulation*. 1992;86:764–773.
 27. Wyman MG, Wyman RM, Cannon DS, Criley JM. Prevention of primary ventricular fibrillation in acute myocardial infarction with prophylactic lidocaine. *Am J Cardiol*. 2004;94:545–551.
 28. Chiriboga D, Yarzebski J, Goldberg RJ, Gore JM, Alpert JS. Temporal trends (1975 through 1990) in the incidence and case-fatality rates of primary ventricular fibrillation complicating acute myocardial infarction: a communitywide perspective. *Circulation*. 1994;89:998–1003.
 29. The Public Access Defibrillation Trial Investigators. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med*. 2004;351:637–646.
 30. Freimark D, Matetzky S, Leor J, Boyko V, Barbash IM, Behar S, Hod H. Timing of aspirin administration as a determinant of survival of patients with acute myocardial infarction treated with thrombolysis. *Am J Cardiol*. 2002;89:381–385.
 31. Barbash IM, Freimark D, Gottlieb S, Hod H, Hasin Y, Battler A, Crystal E, Matetzky S, Boyko V, Mandelzweig L, Behar S, Leor J. Outcome of myocardial infarction in patients treated with aspirin is enhanced by pre-hospital administration. *Cardiology*. 2002;98:141–147.
 32. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet*. 1988;2(8607):349–360.
 33. Casaccia M, Bertello F, De Bernardi A, Sicuro M, Scacciarella P. Prehospital management of acute myocardial infarction in an experimental metropolitan system of medical emergencies [in Italian]. *G Ital Cardiol*. 1996;26:657–672.
 34. Quan D, LoVecchio F, Clark B, Gallagher JV, III. Prehospital use of aspirin rarely is associated with adverse events. *Prehosp Disaster Med*. 2004;19:362–365.
 35. Eisenberg MJ, Topol EJ. Prehospital administration of aspirin in patients with unstable angina and acute myocardial infarction. *Arch Intern Med*. 1996;156:1506–1510.
 36. Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Weatherall M, Beasley R. Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart*. 2009;95:198–202.
 37. Haynes BE, Pritting J. A rural emergency medical technician with selected advanced skills. *Prehosp Emerg Care*. 1999;3:343–346.
 38. Funk D, Groat C, Verdile VP. Education of paramedics regarding aspirin use. *Prehosp Emerg Care*. 2000;4:62–64.
 39. Verheugt FW, van der Laarse A, Funke-Kupper AJ, Sterkman LG, Galema TW, Roos JP. Effects of early intervention with low-dose aspirin (100 mg) on infarct size, reinfarction and mortality in anterior wall acute myocardial infarction. *Am J Cardiol*. 1990;66:267–270.
 40. Bussmann WD, Passek D, Seidel W, Kaltenbach M. Reduction of CK and CK-MB indexes of infarct size by intravenous nitroglycerin. *Circulation*. 1981;63:615–622.
 41. Charvat J, Kuruvilla T, al Amad H. Beneficial effect of intravenous nitroglycerin in patients with non-Q myocardial infarction. *Cardiologia*. 1990;35:49–54.

42. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications. Effect of timing, dosage, and infarct location. *Circulation*. 1988;78:906–919.
43. Madsen JK, Chevalier B, Darius H, Rutsch W, Wojcik J, Schneider S, Allikmets K. Ischaemic events and bleeding in patients undergoing percutaneous coronary intervention with concomitant bivalirudin treatment. *EuroIntervention*. 2008;3:610–616.
44. Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV Jr, Gibler WB, Peterson ED. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J*. 2005;149:1043–1049.
45. Karagounis L, Ipsen SK, Jessop MR, Gilmore KM, Valenti DA, Clawson JJ, Teichman S, Anderson JL. Impact of field-transmitted electrocardiography on time to in-hospital thrombolytic therapy in acute myocardial infarction. *Am J Cardiol*. 1990;66:786–791.
46. Kereiakes DJ, Gibler WB, Martin LH, Pieper KS, Anderson LC. Relative importance of emergency medical system transport and the prehospital electrocardiogram on reducing hospital time delay to therapy for acute myocardial infarction: a preliminary report from the Cincinnati Heart Project. *Am Heart J*. 1992;123(4 Pt 1):835–840.
47. Foster DB, Dufendach JH, Barkdoll CM, Mitchell BK. Prehospital recognition of AMI using independent nurse/paramedic 12-lead ECG evaluation: impact on in-hospital times to thrombolysis in a rural community hospital. *The Am journal of emergency medicine*. 1994;12:25–31.
48. Banerjee S, Rhoden WE. Fast-tracking of myocardial infarction by paramedics. *J R Coll Physicians Lond*. 1998;32:36–38.
49. Melville MR, Gray D, et al. The potential impact of prehospital electrocardiography and telemetry on time to thrombolysis in a United Kingdom center. *Ann Noninvasive Electrocardiol*. 1998;3:327–333.
50. Millar-Craig MW, Joy AV, Adamowicz M, Furber R, Thomas B. Reduction in treatment delay by paramedic ECG diagnosis of myocardial infarction with direct CCU admission. *Heart*. 1997;78:456–461.
51. Brainard AH, Raynovich W, Tandberg D, Bedrick EJ. The prehospital 12-lead electrocardiogram's effect on time to initiation of reperfusion therapy: a systematic review and meta-analysis of existing literature. *Am J Emerg Med*. 2005;23:351–356.
52. Morrison LJ, Brooks S, Sawadsky B, McDonald A, Verbeek PR. Prehospital 12-lead electrocardiography impact on acute myocardial infarction treatment times and mortality: a systematic review. *Acad Emerg Med*. 2006;13:84–89.
53. Adams GL, Campbell PT, Adams JM, Strauss DG, Wall K, Patterson J, Shuping KB, Maynard C, Young D, Corey C, Thompson A, Lee BA, Wagner GS. Effectiveness of prehospital wireless transmission of electrocardiograms to a cardiologist via hand-held device for patients with acute myocardial infarction (from the Timely Intervention in Myocardial Emergency, NorthEast Experience [TIME-NE]). *Am J Cardiol*. 2006;98:1160–1164.
54. Afolabi BA, Novaro GM, Pinski SL, Fromkin KR, Bush HS. Use of the prehospital ECG improves door-to-balloon times in ST segment elevation myocardial infarction irrespective of time of day or day of week. *Emerg Med J*. 2007;24:588–591.
55. Terkelsen CJ, Lassen JF, Norgaard BL, Gerdes JC, Poulsen SH, Bendix K, Ankersen JP, Gotzsche LB, Romer FK, Nielsen TT, Andersen HR. Reduction of treatment delay in patients with ST-elevation myocardial infarction: impact of pre-hospital diagnosis and direct referral to primary percutaneous coronary intervention. *Eur Heart J*. 2005;26:770–777.
56. Wall T, Albright J, Livingston B, Isley L, Young D, Nanny M, Jacobowitz S, Maynard C, Mayer N, Pierce K, Rathbone C, Stuckey T, Savona M, Leibrandt P, Brodie B, Wagner G. Prehospital ECG transmission speeds reperfusion for patients with acute myocardial infarction. *North Carolina Medical Journal*. 2000;61:104–108.
57. Dhruva VN, Abdelhadi SI, Anis A, Gluckman W, Hom D, Dougan W, Kaluski E, Haider B, Klapholz M. ST-Segment Analysis Using Wireless Technology in Acute Myocardial Infarction (STAT-MI) trial. *J Am Coll Cardiol*. 2007;50:509–513.
58. Sekulic M, Hassunizadeh B, McGraw S, David S. Feasibility of early emergency room notification to improve door-to-balloon times for patients with acute ST segment elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2005;66:316–319.
59. Swor R, Hegerberg S, McHugh-McNally A, Goldstein M, McEachin CC. Prehospital 12-lead ECG: efficacy or effectiveness? *Prehosp Emerg Care*. 2006;10:374–377.
60. Campbell PT, Patterson J, Cromer D, Wall K, Adams GL, Albano A, Corey C, Fox P, Gardner J, Hawthorne B, Lipton J, Sejersten M, Thompson A, Wilfong S, Maynard C, Wagner G. Prehospital triage of acute myocardial infarction: wireless transmission of electrocardiograms to the on-call cardiologist via a handheld computer. *J Electrocardiol*. 2005;38(4):300–309.
61. Feldman JA, Brinsfield K, Bernard S, White D, Maciejko T. Real-time paramedic compared with blinded physician identification of ST-segment elevation myocardial infarction: results of an observational study. *Am J Emerg Med*. 2005;23:443–448.
62. Le May MR, Dionne R, Maloney J, Trickett J, Watpool I, Ruest M, Stiell I, Ryan S, Davies RF. Diagnostic performance and potential clinical impact of advanced care paramedic interpretation of ST-segment elevation myocardial infarction in the field. *CJEM*. 2006;8:401–407.
63. van't Hof AW, Rasoul S, van de Wetering H, Ernst N, Suryapranata H, Hoortjje JC, Dambrink JH, Gosselink M, Zijlstra F, Ottervanger JP, de Boer MJ. Feasibility and benefit of prehospital diagnosis, triage, and therapy by paramedics only in patients who are candidates for primary angioplasty for acute myocardial infarction. *Am heart journal*. 2006;151:1255 e1251–1255.
64. Pitt K. Prehospital selection of patients for thrombolysis by paramedics. *Emerg Med J*. 2002;19:260–263.
65. Trivedi K, Schuur JD, Cone DC. Can paramedics read ST-segment elevation myocardial infarction on prehospital 12-lead electrocardiograms? *Prehosp Emerg Care*. 2009;13:207–214.
66. Whitbread M, Leah V, Bell T, Coats TJ. Recognition of ST elevation by paramedics. *Emerg Med J*. 2002;19:66–67.
67. Lloyd G, Roberts A, Bashir I, Mumby M, Kamalvand K, Cooke R. An audit of clinical nurse practitioner led thrombolysis to improve the treatment of acute myocardial infarction. *J Public Health Med*. 2000;22:462–465.
68. Qasim A, Malpass K, O'Gorman DJ, Heber ME. Safety and efficacy of nurse initiated thrombolysis in patients with acute myocardial infarction. *BMJ*. 2002;324(7349):1328–1331.
69. Heath SM, Bain RJ, Andrews A, Chida S, Kitchen SI, Walters MI. Nurse initiated thrombolysis in the accident and emergency department: safe, accurate, and faster than fast track. *Emerg Med J*. 2003;20:418–420.
70. Bouten MJ, Simoons ML, Hartman JA, van Miltenburg AJ, van der Does E, Pool J. Prehospital thrombolysis with alteplase (rt-PA) in acute myocardial infarction. *Eur Heart J*. 1992;13:925–931.
71. Kremser AK, Lyneham J. Can Australian nurses safely assess for thrombolysis on EKG criteria? *J Emerg Nurs*. 2007;33:102–109.
72. Wilmshurst P, Purchase A, Webb C, Jowett C, Quinn T. Improving door to needle times with nurse initiated thrombolysis. *Heart*. 2000;84:262–266.
73. Quinn T. Can nurses safely assess suitability for thrombolytic therapy? A pilot study. *Intensive Crit Care Nurs*. 1995;11:126–129.
74. Ioannidis JP, Salem D, Chew PW, Lau J. Accuracy and clinical effect of out-of-hospital electrocardiography in the diagnosis of acute cardiac ischemia: a meta-analysis. *Ann Emerg Med*. 2001;37:461–470.
75. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. The European Myocardial Infarction Project Group. *N Engl J Med*. 1993;329:383–389.
76. Weaver WD, Cerqueira M, Hallstrom AP, Litwin PE, Martin JS, Kudenchuk PJ, Eisenberg M. Prehospital-initiated vs hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. *JAMA*. 1993;270:1211–1216.
77. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA*. 2000;283:2686–2692.
78. Dussoix P, Reuille O, Verin V, Gaspoz JM, Unger PF. Time savings with prehospital thrombolysis in an urban area. *Eur J Emerg Med*. 2003;10:2–5.
79. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. GREAT Group. *BMJ*. 1992;305(6853):548–553.
80. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol*. 1997;30:1181–1186.
81. Rawles J. Halving of mortality at 1 year by domiciliary thrombolysis in the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol*. 1994;23:1–5.
82. Le May MR, So DY, Dionne R, Glover CA, Froeschl MP, Wells GA, Davies RF, Sherrard HL, Maloney J, Marquis JF, O'Brien ER, Trickett

- J, Poirier P, Ryan SC, Ha A, Joseph PG, Labinaz M. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2008;358:231–240.
83. Stenestrand U, Lindback J, Wallentin L. Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. *Jama*. 2006;296:1749–1756.
 84. Le May MR, Davies RF, Dionne R, Maloney J, Trickett J, So D, Ha A, Sherrard H, Glover C, Marquis JF, O'Brien ER, Stiell IG, Poirier P, Labinaz M. Comparison of early mortality of paramedic-diagnosed ST-segment elevation myocardial infarction with immediate transport to a designated primary percutaneous coronary intervention center to that of similar patients transported to the nearest hospital. *Am J Cardiol*. 2006;98:1329–1333.
 85. Bonnefoy E, Steg PG, Boutitie F, Dubien PY, Lapostolle F, Roncalli J, Dissait F, Vanzetto G, Leizorowicz A, Kirkorian G, Mercier C, McFadden EP, Touboul P. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J*. 2009;30:1598–1606.
 86. Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, Cutlip DE, Bates ER, Frederick PD, Miller DP, Carrozza JP Jr, Antman EM, Cannon CP, Gibson CM. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation*. 2006;114:2019–2025.
 87. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, Morrison LJ, Langer A, Dzavik V, Mehta SR, Lazzam C, Schwartz B, Casanova A, Goodman SG. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med*. 2009;360:2705–2718.
 88. Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, Dimopoulos K, Manari A, Gaspardone A, Ochala A, Zmudka K, Bolognese L, Steg PG, Flather M. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet*. 2008;371(9612):559–568.
 89. Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA, Roumanis SA, Curtis JP, Nallamothu BK, Magid DJ, McNamara RL, Parkosewich J, Loeb JM, Krumholz HM. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med*. 2006;355:2308–2320.
 90. Brown JP, Mahmud E, Dunford JV, Ben-Yehuda O. Effect of pre-hospital 12-lead electrocardiogram on activation of the cardiac catheterization laboratory and door-to-balloon time in ST-segment elevation acute myocardial infarction. *Am J Cardiol*. 2008;101:158–161.
 91. Gross BW, Dauterman KW, Moran MG, Kotler TS, Schnugg SJ, Rostykus PS, Ross AM, Weaver WD. An approach to shorten time to infarct artery patency in patients with ST-segment elevation myocardial infarction. *Am J Cardiol*. 2007;99:1360–1363.
 92. van de Loo A, Saubier B, Kalbhenn J, Koberne F, Zehender M. Primary percutaneous coronary intervention in acute myocardial infarction: direct transportation to catheterization laboratory by emergency teams reduces door-to-balloon time. *Clin Cardiol*. 2006;29:112–116.
 93. Bradley EH, Curry LA, Webster TR, Mattera JA, Roumanis SA, Radford MJ, McNamara RL, Barton BA, Berg DN, Krumholz HM. Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. *Circulation*. 2006;113:1079–1085.
 94. Holmboe ES, Bradley EH, Mattera JA, Roumanis SA, Radford MJ, Krumholz HM. Characteristics of physician leaders working to improve the quality of care in acute myocardial infarction. *Jt Comm J Qual Saf*. 2003;29:289–296.
 95. Huang RL, Donelli A, Byrd J, Mickiewicz MA, Slovis C, Roumie C, Elasy TA, Dittus RS, Speroff T, Disalvo T, Zhao D. Using quality improvement methods to improve door-to-balloon time at an academic medical center. *J Invasive Cardiol*. 2008;20:46–52.
 96. Lipton JA, Broce M, Lucas D, Mimmagh K, Matthews A, Reyes B, Burdette J, Wagner GS, Warren SG. Comprehensive hospital care improvement strategies reduce time to treatment in ST-elevation acute myocardial infarction. *Crit Pathw Cardiol*. 2006;5:29–33.
 97. Ward MR, Lo ST, Herity NA, Lee DP, Yeung AC. Effect of audit on door-to-inflation times in primary angioplasty/stenting for acute myocardial infarction. *Am J Cardiol*. 2001;87:336–338, A339.
 98. Krumholz HM, Bradley EH, Nallamothu BK, Ting HH, Batchelor WB, Kline-Rogers E, Stern AF, Byrd JR, Brush JE Jr. A campaign to improve the timeliness of primary percutaneous coronary intervention: Door-to-Balloon: An Alliance for Quality. *J Am Coll Cardiol Cardiovasc Interv*. 2008;1:97–104.
 99. Bradley EH, Roumanis SA, Radford MJ, Webster TR, McNamara RL, Mattera JA, Barton BA, Berg DN, Portnay EL, Moscovitz H, Parkosewich J, Holmboe ES, Blaney M, Krumholz HM. Achieving door-to-balloon times that meet quality guidelines: how do successful hospitals do it? *J Am Coll Cardiol*. 2005;46:1236–1241.
 100. Jacoby J, Axelband J, Patterson J, Belletti D, Heller M. Cardiac cath lab activation by the emergency physician without prior consultation decreases door-to-balloon time. *J Invasive Cardiol*. 2005;17:154–155.
 101. Khot UN, Johnson ML, Ramsey C, Khot MB, Todd R, Shaikh SR, Berg WJ. Emergency department physician activation of the catheterization laboratory and immediate transfer to an immediately available catheterization laboratory reduce door-to-balloon time in ST-elevation myocardial infarction. *Circulation*. 2007;116:67–76.
 102. Kraft PL, Newman S, Hanson D, Anderson W, Bastani A. Emergency physician discretion to activate the cardiac catheterization team decreases door-to-balloon time for acute ST-elevation myocardial infarction. *Ann Emerg Med*. 2007;50:520–526.
 103. Kurz MC, Babcock C, Sinha S, Tupesis JP, Allegritti J. The impact of emergency physician-initiated primary percutaneous coronary intervention on mean door-to-balloon time in patients with ST-segment-elevation myocardial infarction. *Ann Emerg Med*. 2007;50:527–534.
 104. Lee CH, Ooi SB, Tay EL, Low AF, Teo SG, Lau C, Tai BC, Lim I, Lam S, Lim IH, Chai P, Tan HC. Shortening of median door-to-balloon time in primary percutaneous coronary intervention in Singapore by simple and inexpensive operational measures: clinical practice improvement program. *J Interv Cardiol*. 2008;21:414–423.
 105. Singer AJ, Shembekar A, Visram F, Schiller J, Russo V, Lawson W, Gomes CA, Santora C, Maliszewski M, Wilbert L, Dowdy E, Viccellio P, Henry MC. Emergency department activation of an interventional cardiology team reduces door-to-balloon times in ST-segment-elevation myocardial infarction. *Ann Emerg Med*. 2007;50:538–544.
 106. Thatcher JL, Gilseth TA, Adlis S. Improved efficiency in acute myocardial infarction care through commitment to emergency department-initiated primary PCI. *J Invasive Cardiol*. 2003;15:693–698.
 107. Zarich SW, Sachdeva R, Fishman R, Werdmann MJ, Parniowski M, Bernstein L, Dilella M. Effectiveness of a multidisciplinary quality improvement initiative in reducing door-to-balloon times in primary angioplasty. *J Interv Cardiol*. 2004;17:191–195.
 108. Emergency department: rapid identification and treatment of patients with acute myocardial infarction. National Heart Attack Alert Program Coordinating Committee, 60 Minutes to Treatment Working Group. *Ann Emerg Med*. 1994;23:311–329.
 109. Lambrew CT, Bowlby LJ, Rogers WJ, Chandra NC, Weaver WD. Factors influencing the time to thrombolysis in acute myocardial infarction. Time to Thrombolysis Substudy of the National Registry of Myocardial Infarction-1. *Arch Intern Med*. 1997;157:2577–2582.
 110. Bleeker JK, Simoons ML, Erdman RA, Leenders CM, Kruyssen HA, Lamers LM, van der Does E. Patient and doctor delay in acute myocardial infarction: a study in Rotterdam, The Netherlands. *Br J Gen Pract*. 1995;45(393):181–184.
 111. Goldberg RJ, McGovern PG, Guggina T, Savageau J, Rosamond WD, Luepker RV. Prehospital delay in patients with acute coronary heart disease: concordance between patient interviews and medical records. *Am Heart J*. 135(pt 1):293–299, 1998.
 112. McSweeney JC, Cody M, O'Sullivan P, Elberson K, Moser DK, Garvin BJ. Women's early warning symptoms of acute myocardial infarction. *Circulation*. 2003;108:2619–2623.
 113. Wagner GS, Macfarlane P, Wellens H, Josephson M, Gorgels A, Mirvis DM, Pahlm O, Surawicz B, Kligfield P, Childers R, Gettes LS, Bailey JJ, Deal BJ, Gorgels A, Hancock EW, Kors JA, Mason JW, Okin P, Rautaharju PM, van Herpen G. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction: a scientific statement from the Am Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the Am College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *Journal of the Am College of Cardiology*. 2009;53:1003–1011.
 114. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342–1349.

115. Svensson L, Axelsson C, Nordlander R, Herlitz J. Elevation of biochemical markers for myocardial damage prior to hospital admission in patients with acute chest pain or other symptoms raising suspicion of acute coronary syndrome. *J Intern Med.* 2003;253:311–319.
116. Gust R, Gust A, Bottiger BW, Bohrer H, Martin E. Bedside troponin T testing is not useful for early out-of-hospital diagnosis of myocardial infarction. *Acta Anaesthesiol Scand.* 1998;42:414–417.
117. Newman J, Aulick N, Cheng T, Faynor S, Curtis R, Mercer D, Williams J, Hobbs G. Prehospital identification of acute coronary ischemia using a troponin T rapid assay. *Prehosp Emerg Care.* 1999;3:97–101.
118. Svensson L, Axelsson C, Nordlander R, Herlitz J. Prognostic value of biochemical markers, 12-lead ECG and patient characteristics amongst patients calling for an ambulance due to a suspected acute coronary syndrome. *J Intern Med.* 2004;255:469–477.
119. Schuchert A, Hamm C, Scholz J, Klimmeck S, Goldmann B, Meinertz T. Prehospital testing for troponin T in patients with suspected acute myocardial infarction. *Am Heart J.* 1999;138(1 Pt 1):45–48.
120. Tanaka K, Seino Y, Ohbayashi K, Takano T. Cardiac emergency triage and therapeutic decisions using whole blood rapid troponin T test for patients with suspicious acute coronary syndrome. *Jpn Circ J.* 2001;65:424–428.
121. Al-Mubarak N, Rogers WJ, Lambrew CT, Bowlby LJ, French WJ. Consultation before thrombolytic therapy in acute myocardial infarction. Second National Registry of Myocardial Infarction (NORMI 2) Investigators. *The Am journal of cardiology.* 1999;83:89–93, A88.
122. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the Am College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol.* 2002;40:1366–1374.
123. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the Am College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation.* 2002;106:1893–1900.
124. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, III, Steward DE, Theroux P, Alpert JS, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the Am College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol.* 2000;36:970–1062.
125. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation.* 1994;89:1545–1556.
126. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, Legako RD, Leon DF, Murray JA, Nissen SE, Pepine CJ, Watson RM, Ritchie JL, Gibbons RJ, Cheitlin MD, Gardner TJ, Garson A Jr, Russell RO Jr, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the Am College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation.* 1999;99:2345–2357.
127. King SB, III, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO, Feldman TE, Kern MJ, O'Neill WW, Schaff HV, Whitlow PL, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the Am College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation.* 2008;117:261–295.
128. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Journal of the Am College of Cardiology.* 2000;36:959–969.
129. Pollack CV Jr, Sites FD, Shofer FS, Sease KL, Hollander JE. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population. *Acad Emerg Med.* 2006;13:13–18.
130. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835–842.
131. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation.* 2000;101:2557–2567.
132. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Predictors of hospital mortality in the global registry of acute coronary events. *Archives of internal medicine.* 2003;163:2345–2353.
133. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KAA, for the GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA.* 2004;291:2727–2733.
134. Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation. British Cardiac Society Guidelines and Medical Practice Committee and Royal College of Physicians Clinical Effectiveness and Evaluation Unit. *Heart.* 2001;85:133–142.
135. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. Am College of Emergency Physicians. *Ann Emerg Med.* 2000;35:521–525.
136. Doukky R, Calvin JE. Risk stratification in patients with unstable angina and non-ST segment elevation myocardial infarction: evidence-based review. *J Invasive Cardiol.* 2002;14:215–220.
137. Doukky R, Calvin JE. Part II: risk stratification in patients with unstable angina and non-ST segment elevation myocardial infarction: evidence-based review. *The Journal of Invasive Cardiology.* 2002;14:254–262.
138. Braunwald E, Jones RH, Mark DB, Brown J, Brown L, Cheitlin MD, Concannon CA, Cowan M, Edwards C, Fuster V, et al. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation.* 1994;90:613–622.
139. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)—executive summary: a report of the Am College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation.* 2001;103:3019–3041.
140. Farkouh ME, Smars PA, Reeder GS, Zinsmeister AR, Evans RW, Meloy TD, Kopecky SL, Allen M, Allison TG, Gibbons RJ, Gabriel SE. A clinical trial of a chest-pain observation unit for patients with unstable angina. Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. *N Engl J Med.* 1998;339:1882–1888.
141. Udelson JE, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Handler J, Heller GV, Hendel RC, Pope JH, Ruthazer R, Spiegel EJ, Woolard RH, Selker HP. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA.* 2002;288:2693–2700.

142. Bedetti G, Pasanisi EM, Tintori G, Fonseca L, Tresoldi S, Minneci C, Jambrik Z, Ghelarducci B, Orlandini A, Picano E. Stress echo in chest pain unit: the SPEED trial. *International journal of cardiology*. 2005; 102:461–467.
143. Caragher TE, Fernandez BB, Barr LA. Long-term experience with an accelerated protocol for diagnosis of chest pain. *Archives of pathology & laboratory medicine*. 2000;124:1434–1439.
144. deFilippi CR, Rosanio S, Tocchi M, Parmar RJ, Potter MA, Uretsky BF, Runge MS. Randomized comparison of a strategy of pre-discharge coronary angiography versus exercise testing in low-risk patients in a chest pain unit: in-hospital and long-term outcomes. *Journal of the American College of Cardiology*. 2001;37:2042–2049.
145. Gomez MA, Anderson JL, Karagounis LA, Muhlestein JB, Mooers FB. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). *J Am Coll Cardiol*. 1996;28:25–33.
146. Lee TH, Juarez G, Cook EF, Weisberg MC, Rouan GW, Brand DA, Goldman L. Ruling out acute myocardial infarction. A prospective multicenter validation of a 12-hour strategy for patients at low risk. *N Engl J Med*. 1991;324:1239–1246.
147. Nucifora G, Badano LP, Sarraf-Zadegan N, Karavidas A, Trocino G, Scaffidi G, Pettinati G, Astarita C, Vysniauskas V, Gregori D, Ilerigelen B, Fioretti PM. Effect on quality of life of different accelerated diagnostic protocols for management of patients presenting to the emergency department with acute chest pain. *The American journal of cardiology*. 2009; 103:592–597.
148. Ramakrishna G, Milavetz JJ, Zinsmeister AR, Farkouh ME, Evans RW, Allison TG, Smars PA, Gibbons RJ. Effect of exercise treadmill testing and stress imaging on the triage of patients with chest pain: CHEER substudy. *Mayo Clinic proceedings*. 2005;80:322–329.
149. Roberts RR, Zalenski RJ, Mensah EK, Rydman RJ, Ciavarella G, Gussow L, Das K, Kampe LM, Dickover B, McDermott MF, Hart A, Straus HE, Murphy DG, Rao R. Costs of an emergency department-based accelerated diagnostic protocol vs hospitalization in patients with chest pain: a randomized controlled trial. *JAMA*. 1997; 278:1670–1676.
150. Zalenski RJ, McCarren M, Roberts R, Rydman RJ, Jovanovic B, Das K, Mendez J, el-Khadra M, Fraker L, McDermott M. An evaluation of a chest pain diagnostic protocol to exclude acute cardiac ischemia in the emergency department. *Archives of internal medicine*. 1997;157: 1085–1091.
151. Paventi S, Parafati MA, Luzio ED, Pellegrino CA. Usefulness of two-dimensional echocardiography and myocardial perfusion imaging for immediate evaluation of chest pain in the emergency department. *Resuscitation*. 2001;49:47–51.
152. Conti A, Sammiceli L, Gallini C, Costanzo EN, Antonucci D, Barletta G. Assessment of patients with low-risk chest pain in the emergency department: Head-to-head comparison of exercise stress echocardiography and exercise myocardial SPECT. *Am Heart J*. 2005;149:894–901.
153. Gallagher MJ, Ross MA, Raff GL, Goldstein JA, O'Neil WW, O'Neil B. The diagnostic accuracy of 64-slice computed tomography coronary angiography compared with stress nuclear imaging in emergency department low-risk chest pain patients. *Ann Emerg Med*. 2007;49: 125–136.
154. Forberg JL, Hilmersson CE, Carlsson M, Arheden H, Bjork J, Hjalte K, Ekelund U. Negative predictive value and potential cost savings of acute nuclear myocardial perfusion imaging in low risk patients with suspected acute coronary syndrome: a prospective single blinded study. *BMC Emerg Med*. 2009;9:12.
155. Athappan G, Habib M, Ponniah T, Jeyaseelan L. Multi-detector computerized tomography angiography for evaluation of acute chest pain - A meta analysis and systematic review of literature. *Int J Cardiol*. 2009.
156. Vanhoenacker PK, Decramer I, Bladt O, Sarno G, Bevernage C, Wijns W. Detection of non-ST-elevation myocardial infarction and unstable angina in the acute setting: meta-analysis of diagnostic performance of multi-detector computer tomographic angiography. *BMC Cardiovasc Disord*. 2007;7:39.
157. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, Truong QA, Cury RC, Abbara S, Shapiro MD, Moloo J, Butler J, Ferencik M, Lee H, Jang IK, Parry BA, Brown DF, Udelsom JE, Achenbach S, Brady TJ, Nagurny JT. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol*. 2009;53:1642–1650.
158. Hollander JE, Litt HI, Chase M, Brown AM, Kim W, Baxt WG. Computed tomography coronary angiography for rapid disposition of low-risk emergency department patients with chest pain syndromes. *Acad Emerg Med*. 2007;14:112–116.
159. Goldstein JA, Gallagher MJ, O'Neil WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol*. 2007;49:863–871.
160. Hess EP, Thiruganasambandamoorthy V, Wells GA, Erwin P, Jaffe AS, Hollander JE, Montori VM, Stiell IG. Diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome in the emergency department setting: a systematic review. *Cjem*. 2008;10:373–382.
161. Hamm CW, Goldmann BU, Heeschen C, Kreyman G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med*. 1997;337:1648–1653.
162. Lai C, Noeller TP, Schmidt K, King P, Emerman CL. Short-term risk after initial observation for chest pain. *J Emerg Med*. 2003;25:357–362.
163. Marsan RJ Jr, Shaver KJ, Sease KL, Shofer FS, Sites FD, Hollander JE. Evaluation of a clinical decision rule for young adult patients with chest pain. *Acad Emerg Med*. 2005;12:26–31.
164. Christenson J, Innes G, McKnight D, Thompson CR, Wong H, Yu E, Boychuk B, Grafstein E, Rosenberg F, Gin K, Anis A, Singer J. A clinical prediction rule for early discharge of patients with chest pain. *Ann Emerg Med*. 2006;47:1–10.
165. Challa PK, Smith KM, Conti CR. Initial presenting electrocardiogram as determinant for hospital admission in patients presenting to the emergency department with chest pain: a pilot investigation. *Clin Cardiol*. 2007;30:558–561.
166. Schillinger M, Sodeck G, Meron G, Janata K, Nikfardjam M, Rauscha F, Laggner AN, Domanovits H. Acute chest pain—identification of patients at low risk for coronary events. The impact of symptoms, medical history and risk factors. *Wien Klin Wochenschr*. 2004;116: 83–89.
167. Bassan R, Pimenta L, Scofano M, Gamarski R, Volschan A. Probability stratification and systematic diagnostic approach for chest pain patients in the emergency department. *Crit Pathw Cardiol*. 2004;3:1–7.
168. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation*. 1975;52:360–368.
169. Ribeiro LG, Louie EK, Davis MA, Maroko PR. Augmentation of collateral blood flow to the ischaemic myocardium by oxygen inhalation following experimental coronary artery occlusion. *Cardiovasc Res*. 1979;13:160–166.
170. Kelly RF, Hursley TL, Parrillo JE, Schaer GL. Effect of 100% oxygen administration on infarct size and left ventricular function in a canine model of myocardial infarction and reperfusion. *Am Heart J*. 1995;130: 957–965.
171. Ishikawa K, Kanamasa K, Yamakado T, Katori R. The beneficial effects of 40% and 100% O₂ inhalations on acutely-induced myocardial ischemia in dogs. *The Tohoku journal of experimental medicine*. 1986;149: 107–117.
172. Madias JE, Hood WB Jr. Reduction of precordial ST-segment elevation in patients with anterior myocardial infarction by oxygen breathing. *Circulation*. 1976;53(3 Suppl):I198–I200.
173. Rawles JM, Kenmore AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *BMJ*. 1976;1(6018):1121–1123.
174. Wilson AT, Channer KS. Hypoxaemia and supplemental oxygen therapy in the first 24 hours after myocardial infarction: the role of pulse oximetry. *J R Coll Physicians Lond*. 1997;31:657–661.
175. Gurfinkel EP, Manos EJ, Mejail RI, Cerda MA, Duronto EA, Garcia CN, Daroca AM, Mautner B. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol*. 1995;26:313–318.
176. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71–86.
177. Collaborative overview of randomised trials of antiplatelet therapy—II: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308(6921):81–106.
178. Feldman M, Cryer B. Aspirin absorption rates and platelet inhibition times with 325-mg buffered aspirin tablets (chewed or swallowed intact) and with buffered aspirin solution. *Am J Cardiol*. 1999;84:404–409.

179. Sagar KA, Smyth MR. A comparative bioavailability study of different aspirin formulations using on-line multidimensional chromatography. *J Pharm Biomed Anal.* 1999;21:383–392.
180. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *Jama.* 2006;296:1633–1644.
181. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ (Clinical research ed.)* 2006;332(7553):1302–1308.
182. Gibson IR, Bonfield W. Novel synthesis and characterization of an AB-type carbonate-substituted hydroxyapatite. *J Biomed Mater Res.* 2003;59:697–708.
183. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet.* 1995;345(8951):669–685.
184. Diercks DB, Boghos E, Guzman H, Amsterdam EA, Kirk JD. Changes in the numeric descriptive scale for pain after sublingual nitroglycerin do not predict cardiac etiology of chest pain. *Annals of emergency medicine.* 2005;45:581–585.
185. Henrikson CA, Howell EE, Bush DE, Miles JS, Meininger GR, Friedlander T, Bushnell AC, Chandra-Strobus N. Chest pain relief by nitroglycerin does not predict active coronary artery disease. *Ann Intern Med.* 2003;139:979–986.
186. Steele R, McNaughton T, McConahy M, Lam J. Chest pain in emergency department patients: if the pain is relieved by nitroglycerin, is it more likely to be cardiac chest pain? *CJEM.* 2006;8:164–169.
187. Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Bmj.* 1998;316(7141):1337–1343.
188. Franzosi MG, Santoro E, De Vita C, Geraci E, Lotto A, Maggioni AP, Mauri F, Rovelli F, Santoro L, Tavazzi L, Tognoni G. Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-I study. The GISSI Investigators. *Circulation.* 1998;98:2659–2665.
189. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361(9351):13–20.
190. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet.* 1994;343(8893):311–322.
191. A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med.* 1997;337:1118–1123.
192. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. *Lancet.* 1999;354(9180):716–722.
193. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet.* 1986;1(8478):397–402.
194. Brodie BR, Stuckey TD, Kissling G, Hansen CJ, Weintraub RA, Kelly TA. Importance of infarct-related artery patency for recovery of left ventricular function and late survival after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol.* 1996;28:319–325.
195. Puma JA, Sketch MHJ, Thompson TD, Simes RJ, Morris DC, White HD, Topol EJ, Califf RM. Support for the open-artery hypothesis in survivors of acute myocardial infarction: analysis of 11,228 patients treated with thrombolytic therapy. *Am J Cardiol.* 1999;83:482–487.
196. de Lemos JA, Antman EM, Gibson CM, McCabe CH, Giugliano RP, Murphy SA, Coulter SA, Anderson K, Scherer J, Frey MJ, Van Der Wieken R, Van De Werf F, Braunwald E. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction: observations from the TIMI 14 trial. *Circulation.* 2000;101:239–243.
197. Claeys MJ, Bosmans J, Veenstra L, Jorens P, De R, Vrints CJ. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction: importance of microvascular reperfusion injury on clinical outcome. *Circulation.* 1999;99:1972–1977.
198. Gibson CM, Murphy SA, Rizzo MJ, Ryan KA, Marble SJ, McCabe CH, Cannon CP, Van de Werf F, Braunwald E. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. *Circulation.* 1999;99:1945–1950.
199. Brouwer MA, Martin JS, Maynard C, Wirkus M, Litwin PE, Verheugt FW, Weaver WD. Influence of early prehospital thrombolysis on mortality and event-free survival (the Myocardial Infarction Triage and Intervention [MITI] Randomized Trial). MITI Project Investigators. *Am J Cardiol.* 1996;78:497–502.
200. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med.* 1993;329:673–682.
201. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) Collaborative Group. *Lancet.* 1993;342(8874):767–772.
202. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet.* 1993;342(8874):759–766.
203. Hillis LD, Forman S, Braunwald E. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction. The Thrombolysis in Myocardial Infarction (TIMI) Phase II Co-Investigators. *J Am Coll Cardiol.* 1990;16:313–315.
204. Simoons ML, Maggioni AP, Knatterud G, Leimberger JD, de Jaegere P, van Domburg R, Boersma E, Franzosi MG, Califf R, Schroder R, et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet.* 1993;342(8886–8887):1523–1528.
205. Mahaffey KW, Granger CB, Sloan MA, Thompson TD, Gore JM, Weaver WD, White HD, Simoons ML, Barbash GI, Topol EJ, Califf RM. Risk factors for in-hospital nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolysis: results from GUSTO-I. *Circulation.* 1998;97:757–764.
206. Gore JM, Granger CB, Simoons ML, Sloan MA, Weaver WD, White HD, Barbash GI, Van de Werf F, Aylward PE, Topol EJ, et al. Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation.* 1995;92:2811–2818.
207. White HD, Barbash GI, Califf RM, Simes RJ, Granger CB, Weaver WD, Kleiman NS, Aylward PE, Gore JM, Vahanian A, Lee KL, Ross AM, Topol EJ. Age and outcome with contemporary thrombolytic therapy. Results from the GUSTO-I trial. Global Utilization of Streptokinase and TPA for Occluded coronary arteries trial. *Circulation.* 1996;94:1826–1833.
208. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation.* 2000;101:2239–2246.
209. Collins R, Peto R, Parish S, Sleight P. ISIS-3 and GISSI-2: no survival advantage with tissue plasminogen activator over streptokinase, but a significant excess of strokes with tissue plasminogen activator in both trials. *Am J Cardiol.* 1993;71:1127–1130.
210. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet.* 1998;352(9122):87–92.
211. Selker HP, Griffith JL, D'Agostino RB. A tool for judging coronary care unit admission appropriateness, valid for both real-time and retrospective use. A time-insensitive predictive instrument (TIPI) for acute cardiac ischemia: a multicenter study. *Med Care.* 1991;29:610–627.
212. Magid DJ, Calonge BN, Rumsfeld JS, Canto JG, Frederick PD, Every NR, Barron HV. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA.* 2000;284:3131–3138.
213. Canto JG, Every NR, Magid DJ, Rogers WJ, Malmgren JA, Frederick PD, French WJ, Tiefenbrunn AJ, Misra VK, Kiefe CI, Barron HV. The volume of primary angioplasty procedures and survival after acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *N Engl J Med.* 2000;342:1573–1580.

214. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation*. 2003;108:1809–1814.
215. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300:1423–1431.
216. Nichol G, Aufderheide TP, Eigel B, Neumar RW, Lurie KG, Bufalino VJ, Callaway CW, Menon V, Bass RR, Abella BS, Sayre M, Dougherty CM, Racht EM, Kleinman ME, O'Connor RE, Reilly JP, O'Smann EW, Peterson E. Regional systems of care for out-of-hospital cardiac arrest: A policy statement from the Am Heart Association. *Circulation*. 2010;121:709–729.
217. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, Carli P. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;336:1629–1633.
218. Abu-Laban RB, Christenson JM, Innes GD, van Beek CA, Wanger KP, McKnight RD, MacPhail IA, Puskaric J, Sadowski RP, Singer J, Schechter MT, Wood VM. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. *N Engl J Med*. 2002;346:1522–1528.
219. Bottiger BW, Arntz HR, Chamberlain DA, Bluhmki E, Belmans A, Danays T, Carli PA, Adgey JA, Bode C, Wenzel V. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med*. 2008;359:2651–2662.
220. Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73:29–39.
221. Bendz B, Eritsland J, Nakstad AR, Brekke M, Klow NE, Steen PA, Mangschau A. Long-term prognosis after out-of-hospital cardiac arrest and primary percutaneous coronary intervention. *Resuscitation*. 2004;63:49–53.
222. Engdahl J, Abrahamsson P, Bang A, Lindqvist J, Karlsson T, Herlitz J. Is hospital care of major importance for outcome after out-of-hospital cardiac arrest? Experience acquired from patients with out-of-hospital cardiac arrest resuscitated by the same Emergency Medical Service and admitted to one of two hospitals over a 16-year period in the municipality of Goteborg. *Resuscitation*. 2000;43:201–211.
223. Gorjup V, Radsel P, Kocjancic ST, Erzen D, Noc M. Acute ST-elevation myocardial infarction after successful cardiopulmonary resuscitation. *Resuscitation*. 2007;72:379–385.
224. Garot P, Lefevre T, Eltchaninoff H, Morice MC, Tamion F, Abry B, Lesault PF, Le Tarnec JY, Pougès C, Margenet A, Monchi M, Laurent I, Dumas P, Garot J, Louvard Y. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation*. 2007;115:1354–1362.
225. Lettieri C, Savonitto S, De Servi S, Guagliumi G, Belli G, Repetto A, Piccaluga E, Politi A, Ettori F, Castiglioni B, Fabbiochi F, De Cesare N, Sangiorgi G, Musumeci G, Onofri M, D'Urbano M, Pirelli S, Zanini R, Klugmann S. Emergency percutaneous coronary intervention in patients with ST-elevation myocardial infarction complicated by out-of-hospital cardiac arrest: early and medium-term outcome. *Am Heart J*. 2009;157:569–575 e561.
226. Kahn JK, Glazier S, Swor R, Savas V, O'Neill WW. Primary coronary angioplasty for acute myocardial infarction complicated by out-of-hospital cardiac arrest. *The Am journal of cardiology*. 1995;75:1069–1070.
227. Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation*. 2007;74:227–234.
228. Marcusohn E, Roguin A, Sebbag A, Aronson D, Dragu R, Amikam S, Boulus M, Grenadier E, Kerner A, Nikolsky E, Markiewicz W, Hammerman H, Kapeliovich M. Primary percutaneous coronary intervention after out-of-hospital cardiac arrest: patients and outcomes. *Isr Med Assoc J*. 2007;9:257–259.
229. McCullough PA, Prakash R, Tobin KJ, O'Neill WW, Thompson RJ. Application of a cardiac arrest score in patients with sudden death and ST segment elevation for triage to angiography and intervention. *J Interv Cardiol*. 2002;15:257–261.
230. Nagao K, Hayashi N, Kanmatsuse K, Arima K, Ohtsuki J, Kikushima K, Watanabe I. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. *J Am Coll Cardiol*. 2000;36:776–783.
231. Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, Valskov F, Wanscher M, Friberg H. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand*. 2009;53:926–934.
232. Peels HO, Jessurun GA, van der Horst IC, Arnold AE, Piers LH, Zijlstra F. Outcome in transferred and nontransferred patients after primary percutaneous coronary intervention for ischaemic out-of-hospital cardiac arrest. *Catheter Cardiovasc Interv*. 2008;71:147–151.
233. Pleskot M, Babu A, Hazukova R, Stritecky J, Bis J, Matejka J, Cermakova E. Out-of-hospital cardiac arrests in patients with acute ST elevation myocardial infarctions in the East Bohemian region over the period 2002–2004. *Cardiology*. 2008;109:41–51.
234. Quintero-Moran B, Moreno R, Villarreal S, Perez-Vizcayno MJ, Hernandez R, Conde C, Vazquez P, Alfonso F, Banuelos C, Escaned J, Fernandez-Ortiz A, Azcona L, Macaya C. Percutaneous coronary intervention for cardiac arrest secondary to ST-elevation acute myocardial infarction. Influence of immediate paramedical/medical assistance on clinical outcome. *J Invasive Cardiol*. 2006;18:269–272.
235. Reynolds JC, Callaway CW, El Khoudary SR, Moore CG, Alvarez RJ, Rittenberger JC. Coronary angiography predicts improved outcome following cardiac arrest: propensity-adjusted analysis. *J Intensive Care Med*. 2009;24:179–186.
236. Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, Royle P, Davidson P, Vale L, MacKenzie L. Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation. *Health Technol Assess*. 2005;9:1–99, iii–iv.
237. Peterson LR, Chandra NC, French WJ, Rogers WJ, Weaver WD, Tiefenbrunn AJ. Reperfusion therapy in patients with acute myocardial infarction and prior coronary artery bypass graft surgery (National Registry of Myocardial Infarction-2). *Am J Cardiol*. 1999;84:1287–1291.
238. Dragu R, Behar S, Sandach A, Boyko V, Kapeliovich M, Rispler S, Hammerman H. Should primary percutaneous coronary intervention be the preferred method of reperfusion therapy for patients with renal failure and ST-elevation acute myocardial infarction? *Am J Cardiol*. 2006;97:1142–1145.
239. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thyssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med*. 2003;349:733–742.
240. Scott I, Chan J, Aroney C, Carroll G. Local thrombolysis or rapid transfer for primary angioplasty for patients presenting with ST segment elevation myocardial infarction to hospitals without angioplasty facilities. *Internal medicine journal*. 2004;34:373–377.
241. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med*. 1999;341:625–634.
242. Kent DM, Ruthazer R, Griffith JL, Beshansky JR, Grines CL, Aversano T, Concannon TW, Zalenski RJ, Selker HP. Comparison of mortality benefit of immediate thrombolytic therapy versus delayed primary angioplasty for acute myocardial infarction. *Am J Cardiol*. 2007;99:1384–1388.
243. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol*. 2003;92:824–826.
- 243a. Betriu A, Masotti M. Comparison of mortality rates in acute myocardial infarction treated by percutaneous coronary intervention versus fibrinolysis. *Am J Cardiol*. 2005;95:100–101.
- 243b. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J*. 2006;27:779–788.
- 243c. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kasrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera

- M, Widimsky P, Zamorano JL, Silber S, Aguirre FV, Al-Attar N, Alegria E, Andreotti F, Benzer W, Breithardt O, Danchin N, Di Mario C, Dudek D, Gulba D, Halvorsen S, Kaufmann P, Kornowski R, Lip GY, Rutten F. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2008;29:2909-2945.
- 243d. Nallamothu B, Fox KA, Kannelly BM, Van de Werf F, Gore JM, Steg PG, Granger CB, Dabbous OH, Kline-Rogers E, Eagle KA. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart (British Cardiac Society)*. 2007;93:1552-1555.
244. Holmes DR Jr, Bates ER, Kleiman NS, Sadowski Z, Horgan JH, Morris DC, Califf RM, Berger PB, Topol EJ. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1995;26:668-674.
245. Babaev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *Jama*. 2005;294:448-454.
246. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation*. 2009;119:1211-1219.
247. Hochman JS, Sleeper LA, Webb JG, Dzavik V, Buller CE, Aylward P, Col J, White HD. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *Jama*. 2006;295:2511-2515.
248. Singh M, White J, Hasdai D, Hodgson PK, Berger PB, Topol EJ, Califf RM, Holmes DR Jr. Long-term outcome and its predictors among patients with ST-segment elevation myocardial infarction complicated by shock: insights from the GUSTO-I trial. *J Am Coll Cardiol*. 2007;50:1752-1758.
249. Sleeper LA, Ramanathan K, Picard MH, Lejemtel TH, White HD, Dzavik V, Tormey D, Avis NE, Hochman JS. Functional status and quality of life after emergency revascularization for cardiogenic shock complicating acute myocardial infarction. *J Am Coll Cardiol*. 2005;46:266-273.
250. Califf RM, Bengtson JR. Cardiogenic shock. *N Engl J Med*. 1994;330:1724-1730.
251. Zehender M, Kasper W, Kauder E, Schonthalner M, Geibel A, Olschewski M, Just H. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med*. 1993;328:981-988.
252. Berger PB, Ruocco NA Jr, Ryan TJ, Jacobs AK, Zaret BL, Wackers FJ, Frederick MM, Faxon DP. Frequency and significance of right ventricular dysfunction during inferior wall left ventricular myocardial infarction treated with thrombolytic therapy (results from the thrombolysis in myocardial infarction [TIMI] II trial). The TIMI Research Group. *Am J Cardiol*. 1993;71:1148-1152.
253. Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation*. 1990;82:359-368.
254. Alexander D, Ou FS, Roe MT, Pollack CV Jr, Ohman EM, Cannon CP, Gibler WB, Fintel DJ, Peterson ED, Brown DL. Use of and in-hospital outcomes after early clopidogrel therapy in patients not undergoing an early invasive strategy for treatment of non-ST-segment elevation myocardial infarction: results from Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the Am College of Cardiology/Am Heart Association guidelines (CRUSADE). *Am Heart J*. 2008;156:606-612.
255. Chan AW, Moliterno DJ, Berger PB, Stone GW, DiBattiste PM, Yakubov SL, Sapp SK, Wolski K, Bhatt DL, Topol EJ. Triple antiplatelet therapy during percutaneous coronary intervention is associated with improved outcomes including one-year survival: results from the Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial (TARGET). *J Am Coll Cardiol*. 2003;42:1188-1195.
256. Zeymer U, Gitt AK, Zahn R, Junger C, Bauer T, Koth O, Heer T, Wienbergen H, Gottwik M, Senges J. Clopidogrel in addition to aspirin reduces one-year major adverse cardiac and cerebrovascular events in unselected patients with non-ST segment elevation myocardial infarction. *Acute Card Care*. 2008;10:43-48.
257. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation*. 2004;110:1202-1208.
258. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-2420.
259. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
260. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352:1179-1189.
261. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Lewis BS, Murphy SA, McCabe CH, Braunwald E. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA*. 2005;294:1224-1232.
262. Verheugt FW, Montalescot G, Sabatine MS, Soulat L, Lambert Y, Lapostolle F, Adgey J, Cannon CP. Prehospital fibrinolysis with dual antiplatelet therapy in ST-elevation acute myocardial infarction: a substudy of the randomized double blind CLARITY-TIMI 28 trial. *J Thromb Thrombolysis*. 2007;23:173-179.
263. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607-1621.
264. Zeymer U, Gitt A, Junger C, Bauer T, Heer T, Koeth O, Mark B, Zahn R, Senges J, Gottwik M. Clopidogrel in addition to aspirin reduces in-hospital major cardiac and cerebrovascular events in unselected patients with acute ST segment elevation myocardial. *Thromb Haemost*. 2008;99:155-160.
265. Zeymer U, Gitt AK, Junger C, Heer T, Wienbergen H, Koeth O, Bauer T, Mark B, Zahn R, Gottwik M, Senges J. Effect of clopidogrel on 1-year mortality in hospital survivors of acute ST-segment elevation myocardial infarction in clinical practice. *Eur Heart J*. 2006;27:2661-2666.
266. Lev EI, Kornowski R, Vaknin-Assa H, Brosh D, Fuchs S, Battler A, Assali A. Effect of clopidogrel pretreatment on angiographic and clinical outcomes in patients undergoing primary percutaneous coronary intervention for ST-elevation acute myocardial infarction. *Am J Cardiol*. 2008;101:435-439.
267. Vlaar PJ, Svilaas T, Damman K, de Smet BJ, Tijssen JG, Hillege HL, Zijlstra F. Impact of pretreatment with clopidogrel on initial patency and outcome in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review. *Circulation*. 2008;118:1828-1836.
268. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.
269. Antman EM, Wiviott SD, Murphy SA, Voitek J, Hasin Y, Widimsky P, Chandna H, Macias W, McCabe CH, Braunwald E. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol*. 2008;51:2028-2033.
270. Murphy SA, Antman EM, Wiviott SD, Weerakkody G, Morocutti G, Huber K, Lopez-Sendon J, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. *Eur Heart J*. 2008;29:2473-2479.
271. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, Goodman SG, Corbalan R, Purdy DA, Murphy SA, McCabe CH, Antman EM. Greater clinical benefit of more intensive oral antiplatelet

- therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation*. 2008;118:1626–1636.
272. Wiviott SD, Antman EM, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, Carney RJ, Lazzam C, McKay RG, McCabe CH, Braunwald E. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y₁₂ antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. *Circulation*. 2005;111:3366–3373.
 273. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373(9665):723–731.
 274. Wiviott SD, Braunwald E, McCabe CH, Horvath I, Keltai M, Herrman JP, Van de Werf F, Downey WE, Scirica BM, Murphy SA, Antman EM. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet*. 2008;371(9621):1353–1363.
 275. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet*. 2002;359:189–198.
 276. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med*. 1998;338:1488–1497.
 277. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med*. 1998;339:436–443.
 278. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet*. May 17 1997;349:1429–1435.
 279. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;34:1879–1887.
 280. Stone GW, Ware JH, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, White HD, Feit F, Colombo A, McLaurin BT, Cox DA, Manoukian SV, Fahy M, Clayton TC, Mehran R, Pocock SJ. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA*. 2007;298:2497–2506.
 281. Giugliano RP, White JA, Bode C, Armstrong PW, Montalescot G, Lewis BS, van't Hof A, Berdan LG, Lee KL, Strony JT, Hildemann S, Veltri E, Van de Werf F, Braunwald E, Harrington RA, Califf RM, Newby LK. Early versus delayed, provisional eptifibatid in acute coronary syndromes. *N Engl J Med*. 2009;360:2176–2190.
 282. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med*. 1998;338:1498–1505.
 283. Hamm CW, Heeschen C, Goldmann B, Vahanian A, Adgey J, Miguel CM, Rutsch W, Berger J, Koostra J, Simoons ML. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med*. 1999;340:1623–1629.
 284. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet*. 1999;354:1757–1762.
 285. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879–1887.
 286. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, Hamm CW, Moliterno DJ, Califf RM, White HD, Kleiman NS, Theroux P, Topol EJ. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation*. 2001;104:2767–2771.
 287. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. *Lancet*. 1986;2:57–66.
 288. Hjalmarson A, Herlitz J, Holmberg S, Ryden L, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Waldenstrom J, Wedel H, Wilhelmson L, Wilhelmsson C. The Goteborg metoprolol trial. Effects on mortality and morbidity in acute myocardial infarction: Limitation of infarct size by beta blockers and its potential role for prognosis. *Circulation*. 1983;67(6 Pt 2):126–132.
 289. Reduction of infarct size by the early use of intravenous timolol in acute myocardial infarction. International Collaborative Study Group. *Am J Cardiol*. 1984;54:14E–15E.
 290. Jurgensen HJ, Andersen MP, Bechsgaard P, Frederiksen J, Hansen DA, Nielsen PB, Pedersen F, Pedersen-Bjergaard O, Rasmussen SL. Effect of acute and long-term beta-adrenergic blockade with alprenolol in definite or suspected myocardial infarction. Study design, patient characteristics and conduct of the study. *Acta medica Scandinavica*. 1984;680:8–17.
 291. Galcera-Tomas J, Castillo-Soria FJ, Villegas-Garcia MM, Florenciano-Sanchez R, Sanchez-Villanueva JG, de La Rosa JA, Martinez-Caballero A, Valenti-Aldeguer JA, Jara-Perez P, Parraga-Ramirez M, Lopez-Martinez I, Inigo-Garcia L, Pico-Aracil F. Effects of early use of atenolol or captopril on infarct size and ventricular volume: A double-blind comparison in patients with anterior acute myocardial infarction. *Circulation*. 2001;103:813–819.
 292. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1622–1632.
 293. Herlitz J, Edvardsson N, Holmberg S, Ryden L, Waagstein F, Waldenstrom A, Swedberg K, Hjalmarson A. Goteborg Metoprolol Trial: effects on arrhythmias. *Am J Cardiol*. 1984;53:27D–31D.
 294. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. The MIAMI Trial Research Group. *Eur Heart J*. 1985;6:199–226.
 295. Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC, Willerson JT, Knatterud GL, Forman S, Passamani E, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation*. 1991;83:422–437.
 296. Al-Reesi A, Al-Zadjali N, Perry J, Fergusson D, Al-Shamsi M, Al-Thagafi M, Stiell I. Do beta-blockers reduce short-term mortality following acute myocardial infarction? A systematic review and meta-analysis. *CJEM*. 2008;10:215–223.
 297. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27:335–371.
 298. Basu S, Senior R, Raval U, van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled, randomized trial. *Circulation*. 1997;96:183–191.
 299. Freemantle N, Cleland J, Young P, Mason J, Harrison J. β -Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318(7200):1730–1737.
 300. Murray DP, Murray RG, Rafiqi E, Littler WA. Does acute-phase beta-blockade reduce mortality in acute myocardial infarction by limiting infarct size? *Int J Cardiol*. 1988;20:327–339.
 301. Heidbuechel H, Tack J, Vanneste L, Ballet A, Ector H, Van de Werf F. Significance of arrhythmias during the first 24 hours of acute myocardial infarction treated with alteplase and effect of early administration of a beta-blocker or a bradycardiac agent on their incidence. *Circulation*. 1994;89:1051–1059.
 302. Herlitz J, Hjalmarson A, Swedberg K, Ryden L, Waagstein F. Effects on mortality during five years after early intervention with metoprolol in suspected acute myocardial infarction. *Acta Med Scand*. 1988;223:227–231.

303. TIMI-11B Investigators, Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, Bayes De Luna A, Fox K, Lablanche JM, Radley D, Premmereur J, Braunwald E. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation*. 1999;100:1593-1601.
304. Campos JV, Juarez Herrera U, Rosas Peralta M, Lupi Herrera E, Gonzalez Pacheco H, Martinez Sanchez C, Chuquiure Valenzuela E, Vieyra Herrera G, Cardozo Zepeda C, Barrera Sanchez C, Reyes Corona J, Cortina de la Rosa E, de la Pena Diaz A, Izaguirre Avila R, de la Pena Fernandez A. [Decrease of total hemorrhage with reduced doses of enoxaparin in high risk unstable angina. ENHNAI study. (Enoxaparin vs non-fractionated heparin in unstable angina). Preliminary report]. *Arch Cardiol Mex*. 2002;72:209-219.
305. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med*. 1997;337:447-452.
306. Cohen M, Theroux P, Borzjak S, Frey MJ, White HD, Van Mieghem W, Senatore F, Lis J, Mukherjee R, Harris K, Bigonzi F. Randomized double-blind safety study of enoxaparin versus unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes treated with tirofiban and aspirin: the ACUTE II study. The Anti-thrombotic Combination Using Tirofiban and Enoxaparin. *Am Heart J*. 2002;144:470-477.
307. Goodman SG, Cohen M, Bigonzi F, Gurfinkel EP, Radley DR, Le Iouer V, Fromell GJ, Demers C, Turpie AG, Califf RM, Fox KA, Langer A. Randomized trial of low molecular weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease: one-year results of the ESSENCE Study. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events. *J Am Coll Cardiol*. 2000;36:693-698.
308. Goodman SG, Fitchett D, Armstrong PW, Tan M, Langer A. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatid. *Circulation*. 2003;107:238-244.
309. Malhotra S, Bhargava VK, Grover A, Pandhi P, Sharma YP. A randomized trial to compare the efficacy, safety, cost and platelet aggregation effects of enoxaparin and unfractionated heparin (the ESCAPEU trial). *Int J Clin Pharmacol Ther*. 2001;39:110-115.
310. Blazing MA, de Lemos JA, White HD, Fox KA, Verheugt FW, Ardissino D, DiBattiste PM, Palmisano J, Bilheimer DW, Snapinn SM, Ramsey KE, Gardner LH, Hasselblad V, Pfeffer MA, Lewis EF, Braunwald E, Califf RM. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA*. 2004;292:55-64.
311. Fergusson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, Kereiakes DJ, Langer A, Mahaffey KW, Nessel CC, Armstrong PW, Avezum A, Aylward P, Becker RC, Biasucci L, Borzak S, Col J, Frey MJ, Fry E, Gulba DC, Guneri S, Gurfinkel E, Harrington R, Hochman JS, Kleiman NS, Leon MB, Lopez-Sendon JL, Pepine CJ, Ruzyllo W, Steinhubl SR, Teirstein PS, Toro-Figueroa L, White H. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA*. 2004;292:45-54.
312. Mahaffey KW, Fergusson JJ. Exploring the role of enoxaparin in the management of high-risk patients with non-ST-elevation acute coronary syndromes: the SYNERGY trial. *Am heart journal*. 2005;149(4 Suppl): S81-S90.
313. Mitrovskaja S, Jovanova S. Low-molecular weight heparin enoxaparin in the treatment of acute coronary syndromes without ST segment elevation. *Bratislavské lekarske listy*. 2009;110:45-48.
314. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, Braunwald E. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-essence meta-analysis. *Circulation*. 1999;100:1602-1608.
315. Antman EM, Cohen M, McCabe C, Goodman SG, Murphy SA, Braunwald E. Enoxaparin is superior to unfractionated heparin for preventing clinical events at 1-year follow-up of TIMI 11B and ESSENCE. *Eur Heart J*. 2002;23:308-314.
316. Magee KD, Sevcik W, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. *Cochrane Database Syst Rev*. 2003;CD002132.
317. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, Langer A, Blazing MA, Le-Moigne-Amrani A, de Lemos JA, Nessel CC, Harrington RA, Fergusson JJ, Braunwald E, Califf RM. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-Segment elevation acute coronary syndromes: a systematic overview. *JAMA*. 2004;292:89-96.
318. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet*. 2000;355(9219):1936-1942.
319. Le Nguyen MT, Spencer FA. Low molecular weight heparin and unfractionated heparin in the early pharmacologic management of acute coronary syndromes: a meta-analysis of randomized clinical trials. *J Thromb Thrombolysis*. 2001;12:289-295.
320. Murphy SA, Gibson CM, Morrow DA, Van de Werf F, Menown IB, Goodman SG, Mahaffey KW, Cohen M, McCabe CH, Antman EM, Braunwald E. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. *Eur Heart J*. 2007;28: 2077-2086.
321. Joyner CD, Peters RJ, Afzal R, Chrolavicius S, Mehta SR, Fox KA, Granger CB, Franzosi MG, Flather M, Budaj A, Bassand JP, Yusuf S. Fondaparinux compared to enoxaparin in patients with acute coronary syndromes without ST-segment elevation: outcomes and treatment effect across different levels of risk. *Am Heart J*. 2009;157:502-508.
322. Mehta SR, Granger CB, Eikelboom JW, Bassand JP, Wallentin L, Faxon DP, Peters RJ, Budaj A, Afzal R, Chrolavicius S, Fox KA, Yusuf S. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol*. 2007;50: 1742-1751.
323. Mehta SR, Steg PG, Granger CB, Bassand JP, Faxon DP, Weitz JI, Afzal R, Rush B, Peters RJ, Natarajan MK, Velianou JL, Goodhart DM, Labinaz M, Tanguay JF, Fox KA, Yusuf S. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation (ASPIRE) Pilot Trial. *Circulation*. 2005;111:1390-1397.
324. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354:1464-1476.
325. Mehta SR, Boden WE, Eikelboom JW, Flather M, Steg PG, Avezum A, Afzal R, Piegas LS, Faxon DP, Widimsky P, Budaj A, Chrolavicius S, Rupprecht HJ, Jolly S, Granger CB, Fox KA, Bassand JP, Yusuf S. Antithrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST- and non-ST-segment elevation acute coronary syndromes: an individual patient-level combined analysis of the Fifth and Sixth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5 and 6) randomized trials. *Circulation*. 2008;118:2038-2046.
326. Feit F, Manoukian SV, Ebrahimi R, Pollack CV, Ohman EM, Attubato MJ, Mehran R, Stone GW. Safety and efficacy of bivalirudin monotherapy in patients with diabetes mellitus and acute coronary syndromes: a report from the ACUTY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol*. 2008;51:1645-1652.
327. Lansky AJ, Mehran R, Cristea E, Parise H, Feit F, Ohman EM, White HD, Alexander KP, Bertrand ME, Desmet W, Hamon M, Stone GW. Impact of gender and antithrombin strategy on early and late clinical outcomes in patients with non-ST-elevation acute coronary syndromes (from the ACUTY trial). *Am J Cardiol*. 2009;103:1196-1203.
328. Lopes RD, Alexander KP, Manoukian SV, Bertrand ME, Feit F, White HD, Pollack CV Jr, Hoekstra J, Gersh BJ, Stone GW, Ohman EM. Advanced age, antithrombotic strategy, and bleeding in non-ST-segment elevation acute coronary syndromes: results from the ACUTY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *Journal of the Am College of Cardiology*. 2009;53:1021-1030.
329. Singh S, Molnar J, Arora R. Efficacy and safety of bivalirudin versus heparins in reduction of cardiac outcomes in acute coronary syndrome and percutaneous coronary interventions. *J Cardiovasc Pharmacol Ther*. 2007;12:283-291.

330. Stone GW, Ware JH, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, White HD, Feit F, Colombo A, McLaurin BT, Cox DA, Manoukian SV, Fahy M, Clayton TC, Mehran R, Pocock SJ. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUTY trial. *JAMA*. 2007;298:2497–2506.
331. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358(9282):605–613.
332. Antman EM, Louwrenburg HW, Baars HF, Wesdorp JC, Hamer B, Bassand JP, Bigonzi F, Pisapia G, Gibson CM, Heidebuchel H, Braunwald E, Van de Werf F. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation*. 2002;105:1642–1649.
333. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, Lopez-Sendon JL, Guneri S, Jiang F, White HD, Fox KA, Braunwald E. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354:1477–1488.
334. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation*. 2005;112:3855–3867.
335. Theroux P, Welsh RC. Meta-analysis of randomized trials comparing enoxaparin versus unfractionated heparin as adjunctive therapy to fibrinolysis in ST-elevation acute myocardial infarction. *Am J Cardiol*. 2003;91:860–864.
336. Ross AM, Molhoek P, Lundergan C, Knudtson M, Draoui Y, Regalado L, Le Louer V, Bigonzi F, Schwartz W, De Jong E, Coyne K. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: Second Trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation*. 2001;104:648–652.
337. Sinnaeve PR, Alexander JH, Bogaerts K, Belmans A, Wallentin L, Armstrong P, Adgey JA, Tendera M, Diaz R, Soares-Piegas L, Vahanian A, Granger CB, Van De Werf FJ. Efficacy of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: one-year follow-up results of the Assessment of the Safety of a New Thrombolytic-3 (ASSENT-3) randomized trial in acute myocardial infarction. *Am Heart J*. 2004;147:993–998.
338. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation*. 2003;108:135–142.
339. Armstrong PW, Chang WC, Wallentin L, Goldstein P, Granger CB, Bogaerts K, Danays T, Van de Werf F. Efficacy and safety of unfractionated heparin versus enoxaparin: a pooled analysis of ASSENT-3 and -3 PLUS data. *CMAJ*. 2006;174:1421–1426.
340. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006;295:1519–1530.
341. Ferguson J. Low-molecular-weight heparins and glycoprotein IIb/IIIa antagonists in acute coronary syndromes. *J Invasive Cardiol*. 2004;16:136–144.
342. Zeymer U, Gitt A, Junger C, Bauer T, Heer T, Koeth O, Wienbergen H, Zahn R, Senges J. Efficacy and safety of enoxaparin in unselected patients with ST-segment elevation myocardial infarction. *Thromb Haemost*. 2008;99:150–154.
343. Zeymer U, Gitt A, Zahn R, Junger C, Bauer T, Heer T, Koeth O, Senges J. Efficacy and safety of enoxaparin in combination with and without GP IIb/IIIa inhibitors in unselected patients with ST segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *EuroIntervention*. 2009;4:524–528.
344. Stone GW, Witzentichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218–2230.
345. Mehran R, Lansky AJ, Witzentichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Wong SC, Nikolsky E, Gambone L, Vandertie L, Parise H, Dangas GD, Stone GW. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet*. 2009;374(9696):1149–1159.
346. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet*. 1994;343(8906):1115–1122.
347. Oral captopril versus placebo among 14,962 patients with suspected acute myocardial infarction: a multicenter, randomized, double-blind, placebo controlled clinical trial. Chinese Cardiac Study (CCS-1) Collaborative Group. *Chin Med J (Engl)*. 1997;110:834–838.
348. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction: the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med*. 1995;332:80–85.
349. Borghi C, Marino P, Zardini P, Magnani B, Collatina S, Ambrosioni E. Short- and long-term effects of early fosiopril administration in patients with acute anterior myocardial infarction undergoing intravenous thrombolysis: results from the Fosiopril in Acute Myocardial Infarction Study. FAMIS Working Party. *Am Heart J*. 1998;136:213–225.
350. Oral captopril versus placebo among 13,634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet*. 1995;345(8951):686–687.
351. Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT, Menapace FJ Jr, Rapaport E, Ridker PM, Rouleau JL, Solomon SD, Hennekens CH. Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. *Circulation*. 1997;95:2643–2651.
352. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation*. 1998;97:2202–2212.
353. Teo KK, Yusuf S, Pfeffer M, Torp-Pedersen C, Kober L, Hall A, Pogue J, Latini R, Collins R. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet*. 2002;360(9339):1037–1043.
354. Latini R, Maggioni AP, Flather M, Sleight P, Tognoni G. ACE inhibitor use in patients with myocardial infarction. Summary of evidence from clinical trials. *Circulation*. 1995;92:3132–3137.
355. Latini R, Tognoni G, Maggioni AP, Baigent C, Braunwald E, Chen ZM, Collins R, Flather M, Franzosi MG, Kjekshus J, Kober L, Liu LS, Peto R, Pfeffer M, Pizzetti F, Santoro E, Sleight P, Swedberg K, Tavazzi L, Wang W, Yusuf S. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group. *J Am Coll Cardiol*. 2000;35:1801–1807.
356. Lu CY [Treatment of acute myocardial infarction with oral captopril. A randomized, double blind and placebo controlled pilot study]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 1993;21:74–76, 121–122.
357. Ray SG, Pye M, Oldroyd KG, Christie J, Connelly DT, Northridge DB, Ford I, Morton JJ, Dargie HJ, Cobbe SM. Early treatment with captopril after acute myocardial infarction. *Br Heart J*. 1993;69:215–222.
358. Di Pasquale P, Paterna S, Cannizzaro S, Bucca V. Does captopril treatment before thrombolysis in acute myocardial infarction attenuate reperfusion damage? Short-term and long-term effects. *Int J Cardiol*. 1994;43:43–50.
359. Spinar J, Vitovec J, Pluhacek L, Spinarova L, Fischerova B, Toman J. First dose hypotension after angiotensin converting enzyme inhibitor captopril and angiotensin II blocker losartan in patients with acute myocardial infarction. *Int J Cardiol*. 75(2–3):197–204, 2000.
360. Wagner A, Herkner H, Schreiber W, Bur A, Woisetschlager C, Stix G, Laggner AN, Hirschl MM. Ramipril prior to thrombolysis attenuates the early increase of PAI-1 in patients with acute myocardial infarction. *Thromb Haemost*. 2002;88:180–185.
361. Mehta PM, Przyklenk K, Kloner RA. Cardioprotective effects of captopril in myocardial ischaemia, ischaemia/reperfusion and infarction. *Eur Heart J*. 1990;11 Suppl B:94–99.
362. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan,

- captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med.* 2003;349:1893–1906.
363. Di Pasquale P, Bucca V, Scalzo S, Cannizzaro S, Giubilato A, Paterna S. Does the addition of losartan improve the beneficial effects of ACE inhibitors in patients with anterior myocardial infarction? A pilot study. *Heart (British Cardiac Society).* 1999;81:606–611.
 364. Kingma JH, van Gilst WH, Peels CH, Dambrink JH, Verheugt FW, Wielenga RP. Acute intervention with captopril during thrombolysis in patients with first anterior myocardial infarction. Results from the Captopril and Thrombolysis Study (CATS). *Eur Heart J.* 1994;15:898–907.
 365. van Gilst WH, Kingma JH, Peels KH, Dambrink JH, St John Sutton M. Which patient benefits from early angiotensin-converting enzyme inhibition after myocardial infarction? Results of one-year serial echocardiographic follow-up from the Captopril and Thrombolysis Study (CATS). *J Am Coll Cardiol.* 1996;28:114–121.
 366. de Kam PJ, Voors AA, van den Berg MP, van Veldhuisen DJ, Brouwer J, Crijns HJ, Borghi C, Ambrosioni E, Hochman JS, LeJemtel TH, Kingma JH, Sutton MS, van Gilst WH. Effect of very early angiotensin-converting enzyme inhibition on left ventricular dilation after myocardial infarction in patients receiving thrombolysis: results of a meta-analysis of 845 patients. FAMIS, CAPTIN and CATS Investigators. *Journal of the Am College of Cardiology.* 2000;36:2047–2053.
 367. Voors AA, de Kam PJ, van den Berg MP, Borghi C, Hochman JS, van Veldhuisen DJ, van Gilst WH. Acute administration of angiotensin converting enzyme inhibitors in thrombolysed myocardial infarction patients is associated with a decreased incidence of heart failure, but an increased re-infarction risk. *Cardiovasc Drugs Ther.* 2005;19:119–124.
 368. Kayikcioglu M, Can L, Kultursay H, Payzin S, Turkoglu C. Early use of pravastatin in patients with acute myocardial infarction undergoing coronary angioplasty. *Acta Cardiol.* 2002;57:295–302.
 369. Kayikcioglu M, Can L, Evrengul H, Payzin S, Kultursay H. The effect of statin therapy on ventricular late potentials in acute myocardial infarction. *Int J Cardiol.* 2003;90:63–72.
 370. Kinlay S, Schwartz GG, Olsson AG, Rifai N, Leslie SJ, Sasiela WJ, Szarek M, Libby P, Ganz P. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation.* 2003;108:1560–1566.
 371. Correia LC, Sposito AC, Lima JC, Magalhaes LP, Passos LC, Rocha MS, D'Oliveira A, Esteves JP. Anti-inflammatory effect of atorvastatin (80 mg) in unstable angina pectoris and non-Q-wave acute myocardial infarction. *Am J Cardiol.* 2003;92:298–301.
 372. Heesch C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation.* 2002;105:1446–1452.
 373. Chan AW, Bhatt DL, Chew DP, Reginelli J, Schneider JP, Topol EJ, Ellis SG. Relation of inflammation and benefit of statins after percutaneous coronary interventions. *Circulation.* 2003;107:1750–1756.
 374. Cuculi F, Radovanovic D, Eberli FR, Stauffer JC, Bertel O, Erne P. The impact of statin treatment on presentation mode and early outcomes in acute coronary syndromes. *Cardiology.* 2008;109:156–162.
 375. Daskalopoulou SS, Delaney JA, Filion KB, Brophy JM, Mayo NE, Suissa S. Discontinuation of statin therapy following an acute myocardial infarction: a population-based study. *Eur Heart J.* 2008.
 376. Fonarow GC, Wright RS, Spencer FA, Fredrick PD, Dong W, Every N, French WJ. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. *Am J Cardiol.* 2005;96:611–616.
 377. Lenderink T, Boersma E, Gitt AK, Zeymer U, Wallentin L, Van de Werf F, Hasdai D, Behar S, Simoons ML. Patients using statin treatment within 24 h after admission for ST-elevation acute coronary syndromes had lower mortality than non-users: a report from the first Euro Heart Survey on acute coronary syndromes. *Eur Heart J.* 2006;27:1799–1804.
 378. Saab FA, Petrina M, Kline-Rogers E, Fang J, Otten R, Mukherjee D, Eagle KA. Early statin therapy in elderly patients presenting with acute coronary syndrome causing less heart failure. *Indian Heart J.* 2006;58:321–324.
 379. Spencer FA, Fonarow GC, Frederick PD, Wright RS, Every N, Goldberg RJ, Gore JM, Dong W, Becker RC, French W. Early withdrawal of statin therapy in patients with non-ST-segment elevation myocardial infarction: national registry of myocardial infarction. *Arch Intern Med.* 2004;164:2162–2168.
 380. Kiyokuni M, Kosuge M, Ebina T, Hibi K, Tsukahara K, Okuda J, Iwahashi N, Maejima N, Kusama I, Komura N, Nakayama N, Umemura S, Kimura K. Effects of pretreatment with statins on infarct size in patients with acute myocardial infarction who receive fibrinolytic therapy. *Circ J.* 2009;73:330–335.
 381. Wright RS, Bybee K, Miller WL, Laudon DA, Murphy JG, Jaffe AS. Reduced risks of death and CHF are associated with statin therapy administered acutely within the first 24 h of AMI. *Int J Cardiol.* 2006;108:314–319.
 382. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. *Circulation.* 2004;110:674–678.
 383. Briguori C, Colombo A, Airolfi F, Violante A, Focaccio A, Balestrieri P, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Librera M, Bonizzoni E, Ricciardelli B. Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. *European heart journal.* 2004;25:1822–1828.
 384. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, Montinaro A, Di Sciascio G. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol.* 2007;49:1272–1278.
 385. Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D, Paolasso E, Ahmed R, Xie C, Kazmi K, Tai J, Orlandini A, Pogue J, Liu L. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA.* 2005;293:437–446.
 386. Timmer J. Glucose-insulin-potassium study in patients with ST-elevation myocardial infarction without signs of heart failure: The Gips-II Trial. paper presented at Late-Breaking Clinical Trials III. Paper presented at: Am College of Cardiology Scientific Sessions, March 9, 2005; Orlando, Fla.
 387. Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. *Lancet.* 1967;2(7510):271–273.
 388. Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death [published correction appears in *Am J Cardiol.* 1998;81:260]. *Am J Cardiol.* 1997;79:1512–1516.
 389. Colquhoun MC, Julien DG. Sudden death in the community—the arrhythmia causing cardiac arrest and results of immediate resuscitation. *Resuscitation.* 1992;24:177A.
 390. Campbell RW, Murray A, Julian DG. Ventricular arrhythmias in first 12 hours of acute myocardial infarction: natural history study. *Br Heart J.* 1981;46:351–357.
 391. O'Doherty M, Tayler DI, Quinn E, Vincent R, Chamberlain DA. Five hundred patients with myocardial infarction monitored within one hour of symptoms. *BMJ.* 1983;286(6375):1405–1408.
 392. Lie KI, Wellens HJ, Downar E, Durrer D. Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction. *Circulation.* 1975;52:755–759.
 393. MacMahon S, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA.* 1988;260:1910–1916.
 394. Elizari MV, Martinez JM, Belziti C, Ciruzzi M, Perez de la Hoz R, Sinisi A, Carbajales J, Scapin O, Garguichevich J, Girotti L, Cagide A. Morbidity and mortality following early administration of amiodarone in acute myocardial infarction. GEMICA study investigators, GEMA Group, Buenos Aires, Argentina. Grupo de Estudios Multicentricos en Argentina. *Eur Heart J.* 2000;21:198–205. Copyright 2010 American Heart Association, Inc., European Resuscitation Council, and International Liaison Committee on Resuscitation.

KEY WORDS: acute coronary syndrome ■ myocardial infarction ■ non-ST-segment elevation acute coronary syndromes