

ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction: Executive Summary. A Report of the American College of Cardiology/American 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)

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ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: Executive Summary

A Report of the American College of Cardiology/American 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 American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine

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Preamble

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies as they are introduced and tested in the detection, management, or prevention of disease states. Rigorous and expert analysis of the available data documenting absolute and relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. The American College of Cardiology (ACC)/AHA Task Force on Practice Guidelines, whose charge is to develop, update, or revise practice guidelines for important cardiovascular diseases and procedures, directs this effort. Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop, update, or revise written recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups when appropriate. Writing committees are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities and issues of patient preference that might influence the choice of particular tests or therapies are considered as well as frequency of follow-up and costeffectiveness. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical outcomes will constitute the primary basis for preparing recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or perceived conflict of interest that may arise as a result of an industry relationship or personal interest of the Writing Committee. Specifically, all members of the Writing Committee, as well as peer reviewers of the document, were asked to provide disclosure statements of all such relationships that may be perceived as real or potential conflicts of interest. Writing Committee members are also strongly encouraged to declare a previous relationship with industry that might be perceived as relevant to guideline development. If a Writing Committee member develops a new relationship with industry during their tenure, they are required to notify guideline staff in writing. The continued

participation of the Writing Committee member will be reviewed. These statements are reviewed by the parent task force, reported orally to all members of the Writing Committee at each meeting, and updated and reviewed by the Writing Committee as changes occur. Please refer to the methodology manual for ACC/AHA Guideline Writing Committees for further description of the relationships with industry policy, available on ACC and AHA World Wide Web sites (http://www.acc.org/clinical/manual/manual_introltr.htm and <http://circ.ahajournals.org/manual/>). Please see Appendix 1 for author relationships with industry and Appendix 2 for peer reviewer relationships with industry that are pertinent to these guidelines.

These practice guidelines are intended to assist health care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management and prevention of specific diseases or conditions. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care.

Patient adherence to prescribed and agreed upon medical regimens and lifestyles is an important aspect of treatment. Prescribed courses of treatment in accordance with these recommendations will only be effective if they are followed. Since lack of patient understanding and adherence may adversely affect treatment outcomes, physicians and other health care providers should make every effort to engage the patient in active participation with prescribed medical regimens and lifestyles.

If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the health care provider and the patient in light of all of the circumstances presented by that patient. There are circumstances in which deviations from these guidelines are appropriate.

The guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and will be considered current unless they are updated, revised, or sunsetted and withdrawn from distribution. The executive summary and recommendations are published in the August 14, 2007, issue of the *Journal of the American College of Cardiology* and the August 14, 2007, issue of *Circulation*. The full-text guidelines are e-published in the same issue of the journals noted above, as well as posted on the ACC (www.acc.org) and AHA (www.americanheart.org) World Wide Web sites. Copies of the full text and the executive summary are available from both organizations.

Sidney C. Smith, Jr., MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

I. Introduction

A. Organization of Committee and Evidence Review

The ACC/AHA Task Force on Practice Guidelines was formed to make recommendations regarding the diagnosis and treatment of patients with known or suspected cardiovascular disease. Coronary artery disease (CAD) is the leading cause of death in the United States. Unstable angina (UA) and the closely related condition of non-ST-segment elevation myocardial infarction (NSTEMI) are very common manifestations of this disease.

The committee members reviewed and compiled published reports through a series of computerized literature searches of the English-language literature since 2002 and a final manual search of selected articles. Details of the specific searches conducted for particular sections are provided when appropriate. Detailed evidence tables were developed whenever necessary with the specific criteria outlined in the individual sections. The recommendations made were based primarily on these published data. The weight of the evidence was ranked highest (A) to lowest (C). The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention in patients with UA/NSTEMI summarize both clinical evidence and expert opinion.

Classification of Recommendations

The schema for classification of recommendations and level of evidence is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size of the treatment effect and an estimate of the certainty of the treatment effect.

The Writing Committee consisted of acknowledged experts in general internal medicine representing the American College of Physicians, family medicine from the American Academy of Family Physicians, emergency medicine from the American College of Emergency Physicians, thoracic surgery from the Society of Thoracic Surgeons, interventional cardiology from the Society for Cardiovascular Angiography and Interventions (SCAI), and general and critical care cardiology, as well as individuals with recognized expertise in more specialized areas, including noninvasive testing, preventive cardiology, coronary intervention, and cardiovascular surgery. Both the academic and private practice sectors were represented. This document was reviewed by 2 outside reviewers nominated by each of the ACC and AHA.

B. Changes Since Publication of These Guidelines in 2002

The writing committee considered evidence published since 2002 and drafted revised recommendations to incorporate results from major clinical trials. The text has been reorganized and rewritten to reflect these developments. Greater

Table 1. Applying Classification of Recommendations and Level of Evidence†

		SIZE OF TREATMENT EFFECT →			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives</i> needed IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives</i> needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>Risk ≥ Benefit</i> No additional studies needed Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple (3-5) population risk strata evaluated* General consistency of direction and magnitude of effect	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
	LEVEL B Limited (2-3) population risk strata evaluated*	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Limited evidence from single randomized trial or nonrandomized studies
	LEVEL C Very limited (1-2) population risk strata evaluated*	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care
Suggested phrases for writing recommendations†		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

Fighting Heart Disease and Stroke

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. †In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

emphasis is placed on earlier access to medical evaluation of the acute coronary syndrome (ACS) patient, including avoidance of delays inherent in patient self-medication, as well as facilitated emergency department (ED) diagnosis and triage. New imaging tests (cardiac magnetic resonance imaging and coronary computed tomographic [CT] angiography) have emerged as diagnostic options in selected patients. Troponins have become the dominant cardiac biomarker of necrosis, have redefined NSTEMI, and have changed its demographics and prognosis. B-type natriuretic peptide (BNP) now may be added to the list of biomarkers that are potentially useful in risk assessment. Clinical trials data continue to build support for an initial invasive strategy for higher-risk UA/NSTEMI patients (as assessed by troponin positivity or a formal risk score); in contrast, such a strategy is not of benefit and may be harmful in low-risk women, in whom an initially conservative strategy is rec-

ommended. Two new anticoagulants, fondaparinux and bivalirudin, have undergone favorable testing in clinical trials and are recommended as alternatives to unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) for specific or more general applications. Support for thienopyridine use (primarily with clopidogrel) continues to grow, including higher loading-dose options, earlier (upstream) administration, and longer administration (especially after drug-eluting stent placement). The question of how best to integrate thienopyridine use with parenteral glycoprotein (GP) IIb/IIIa antagonists to provide optimal antiplatelet therapy early in the course of UA/NSTEMI therapy, including cardiac catheterization, is an evolving subject and continues to present a challenge. These guidelines incorporate changes based on recent updates for percutaneous coronary intervention (PCI) and for secondary prevention as they impact patients with UA/NSTEMI. An

expanded section on special patient groups recognizes the need to highlight specific diagnostic and therapeutic considerations in patients with diverse characteristics. Care processes are highlighted as another area important to patient outcomes. These and other developments and advances also highlight important knowledge and treatment gaps, which should stimulate continued progress in UA/NSTEMI through research and clinical application.

1. Purpose of These Guidelines

These guidelines address the diagnosis and management of patients with UA and the closely related condition of NSTEMI. These potentially life-threatening disorders are a major cause of emergency medical care and hospitalization in the United States. In 2004, the National Center for Health Statistics reported 1,565,000 hospitalizations for primary or secondary diagnosis of an ACS, 669,000 for UA and 896,000 for myocardial infarction (MI) (1). These guidelines are intended to assist both cardiovascular specialists and nonspecialists in the proper evaluation and management of patients with an acute onset of symptoms suggestive of these conditions. These clinical practice guidelines also provide recommendations and supporting evidence for the continued management of patients with these conditions in both inpatient and outpatient settings.

C. Recommendations for Management of Patients With UA/NSTEMI

Classification of recommendations and level of evidence are expressed in the ACC/AHA format as described above and in Table 1. Recommendations are evidence-based and derived primarily from published data. The reader is referred to the full-text guidelines for a complete description of the rationale and evidence supporting these recommendations.

RECOMMENDATIONS

1. Identification of Patients at Risk of UA/NSTEMI

CLASS I

1. Primary care providers should evaluate the presence and status of control of major risk factors for coronary heart disease (CHD) for all patients at regular intervals (approximately every 3 to 5 years). (Level of Evidence: C)
2. Ten-year risk (National Cholesterol Education Program global risk) of developing symptomatic CHD should be calculated for all patients who have 2 or more major risk factors to assess the need for primary prevention strategies (2,3). (Level of Evidence: B)
3. Patients with established CHD should be identified for secondary prevention efforts, and patients with a CHD risk equivalent (e.g., atherosclerosis in other vascular beds, diabetes mellitus, chronic kidney disease, or 10-year risk greater than 20% as calculated by Framingham equations) should receive equally intensive risk factor intervention as those with clinically apparent CHD. (Level of Evidence: A)

2. Initial Evaluation and Management

A. CLINICAL ASSESSMENT

CLASS I

1. Patients with symptoms that may represent ACS (Table 2) should not be evaluated solely over the telephone but should be referred to a facility that allows evaluation by a physician and the recording of a 12-lead ECG and biomarker determination (e.g., an ED or other acute care facility). (Level of Evidence: C)
2. Patients with symptoms of ACS (chest discomfort with or without radiation to the arm[s], back, neck, jaw, or epigastrium; shortness of breath; weakness; diaphoresis; nausea; lightheadedness) should be instructed to call 9-1-1 and should be transported to the hospital by ambulance rather than by friends or relatives. (Level of Evidence: B)
3. Health care providers should actively address the following issues regarding ACS with patients with or at risk for CHD and their families or other responsible caregivers:
 - a. The patient's heart attack risk; (Level of Evidence: C)
 - b. How to recognize symptoms of ACS; (Level of Evidence: C)
 - c. The advisability of calling 9-1-1 if symptoms are unimproved or worsening after 5 min, despite feelings of uncertainty about the symptoms and fear of potential embarrassment; (Level of Evidence: C)
 - d. A plan for appropriate recognition and response to a potential acute cardiac event, including the phone number to access emergency medical services (EMS), generally 9-1-1 (4). (Level of Evidence: C)
4. Prehospital EMS providers should administer 162 to 325 mg of aspirin (ASA; chewed) to chest pain patients suspected of having ACS unless contraindicated or already taken by the patient. Although some trials have used enteric-coated ASA for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. (Level of Evidence: C)
5. Health care providers should instruct patients with suspected ACS for whom nitroglycerin (NTG) has been prescribed previously to take not more than 1 dose of NTG sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or is worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or family member/friend/caregiver call 9-1-1 immediately to access EMS before taking additional NTG. In patients with chronic stable angina, if symptoms are significantly improved by 1 dose of NTG, it is appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not resolved completely. (Level of Evidence: C)
6. Patients with a suspected ACS with chest discomfort or other ischemic symptoms at rest for greater than 20 min, hemodynamic instability, or recent syncope or presyncope should be referred immediately to an ED. Other patients with a suspected ACS who are experiencing less severe symptoms and who have none of the above high-risk features, including those who respond to an NTG dose, may be seen initially in an ED or an outpatient facility able to provide an acute evaluation. (Level of Evidence: C)

CLASS IIa

1. It is reasonable for health care providers and 9-1-1 dispatchers to advise patients without a history of ASA allergy who have symptoms of ACS to chew ASA (162 to 325 mg) while awaiting arrival of prehospital EMS providers. Although some trials have used enteric-

coated ASA for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. (Level of Evidence: B)

2. It is reasonable for health care providers and 9-1-1 dispatchers to advise patients who tolerate NTG to repeat NTG every 5 min for a maximum of 3 doses while awaiting ambulance arrival. (Level of Evidence: C)
3. It is reasonable that all prehospital EMS providers perform and evaluate 12-lead electrocardiograms (ECGs) in the field (if available) on chest pain patients suspected of ACS to assist in triage decisions. Electrocardiographs with validated computer-generated interpretation algorithms are recommended for this purpose. (Level of Evidence: B)
4. If the 12-lead ECG shows evidence of acute injury or ischemia, it is reasonable that prehospital ACLS providers relay the ECG to a predetermined medical control facility and/or receiving hospital. (Level of Evidence: B)

B. EARLY RISK STRATIFICATION

CLASS I

1. A rapid clinical determination of the likelihood risk of obstructive CAD (i.e., high, intermediate, or low) should be made in all patients with chest discomfort or other symptoms suggestive of an ACS and considered in patient management. (Level of Evidence: C)
2. Patients who present with chest discomfort or other ischemic symptoms should undergo early risk stratification for the risk of cardiovascular events (e.g., death or [re]MI) that focuses on history, including anginal symptoms, physical findings, ECG findings, and biomarkers of cardiac injury and results should be considered in patient management. (Level of Evidence: C)
3. A 12-lead ECG should be performed and shown to an experienced emergency physician as soon as possible after ED arrival, with a goal of within 10 min of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of ACS. (Level of Evidence: B)
4. If the initial ECG is not diagnostic but the patient remains symptomatic and there is high clinical suspicion for ACS, serial ECGs, initially at 15- to 30-min intervals, should be performed to detect the potential for development of ST-segment elevation or depression. (Level of Evidence: B)
5. Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with ACS. (Level of Evidence: B)
6. A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients who present with chest discomfort consistent with ACS. (Level of Evidence: B)
7. Patients with negative cardiac biomarkers within 6 h of the onset of symptoms consistent with ACS should have biomarkers remeasured in the time frame of 8 to 12 h after symptom onset. (The exact timing of serum marker measurement should take into account the uncertainties often present with the exact timing of onset of pain and the sensitivity, precision, and institutional norms of the assay being utilized as well as the release kinetics of the marker being measured.) (Level of Evidence: B)
8. The initial evaluation of the patient with suspected ACS should include the consideration of noncoronary causes for the development of unexplained symptoms. (Level of Evidence: C)

CLASS IIa

1. Use of risk-stratification models, such as the Thrombolysis In Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) risk score or the Platelet Glycoprotein IIb/IIIa in Unstable

Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk model, can be useful to assist in decision making with regard to treatment options in patients with suspected ACS. (Level of Evidence: B)

2. It is reasonable to remeasure positive biomarkers at 6- to 8-h intervals 2 to 3 times or until levels have peaked, as an index of infarct size and dynamics of necrosis. (Level of Evidence: B)
3. It is reasonable to obtain supplemental ECG leads V₇ through V₉ in patients whose initial ECG is nondiagnostic to rule out MI due to left circumflex occlusion. (Level of Evidence: B)
4. Continuous 12-lead ECG monitoring is a reasonable alternative to serial 12-lead recordings in patients whose initial ECG is nondiagnostic. (Level of Evidence: B)

CLASS IIb

1. For patients who present within 6 h of the onset of symptoms consistent with ACS, assessment of an early marker of cardiac injury (e.g., myoglobin) in conjunction with a late marker (e.g., troponin) may be considered. (Level of Evidence: B)
2. For patients who present within 6 h of symptoms suggestive of ACS, a 2-h delta CK-MB mass in conjunction with 2-h delta troponin may be considered. (Level of Evidence: B)
3. For patients who present within 6 h of symptoms suggestive of ACS, myoglobin in conjunction with CK-MB mass or troponin when measured at baseline and 90 min may be considered. (Level of Evidence: B)
4. Measurement of BNP or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. (Level of Evidence: B)

CLASS III

Total CK (without MB), aspartate aminotransferase (AST, SGOT), alanine transaminase, beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be utilized as primary tests for the detection of myocardial injury in patients with chest discomfort suggestive of ACS. (Level of Evidence: C)

C. IMMEDIATE MANAGEMENT

CLASS I

1. The history, physical examination, 12-lead ECG, and initial cardiac biomarker tests should be integrated to assign patients with chest pain into 1 of 4 categories: a noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS. (Level of Evidence: C)
2. Patients with probable or possible ACS but whose initial 12-lead ECG and cardiac biomarker levels are normal should be observed in a facility with cardiac monitoring (e.g., chest pain unit or hospital telemetry ward), and repeat ECG (or continuous 12-lead ECG monitoring) and repeat cardiac biomarker measurement(s) should be obtained at predetermined, specified time intervals (see Section III.B). (Level of Evidence: B)
3. In patients with suspected ACS in whom ischemic heart disease is present or suspected, if the follow-up 12-lead ECG and cardiac biomarkers measurements are normal, a stress test (exercise or pharmacological) to provoke ischemia should be performed in the ED, in a chest pain unit, or on an outpatient basis in a timely fashion (within 72 h) as an alternative to inpatient admission. Low-risk patients with a negative diagnostic test can be managed as outpatients. (Level of Evidence: C)
4. In low-risk patients who are referred for outpatient stress testing (see above), precautionary appropriate pharmacotherapy (e.g., ASA,

sublingual NTG, and/or beta blockers) should be given while awaiting results of the stress test. (Level of Evidence: C)

5. Patients with definite ACS and ongoing ischemic symptoms, positive cardiac biomarkers, new ST-segment deviations, new deep T-wave inversions, hemodynamic abnormalities, or a positive stress test should be admitted to the hospital for further management. Admission to the critical care unit is recommended for those with active, ongoing ischemia/injury and hemodynamic or electrical instability. Otherwise, a telemetry step-down unit is reasonable. (Level of Evidence: C)
6. Patients with possible ACS and negative cardiac biomarkers who are unable to exercise or who have an abnormal resting ECG should undergo a pharmacological stress test. (Level of Evidence: B)
7. Patients with definite ACS and ST-segment elevation in leads V₇ to V₉ due to left circumflex should be evaluated for immediate reperfusion therapy. (Level of Evidence: A)
8. Patients discharged from the ED or chest pain unit should be given specific instructions for activity, medications, additional testing, and follow-up with a personal physician. (Level of Evidence: C)

CLASS IIa

In patients with suspected ACS with a low or intermediate probability of CAD, in whom the follow-up 12-lead ECG and cardiac biomarker measurements are normal, performance of a noninvasive coronary imaging test (i.e., coronary CT angiography) is reasonable as an alternative to stress testing. (Level of Evidence: B)

3. Early Hospital Care

A. ANTI-ISCHEMIC AND ANALGESIC THERAPY

CLASS I

1. Bed/chair rest with continuous ECG monitoring is recommended for all UA/NSTEMI patients during the early hospital phase. (Level of Evidence: C)
2. Supplemental oxygen should be administered to patients with UA/NSTEMI with an arterial saturation less than 90%, respiratory distress, or other high-risk features for hypoxemia. (Pulse oximetry is useful for continuous measurement of SaO₂.) (Level of Evidence: B)
3. Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated. (Level of Evidence: C)
4. Intravenous NTG is indicated in the first 48 h after UA/NSTEMI for treatment of persistent ischemia, heart failure (HF), or hypertension. The decision to administer intravenous NTG and the dose used should not preclude therapy with other proven mortality-reducing interventions such as beta blockers or angiotensin-converting enzyme (ACE) inhibitors. (Level of Evidence: B)
5. Oral beta-blocker therapy should be initiated within the first 24 h for patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 s, second or third degree heart block, active asthma, or reactive airway disease). (Level of Evidence: B)

6. In UA/NSTEMI patients with continuing or frequently recurring ischemia and in whom beta blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant left ventricular (LV) dysfunction or other contraindications. (Level of Evidence: B)
7. An ACE inhibitor should be administered orally within the first 24 h to UA/NSTEMI patients with pulmonary congestion or LV ejection fraction (LVEF) less than or equal to 0.40, in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. (Level of Evidence: A)
8. An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of HF or LVEF less than or equal to 0.40. (Level of Evidence: A)
9. Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, nonsteroidal anti-inflammatory drugs (NSAIDs), except for ASA, whether nonselective or cyclooxygenase (COX)-2-selective agents, should be discontinued at the time a patient presents with UA/NSTEMI. (Level of Evidence: C)

CLASS IIa

1. It is reasonable to administer supplemental oxygen to all patients with UA/NSTEMI during the first 6 h after presentation. (Level of Evidence: C)
2. In the absence of contradictions to its use, it is reasonable to administer morphine sulfate intravenously to UA/NSTEMI patients if there is uncontrolled ischemic chest discomfort despite NTG, provided that additional therapy is used to manage the underlying ischemia. (Level of Evidence: B)
3. It is reasonable to administer intravenous (IV) beta blockers at the time of presentation for hypertension to UA/NSTEMI patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 s, second or third degree heart block, active asthma, or reactive airway disease). (Level of Evidence: B)
4. Oral long-acting nondihydropyridine calcium antagonists are reasonable for use in UA/NSTEMI patients for recurrent ischemia in the absence of contraindications after beta blockers and nitrates have been fully used. (Level of Evidence: C)
5. An ACE inhibitor administered orally within the first 24 h of UA/NSTEMI can be useful in patients without pulmonary congestion or LVEF less than or equal to 0.40 in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. (Level of Evidence: B)
6. Intra-aortic balloon pump counterpulsation is reasonable in UA/NSTEMI patients for severe ischemia that is continuing or recurs frequently despite intensive medical therapy, for hemodynamic instability in patients before or after coronary angiography, and for mechanical complications of MI. (Level of Evidence: C)

CLASS IIb

1. The use of extended-release forms of nondihydropyridine calcium antagonists instead of a beta blocker may be considered in patients with UA/NSTEMI. (Level of Evidence: B)

*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock): age greater than 70 years, systolic blood pressure less than 120 mm Hg, sinus tachycardia greater than 110 or heart rate less than 60, increased time since onset of symptoms of UA/NSTEMI.

2. Immediate-release dihydropyridine calcium antagonists in the presence of adequate beta blockade may be considered in patients with UA/NSTEMI with ongoing ischemic symptoms or hypertension. (Level of Evidence: B)

CLASS III

1. Nitrates should not be administered to UA/NSTEMI patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 beats per min), tachycardia (more than 100 beats per min) in the absence of symptomatic HF, or right ventricular infarction. (Level of Evidence: C)
2. Nitroglycerin or other nitrates should not be administered to patients with UA/NSTEMI who had received a phosphodiesterase inhibitor for erectile dysfunction within 24 h of sildenafil or 48 h of tadalafil use. The suitable time for the administration of nitrates after vardenafil has not been determined. (Level of Evidence: C)
3. Immediate-release dihydropyridine calcium antagonists should not be administered to patients with UA/NSTEMI in the absence of a beta blocker. (Level of Evidence: A)
4. An intravenous ACE inhibitor should not be given to patients within the first 24 h of UA/NSTEMI because of the increased risk of hypotension. (A possible exception may be patients with refractory hypertension.) (Level of Evidence: B)
5. It may be harmful to administer IV beta blockers to UA/NSTEMI patients who have contraindications to beta blockade, signs of HF or low-output state, or other risk factors* for cardiogenic shock. (Level of Evidence: A)
6. Nonsteroidal anti-inflammatory drugs (except for ASA), whether nonselective or COX-2-selective agents, should not be administered during hospitalization for UA/NSTEMI because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use. (Level of Evidence: C)

B. ANTIPLATELET/ANTICOAGULANT THERAPY IN PATIENTS FOR WHOM

DIAGNOSIS OF UA/NSTEMI IS LIKELY OR DEFINITE

Recommendations are written as the reader follows through the algorithm for Antiplatelet/Anticoagulant Therapy and Triage for Angiography (Figs. 6, 7, and 8). Letters after recommendations refer to the specific box in the algorithm. See Table 6 for dosing recommendations.

I. ANTIPLATELET THERAPY

CLASS I

1. Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication. (Level of Evidence: A) (Figs. 6 and 7; Box A)
2. Clopidogrel (loading dose followed by daily maintenance dose)† should be administered to UA/NSTEMI patients who are unable to

take ASA because of hypersensitivity or major gastrointestinal intolerance. (Level of Evidence: A) (Figs. 6 and 7; Box A)

3. In UA/NSTEMI patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly. (Level of Evidence: B)
4. For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose)† or an IV GP IIb/IIIa inhibitor. (Level of Evidence: A) Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor. (Level of Evidence: B)
5. For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected (see Section IV.C), clopidogrel (loading dose followed by daily maintenance dose)† should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (Level of Evidence: A) and ideally up to 1 year. (Level of Evidence: B) (Fig. 7; Box C2)
6. For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, HF, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed (Level of Evidence: A) (Fig. 7; Box D). Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban; Level of Evidence: A) or clopidogrel (loading dose followed by daily maintenance dose; Level of Evidence: A)† should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream). (Level of Evidence: C)

CLASS IIa

1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography. (Level of Evidence: C)
2. For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with both clopidogrel (loading dose followed by daily maintenance dose)† and an IV GP IIb/IIIa inhibitor (Level of Evidence: B). Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor.‡ (Level of Evidence: B)
3. For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an IV GP IIb/IIIa antagonist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier than planned catheterization or PCI. (Level of Evidence: B)

CLASS IIb

For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or

*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock): age greater than 70 years, systolic blood pressure less than 120 mm Hg, sinus tachycardia greater than 110 or heart rate less than 60, increased time since onset of symptoms of UA/NSTEMI.

†Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

‡Factors favoring administration of both clopidogrel and GP IIa/IIb inhibitor include: delay to angiography, high-risk features, and early recurrent ischemic discomfort.

tirofiban to anticoagulant and oral antiplatelet therapy. (Level of Evidence: B) (Fig. 7; Box C2)

CLASS III

Abciximab should not be administered to patients in whom PCI is not planned. (Level of Evidence: A)

II. ANTICOAGULANT THERAPY

Recommendations are written as the reader follows through the algorithm for Antiplatelet/Anticoagulant Therapy and Triage for Angiography (Figs. 6, 7, and 8). Letters after recommendations refer to the specific box in the algorithm. See Table 6 for dosing recommendations.

CLASS I

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.

- For patients in whom an invasive strategy is selected, regimens with established efficacy at a Level of Evidence: A include enoxaparin and UFH (Fig. 6; Box B1), and those with established efficacy at a Level of Evidence: B include bivalirudin and fondaparinux (Fig. 7; Box B1).
- For patients in whom a conservative strategy is selected, regimens using either enoxaparin* or UFH (Level of Evidence: A) or fondaparinux (Level of Evidence: B) have established efficacy. (Fig. 8; Box C1)* See also Class IIa recommendation below.
- In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable. (Level of Evidence: B) (Fig. 7; Box C1)

CLASS IIa

For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin* or fondaparinux is preferable to UFH as anticoagulant therapy, unless coronary artery bypass graft surgery (CABG) is planned within 24 h. (Level of Evidence: B)

III. ADDITIONAL MANAGEMENT CONSIDERATIONS FOR ANTIPLATELET AND ANTICOAGULANT THERAPY

Recommendations are written as the reader follows through the algorithm for Antiplatelet/Anticoagulant Therapy and Triage for Angiography (Figs. 6, 7, and 8). Letters after recommendations refer to the specific box in the algorithm. See Table 6 for dosing recommendations.

CLASS I

- For UA/NSTEMI patients in whom an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), a stress test should be performed. (Level of Evidence: B) (Fig. 7; Box O)
 - If, after stress testing, the patient is classified as not at low risk, diagnostic angiography should be performed. (Level of Evidence: A) (Fig. 7; Box E1)
 - If, after stress testing, the patient is classified as being at low risk (Fig. 7; Box E2), the instructions noted below should be followed in preparation for discharge (Fig. 7; Box K) (Level of Evidence: A):
 - Continue ASA indefinitely. (Level of Evidence: A)
 - Continue clopidogrel for at least 1 month (Level of Evidence: A) and ideally up to 1 year. (Level of Evidence: B)

- Discontinue IV GP IIb/IIIa inhibitor if started previously. (Level of Evidence: A)

- Continue UFH for 48 h or administer enoxaparin or fondaparinux for the duration of hospitalization, up to 8 d, and then discontinue anticoagulant therapy. (Level of Evidence: A)

- For UA/NSTEMI patients in whom CABG is selected as a postangiography management strategy, the instructions noted below should be followed (Fig. 8; Box G).

- Continue ASA. (Level of Evidence: A)
- Discontinue clopidogrel 5 to 7 d before elective CABG. (Level of Evidence: B) More urgent surgery, if necessary, may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable. (Level of Evidence: C)
- Discontinue IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) 4 h before CABG. (Level of Evidence: B)
- Anticoagulant therapy should be managed as follows:
 - Continue UFH. (Level of Evidence: B)
 - Discontinue enoxaparin* 12 to 24 h before CABG and dose with UFH per institutional practice. (Level of Evidence: B)
 - Discontinue fondaparinux 24 h before CABG and dose with UFH per institutional practice. (Level of Evidence: B)
 - Discontinue bivalirudin 3 h before CABG and dose with UFH per institutional practice. (Level of Evidence: B)

- For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, the instructions noted below should be followed (Fig. 8 C; Box H):

- Continue ASA. (Level of Evidence: A)
- Administer a loading dose of clopidogrel† if not started before diagnostic angiography. (Level of Evidence: A)
- Administer an IV GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) if not started before diagnostic angiography for troponin-positive and other high-risk patients. (Level of Evidence: A) See Class IIa recommendation below if bivalirudin was selected as the anticoagulant.
- Discontinue anticoagulant therapy after PCI for uncomplicated cases. (Level of Evidence: B)

- For UA/NSTEMI patients in whom medical therapy is selected as a postangiography management strategy and in whom no significant obstructive CAD on angiography was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician. (Level of Evidence: C) For patients in whom evidence of coronary atherosclerosis is present (e.g., luminal irregularities or intravascular ultrasound–demonstrated lesions), albeit without flow-limiting stenoses, long-term treatment with ASA and other secondary prevention measures should be prescribed. (Fig. 8; Box I) (Level of Evidence: C)

- For UA/NSTEMI patients in whom medical therapy is selected as a postangiography management strategy and in whom CAD was found on angiography, the following approach is recommended (Fig. 8; Box J):

- Continue ASA. (Level of Evidence: A)
- Administer a loading dose of clopidogrel† if not given before diagnostic angiography. (Level of Evidence: A)

*Limited data are available for the use of other LMWHs (e.g., dalteparin; see Tables 6 and 7) in UA/NSTEMI.

†Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

- c. Discontinue IV GP IIb/IIIa inhibitor if started previously. (Level of Evidence: B)
- d. Anticoagulant therapy should be managed as follows:
 1. Continue IV UFH for at least 48 h or until discharge if given before diagnostic angiography. (Level of Evidence: A)
 2. Continue enoxaparin for duration of hospitalization, up to 8 d, if given before diagnostic angiography. (Level of Evidence: A)
 3. Continue fondaparinux for duration of hospitalization, up to 8 d, if given before diagnostic angiography. (Level of Evidence: B)
 4. Either discontinue bivalirudin or continue at a dose of 0.25 mg per kg per h for up to 72 h at the physician's discretion, if given before diagnostic angiography. (Level of Evidence: B)
6. For UA/NSTEMI patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, the instructions noted below should be followed (Fig. 7; Box K):
 - a. Continue ASA indefinitely. (Level of Evidence: A)
 - b. Continue clopidogrel for at least 1 month (Level of Evidence: A) and ideally up to 1 year. (Level of Evidence: B)
 - c. Discontinue IV GP IIb/IIIa inhibitor if started previously. (Level of Evidence: A)
 - d. Continue UFH for 48 h or administer enoxaparin or fondaparinux for the duration of hospitalization, up to 8 d, and then discontinue anticoagulant therapy. (Level of Evidence: A)
7. For UA/NSTEMI patients in whom an initial conservative strategy is selected and in whom no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), LVEF should be measured. (Level of Evidence: B) (Fig. 7; Box L)

CLASS IIa

1. For UA/NSTEMI patients in whom PCI is selected as a postangiography management strategy, it is reasonable to omit administration of an IV GP IIb/IIIa antagonist if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier. (Level of Evidence: B) (Fig. 8)
2. If LVEF is less than or equal to 0.40, it is reasonable to perform diagnostic angiography. (Level of Evidence: B) (Fig. 7; Box M)
3. If LVEF is greater than 0.40, it is reasonable to perform a stress test. (Level of Evidence: B) (Fig. 7; Box N)

CLASS IIb

For UA/NSTEMI patients in whom PCI is selected as a postangiography management strategy, it may be reasonable to omit an IV GP IIb/IIIa inhibitor if not started before diagnostic angiography for troponin-negative patients without other clinical or angiographic high-risk features. (Level of Evidence: C)

CLASS III

Intravenous fibrinolytic therapy is not indicated in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block. (Level of Evidence: A)

C. INITIAL CONSERVATIVE VERSUS INITIAL INVASIVE STRATEGIES**CLASS I**

1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability

(without serious comorbidities or contraindications to such procedures). (Level of Evidence: B)

2. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in initially stabilized UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (see Table 5 and Sections III.B and IV.C.5). (Level of Evidence: A)

CLASS IIb

1. In initially stabilized patients, an initially conservative (i.e. a selectively invasive) strategy may be considered as a treatment strategy for UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (see Table 5 and Sections III.B and IV.C.5) including those who are troponin positive. (Level of Evidence: B) The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may be made by considering physician and patient preference. (Level of Evidence: C)
2. An invasive strategy may be reasonable in patients with chronic renal insufficiency. (Level of Evidence: C)

CLASS III

1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with extensive comorbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. (Level of Evidence: C)
2. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with acute chest pain and a low likelihood of ACS. (Level of Evidence: C)
3. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) should not be performed in patients who will not consent to revascularization regardless of the findings. (Level of Evidence: C)

D. RISK STRATIFICATION BEFORE DISCHARGE**CLASS I**

1. Noninvasive stress testing is recommended in low-risk patients (Table 3) who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h. (Level of Evidence: C)
2. Noninvasive stress testing is recommended in patients at intermediate risk (Table 3) who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h. (Level of Evidence: C)
3. Choice of stress test is based on the resting ECG, ability to perform exercise, local expertise, and technologies available. Treadmill exercise is useful in patients able to exercise in whom the ECG is free of baseline ST-segment abnormalities, bundle-branch block, LV hypertrophy, intraventricular conduction defect, paced rhythm, pre-excitation, and digoxin effect. (Level of Evidence: C)
4. An imaging modality should be added in patients with resting ST-segment depression (greater than or equal to 0.10 mV), LV hypertrophy, bundle-branch block, intraventricular conduction defect, preexcitation, or digoxin who are able to exercise. In patients undergoing a low-level exercise test, an imaging modality can add sensitivity. (Level of Evidence: B)
5. Pharmacological stress testing with imaging is recommended when physical limitations (e.g., arthritis, amputation, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, or

general debility) preclude adequate exercise stress. (*Level of Evidence: B*)

6. Prompt angiography without noninvasive risk stratification should be performed for failure of stabilization with intensive medical treatment. (*Level of Evidence: B*)
7. A noninvasive test (echocardiogram or radionuclide angiogram) is recommended to evaluate LV function in patients with definite ACS who are not scheduled for coronary angiography and left ventriculography. (*Level of Evidence: B*)

4. Revascularization With PCI and CABG in Patients With UA/NSTEMI

A. PERCUTANEOUS CORONARY INTERVENTION

CLASS I

1. An early invasive PCI strategy is indicated for patients with UA/NSTEMI who have no serious comorbidity and who have coronary lesions amenable to PCI and any of the high-risk features listed in Section IV.5. (See Section 3.C for specific recommendations and their Level of Evidence.)
2. Percutaneous coronary intervention (or CABG) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (*Level of Evidence: B*)
3. Percutaneous coronary intervention (or CABG) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. (*Level of Evidence: A*)
4. An intravenous platelet GP IIb/IIIa inhibitor is generally recommended in UA/NSTEMI patients undergoing PCI. (*Level of Evidence: A*) See Section IV.B.3. and Figures 6, 7, and 8 for details on timing and dosing recommendations (see Table 6).

CLASS IIa

1. Percutaneous coronary intervention is reasonable for focal saphenous vein graft (SVG) lesions or multiple stenoses in UA/NSTEMI patients who are undergoing medical therapy and who are poor candidates for reoperative surgery. (*Level of Evidence: C*)
2. Percutaneous coronary intervention (or CABG) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. (*Level of Evidence: B*)
3. Percutaneous coronary intervention (or CABG) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal left anterior descending CAD. (*Level of Evidence: B*)
4. Use of PCI is reasonable in patients with UA/NSTEMI with significant left main CAD (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG or who require emergent intervention at angiography for hemodynamic instability. (*Level of Evidence: B*)

CLASS IIb

1. In the absence of high-risk features associated with UA/NSTEMI, PCI may be considered in patients with single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more lesions to be dilated with a reduced likelihood of success. (*Level of Evidence: B*)

2. Percutaneous coronary intervention may be considered for UA/NSTEMI patients who are undergoing medical therapy who have 2- or 3-vessel disease, significant proximal left anterior descending CAD, and treated diabetes or abnormal LV function, with anatomy suitable for catheter-based therapy. (*Level of Evidence: B*)

CLASS III

1. Percutaneous coronary intervention (or CABG) is not recommended for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. (*Level of Evidence: C*)
2. In the absence of high-risk features associated with UA/NSTEMI, PCI is not recommended for patients with UA/NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have 1 or more of the following:
 - a. Only a small area of myocardium at risk. (*Level of Evidence: C*)
 - b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success. (*Level of Evidence: C*)
 - c. A high risk of procedure-related morbidity or mortality. (*Level of Evidence: C*)
 - d. Insignificant disease (less than 50% coronary stenosis). (*Level of Evidence: C*)
 - e. Significant left main CAD and candidacy for CABG. (*Level of Evidence: B*)
3. A PCI strategy in stable patients with persistently occluded infarct-related coronary arteries after NSTEMI is not indicated. (*Level of Evidence: B*)

B. CABG

CLASS I

1. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with significant left main CAD (greater than 50% stenosis). (*Level of Evidence: A*)
2. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with 3-vessel disease; the survival benefit is greater in patients with abnormal LV function (LVEF less than 0.50). (*Level of Evidence: A*)
3. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with 2-vessel disease with significant proximal left anterior descending CAD and either abnormal LV function (LVEF less than 0.50) or ischemia on noninvasive testing. (*Level of Evidence: A*)
4. Coronary artery bypass graft surgery is recommended for UA/NSTEMI in patients in whom percutaneous revascularization is not optimal or possible and who have ongoing ischemia not responsive to maximal nonsurgical therapy. (*Level of Evidence: B*)
5. Coronary artery bypass graft surgery (or PCI) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (*Level of Evidence: B*)
6. Coronary artery bypass graft surgery (or PCI) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. (*Level of Evidence: A*)

CLASS IIa

1. For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes. (*Level of Evidence: B*)

2. It is reasonable to perform CABG with the internal mammary artery for UA/NSTEMI patients with multivessel disease and treated diabetes mellitus. (*Level of Evidence: B*)
3. Repeat CABG is reasonable for UA/NSTEMI patients with multiple SVG stenoses, especially when there is significant stenosis of a graft that supplies the left anterior descending coronary artery (LAD). (*Level of Evidence: C*)
4. Coronary artery bypass graft surgery (or PCI) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. (*Level of Evidence: B*)
5. Coronary artery bypass graft surgery (or PCI) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal left anterior descending CAD. (*Level of Evidence: B*)
6. Coronary artery bypass graft surgery (or PCI) with stenting is reasonable for patients with multivessel disease and symptomatic myocardial ischemia. (*Level of Evidence: B*)

CLASS IIb

Coronary artery bypass graft surgery may be considered in patients with UA/NSTEMI who have 1- or 2-vessel disease not involving the proximal LAD with a modest area of ischemic myocardium when percutaneous revascularization is not optimal or possible. (If there is a large area of viable myocardium and high-risk criteria on noninvasive testing, this recommendation becomes a Class I recommendation.) (*Level of Evidence: B*)

CLASS III

Coronary artery bypass graft surgery (or PCI) is not recommended for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. (*Level of Evidence: C*)

5. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge Care

A. MEDICAL REGIMEN AND USE OF MEDICATIONS

RECOMMENDATIONS**CLASS I**

1. Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with UA/NSTEMI who do not undergo coronary revascularization, patients with unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Upward or downward titration of the doses may be required. (*Level of Evidence: C*)
2. All post-UA/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. (*Level of Evidence: C*)
3. Before hospital discharge, patients with UA/NSTEMI should be informed about symptoms of worsening myocardial ischemia and MI and should be instructed in how and when to seek emergency care and assistance if such symptoms occur. (*Level of Evidence: C*)
4. Before hospital discharge, post-UA/NSTEMI patients and/or designated responsible caregivers should be provided with supportable, easily understood, and culturally sensitive instructions with

respect to medication type, purpose, dose, frequency, and pertinent side effects. (*Level of Evidence: C*)

5. In post-UA/NSTEMI patients, anginal discomfort lasting more than 2 or 3 min should prompt the patient to discontinue physical activity or remove himself or herself from any stressful event. If pain does not subside immediately, the patient should be instructed to take 1 dose of NTG sublingually. If the chest discomfort/pain is unimproved or worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or a family member/friend call 9-1-1 immediately to access EMS. While activating EMS access, additional NTG (at 5-min intervals 2 times) may be taken while lying down or sitting. (*Level of Evidence: C*)
6. If the pattern or severity of anginal symptoms changes, which suggests worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or now occurs at rest), the patient should contact his or her physician without delay to assess the need for additional treatment or testing. (*Level of Evidence: C*)

B. LONG-TERM MEDICAL THERAPY AND SECONDARY PREVENTION

I. ANTIPLATELET THERAPY

CLASS I

1. For UA/NSTEMI patients treated medically without stenting, aspirin* (75 to 162 mg per day) should be prescribed indefinitely (*Level of Evidence: A*) clopidogrel† (75 mg per day) should be prescribed for at least 1 month (*Level of Evidence: A*) and ideally for up to 1 year. (*Level of Evidence: B*)
2. For UA/NSTEMI patients treated with bare-metal stents, aspirin* 162 to 325 mg per day should be prescribed for at least 1 month (*Level of Evidence: B*), then continued indefinitely at a dose of 75 to 162 mg per day (*Level of Evidence: A*); clopidogrel should be prescribed at a dose of 75 mg per day for a minimum of 1 month and ideally for up to 1 year (unless the patient is at increased risk of bleeding, then it should be given for a minimum of 2 weeks). (*Level of Evidence: B*)
3. For UA/NSTEMI patients treated with DES, aspirin* 162 to 325 mg per day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation then continued indefinitely at a dose of 75 to 162 mg per day. (*Level of Evidence: B*) Clopidogrel 75 mg daily should be given for at least 12 months to all post-PCI patients receiving DES. (*Level of Evidence: B*)
4. Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when ASA is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as proton-pump inhibitors). (*Level of Evidence: A*)

CLASS IIa

For UA/NSTEMI patients in whom the physician is concerned about the risk of bleeding, a lower initial aspirin dose after PCI of 75 to 162 mg per day is reasonable. (*Level of Evidence: C*)

*For ASA-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.

†For clopidogrel-allergic patients, use ticlopidine 250 mg by mouth twice daily.

CLASS IIb

For UA/NSTEMI patients who have an indication for anticoagulation, add warfarin* to maintain an international normalization ratio of 2.0 to 3.0.† (Level of Evidence: B)

CLASS III

Dipyridamole is not recommended as an antiplatelet agent in post-UA/NSTEMI patients because it has not been shown to be effective. (Level of Evidence: A)

II. BETA BLOCKERS

CLASS I

1. Beta blockers are indicated for all patients recovering from UA/NSTEMI unless contraindicated. (For those at low risk, see Class IIa recommendation below). Treatment should begin within a few days of the event, if not initiated acutely, and should be continued indefinitely. (Level of Evidence: B)
2. Patients recovering from UA/NSTEMI with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme. (Level of Evidence: B)

CLASS IIa

It is reasonable to prescribe beta blockers to low-risk patients (i.e., normal LV function, revascularized, no high-risk features) recovering from UA/NSTEMI in the absence of absolute contraindications. (Level of Evidence: B)

III. INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

CLASS I

1. Angiotensin-converting enzyme inhibitors should be given and continued indefinitely for patients recovering from UA/NSTEMI with HF, LV dysfunction (ejection fraction less than 0.40), hypertension, or diabetes mellitus unless contraindicated. (Level of Evidence: A)
2. An angiotensin receptor blocker should be prescribed at discharge to those UA/NSTEMI patients who are intolerant of an ACE inhibitor and who have either clinical or radiological signs of HF and LVEF less than 0.40. (Level of Evidence: A)
3. Long-term aldosterone receptor blockade should be prescribed for UA/NSTEMI patients without significant renal dysfunction (estimated creatinine clearance should be greater than 30 ml per min) or hyperkalemia (potassium should be less than or equal to 5 mEq per liter) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either symptomatic HF or diabetes mellitus. (Level of Evidence: A)

CLASS IIa

1. Angiotensin-converting enzyme inhibitors are reasonable for patients recovering from UA/NSTEMI in the absence of LV dysfunction, hypertension, or diabetes mellitus unless contraindicated. (Level of Evidence: A)
2. Angiotensin-converting enzyme inhibitors are reasonable for patients with HF and LVEF greater than 0.40. (Level of Evidence: A)
3. In UA/NSTEMI patients who do not tolerate ACE inhibitors, an angiotensin receptor blocker can be useful as an alternative to ACE inhibitors in long-term management provided there are either clinical

or radiological signs of HF and LVEF less than 0.40. (Level of Evidence: B)

CLASS IIb

The combination of an ACE inhibitor and an angiotensin receptor blocker may be considered in the long-term management of patients recovering from UA/NSTEMI with persistent symptomatic HF and LVEF less than 0.40‡ despite conventional therapy including an ACE inhibitor or angiotensin receptor blocker alone. (Level of Evidence: B)

IV. NITROGLYCERIN

CLASS I

Nitroglycerin to treat ischemic symptoms is recommended. (Level of Evidence: C)

V. CALCIUM CHANNEL BLOCKERS

CLASS I

1. Calcium channel blockers§ are recommended for ischemic symptoms when beta blockers are not successful. (Level of Evidence: B)
2. Calcium channel blockers§ are recommended for ischemic symptoms when beta blockers are contraindicated or cause unacceptable side effects. (Level of Evidence: C)

VI. WARFARIN THERAPY

CLASS I

Use of warfarin in conjunction with ASA and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. (Level of Evidence: A)

CLASS IIb

Warfarin either without (international normalized ratio 2.5 to 3.5) or with low-dose ASA (75 to 81 mg per d; international normalized ratio 2.0 to 2.5) may be reasonable for patients at high CAD risk and low bleeding risk who do not require or are intolerant of clopidogrel. (Level of Evidence: B)

VII. LIPID MANAGEMENT

CLASS I

1. The following lipid recommendations are beneficial:
 - a. Lipid management should include assessment of a fasting lipid profile for all patients, within 24 h of hospitalization. (Level of Evidence: C)
 - b. Hydroxymethyl glutaryl-coenzyme A reductase inhibitors (statins), in the absence of contraindications, regardless of baseline LDL-C and diet modification, should be given to post-UA/NSTEMI patients, including postrevascularization patients. (Level of Evidence: A)
 - c. For hospitalized patients, lipid-lowering medications should be initiated before discharge. (Level of Evidence: A)
 - d. For UA/NSTEMI patients with elevated LDL-C (greater than or equal to 100 mg per dL), cholesterol-lowering therapy should be initiated or intensified to achieve an LDL-C of less than 100 mg per dL. (Level of Evidence: A) Further titration to less than 70 mg per dL is reasonable. (Class IIa, Level of Evidence: A)
 - e. Therapeutic options to reduce non-HDL-C|| are recommended,

*Continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; or cerebral, venous, or pulmonary emboli.

†An international normalized ratio of 2.0 to 2.5 is preferable while given with ASA and clopidogrel, especially in older patients and those with other risk factors for bleeding.

‡The safety of this combination has not been proven in patients also on aldosterone antagonist and is not recommended.

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

||Non-HDL-C = total cholesterol minus HDL-C.

including more intense LDL-C-lowering therapy. (Level of Evidence: B)

- f. Dietary therapy for all patients should include reduced intake of saturated fats (to less than 7% of total calories), cholesterol (to less than 200 mg per d), and trans fat (to less than 1% of energy). (Level of Evidence: B)
- g. Promoting daily physical activity and weight management are recommended. (Level of Evidence: B)

2. Treatment of triglycerides and non-HDL-C is useful, including the following:

- a. If triglycerides are 200 to 499 mg per dL, non-HDL-C* should be less than 130 mg per dL. (Level of Evidence: B)
- b. If triglycerides are greater than or equal to 500 mg per dL†, therapeutic options to prevent pancreatitis are fibrate‡ or niacin‡ before LDL-lowering therapy is recommended. It is also recommended that LDL-C be treated to goal after triglyceride-lowering therapy. Achievement of a non-HDL-C* less than 130 mg per dL (i.e., 30 mg per dL greater than LDL-C target) if possible is recommended. (Level of Evidence: C)

CLASS IIa

The following lipid management strategies can be beneficial:

- a. Further reduction of LDL-C to less than 70 mg per dL is reasonable. (Level of Evidence: A)
- b. If baseline LDL cholesterol is 70 to 100 mg per dL, it is reasonable to treat LDL-C to less than 70 mg per dL. (Level of Evidence: B)
- c. Further reduction of non-HDL-C* to less than 100 mg per dL is reasonable; if triglycerides are 200 to 499 mg per dL, non-HDL-C target is less than 130 mg per dL. (Level of Evidence: B)
- d. Therapeutic options to reduce non-HDL-C* (after LDL-C lowering) include niacin‡ or fibrate‡ therapy.
- e. Nicotinic acid (niacin)‡ and fibric acid derivatives (fenofibrate, gemfibrozil)† can be useful as therapeutic options (after LDL-C-lowering therapy) for HDL-C less than 40 mg per dL. (Level of Evidence: B)
- f. Nicotinic acid (niacin)‡ and fibric acid derivatives (fenofibrate, gemfibrozil)† can be useful as therapeutic options (after LDL-C-lowering therapy) for triglycerides greater than 200 mg per dL. (Level of Evidence: B)
- g. The addition of plant stanol/sterols (2 g per d) and/or viscous fiber (more than 10 g per d) is reasonable to further lower LDL-C. (Level of Evidence: A)

CLASS IIb

Encouraging consumption of omega-3 fatty acids in the form of fish§ or in capsule form (1 g per d) for risk reduction may be reasonable. For treatment of elevated triglycerides, higher doses (2 to 4 g per d) may be used for risk reduction. (Level of Evidence: B)

VIII. BLOOD PRESSURE CONTROL

CLASS I

Blood pressure control according to Joint National Committee on

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines|| is recommended (i.e., blood pressure less than 140/90 mm Hg or less than 130/80 mm Hg if the patient has diabetes mellitus or chronic kidney disease). (Level of Evidence: A) Additional measures recommended to treat and control blood pressure include the following:

- a. Patients should initiate and/or maintain lifestyle modifications, including weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. (Level of Evidence: B)
- b. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for individuals with chronic kidney disease or diabetes mellitus), it is useful to add blood pressure medication as tolerated, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve target blood pressure. (Level of Evidence: A)

IX. DIABETES MELLITUS

CLASS I

Diabetes management should include lifestyle and pharmacotherapy measures to achieve a near-normal hemoglobin A1c level of less than 7%. (Level of Evidence: B) Diabetes management should also include the following:

- a. Vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management) as recommended should be initiated and maintained. (Level of Evidence: B)
- b. It is useful to coordinate the patient's diabetic care with the patient's primary care physician or endocrinologist. (Level of Evidence: C)

X. SMOKING CESSATION

CLASS I

Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home are recommended. Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement) is useful, as is adopting a stepwise strategy aimed at smoking cessation (the 5 As are: Ask, Advise, Assess, Assist, and Arrange). (Level of Evidence: B)

XI. WEIGHT MANAGEMENT

CLASS I

Weight management, as measured by body mass index and/or waist circumference, should be assessed on each visit. A body mass index of 18.5 to 24.9 kg per m² and a waist circumference (measured horizontally at the iliac crest) of less than 40 inches for men and less than 35 inches for women is recommended. (Level of Evidence: B) Additional weight management practices recommended include the following:

- a. On each patient visit, it is useful to consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg per m². (Level of Evidence: B)
- b. If waist circumference is 35 inches or more in women or 40 inches

*Non-HDL-C = total cholesterol minus HDL-C.

†Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrants is relatively contraindicated when triglycerides are greater than 200 mg per dL.

‡The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

§Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

||Chobanian AV, Bakris GL, Black HR, et al., for the National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72 (6).

or more in men, it is beneficial to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. (Level of Evidence: B)

- c. The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. (Level of Evidence: B)

XII. PHYSICAL ACTIVITY

CLASS I

1. The patient's risk after UA/NSTEMI should be assessed on the basis of an in-hospital determination of risk. A physical activity history or an exercise test to guide initial prescription is beneficial. (Level of Evidence: B)
2. Guided/modified by an individualized exercise prescription, patients recovering from UA/NSTEMI generally should be encouraged to achieve physical activity duration of 30 to 60 min per d, preferably 7 (but at least 5) d per week of moderate aerobic activity, such as brisk walking, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work). (Level of Evidence: B)
3. Cardiac rehabilitation/secondary prevention programs are recommended for patients with UA/NSTEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is particularly warranted. (Level of Evidence: B)

CLASS IIb

The expansion of physical activity to include resistance training on 2 d per week may be reasonable. (Level of Evidence: C)

XIII. PATIENT EDUCATION

CLASS I

Beyond the detailed instructions for daily exercise, patients should be given specific instruction on activities (e.g., heavy lifting, climbing stairs, yard work, and household activities) that are permissible and those that should be avoided. Specific mention should be made regarding resumption of driving, return to work, and sexual activity. (Level of Evidence: C) Specific recommendations for physical activity follow in Section VI.E.

XIV. INFLUENZA

CLASS I

An annual influenza vaccination is recommended for patients with cardiovascular disease. (Level of Evidence: B)

XV. DEPRESSION

CLASS IIa

It is reasonable to consider screening UA/NSTEMI patients for depression and refer/treat when indicated. (Level of Evidence: B)

XVI. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

CLASS I

At the time of preparation for hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed, and a stepped-care approach to treatment should be used for selection of treatments (see Fig. 21 in the full-text guideline). Pain relief should begin with acetaminophen, small doses of narcotics, or nonacetylated salicylates. (Level of Evidence: C)

CLASS IIa

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

CLASS IIb

Nonsteroidal anti-inflammatory drugs with increasing degrees of relative COX-2 selectivity may be considered for pain relief only for situations in which intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, small doses of narcotics, nonacetylated salicylates, or nonselective NSAIDs. In all cases, the lowest effective doses should be used for the shortest possible time. (Level of Evidence: C)

CLASS III

Nonsteroidal anti-inflammatory drugs with increasing degrees of relative COX-2 selectivity should not be administered to UA/NSTEMI patients with chronic musculoskeletal discomfort when therapy with acetaminophen, small doses of narcotics, nonacetylated salicylates, or nonselective NSAIDs provides acceptable levels of pain relief. (Level of Evidence: C)

XVII. HORMONE THERAPY

CLASS III

1. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given de novo to postmenopausal women after UA/NSTEMI for secondary prevention of coronary events. (Level of Evidence: A)
2. Postmenopausal women who are already taking estrogen plus progestin, or estrogen alone, at the time of UA/NSTEMI in general should not continue hormone therapy. However, women who are more than 1 to 2 years past the initiation of hormone therapy who wish to continue such therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of cardiovascular events and breast cancer (combination therapy) or stroke (estrogen). Hormone therapy should not be continued while patients are on bedrest in the hospital. (Level of Evidence: B)

XVIII. ANTIOXIDANT VITAMINS AND FOLIC ACID

CLASS III

1. Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) should not be used for secondary prevention in UA/NSTEMI patients. (Level of Evidence: A)
2. Folic acid, with or without B6 and B12, should not be used for secondary prevention in UA/NSTEMI patients. (Level of Evidence: A)

C. POSTDISCHARGE FOLLOW-UP

RECOMMENDATIONS

CLASS I

1. Detailed discharge instructions for post-UA/NSTEMI patients should include education on medications, diet, exercise, and smoking cessation counseling (if appropriate), referral to a cardiac rehabilitation/secondary prevention program (when appropriate), and the scheduling of a timely follow-up appointment. Low-risk medically treated patients and revascularized patients should return in 2 to 6 weeks, and higher risk patients should return within 14 d. (Level of Evidence: C)
2. Patients with UA/NSTEMI managed initially with a conservative strategy who experience recurrent signs or symptoms of UA or

severe (Canadian Cardiovascular Society class III) chronic stable angina despite medical management who are suitable for revascularization should undergo timely coronary angiography. (Level of Evidence: B)

3. Patients with UA/NSTEMI who have tolerable stable angina or no anginal symptoms at follow-up visits should be managed with long-term medical therapy for stable CAD. (Level of Evidence: B)
4. Care should be taken to establish effective communication between the post-UA/NSTEMI patient and health care team members to enhance long-term compliance with prescribed therapies and recommended lifestyle changes. (Level of Evidence: B)

D. CARDIAC REHABILITATION

CLASS I

Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with UA/NSTEMI, particularly those with multiple modifiable risk factors and those moderate- to high-risk patients in whom supervised or monitored exercise training is warranted. (Level of Evidence: B)

6. Special Groups

A. WOMEN

CLASS I

1. Women with UA/NSTEMI should be managed with the same pharmacological therapy as men both in the hospital and for secondary prevention, with attention to antiplatelet and anticoagulant doses based on weight and renal function; doses of renally cleared medications should be based on estimated creatinine clearance. (Level of Evidence: B)
2. Recommended indications for noninvasive testing in women with UA/NSTEMI are similar to those for men. (Level of Evidence: B)
3. For women with high-risk features for invasive strategy, recommendations are similar to those for men. (Level of Evidence: B)
4. In women with low-risk features, a conservative strategy is recommended. (Level of Evidence: B)

B. DIABETES MELLITUS

CLASS I

1. Medical treatment in the acute phase of UA/NSTEMI and decisions on whether to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus. (Level of Evidence: A)
2. In all patients with diabetes mellitus and UA/NSTEMI, attention should be directed toward aggressive glycemic management in accordance with current standards of diabetes care endorsed by the American Diabetes Association and the American College of Endocrinology. Goals of therapy should include a preprandial glucose target of less than 110 mg per dL and a maximum daily target of less than 180 mg per dL. The postdischarge goal of therapy should be hemoglobin A1c less than 7%, which should be addressed by primary care and cardiac caregivers at every visit. (Level of Evidence: B)
3. An intravenous platelet GP IIb/IIIa inhibitor should be administered for patients with diabetes mellitus as recommended for all UA/NSTEMI patients (Sections I.C.3.A and IV.B). (Level of Evidence: A) The benefit may be enhanced in patients with diabetes mellitus. (Level of Evidence: B)

CLASS IIa

1. For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes mellitus. (Level of Evidence: B)
2. Percutaneous coronary intervention is reasonable for UA/NSTEMI patients with diabetes mellitus with single-vessel disease and inducible ischemia. (Level of Evidence: B)
3. In patients with UA/NSTEMI and diabetes mellitus, it is reasonable to administer aggressive insulin therapy to achieve a glucose less than 150 mg per dL during the first 3 hospital (intensive care unit) days and between 80 and 110 mg per dL thereafter whenever possible. (Level of Evidence: B)

Please see Section V for further explanation of revascularization strategies.

C. POST-CABG PATIENTS

CLASS I

1. Medical treatment for UA/NSTEMI patients after CABG should follow the same guidelines as for non-post-CABG patients with UA/NSTEMI. (Level of Evidence: C)
2. Because of the many anatomic possibilities that might be responsible for recurrent ischemia, there should be a low threshold for angiography in post-CABG patients with UA/NSTEMI. (Level of Evidence: C)

CLASS IIa

1. Repeat CABG is reasonable for UA/NSTEMI patients with multiple SVG stenoses, especially when there is significant stenosis of a graft that supplies the LAD. Percutaneous coronary intervention is reasonable for focal saphenous vein stenosis. (Level of Evidence: C) (Note that an intervention on a native vessel is generally preferable to that on a vein graft that supplies the same territory, if possible.)
2. Stress testing with imaging in UA/NSTEMI post-CABG patients is reasonable. (Level of Evidence: C)

D. OLDER ADULTS

CLASS I

1. Older patients with UA/NSTEMI should be evaluated for appropriate acute and long-term therapeutic interventions in a similar manner as younger patients with UA/NSTEMI. (Level of Evidence: A)
2. Decisions on management of older patients with UA/NSTEMI should not be based solely on chronologic age but should be patient centered, with consideration given to general health, functional and cognitive status, comorbidities, life expectancy, and patient preferences and goals. (Level of Evidence: B)
3. Attention should be given to appropriate dosing (i.e., adjusted by weight and estimated creatinine clearance) of pharmacological agents in older patients with UA/NSTEMI, because they often have altered pharmacokinetics (due to reduced muscle mass, renal and/or hepatic dysfunction, and reduced volume of distribution) and pharmacodynamics (increased risks of hypotension and bleeding). (Level of Evidence: B)
4. Older UA/NSTEMI patients face increased early procedural risks with revascularization relative to younger patients, yet the overall benefits from invasive strategies are equal to or perhaps greater in older adults and are recommended. (Level of Evidence: B)
5. Consideration should be given to patient and family preferences, quality-of-life issues, end-of-life preferences, and sociocultural differences in older patients with UA/NSTEMI. (Level of Evidence: C)

E. CHRONIC KIDNEY DISEASE

CLASS I

1. Creatinine clearance should be estimated in UA/NSTEMI patients, and the doses of renally cleared drugs should be adjusted appropriately. (Level of Evidence: B)
2. In chronic kidney disease patients undergoing angiography, isosmolar contrast agents are indicated and are preferred. (Level of Evidence: A)

F. COCAINE AND METHAMPHETAMINE USERS

CLASS I

1. Administration of sublingual or intravenous NTG and intravenous or oral calcium antagonists is recommended for patients with ST-segment elevation or depression that accompanies ischemic chest discomfort after cocaine use. (Level of Evidence: C)
2. Immediate coronary angiography, if possible, should be performed in patients with ischemic chest discomfort after cocaine use whose ST segments remain elevated after NTG and calcium antagonists; PCI is recommended if occlusive thrombus is detected. (Level of Evidence: C)
3. Fibrinolytic therapy is useful in patients with ischemic chest discomfort after cocaine use if ST segments remain elevated despite NTG and calcium antagonists, if there are no contraindications, and if coronary angiography is not possible. (Level of Evidence: C)

CLASS IIa

1. Administration of NTG or oral calcium channel blockers can be beneficial for patients with normal ECGs or minimal ST-segment deviation suggestive of ischemia after cocaine use. (Level of Evidence: C)
2. Coronary angiography, if available, is probably recommended for patients with ischemic chest discomfort after cocaine use with ST-segment depression or isolated T-wave changes not known to be previously present and who are unresponsive to NTG and calcium antagonists. (Level of Evidence: C)
3. Management of UA/NSTEMI patients with methamphetamine use similar to that of patients with cocaine use is reasonable. (Level of Evidence: C)

CLASS IIb

Administration of combined alpha- and beta-blocking agents (e.g., labetalol) may be reasonable for patients after cocaine use with hypertension (systolic blood pressure greater than 150 mm Hg) or those with sinus tachycardia (pulse greater than 100 beats per min) provided that the patient has received a vasodilator, such as NTG or a calcium antagonist, within close temporal proximity (i.e., within the previous hour). (Level of Evidence: C)

CLASS III

Coronary angiography is not recommended in patients with chest pain after cocaine use without ST-segment or T-wave changes and with a negative stress test and cardiac biomarkers. (Level of Evidence: C)

G. VARIANT (PRINZMETAL'S) ANGINA

CLASS I

1. Diagnostic investigation is indicated in patients with a clinical picture suggestive of coronary spasm, with investigation for the presence of transient myocardial ischemia and ST-segment elevation during chest pain. (Level of Evidence: A)
2. Coronary angiography is recommended in patients with episodic chest pain accompanied by transient ST-segment elevation. (Level of Evidence: B)

3. Treatment with nitrates and calcium channel blockers is recommended in patients with variant angina whose coronary angiograms show no or nonobstructive coronary artery lesions. Risk factor modification is recommended, with patients with atherosclerotic lesions considered to be at higher risk. (Level of Evidence: B)

CLASS IIb

1. Percutaneous coronary intervention may be considered in patients with chest pain and transient ST-segment elevation and a significant coronary artery stenosis. (Level of Evidence: B)
2. Provocative testing may be considered in patients with no significant angiographic CAD and no documentation of transient ST-segment elevation when clinically relevant symptoms possibly explained by coronary artery spasm are present. (Level of Evidence: C)

CLASS III

Provocative testing is not recommended in patients with variant angina and high-grade obstructive stenosis on coronary angiography. (Level of Evidence: B)

H. CARDIOVASCULAR "SYNDROME X"

CLASS I

1. Medical therapy with nitrates, beta blockers, and calcium channel blockers, alone or in combination, is recommended in patients with cardiovascular syndrome X. (Level of Evidence: B)
2. Risk factor reduction is recommended in patients with cardiovascular syndrome X. (Level of Evidence: B)

CLASS IIb

1. Intracoronary ultrasound to assess the extent of atherosclerosis and rule out missed obstructive lesions may be considered in patients with syndrome X. (Level of Evidence: B)
2. If no ECGs during chest pain are available and coronary spasm cannot be ruled out, coronary angiography and provocative testing with acetylcholine, adenosine, or methacholine and 24-h ambulatory ECG may be considered. (Level of Evidence: C)
3. If coronary angiography is performed and does not reveal a cause of chest discomfort, and if syndrome X is suspected, invasive physiological assessment (i.e., coronary flow reserve measurement) may be considered. (Level of Evidence: C)
4. Imipramine or aminophylline may be considered in patients with syndrome X for continued pain despite implementation of Class I measures. (Level of Evidence: C)
5. Transcutaneous electrical nerve stimulation and spinal cord stimulation for continued pain despite the implementation of Class I measures may be considered for patients with syndrome X. (Level of Evidence: B)

CLASS III

Medical therapy with nitrates, beta blockers, and calcium channel blockers for patients with noncardiac chest pain is not recommended. (Level of Evidence: C)

II. Overview of the Acute Coronary Syndromes

A. Definition of Terms

Unstable angina/NSTEMI constitutes a clinical syndrome subset of ACS that is usually, but not always, caused by atherosclerotic CAD and is associated with an increased risk of cardiac death and subsequent MI. In the spectrum of ACS, UA/NSTEMI is defined by ECG ST-segment de-

pression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent).

“Acute coronary syndrome” has evolved as a useful operational term to refer to any constellation of clinical symptoms that are compatible with acute myocardial ischemia. It encompasses MI (STEMI and NSTEMI) and UA. These guidelines focus on 2 components of ACS: UA and NSTEMI. The “Act in Time” initiative of the National Heart Attack Alert Program (7) summarizes the clinical information needed to make the diagnosis of probable ACS at the earliest phase of clinical evaluation and can be accessed at <http://www.nhlbi.nih.gov/actintime/index.htm>. The implication of this early provisional diagnosis is that patients should be placed in an environment with continuous ECG monitoring and defibrillation capability, where a 12-lead ECG can be obtained and interpreted expeditiously. The most urgent priority is to identify patients with STEMI who should be considered for immediate reperfusion therapy and managed according to the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (8) and to recognize other potentially catastrophic causes of patient symptoms, such as aortic dissection. In these guidelines, UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar but of differing severity, that is, whether the ischemia is severe enough to cause myocardial injury with the release of a marker of myocardial injury, most commonly troponin I, troponin T, or CK-MB. The appearance of these biomarkers may be delayed by up to several hours after the onset of ischemic symptoms, after which the differentiation between UA (i.e., no biomarkers in circulation; usually transient, if any, ECG changes of ischemia) and NSTEMI (i.e., elevated biomarkers) can be made definitively.

B. Pathogenesis of UA/NSTEMI

These conditions are characterized by an imbalance between myocardial oxygen supply and demand. A relatively few nonexclusive causes are recognized (9). A reduction in oxygen supply is more commonly the principal mechanism than an increased requirement for oxygen.

- The most common cause of UA/NSTEMI is reduced myocardial perfusion due to coronary artery narrowing caused by a thrombus, usually nonocclusive, that develops on a disrupted atherosclerotic plaque. The release of myocardial markers can be caused by microembolization of platelet aggregates and plaque components. The most common underlying molecular and cellular pathophysiology of disrupted atherosclerotic plaque is arterial inflammation.
- A less common cause is dynamic obstruction (i.e., intense focal epicardial coronary artery spasm, spasm on top of plaque, or dynamic microvascular dysfunction/spasm).

- A third cause is severe narrowing alone (e.g., to progressive atherosclerosis or restenosis after a PCI).
- A fourth cause is coronary artery dissection (e.g., as a cause of ACS in periparturient women).
- The fifth mechanism is secondary UA, in which the precipitating condition is extrinsic to the coronary arterial bed, such as with fever, tachycardia, or thyrotoxicosis; anemia; hypoxemia; or hypotension. Often there is associated coronary atherosclerotic narrowing.

C. Presentations of UA and NSTEMI

There are 3 principal presentations of UA: 1) rest angina, 2) new-onset (less than 2 months) severe angina, and 3) increasing angina (in intensity, duration, and/or frequency) (10). Angina is graded according to the Canadian Cardiovascular Society classification (11). Non-ST-elevation MI generally presents as prolonged, more intense rest angina or angina equivalent.

D. Prevention of UA/NSTEMI

The major risk factors for development of CHD and UA/NSTEMI are well established. Modification of these risk factors can prevent the development of CHD (primary prevention) or reduce the risk of experiencing UA/NSTEMI in patients who have CHD (secondary prevention). The reader is referred to contemporary prevention guidelines for the evidence base and discussion supporting these guidelines (3,12,13). All practitioners should emphasize appropriate long-term preventive care.

E. Onset of UA/NSTEMI

1. Recognition of Symptoms by Patient

Recognition of symptoms of UA/NSTEMI must occur before evaluation and treatment can be pursued. Many people are unaware that symptoms besides chest discomfort, such as shortness of breath (14), diaphoresis (15), or extreme fatigue, can represent anginal equivalents (16,17). The average UA/NSTEMI patient does not seek medical care for approximately 2 h after symptom onset (17). Reasons for this delay have been studied and include a mismatch between expectation and actual symptoms (18–20) and an impression that symptoms are self-limited or are due to other chronic conditions (21).

2. Silent and Unrecognized Events

As many as one-half of all AMIs are clinically silent or unrecognized, and one third present with symptoms other than chest discomfort (22). Patients without chest discomfort are more likely to be older, to be women, to have diabetes mellitus, to have prior HF, and to delay going to the hospital. They also are less likely to be diagnosed correctly initially and to receive appropriate therapies. Unexplained dyspnea, even without angina, is a common and

serious symptom of atypical ischemia/infarction (14). Health care providers should maintain a high index of suspicion when evaluating groups at high risk for silent or unrecognized UA/MI.

III. Initial Evaluation and Management

A. Clinical Assessment

Morbidity and mortality from ACS can be reduced significantly if patients and bystanders recognize symptoms early, activate the EMS system, and shorten the time to definitive treatment. Educational materials are available on the "Act in Time" Web page (www.nhlbi.nih.gov/health/public/heart/mi/core_bk.pdf) (7). For symptoms of ACS, see Table 2.

When the patient makes contact with the medical care system, the health care provider must assess whether the symptoms are potentially a manifestation of an ACS. Health care providers should advise patients with possible ACS that an evaluation cannot be performed solely via the telephone, and they should especially target those with known CHD or CHD risk equivalents (24). They should also be sensitive to anginal risk equivalents, especially in older and diabetic patients (22). Patients with known CHD should be instructed to proceed rapidly to an ED when symptoms occur. When symptoms are moderate to severe or sustained and MI is suspected, they should be instructed to access the EMS system directly by calling 9-1-1 and to be transported to the hospital by ambulance (25,26). Every community should have a written protocol that guides EMS transport to appropriate care facilities (8). All patients presenting to the ED with symptoms suggestive of ACS should be considered high-priority and should be evaluated with a predetermined protocol (Fig. 1) (27). Patients should be placed on a cardiac monitor, with emergency resuscitation and defibrillation equipment nearby. An ECG should be performed and interpreted as soon as possible, with a goal of within 10 min of ED arrival. If STEMI is present, a primary reperfusion strategy should be implemented (8).

The recommendation for self-medication has been to encourage earlier contacting of the EMS system, that is, after taking 1 dose of NTG for unrelieved symptoms suggestive of ACS (Fig. 2) (8). (While awaiting ambulance arrival, patients tolerating NTG can be instructed to take additional NTG every 5 min, up to 3 doses.) Patients may be advised to chew ASA (162 to 325 mg) while emergency personnel are en route, may receive ASA en route to the hospital, or may be given ASA on arrival at the hospital.

1. Patient Transportation and ED or Outpatient Facility Evaluation

Patients with chest discomfort at rest or other symptoms of ACS for more than 20 min, hemodynamic instability, or

Table 2. Guidelines for the Identification of ACS Patients by ED Registration Clerks or Triage Nurses

Registration/clerical staff

Patients with the following chief complaints require immediate assessment by the triage nurse and should be referred for further evaluation:

- Chest pain, pressure, tightness, or heaviness; pain that radiates to neck, jaw, shoulders, back, or 1 or both arms
- Indigestion or "heartburn"; nausea and/or vomiting associated with chest discomfort
- Persistent shortness of breath
- Weakness, dizziness, lightheadedness, loss of consciousness

Triage nurse

Patients with the following symptoms and signs require immediate assessment by the triage nurse for the initiation of the ACS protocol:

- Chest pain or severe epigastric pain, nontraumatic in origin, with components typical of myocardial ischemia or MI:
 - Central/substernal compression or crushing chest pain
 - Pressure, tightness, heaviness, cramping, burning, aching sensation
 - Unexplained indigestion, belching, epigastric pain
 - Radiating pain in neck, jaw, shoulders, back, or 1 or both arms
 - Associated dyspnea
 - Associated nausea and/or vomiting
 - Associated diaphoresis
- If these symptoms are present, obtain stat ECG.

Medical history

The triage nurse should take a brief, targeted, initial history with an assessment of current or past history of:

- CABG, PCI, CAD, angina on effort, or MI
- NTG use to relieve chest discomfort
- Risk factors, including smoking, hyperlipidemia, hypertension, diabetes mellitus, family history, and cocaine or methamphetamine use
- Regular and recent medication use

The brief history must not delay entry into the ACS protocol.

Special considerations

Women may present more frequently than men with atypical chest pain and symptoms.

Diabetic patients may have atypical presentations due to autonomic dysfunction.

Elderly patients may have atypical symptoms such as generalized weakness, stroke, syncope, or a change in mental status.

Adapted from National Heart Attack Alert Program. Emergency Department: rapid identification and treatment of patients with acute myocardial infarction. Bethesda, MD: US Department of Health and Human Services. US Public Health Service. National Institutes of Health. National Heart, Lung and Blood Institute, September 1993. NIH Publication No. 93-3278 (23).

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; ECG = electrocardiogram; ED = emergency department; MI = myocardial infarction; NTG = nitroglycerin; PCI = percutaneous coronary intervention.

recent syncope/presyncope should be referred immediately to an ED. Patients with less severe symptoms and without high-risk features should be seen initially in an ED or an appropriate outpatient facility. High-risk patients should seek emergency transportation if available in less than 20 to 30 min.

The initial evaluation should answer 2 questions: what is the likelihood that the signs and symptoms represent ACS secondary to obstructive CAD, and what is the likelihood of an adverse clinical outcome? Traditional risk factors for CAD are less important than are symptoms, ECG findings, and cardiac biomarkers.

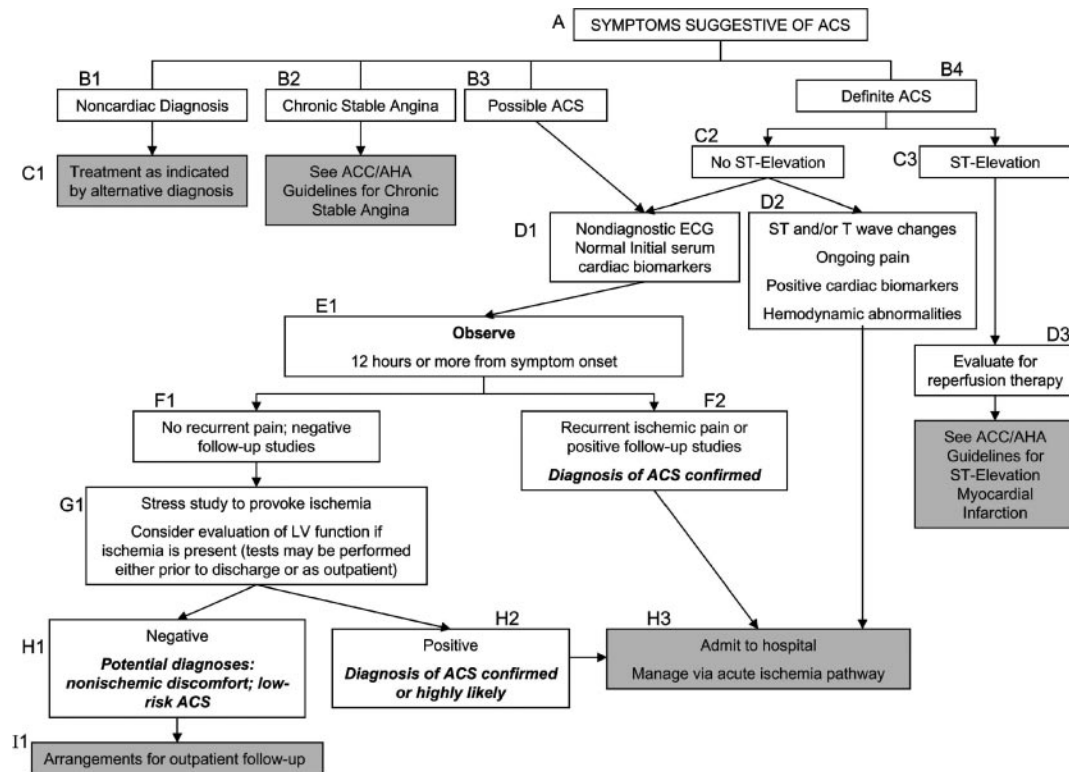


Figure 1. Algorithm for Evaluation and Management of Patients Suspected of Having ACS

To facilitate interpretation of this algorithm and a more detailed discussion in the text, each box is assigned a letter code that reflects its level in the algorithm and a number that is allocated from left to right across the diagram on a given level. ACC/AHA = American College of Cardiology/American Heart Association; ACS = acute coronary syndrome; ECG = electrocardiogram; LV = left ventricular.

B. Early Risk Stratification

1. Estimation of the Level of Risk

The initial medical history, physical examination, ECG, assessment of renal function, and cardiac biomarker measurements in patients with symptoms suggestive of ACS can be integrated into an estimation of the risk of death and nonfatal cardiac events (Table 3). An estimation of risk is useful in selection of the site of care and selection of initial medical and interventional therapies. The TIMI, GRACE, and PURSUIT risk scores, developed for short- and longer-term risk assessment, are discussed in Section III.B.3 below. Overall, risk is highest at the time of presentation and subsequently declines but remains elevated beyond the acute phase.

2. History

The 5 most important factors on the initial history, in order of importance, are 1) the nature of the anginal symptoms, 2) prior history of CAD, 3) sex (male), 4) older age, and 5) an increasing number of traditional risk factors (29,30). In patients without preexisting clinical CHD, older age is the most important factor.

Patients with UA/NSTEMI may have discomfort typical of chronic angina (31) except that the episodes are more severe, are prolonged, occur at rest, or are precipitated by less exertion.

Patients often do not perceive anginal symptoms to be true “chest pain”; hence, “chest discomfort” is preferentially used in these guidelines. Some patients have no chest discomfort but present solely with jaw, neck, arm, shoulder, back, or epigastric discomfort or with unexplained dyspnea without discomfort (14,32,33). Features of discomfort not characteristic of UA include pleuritic pain (i.e., sharp pain brought on by respiration or cough); primary or sole location in the middle or lower abdominal region; pain localized to a fingertip; pain reproduced with movement or palpation; very brief episodes (e.g., a few seconds or less); and radiation into the lower extremities. Nevertheless, uncharacteristic features do not entirely exclude ACS (34), and the relief of chest discomfort by sublingual NTG is not reliably predictive of ACS (35), nor does the relief of discomfort by a “GI cocktail” reliably predict its absence (36).

A history of MI increases the risk of obstructive and multivessel CAD. Presentations also can differ by sex (see Section VII.A) and age (see Section VII.D). Traditional risk factors are only weakly predictive of the likelihood of acute ischemia (37), and they are less important than symptoms, ECG findings, and cardiac biomarkers. However, diabetes mellitus and extracardiac disease are major risk factors for poor outcomes in patients with ACS.

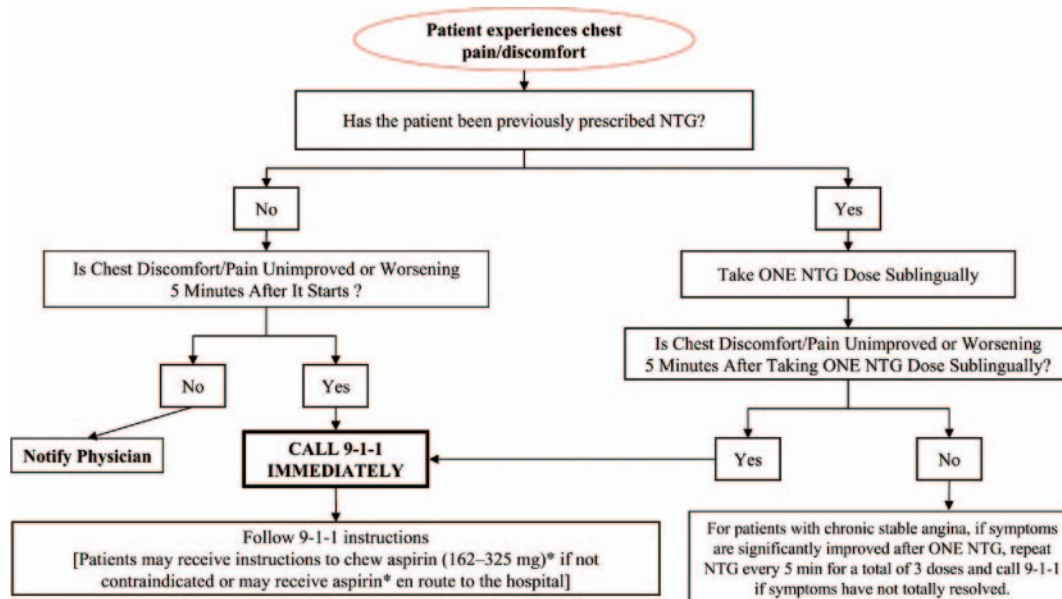


Figure 2. Patient (Advance) Instructions for NTG Use and EMS Contact in the Setting of Non-Trauma-Related Chest Discomfort/Pain

If patients experience chest discomfort/pain and have been previously prescribed NTG and have it available (right side of algorithm), it is recommended that they be instructed (in advance) to take 1 dose of NTG immediately in response to symptoms. If chest discomfort/pain is unimproved or worsening 5 min after taking 1 NTG sublingually, it is recommended that the patient call 9-1-1 immediately to access EMS. In patients with chronic stable angina, if the symptoms are significantly improved after taking 1 NTG, it is appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 minutes for a maximum of 3 doses and call 9-1-1 if symptoms have not totally resolved. If patients are not previously prescribed NTG (left side of algorithm), it is recommended that they call 9-1-1 if chest discomfort/pain is unimproved or worsening 5 min after it starts. If the symptoms subside within 5 min of when they began, patients should notify their physician of the episode. (For those patients with new-onset chest discomfort who have not been prescribed NTG, it is appropriate to discourage them from seeking someone else's NTG [e.g., from a neighbor, friend, or relative].) *Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. EMS = emergency medical services; NTG = nitroglycerin.

3. Tools to Estimate Risk at Presentation

The TIMI risk score tool, composed of 7 (1-point) risk indicators rated on presentation (Table 4), has been developed and validated for UA/NSTEMI patients (38,46) and is available at www.timi.org. It is useful to predict both 30-d and 1-year mortality. A second model is based on the PURSUIT trial (39). Risk models based on the GRACE database have been developed and validated for in-hospital and 6-month outcomes (40,47). The sum of 9 scores is applied to a reference monogram to determine risk of all-cause mortality (Fig. 3). The GRACE clinical application tool is available at www.outcomes-umassmed.org/grace. Among patients with UA/NSTEMI, there is progressively greater benefit with increasing risk score from more aggressive therapies, such as LMWH (41,42), platelet GP IIb/IIIa inhibition (43), and an invasive strategy with increasing risk score (44). Dynamic risk modeling promises more sophisticated predictive modeling in the future (45).

4. Electrocardiogram

The 12-lead ECG is central to the diagnostic and triage pathway for ACS (Fig. 1) and provides important prognostic information (48). Transient ST-segment changes (greater than or equal to 0.05 mV [ie, 0.5 mm]) that develop during a symptomatic episode at rest strongly suggest acute ischemia

due to severe CAD. Patients who present with ST-segment depression can have either UA or NSTEMI, the distinction being based on the later detection of biomarkers of myocardial necrosis. Inverted T waves, especially if marked (greater than or equal to 2 mm [0.2 mV]), also can indicate UA/NSTEMI (49). Q waves suggesting prior MI indicate a high likelihood of CAD. However, a normal ECG does not completely exclude ACS: 1% to 6% of such patients prove to have had an NSTEMI, and at least 4% will be found to have UA (50).

Approximately 4% of MI patients show ST elevation isolated to the posterior chest leads V₇ through V₉ (51). Posterior ST elevation is diagnostically important because it qualifies the patient for reperfusion therapy as a STEMI patient (8,52).

Serial or continuous ECGs increase diagnostic sensitivity, although the yield is greater with serial cardiac biomarker measurements (53–55). Electrocardiogram monitoring is also recommended, because ST elevation on 12-lead ECG is the principal criterion for reperfusion therapy.

5. Physical Examination

The major objectives of the physical examination are to identify potential precipitating causes of myocardial ischemia, such as uncontrolled hypertension, thyrotoxicosis, or gastrointestinal bleeding, and comorbid conditions that

Table 3. Short-Term Risk of Death or Nonfatal MI in Patients With UA/NSTEMI*

Feature	High Risk <i>At least 1 of the following features must be present:</i>	Intermediate Risk <i>No high-risk feature, but must have 1 of the following:</i>	Low Risk <i>No high- or intermediate-risk feature but may have any of the following features:</i>
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (greater than 20 min) rest pain	Prolonged (greater than 20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (greater than 20 min) or relieved with rest or sublingual NTG Nocturnal angina New-onset or progressive CCS class III or IV angina in the past 2 weeks without prolonged (greater than 20 min) rest pain but with intermediate or high likelihood of CAD (see Table 6)	Increased angina frequency, severity, or duration Angina provoked at a lower threshold New onset angina with onset 2 weeks to 2 months prior to presentation
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S ₃ or new/worsening rales Hypotension, bradycardia, tachycardia Age greater than 75 years	Age greater than 70 years	
ECG	Angina at rest with transient ST-segment changes greater than 0.5 mm Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes Pathological Q waves or resting ST-depression less than 1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged ECG
Cardiac markers	Elevated cardiac TnT, TnI, or CK-MB (e.g., TnT or TnI greater than 0.1 ng per ml)	Slightly elevated cardiac TnT, TnI, or CK-MB (e.g., TnT greater than 0.01 but less than 0.1 ng per ml)	Normal

*Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA (or NSTEMI) is a complex multivariable problem that cannot be fully specified in a table such as this; therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms. Adapted from AHA/ACC Clinical Practice Guidelines No. 10, Unstable Angina: Diagnosis and Management, May 1994 (28).

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CK-MB = creatine kinase, MB fraction; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation; NTG = nitroglycerin; TnI = troponin I; TnT = troponin T; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction.

could impact therapeutic risk and decision making, such as pulmonary disease and malignancies, as well as to assess the hemodynamic impact of the ischemic event. In every patient

Table 4. TIMI Risk Score for Unstable Angina/Non-ST-Elevation MI

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

The TIMI risk score is determined by the sum of the presence of 7 variables at admission; 1 point is given for each of the following variables: age 65 y or older; at least 3 risk factors for CAD; prior coronary stenosis of 50% or more; ST-segment deviation on ECG presentation; at least 2 anginal events in prior 24 h; use of aspirin in prior 7 d; elevated serum cardiac biomarkers. Prior coronary stenosis of 50% or more remained relatively insensitive to missing information and remained a significant predictor of events. Reprinted with permission from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835-42 (46). Copyright © 2000 American Medical Association.

CAD = coronary artery disease; ECG = electrocardiogram; MI = myocardial infarction; y = year.

with suspected ACS, vital signs should be routinely measured (blood pressure, in both arms if dissection is suspected; heart rate; temperature), and such patients should undergo a focused but thorough cardiovascular examination. The physical examination can also lead to important alternative diagnoses, such as aortic dissection (unequal pulses) or acute pericarditis (friction rub). Cardiogenic shock manifested by hypotension and evidence of organ hypoperfusion can occur in patients with NSTEMI or STEMI and constitutes a medical emergency (56).

6. Noncardiac Causes of Symptoms and Secondary Causes of Myocardial Ischemia

Three fourths of patients evaluated in the ED for suspected ACS will be found not to have acute ischemia (57). This includes patients with noncardiac pain (e.g., pulmonary embolism, musculoskeletal or esophageal discomfort) or cardiac pain not caused by myocardial ischemia (e.g., acute pericarditis). The remaining patients should be evaluated for secondary causes of UA, for example, aortic stenosis and hypertrophic cardiomyopathy; anemia due to gastrointestinal bleeding; hypoxemia due to worsening of chronic obstructive pulmonary disease; fever; hyperthyroidism;

Risk Calculator for 6-Month Postdischarge Mortality After Hospitalization for Acute Coronary Syndrome

Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the total score on the x-axis of the nomogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 months.

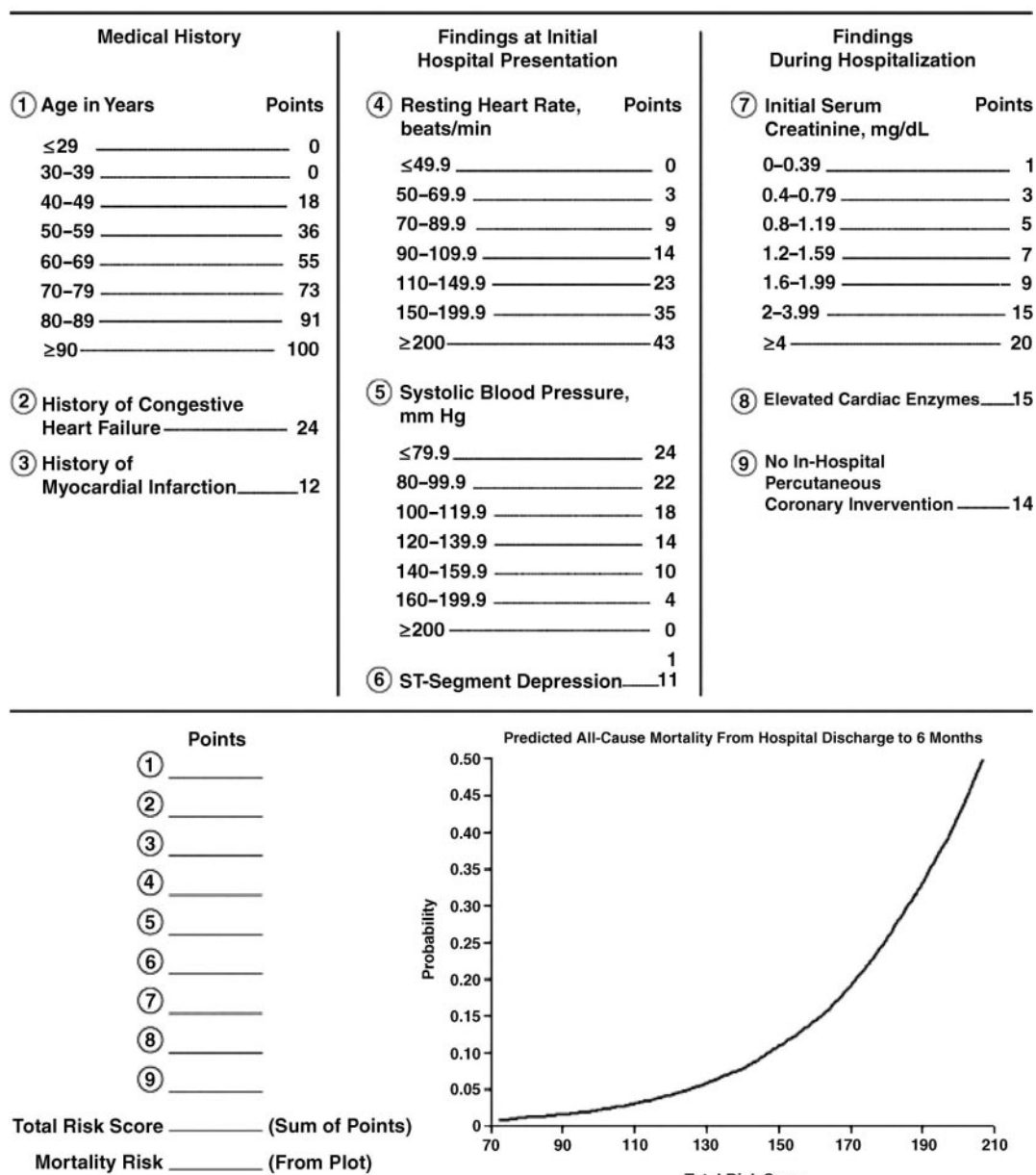


Figure 3. GRACE Prediction Score Card and Nomogram for All-Cause Mortality From Discharge to 6 Months

Reprinted with permission from Eagle KA, Lim MJ, Dabbous OH, et al. 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;291:2727–33 (47). Copyright © 2004 American Medical Association.

tachyarrhythmias; severe hypertension; and arteriovenous fistula placed for renal dialysis.

7. Cardiac Biomarkers of Necrosis and the Redefinition of AMI

Cardiac biomarkers have proliferated to address various facets of ACS pathophysiology. Favorable biomarker fea-

tures of biomarkers of necrosis are high concentrations in the myocardium and absence in nonmyocardial tissue, release into the blood within a convenient diagnostic time window and in proportion to the extent of myocardial injury, and quantification with reproducible, inexpensive, rapid, and easily applied assays (58). The cardiac troponins

possess many of these features, have gained wide acceptance as the biomarkers of choice, and have inspired redefinitions of MI (59). Myocardial necrosis now is defined by an elevation of troponin above the 99th percentile of normal. Myocardial infarction, which is necrosis related to ischemia, is further defined by the addition of at least 1 of the following criteria: ischemic ST and T-wave changes, new left bundle-branch block, new Q waves, PCI-related marker elevation, or imaging showing a new loss of myocardium.

A. CREATINE KINASE-MB

Creatine kinase-MB, long a standard marker for the diagnosis of MI, is less sensitive and specific for MI than the cardiac troponins; however, it remains useful for the diagnosis of early infarct extension (reinfarction) and periprocedural MI because its short half-life better permits the detection of secondary increases in marker levels (60).

B. CARDIAC TROPONINS

The troponin subunits T and I are derived from heart-specific genes; hence, the term “cardiac troponins” (cTn) specifically refers to cardiac troponin T (cTnT) or I (cTnI). Because cTnT and cTnI generally are not detected in the blood of healthy persons, the cutoff values for elevated cTnT and cTnI levels may be set to slightly above the upper limits of the performance characteristics of the assay for a normal healthy population. Assays for cTnI and cTnT have evolved through several generations (61); hence, physicians need to know the characteristics of tests used in their hospitals.

C. MYOGLOBIN

Myoglobin, a low-molecular-weight heme protein found in both cardiac and skeletal muscle, is not cardiac specific, but it is released rapidly (as early as 2 h) after the onset of myocardial necrosis. Because it is not cardiac specific, it may be more useful to assist in rapidly “ruling out” rather than “ruling in” NSTEMI, which should be confirmed by troponin measurements (62).

D. CLINICAL USE

Although troponins can be detected in blood as early as 2 to 4 h after the onset of symptoms, elevation can be delayed for up to 8 to 12 h. This timing of elevation is similar to that of CK-MB but persists longer, for up to 5 to 14 days (Fig. 4). Approximately 30% to 40% of ACS patients without ST-segment elevation who would be diagnosed as having UA on the basis of the absence of CK-MB elevation have NSTEMI when assessed by troponin assays. The result is a change in case mix and overall survival by a troponin-based definition of NSTEMI (63). Troponin elevation also conveys prognostic information incremental to clinical characteristics, the ECG, and the predischarge exercise test (64–68) (Fig. 5). Although cTn accurately identifies myocardial necrosis, it does not inform as to the cause(s) of necrosis, which can be multiple (69). Therefore, in making the diagnosis of NSTEMI, cardiac troponins should be used in conjunction with other criteria.

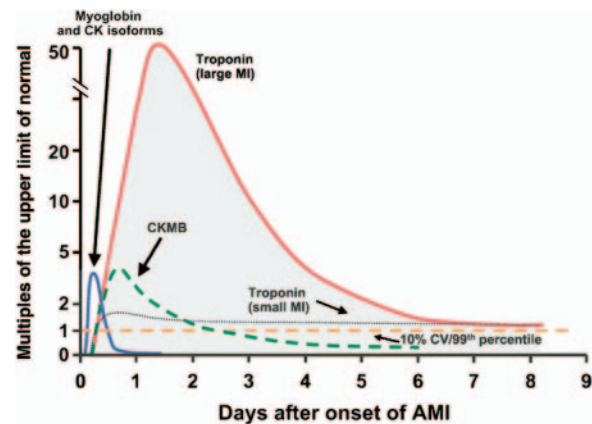


Figure 4. Timing of Release of Various Biomarkers After Acute Ischemic Myocardial Infarction

The biomarkers are plotted showing the multiples of the cutoff for acute myocardial infarction (AMI) over time. The dashed horizontal line shows the upper limit of normal (ULN; defined as the 99th percentile from a normal reference population without myocardial necrosis; the coefficient of variation of the assay should be 10% or less). The earliest rising biomarkers are myoglobin and CK isoforms (leftmost curve). CKMB (dashed curve) rises to a peak of 2 to 5 times the ULN and typically returns to the normal range within 2 to 3 d after AMI. The cardiac-specific troponins show small elevations above the ULN in small infarctions (e.g., as is often the case with NSTEMI) but rise to 20 to 50 times the ULN in the setting of large infarctions (e.g., as is typically the case in STEMI). The troponin levels may stay elevated above the ULN for 7 d or more after AMI. Modified from Shapiro BP, Jaffe AS. Cardiac biomarkers. In: Murphy JG, Lloyd MA, editors. Mayo Clinic Cardiology: Concise Textbook. 3rd ed. Rochester, MN: Mayo Clinic Scientific Press and New York: Informa Healthcare USA, 2007:773–80 (70). Used with permission of Mayo Foundation for Medical Education and Research. CK = creatine kinase; CKMB = MB fraction of creatine kinase; CV = coefficient of variation; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction.

Troponin elevation also permits the identification of high-risk patients who will benefit from aggressive therapies such as the LMWHs (vs. UFH) (41,42,71) and platelet GP IIb/IIIa inhibitors, alone (72,73) or in addition to clopidogrel (74), and in conjunction with overall risk assessment, a routine invasive strategy (75,76). When troponin and CK-MB are used together, those with both markers positive are at highest short-term risk, those with troponin elevation alone are at intermediate risk, and those with isolated CK-MB are at lowest risk, equivalent to those with normal marker levels (77). Equivalent diagnostic and prognostic information is provided by cTnI and cTnT except in patients with renal dysfunction (78), in whom cTnT is less specific but retains predictive ability (79).

Cardiac markers can be measured in the central chemistry laboratory or with point-of-care instruments in the ED (64). To date, bedside testing has not succeeded in becoming widely accepted or applied.

CLINICAL USE OF MARKER CHANGE SCORES

A newer method aims to identify or exclude MI within 6 h of symptoms by relying on changes in serum marker levels (delta values) over an abbreviated time interval (e.g., 2 h). This method focuses on increasing values while still in their

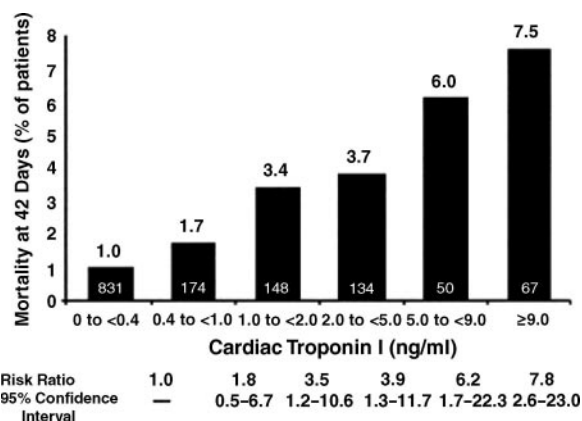


Figure 5. Troponin I Levels to Predict the Risk of Mortality in Acute Coronary Syndromes

Mortality rates are at 42 d (without adjustment for baseline characteristics) in patients with acute coronary syndrome. The numbers at the bottom of each bar are the numbers of patients with cardiac troponin I levels in each range, and the numbers above the bars are percentages. p less than 0.001 for the increase in the mortality rate (and the risk ratio for mortality) with increasing levels of cardiac troponin I at enrollment. Reprinted with permission from Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342–9 (66). Copyright © 1996 Massachusetts Medical Society. All rights reserved.

normal ranges, which potentially permits the earlier selection of patients for more aggressive anti-ischemic therapies (54,55).

8. Other Markers and Multimarker Approaches

Besides biomarkers of myocardial necrosis, markers of other pathophysiological mechanisms implicated in ACS are under investigation, including markers of ischemia, coagulation, platelet activation, inflammation, and HF. B-type natriuretic peptide, one of these newer biomarkers (measured as BNP or N-terminal proBNP), has been shown to provide incremental prognostic value in patient cohorts with STEMI and UA/NSTEMI (80–82) and is now included as possibly useful in guideline recommendations. A multimarker approach to risk stratification of UA/NSTEMI (e.g., simultaneous assessment of cTnI, C-reactive protein, and BNP) has been advocated as a potential advance over single biomarker assessment (83) but will require further assessment.

C. Immediate Management

By integrating information from the history, physical examination, 12-lead ECG, and initial cardiac biomarker tests, clinicians can assign patients to 1 of 4 categories: noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS, which is further divided into UA/NSTEMI and STEMI, based on the initial ECG (Fig. 1). Patients with a low likelihood of CAD should be evaluated for noncoronary presentations (Fig. 1, B1). Patients found to have an alternative diagnosis should be referred for appropriate follow-up care

(Fig. 1, C1). Chronic stable angina diagnosed in this setting (Fig. 1, B2) should be managed according to the ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina (31). Patients with possible ACS (Fig. 1, B3 and D1) are candidates for additional observation (Fig. 1, E1). Those with definite ACS (Fig. 1, B4) are triaged based on the 12-lead ECG. Patients with ST-segment elevation (Fig. 1, C3) are evaluated for reperfusion therapy (Fig. 1, D3) and managed according to the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (8), whereas those without ST-segment elevation (Fig. 1, C2) are either managed by additional observation (Fig. 1, E1) or admitted to the hospital (Fig. 1, H3). Patients with low-risk ACS (negative initial testing) (Fig. 1, H1) may be discharged and treated as outpatients (Fig. 1, I1).

1. Chest Pain Units

To facilitate appropriate evaluation while avoiding both unnecessary hospital admissions and ED discharges, special ED “chest pain units” have been established (84,85). Here, patients at low risk of ACS undergo a predetermined observation period with serial cardiac biomarkers and ECGs, are reevaluated, and may then undergo functional cardiac testing or a noninvasive coronary imaging study (i.e., coronary CT angiography). Those with abnormal findings are admitted for inpatient management (Fig. 1, H3).

Extension of the use of chest pain units to intermediate-risk patients has been favorably tested (86). Such a strategy is facilitated by making available diagnostic (stress/imaging) testing 7 d per week. An appropriate inpatient telemetry unit may serve as an alternative to an ED-based chest pain unit when the latter is not available.

Patients with positive findings during ED/chest pain unit initial evaluation or follow-up observation (Fig. 1, D2, F2) should be admitted to the hospital (Fig. 1, H3) and managed as described in Section IV. Patients at low ACS risk (Fig. 1, F1) may be considered for a pre-discharge stress test or coronary CT angiography (Fig. 1, G1). Alternatively, the patient may be discharged, with appropriate precautionary medication and instructions, and return for testing within 72 h. In general, a physician should see patients as soon after discharge from the ED or chest pain unit as practical and appropriate, that is, usually within 72 h.

Two newer imaging modalities, cardiac magnetic resonance and multidetector CT for coronary calcification and coronary CT angiography, are undergoing clinical validation and application and hold promise as alternative or supplementary imaging modalities for the assessment of patients presenting with chest pain syndromes (87–89). Coronary CT angiography may be particularly appropriate for those with acute chest pain syndromes with low to intermediate pretest probability of CAD in the setting of nondiagnostic ECG and negative cardiac biomarkers (88).

Table 5. Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy

Preferred Strategy	Patient Characteristics
Invasive	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 (e.g., TIMI, GRACE)
Conservative	Reduced left ventricular function (LVEF less than 40%)
	Low risk score (e.g., TIMI, GRACE)
	Patient or physician preference in the absence of high-risk features

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

IV. Early Hospital Care

Patients with definite or probable UA/NSTEMI who are stable hemodynamically should be admitted to an inpatient unit for bed rest with continuous rhythm monitoring and careful observation for recurrent ischemia and managed with either an invasive or conservative strategy (Fig. 1, Table 5). High-risk patients, including those with continuing discomfort and/or hemodynamic instability, should be hospitalized in a coronary care unit and observed for at least 24 h without any major complications. (Shorter periods might be appropriate for patients who are successfully reperfused, have normal LV function, and have minimal or no necrosis.)

After admission, standard medical therapy is indicated. The optimal management of UA/NSTEMI has the twin goals of relief of ischemia and prevention of serious adverse outcomes. This is accomplished with anti-ischemic therapy, anticoagulant therapy, ongoing risk stratification, and appropriate use of invasive procedures. Unless contraindicated, treatment generally should include ASA, a beta blocker, anticoagulant therapy, a GP IIb/IIIa receptor antagonist, and a thienopyridine (i.e., clopidogrel; initiation may be deferred until a revascularization decision is made). A critical early decision is the choice of an angiographic (invasive) or an initially conservative strategy (Table 5). Assessment of LV function, which can influence management, is recommended.

A. Anti-Ischemic and Analgesic Therapy

1. General Care

Patients should be placed on bed rest initially but can be mobilized to a chair and use a bedside commode when symptom free. Subsequent activity should be liberalized

when response to treatment occurs. Patients with or at risk for hypoxemia should receive supplemental oxygen. A short period of initial routine oxygen supplementation is reasonable during stabilization of the patient. Patients should undergo continuous ECG monitoring during their early hospital phases, because ventricular fibrillation is the major preventable cause of early death.

2. Use of Anti-Ischemic Therapies

A. NITRATES

The rationale for NTG use in UA/NSTEMI is extrapolated from STEMI and from pathophysiological principles and extensive clinical observations (90). Nitroglycerin is an endothelium-independent vasodilator with both peripheral and coronary vascular effects that result in reduction in myocardial oxygen demand and enhancement of myocardial oxygen delivery. Nitroglycerin promotes the dilation of large coronary arteries, as well as collateral flow and redistribution of coronary blood flow to ischemic regions.

Intravenous NTG can benefit patients who are unresponsive to sublingual NTG and beta blockers. Intravenous NTG is also useful in patients with HF or hypertension. Side effects include headache and hypotension.

Intravenous NTG may be initiated at a rate of 10 mcg per min and increased by 10 mcg per min every 3 to 5 min until relief of symptoms or blood pressure response is noted. A ceiling dose of 200 mcg per min is commonly used. Systolic blood pressure generally should not be reduced to less than 110 mm Hg in previously normotensive patients or to more than 25% below the starting mean arterial blood pressure if hypertension was present. Nitroglycerin should be avoided in patients with initial systolic blood pressure less than 90 mm Hg or 30 mm Hg or more below their baseline, or with marked bradycardia or tachycardia.

Topical or oral nitrates are acceptable alternatives for patients without ongoing refractory ischemic symptoms. After medical stabilization, intravenous NTG generally should be converted within 24 h to a nonparenteral alternative administered in a non-tolerance-producing regimen (lower and/or intermittent dosing) if ongoing therapy is required (91).

B. MORPHINE SULFATE

Morphine sulfate (1 to 5 mg intravenously [IV]) is reasonable for patients whose symptoms either are not relieved despite NTG or recur despite adequate anti-ischemic therapy. Hypotension, nausea, and respiratory depression are potential adverse effects of morphine. A large observational registry that included patients with UA/NSTEMI suggested a higher adjusted likelihood of death with morphine use (92). Although subject to uncontrolled selection biases, these results raise a safety concern and suggest the need for a randomized trial. Meanwhile, the recommendation for morphine use has been downgraded from a class I to a class IIa recommendation.

C. BETA-ADRENERGIC BLOCKERS

Beta blockers act by competitively blocking the effects of catecholamines on cell membrane beta receptors. The benefits of routine early intravenous use of beta blockers in earlier studies in AMI have been less impressive based on data in the reperfusion era (93,94). In the 45,852-patient Chinese COMMIT study (93% with STEMI, 7% with NSTEMI) (94), neither the composite of death, reinfarction, or cardiac arrest nor death alone was reduced for up to 28 d in the hospital. A modest reduction in reinfarction and ventricular fibrillation was counterbalanced by an increase in cardiogenic shock, primarily in those who were hemodynamically compromised. Thus, early aggressive beta blockade poses a net hazard in hemodynamically unstable patients and should be avoided. In an attempt to balance the evidence base overall for UA/NSTEMI patients, beta blockers are recommended to be initiated orally, in the absence of contraindications (e.g., HF), within the first 24 h. Greater caution is suggested in the early use of intravenous beta blockers, which should be targeted to specific indications and should be avoided with HF, hypotension, and hemodynamic instability. (In contrast, oral beta blockers are strongly recommended for secondary prevention before hospital discharge in those with compensated HF or LV systolic dysfunction) (95,96).

The rationale for use of beta blockers for secondary prevention after UA and NSTEMI derives from limited trial data and extrapolations from chronic angina, HF, and STEMI studies (95). Pooled results from relatively contemporary anticoagulant therapy trials in patients with ACS undergoing PCI and given beta-blocker therapy have shown reduced death rates at 30 d (0.6% vs. 2.0%) and 6 months (1.7% vs. 3.7%; both *p* less than 0.001) (96). High- or intermediate-risk patients undergoing cardiac or noncardiac surgery also have been shown to benefit (97).

D. CALCIUM CHANNEL BLOCKERS

Although members of the calcium channel blocker class of drugs are structurally diverse, the superiority of 1 agent over another in UA/NSTEMI has not been demonstrated, except for the increased risk posed by rapid-release nifedipine (98,99). The calcium channel blocker evidence base for benefit is greatest for verapamil and diltiazem (100,101). Beneficial effects in UA/NSTEMI are believed to be due to decreased myocardial oxygen demand and improved myocardial flow (90). Side effects include hypotension, worsening HF, bradycardia, and atrioventricular block.

Calcium channel blockers may be used to control ischemia-related symptoms in patients unresponsive to or intolerant of nitrates and beta blockers and in patients with variant angina. Rapid-release, short-acting dihydropyridines (e.g., nifedipine) must be avoided in the absence of concomitant beta blockade (98,99). Verapamil and diltiazem should be avoided in patients with pulmonary edema or severe LV dysfunction (100,101). Caution is indicated when a beta-blocker and calcium channel blocker are combined,

because they act in synergy to depress LV function and sinus and atrioventricular node conduction.

E. INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Angiotensin-converting enzyme inhibitors have been shown to reduce mortality rates in patients with AMI and in those who recently had an MI and have LV systolic dysfunction (102), in patients with diabetes mellitus with LV dysfunction (103), and in a broad spectrum of patients with high-risk chronic CAD, including patients with normal LV function (104). Angiotensin receptor blockers may be useful in post-MI and ischemic HF patients intolerant of ACE inhibitors (105,106).

The selective aldosterone receptor blocker eplerenone, used in patients with MI complicated by LV dysfunction and either HF or diabetes mellitus, has been shown to reduce morbidity and mortality (107). Spironolactone decreased morbidity and death in patients with severe HF, one-half of whom had an ischemic origin of the HF (108).

F. INTRA-AORTIC BALLOON COUNTERPULSATION

Intra-aortic balloon counterpulsation has been used for more than 30 years for refractory UA after MI, for cardiogenic shock, for hemodynamic support during catheterization and/or angioplasty, before high-risk surgery, and for mechanical complications of MI (109), although randomized data to support its benefit are limited.

G. ANALGESIC THERAPY

Because of the known increased risk of cardiovascular events among patients taking COX-2 inhibitors and NSAIDs (110–112), patients who are taking them at the time of UA/NSTEMI should discontinue them immediately (see Section 5.2.16 in the full text for additional discussion). A secondary analysis of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT)-TIMI-25 data (113) demonstrated an increased risk of death, reinfarction, HF, or shock among patients who were taking NSAIDs within 7 d of enrollment. Longer-term management is considered in Section VI.C.

B. Antiplatelet/Anticoagulant Therapy in Patients With Likely or Definite UA/NSTEMI

Anticoagulant therapy is essential to modify the ACS disease process and its adverse consequences. A combination of ASA, an anticoagulant, and additional antiplatelet therapy represents the most effective therapy. The intensity of treatment is tailored to individual risk, and triple-anticoagulant treatment is used in patients with continuing ischemia or with other high-risk features and in patients oriented to an early invasive strategy (see Table 5 and Figs. 6, 7, and 8). Table 6 shows the recommended doses of the various agents. A problematic group of patients are those who present with UA/NSTEMI but who are therapeutically anticoagulated with warfarin. In such patients, clinical judgment is needed.

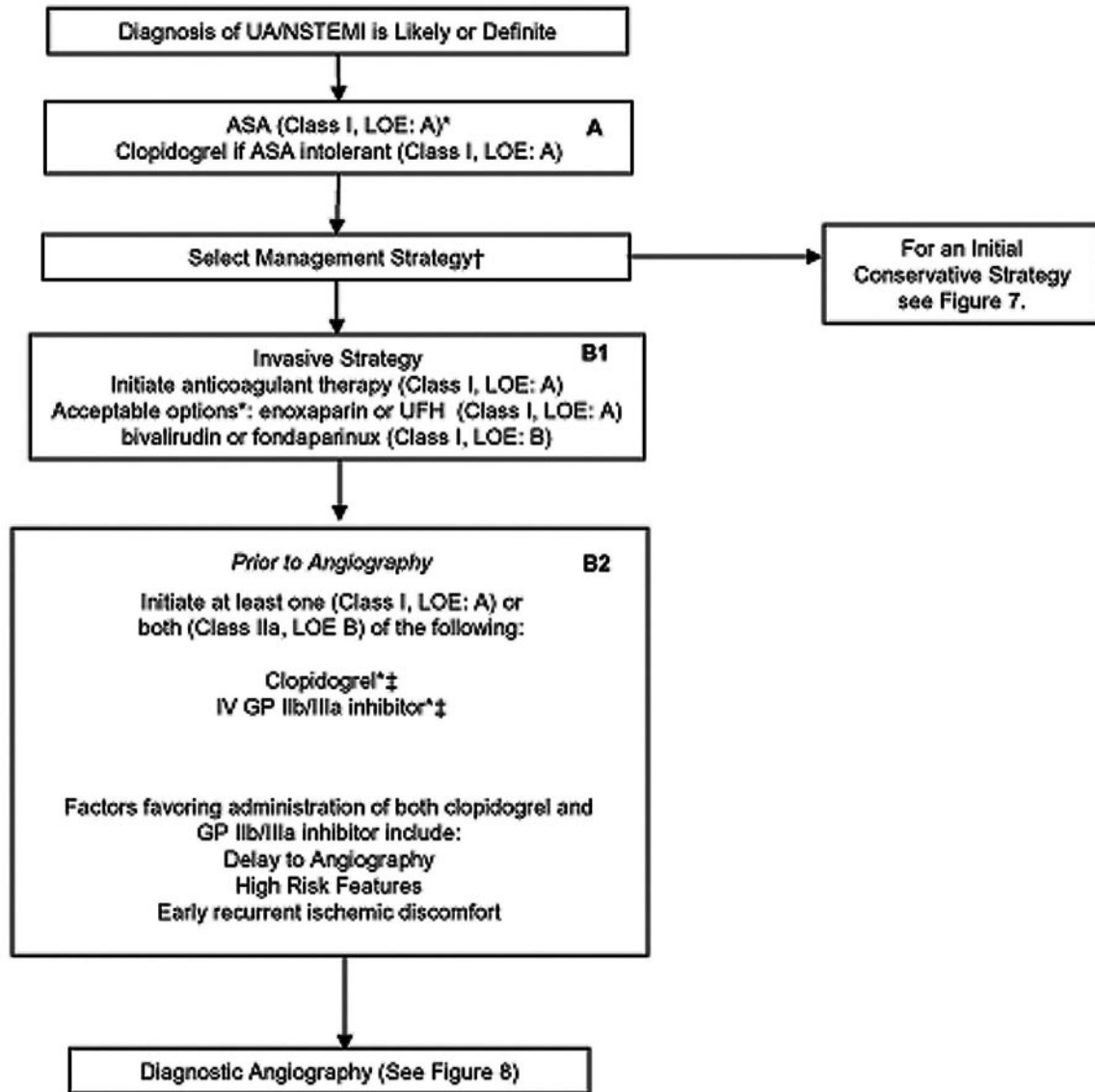


Figure 6. Algorithm for Patients With UA/NSTEMI Managed by an Initial Invasive Strategy

When multiple drugs are listed, they are in alphabetical order and not in order of preference (e.g., Boxes B, B1, and B2). *See dosing Table 6. †See Table 5 for selection of management strategy. ‡Evidence exists that GP IIb/IIIa inhibitors may not be necessary if the patient received a preloading dose of at least 300 mg of clopidogrel at least 6 h earlier (Class I, Level of Evidence B for clopidogrel administration) and bivalirudin is selected as the anticoagulant (Class IIa, Level of Evidence B). ASA = aspirin; GP = glycoprotein; IV = intravenous; LOE = level of evidence; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction; UFH = unfractionated heparin.

1. Antiplatelet Therapy (Aspirin, Ticlopidine, Clopidogrel)

A. ASPIRIN

Trials of ASA in UA/NSTEMI have consistently documented a benefit to its use compared with placebo (114–117). Platelets represent one of the principal participants in thrombus formation after plaque disruption. Aspirin acts promptly to inhibit COX-1 within platelets, which prevents the formation of thromboxane A₂, diminishing the platelet aggregation promoted by this pathway. Indirect comparisons of doses ranging from less than 75 to 1,500 mg per day

have shown similar reductions in the odds of vascular events; however, there is a dose-dependent increase in bleeding (118). Therefore, maintenance doses of 75 to 162 mg of ASA are recommended.

It is recommended that ASA be initiated as soon as the diagnosis of ACS is made or suspected unless contraindicated and that it be continued indefinitely. On the basis of prior randomized trial protocols and clinical experience, the initial dose of ASA should be between 162 and 325 mg. More rapid buccal absorption occurs with non-enteric-coated formulations than with enteric-coated formulations

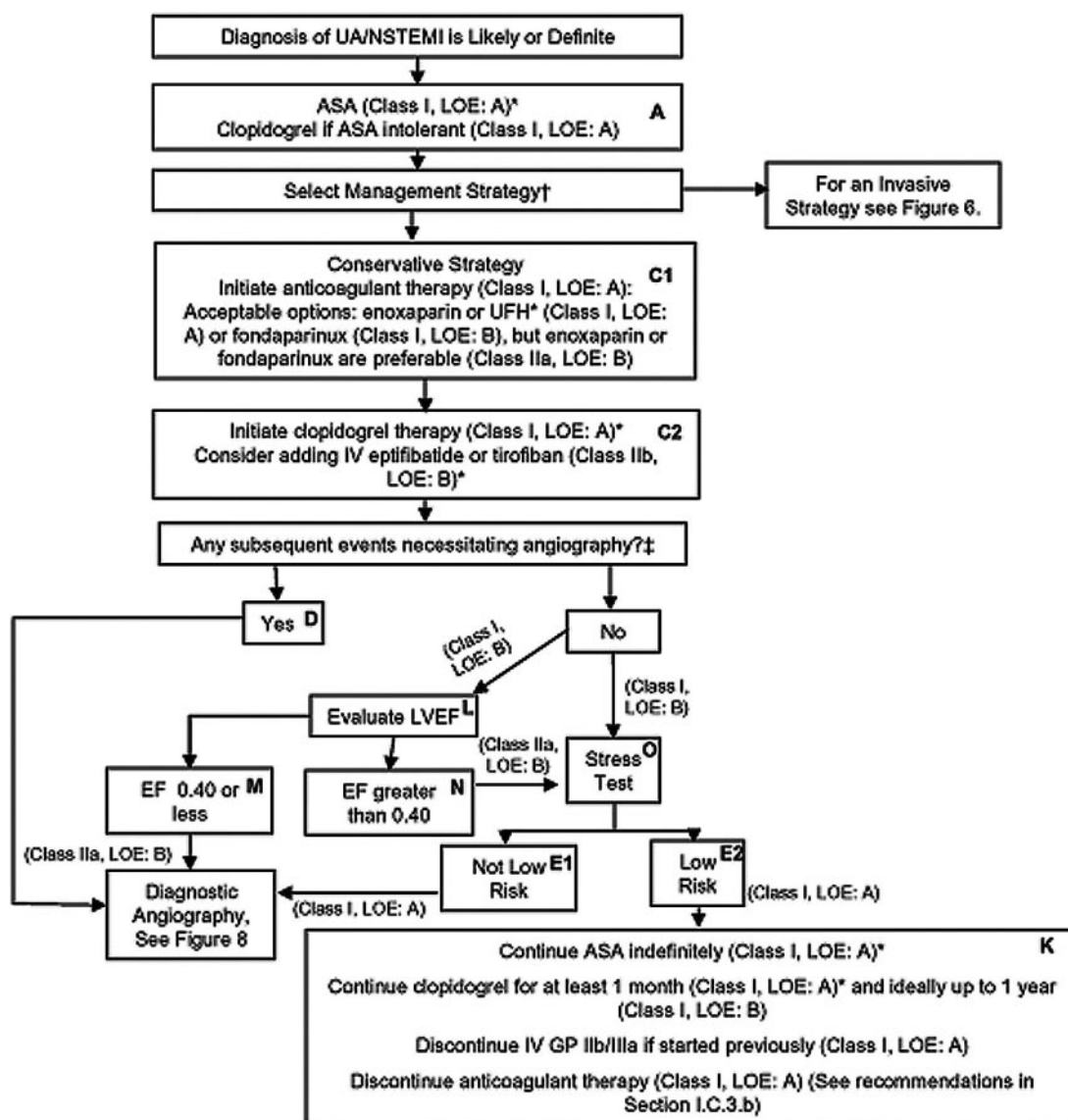


Figure 7. Algorithm for Patients With UA/NSTEMI Managed by an Initial Conservative Strategy

When multiple drugs are listed, they are in alphabetical order and not in order of preference (e.g., Boxes C1, and C2). *See dosing Table 6. †See Table 5 for selection of management strategy. ‡Recurrent symptoms/ischemia, heart failure, serious arrhythmia. ASA = aspirin; EF = ejection fraction; GP = glycoprotein; IV = intravenous; LOE = level of evidence; LVEF = left ventricular ejection fraction; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction; UFH = unfractionated heparin.

(119). After stenting, a higher initial maintenance dose of ASA of 325 mg per day has been recommended for 1 month after bare-metal stent implantation and 3 to 6 months after drug-eluting stent implementation, which had been modified to an initial dose range of 162 to 325 mg per day based on the risk of excess bleeding with higher doses and an update of current evidence of outcomes after PCI (Table 6, Fig. 9).

Because of an interaction between ibuprofen and ASA, an alternative NSAID should be used, or ibuprofen should be taken at least 30 min after or at least 8 h before ASA (www.fda.gov/drug/infopage/ibuprofen/science_paper.html).

A reported interaction of ASA and ACE inhibitors does not appear to interfere importantly with clinical benefits (120).

B. ADENOSINE DIPHOSPHATE RECEPTOR ANTAGONISTS AND OTHER ANTIPLATELET AGENTS

Two thienopyridines—ticlopidine and clopidogrel—are adenosine diphosphate receptor (P2Y₁₂) antagonists approved for antiplatelet therapy. The platelet effects of ticlopidine and clopidogrel are irreversible but take several days to achieve maximal effect in the absence of a loading dose. Ticlopidine has been used successfully for the secondary prevention of stroke and MI and for the prevention of

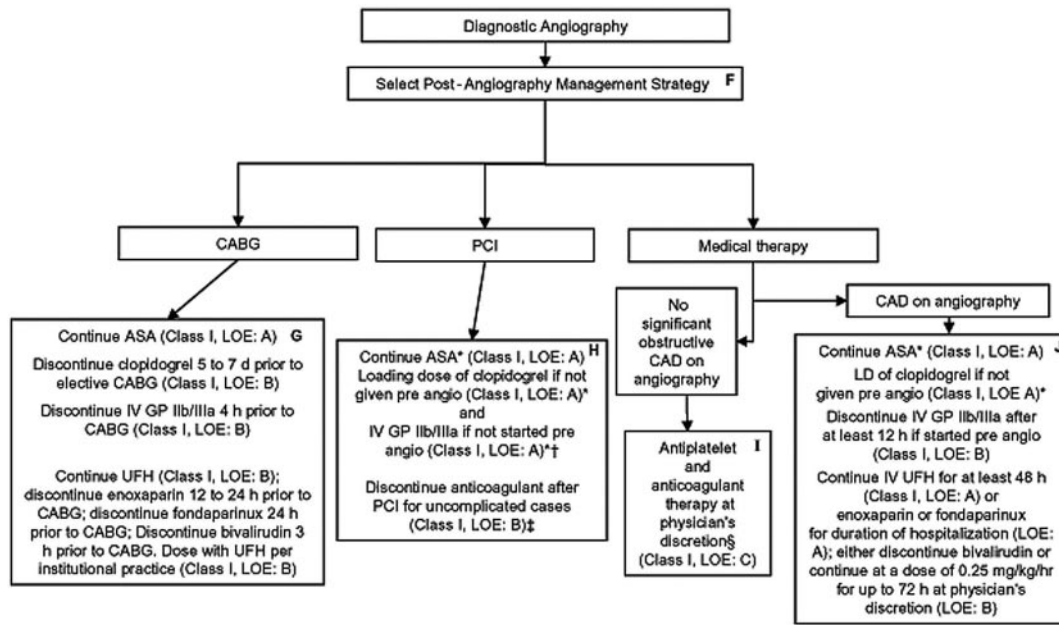


Figure 8. Management After Diagnostic Angiography in Patients With UA/NSTEMI

*See dosing Table 6. †Evidence exists that GP IIb/IIIa inhibitors may not be necessary if the patient received a preloading dose of at least 300 mg of clopidogrel at least 6 h earlier (Class I, Level of Evidence B for clopidogrel administration) and bivalirudin is selected as the anticoagulant (Class IIa, Level of Evidence B). ‡Additional bolus of UFH is recommended if fondaparinux is selected as the anticoagulant (see dosing Table 6). §For patients in whom the clinician believes coronary atherosclerosis is present, albeit without any significant, flow-limiting stenoses, long-term treatment with antiplatelet agents and other secondary prevention measures should be considered. ASA = aspirin; CABG = coronary artery bypass graft; CAD = coronary artery disease; GP = glycoprotein; IV = intravenous; LD = loading dose; PCI = percutaneous coronary intervention; pre angio = before angiography; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction; UFH = unfractionated heparin.

stent closure and graft occlusion (121); however, the adverse potential of ticlopidine (i.e., neutropenia and, rarely, thrombotic thrombocytopenic purpura) (122) has limited its use.

Clopidogrel has undergone extensive clinical testing and application. For secondary prevention, clopidogrel alone was at least as effective as or modestly more effective than ASA in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial (123). Thus, clopidogrel is indicated in patients with UA/NSTEMI who are unable to tolerate ASA. In patients with a history of gastrointestinal bleeding while taking ASA, drugs to minimize the risk of recurrent bleeding (e.g., proton-pump inhibitors) should be prescribed when a thienopyridine is administered (124).

In the acute setting, an oral loading dose of clopidogrel is typically used to achieve more rapid platelet inhibition. A large evidence base exists for the approved loading dose of 300 mg. Small to moderate-sized trials have reported favorable outcomes with a 600- versus a 300-mg loading dose in patients undergoing PCI (125); however, larger-scale randomized trials are needed to rigorously establish the optimal loading dose.

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial randomized 12,562 patients with UA and NSTEMI presenting within 24 h to placebo or clopidogrel (loading dose of 300 mg followed by 75 mg daily) and followed them for 3 to 12 months (118). All patients received ASA. Cardiovascular death, MI, or stroke

occurred in 11.5% of placebo and 9.3% of clopidogrel patients (risk ratio [RR] = 0.80, p less than 0.001). Clopidogrel also reduced in-hospital severe ischemia and revascularization. A benefit was observed across subgroups and began within the first few hours. A small excess in bleeding was noted, which was increased in patients undergoing CABG surgery within 5 d of stopping clopidogrel.

The PCI-CURE study was an observational substudy of the 2,658 patients undergoing PCI within the CURE trial (126). Clopidogrel reduced the primary end point (a composite of cardiovascular death, MI, or urgent target-vessel revascularization within 30 d of PCI) by 30% ($p = 0.03$) and reduced the incidence of cardiovascular death or MI by 31% ($p = 0.002$). Therefore, clopidogrel is recommended in patients who undergo PCI.

The Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment (ISAR-REACT)-2 trial tested whether patients undergoing PCI who were preloaded with clopidogrel 600 mg at least 2 h before the procedure, as well as ASA, would derive additional benefit from GP IIb/IIIa receptor antagonist therapy (74). The study randomized 2,022 patients to abciximab or placebo. The primary end point was reached in 90 patients (8.9%) assigned to abciximab versus 120 patients (11.9%) assigned to placebo, a 25% reduction in risk with abciximab (RR 0.75, 95% confidence interval [CI] 0.58 to 0.97, $p = 0.03$) (74). However, this benefit was limited to patients

Table 6. Dosing Table for Antiplatelet and Anticoagulant Therapy in Patients With UA/NSTEMI

Drug*	During PCI			At Hospital Discharge
	Initial Medical Treatment	Patient Received Initial Medical Treatment	Patient Did Not Receive Initial Medical Treatment	
		Oral Antiplatelet Therapy		
Aspirin	162 to 325 mg nonenteric formulation, orally or chewed	No additional treatment	162 to 325 mg nonenteric formulation orally or chewed	162 to 325 mg daily should be given† for at least 1 month after BMS implantation, 3 months after SES implantation, and 6 months after PES implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg
Clopidogrel	LD of 300 to 600 mg orally MD of 75 mg orally per day	A second LD of 300 mg orally may be given to supplement a prior LD of 300 mg	LD of 300 to 600 mg orally	For BMS: 75 mg daily for at least 1 month and ideally up to 1 year. For DES, 75 mg daily for at least 1 year (in patients who are not at high risk of bleeding) (See Fig. 9)
Ticlopidine	LD of 500 mg orally MD of 250 mg orally twice daily	No additional treatment	LD of 500 mg orally	MD of 250 mg orally twice daily
		Anticoagulants		
Bivalirudin	0.1 mg per kg bolus, 0.25 mg per kg per h infusion	0.5 mg per kg bolus, increase infusion to 1.75 mg per kg per h	0.75 mg per kg bolus, 1.75 mg per kg per h infusion	No additional treatment or continue infusion for up to 4 h
Dalteparin	120 IU per kg SC every 12 h (maximum 10,000 IU twice daily)‡	IV GP IIb/IIIa planned: target ACT 200 s using UFH No IV GP IIb/IIIa planned: target ACT 250 to 300 s for HemoTec; 300 to 350 s for Hemochron using UFH	IV GP IIb/IIIa planned: 60 to 70 U per kg§ of UFH No IV GP IIb/IIIa planned: 100 to 140 U per kg of UFH	No additional treatment
Enoxaparin	LD of 30 mg IV bolus may be given MD = 1 mg per kg SC every 12 h ; extend dosing interval to 1 mg per kg every 24 h if estimated creatinine clearance less than 30 mL per min	Last SC dose less than 8 h: no additional treatment Last SC dose greater than 8 h: 0.3 mg per kg IV bolus	0.5 to 0.75 mg per kg IV bolus	No additional treatment
Fondaparinux	2.5 mg SC once daily. Avoid for creatinine clearance less than 30 mL per min	50 to 60 U per kg IV bolus of UFH is recommended by the OASIS 5 Investigators¶	50 to 60 U per kg IV bolus of UFH is recommended by the OASIS 5 Investigators¶	No additional treatment

Continued on next page

Table 6. Continued

Drug*	During PCI				At Hospital Discharge
	Initial Medical Treatment	Patient Received Initial Medical Treatment	Patient Did Not Receive Initial Medical Treatment	After PCI	
Unfractionated heparin	LD of 60 U per kg (max 4,000 U) as IV bolus MD of IV infusion of 12 U per kg per h (max 1,000 U per h) to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s)	IV GP IIb/IIIa planned: target ACT 200 s No IV GP IIb/IIIa planned: target ACT 250 to 300 s for HemoTec; 300 to 350 s for Hemochron	IV GP IIb/IIIa planned: 60 to 70 U per kg§ No IV GP IIb/IIIa planned: 100 to 140 U per kg	No additional treatment	
Intravenous Antiplatelet Therapy					
Abciximab	Not applicable	Not applicable	LD of 0.25 mg per kg IV bolus MD of 0.125 mcg per kg per min (max 10 mcg per min)	Continue MD infusion for 12 h	
Eptifibatide	LD of IV bolus of 180 mcg per kg MD of IV infusion of 2.0 mcg per kg per min; reduce infusion by 50% in patients with estimated creatinine clearance less than 50 mL per min	Continue infusion	LD of IV bolus of 180 mcg per kg followed 10 min later by second IV bolus of 180 mcg per kg MD of 2.0 mcg per kg per min; reduce infusion by 50% in patients with estimated creatinine clearance less than 50 mL per min	Continue MD infusion for 18 to 24 h	
Tirofiban	LD of IV infusion of 0.4 mcg per kg per min for 30 min MD of IV infusion of 0.1 mcg per kg per min; reduce rate of infusion by 50% in patients with estimated creatinine clearance less than 30 mL per min	Continue infusion	LD of IV infusion of 0.4 mcg per kg per min for 30 min MD of IV infusion of 0.1 mcg per kg per min; reduce rate of infusion by 50% in patients with estimated creatinine clearance less than 30 mL per min	Continue MD infusion for 18 to 24 h	

Additional considerations include the possibility that a conservatively managed patient may develop a need for PCI, in which case an intravenous bolus of 50 to 60 U per kg is recommended if fondaparinux was given for initial medical treatment; the safety of this drug combination is not well established. For conservatively managed patients in whom enoxaparin was the initial medical treatment, as noted in the table, additional intravenous enoxaparin is an acceptable option. *This list is in alphabetical order and is not meant to indicate a particular therapy preference. †In patients in whom the physician is concerned about the risk of bleeding, a lower initial ASA dose after PCI of 75 to 162 mg/d is reasonable (Class IIa, LOE: C). ‡Dalteparin was evaluated for management of patients with UA/NSTEMI in an era before the widespread use of important therapies such as stents, clopidogrel, and GP IIb/IIIa inhibitors. Its relative efficacy and safety in the contemporary management era is not well established. §Some operators use less than 60 U per kg of UFH with GP IIb/IIIa blockade, although no clinical trial data exist to demonstrate the efficacy of doses below 60 U per kg in this setting. ||For patients managed by an initial conservative strategy, agents such as enoxaparin and fondaparinux offer the convenience advantage of SC administration compared with an intravenous infusion of UFH. They are also less likely to provoke heparin-induced thrombocytopenia than UFH. Available data suggest fondaparinux is associated with less bleeding than enoxaparin in conservatively managed patients using the regimens listed. ¶Personal communication, OASIS 5 Investigators, July 7, 2006. Note that this regimen has not been rigorously tested in prospective randomized trials.

ACT = activated clotting time; BMS = bare-metal stent; GP = glycoprotein; IU = international unit; IV = intravenous; LD = loading dose; MD = maintenance dose; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SC = subcutaneous; SES = sirolimus-eluting stent; U = units; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction; UFH = unfractionated heparin.

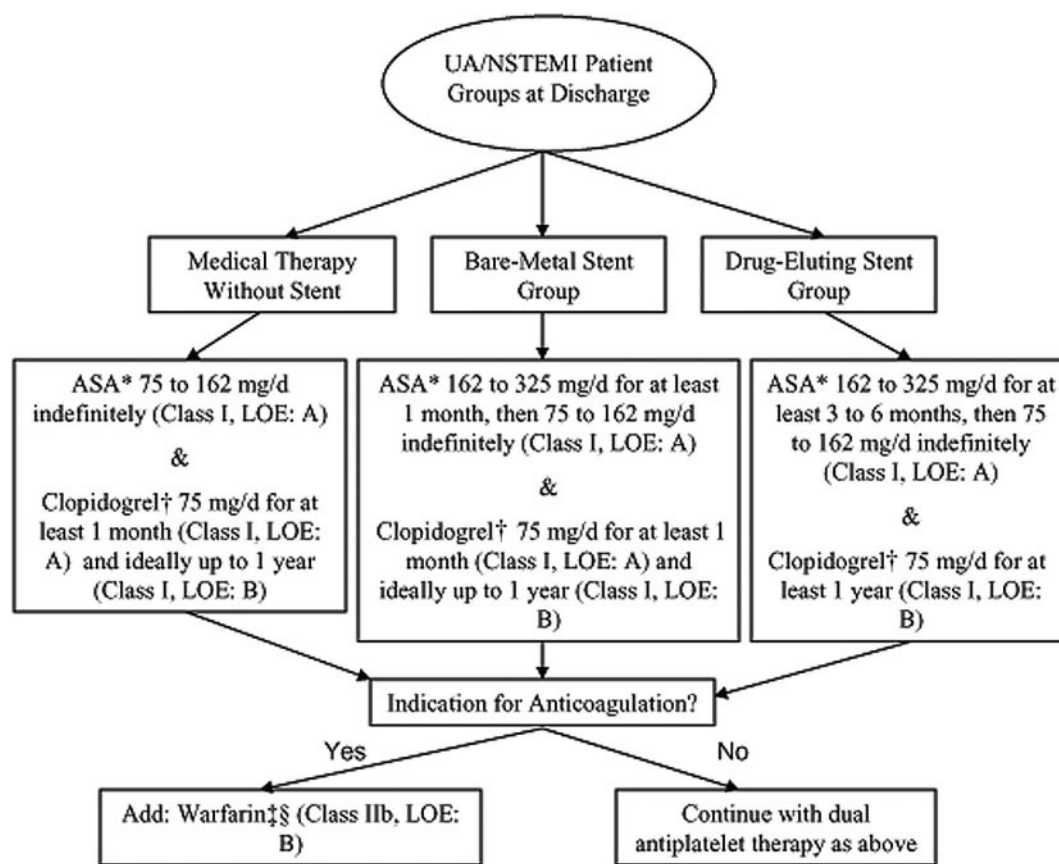


Figure 9. Long-Term Anticoagulant Therapy at Hospital Discharge After UA/NSTEMI

*For aspirin (ASA) allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization. †For clopidogrel-allergic patients, use ticlopidine 250 mg by mouth twice daily. ‡Continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; or cerebral, venous, or pulmonary emboli. §§When warfarin is added to aspirin plus clopidogrel, an INR of 2.0 to 2.5 is recommended. INR = international normalized ratio; LOE = level of evidence; LV = left ventricular; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction.

with an elevated cTn level (13.1% vs. 18.3% event rate, RR 0.71, 95% CI 0.54 to 0.95, $p = 0.02$ [$p = 0.07$ for interaction]). Bleeding rates were similar in the 2 arms. Thus, it appears beneficial to add an intravenous GP IIb/IIIa inhibitor to thienopyridine treatment if an invasive strategy is planned in patients with high-risk features (e.g., elevated cTn level; Figs. 6, 7, and 8).

The optimal timing of administration (“upstream” vs. “in-lab”) of the loading dose of clopidogrel for those who are managed with an early invasive strategy cannot be determined with certainty from the PCI-CURE trial. Given the early separation of the curves, clopidogrel is recommended as initial, upstream therapy when there is a delay to coronary angiography (Figs. 6, 7, and 8).

Although clopidogrel has a role in patients with UA/NSTEMI managed both conservatively and invasively (127), the optimal duration of therapy is uncertain. Most of the incremental benefit of clopidogrel in CURE occurred within the first 1 to 3 months, but favorable results were observed over the entire trial period, which averaged 9 months, and for up to 1 year (118,128). Pathological (129)

and clinical evidence (130,131) suggests the need for longer-term therapy, that is, at least 1 year, in patients who receive drug-eluting stents. Drug-eluting stents delay neointimal coverage of stent struts, increase late thrombotic events (by approximately 0.5%), and prevent restenosis. In contrast, clopidogrel was not beneficial in a large trial of high-risk primary prevention patients (132).

Because clopidogrel increases the risk of bleeding during major surgery, it has been recommended that it be withheld for at least 5 d in patients scheduled for elective CABG (133,134). Thus, many hospitals that use an early invasive approach for UA/NSTEMI delay starting clopidogrel until diagnostic angiography clarifies whether early CABG is indicated. However, when clopidogrel is given before catheterization, and urgent surgical intervention is indicated, some experience suggests that “early” bypass surgery may be undertaken by experienced surgeons at acceptable incremental bleeding risk (135). More data are needed to formulate definitive recommendations on this issue.

Sulfinpyrazone, dipyridamole, prostacyclin, and prostacyclin analogs have not been demonstrated to be of benefit in

UA or NSTEMI and are not recommended. The thromboxane synthase blockers and thromboxane A₂ receptor antagonists have been evaluated in ACS and have not shown any advantage over ASA. A number of other antiplatelet drugs are currently available, and still others are under active investigation.

Considerable interpatient variability in inhibition of platelet aggregation to a specific dose of clopidogrel has been observed (136). Patients with diminished responsiveness appear to be at increased risk of ischemic events (137,138). Optimal strategies to avoid or overcome poor responsiveness remain to be established but might involve monitoring of individual responsiveness and dose adjustments (139,140).

2. Anticoagulants

An increasing number of anticoagulants (previously referred to as antithrombins) have become available for management of patients with UA/NSTEMI. Anticoagulant strategies recommended (class I or IIa) on the basis of the current data set are given in Figures 6, 7, and 8. Although each agent or regimen reviewed (UFH, enoxaparin, fondaparinux, and bivalirudin [invasive strategy only]) satisfies criteria for effectiveness, it is often difficult to conclude that one antithrombotic strategy is preferred over another, given differing study designs (blinded vs. unblinded; superiority vs. noninferiority) and questions of equipotent dosing; differing patient populations (higher vs. lower risk), durations of therapy, and strategies (invasive vs. conservative); confounding by open-label and crossover use of anticoagulants; differing antiplatelet strategies; and differing clinical versus study protocols. The limitations of noninferiority trials also must be noted (141). It is suggested that each institution agree on an approved anticoagulant approach most consistent with local practice and preference.

A. UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) is a heterogeneous mixture of polysaccharide chains of molecular weights that range from 5,000 to 30,000 Daltons and that have varying anticoagulant activity (142). Unfractionated heparin accelerates the action of circulating antithrombin, which inactivates factor IIa (thrombin), factor IXa, and factor Xa. Unfractionated heparin prevents thrombus propagation but does not lyse existing thrombi.

Meta-analysis of a relatively small, randomized database suggests a reduction of 33% to 56% ($p = 0.06$ to 0.03) in early ischemic events by the addition of UFH (143,144). Most of the benefit is short term, with reactivation of the thrombotic process ("rebound") after the discontinuation of UFH contributing to the loss of early gain (145).

Unfractionated heparin binds to a number of plasma proteins, blood cells, and endothelial cells, leading to the poor bioavailability, especially at low doses, and marked variability in anticoagulant response. As a consequence, the anticoagulant effect of heparin requires monitoring with the

activated partial thromboplastin time (aPTT). A weight-adjusted dosing regimen provides more predictable anticoagulation than a fixed-dose regimen (146,147). An initial bolus of 60 U per kg (maximum 4,000 U) is followed by an initial infusion of 12 U per kg per hour (maximum 1,000 U per hour). Older age and female sex decrease UFH requirements. A therapeutic range equivalent to heparin levels of 0.3 to 0.7 U/mL, assessed by anti-factor Xa determinations, which correlates with aPTT values between 60 and 80 seconds, has been recommended (142). Nomograms should be established at each institution to achieve aPTT values in the target range of 1.5 to 2.5 times control aPTT values. Measurements should be made 6 h after any dosage change and whenever there are significant changes in clinical status and used to adjust UFH infusion until the aPTT exhibits a therapeutic level.

During UFH therapy, complete blood counts and platelet counts are recommended to monitor for anemia and heparin-induced thrombocytopenia, especially after prolonged (several days) infusions. The duration of UFH therapy in most UA/NSTEMI trials has been 2 to 5 d. The optimal duration of therapy is uncertain and likely varies by strategy.

B. LOW-MOLECULAR-WEIGHT HEPARIN

The LMWHs are obtained through chemical or enzymatic depolymerization of the polysaccharide chains of heparin to provide chains with different molecular-weight distributions (142,148). Approximately 25% to 50% of the pentasaccharide-containing chains of LMWH preparations contain more than 18 saccharide units, which inactivate both thrombin and factor Xa; LMWH chains of fewer than 18 saccharide units inactivate factor Xa but not thrombin. Therefore, LMWHs are relatively more potent in inhibiting factor Xa than inactivating thrombin. Advantages of LMWH over UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance, with a longer half-life. This results in more predictable and sustained anticoagulation with once- or twice-a-day subcutaneous administration that usually does not require laboratory monitoring. Different preparations of LMWHs vary in mean molecular weights (ranging from 4,200 to 6,000 Daltons) and corresponding ratios of anti-Xa factor to anti-IIa factor (1.9 to 3.8) (148).

Unstable angina/NSTEMI trials of LMWH and ASA compared with ASA alone or with UFH have generally shown favorable results. Eight randomized trials have directly compared an LMWH with UFH (Table 7). Trials with dalteparin and nadroparin reported similar rates of death or nonfatal MI compared with UFH, whereas 5 of 6 trials of enoxaparin found point estimates for death or nonfatal MI that favored enoxaparin; the pooled OR was 0.91 (95% CI 0.83 to 0.99). This incremental benefit of enoxaparin appeared to be driven largely by a reduction in nonfatal MI. With an early invasive strategy, outcomes with

Table 7. Trials of LMWH Versus UFH in UA/NSTEMI

Trial (Reference)	n	LMWH/Dose	UFH	End Point/Drug Effect	Analysis	95% CI	p	Major Bleeding (p)
FRISC (150)	1,506	(a) 6 d*: dalteparin 120 IU per kg† SC twice daily (maximum 10,000 IU) (b) During first 40 d: dalteparin 7,500 IU SC once per day	(a) 6 d: placebo (b) During first 40 d: placebo	(a) Death or new MI (6 d): LMWH 1.8%, Placebo 4.8% (b) Death or new MI (during first 40 d†): LMWH 8%, placebo 10.7%	(a) RR 0.37 ARR 3% (b) RR 0.75 ARR 2.7%	(a) 0.20 to 0.68 (b) 0.54 to 1.03	(a) 0.001 (b) 0.07	(a) LMWH 0.8%, placebo 0.5%; ARR −0.3% (p = NR) (b) During first 40 d: LMWH 0.3%, placebo 0.3%; ARR 0% (p = NR)
ESSENCE (41)	3,171	Enoxaparin 1 mg per kg SC twice daily (minimum 48 h, maximum 8 d)	UFH IV bolus (usually 5,000 units) and continued IV infusion	(a) Death, MI, or recurrent angina at 14 d: LMWH 16.6%, UFH 19.8% (b) Death, MI, or recurrent angina at 30 d: LMWH 19.8%, UFH 23.3%	(a) OR at 14 d = 0.80 ARR 3.2% (b) OR at 30 d = 0.81 ARR 3.5%	(a) 0.67 to 0.96 (b) 0.68 to 0.96	(a) 0.019 (b) 0.016	At 30 d: LMWH 6.5%, UFH 7%; ARR 0.5% (p = 0.57)
FRIC (151)	1,482	(a) Days 1 to 6: dalteparin 120 IU per kg SC twice daily (b) Days 6 to 45§: dalteparin 7,500 IU SC once per day	(a) Days 1 to 6: UFH 5,000 units IV bolus and IV infusion of 1,000 units per h for 48 h (b) Days 6 to 45: placebo SC once daily	(a) Death, MI, or recurrence of angina (Days 1 to 6): LMWH 9.3%, UFH 7.6% (b) Death, MI, or recurrence of angina (Days 6 to 45): 12.3% in both the LMWH and UFH groups (a) Death or MI (Days 1 to 6): LMWH 3.9%, UFH 3.6% (b) Death or MI (Days 6 to 45): LMWH 4.3%, placebo 4.7%	(a) RR 1.18 ARR −1.7% (b) RR 1.01 ARR 0% (a) RR 1.07 ARR −0.3% (b) RR 0.92 ARR 0.4%	(a) 0.84 to 1.66 (b) 0.74 to 1.38 (a) 0.63 to 1.80 (b) 0.54 to 1.57	(a) 0.33 (b) 0.96 (a) 0.80 (b) 0.76	(a) Days 1 to 6: LMWH 1.1%, UFH 1.0%; ARR −0.1% (p = NR) (b) Days 6 to 45: LMWH 0.5%, placebo 0.4%; ARR −0.1% (p = NR)
FRAX.I.S. (152)	3,468	(a) Nadroparin 6 d: nadroparin 86 anti-Xa IU per kg IV bolus, followed by nadroparin 86 anti-Xa IU per kg SC twice daily for 6 d (b) Nadroparin 14 d: nadroparin 86 anti-Xa IU per kg IV bolus, followed by nadroparin 86 anti-Xa IU per kg SC twice daily for 14 d	(a) + (b) UFH 5,000 units IV bolus and UFH infusion at 1,250 units per h IV for 6 d (plus or minus 2 d)	Cardiac death, MI, refractory angina, recurrence of UA at Day 14: LMWH 6 d 17.8%, LMWH 14 d 20.0% UFH 18.1%	(a) ARR 0.3% (b) ARR −1.9%	(a) −2.8 to 3.4 (b) −5.1 to 1.3	(a) 0.85 (b) 0.24	At 6 d: UFH 1.6%, LMWH 1.5%, ARR 0.1% At 14 d: UFH 1.6%, LMWH 3.5%, ARR −1.9% (p = 0.0035)

Continued on next page

Table 7. Continued

Trial (Reference)	n	LMWH/Dose	UFH	End Point/Drug Effect	Analysis	95% CI	p	Major Bleeding (p)
TIMI 11B (42)	3,910	(a) Inpatient: enoxaparin 30 mg IV bolus immediately followed by 1 mg per kg SC every 12 h (b) Outpatient: enoxaparin 40 mg SC twice per day (patients weighing less than 65 kg) or 60 mg SC twice per day (patients weighing at least 65 kg)	(a) Inpatient: UFH 70 units per kg bolus and infusion at 15 units per h titrated to aPTT (treatment maintained for a minimum of 3 and maximum of 8 d at physician's discretion) (b) Outpatient: placebo SC twice per day	Death, MI, urgent revascularization (a) At 48 h; LMWH 5.5% UFH 7.3% (b) 8 d: LMWH 12.4%, UFH 14.5% (c) 14 d: LMWH 14.2%, UFH 16.7% (d) 43 d: LMWH 17.3%, UFH 19.7%	(a) OR 0.75 ARR 1.8% (b) OR 0.83 ARR 2.1% (c) OR 0.82 ARR 2.5% (d) OR 0.85 ARR 2.4%	(a) 0.58 to 0.97 (b) 0.69 to 1.00 (c) 0.69 to 0.98 (d) 0.72 to 1.00	(a) 0.026 (b) 0.048 (c) 0.029 (d) 0.048	At 48 h: LMWH 0.8%, UFH 0.7%, ARR −0.1% (p = 0.14) End of initial hospitalization: LMWH 1.5%, UFH 1%; ARR −0.5% (p = 0.143) Between day 8 and day 43: LMWH 2.9%, placebo 2.9%; ARR 0% (p = 0.021)
ACUTE II (153)	525	Enoxaparin 1 mg per kg SC every 12 h	UFH 5,000 units IV bolus and maintenance infusion at 1,000 units per h IV adjusted to aPTT	(a) Death or (b) MI at 30 d (a) LMWH 2.5%, UFH 1.9% (b) LMWH 6.7%, UFH 7.1%	(a) RR −1.3 ARR −0.6% (b) RR 0.94 ARR 0.4%	(a) 0.06 to 3.93 (b) 0.45 to 2.56	(a) 0.77 (b) 0.86	LMWH 0.3%, UFH 1%; ARR 0.7% (p = 0.57)
INTERACT¶ (154)	746	Enoxaparin 1 mg per kg SC every 12 h	UFH 70 units per kg IV bolus followed by continuous infusion at 15 units per kg per h	Death or MI at 30 d: LMWH 5.0%, UFH 9.0%	RR 0.55 ARR 4%	0.30 to 0.96	0.031	At 96 h: LMWH 1.8%; UFH 4.6%; ARR 2.8% (p = 0.03)
A to Z** (155)	3,987	Enoxaparin 1 mg per kg SC every 12 h	UFH 4,000 units IV bolus followed by 900 units per h IV infusion for patients weighing at least 70 kg UFH 60 units per kg (maximum 4,000 units) IV bolus followed by 12 units per kg per h IV infusion for patients weighing less than 70 kg	All-cause death, MI, or refractory ischemia within 7 d of tirofiban initiation: LMWH 8.4%, UFH 9.4%	HR 0.88 ARR 1%	0.71 to 1.08	NR	LMWH 0.9%, UFH 0.4%; ARR −0.5% (p = 0.05)



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Table 7. Continued

Trial (Reference)	n	LMWH/Dose	UFH	End Point/Drug Effect	Analysis	95% CI	p	Major Bleeding (p)
SYNERGY†† (156)	9,978	Enoxaparin 1 mg per kg SC every 12 h	UFH 60 units per kg IV bolus (maximum of 5,000 units) and followed by IV infusion of 12 units per kg per h (maximum of 1,000 units per h initially)	Death or nonfatal MI during first 30 d after randomization LMWH 14.0%, UFH 14.5%,	HR 0.96 ARR 0.5%	0.86 to 1.06	0.40	TIMI minor: LMWH 12.5%, UFH 12.3%; ARR –0.2% (p = 0.80) TIMI major: LMWH 9.1%, UFH 7.6% ARR –1.5% (p = 0.008) GUSTO severe: LMWH 2.7%, UFH 2.2%; ARR –0.5% (p = 0.08)

For specific interventions and additional medications during the study, see individual study references. Major bleeding was classified as follows in the various trials: A to Z: decrease in hemoglobin of more than 5 mg per dL or intracranial or pericardial bleeding. ESSENCE: Major hemorrhage was defined as bleeding resulting in death, transfusion of at least 2 U of blood, a fall in hemoglobin of 30 g per liter or more, or a retroperitoneal, intracranial, or intraocular hemorrhage. TIMI 11B: Overt bleed resulting in death; a bleed in a retroperitoneal, intracranial, or intraocular location; a hemoglobin drop of greater than or equal to 3 g per dL; or the requirement of transfusion of at least 2 U of blood. SYNERGY: TIMI and GUSTO criteria. ACUTE II: Severity was recorded on the basis of the TIMI trial bleeding criteria. TIMI major bleeding involved a hemoglobin drop greater than 5 g per dL (with or without an identified site, not associated with coronary artery bypass grafting) or intracranial hemorrhage or cardiac tamponade. INTERACT: Major bleeding included bleeding resulting in death, or retroperitoneal hemorrhage, or bleeding at a specific site accompanied by a drop in hemoglobin greater than or equal to 3 g per dL. FRIC: A bleeding event was classified as major if it led to a fall in the hemoglobin level of at least 20 g per liter, required transfusion, was intracranial, or caused death or cessation of the study treatment. *Primary study end point was first 6 d. †Initial trial dose of 150 IU per kg SC twice daily decreased to 120 IU per kg SC twice daily due to increased bleeding during first 6 d (4 patients or 6% major bleeding episodes and 9 patients or 14% minor episodes among 63 actively treated patients). ‡Follow-up incomplete in 13 patients (8 dalteparin, 5 placebo) at their request. §Primary study outcome was Days 6 to 45. ||All patients in ACUTE II received a tirofiban loading dose of 0.4 mcg per kg per min over 30 min, followed by a maintenance infusion at 0.1 mcg per kg per min. ¶All patients in INTERACT received eptifibatide 180 mcg per kg bolus followed by a 2.0 mcg per kg per min infusion for 48 h. **All patients enrolled in the A to Z Trial received aspirin and tirofiban. ††Patients also received glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel; patients eligible for enrollment even if LMWH or UFH given before enrollment, adjustments made to enoxaparin and UFH during percutaneous coronary intervention.

A to Z = Aggrastat to Zocor study; ACUTE II = Antithrombotic Combination Using Tirofiban and Enoxaparin; aPTT = activated partial thromboplastin time; ARR = absolute risk reduction; CI = confidence interval; ESSENCE = Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave Myocardial Infarction; FRIC = FRagmin In unstable Coronary disease; HR = hazard ratio; INTERACT = Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment; IU = international units; IV = intravenous; LD = loading dose; MD = maintenance dose; N = number of patients; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NR = not reported; RR = relative risk; SC = subcutaneous; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; TIMI 11B = Thrombolysis In Myocardial Infarction 11B; U = unit; UA = unstable angina; UFH = unfractionated heparin.

UFH and LMWH (enoxaparin) were similar (156) (Fig. 10).

The Enoxaparin Versus Tinzaparin (EVET) trial directly compared 2 LMWHs, enoxaparin and tinzaparin, in 436 patients with UA/NSTEMI. Enoxaparin was associated with a lower rate of death/MI/recurrent angina at 7 and 30 d than tinzaparin (149). Bleeding rates were similar.

Four trials evaluated the potential benefit of prolonged administration of LMWH after hospital discharge, with little or no benefit beyond the acute phase (see Table 7) (157). In addition to providing ease of administration and eliminating the need for monitoring, LMWHs stimulate platelets less than UFH (158) and less frequently cause heparin-induced thrombocytopenia (159). They are associated with more frequent minor but not major bleeding. A post hoc analysis from the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial (Fig. 10) (156) suggested that some of the excess bleeding seen with enoxaparin could be explained by crossover to UFH at the time of PCI. It thus appears reasonable to maintain consistent anticoagulant therapy from the pre-PCI phase throughout the procedure itself. For patients in whom CABG is planned, it is recommended that LMWH be discontinued and UFH used during the operation.

C. DIRECT THROMBIN INHIBITORS

Hirudin, the prototype direct thrombin inhibitor, has been studied extensively but with mixed results, including excess bleeding with higher doses (160,161). Bivalirudin is a synthetic analog of hirudin that binds reversibly to thrombin and inhibits clot-bound thrombin. Bivalirudin was investigated in 13,819 patients with UA/NSTEMI in the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial (162). In a 2 × 2 factorial design, a heparin (UFH or enoxaparin), with or without upstream GP IIb/IIIa inhibition, was compared to bivalirudin, with or without upstream GP IIb/IIIa inhibition; a third arm with bivalirudin alone and provisional GP IIb/IIIa inhibition was also included. The study was randomized but open-label. Bivalirudin compared with heparin (both with GP IIb/IIIa inhibitors) gave noninferior 30-d rates of composite ischemia (7.7% vs. 7.3%), major bleeding (5.3% vs. 5.7%), and net clinical outcomes (11.8% vs. 11.7%; Fig. 11). Bivalirudin alone was comparable to heparin plus GP IIb/IIIa inhibition for the subgroup of patients who received a thienopyridine before angiography or PCI (composite ischemic end-point rate 7.0% vs. 7.3%), but it was inferior in patients who did not (ischemic event rate 9.1% vs. 7.1%, RR 1.29, 95% CI 1.03 to 1.63; p for interaction = 0.054) (Fig. 12). Bleeding rates were lower with bivalirudin alone. In sum-

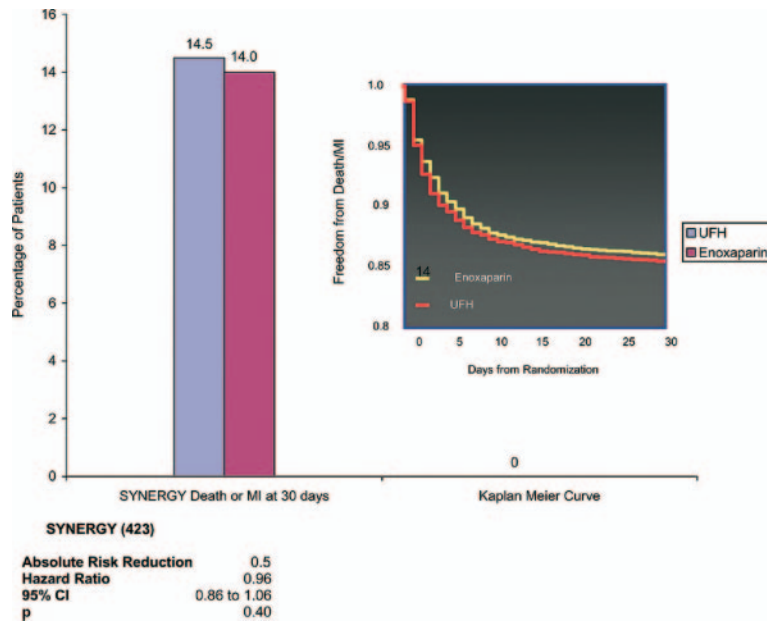


Figure 10. SYNERGY Primary Outcomes at 30 D

CI = confidence interval; MI = myocardial infarction; SYNERGY = Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; UFH = unfractionated heparin.

mary, UA/NSTEMI patients should be treated with concomitant GP IIb/IIIa inhibition or a thienopyridine, administered before angiography, to optimize outcomes if a bivalirudin-based anticoagulant strategy is used.

D. FACTOR Xa INHIBITORS

Factor Xa inhibitors act proximally in the coagulation cascade to inhibit the multiplier effects of the downstream reactions, thereby suppressing thrombin generation. Advan-

tages of the pentasaccharide factor Xa inhibitor fondaparinux over UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance with a longer half-life, which results in more predictable and sustained anticoagulation and allows fixed-dose, once-daily subcutaneous administration. As with the LMWHs, fondaparinux does not require laboratory monitoring. Fondaparinux is renally cleared. The factor Xa inhibitors do

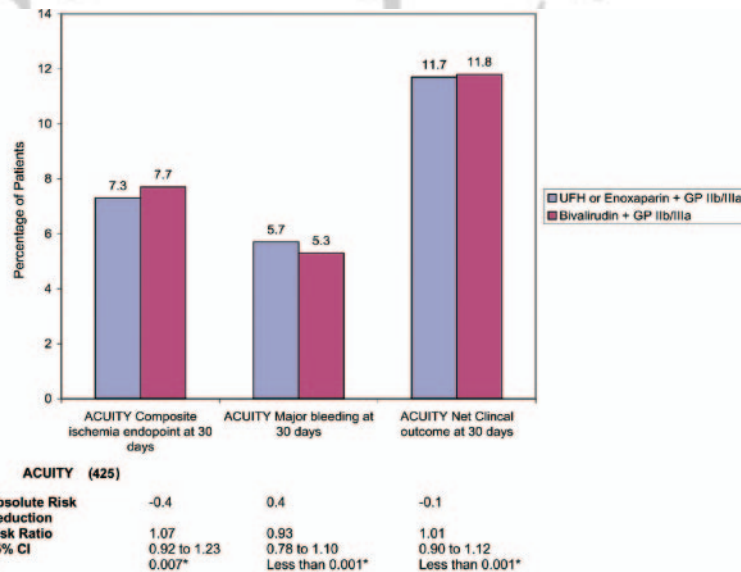


Figure 11. ACUTY Clinical Outcomes at 30 D

*p for noninferiority. ACUTY = Acute Catheterization and Urgent Intervention Triage strategy; CI = confidence interval; GP = glycoprotein; UFH = unfractionated heparin.

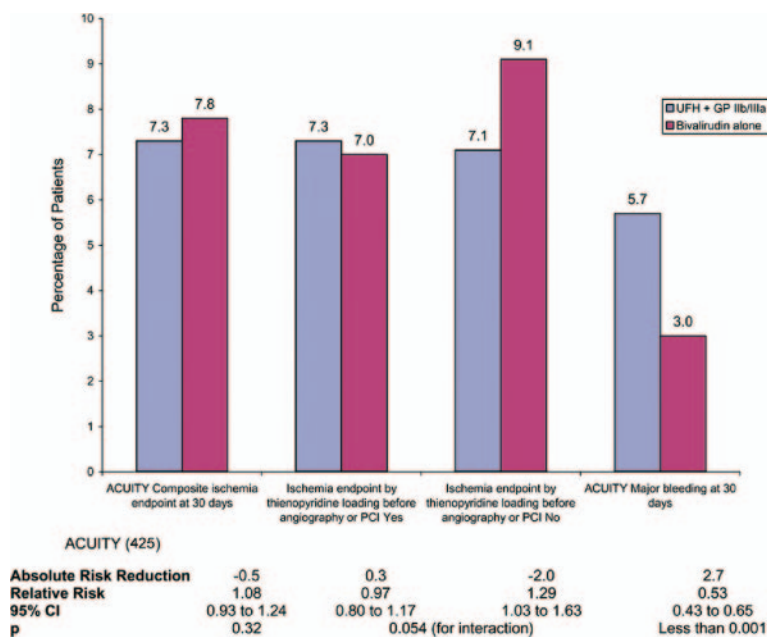


Figure 12. ACUITY Composite Ischemia and Bleeding Outcomes

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CI = confidence interval; GP = glycoprotein; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

not have any action against thrombin that is already formed, a possible explanation for the increased rate of catheter-associated thrombosis with fondaparinux.

The Organization to Assess Strategies for Ischaemic Syndromes (OASIS)-5 investigators evaluated the use of fondaparinux in 20,078 patients with UA/NSTEMI (163). Patients were randomized (double-blind, double-dummy design) to a control strategy of enoxaparin 1.0 mg per kg subcutaneous twice daily (reduced to 1.0 mg per kg once daily for patients with an estimated creatinine clearance less than 30 mL per min) or to fondaparinux 2.5 mg SC once daily. Unfractionated heparin initially was not used with PCI, but because of an increased incidence of catheter-associated thrombus, the protocol was amended to permit the use of open-label UFH at the investigator's discretion. The OASIS-5 primary composite outcome (death, MI, or refractory ischemia at 9 d) was similar in the 2 groups (579 with fondaparinux [5.8%] vs. 573 with enoxaparin [5.7%]; hazard ratio [HR] 1.01; 95% CI 0.90 to 1.13), which satisfied prespecified noninferiority criteria (Fig. 13). Rates of major bleeding at 9 d were lower with fondaparinux (2.2% vs. 4.1%, p less than 0.001), which yielded a lower efficacy plus safety composite (Fig. 13). Primary composite events trended lower in the fondaparinux group at 30 d and 6 months; 6-month rates of death (5.8% vs. 6.5%) and death, MI, and stroke (11.3% vs. 12.5%) were also lower at 6 months with fondaparinux.

At present, on the basis of limited experience in OASIS-5 and concerns raised by OASIS-6 (164), UFH (50 to 60 U per kg IV) is recommended with a fondaparinux

strategy during angiography/PCI. Fondaparinux appears to represent a preferred anticoagulant strategy in those at higher risk of bleeding managed with a noninvasive strategy.

E. LONG-TERM ANTICOAGULATION

The long-term administration of warfarin or other coumarins after UA/NSTEMI or STEMI has been evaluated in several small and a few moderate-size trials with variable results (165). Moderate-intensity warfarin with low-dose ASA appears to be modestly more effective than ASA alone when applied to post-MI patients treated primarily with a noninterventional approach, but it is associated with a higher risk of bleeding (166,167). The relevance of routine long-term anticoagulation with warfarin to contemporary practice is unclear given the current routine use of clopidogrel and the much more frequent use of an invasive strategy.

In contrast, occasional UA/NSTEMI patients present with a specific indication for oral anticoagulant therapy with warfarin (i.e., atrial fibrillation, mechanical prosthetic valve, or LV thrombus) in addition to ASA plus clopidogrel. The evidence base for such "triple-anticoagulant therapy" remains small. When triple-combination therapy is selected for clear indications, on the basis of clinical judgment that the benefit will outweigh the incremental risk of bleeding, therapy should be given for the minimum time and doses necessary to achieve protection.

3. Platelet GP IIb/IIIa Receptor Antagonists

When platelets are activated by a number of mechanisms, their GP IIb/IIIa cell membrane receptors undergo a

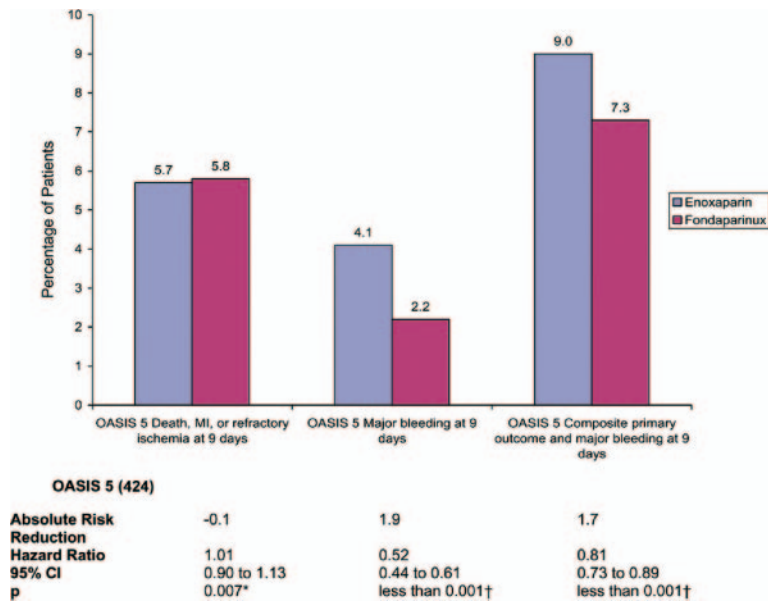


Figure 13. OASIS Cumulative Risks of Death, MI, or Refractory Ischemia

**p* for noninferiority. †*p* for superiority. CI = confidence interval; MI = myocardial infarction; OASIS 5 = Fifth Organization to Assess Strategies for Ischemic Syndromes.

conformation change that increases receptor affinity for fibrinogen (168). The binding of fibrinogen molecules to receptors on adjacent platelets results in platelet aggregation. The platelet GP IIb/IIIa receptor antagonists act by occupying the receptors, preventing fibrinogen from binding and thereby preventing platelet aggregation. Experimental and clinical studies have suggested that occupancy of 80% or more of the receptor population and inhibition of platelet aggregation to adenosine diphosphate (5 to 20 micromoles per liter) by 80% or more results in potent anticoagulant effects (169).

The 3 approved GP IIb/IIIa antagonists differ in pharmacokinetic and pharmacodynamic properties (170). Abciximab is a Fab fragment of a humanized murine antibody that has a short plasma half-life but strong affinity for the receptor. Platelet aggregation gradually returns to normal 24 to 48 h after discontinuation. Eptifibatide is a cyclic heptapeptide that contains the KGD (Lys-Gly-Asp) sequence; tirofiban is a nonpeptide mimetic of the RGD (Arg-Gly-Asp) sequence of fibrinogen. They bind with high specificity to the GP IIb/IIIa receptor, but platelet aggregation returns to normal 4 to 8 h after discontinuation of these 2 drugs, consistent with their relatively short half-lives of 2 to 3 h (171).

The efficacy of GP IIb/IIIa antagonists for the prevention of PCI-related complications has been documented in several trials, many composed primarily of patients with UA (Table 8). Abciximab has been studied primarily in PCI trials, in which it consistently reduced rates of MI and the need for urgent revascularization. In subgroups of patients who had ACS, abciximab reduced the 30-d risk of ischemic complications after PCI by 60% to 80%. Two trials specif-

ically studied patients with ACS. In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial (172), abciximab reduced the rate of death, MI, or urgent revascularization within 30 d from 15.9% to 11.3% (RR 0.71, *p* = 0.012). Hence, abciximab is approved for the treatment of UA/NSTEMI as an adjunct to PCI or when PCI is planned within 24 h. In contrast, the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IV-ACS trial (173) enrolled 7,800 patients with UA/NSTEMI in whom early (less than 48 h) revascularization was not intended and found no benefit or adverse trends in rates of death or MI. Although the explanation for these results is not clear, abciximab should not be used in the management of patients with UA/NSTEMI in whom an early invasive management strategy is not planned.

Tirofiban was studied in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) (182) and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) (181) trials (Table 8). The PRISM trial compared tirofiban with heparin in 3,232 patients with UA/NSTEMI. The primary composite outcome (death, MI, or refractory ischemia at the end of a 48-h infusion) was reduced from 5.6% to 3.8% (RR 0.67, *p* = 0.01). At 30 days, the frequency of the composite outcome was similar in the 2 groups, but the rate of death or MI trended lower with tirofiban (7.1% vs. 5.8%), and mortality was reduced (3.6% vs. 2.3%, *p* = 0.02). Benefit primarily occurred in patients with elevated troponin. PRISM-PLUS randomized 1,915 UA/NSTEMI patients to tirofiban alone, UFH alone, or the combination for 48 to 108 h (181). The tirofiban-alone arm was dropped during the trial because of an adverse early

Table 8. UA/NSTEMI Outcome of Death or Myocardial Infarction in Clinical Trials of GP IIb/IIIa Antagonists Involving More Than 1,000 Patients

Trial (Year)	Study Population	Drugs	Results							
			Placebo		GP IIb/IIIa		ARR, %	RR	95% CI	p
			n	%	n	%				
PCI trials										
EPIC (1994) (174)	High-risk PTCA	Abciximab	72/696	10.3	49/708	6.9*	3.4	0.68	0.47 to 0.95	0.022
EPILOG (1997) (175)	All PTCA	Abciximab	85/939	9.1	35/935	3.7*	5.4	0.41	0.28 to 0.61	Less than 0.001
CAPTURE (1997) (172)	UA	Abciximab	57/635	9.0	30/630	4.8	4.2	0.53	0.35 to 0.81	0.003
IMPACT II (1997) (176)	All PTCA	Eptifibatide	112/1328	8.4	93/1349	6.9	1.5	0.83	0.63 to 1.06	0.134
RESTORE (1997) (177)	UA	Tirofiban	69/1070	6.4	54/1071	5.0	1.4	0.78	0.55 to 1.10	0.162
EPISTENT (1998) (178)	Elective stenting	Abciximab	83/809	10.2	38/794	4.8*	5.4	0.46	0.32 to 0.68	Less than 0.001
ESPRIT (2000) (179)	Elective stenting	Eptifibatide	104/1024	10.2	66/1040	6.3	3.9	0.62	0.46 to 0.84	0.0016
ISAR-REACT (2004) (180)	Elective stenting with clopidogrel pretreatment	Abciximab	42/1080	3.9	43/1079	4.0	-0.1	1.02	0.68 to 1.55	0.91
ACS trials										
PRISM-PLUS (1998) (181)	UA/NQWMI	Tirofiban	95/797	11.9	67/733*	9.1*	2.8	0.70	0.51 to 0.96	0.03
PRISM (1998) (182)	UA/NQWMI	Tirofiban	115/1616	7.1	94/1616	5.8†	1.3	0.82	0.61 to 1.05	0.11
PURSUIT (1998) (183)	UA/NQWMI	Eptifibatide	744/4739	15.7	67/4722	1.4*	14.3	0.09	0.07 to 0.12	Less than 0.0001
PARAGON A (1998) (184)	UA/NQWMI	Lamifiban	89/758	11.7	80/755	10.6**†	1.1	0.90	0.68 to 1.20	0.48
GUSTO IV ACS (2001) (173)	UA/NQWMI	Abciximab	209/2598	8.0	450/5202‡	8.7	-0.7	1.08	0.92 to 1.26	0.36
PARAGON B (2002) (185)	UA/NQWMI	Lamifiban	296/2597	11.4	278/2628	10.6	0.8	0.94	0.77 to 1.09	0.32
ISAR-REACT (2006) (74)	UA/NSTEMI§	Abciximab	116/1010	11.5	87/1012	8.6	2.9	0.75	1.57 to 0.92	0.03
All PCI trials			624/7581	8.2	408/7606	5.4	2.8	0.65	0.58 to 0.74	Less than 0.0001
All ACS trials			1548/13 105	11.8	1036/15 656	6.6	5.2	0.56	0.52 to 0.60	Less than 0.0001
All PCI and ACS trials			2172/20 686	10.5	1444/23 262	6.2	4.3	0.59	0.55 to 0.63	Less than 0.0001

*Best treatment group selected for analysis. †Platelet GP IIb/IIIa antagonist without heparin. ‡Pooled results for 24- and 48-h infusion arms. §Used an invasive (PCI) strategy; all patients received clopidogrel.

ACS = acute coronary syndrome; CAPTURE = c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina; CI = confidence interval; EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications; EPICLOG = Evaluation of PTCA and Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade; EPISTENT = Evaluation of Platelet IIb/IIIa Inhibitor for STENTING; ESPRIT = Enhanced Suppression of Platelet Receptor GP IIb/IIIa using Integrilin Therapy; GUSTO IV ACS = Global Use of Strategies to Open Occluded Coronary Arteries IV; IMPACT II = Integrilin to Minimize Platelet Aggregation and Coronary Thrombolysis II; ISAR-REACT = Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment; NQWMI = non-Q-wave myocardial infarction; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; PCI = percutaneous coronary intervention; PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable 16 Angina: Receptor Suppression Using Integrilin Therapy; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; RR = risk ratio; UA = unstable angina; UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction.

mortality trend. The combination of tirofiban and UFH compared with UFH alone reduced the primary composite end point of death, MI, or refractory ischemia at 7 d (from 17.9% to 12.9% RR 0.68, $p = 0.004$), as well as at 30 days (by 22%, $p = 0.03$) and at 6 months (19%, $p = 0.02$). Death or nonfatal MI was reduced at 7 d (43%, $p = 0.006$), at 30 d (30%, $p = 0.03$), and at 6 months (22%, $p = 0.06$). Incremental benefit was observed both before and after PCI. Analysis of coronary angiograms, obtained after 48 h, showed reduced thrombus burden and improved coronary flow (186). Tirofiban, in combination with heparin, is approved for the treatment of patients with ACS, including patients managed medically and those undergoing PCI.

Eptifibatide, added to standard management until hospital discharge or for 72 h, was studied in the PURSUIT trial, which enrolled 10,948 UA/NSTEMI patients (183). The primary outcome of death or nonfatal MI at 30 days was reduced from 15.7% to 14.2% with eptifibatide (RR 0.91, $p = 0.042$). Event rate reduction (31%) was substantially greater in those undergoing PCI within 72 h (16.7% to 11.6%). Benefits were maintained at 6-month follow-up. Eptifibatide is approved for the treatment of patients with ACS (UA/NSTEMI) who are treated medically or with PCI.

In summary, the CAPTURE, PRISM-PLUS, and PURSUIT trials each showed a significant reduction in the rate of death or MI during the phase of medical management and an augmented benefit after PCI. A meta-analysis of the 6 large, placebo-controlled GP IIb/IIIa antagonist trials (including GUSTO IV) involving 31,402 patients with UA/NSTEMI not routinely scheduled to undergo coronary revascularization suggested a modest overall benefit in reducing the risk of death or MI by 30 d (11.8% vs. 10.8%, OR 0.91 and 95% CI 0.84 to 0.98, respectively; $p = 0.015$) at a modest increase (from 1.4% to 2.4%) in major bleeding events (187). Treatment effect was greater among higher-risk patients with troponin elevation and ST-segment depression. These and other data have elevated troponin level to a major factor in decision making for the use of these agents in UA/NSTEMI. Although not specified in these trials, PCI or CABG was performed in 19% of patients within 5 d and in 38% within 30 d. These subgroups noted a greater risk reduction (OR 0.79, 95% CI 0.68 to 0.91 and OR 0.89, 95% CI 0.80 to 0.98, respectively) than in those not undergoing intervention (OR 0.95, 95% CI 0.86 to 1.05). These findings in the context of other PCI trial data suggest that GP IIb/IIIa inhibitors are of substantial benefit in patients with UA/NSTEMI who undergo PCI, are of modest benefit in patients who are not routinely scheduled to undergo revascularization (but who may do so), and are of questionable benefit in patients who do not undergo revascularization.

Glycoprotein IIb/IIIa antagonists increase the risk of bleeding, most commonly mucocutaneous or vascular access site bleeding. No trials have shown an excess of intracranial bleeding. Aspirin has been used with the intravenous GP

IIb/IIIa receptor blockers in all trials, and adjunctive UFH appears beneficial (181,183). Hence, clinical recommendations call for the concomitant use of heparin with GP IIb/IIIa inhibitors. Lower heparin doses diminish the bleeding risk associated with GP IIb/IIIa blockade in the setting of PCI and likely the medical phase of management as well. Thrombocytopenia is an uncommon (less than 0.5%) complication of these agents that is reversible but is associated with increased bleeding risk.

Several trials have demonstrated that GP IIb/IIIa inhibitors can be used with LMWH in ACS patients (155,156). The A to Z Trial (Aggrastat to Zocor; 3,987 patients) found nonsignificant trends toward fewer ischemic end points but more frequent bleeding with enoxaparin than with UFH (155). In the larger SYNERGY trial, 10,027 patients with high-risk ACS were randomized to UFH or enoxaparin. Glycoprotein IIb/IIIa antagonists were administered to 57% of patients, and 92% underwent coronary angiography. Rates of the primary end point of death or MI by 30 d were similar (14.0% vs. 14.5%) (Fig. 10), and the therapies offered similar protection against ischemic events during PCI, although enoxaparin was associated with a 1.5% increase in bleeding events (156).

A challenge for the current guidelines is the integration of the GP IIb/IIIa antagonist studies from the 1990s with more recent studies using preangiography clopidogrel loading and newer anticoagulants. The current evidence base and expert opinion suggest that for UA/NSTEMI patients in whom an initial invasive strategy is selected, either an intravenous GP IIb/IIIa inhibitor or clopidogrel should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream) for lower-risk, troponin-negative patients, and that both should be given before angiography for high-risk, troponin-positive patients (Class I recommendations). For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, the evidence for benefit is less; for this strategy, the addition of eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy may be reasonable for high-risk UA/NSTEMI patients (Class IIb recommendation). The randomized trial database has shown no benefit of fibrinolysis versus standard therapy in UA/NSTEMI patients (191). Fibrinolytic therapy is not recommended for the management of ACS patients without ST-segment elevation, a posterior-wall MI, or a presumably new left bundle-branch block.

C. Initial Conservative Versus Initial Invasive Strategies

1. General Principles and Care Objectives

Two treatment pathways have emerged for treating UA/NSTEMI patients: the early "invasive strategy" and an initial "conservative strategy" (192,192a). Patients treated with an invasive strategy generally will undergo coronary angiography within 4 to 24 h of admission. The invasive strategy can be subdivided into 2 groups. The

first group consists of patients requiring urgent angiography/revascularization urgently because of ongoing ischemic symptoms or hemodynamic or rhythm instability. With these patients, GP IIb/IIIa antagonists or clopidogrel may be delayed at the physician's discretion until the time of angiography (Figs. 6, 7, and 8). The second, larger group comprises others with UA/NSTEMI who are designated by patient/physician discretion or after risk assessment to benefit from "early" but nonurgent angiography/intervention. For these patients, "upstream" therapy with GP IIb/IIIa antagonists and/or clopidogrel is recommended, with greater delays to angiography being associated with greater incremental benefit of aggressive antiplatelet therapy. In contrast, the "conservative strategy" (or "selective invasive management") calls for invasive evaluation only with symptomatic failure of medical therapy or other objective evidence of recurrent or latent ischemia.

The primary objective in selecting a treatment strategy in UA/NSTEMI is to yield the best long-term clinical outcome. Estimating the risk for an adverse outcome is paramount for determining which strategy is best applied to individual patients. General characteristics favoring one or the other strategy are presented in Table 5. Although general guidelines can be offered, individual judgment is required.

2. Rationale for the Conservative Strategy

The conservative strategy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability. With this strategy, an early echocardiogram should be considered to identify significant LV dysfunction. In addition, an exercise or pharmacological stress test is recommended before or shortly after discharge to identify patients with latent ischemia who could benefit from revascularization. The use of aggressive anticoagulant and antiplatelet agents has reduced the incidence of adverse outcomes in patients managed conservatively.

3. Rationale for the Invasive Strategy

The routine use of angiography within 24 h of hospital admission provides an invasive approach to risk stratification. It can identify the 10% to 20% of patients with no significant coronary stenoses as well as the approximately 20% with 3-vessel disease with LV dysfunction or left main CAD who derive a substantial survival benefit from CABG (Section V). For the other approximately 60% to 70%, PCI of the culprit lesion can reduce subsequent hospitalizations and the need for multiple antianginal drugs. Contemporary anticoagulant and antiplatelet therapies have lessened the early hazard of PCI. Excluding those in need of urgent intervention, 2 alternatives for the invasive approach have emerged: early ("immediate") or deferred angiography (i.e., before or after a 12- to 48-h window). Support for immediate angiography comes from the Intracoronary Stenting with Antithrombotic Regimen Cooling-off Study (ISAR-

COOL) trial (193). In that trial, all 410 UA/NSTEMI patients were treated with intensive medical therapy, including ASA, heparin, clopidogrel (600-mg loading dose), and the intravenous GP IIb/IIIa receptor inhibitor tirofiban, and were randomized to immediate angiography (median time 2.4 h) or delayed angiography after a prolonged "cooling off" period (median 86 h) before catheterization. Patients randomized to immediate angiography had fewer deaths or MIs at 30 d (5.9% vs. 11.6%, $p = 0.04$). Importantly, this difference was attributed to events that occurred before catheterization. Additional data comparing these 2 invasive strategies are needed.

4. Comparison of Invasive and Conservative Strategies

Prior meta-analyses have concluded that routine invasive therapy is better than a conservative or selectively invasive approach (194). In contrast, the Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial (192) favored a strategy of selective invasive therapy. ICTUS randomized 1,200 UA/NSTEMI patients to routine invasive or selective invasive management. At the end of 1 year, there was no significant difference in the composite ischemic end point. Results were unchanged during 3-year follow-up (192a). ICTUS required troponin positivity. Thus, troponin alone might not be an adequate single criterion for strategy selection. Proposed explanations for the lack of incremental benefit with an invasive strategy include the high rate of revascularization in the selective invasive therapy arm (47%), more aggressive medical therapy (statins, clopidogrel) in both arms, routine use of clopidogrel in the conservative arm, and limited power owing to the relatively low rate of hard end points (195). Given the results of ICTUS, these guidelines recognize that an initially conservative (selective invasive) strategy may be considered as a treatment option in stabilized UA/NSTEMI patients. Additional comparative trials of a selective versus a routine invasive strategy are encouraged using aggressive contemporary medical therapies in both arms.

In the RITA-3 trial (Third Randomized Intervention Treatment of Angina), 1,810 UA/NSTEMI patients were randomized to interventional versus conservative treatment. At 1 year, death and MI rates were similar, but at 5 years, a significant reduction in death or MI emerged in the early invasive treatment arm (196). Benefits were seen mainly in high-risk patients, which supports appropriate risk stratification. Long-term outcomes of the FRagmin and fast revascularization during InStability in Coronary artery disease (FRISC II) trial have also been published (197). At 5 years, the invasive strategy was favored for the primary end point of death or nonfatal MI (HR 0.81, $p = 0.009$). Benefit was confined to men, nonsmokers, and patients with 2 or more risk factors.

A contemporary meta-analysis of 7 randomized trials of management strategies in UA/NSTEMI, including ICTUS, supports the long-term benefit of an early invasive strategy (Fig. 14) (198). Among 8,375 patients, the inci-

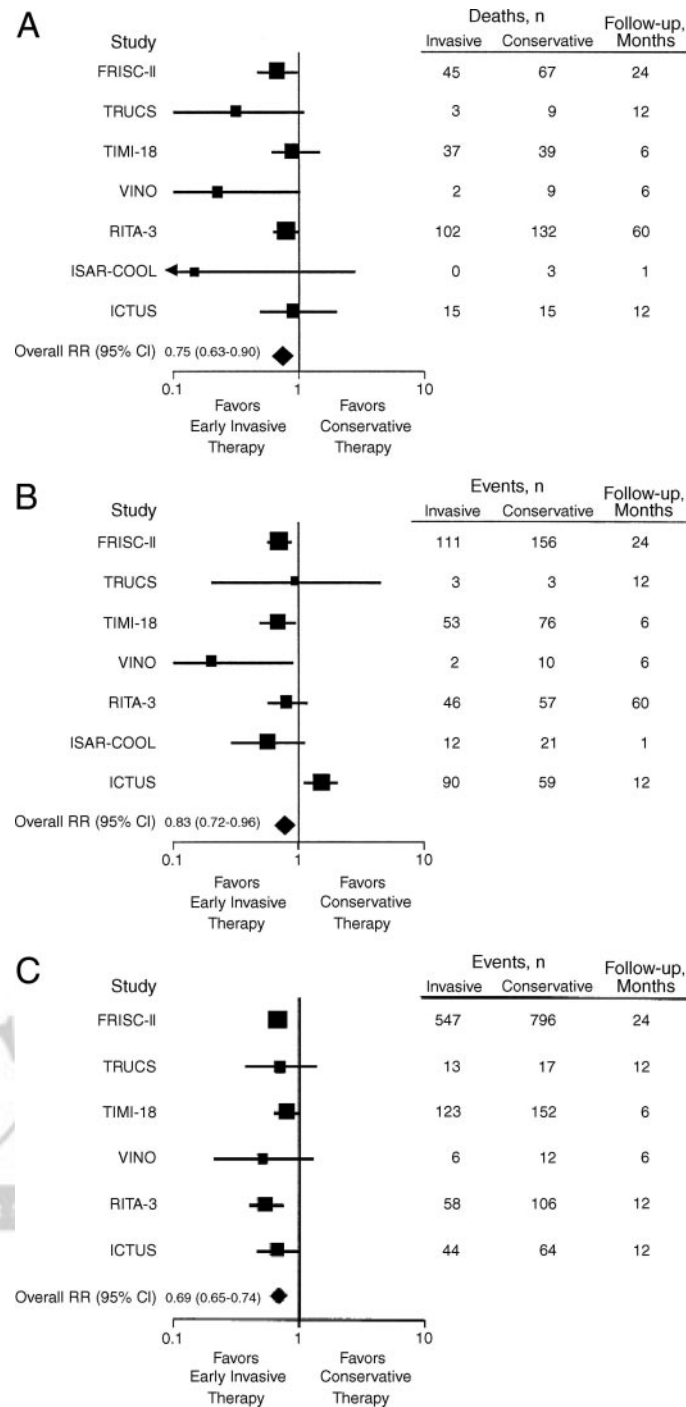


Figure 14. Relative Risk of Outcomes With Early Invasive Versus Conservative Therapy in UA/NSTEMI

A: Relative risk of all-cause mortality for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. B: Relative risk of recurrent nonfatal myocardial infarction for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. C: Relative risk of recurrent unstable angina resulting in rehospitalization for early invasive therapy compared with conservative therapy at a mean follow-up of 13 months. Modified from the Journal of the American College of Cardiology, 48, Bavy AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes a meta-analysis of contemporary randomized clinical trials, 1319–25, Copyright 2006, with permission from Elsevier (198). CI = confidence interval; FRISC-II = FRagmin and fast Revascularization during InStability in Coronary artery disease; ICTUS = Invasive versus Conservative Treatment in Unstable coronary Syndromes; ISAR-COOL = Intracoronary Stenting with Antithrombotic Regimen COOLing-off study; RITA-3 = Third Randomized Intervention Treatment of Angina trial; RR = risk ratio; TIMI-18 = Thrombolysis In Myocardial Infarction-18; TRUCS = Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery; VINO = Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction: Open multicenter randomized trial.

dence of all-cause mortality at 2 years was 4.9% in the early invasive group compared with 6.5% in the conservative groups (RR 0.75, 95% CI 0.63 to 0.90, $p = 0.001$). Nonfatal MI (7.6% vs. 9.1%, respectively, RR 0.83, 95% CI 0.72 to 0.96, $p = 0.012$) and hospitalization (RR 0.69, 95% CI 0.65 to 0.74, p less than 0.0001) also were reduced. See the full-text guidelines for discussion of individual trials.

A. SUBGROUPS

Caveats about the application of invasive and conservative strategies in several subgroups of interest, including women (Section VII.A), diabetics (Section VII.B), older patients (Section VII.D), and those with chronic kidney disease (Section VII.E), are addressed in Section VII. Patients with PCI within the previous 6 months and those with prior CABG represent subgroups for which coronary angiography without preceding functional testing is generally indicated.

Management decisions must account for extensive comorbidities, such as 1) advanced or metastatic malignancy with a limited life expectancy, 2) intracranial pathology that contraindicates the use of systemic anticoagulation or causes severe cognitive or physical limitations, 3) end-stage cirrhosis, and 4) CAD that is known from previous angiography not to be amenable to revascularization.

5. Risk Stratification Before Discharge

A. GENERAL PRINCIPLES AND CARE OBJECTIVES

Important predischarge prognostication is derived from careful initial assessment, the patient's hospital course, and response to anti-ischemic and anticoagulant therapy. Formal risk assessment tools, such as GRACE and TIMI, can be useful not only for in-hospital and short-term assessments but also for longer term (6-month) assessment of risk (Table 4, Fig. 3). Coronary angiography and revascularization represent powerful modifiers of risk and tools for prognostication. Cardiac biomarkers (i.e., troponins and BNP) add to the assessment of postdischarge and in-hospital risk. An assessment of LV function by any of several methods is generally recommended to guide therapy and assess prognosis. Noninvasive stress testing before or shortly after discharge also provides very useful supplemental information to clinically based risk assessment (Table 9).

The goals of noninvasive testing are to 1) determine the presence or absence of ischemia in patients with a low or intermediate likelihood of CAD and 2) estimate prognosis. A detailed discussion of noninvasive stress testing in CAD is presented in the ACC/AHA Guidelines for Exercise Testing, the ACC/AHA Guidelines for the Clinical Use of Cardiac Radionuclide Imaging, and the ACC/AHA Guidelines for the Clinical Application of Echocardiography (Table 9) (31,199–201). Noninvasive criteria for estimating risk as high, intermediate, or low are summarized in Table 9.

Stress echocardiography and nuclear ventriculography represent important alternatives. Myocardial perfusion im-

Table 9. Noninvasive Risk Stratification

High risk (greater than 3% annual mortality rate)
Severe resting LV dysfunction (LVEF less than 0.35)
High-risk treadmill score (score ≤ -11 or less)
Severe exercise LV dysfunction (exercise LVEF less than 0.35)
Stress-induced large perfusion defect (particularly if anterior)
Stress-induced multiple perfusion defects of moderate size
Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
Echocardiographic wall-motion abnormality (involving more than 2 segments) developing at low dose of dobutamine (10 mg per kg per min or less) or at a low heart rate (less than 120 beats per min)
Stress echocardiographic evidence of extensive ischemia
Intermediate risk (1% to 3% annual mortality rate)
Mild/moderate resting LV dysfunction (LVEF = 0.35 to 0.49)
Intermediate-risk treadmill score (≤ -11 to 5)
Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
Limited stress echocardiographic ischemia with a wall-motion abnormality only at higher doses of dobutamine involving less than or equal to 2 segments
Low risk (less than 1% annual mortality rate)
Low-risk treadmill score (score 5 or greater)
Normal or small myocardial perfusion defect at rest or with stress*
Normal stress echocardiographic wall motion or no change of limited resting wall-motion abnormalities during stress*

*Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF less than 0.35). Reproduced from Table 23 in Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients With Chronic Stable Angina). 2002. Available at: <http://www.acc.org/qualityandscience/clinical/statements.htm> (2003).

LV = left ventricular; LVEF = left ventricular ejection fraction.

aging with pharmacological stress is particularly useful in patients who are unable to exercise. Cardiac magnetic resonance is a newer imaging modality that can effectively and simultaneously assess cardiac function, perfusion (i.e., with adenosine stress), and viability (202).

B. NONINVASIVE TEST SELECTION

There are no conclusive data comparing various noninvasive tests. Furthermore, prognostic information is largely extrapolated from studies in stable angina/chronic CAD populations. Hence, test selection may be based primarily on individual patient characteristics, physician judgment, and test expertise and availability (204). Low- and intermediate-risk patients may undergo symptom-limited stress testing if they have been clinically stable for 12 to 24 h. Earlier stress testing (i.e., within 3 to 7 d after UA/NSTEMI) is superior to later testing (i.e., at 1 month) (205) in that it identifies patients at risk for adverse events within the first month.

C. SELECTION FOR CORONARY ANGIOGRAPHY

Coronary angiography provides detailed structural information as the basis for assessing prognosis and directing management. When combined with LV angiography, it also

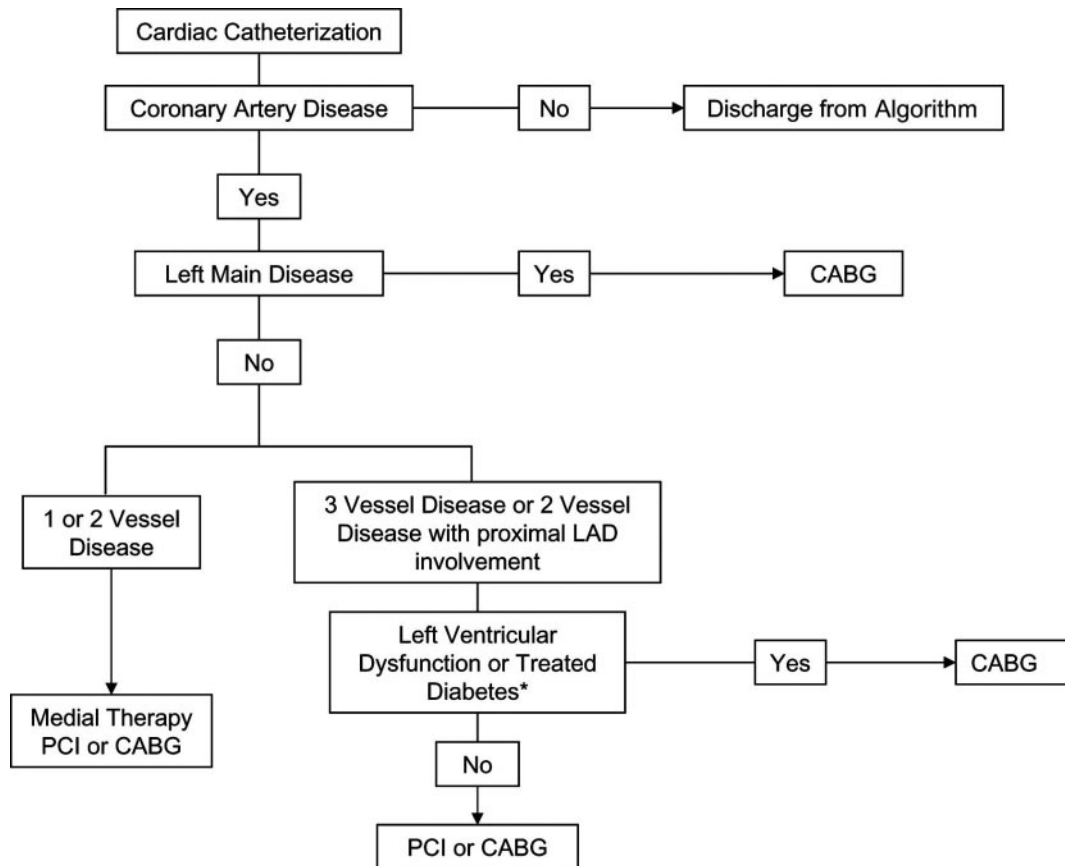


Figure 15. Revascularization Strategy in UA/NSTEMI

*There is conflicting information about these patients. Most consider CABG to be preferable to PCI. CABG = coronary artery bypass graft; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

provides an assessment of global and regional LV function. Indications for coronary angiography are interwoven with indications for possible therapeutic plans such as PCI or CABG. In contemporary practice, many intermediate- and high-risk patients receive coronary angiography as part of an invasive management strategy. In addition, coronary angiography is usually indicated in other UA/NSTEMI patients who have either recurrent symptoms or ischemia despite adequate medical therapy or who develop high-risk features clinically (Tables 5 and 9) (205a).

V. Coronary Revascularization

A. General Principles and Care Objectives

As discussed in Section IV, coronary angiography is useful for defining the coronary artery anatomy in patients with UA/NSTEMI and for identifying subsets of high-risk patients who can benefit from early revascularization. Coronary revascularization (PCI or CABG) is performed to improve prognosis, relieve symptoms, prevent ischemic complications, and improve functional capacity. The indications for coronary revascularization in patients with UA/NSTEMI are similar to those

for patients with chronic stable angina and are presented in greater detail in the ACC/AHA Guidelines for the Management of Patients With Chronic Stable Angina (31) and in the ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery (206) and the 2005 ACC/AHA/SCAI Guidelines Update for Percutaneous Coronary Intervention (5). These indications are tempered by individual patient characteristics. Selection criteria for coronary revascularization in patients with UA/NSTEMI are, in general, similar to those for patients with stable angina (122). Revascularization appears to be of most benefit when performed early in the hospital course, particularly in those with high-risk characteristics. See Figure 15 for details of the decision tree.

In recent years, stenting, other technological advances, and the use of improved antiplatelet and anticoagulant agents have improved the safety and durability of PCI in UA/NSTEMI. Stenting has reduced the risks of both acute vessel closure and late restenosis. Drug-eluting stents have reduced the risk of restenosis but modestly increase the risk of late coronary thrombotic events (129–131).

Published success rates of PCI in patients with UA/NSTEMI are high overall. Outcomes have approached those

of elective surgery with the use of stents and potent antiplatelet therapy (207–209). The use of drug-eluting stents for UA/NSTEMI has increased dramatically in recent years, with favorable rates of early death and recurrent infarction (210).

1. Platelet Inhibitors and PCI

Glycoprotein IIb/IIIa receptor antagonists and thienopyridines represent important therapeutic advances in patients with UA/NSTEMI, particularly in the setting of PCI, as reviewed in Section IV.B. Key trials of these agents in the settings of PCI and UA/NSTEMI are summarized in Table 8. Only 1 comparative trial (TARGET: Do Tirofiban And ReoPro Give similar Efficacy Trial) directly compared these agents (tirofiban vs. abciximab) in patients undergoing PCI with intended stenting. An advantage of abciximab in preventing early ischemic events was observed among the subgroup presenting with UA/NSTEMI (211). An insufficient loading dose of tirofiban to achieve an optimal early (periprocedural) antiplatelet effect has been proposed as a possible explanation for this difference (212).

Whether GP IIb/IIIa inhibition is still useful in UA/NSTEMI patients undergoing PCI who have received a high loading dose (600 mg) of clopidogrel was raised by a study in an elective setting (ISAR-REACT) (213). To address this issue, ISAR-REACT 2 enrolled patients with UA/NSTEMI undergoing PCI, loaded them with clopidogrel 600 mg at least 2 h before the procedure, and then randomized them to receive either abciximab or placebo at the time of PCI (74). As discussed earlier, the primary end point of death, nonfatal reinfarction, or urgent target-vessel revascularization within 30 d was reduced by 25% in the abciximab group, an advantage limited entirely to patients with an elevated troponin level. These findings have been incorporated into the overall UA/NSTEMI treatment algorithm shown in Figures 6, 7, and 8.

Comparisons of PCI and CABG are summarized in the next section.

B. Surgical Revascularization

Dramatic changes in surgical technique and in medical and percutaneous therapies have occurred over the past 2 decades, limiting the implications of older trial results for contemporary practice. The Bypass Angioplasty Revascularization Investigation (BARI) trial, the largest randomized comparison of CABG and percutaneous transluminal coronary angioplasty (PTCA) in multivessel CAD (214, 215), observed a survival benefit with CABG that was confined to patients with diabetes mellitus. The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) also showed a survival benefit for CABG in patients with diabetes and multivessel CAD (216). An Emory University study also was confirmatory (217). However, a CABG-related advantage was not reproduced in the BARI registry (218), which suggests that physicians might be able to recognize characteristics of CAD in diabetic patients that permits the safe selection of either revascularization therapy.

Hannan et al. (219) compared 3-year risk-adjusted survival rates in 29,646 CABG patients and 29,930 PTCA patients undergoing revascularization in the state of New York in 1993. Anatomic extent of disease was the only variable that interacted with revascularization therapy to influence survival. Patients with 1-vessel disease not involving the LAD had higher survival rates with PTCA, whereas patients with proximal LAD stenosis and 3-vessel disease had higher survival rates with CABG. A follow-up study using the same registry compared 37,212 patients who underwent CABG with 22,102 patients who underwent PCI using stents (220). The unanticipated finding was that the risk-adjusted long-term mortality of patients in all 5 anatomic subsets assessed was lower with CABG.

The most recent randomized comparisons of PCI and CABG surgery can be summarized as follows: The Angina With Extremely Serious Operative Mortality Evaluation [AWESOME] trial found comparable survival with CABG and PCI, which included stenting or atherectomy (221). Similarly, the ARTS trial (Arterial Revascularization Therapy Study), which compared coronary stenting with CABG (222) and which included but was not limited to patients with UA, found identical 3-year survival rates free of stroke and MI (222). A meta-analysis of 4 trials of CABG versus PCI with bare-metal stenting for multivessel disease between 1995 and 2000 also reported no difference in the primary composite end point of death, MI, and stroke or death alone between the CABG and the stent groups. None of these trials adequately reflect current interventional cardiology practice, which includes a broad use of drug-eluting stents, double- or triple-antiplatelet therapy, and newer anticoagulants. Surgical management also has evolved, and risk-adjusted mortality for CABG has declined progressively (223).

Nevertheless, when data from available trials and cohort studies are combined, these data suggest that it is reasonable to consider CABG to be a preferred revascularization strategy for most patients with 3-vessel disease, especially if it involves the proximal LAD, and for patients with multivessel disease and treated diabetes mellitus or LV dysfunction (Fig. 15). However, it would be unwise to deny contemporary PCI to a patient with diabetes mellitus and less severe CAD on the basis of the current information (224,225).

VI. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge Care

A. General Principles and Care Objectives

Two broad goals during the hospital discharge phase are 1) to prepare the patient for normal activities to the extent possible and 2) to use the acute event as an opportunity to reevaluate care, focusing on lifestyle and aggressive risk factor modification. Patients who have undergone successful PCI with an uncomplicated course are usually discharged

the next day. Patients who undergo uncomplicated CABG generally are discharged 4 to 7 d later. Low-risk patients may be discharged soon after noninvasive testing or coronary angiography. Management of high-risk, unstable patients often requires more prolonged and vigilant inpatient care.

Inpatient oral anti-ischemic, antiplatelet, and other secondary preventive medications used in the nonintensive phase generally should be continued after discharge. A multidisciplinary team is ideal to prepare the patient for discharge.

1. Long-Term Medical Therapy

Patients with UA/NSTEMI require secondary prevention at discharge. The acute phase of UA/NSTEMI is usually over within 1 to 3 months, after which most patients assume a course of chronic CAD. Therefore, chronic secondary prevention measures are similar to those for other CAD patients (3,8,12,13,31) (see Section VI.C below). Recommendations for lipid lowering are fully discussed elsewhere (3,12,13).

B. Postdischarge Risk Assessment and Follow-Up

Patient-specific risk within 1 year can be predicted on the basis of clinical information and the ECG. The PURSUIT, TIMI, and GRACE risk models, introduced in Section III.B, are also useful for postdischarge risk assessment (see Fig. 3).

At discharge, detailed discharge instructions for post-UA/NSTEMI patients should include education on medications, diet, exercise, and smoking cessation (if appropriate); referral to a cardiac rehabilitation/secondary prevention program (when appropriate); and the scheduling of a timely follow-up appointment. Low-risk medically treated patients and revascularized patients should return in 2 to 6 weeks, and higher-risk patients should return within 14 d. When stable, typically by 1 to 3 months after discharge, patients may be followed up as for stable CAD.

Minimizing the risk of recurrent cardiovascular events requires optimizing patient compliance with prescribed therapies and recommended lifestyle modifications.

C. Risk Factor Modification

A health care team with expertise in aggressively managing CAD risk factors should work with patients and their families, including patients who have undergone revascularization (226), to educate them in detail regarding specific targets for LDL-C and HDL-C (3,12,13), blood pressure (6), diabetes mellitus, diet and weight management (12), physical activity (12), tobacco cessation (12), and other appropriate lifestyle modifications (226,228). There is a wealth of evidence that cholesterol-lowering therapy reduces vascular events in patients with CAD and hypercholesterolemia (229) or mild cholesterol elevation after MI (230,231). Indeed, there is mounting evidence that statin therapy is beneficial regardless of baseline LDL-C levels

(232–234). More aggressive lipid lowering further lowers cardiovascular event rates and is safe, although the incremental impact on mortality over moderate lipid-lowering remains to be clearly established (235).

Data on the utility of ACE inhibitors in stable CAD in the absence of HF or LV dysfunction have been conflicting. A meta-analysis of 3 major trials (HOPE [Heart Outcomes Prevention Evaluation], EUROPA [EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease], and PEACE [Prevention of Events with Angiotensin Converting Enzyme Inhibition]) supports a benefit across the risk spectrum studied (236); however, the absolute benefit is proportional to disease-related risk, with those at lowest risk benefiting least (236,237). All patients with elevated systolic or diastolic blood pressures should be educated and motivated to achieve systolic and diastolic blood pressures in the normal range (i.e., less than 140/90 mm Hg; 130/80 mm Hg if the patient has diabetes or chronic kidney disease) (6,12).

For patients who smoke, tobacco cessation has substantial potential to improve survival (238). Physician counseling, referral to a smoking cessation program, and the use of pharmacological agents (239–242) are recommended (239).

Overweight patients should be instructed in a weight loss regimen, with emphasis on the importance of regular exercise and a lifelong prudent diet to maintain ideal body mass index.

Glycemic control is discussed in Section VII.B.

The use of NSAIDs and COX-2-selective inhibitors should be minimized in post-UA/NSTEMI patients because of an increase in cardiovascular risk (112,243,244). Cardiovascular risk associated with NSAID use may be lowest with naproxen, which has antiplatelet activity (111,243). An AHA scientific statement on the use of NSAIDs has recommended a stepped-care approach to musculoskeletal pain control to minimize risk (245).

Folic acid/B-vitamin supplementation given to reduce homocysteine levels did not reduce the risk of CAD events in 2 major trials (246,247), and its routine use for secondary prevention is not recommended. Antioxidant vitamins (C, E, beta carotene) also have not demonstrated benefit in secondary prevention and are not recommended (13).

See Section I.C.5.B for lipid lowering and other risk factor modification recommendations.

D. Physical Activity

Regular physical activity is important to improving functional capacity and well-being, losing weight and maintaining weight loss, and reducing other risk factors such as insulin resistance (248,249). Exercise training generally can begin within 1 to 2 weeks after revascularized UA/NSTEMI (249). Unsupervised exercise may target a heart rate range of 60% to 75% of maximum predicted; supervised training (see next section) may target a somewhat higher heart rate (70% to 85% of maximum) (249). Additional restrictions apply when residual ischemia is

present. Activity questionnaires and nomograms have been developed for cardiac and general populations to help guide exercise prescriptions (250). In addition to aerobic training, mild- to moderate-resistance training may be considered and may start 2 to 4 weeks after aerobic training has begun (251).

E. Cardiac Rehabilitation

Cardiac rehabilitation has been shown to improve exercise tolerance without increasing cardiovascular complications, to improve exercise tolerance and reduce cardiovascular symptoms, and to improve blood lipid levels; it has also been shown to reduce cigarette smoking in conjunction with a smoking cessation program, to decrease stress, and to improve psychosocial well-being (252). A limited, controlled evidence base also suggests a beneficial potential on cardiovascular outcomes (253,254). The benefits of rehabilitation after uncomplicated UA/NSTEMI with revascularization and modern medical therapy are less clear in comparison with STEMI or complicated NSTEMI, and physician judgment is recommended. Comprehensive cardiac rehabilitation involves individualized risk factor assessment, education, and modification, as well as prescribed exercise, and may occur in a variety of settings (255). Alternative approaches, including home exercise, Internet-based programs, and transtelephonic monitoring/supervision, also can be implemented effectively and safely for selected patients (256).

F. Return to Work and Disability

Cardiac functional status and LVEF are not strong predictors of return to work, although physical requirements of work play a role (257,258). Psychological variables such as trust, job security, feelings about disability, absence of depression, pre-event functional independence, and expectations of recovery are more predictive (257,259). Resumption of full employment also is lower with diabetes mellitus, older age, Q-wave MI, and preinfarction angina (258). Cardiac rehabilitation programs can contribute to return to work (260). Contemporary information on the impact of current aggressive interventional treatment of UA/NSTEMI, with shortened hospital length of stay and early rehabilitation, on return to work and disability is needed. In PAMI (Primary Angioplasty in Myocardial Infarction)-II, a study of primary PTCA in low-risk patients with MI, patients were encouraged to return to work at 2 weeks (261). Although the actual timing of return to work was not reported, no adverse events occurred as a result of this strategy.

G. Other Activities

Daily walking can be encouraged immediately in all patients. In stable patients without complications, sexual activity with the usual partner can be resumed within 1 week to 10 d. For stable patients, driving can begin 1

week after discharge if otherwise in compliance with state laws. After complicated MI, driving should be delayed until 2 to 3 weeks after symptoms have resolved. Air travel within the first 2 weeks of MI should be undertaken only if a patient has no angina, dyspnea, or hypoxemia at rest or fear of flying, flies with a companion, carries NTG, and avoids rushing and increased physical demands of travel. Low-risk patients with UA/NSTEMI who are revascularized and otherwise stable may accelerate their return to work, driving, flying, and other normal activities (often, within a few days).

H. Patient Records and Other Information Systems

Effective medical record systems, including electronic systems, that document the course and plan of care should be established or enhanced. Tools such as the ACC's "Guidelines Applied in Practice" and the AHA's "Get With the Guidelines" can improve quality of care and patient safety. Reliable health care information relevant to UA/NSTEMI patients is available, and patient access to it should be encouraged (<http://www.hearthaauthority.com>; <http://www.nhlbi.nih.gov/health/dci/index.html>; <http://www.nlm.nih.gov/medlineplus/tutorial.html>; <http://www.fda.gov/hearthealth/index.html>).

VII. Special Groups

A. Women

1. Profile of UA/NSTEMI in Women

Women present at an older age but account for a considerable proportion of UA/NSTEMI. Women are more likely to have hypertension, diabetes mellitus, and HF with preserved systolic function; to manifest UA rather than NSTEMI; to have atypical symptoms (e.g., primarily dyspnea); and to have causes unrelated to CAD (22,32,262–265,266). Women have similar rates of ST depression but less often have elevated biomarkers (267). Nevertheless, the prognostic value of elevated biomarkers is similar in women and men (268). Coronary angiography reveals less extensive CAD in women and a higher proportion (as high as 37%) with nonobstructive CAD (262,269). This profile makes it challenging to confirm the diagnosis of UA/NSTEMI and is a likely cause of underutilization or overutilization of therapies in women (267). Unlike STEMI, female sex is not a risk factor for adverse outcomes for UA/NSTEMI when adjusted for baseline characteristics (22,203,267,270–277).

2. Stress Testing

Indications for noninvasive testing in women are the same as in men (203,270). Exercise ECG testing is less predictive in women, however, primarily because of the lower pretest probability of CAD (271–273). Perfusion studies with sestamibi have good sensitivity and specificity in women

(275). The Duke Treadmill Score performs well in women for the exclusion of CAD (276).

3. Management

A. PHARMACOLOGICAL THERAPY

Women derive the same treatment benefit as men from ASA, clopidogrel, anticoagulants, beta blockers, ACE inhibitors, and statins, but they are given ASA and other anticoagulant less frequently (278). A meta-analysis of GP IIb/IIIa antagonists in UA/NSTEMI reported an apparent lack of efficacy and possible harm in women (187); however, women with elevated troponin levels received the same beneficial effect as men. Higher rates of dosing errors and subsequent bleeding with antiplatelet and anticoagulant therapy have been reported for women than for men (279). Creatinine clearance (Cockcroft-Gault formula) and weight-based adjustments of medications, where recommended, can reduce this risk.

B. CORONARY ARTERY REVASCLARIZATION

Angiographic success and late outcomes after PCI for women, including those presenting with UA/NSTEMI, have improved and are generally similar to men, although in some series, early complications occurred more frequently in women (264,280,281). Similarly, more recent studies show a favorable outlook for women with ACS undergoing CABG (262,282,282a).

C. INITIAL INVASIVE VERSUS INITIAL CONSERVATIVE STRATEGY

Clinical trials of UA/NSTEMI have consistently demonstrated a benefit with an invasive strategy for men (see Section IV.C), but results in women have been conflicting. A meta-analysis of trials in the era of stents and GP IIb/IIIa antagonists has failed to show a survival benefit of a direct invasive strategy in women at 6 to 12 months (OR for women 1.07, 95% CI 0.82 to 1.41; OR for men 0.68, 95% CI 0.57 to 0.81) (283).

In TACTICS (Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy) TIMI-18, there was a reduction in the composite risk of death, nonfatal MI, or rehospitalization for UA in women with intermediate (3 to 4) or high (5 to 7) TIMI risk scores undergoing an early invasive strategy that was similar to that in men (284). In contrast, women with a low TIMI risk score had an increased risk of events (OR 1.59, 95% CI 0.69 to 3.67) with the invasive versus the conservative strategy, whereas low-risk men had similar outcomes with the 2 strategies. However, the number of events was small ($n = 26$ events), and the probability value for interaction did not achieve significance ($p = 0.09$). Similarly, women with an elevated troponin T benefited from an invasive strategy (adjusted OR 0.47, 95% CI 0.26 to 0.83), whereas the primary end point was significantly more frequent in women (but not men) treated invasively with a negative troponin (OR 1.46, 95% CI 0.78 to 2.72) (284). The FRISC II (197) and RITA-3 (196,269,285) randomized trials reported im-

proved outcomes with an invasive strategy only in men, but a high percentage of women were low risk, and an assessment of outcomes by risk or troponin status has not been reported.

In summary, women with UA/NSTEMI and high-risk features, including elevated cardiac biomarkers, appear to benefit from an invasive strategy with adjunctive GP IIb/IIIa antagonist use, although more data are needed. There is no benefit of a direct invasive strategy for low-risk women, and the weight of evidence suggests that there may be excess risk in this group, for which a conservative strategy is recommended.

B. Diabetes Mellitus

1. Profile and Initial Management of Diabetic and Hyperglycemic Patients With UA/NSTEMI

Coronary artery disease accounts for 75% of deaths in patients with diabetes, and approximately 20% to 25% of patients with UA/NSTEMI have diabetes mellitus (215,286). Diabetic patients with UA/NSTEMI have more severe CAD (286–288), more ulcerated plaques and intracoronary thrombi (289), more vascular comorbidities, and are more often post-CABG patients (290). Diabetic autonomic dysfunction raises the threshold for the perception of angina, which confounds the diagnosis of UA/NSTEMI (291). Importantly, diabetes mellitus is an independent predictor of death, MI, or readmission with UA (292).

Glucose level on admission to the hospital is a significant predictor of 1-year mortality (293); however, the optimal approach to managing hyperglycemia remains uncertain (294–296). Pending additional trials that include ACS patients, a reasonable approach may be to target a blood glucose goal of less than 150 mg per dL during the first 3 d in the intensive care unit/critical care unit in very ill patients (e.g., those with ventilators or on parenteral feeding) (297). Thereafter, or in less ill patients, a more intensive insulin regimen could be instituted, with a goal of normoglycemia (80 to 110 mg per dL).

2. Coronary Revascularization

An advantage for CABG over PTCA was found in treated patients with diabetes mellitus in the randomized BARI (286), CABRI (216), and Emory University trials (217), as discussed in Section V.C. Specifically, mortality was lower in patients who received internal thoracic artery grafts. However, a CABG-related advantage was not reproduced in the BARI registry population (218), which suggests that physicians might be able to recognize characteristics of CAD in diabetic patients that permit the safe selection of either revascularization therapy. Similarly, in the Duke University registry study, although outcome was worse in diabetic patients, there was no differential effect of PCI versus CABG (298).

Stents have improved the outcome of patients with diabetes mellitus who undergo PCI. In a study with histor-

ical controls, the outcome after coronary stenting was superior to that after PTCA, and the restenosis rate was reduced (63% vs. 36%, diabetes vs. no diabetes, with balloon PTCA at 6 months [$p = 0.0002$] compared with 25% and 27% with stents [$p = \text{NS}$]) (299). Nevertheless, “BARI-like” comparisons of long-term survival after PCI with frequent stenting versus CABG have reported better risk-adjusted long-term survival in diabetic subgroups with 3-vessel disease treated with CABG (300).

Glycoprotein IIb/IIIa antagonists improve the outcome of PCI in patients with diabetes mellitus. In the Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade (EPILOG), abciximab resulted in a greater decline in death/MI over 6 months after PCI in patients with diabetes mellitus (HR 0.36, 95% CI 0.21 to 0.61) than in those without diabetes (HR 0.60, 95% CI 0.44 to 0.829) (301). A similar differential benefit in diabetic patients has been reported for tirofiban (225). In the Evaluation of IIb/IIIa Platelet Inhibitor for STENTing (EPISTENT) trial, which studied 2,399 patients, 21% with diabetes and 20% with UA (178), abciximab reduced the 30-d event rate (death, MI, or urgent revascularization) in diabetic patients from 12.1% (stent plus placebo) to 5.6% (stent plus abciximab; $p = 0.040$). At 6 months, revascularization of target arteries was reduced by more than 50% (16.6% vs. 8.1%, $p = 0.02$). Death or MI was reduced to a similar degree in diabetic and nondiabetic patients (303), and benefits were maintained at 1 year (304).

Data on outcomes in diabetic patients with the contemporary use of drug-eluting stents, GP IIb/IIIa inhibitors, and long-term clopidogrel are limited. However, given the diffuse nature of diabetic CAD, the relative benefits of CABG over PCI may persist for diabetic patients, even in the era of drug-eluting stents.

C. Post-CABG Patients

Overall, up to 20% of patients presenting with UA/NSTEMI have previously undergone CABG (290). Conversely, approximately 20% of post-CABG patients develop UA/NSTEMI during an interval of 7.5 years (305). Post-CABG patients who present with UA/NSTEMI are at higher risk than those who have not undergone surgery.

1. Pathological Findings

Pathologically, post-CABG patients have a particular tendency for atherosclerotic and thrombotic lesions to develop in SVGs, as well as native-vessel progression, which can lead to UA/NSTEMI (306). Angiographically, SVGs more frequently have friable plaques, complex lesions, thrombi, and total occlusions than native vessels (307). Approximately 50% of SVGs develop obstructive lesions within 5 years and more than 90% at greater than 10 years (307), and there is a high rate of early graft failure in current practice (occlusion in up to one third at 1 year). Thus, SVG disease is a serious and unstable process.

2. Clinical Findings and Approach

Post-CABG patients are more frequently male, older, and diabetic; have more extensive CAD; and have more prior MIs and LV dysfunction than non-CABG patient presenting with UA/NSTEMI. Resting ECG abnormalities often limit the utility of ECG stress testing, but myocardial stress perfusion imaging or dobutamine echocardiography can help to identify and define areas of ischemia. Given complex disease with many anatomic possibilities that cause ischemia, there should be a low threshold for angiography in post-CABG patients with UA/NSTEMI.

Revascularization with either PCI or reoperation may be considered in post-CABG patients with UA/NSTEMI on the basis of individual characteristics. Stents are generally preferred to balloon angioplasty of SVGs (308). When possible, PCI of a native vessel is preferred to PCI of an SVG. Embolization of friable atherosclerotic can increase the risk of PCI-related complications (309). Despite relatively similar early outcomes, post-CABG patients experience up to twice the incidence of adverse events (death, MI, or recurrent UA) during the first year, which is attributable, at least in part, to a lower rate of complete revascularization (305,310).

D. Older Adults

The terms “elderly” or “older adults” are often used to refer to those aged 75 years and older. Older adults account for more than one-third of UA/NSTEMI patients (311) and present with special challenges. First, they more often present with atypical symptoms, including dyspnea and confusion (312). Second, they are more likely to have altered cardiovascular physiology, including hypertension or hypotension, cardiac hypertrophy, and HF and LV dysfunction, especially diastolic dysfunction (313), and they more frequently have other cardiac comorbidities. Third, older patients tend to be treated with a greater number of medications, have reduced renal function, and are at greater risk for adverse drug interactions. Hence, older age is associated with both higher disease severity and greater treatment risk (311).

1. Pharmacological Management

Overall, older subgroups in clinical trials have relative or absolute risk reductions that are relatively similar to those of younger patients for many commonly used treatments for UA/NSTEMI. Despite this, older patients less often receive an early invasive strategy and key pharmacotherapies, including anticoagulants, beta blockers, clopidogrel, and GP IIb/IIIa inhibitors (44,311,314). With this said, proper drug selection and dose adjustment are needed to account for altered drug metabolism, distribution, and elimination, as well as exaggerated drug effects. In a community-based registry, 38% of UA/NSTEMI patients aged 75 years or older received an excessive dose of UFH, 17% received excessive LMWH, and 65%

received an excessive dose of a GP IIb/IIIa antagonist (311); 15% of major bleeding could be attributed to excess dosing (279). Mortality and length of stay were greater with excessive dosing. Altered pharmacodynamic responses to drugs also result from lower cardiac output, plasma volume, and vasomotor tone and responsiveness.

2. Functional Studies

Older persons often have difficulty performing exercise testing and have a higher prevalence of preexisting ECG abnormalities. In such patients, pharmacological stress testing with cardiac imaging can be useful.

3. Contemporary Revascularization Strategies in Older Patients

Experience has shown that coronary stenting can be performed in older patients with high procedural success and acceptably low complication rates (315). Similarly, an invasive strategy in UA/NSTEMI can benefit older patients with UA/NSTEMI. In the TACTICS TIMI-18 trial (316), the early invasive strategy conferred an absolute reduction in total ischemic events of 10.8 percentage points and a relative risk reduction of 50% (10.8% vs. 21.6%; $p = 0.016$) in patients older than 75 years. Benefits came with an increased risk of major bleeding events (16.6% vs. 6.5%; $p = 0.009$). Thus, selection of older patients for an early invasive strategy remains challenging and requires clinical judgment and individual application; however, age alone should not preclude the use of a PCI-based strategy.

Operative morbidity and mortality rates also increase for CABG with advanced age, but outcomes have progressively improved and are favorable compared with medical therapy; quality of life improves as well (317). A contemporary review of 662,033 patients enrolled in the Society of Thoracic Surgeons National Cardiac Database (318) found a CABG operative mortality rate of 2.8% for patients 50 to 79 years of age, 7.1% for patients 80 to 89 years of age, and 11.8% for patients aged 90 years or greater. Risk was lower in the absence of certain factors (renal failure, emergency surgery, and noncoronary vascular disease). Thus, with appropriate selection, CABG surgery can be an appropriate revascularization strategy, even in the oldest patient subgroups.

E. Chronic Kidney Disease

Chronic kidney disease is a potent risk factor for cardiovascular disease and qualifies as a coronary risk equivalent (319). Chronic kidney disease is also a risk factor for adverse outcomes after MI, including NSTEMI (47,320,321). Of concern, however, is the underrepresentation of patients with renal disease in randomized controlled trials (322). Limited evidence and current opinion suggest that when appropriately monitored, cardiovascular medications and interventional strategies can be safely applied to these patients (320). However, bleeding risk is higher because of platelet dysfunction and dosing errors (279). Renin-

angiotensin-aldosterone inhibitors can impose a greater risk of hyperkalemia and worsening renal function. Angiography carries an increased risk of contrast-induced nephropathy, and PCI is associated with a higher rate of early and late complications (322). Thus, chronic kidney disease carries a far worse prognosis, but unlike in several other high-risk subsets, the value of aggressive therapeutic interventions is less certain and should be further studied.

In patients with chronic kidney disease or chronic kidney disease and diabetes mellitus who are undergoing angiography, isosmolar contrast material has been shown to lessen the rise in creatinine: It reduced the risk of contrast-induced nephropathy in both a randomized clinical trial (RECOVER [Renal Toxicity Evaluation and Comparison Between Visipaque (Iodixanol) and Hexabrix (Ioxaglate) in Patients With Renal Insufficiency Undergoing Coronary Angiography]) comparing iodixanol with ioxaglate (323) and a meta-analysis of 2,727 patients from 16 randomized clinical trials (324).

An assessment of renal function is critical to proper medical therapy of UA/NSTEMI. Many cardiovascular drugs used in UA/NSTEMI patients are renally cleared; their doses should be adjusted for estimated creatinine clearance. Clinical studies and labeling that defines adjustments for several of these drugs have been based on the Cockcroft-Gault formula for estimating creatinine clearance, which should be used to generate dose adjustments.

F. Cocaine and Methamphetamine Users

The widespread use of cocaine and, more recently, methamphetamines and their known association with UA/NSTEMI makes it mandatory to consider these drugs as a potential cause of UA/NSTEMI, because pathophysiology and therapy for these drugs are distinctive.

1. Pathophysiology and Presentation

The potential of cocaine to induce coronary spasm has been demonstrated both *in vitro* (325) and *in vivo* (326–328). Treatment with calcium antagonists inhibits or reverses cocaine-induced vasoconstriction (328,329). Cocaine also increases platelet responsiveness and reduces anticoagulant factors, which predisposes the individual to coronary thrombosis (326,330).

Cocaine users can develop chest discomfort that is indistinguishable from UA/NSTEMI secondary to coronary atherosclerosis. Thus, UA/NSTEMI patients should be questioned about the use of cocaine and methamphetamines (331).

2. Treatment

Initial management of cocaine-induced ACS should include sublingual NTG and a calcium antagonist (e.g., diltiazem 20 mg IV) (326,332). If ST-segment elevation is present and the patient is unresponsive to initial treatment, immediate coronary angiography is preferred over fibrinolytic therapy. After cocaine use, increased motor activity causing CK and CK-MB

elevations can occur in the absence of MI (333); hence, troponin levels should be used to assess myocardial injury. The use of beta blockers for cocaine-induced ischemia is controversial (334). If used, labetalol, an alpha and beta blocker, has been advocated, because it has been shown not to induce coronary artery vasoconstriction (335). However, NTG and calcium antagonists are preferred (332,334). Cocaine users with possible/probable UA/NSTEMI should be observed and managed medically for 9 to 24 h. Thereafter, if the ECG and biomarkers are normal and the patient is stable, the patient can be discharged (336).

3. Methamphetamine Use and UA/NSTEMI

Although methamphetamine abuse has increased dramatically, the evidence base for UA/NSTEMI after methamphetamine use and its treatment is limited to a few publications of case reports and small series (337–339). These suggest a clinical presentation that resembles cocaine-associated ACS. Therapy similar to that for cocaine-induced UA/NSTEMI is reasonable pending information more specific to methamphetamine use.

G. Variant (Prinzmetal's) Angina

Variant angina (Prinzmetal's angina, periodic angina) is an unusual form of UA that usually occurs spontaneously, is classically characterized by transient ST-segment elevation, and spontaneously resolves or resolves with NTG use, usually without progression to MI.

1. Clinical Picture, Pathogenesis, and Diagnosis

Anginal discomfort usually occurs at rest, simulating UA/NSTEMI. Attacks can be precipitated by emotional stress, hyperventilation, exercise, or exposure to cold and occur more frequently in the early morning. Patients with variant angina are generally younger and, except for smoking, have fewer coronary risk factors (340,341). Occasionally, prolonged vasospasm can result in MI, atrioventricular block, ventricular tachycardia, or sudden death (342,343).

The cause of variant angina is epicardial coronary artery spasm, most commonly focal but potentially at more than 1 site (344). ST-segment elevation implies transmural ischemia associated with complete or near-complete coronary occlusion. These sites can be angiographically normal (presumably with endothelial dysfunction or inapparent plaques) (345) or may show nonobstructive or obstructive CAD (346). The key to diagnosis is the documentation of transient ST-segment elevation during chest discomfort. Both noninvasive tests (ambulatory ECG recording, morning treadmill exercise) and coronary angiography (which can include pharmacological provocation) can be useful in diagnosis.

2. Treatment and Prognosis

Variant angina is usually responsive to NTG, long-acting nitrates, and calcium antagonists (347–349), which are

considered first-line therapies. (Beta blockers have theoretical adverse potential, and their clinical effect is controversial.) Smoking should be discontinued. Patients with very active disease can require a combination of nitrates and 2 calcium antagonists of different classes (i.e., a dihydropyridine with verapamil or diltiazem). Alpha-receptor blockers may be tried in resistant patients (350). Coronary spasm (with or without provocation) that occurs during coronary angiography should be treated with 0.3 mg of NTG infused directly into the coronary artery involved. Prognosis with medical therapy is usually good in the presence of a normal or near-normal coronary arteriogram (351) but is worse in the presence of CAD (352).

H. Cardiovascular "Syndrome X"

1. Definition and Clinical Picture

Cardiovascular "syndrome X" refers to with a syndrome of angina or angina-like discomfort with exercise, ST-segment depression on exercise testing or other objective signs of ischemia (353), and normal or nonobstructed coronary arteries on arteriography (354). Syndrome X is more common in women than in men (354–357). Chest discomfort can be typical or atypical (356), may occur with activity or at rest, and may or may not respond to NTG (358). Prolonged episodes can simulate UA/NSTEMI. The cause of syndrome X is not well understood but has been postulated to involve microvascular dysfunction and/or abnormal pain perception (359,360). Recent data from the Women's Ischemia Syndrome Evaluation (WISE) (361,362) suggest that long-term prognosis might not be as benign as previously thought: Women with no or minimal obstructive disease had a 9.4% occurrence of MI or death by 4 years.

2. Treatment

Persistence of symptoms is common, and many patients do not return to work (358). The demonstration of normal coronary arteries on angiography can be reassuring. Beta blockers and calcium antagonists can reduce the number of episodes of chest discomfort (363,364). Nitrates are effective in one-half of patients. Imipramine 50 mg daily can benefit patients with chronic pain syndromes, including syndrome X (365). Estrogen in postmenopausal women can reduce the frequency of chest pain episodes (366) but can increase cardiovascular risk. Statin therapy and exercise training can improve exercise capacity, endothelial function, and symptoms (367,368). Cognitive behavioral therapy can be beneficial (369). Other causes of chest discomfort, especially esophageal dysmotility, should be ruled out. Coronary risk factor reduction is appropriate, especially if even minimal CAD is present. Transcutaneous electrical nerve stimulation and spinal cord stimulation have been used for pain control in highly symptomatic, refractory cases (370).

APPENDIX 1. RELATIONSHIPS WITH INDUSTRY—ACC/AHA COMMITTEE TO UPDATE THE 2002 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/NON-ST-ELEVATION MYOCARDIAL INFARCTION

Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/ Advisory Member
Cynthia D. Adams	None	<ul style="list-style-type: none"> • GlaxoSmithKline • Guidant • Medtronic • Pfizer 	None	<ul style="list-style-type: none"> • CHF Technologies
Jeffery L. Anderson	<ul style="list-style-type: none"> • AstraZeneca • Bristol-Myers Squibb* 	<ul style="list-style-type: none"> • Merck* 		<ul style="list-style-type: none"> • Bristol-Myers Squibb • Merck* • Sanofi • ThromboVision
Elliott M. Antman	<ul style="list-style-type: none"> • Accumetrics • Amgen, Inc. • AstraZeneca • Bayer Healthcare LLC • Biosite • Boehringer Mannheim • Beckman Coulter, Inc. • Bristol-Myers Squibb • Centocor • CV Therapeutics • Dade • Dendron • Eli Lilly* • Genetech • GlaxoSmithKline • Inotek Pharmaceuticals Corp. • Integrated Therapeutics Corp. • Merck • Millennium* • Novartis Pharmaceuticals • Nuvelo, Inc. • Ortho-Clinical Diagnostics, Inc. • Pfizer, Inc. • Roche Diagnostics GmbH • Sanofi-Aventis Research Institute • Sanofi-Synthelabo Recherche • Schering-Plough • Sunoz Molecular • The National Institutes of Health 	None	None	<ul style="list-style-type: none"> • Eli Lilly • Sanofi-Aventis
Charles R. Bridges	None	None	None	None



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Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/ Advisory Member
Robert M. Califf	<ul style="list-style-type: none"> • Abbott Laboratories • Abbott Vascular Devices • Acorn Cardiovascular • Actelion • Acushphere, Inc • Advanced CV Systems • Advanced Stent Tech • Agilent Technologies • Ajinomoto • Alexion • Allergan • Alsius • Amgen • Amylin Pharmaceuticals Inc. • Anadys • ANGES MG, Inc. • Argionx Pharmaceuticals • Ark Therapeutics, Ltd. • AstraZeneca • Aventis • Aviron Flu Mist • Bayer AG • Bayer Corp. • Berlex • Biocompatibles, Ltd. • Biogen • Bioheart • Biomarin • Biosense Webster, Inc. • Biosite • Biotronik • Biotechnology General Corp. • Boehringer Ingelheim • Boston Scientific • Bracco Diagnostics • Bristol-Myers Squibb • CanAm Bioresearch, Inc. • Cardiac Science, Inc. • Cardiodynamics • CardioKinetix, Inc. • Caro Research 	<ul style="list-style-type: none"> • Bristol-Myers Squibb • Conceptis • Guilford Pharmaceuticals • Novartis Pharmaceutical • Pfizer • Sanofi-Aventis • Schering-Plough • The Medicines Company • Yamanouchi 	<ul style="list-style-type: none"> • NITROX 	<ul style="list-style-type: none"> • Conceptis



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Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/ Advisory Member
Robert M. Califf (continued)	<ul style="list-style-type: none"> • Celsion Corp. • Centocor • Chase Medical • Chugai Biopharmaceuticals, Inc. • Coley Pharma Group • Conor Medsystems, Inc. • Corautus Genetics, Inc. • Cordis • Corgentech • Covalent Group • Critical Therapeutics, Inc. • CryoVascular Systems, Inc. • CTS Durham • Cubist Pharmaceuticals • CV Therapeutics, Inc. • Dade Behring • Daiichi • Dupont • Dyax • Echosens, Inc. • Eclipse Surgical Technologies • Edwards Lifesciences • Enzon • Ernst and Young • Esai • Ev3, Inc. • Evalve, Inc. • First Circle Medical, Inc. • First Horizon • Flow Cardia, Inc. • Fox Hollow Pharmaceuticals • Fujisawa • Genentech • General Electric Healthcare • General Electric Medical Systems • Genome Canada • Genzyme Corporation • Gilead • GlaxoSmithKline • Guidant • Guilford Pharmaceuticals • Hemosol • Hewlett Packard • Human Genome Sciences • Humana • IDB Medical • Idun Pharmaceuticals, Inc. • Immunex • Indenix Pharmaceuticals • INFORMD, Inc. • InfraReDx • Inhibitex • INO Therapeutics • Integris • InterMune Pharmaceuticals • ISIS Pharmaceuticals • IOMED • Johnson & Johnson • Jomed, Inc. • KAI Pharmaceuticals • Kerberos Proximal Inc. • King Pharmaceuticals • Kuhera • Lilly • Lumen Biomedical • MedAcoustics • Medco Health Solutions 			



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Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/ Advisory Member
Robert M. Califf (continued)	<ul style="list-style-type: none"> • Medisure • Medi-Flex, Inc. • Medimmune • Medtronic • Medtronic Vascular, Inc. • Merck • MicroMed Tech, Inc. • Millenium Pharmaceutical • Mitsubishi • Mycosol, Inc. • Myogen • NABI • NitroMed • NovaCardia, Inc. • Novartis AG Group • Novartis Pharmaceutical • Organon International • Ortho Biotech • Osiris Therapeutics, Inc. • Otsuka America Pharmaceutical, Inc. • Pathway Medical Tech • Pfizer • Pharmacia/Upjohn • Pharmanetics, Inc. • Pharsight • Procter & Gamble • Prometheus • Recom Managed Systems • Regado Biosciences, Inc. • Roche Diagnostic Corp. • Roche Holdings, Ltd. • Roche Labs • Salix Pharmaceuticals • Sanofi Pasteur • Sanofi-Aventis • Sanofi-Synthelabo • Schering-Plough • Scios • Searle • Sidel Technologies • Siemens • SmithKlineBeecham • Spectranetics • Summit • Sunels • Synaptic • Synthetic Blood International • Terumo Corp • The Medicines Company • Theravance • TherOx, Inc. • Titan Pharmaceuticals, Inc. • Valeant Pharmaceuticals • Valentis, Inc. • Velocimed • Veridex • Vertex Pharmaceuticals • VIASYS Helathcare Inc. • Vicuron Pharmaceutical • Wyeth-Ayerst • XOMA • Xsira Pharmaceuticals • XTL Biopharmaceuticals • Xylum • Yamanouchi 			



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Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/ Advisory Member
Donald E. Casey, Jr.	None	None	<ul style="list-style-type: none"> Johnson & Johnson Merck Pfizer 	None
William E. Chavey II	None	NitroMed	None	None
Francis M. Fesmire	<ul style="list-style-type: none"> Cor Therapeutics Dupont Hewlett-Packard Radiopharmaceuticals 	<ul style="list-style-type: none"> Dadle Millenium 	None	<ul style="list-style-type: none"> CRUSADE
Judith S. Hochman	<ul style="list-style-type: none"> Arginox Pharmaceuticals CV Therapeutics Eli Lilly Millennium Procter & Gamble 	<ul style="list-style-type: none"> Network for Continuing Medical Education (supported by Bristol-Myers Squibb/Sanofi) 	None	<ul style="list-style-type: none"> Datascope Eli Lilly GlaxoSmithKline Merck Schering-Plough
Thomas N. Levin	None	<ul style="list-style-type: none"> Bristol-Myers Squibb/Sanofi Foxhollow Schering-Plough 	<ul style="list-style-type: none"> Boston Scientific Foxhollow Johnson & Johnson Medtronic Pfizer 	None
A. Michael Lincoff	<ul style="list-style-type: none"> Alexion Pharm* Amer Bioscience* AstraZeneca* Atherogenics* Biosite* Centocor* Converge Medical* Cordis* Dr. Reddy's Laboratory* Eli Lilly* GlaxoSmithKline* Glaxo Wellcome* Guilford* Medtronic* Novartis* Pfizer* Pharmacia Upjohn* Phillips* Orphan Therapeutic* Sankyo* Sanofi* Scios* Takeda America* The Medicines Company* Vasogenix* 	<ul style="list-style-type: none"> The Medicines Company* 	None	None
Eric D. Peterson	<ul style="list-style-type: none"> Bristol-Myers Squibb/Sanofi Millennium Pharmaceuticals Schering-Plough 	<ul style="list-style-type: none"> Millennium Pharmaceuticals Schering-Plough 	None	None
Pierre Theroux	<ul style="list-style-type: none"> AstraZeneca Sanofi-Aventis 	None	<ul style="list-style-type: none"> AstraZeneca Boston Scientific Cardiovascular Therapeutics Therapeutics Medtronic Merck Procter & Gamble Sanofi-Aventis 	<ul style="list-style-type: none"> AstraZeneca Procter & Gamble Sanofi-Aventis



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Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/ Advisory Member
Nanette Kass Wenger	• Pfizer	<ul style="list-style-type: none"> • Bristol-Myers Squibb • CV Therapeutics • Eli Lilly • Merck • NitroMed • Novartis • Pfizer 	None	<ul style="list-style-type: none"> • Abbott • AstraZeneca AB • Bristol Myers Squibb • CV Therapeutics* • GlaxoSmithKline • NitroMed Heart Failure Advisory Board • Sanofi-Aventis • Schering-Plough
R. Scott Wright	• Centocor*	None	None	<ul style="list-style-type: none"> • Merck/Schering-Plough • Novartis • Pfizer

This table represents the actual or potential relationships with industry that were reported as of February 13, 2007. This table was updated in conjunction with all meetings and conference calls of the writing committee. *Indicates significant (greater than \$10,000) relationship.

APPENDIX 2. RELATIONSHIPS WITH INDUSTRY—EXTERNAL PEER REVIEW FOR THE ACC/AHA COMMITTEE TO UPDATE THE 2002 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/NON-ST-ELEVATION MYOCARDIAL INFARCTION

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Eugene Braunwald	• Official	<ul style="list-style-type: none"> • AstraZeneca • Bayer Healthcare • Daiichi Sankyo • Merck and Co. • Momenta • Pfizer • Sanofi-Aventis • Schering-Plough • Scios† 	None	None	<ul style="list-style-type: none"> • AccuMetrics, Inc.† • AstraZeneca† • Bayer Healthcare† • Beckman Coulter† • Bristol-Myers Squibb† • CV Therapeutics† • Eli Lilly† • Inotek Pharmaceuticals† • Johnson & Johnson† • Merck and Co.† • National Institutes of Health† • Novartis† • Nuucid† • Pfizer† • Roche Diagnostics† • Sanofi-Aventis† • Schering-Plough† 	None
Bernard Gersh	• Official-AHA	<ul style="list-style-type: none"> • Abbott • Asnocyte Inc. • AstraZeneca • Boston Scientific • Bristol-Myers Squibb • Cardiovascular Therapeutics† 	None	None	None	None

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Chris Granger	• Official-AHA	• AstraZeneca† • GlaxoSmithKline† • Medicores Co. • Sanofi-Aventis†	None	None	• Alexion† • AstraZeneca† • Berlex† • Boehringer Ingelheim† • Bristol-Myers Squibb† • Genetech† • GlaxoSmithKline† • Novartis† • Procter & Gamble† • Sanofi-Aventis†	None
David Holmes	• Official-ACC Board of Trustees	None	None	None	None	None
Kristen Newby	• Official-AHA	• Biosite • CV Therapeutics • Eli Lilly • Inverness Medical • Procter & Gamble	• BMS-Sanofi	None	• Bristol-Myers Squibb/Sanofi† • Millennium Pharmaceuticals† • Roche Diagnostics† • Schering-Plough†	None
Rick Nishimura	• Official-ACC Lead Task Force Reviewer	None	None	None	None	None
Eugene Sherman	• Official-ACC Board of Governors	None	• Abbott • GlaxoSmithKline • Novartis • Sanofi-Aventis • Takeba	• General Electric† • Johnson & Johnson† • Pfizer†	None	None
William Brady	• Organizational-American College of Emergency Physicians	• HeartScape • MedicoLegal Review	None	None	None	None
Deborah Diercks	• Organizational-American College of Emergency Physicians	• Astellas • Inovise Technology • Medicines Company • Sanofi-Aventis†	• Bristol-Myers Squibb • Sanofi-Aventis† • Schering-Plough	None	• The Medicines Company	None
Lakshmi Halasyamani	• Organizational-American College of Physicians‡	None	None	None	None	None
Robert Higgins	• Organizational-Society of Thoracic Surgeons‡	None	None	None	None	None
Morton Kern	• Organizational-Society for Cardiovascular Angiography and Interventions and ACC/ AHA/SCAI PCI Guidelines Writing Committee‡	• Merrit Medical • Therox Inc.	None	None	None	None
Marjorie King	• Organizational-American Association of Cardiovascular and Pulmonary Rehabilitation‡	None	None	None	None	None

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Michael Lim	• Organizational–Society for Cardiovascular Angiography and Interventions‡	None	• Bristol-Myers Squibb • Merck • Sanofi-Aventis	None	None	None
Walter Merrill	• Organizational–Society of Thoracic Surgeons‡	None	None	None	None	None
Charles Pollack	• Organizational–Society for Academic Emergency Medicine‡	• Bristol-Myers Squibb • Sanofi-Aventis • Schering-Plough • The Medicines Company	• Sanofi-Aventis • Schering-Plough	None	• GlaxoSmithKline†	• Spouse employed by The Medicines Company†
Mazen Abu-Fadel	• Content–ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None	None
Paul Armstrong	• Content–ACC/AHA STEMI Guidelines Writing Committee	• Abbott Laboratories • ArgiNOx • Boehringer Ingelheim • Hoffmann LaRoche Canada • Sanofi-Aventis • TarGen	None		• Boehringer Ingelheim† • Hoffmann LaRoche Canada† • Procter & Gamble/Alexion† • Sanofi-Aventis†	• Mediscure†
Eric Bates	• Content–ACC/AHA STEMI Guidelines Writing Committee	• AstraZeneca • Eli Lilly • GlaxoSmithKline • Sanofi-Aventis • Schering-Plough	None	None	• Eli Lilly	None
Alexander Battler	• Content–ACC/AHA Acute Coronary Syndromes Data Standards Writing Committee	None	None	None	None	None
Vera Bittner	• Content–ACCF Prevention of Cardiovascular Disease Committee	• CV Therapeutics • Pfizer • Reliant	None	None	• Atherogenics† • NHLBI† • Pfizer†	None



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Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Christopher Cannon	• Content-ACC/AHA Acute Coronary Syndromes Data Standards Writing Committee	• AstraZeneca† • BGB New York • Bristol-Myers Squibb† • DIME • GlaxoSmithKline† • Merck† • NCME • Pfizer† • Sanofi-Aventis† • Schering-Plough†	• Accumetrics† • AstraZeneca† • Bristol-Myers Squibb† • Merck† • Pfizer† • Sanofi-Aventis† • Schering-Plough†	None	• Accumetrics† • Amgen • AstraZeneca† • Bayer Healthcare • Beckman Coulter, Inc. • Biosite Inc. • Bristol-Myers Squibb Pharmaceutical Research Inst. • CV Therapeutics • Eli Lilly and Co. • GlaxoSmithKline • Inotek Pharmaceuticals • Integrated Therapeutics Corp. • Merck† • Millenium Pharmaceuticals Inc. • Novartis Pharmaceuticals • Nuvelo, Inc. • Ortho-Clinical Diagnostics • Pfizer • Roche Diagnostics • Sanofi-Aventis • Sanofi-Synthelabo Recherche • Schering-Plough† • The National Institutes of Health	None
Bernard Chaitman	• Content-ACC/AHA Acute Coronary Syndromes Data Standards Writing Committee	• Merck† • CV Therapeutics†	• Pfizer†	None	• CV Therapeutics†	None
Jose Diez	• Content-ACCF Cardiac Catheterization and Intervention Committee	• Sanofi-Aventis	None	None	None	None
Stephen Ellis	• Content-ACC/AHA Acute Coronary Syndromes Data Standards Writing Committee	• Abbott • Boston Scientific • Cordis • Viacor	None	None	• Centocor	None
James Ferguson	• Content-ACCF Cardiac Catheterization and Intervention Committee	• Bristol-Myers Squibb • Eisai† • GlaxoSmithKline • Prism • Sanofi-Aventis† • Schering-Plough • Takeda • The Medicus Co. • Therox	• Bristol-Myers Squibb • Sanofi-Aventis† • Schering-Plough	None	• Eisai • The Medicus Co. • Vitatron/Medtronic	None

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Gregg Fonarow	• Content-ACCF Prevention of Cardiovascular Disease Committee	• AstraZeneca • Bristol-Myers Squibb/Sanofi† • GlaxoSmithKline† • Guidant • Medtronic† • Merck/Schering- Plough† • Pfizer† • St. Jude	• AstraZeneca • Bristol-Myers Squibb/Sanofi† • GlaxoSmithKline† • Medtronic† • Merck/Schering- Plough† • Pfizer†	None	• Guidant • Medtronic† • Pfizer† • St. Jude	None
Robert Harrington	• Content-ACC/AHA Acute Coronary Syndromes Data Standards Writing Committee	None	None	None	• AstraZeneca† • Bristol-Myers Squibb† • Lilly† • JMC† • Merck† • Sanofi-Aventis† • Schering-Plough†	None
Edward Havranek	• Content-ACC/AHA Task Force on Data Standards	• CV Therapeutics • McKesson	None	None	None	None
Harlan Krumholz	• Content-ACC/AHA STEMI Guidelines Writing Committee, ACC/AHA Acute Coronary Syndromes Data Standards Writing Committee	• CV Therapeutics • United Healthcare†	None	None	None	None
Janet Long	• Content-ACCF Prevention of Cardiovascular Disease Committee	None	• AstraZeneca	None	None	None
C. Noel Bairey Merz	• Content-Individual Reviewer	• AstraZeneca • Bayer† • KOS • Merck • Pfizer	None	• Eli Lilly† • Johnson & Johnson† • Medtronic†	• Merck • Pfizer†	None
Debabrata Mukherjee	• Content-ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None	None
Charles Mullany	• Content-ACC/AHA STEMI Guidelines Writing Committee	None	None	None	• AstraZeneca • Atricure • Avant Immunotherapeutics • Baxter • Carbomedics/Sorin Group • CryoLife • Jarvik Heart • Medtronic • St. Jude Medical • Thoratec Corporation • TransTech Pharma • W.L. Gore and Associates	None

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Magnus Ohman	• Content-ESC Guidelines on Non-ST-Elevation Acute Coronary Syndromes Writing Committee	• Inovise† • Liposcience • Response Biomedical • Savacor† • The Medicines Company	None	• Inovise† • Medtronic† • Savacor†	• Berlex† • Bristol-Myers Squibb† • Eli Lilly† • Millenium Pharmaceuticals† • Sanofi-Aventis† • Schering-Plough†	None
Joseph Ornato	• Content-ACC/AHA STEMI Guidelines Writing Committee	• Boehringer Ingelheim • Bristol-Myers Squibb • Genetech • PDL BioPharma, Inc. • ZOLL	None	None	None	None
Rita Redberg	• Content-ACCF Prevention of Cardiovascular Disease Committee	None	None	None	None	None
Charanjit Rihal	• Content-ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None	None
David Williams	• Content-ACC/AHA/SCAI PCI Guidelines Writing Committee	• Abbott • Cordis†	None	None	• Cordis Guidant	None
Kim Williams	• Content-ACCF Cardiovascular Imaging Committee	• CV Therapeutics† • GE Healthcare† • King Pharmaceuticals†	• Astellas • GE Healthcare† • GE Healthcare†	None	• Bristol-Myers Squibb† • CV Therapeutics† • GE Healthcare† • Molecular Insight Pharmaceuticals†	

This table represents the relationships of peer reviewers with industry that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication. *Names are listed in alphabetical order with each category of review. †Indicates a significant relationship (valued at \$10,000 or more). ‡Participation in the peer review process does not imply endorsement of this document.

ACC = American College of Cardiology; ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ESC = European Society of Cardiology; NHLBI = National Heart, Lung, and Blood Institute; SCAI = Society for Cardiovascular Angiography and Interventions.

REFERENCES

- Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:e85–151.
- Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–39.
- Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–421.
- Dracup K, Alonzo AA, Atkins JM, et al. The physician's role in minimizing prehospital delay in patients at high risk for acute myocardial infarction: recommendations from the National Heart Attack Alert Program. Working Group on Educational Strategies to Prevent Prehospital Delay in Patients at High Risk for Acute Myocardial Infarction. *Ann Intern Med* 1997;126:645–51.
- Smith SC Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2006;47:e1–121.
- Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.
- National Heart, Lung and Blood Institute, National Institutes of Health. Act in time to heart attack signs. Available at http://www.nhlbi.nih.gov/health/public/heart/mi/core_pk.pdf. Accessed November 27, 2006.
- Antman EM, Anbe DT, Armstrong PW, 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). *J Am Coll Cardiol* 2004;44:e1–211.
- Braunwald E. Unstable angina: an etiologic approach to management [editorial]. *Circulation* 1998;98:2219–22.
- Braunwald E. Unstable angina: a classification. *Circulation* 1989;80:410–4.
- Campeau L. Letter: grading of angina pectoris. *Circulation* 1976;54:522–3.
- Smith SC Jr., Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol* 2006;47:2130–9.

13. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *J Am Coll Cardiol* 2007;49:1230–50.
14. Abidov A, Rozanski A, Hachamovitch R, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med* 2005;353:1889–98.
15. Goff DC Jr., Sellers DE, McGovern PG, et al. Knowledge of heart attack symptoms in a population survey in the United States: the REACT trial. Rapid Early Action for Coronary Treatment. *Arch Intern Med* 1998;158:2329–38.
16. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:161–72.
17. Goff DC Jr., Feldman HA, McGovern PG, et al. Prehospital delay in patients hospitalized with heart attack symptoms in the United States: the REACT trial. Rapid Early Action for Coronary Treatment (REACT) Study Group. *Am Heart J* 1999;138:1046–57.
18. Finnegan JR Jr., Meischke H, Zapka JG, et al. Patient delay in seeking care for heart attack symptoms: findings from focus groups conducted in five U.S. regions. *Prev Med* 2000;31:205–13.
19. Luepker RV, Raczynski JM, Osganian S, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: the Rapid Early Action for Coronary Treatment (REACT) Trial. *JAMA* 2000;284:60–7.
20. Feldman HA, Proschan MA, Murray DM, et al. Statistical design of REACT (Rapid Early Action for Coronary Treatment), a multisite community trial with continual data collection. *Control Clin Trials* 1998;19:391–403.
21. Rucker D, Brennan T, Burstin H. Delay in seeking emergency care. *Acad Emerg Med* 2001;8:163–9.
22. Canto JG, Shlipak MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000;283:3223–9.
23. National Heart Attack Alert Program. Emergency Department: rapid identification and treatment of patients with acute myocardial infarction. US Department of Health and Human Services. US Public Health Service. National Institutes of Health. National Heart, Lung and Blood Institute; September 1993; NIH Publication No. 93-3278.
24. McDermott MM, Mandapat AL, Moates A, et al. Knowledge and attitudes regarding cardiovascular disease risk and prevention in patients with coronary or peripheral arterial disease. *Arch Intern Med* 2003;163:2157–62.
25. Canto JG, Zalenski RJ, Ornato JP, et al. Use of emergency medical services in acute myocardial infarction and subsequent quality of care: observations from the National Registry of Myocardial Infarction 2. *Circulation* 2002;106:3018–23.
26. Hutchings CB, Mann NC, Daya M, et al. Patients with chest pain calling 9-1-1 or self-transporting to reach definitive care: which mode is quicker? *Am Heart J* 2004;147:35–41.
27. Braunwald E, Antman EM, Beasley JW, et al. 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 American 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;40:1366–74.
28. Braunwald E, Mark DB, Jones RH, et al. Unstable Angina: Diagnosis and Management. 3-1-1994;AHCPR Publication No. 94-0602:1-154.
29. Morise AP, Haddad WJ, Beckner D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. *Am J Med* 1997;102:350–6.
30. Ho KT, Miller TD, Hodge DO, Bailey KR, Gibbons RJ. Use of a simple clinical score to predict prognosis of patients with normal or mildly abnormal resting electrocardiographic findings undergoing evaluation for coronary artery disease. *Mayo Clin Proc* 2002;77:515–21.
31. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 2003;41:159–68.
32. Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? *Am Heart J* 2004;148:27–33.
33. McSweeney JC, Cody M, O'Sullivan P, Elberson K, Moser DK, Garvin BJ. Women's early warning symptoms of acute myocardial infarction. *Circulation* 2003;108:2619–23.
34. Lee TH, Cook EF, Weisberg M, Sargent RK, Wilson C, Goldman L. Acute chest pain in the emergency room: identification and examination of low-risk patients. *Arch Intern Med* 1985;145:65–9.
35. Henrikson CA, Howell EE, Bush DE, et al. Chest pain relief by nitroglycerin does not predict active coronary artery disease. *Ann Intern Med* 2003;139:979–86.
36. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA* 2005;294:2623–9.
37. Jayes RLJ, Beshansky JR, D'Agostino RB, Selker HP. Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? A multicenter study. *J Clin Epidemiol* 1992;45:621–6.
38. 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;13:13–8.
39. Boersma E, Pieper KS, Steyerberg EW, et al. 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;101:2557–67.
40. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345–53.
41. Cohen M, Demers C, Gurfinkel EP, et al. 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;337:447–52.
42. Antman EM, McCabe CH, Gurfinkel EP, et al. 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;100:1593–601.
43. Morrow DA, Antman EM, Snapinn SM, McCabe CH, Theroux P, Braunwald E. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes. Application of the TIMI Risk Score for UA/NSTEMI in PRISM-PLUS. *Eur Heart J* 2002;23:223–9.
44. Cannon CP, Weintraub WS, Demopoulos LA, et al. 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;344:1879–87.
45. Chang WC, Kaul P, Fu Y, et al. Forecasting mortality: dynamic assessment of risk in ST-segment elevation acute myocardial infarction. *Eur Heart J* 2006;27:419–26.
46. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–42.
47. Eagle KA, Lim MJ, Dabbous OH, et al. 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;291:2727–33.
48. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA* 1999;281:707–13.
49. de Zwaan C, Bar FW, Janssen JH, et al. Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am Heart J* 1989;117:657–65.
50. Slater DK, Hlatky MA, Mark DB, Harrell FEJ, Pryor DB, Calif RM. Outcome in suspected acute myocardial infarction with normal or minimally abnormal admission electrocardiographic findings. *Am J Cardiol* 1987;60:766–70.
51. Matetzky S, Freimark D, Feinberg MS, et al. Acute myocardial infarction with isolated ST-segment elevation in posterior chest leads

- V7-9: "hidden" ST-segment elevations revealing acute posterior infarction. *J Am Coll Cardiol* 1999;34:748-53.
52. Matetzky S, Freimark D, Chouraqui P, et al. Significance of ST segment elevations in posterior chest leads (V7 to V9) in patients with acute inferior myocardial infarction: application for thrombolytic therapy. *J Am Coll Cardiol* 1998;31:506-11.
53. Hedges JR, Young GP, Henkel GF, Gibler WB, Green TR, Swanson JR. Serial ECGs are less accurate than serial CK-MB results for emergency department diagnosis of myocardial infarction. *Ann Emerg Med* 1992;21:1445-50.
54. Fesmire FM. Delta CK-MB outperforms delta troponin I at 2 hours during the ED rule out of acute myocardial infarction. *Am J Emerg Med* 2000;18:1-8.
55. Fesmire FM, Hughes AD, Fody EP, et al. The Erlanger chest pain evaluation protocol: a one-year experience with serial 12-lead ECG monitoring, two-hour delta serum marker measurements, and selective nuclear stress testing to identify and exclude acute coronary syndromes. *Ann Emerg Med* 2002;40:584-94.
56. Holmes DR Jr., Berger PB, Hochman JS, et al. Cardiogenic shock in patients with acute ischemic syndromes with and without ST-segment elevation. *Circulation* 1999;100:2067-73.
57. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia: a multicenter, controlled clinical trial. *Ann Intern Med* 1998;129:845-55.
58. Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes RJ. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. *Clin Chem* 1999;45:1104-21.
59. 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. *J Am Coll Cardiol* 2000;36:959-69.
60. Christenson RH, Vaidya H, Landt Y, et al. Standardization of creatine kinase-MB (CK-MB) mass assays: the use of recombinant CK-MB as a reference material. *Clin Chem* 1999;45:1414-23.
61. Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem* 2004;50:327-32.
62. Eggers KM, Oldgren J, Nordenskjöld A, Lindahl B. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *Am Heart J* 2004;148:574-81.
63. Roger VL, Killian JM, Weston SA, et al. Redefinition of myocardial infarction: prospective evaluation in the community. *Circulation* 2006;114:790-7.
64. 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;337:1648-53.
65. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* 1996;335:1333-41.
66. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342-9.
67. Galvani M, Ottani F, Ferrini D, et al. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. *Circulation* 1997;95:2053-9.
68. Lindahl B, Andren B, Ohlsson J, Venge P, Wallentin L. Risk stratification in unstable coronary artery disease: additive value of troponin T determinations and pre-discharge exercise tests. FRISK Study Group. *Eur Heart J* 1997;18:762-70.
69. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol* 2006;48:1-11.
70. Shapiro BP, Jaffe AS. Cardiac biomarkers. In: Murphy JG, Lloyd MA, editors. *Mayo Clinic Cardiology: Concise Textbook*. 3rd ed. Rochester, MN: Mayo Clinic Scientific Press and New York: Informa Healthcare USA, 2007;773-80.
71. Lindahl B, Venge P, Wallentin L. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. Fragmin in Unstable Coronary Artery Disease (FRISC) Study Group. *J Am Coll Cardiol* 1997;29:43-8.
72. Hamm CW, Heeschen C, Goldmann B, et al. 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;340:1623-9.
73. 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. *Lancet* 1999;354:1757-62.
74. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006;295:1531-8.
75. Fragmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:708-15.
76. Kleiman NS, Lakkis N, Cannon CP, et al. Prospective analysis of creatine kinase muscle-brain fraction and comparison with troponin T to predict cardiac risk and benefit of an invasive strategy in patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol* 2002;40:1044-50.
77. Rao SV, Ohman EM, Granger CB, et al. Prognostic value of isolated troponin elevation across the spectrum of chest pain syndromes. *Am J Cardiol* 2003;91:936-40.
78. Freda BJ, Tang WH, Van LF, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol* 2002;40:2065-71.
79. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 2002;346:2047-52.
80. Galvani M, Ottani F, Oltrona L, et al. N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004;110:128-34.
81. Palazzuoli A, Deckers J, Calabro A, et al. Brain natriuretic peptide and other risk markers for outcome assessment in patients with non-ST-elevation coronary syndromes and preserved systolic function. *Am J Cardiol* 2006;98:1322-8.
82. Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. *J Am Coll Cardiol* 2003;41:1264-72.
83. Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation* 2002;105:1760-3.
84. Cannon CP, O'Gara PT. Critical pathways for acute coronary syndromes. In: Cannon CP, editor. *Management of Acute Coronary Syndromes*. Totowa, NJ: Humana Press, 1999:611-27.
85. Gibler WB, Runyon JP, Levy RC, et al. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med* 1995;25:1-8.
86. Farkouh ME, Smars PA, Reeder GS, et al. 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;339:1882-8.
87. Fuster V, Kim RJ. Frontiers in cardiovascular magnetic resonance. *Circulation* 2005;112:135-44.
88. Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006;48:1475-97.

89. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006;114:1761–91.
90. Armstrong PW. Stable ischemic syndromes. In: Topol EJ, editor. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott-Raven, 1998:349–50.
91. Esposito GA, Dunham G, Granger BB, Tudor GE, Granger CB. Converting i.v. nitroglycerin therapy to nitroglycerin ointment therapy: a comparison of two methods. *Am J Crit Care* 1998;7:123–30.
92. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J* 2005;149:1043–9.
93. Roberts R, Rogers WJ, Mueller HS, 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;83:422–37.
94. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1622–32.
95. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385–90.
96. Ellis K, Tcheng JE, Sapp S, Topol EJ, Lincoff AM. Mortality benefit of beta blockade in patients with acute coronary syndromes undergoing coronary intervention: pooled results from the Epic, Epilog, Epistent, Capture and Rapport Trials. *J Interv Cardiol* 2003;16:299–305.
97. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for non-cardiac surgery: focused update on perioperative beta-blocker therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2006;47:2343–55.
98. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326–31.
99. Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol* 1987;60:18A–25A.
100. Gibson RS, Boden WE, Theroux P, et al. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. Results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986;315:423–9.
101. Hansen JF, Hagerup L, Sigurd B, et al. Cardiac event rates after acute myocardial infarction in patients treated with verapamil and trandolapril versus trandolapril alone. Danish Verapamil Infarction Trial (DAVIT) Study Group. *Am J Cardiol* 1997;79:738–41.
102. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation* 1998;97:2202–12.
103. Gustafsson I, Torp-Pedersen C, Kober L, Gustafsson F, Hildebrandt P. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. Trace Study Group. *J Am Coll Cardiol* 1999;34:83–9.
104. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–53.
105. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893–906.
106. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759–66.
107. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–21.
108. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709–17.
109. Stone GW, Ohman EM, Miller MF, et al. Contemporary utilization and outcomes of intra-aortic balloon counterpulsation in acute myocardial infarction: the benchmark registry. *J Am Coll Cardiol* 2003;41:1940–5.
110. 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* 2006;332:1302–8.
111. 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;296:1633–44.
112. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation* 2006;113:2906–13.
113. Gibson CM, Braunwald B. Association of treatment with non-steroidal anti-inflammatory agents (NSAIDs) on study entry with 30 day adverse outcomes among ST Elevation MI (STEMI) patients treated with fibrinolytic agent. An EXTRACT-TIMI 25 analysis (abstr). *Circulation* 2006;114 Suppl II:697.
114. Lewis HDJ, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1983;309:396–403.
115. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina: results of a Canadian multicenter trial. *N Engl J Med* 1985;313:1369–75.
116. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105–11.
117. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827–30.
118. 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.
119. Sagar KA, Smyth MR. A comparative bioavailability study of different aspirin formulations using on-line multidimensional chromatography. *J Pharm Biomed Anal* 1999;21:383–92.
120. Song KH, Fedyk R, Hoover R. Interaction of ACE inhibitors and aspirin in patients with congestive heart failure. *Ann Pharmacother* 1999;33:375–7.
121. Balsano F, Rizzon P, Violi F, et al. Antiplatelet treatment with ticlopidine in unstable angina: a controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990;82:17–26.
122. Love BB, Biller J, Gent M. Adverse haematological effects of ticlopidine. Prevention, recognition and management. *Drug Saf* 1998;19:89–98.
123. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329–39.
124. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352:238–44.
125. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di SG. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2005;111:2099–106.
126. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527–33.

127. Fox KA, Mehta SR, Peters R, et al. 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;110:1202-8.
128. Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003;107:966-72.
129. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol* 2006;47:2108-11.
130. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584-91.
131. Bavy AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006;119:1056-61.
132. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
133. Physicians Desk Reference. 56 edition. Montvale, NJ: Medical Economics Company, Inc., 2002:3085.
134. Chu MW, Wilson SR, Novick RJ, Stitt LW, Quantz MA. Does clopidogrel increase blood loss following coronary artery bypass surgery? *Ann Thorac Surg* 2004;78:1536-41.
135. Mehta RH, Califf RM, Garg J, et al. The impact of anthropomorphic indices on clinical outcomes in patients with acute ST-elevation myocardial infarction. *Eur Heart J* 2007;28:415-24.
136. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol* 2005;45:246-51.
137. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109:3171-5.
138. Wiviott SD, Antman EM. Clopidogrel resistance: a new chapter in a fast-moving story. *Circulation* 2004;109:3064-7.
139. Cannon CP. Evolving management of ST-segment elevation myocardial infarction: update on recent data. *Am J Cardiol* 2006;98:S10-21.
140. Gurbel PA, Bliden KP, Hayes KM, Yoho JA, Herzog WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. *J Am Coll Cardiol* 2005;45:1392-6.
141. Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. *Ann Intern Med* 2006;145:62-9.
142. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:188S-203S.
143. Cohen M, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users: primary end points analysis from the ATACS trial. *Antithrombotic Therapy in Acute Coronary Syndromes Research Group. Circulation* 1994;89:81-8.
144. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996;276:811-5.
145. Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med* 1992;327:141-5.
146. Hassan WM, Flaker GC, Feutz C, Petroski GF, Smith D. Improved anticoagulation with a weight-adjusted heparin nomogram in patients with acute coronary syndromes: a randomized trial. *J Thromb Thrombolysis* 1995;2:245-9.
147. Becker RC, Ball SP, Eisenberg P, et al. A randomized, multicenter trial of weight-adjusted intravenous heparin dose titration and point-of-care coagulation monitoring in hospitalized patients with active thromboembolic disease: Antithrombotic Therapy Consortium Investigators. *Am Heart J* 1999;137:59-71.
148. Weitz JI. Low-molecular-weight heparins [published erratum appears in *N Engl J Med* 1997 Nov 20;337:1567]. *N Engl J Med* 1997;337:688-98.
149. Michalis LK, Katsouras CS, Papamichael N, et al. Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: the EVET trial. *Am Heart J* 2003;146:304-10.
150. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. *Lancet* 1996;347:561-8.
151. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC) [published erratum appears in *Circulation* 1998 Feb 3;97:413]. *Circulation* 1997;96:61-8.
152. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q-wave myocardial infarction: FRAX.I.S. (FRAXiparine in Ischaemic Syndrome). *Eur Heart J* 1999;20:1553-62.
153. Cohen M, Theroux P, Borzak S, et al. 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 Antithrombotic Combination Using Tirofiban and Enoxaparin. *Am Heart J* 2002;144:470-7.
154. 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 eptifibatide. *Circulation* 2003;107:238-44.
155. Blazing MA, de Lemos JA, White HD, et al. 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.
156. Ferguson JJ, Califf RM, Antman EM, et al. 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.
157. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701-7.
158. Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 1998;97:251-6.
159. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-5.
160. Antman EM. Hirudin in acute myocardial infarction: Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* 1996;94:911-21.
161. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999;353:429-38.
162. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203-16.
163. Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;354:1464-76.
164. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;295:1519-30.
165. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999;282:2058-67.
166. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;360:109-13.
167. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347:969-74.

168. Lefkowitz J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995;332:1553–9.
169. Collier BS. Monitoring platelet GP IIb/IIIa [corrected] antagonist therapy [editorial] [corrected and republished in *Circulation* 1998 Jan 6–13;97(1):5–9]. *Circulation* 1997;96:3828–32.
170. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb–IIIa blockers. *Lancet* 1999;353:227–31.
171. Theroux P. Tirofiban. *Drugs Today (Barc)* 1999;35:59–73.
172. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study [published erratum appears in *Lancet* 1997 Sep 6;350(9079):744]. *Lancet* 1997;349:1429–35.
173. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV–ACS randomised trial. *Lancet* 2001;357:1915–24.
174. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 1994;330:956–61.
175. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689–96.
176. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997;349:1422–8.
177. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997;96:1445–53.
178. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;352:87–92.
179. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;356:2037–44.
180. Gratsianskii NA. [Do low risk patients undergoing percutaneous coronary intervention after pretreatment with clopidogrel need abciximab infusion? Results of ISAR-REACT study]. *Kardiologiya* 2004;44:80–1.
181. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction [published erratum appears in *N Engl J Med* 1998 Aug 6;339(6):415]. *N Engl J Med* 1998;338:1488–97.
182. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;338:1498–505.
183. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;339:436–43.
184. The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation* 1998;97:2386–95.
185. Mukherjee D, Mahaffey KW, Moliterno DJ, et al. Promise of combined low-molecular-weight heparin and platelet glycoprotein IIb/IIIa inhibition: results from Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network B (PARAGON B). *Am Heart J* 2002;144:995–1002.
186. Zhao XQ, Theroux P, Snapinn SM, Sax FL. Intracoronary thrombus and platelet glycoprotein IIb/IIIa receptor blockade with tirofiban in unstable angina or non-Q-wave myocardial infarction: angiographic results from the PRISM-PLUS trial. *Circulation* 1999;100:1609–15.
187. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189–98.
188. Deleted in proof.
189. Deleted in proof.
190. Deleted in proof.
191. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. 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. *Lancet* 1994;343:311–22.
192. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;353:1095–104.
- 192a. Hirsch A, Windhausen F, Tijssen JGP, Verheugt FWA, Hein Cornel J, de Winter RJ, for the Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) Investigators. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. *Lancet* 2007;367:827–35.
193. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:1593–9.
194. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908–17.
195. Giugliano RP, Braunwald E. The year in non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2005;46:906–19.
196. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914–20.
197. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006;368:998–1004.
198. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;48:1319–25.
199. Chaitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation* 2003;108:1146–62.
200. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 2003;108:1404–18.
201. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002;106:1883–92.
202. Klem I, Heitner JF, Shah DJ, et al. Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. *J Am Coll Cardiol* 2006;47:1630–8.
203. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol* 1999;33:2092–197.
204. Manning WJ. Stress echocardiography in the diagnosis and prognosis of coronary heart disease. UpToDate Patient Information 2006 Sept; 15. Available at: <http://patients.uptodate.com/topic.asp?file=chd/55189>. Accessed January 11, 2007.

205. Larsson H, Areskog M, Areskog NH, et al. Should the exercise test (ET) be performed at discharge or one month later after an episode of unstable angina or non-Q-wave myocardial infarction? *Int J Card Imaging* 1991;7:7-14.
- 205a. Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. *JAMA* 2007;297:1985-91.
206. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 2004;110:e340-437.
207. Malosky SA, Hirshfeld JWJ, Herrmann HC. Comparison of results of intracoronary stenting in patients with unstable vs. stable angina. *Cathet Cardiovasc Diagn* 1994;31:95-101.
208. Marzocchi A, Piovaccari G, Marzocchi C, et al. Results of coronary stenting for unstable versus stable angina pectoris. *Am J Cardiol* 1997;79:1314-8.
209. Schühlen H, Kastrati A, Dirschinger J, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. *Circulation* 1998;98:104-11.
210. Kandzari DE, Roe MT, Ohman EM, et al. Frequency, predictors, and outcomes of drug-eluting stent utilization in patients with high-risk non-ST-segment elevation acute coronary syndromes. *Am J Cardiol* 2005;96:750-5.
211. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;344:1888-94.
212. Kabbani SS, Aggarwal A, Terrien EF, DiBattiste PM, Sobel BE, Schneider DJ. Suboptimal early inhibition of platelets by treatment with tirofiban and implications for coronary interventions. *Am J Cardiol* 2002;89:647-50.
213. Kastrati A, Mehilli J, Schühlen H, et al. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004;350:232-8.
214. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease: a multicenter randomized trial. *JAMA* 1997;277:715-21.
215. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease [published erratum appears in *N Engl J Med* 1997 Jan 9;336(2):147]. *N Engl J Med* 1996;335:217-25.
216. CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). *Lancet* 1995;346:1179-84.
217. Weintraub WS, Stein B, Kosinski A, et al. Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. *J Am Coll Cardiol* 1998;31:10-9.
218. Detre KM, Guo P, Holubkov R, et al. Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1999;99:633-40.
219. Hannan EL, Racz MJ, McCallister BD, et al. A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1999;33:63-72.
220. Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 2005;352:2174-83.
221. Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol* 2001;38:143-9.
222. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344:1117-24.
223. Ferguson, TB Jr., Hammill BG, Peterson, ED, DeLong, ER, Grover, FL. A decade of change—risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990–1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Society of Thoracic Surgeons. *Ann Thorac Surg* 2002;73:480-9.
224. Bhatt DL, Topol EJ. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *JAMA* 2000;284:1549-58.
225. Theroux P, Alexander J Jr., Pharand C, et al. Glycoprotein IIb/IIIa receptor blockade improves outcomes in diabetic patients presenting with unstable angina/non-ST-elevation myocardial infarction: results from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. *Circulation* 2000;102:2466-72.
226. Flaker GC, Warnica JW, Sacks FM, et al. Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. Cholesterol and Recurrent Events CARE Investigators. *J Am Coll Cardiol* 1999;34:106-12.
227. Deleted in proof.
228. Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82-96.
229. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
230. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
231. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.
232. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
233. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307-16.
234. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
235. Briel M, Schwartz GG, Thompson PL, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. *JAMA* 2006;295:2046-56.
236. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;368:581-8.
237. Pitt B. ACE inhibitors for patients with vascular disease without left ventricular dysfunction—may they rest in PEACE? *N Engl J Med* 2004;351:2115-7.
238. Daly LE, Mulcahy R, Graham IM, Hickey N. Long term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *Br Med J (Clin Res Ed)* 1983;287:324-6.
239. U.S. Department of Health and Human Services, Public Health Service Agency. Clinical Practice Guidelines: Number 18: Smoking Cessation. 1996; AHCPR Publication No. 96-0692.
240. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006;296:64-71.
241. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:56-63.
242. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release

- bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47–55.
243. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclooxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005;365:475–81.
 244. Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation* 2005;112:759–70.
 245. Antman E, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs (NSAIDs): an update for clinicians: a scientific statement from the American Heart Association. *Circulation* 2007;115:1634–42.
 246. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567–77.
 247. Bona KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578–88.
 248. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation* 2003;107:3109–16.
 249. Thompson PD. Exercise prescription and proscription for patients with coronary artery disease. *Circulation* 2005;112:2354–63.
 250. Gondoni LA, Liuzzi A, Tilton AM, et al. A simple tool to predict exercise capacity of obese patients with ischaemic heart disease. *Heart* 2006;92:899–904.
 251. Pollock ML, Franklin BA, Balady GJ, et al. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation* 2000;101:828–33.
 252. Balady GJ, Ades PA, Comoss P, et al. Core components of cardiac rehabilitation/secondary prevention programs: a statement for health-care professionals from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation Writing Group. *Circulation* 2000;102:1069–73.
 253. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2001;CD001800.
 254. Witt BJ, Jacobsen SJ, Weston SA, et al. Cardiac rehabilitation after myocardial infarction in the community. *J Am Coll Cardiol* 2004;44:988–96.
 255. King ML, Williams MA, Fletcher GF, et al. Medical director responsibilities for outpatient cardiac rehabilitation/secondary prevention programs: a scientific statement from the American Heart Association/American Association for Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2005;112:3354–60.
 256. DeBusk RF, Miller NH, Superko HR, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med* 1994;120:721–9.
 257. Mittag O, Kolenda KD, Nordman KJ, Bernien J, Maurischat C. Return to work after myocardial infarction/coronary artery bypass grafting: patients' and physicians' initial viewpoints and outcome 12 months later. *Soc Sci Med* 2001;52:1441–50.
 258. Froom P, Cohen C, Rashcupkin J, et al. Referral to occupational medicine clinics and resumption of employment after myocardial infarction. *J Occup Environ Med* 1999;41:943–7.
 259. Boudrez H, De BG. Recent findings on return to work after an acute myocardial infarction or coronary artery bypass grafting. *Acta Cardiol* 2000;55:341–9.
 260. Petrie KJ, Cameron LD, Ellis CJ, Buick D, Weinman J. Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosom Med* 2002;64:580–6.
 261. Grines CL, Marsalese DL, Brodie B, et al. Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. PAMI-II Investigators. Primary Angioplasty in Myocardial Infarction. *J Am Coll Cardiol* 1998;31:967–72.
 262. Hochman JS, McCabe CH, Stone PH, et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. TIMI Investigators. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol* 1997;30:141–8.
 263. Stone PH, Thompson B, Anderson HV, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: the TIMI III registry. *JAMA* 1996;275:1104–12.
 264. Keelan ET, Nunez BD, Grill DE, Berger PB, Holmes DRJ, Bell MR. Comparison of immediate and long-term outcome of coronary angioplasty performed for unstable angina and rest pain in men and women. *Mayo Clin Proc* 1997;72:5–12.
 265. Robertson T, Kennard ED, Mehta S, et al. Influence of gender on in-hospital clinical and angiographic outcomes and on one-year follow-up in the New Approaches to Coronary Intervention (NACI) registry. *Am J Cardiol* 1997;80:26K–39K.
 266. DeVon HA, Zerwic JJ. Symptoms of acute coronary syndromes: are there gender differences? A review of the literature. *Heart Lung* 2002;31:235–45.
 267. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;45:832–7.
 268. Wiviott SD, Cannon CP, Morrow DA, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. *Circulation* 2004;109:580–6.
 269. Clayton TC, Pocock SJ, Henderson RA, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA 3 trial. *Eur Heart J* 2004;25:1641–50.
 270. Melin JA, Wijns W, Vanbutssele RJ, et al. Alternative diagnostic strategies for coronary artery disease in women: demonstration of the usefulness and efficiency of probability analysis. *Circulation* 1985;71:535–42.
 271. Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and coST-efficient technique for detection of coronary artery disease in women. *J Am Coll Cardiol* 1995;26:335–41.
 272. Morise AP, Diamond GA. Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased populations of men and women. *Am Heart J* 1995;130:741–7.
 273. Williams MJ, Marwick TH, O'Gorman D, Foale RA. Comparison of exercise echocardiography with an exercise score to diagnose coronary artery disease in women. *Am J Cardiol* 1994;74:435–8.
 274. Robert AR, Melin JA, Detry JM. Logistic discriminant analysis improves diagnostic accuracy of exercise testing for coronary artery disease in women. *Circulation* 1991;83:1202–9.
 275. Shaw LJ, Hendel R, Borges-Neto S, et al. Prognostic value of normal exercise and adenosine (99m)Tc-tetrofosmin SPECT imaging: results from the multicenter registry of 4,728 patients. *J Nucl Med* 2003;44:134–9.
 276. Alexander KP, Shaw LJ, DeLong ER, Mark DB, Peterson ED. Value of exercise treadmill testing in women. *J Am Coll Cardiol* 1998;32:1657–64.
 277. Lewis JF, Lin L, McGorray S, et al. Dobutamine stress echocardiography in women with chest pain: pilot phase data from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). *J Am Coll Cardiol* 1999;33:1462–8.
 278. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;108:1682–7.
 279. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 2005;294:3108–16.

280. Weintraub WS, Wenger NK, Kosinski AS, et al. Percutaneous transluminal coronary angioplasty in women compared with men. *J Am Coll Cardiol* 1994;24:81-90.
281. Welty FK, Mittelman MA, Healy RW, Muller JE, Shubrooks SJJ. Similar results of percutaneous transluminal coronary angioplasty for women and men with postmyocardial infarction ischemia. *J Am Coll Cardiol* 1994;23:35-9.
282. Mikhail GW. Coronary revascularisation in women. *Heart* 2006;92 Suppl 3:iii19-23.
- 282a. Humphries KH, Gao M, Pu A, Lichtenstein S, Thompson CR. Significant improvement in short-term mortality in women undergoing coronary artery bypass surgery (1991 to 2004). *J Am Coll Cardiol* 2007;49:1552-8.
283. Bavry AA, Kumbhani DJ, Quiroz R, Ramchandani SR, Kenchaiah S, Antman EM. Invasive therapy along with glycoprotein IIb/IIIa inhibitors and intracoronary stents improves survival in non-ST-segment elevation acute coronary syndromes: a meta-analysis and review of the literature. *Am J Cardiol* 2004;93:830-5.
284. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA* 2002;288:3124-9.
285. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 2002;360:743-51.
286. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1997;96:1761-9.
287. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1996;94:1818-25.
288. Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 1995;91:979-89.
289. Silva JA, Escobar A, Collins TJ, Ramee SR, White CJ. Unstable angina: a comparison of angiographic findings between diabetic and nondiabetic patients. *Circulation* 1995;92:1731-6.
290. Theroux P, Waters D. Unstable angina: special considerations in the post-bypass patient. In: Waters D, Bourassa MG, Brest AN, editors. *Care of the Patient with Previous Coronary Bypass Surgery*. Philadelphia, PA: FA Davis, 1991:169-91.
291. Zola B, Kahn JK, Juni JE, Vinik AI. Abnormal cardiac function in diabetic patients with autonomic neuropathy in the absence of ischemic heart disease. *J Clin Endocrinol Metab* 1986;63:208-14.
292. Fava S, Azzopardi J, Agius-Muscat H. Outcome of unstable angina in patients with diabetes mellitus. *Diabet Med* 1997;14:209-13.
293. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;355:773-8.
294. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650-61.
295. Van den BG, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345:1359-67.
296. Van den BG, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449-61.
297. Malhotra A. Intensive insulin in intensive care. *N Engl J Med* 2006;354:516-8.
298. Barsness GW, Peterson ED, Ohman EM, et al. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. *Circulation* 1997;96:2551-6.
299. King SB III, Kosinski A, Guyton RA, Lembo NJ, Weintraub WS. Eight year mortality in the Emory Angioplasty vs Surgery Trial (EAST). *J Am Coll Cardiol* 2000;35:1116-21.
300. Malenka DJ, Leavitt BJ, Hearne MJ, et al. Comparing long-term survival of patients with multivessel coronary disease after CABG or PCI: analysis of BARI-like patients in northern New England. *Circulation* 2005;112:1371-6.
301. Kleiman NS, Lincoff AM, Kereiakes DJ, et al. Diabetes mellitus, glycoprotein IIb/IIIa blockade, and heparin: evidence for a complex interaction in a multicenter trial. EPILOG Investigators. *Circulation* 1998;97:1912-20.
302. Deleted in proof.
303. Lincoff AM, Califf RM, Anderson KM, et al. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. EPIC Investigators. Evaluation of 7E3 in Preventing Ischemic Complications. *J Am Coll Cardiol* 1997;30:149-56.
304. Topol EJ, Mark DB, Lincoff AM, et al. Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1999;354:2019-24.
305. Lambert M, Kouz S, Campeau L. Preoperative and operative predictive variables of late clinical events following saphenous vein coronary artery bypass graft surgery. *Can J Cardiol* 1989;5:87-92.
306. Hwang MH, Meadows WR, Palac RT, et al. Progression of native coronary artery disease at 10 years: insights from a randomized study of medical versus surgical therapy for angina. *J Am Coll Cardiol* 1990;16:1066-70.
307. Chen L, Theroux P, Lesperance J, Shabani F, Thibault B, de Guise P. Angiographic features of vein grafts versus ungrafted coronary arteries in patients with unstable angina and previous bypass surgery. *J Am Coll Cardiol* 1996;28:1493-9.
308. Savage MP, Douglas JSJ, Fischman DL, et al. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. *N Engl J Med* 1997;337:740-7.
309. Carlino M, De Gregorio J, di Mario C, et al. Prevention of distal embolization during saphenous vein graft lesion angioplasty. Experience with a new temporary occlusion and aspiration system. *Circulation* 1999;99:3221-3.
310. Kleiman NS, Anderson HV, Rogers WJ, Theroux P, Thompson B, Stone PH. Comparison of outcome of patients with unstable angina and non-Q-wave acute myocardial infarction with and without prior coronary artery bypass grafting (Thrombolysis in Myocardial Ischemia III Registry). *Am J Cardiol* 1996;77:227-31.
311. Alexander KP, Roe MT, Chen AY, et al. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;46:1479-87.
312. Nadelmann J, Frishman WH, Ooi WL, et al. Prevalence, incidence and prognosis of recognized and unrecognized myocardial infarction in persons aged 75 years or older: The Bronx Aging Study. *Am J Cardiol* 1990;66:533-7.
313. Lakatta EG, Gerstenblith G, Weisfeldt ML. The aging heart: structure, function, and disease. In: Braunwald E, editor. *Heart Disease*. Philadelphia, PA: W.B. Saunders Company, 1997:1687-703.
314. Avezum A, Makdisse M, Spencer F, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2005;149:67-73.
315. Nasser TK, Fry ET, Annan K, et al. Comparison of six-month outcome of coronary artery stenting in patients <65, 65-75, and >75 years of age. *Am J Cardiol* 1997;80:998-1001.
316. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med* 2004;141:186-95.
317. Peterson ED, Jollis JG, Bechuk JD, et al. Changes in mortality after myocardial revascularization in the elderly: the national Medicare experience. *Ann Intern Med* 1994;121:919-27.
318. Bridges CR, Edwards FH, Peterson ED, Coombs LP, Ferguson TB. Cardiac surgery in nonagenarians and centenarians. *J Am Coll Surg* 2003;197:347-56.
319. Brosius FC III, Hostetter TH, Kelepouris E, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart

- Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. *Circulation* 2006;114:1083-7.
320. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;351:1285-95.
 321. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
 322. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA* 2006;296:1377-84.
 323. Jo SH, Youn TJ, Koo BK, et al. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. *J Am Coll Cardiol* 2006;48:924-30.
 324. McCullough PA, Bertrand ME, Brinker JA, Stacul F. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol* 2006;48:692-9.
 325. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989;4:174-85.
 326. Isner JM, Chokshi SK. Cardiovascular complications of cocaine. *Curr Probl Cardiol* 1991;16:89-123.
 327. Flores ED, Lange RA, Cigarroa RG, Hillis LD. Effect of cocaine on coronary artery dimensions in atherosclerotic coronary artery disease: enhanced vasoconstriction at sites of significant stenoses. *J Am Coll Cardiol* 1990;16:74-9.
 328. Lange RA, Cigarroa RG, Yancy CWJ, et al. Cocaine-induced coronary-artery vasoconstriction. *N Engl J Med* 1989;321:1557-62.
 329. Vitullo JC, Karam R, Mekhail N, Wicker P, Engelmann GL, Khairallah PA. Cocaine-induced small vessel spasm in isolated rat hearts. *Am J Pathol* 1989;135:85-91.
 330. Stenberg RG, Winniford MD, Hillis LD, Dowling GP, Buja LM. Simultaneous acute thrombosis of two major coronary arteries following intravenous cocaine use. *Arch Pathol Lab Med* 1989;113:521-4.
 331. Pitts WR, Lange RA, Cigarroa JE, Hillis LD. Cocaine-induced myocardial ischemia and infarction: pathophysiology, recognition, and management. *Prog Cardiovasc Dis* 1997;40:65-76.
 332. Brogan WC, Lange RA, Kim AS, Moliterno DJ, Hillis LD. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. *J Am Coll Cardiol* 1991;18:581-6.
 333. Tokarski GF, Paganussi P, Urbanski R, Carden D, Foreback C, Tomlanovich MC. An evaluation of cocaine-induced chest pain. *Ann Emerg Med* 1990;19:1088-92.
 334. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med* 1990;112:897-903.
 335. Boehrer JD, Moliterno DJ, Willard JE, Hillis LD, Lange RA. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. *Am J Med* 1993;94:608-10.
 336. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995;333:1267-72.
 337. Turnipseed SD, Richards JR, Kirk JD, Diercks DB, Amsterdam EA. Frequency of acute coronary syndrome in patients presenting to the emergency department with chest pain after methamphetamine use. *J Emerg Med* 2003;24:369-73.
 338. Wijetunga M, Bhan R, Lindsay J, Karch S. Acute coronary syndrome and crystal methamphetamine use: a case series. *Hawaii Med J* 2004;63:8-13, 25.
 339. Watts DJ, McColester L. Methamphetamine-induced myocardial infarction with elevated troponin I. *Am J Emerg Med* 2006;24:132-4.
 340. Nobuyoshi M, Abe M, Nosaka H, et al. Statistical analysis of clinical risk factors for coronary artery spasm: identification of the most important determinant. *Am Heart J* 1992;124:32-8.
 341. Sugiishi M, Takatsu F. Cigarette smoking is a major risk factor for coronary spasm. *Circulation* 1993;87:76-9.
 342. Fukai T, Koyanagi S, Takeshita A. Role of coronary vasospasm in the pathogenesis of myocardial infarction: study in patients with no significant coronary stenosis. *Am Heart J* 1993;126:1305-11.
 343. MacAlpin RN. Cardiac arrest and sudden unexpected death in variant angina: complications of coronary spasm that can occur in the absence of severe organic coronary stenosis. *Am Heart J* 1993;125:1011-7.
 344. Ozaki Y, Keane D, Serruys PW. Fluctuation of spastic location in patients with vasospastic angina: a quantitative angiographic study. *J Am Coll Cardiol* 1995;26:1606-14.
 345. Yamagishi M, Miyatake K, Tamai J, Nakatani S, Koyama J, Nissen SE. Intravascular ultrasound detection of atherosclerosis at the site of focal vasospasm in angiographically normal or minimally narrowed coronary segments. *J Am Coll Cardiol* 1994;23:352-7.
 346. Maseri A, Severi S, Nes MD, et al. "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. *Am J Cardiol* 1978;42:1019-35.
 347. Opie LH. Calcium channel antagonists in the management of anginal syndromes: changing concepts in relation to the role of coronary vasospasm. *Prog Cardiovasc Dis* 1996;38:291-314.
 348. Chahine RA, Feldman RL, Giles TD, et al. Randomized placebo-controlled trial of amlodipine in vasospastic angina. Amlodipine Study 160 Group. *J Am Coll Cardiol* 1993;21:1365-70.
 349. Lombardi M, Morales MA, Michelassi C, Moscarelli E, Distante A, L'Abbate A. Efficacy of isosorbide-5-mononitrate versus nifedipine in preventing spontaneous and ergonovine-induced myocardial ischemia: a double-blind, placebo-controlled study. *Eur Heart J* 1993;14:845-51.
 350. Yasue H, Touyama M, Kato H, Tanaka S, Akiyama F. Prinzmetal's variant form of angina as a manifestation of alpha-adrenergic receptor-mediated coronary artery spasm: documentation by coronary arteriography. *Am Heart J* 1976;91:148-55.
 351. Yasue H, Takizawa A, Nagao M, et al. Long-term prognosis for patients with variant angina and influential factors. *Circulation* 1988;78:1-9.
 352. Rovai D, Bianchi M, Baratto M, et al. Organic coronary stenosis in Prinzmetal's variant angina. *J Cardiol* 1997;30:299-305.
 353. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346:1948-53.
 354. Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). *Circulation* 2004;109:568-72.
 355. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *BMJ* 1994;308:883-6.
 356. Rosen SD, Uren NG, Kaski JC, Tousoulis D, Davies GJ, Camici PG. Coronary vasodilator reserve, pain perception, and sex in patients with syndrome X. *Circulation* 1994;90:50-60.
 357. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA* 2005;293:477-84.
 358. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function: long-term follow-up study. *J Am Coll Cardiol* 1995;25:807-14.
 359. Cannon RO, Camici PG, Epstein SE. Pathophysiological dilemma of syndrome X. *Circulation* 1992;85:883-92.
 360. Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998;351:1165-9.
 361. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006;47:S21-9.
 362. Handberg E, Johnson BD, Arant CB, et al. Impaired coronary vascular reactivity and functional capacity in women: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE) Study. *J Am Coll Cardiol* 2006;47:S44-9.

363. Cannon RO, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. *Am J Cardiol* 1985;56:242-6.
364. Bugiardini R, Borghi A, Biagetti L, Puddu P. Comparison of verapamil versus propranolol therapy in syndrome X. *Am J Cardiol* 1989;63:286-90.
365. Cannon RO, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994;330:1411-7.
366. Rosano GM, Peters NS, Lefroy D, et al. 17-beta-Estradiol therapy lessens angina in postmenopausal women with syndrome X. *J Am Coll Cardiol* 1996;28:1500-5.
367. Kayikcioglu M, Payzin S, Yavuzgil O, Kultursay H, Can LH, Soydan I. Benefits of statin treatment in cardiac syndrome-X1. *Eur Heart J* 2003;24:1999-2005.
368. Eriksson BE, Tyni-Lenne R, Svedenhag J, et al. Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X. *J Am Coll Cardiol* 2000;36:1619-25.
369. Mayou RA, Bryant BM, Sanders D, Bass C, Klimes I, Forfar C. A controlled trial of cognitive behavioural therapy for non-cardiac chest pain. *Psychol Med* 1997;27:1021-31.
370. Eliasson T, Albertsson P, Hardhammar P, Emanuelsson H, Augustinsson LE, Mannheimer C. Spinal cord stimulation in angina pectoris with normal coronary arteriograms. *Coron Artery Dis* 1993;4:819-27.



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