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ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

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)

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PREAMBLE

It is important that members of the medical profession play a significant role in the critical evaluation of the use of diagnostic procedures and therapies in the management and prevention of disease states. Rigorous and expert analysis of the available data that document the 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 through a focus of resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. This effort is directed by the ACC/AHA Task Force on Practice Guidelines, whose charge is to develop and revise practice guidelines for important cardiovascular diseases and procedures. Experts in the subject under consideration are selected from both organizations to examine subject-specific data and to write guidelines. The process includes additional representatives from other medical practitioner and specialty groups where appropriate. Writing groups are specifically charged to perform a formal literature review, to weigh the strength of evidence for or against a particular treatment or procedure, and to 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 cost-effectiveness.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or a personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that

might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated as changes occur.

These practice guidelines are intended to assist physicians in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines represent an attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding the care of a particular patient must be made by the physician and patient in light of all of the available information and the circumstances presented by that patient.

These guidelines were published in the Journal of the American College of Cardiology and Circulation in September 2000. The committee has continuously monitored the literature since the 2000 report to ensure relevancy of its recommendations. The guidelines have been updated in 2002 via the ACC and AHA web sites to include the most significant advances that have occurred in the management of patients with UA/NSTEMI since the 2000 report. A summary article highlighting the changes to the guidelines will be published in a subsequent issue of the Journal of the American College of Cardiology and Circulation. The 2000 guidelines were officially endorsed by the American College of Emergency Physicians (ACEP)* and the Society for Cardiac Angiography and Interventions.

Raymond J. Gibbons, MD, FACC
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 non–ST-segment elevation myocardial infarction (NSTEMI) are very common manifestations of this disease. In recognition of the importance of the management of this common entity and of the rapid advances in the management of this condition, the need to revise guidelines published by the Agency for Health Care Policy and Research (AHCPR) and the National Heart, Lung, and Blood Institute (NHLBI) in 1994 (1) was evident. This Task Force therefore formed the current committee to develop guidelines for the management of UA and NSTEMI, supported by the Agency for Healthcare Research and Quality's UCSF-Stanford Evidence-Based Practice Center. This document should serve as a useful successor to the 1994 AHCPR guideline.

The committee members reviewed and compiled published reports through a series of computerized literature searches of the English-language literature since 1994 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) if the data were derived from multiple randomized clinical trials that involved large numbers of patients and intermediate (B) if the data were derived from a limited number of randomized trials that involved small numbers of patients or from careful analyses of nonrandomized studies or observational registries. A lower rank (C) was given when expert consensus was the primary basis for the recommendation.

The customary ACC/AHA classifications I, II, and III are used in tables that summarize both the evidence and expert opinion and provide final recommendations for both patient evaluation and therapy:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy

Class IIb: Usefulness/efficacy is less well established by evidence/opinion

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

A complete list of the thousands of publications on various aspects of this subject is beyond the scope of these guidelines; only selected references are included. The Committee consisted of acknowledged experts in general internal medicine representing the American College of Physicians–American Society of Internal Medicine (ACP-ASIM), family medicine from the American Academy of Family Physicians (AAFP), emergency medicine from the American College of Emergency Physicians (ACEP), thoracic surgery from the Society of Thoracic Surgeons (STS), and general 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. The Agency for Healthcare Research and Quality UCSF-Stanford Evidence-Based Practice Center

*Endorsement by the ACEP means that the ACEP agrees with the general concepts in the guidelines and believes that the developers have begun to define a process of care that considers the best interests of patients with unstable angina and non–ST-segment elevation myocardial infarction.

provided support for the guidelines. The original 2000 document was reviewed by 3 outside reviewers nominated by each of the ACC, AHA, and ACEP; 1 outside reviewer nominated by each of the AAFP, ACP-ASIM, European Society of Cardiology, and STS; and 29 outside reviewers nominated by the Committee. The 2002 update was reviewed by 2 outside reviewers nominated by each of the ACC and AHA. This document was approved for publication by the governing bodies of ACC and AHA. These guidelines will be reviewed 1 year after publication and yearly thereafter by the Task Force to determine whether revision is necessary. These guidelines will be considered current unless the Task Force revises them or withdraws them from distribution.

These guidelines overlap several previously published ACC/AHA practice guidelines, including the ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction and the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina.

B. Purpose of These Guidelines

These guidelines address the diagnosis and management of patients with UA and the closely related condition NSTEMI. These life-threatening disorders are a major cause of emergency medical care and hospitalization in the United States. In 1996 alone, the National Center for Health Statistics reported 1,433,000 hospitalizations for UA or NSTEMI (2). Nearly 60% of hospital admissions of patients with UA as the primary diagnosis were among persons greater than 65 years old, and 46% of such patients of all ages were women. In 1997, there were 5,315,000 visits to US emergency departments (EDs) for the evaluation of chest pain and related symptoms (3). The prevalence of this presentation of CAD ensures that many healthcare providers who are not cardiovascular specialists will encounter patients with UA/NSTEMI in the course of the treatment of other diseases, especially in outpatient and ED settings. 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. The diagnostic and therapeutic strategies that are recommended are supported by the best available evidence and expert opinion. The application of these principles with carefully reasoned clinical judgment reduces, but does not eliminate, the risk of cardiac damage and death in patients who present with symptoms suggestive of UA.

C. Overview of the Acute Coronary Syndrome

1. Definition of Terms

UA/NSTEMI constitutes a clinical syndrome that is usually, but not always, caused by atherosclerotic CAD and associated with an increased risk of cardiac death and myocardial infarction (MI). The results of angiographic and angioscopic studies suggest that UA/NSTEMI often results from the disruption of an atherosclerotic plaque and a subsequent cascade of pathological processes that decrease coronary blood flow. Most patients who die during UA/NSTEMI do so because of sudden death or the development (or recurrence) of acute MI (AMI). The efficient diagnosis and optimal management of these patients must derive from information readily available at the time of the initial clinical presentation. The clinical presentation of patients with a life-threatening acute coronary syndrome (ACS) often overlaps that of patients subsequently found not to have CAD. Moreover, some forms of MI cannot always be differentiated from UA at the time of initial presentation.

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 (Fig. 1). It encompasses AMI (ST-segment elevation and depression, Q wave and non–Q wave) as well as UA. These guidelines focus on 2 components of this syndrome: UA and NSTEMI. In practice, the term *possible ACS* is often assigned first by ancillary personnel, such as emergency medical technicians and triage nurses, early in the evaluation process. A guideline of the National Heart Attack Alert Program (NHAAP) (4) summarizes the clinical information needed to make the diagnosis of possible ACS at the earliest phase of clinical evaluation (Table 1). The implication of this early diagnosis for clinical management is that a patient who is considered to have an ACS should be placed in an environment with continuous electrocardiographic (ECG) monitoring and defibrillation capability, where a 12-lead ECG can be obtained expeditiously and definitively interpreted within 10 min. The most urgent priority of early evaluation is to identify patients with AMI who should be considered for immediate reperfusion therapy and to recognize other potentially catastrophic causes of sudden patient decompensation, such as aortic dissection.

Patients diagnosed as having an AMI suitable for reperfusion (with ST-segment elevation) are excluded from management according to these guidelines and should be managed as indicated according to the ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction (5). The management of patients who experience periprocedural myocardial damage that is reflected in release of the MB isoenzyme of creatine phosphokinase (CK-MB) also is not considered here. Patients with AMI and with definite ischemic ECG changes who are not suitable for acute reperfusion should be diagnosed and managed as patients with UA. The residual group of patients with an initial diagnosis of ACS will include many patients who will ultimately be proven to have a noncardiac cause for the initial clinical presentation that was *suggestive* of ACS. Therefore, at the conclusion of the initial evaluation, which is frequently carried out in the ED but sometimes occurs during the initial hours of inpatient hospitalization, each patient should have a provisional diagnosis of 1) ACS, which in turn is classified as a) ST-segment elevation MI (STEMI), a condition for which

Table 1. 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:*

Chief Complaint
- 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:*

Chief Complaint

- 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, angioplasty, CAD, angina on effort, or AMI
- NTG use to relieve chest discomfort
- Risk factors, including smoking, hyperlipidemia, hypertension, diabetes mellitus, family history, and cocaine use

This 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. 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.

immediate reperfusion therapy (thrombolysis or percutaneous coronary intervention [PCI]) should be considered; b) NSTEMI; or c) UA; 2) a non-ACS cardiovascular condition (e.g., acute pericarditis); 3) a noncardiac condition with another specific disease (e.g., chest pain secondary to esophageal spasm); and 4) a noncardiac condition that is undefined. In addition, the initial evaluation should be used to determine risk and to treat life-threatening events.

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, they differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly troponin I (TnI), troponin T (TnT), or CK-MB. Once it has been established that no biochemical marker of myocardial necrosis has been released (with a reference limit of the 99th percentile of the normal population) (6), the patient with ACS may be considered to have experienced UA, whereas the diagnosis of NSTEMI is established if a marker has been released. In the latter condition, ECG ST-segment or T-wave changes may be persistent, whereas they may or may not occur in patients with UA, and if they do, they are usually transient. Markers of myocardial injury may be detected in the bloodstream hours after the onset of ischemic chest pain, which allows the differentiation between UA (i.e., no markers in circulation; usually transient, if any, ECG changes of

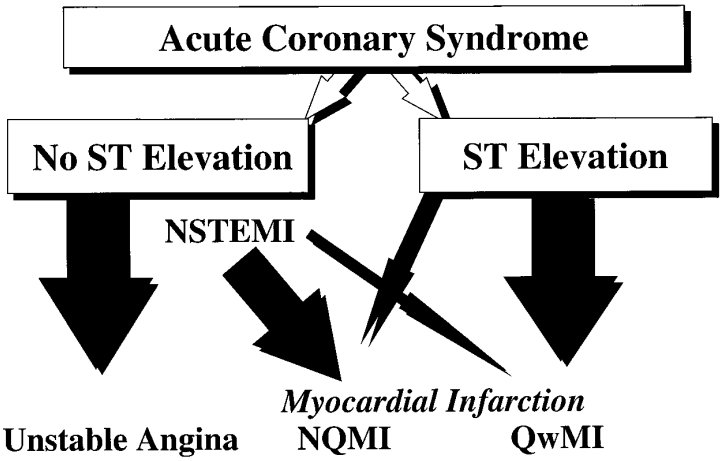


Figure 1. Nomenclature of ACSs. Patients with ischemic discomfort may present with or without ST-segment elevation on the ECG. The majority of patients with ST-segment elevation (large arrows) ultimately develop a Q-wave AMI (QwMI), whereas a minority (small arrow) develop a non–Q-wave AMI (NQMI). Patients who present without ST-segment elevation are experiencing either UA or an NSTEMI. The distinction between these 2 diagnoses is ultimately made based on the presence or absence of a cardiac marker detected in the blood. Most patients with NSTEMI do not evolve a Q wave on the 12-lead ECG and are subsequently referred to as having sustained a non–Q-wave MI (NQMI); only a minority of NSTEMI patients develop a Q wave and are later diagnosed as having Q-wave MI. Not shown is Prinzmetal's angina, which presents with transient chest pain and ST-segment elevation but rarely MI. The spectrum of clinical conditions that range from US to non–Q-wave AMI and Q-wave AMI is referred to as ACSs. Adapted from Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald EB, ed. Heart disease: a textbook of cardiovascular medicine. Philadelphia, PA: WB Saunders, 1997.

ischemia) and NSTEMI (i.e., elevated biochemical markers). Thus, at the time of presentation, patients with UA and NSTEMI may be indistinguishable and therefore are considered together in these guidelines.

2. Pathogenesis of UA/NSTEMI

These conditions are characterized by an imbalance between myocardial oxygen supply and demand. They are not specific diseases such as pneumococcal pneumonia, but rather a syndrome, analogous to hypertension. Five nonexclusive causes are recognized (7) (Table 2).

Table 2. Causes of UA*

Nonocclusive thrombus on pre-existing plaque
Dynamic obstruction (coronary spasm or vasoconstriction)
Progressive mechanical obstruction
Inflammation and/or infection
Secondary UA

*These causes are not mutually exclusive; some patients have greater than or equal to 2 causes.
Reprinted with permission from Braunwald E. Unstable angina: an etiologic approach to management. Circulation 1998;98:2219–22.

With the first 4 causes, the imbalance is caused primarily by a reduction in oxygen supply to the myocardium, whereas with the fifth cause, the imbalance is due principally to increased myocardial oxygen requirements, usually in the presence of a fixed restricted oxygen supply.

- The most common cause of UA/NSTEMI is reduced myocardial perfusion that results from coronary artery narrowing caused by a nonocclusive thrombus that developed on a disrupted atherosclerotic plaque and is usually nonocclusive. Microembolization of platelet aggregates and components of the disrupted plaque is believed to be responsible for the release of myocardial markers in many of these patients.
- A less common cause is dynamic obstruction, which may be caused by intense focal spasm of a segment of an epicardial coronary artery (Prinzmetal's angina) (see Section VI. F). This local spasm is caused by hypercontractility of vascular smooth muscle and/or by endothelial dysfunction. Dynamic coronary obstruction can also be caused by the abnormal constriction of small intramural resistance vessels.
- A third cause of UA is severe narrowing without spasm or thrombus. This occurs in some patients with progressive atherosclerosis or with restenosis after a PCI.
- The fourth cause is arterial inflammation, perhaps caused by or related to infection, which may be responsible for arterial narrowing, plaque destabilization, rupture, and thrombogenesis. Activated macrophages and T-lymphocytes located at the shoulder of a plaque increase the expression of enzymes such as metalloproteinases that may cause thinning and disruption of the plaque, which in turn may lead to UA/NSTEMI.
- The fifth cause is *secondary* UA, in which the precipitating condition is *extrinsic* to the coronary arterial bed. These patients have underlying coronary atherosclerotic narrowing that limits myocardial perfusion, and they often have chronic stable angi-

na. Secondary UA is precipitated by conditions that 1) increase myocardial oxygen requirements, such as fever, tachycardia, and thyrotoxicosis; 2) reduce coronary blood flow, such as hypotension; or 3) reduce myocardial oxygen delivery, such as anemia or hypoxemia.

These 5 causes of UA/NSTEMI are not mutually exclusive (Fig. 2).

3. Presentations of UA

There are 3 principal presentations of UA: 1) rest angina (angina commencing when the patient is at rest), 2) new-onset severe angina, and 3) increasing angina (Table 3) (8). Criteria for the diagnosis of UA are based on the duration and intensity of angina as graded according to the Canadian Cardiovascular Society (CCS) classification (Table 4) (9).

The strictness of the criteria used to define UA/NSTEMI, the rigor used in consistent application of these criteria, and the presence of comorbid conditions all greatly influence reported mortality rates. Published series commonly include only patients for whom a definitive diagnosis of UA has been established and do not include all patients from the time of onset of symptoms. Therefore, mortality rates observed in any series of carefully defined patients with UA/NSTEMI will tend to understate the risk. Data that depict survival rates and survival rates without MI, obtained from 1 large trial (10) carried out with patients with UA/NSTEMI, indicate that the risk associated with an ACS is greatest during the first 30 days after presentation and thereafter stabilizes at a lower rate (Fig. 3).

Table 3. Three Principal Presentations of UA

Rest angina*	Angina occurring at rest and prolonged, usually >20 minutes
New-onset angina	New-onset angina of at least CCS Class III severity
Increasing angina	Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by greater than or equal to 1 CCS class to at least CCS Class III severity)

*Patients with NSTEMI usually present with angina at rest.
Adapted from Braunwald E. Unstable angina: a classification. Circulation 1989;80:410-4.

II. INITIAL EVALUATION AND MANAGEMENT

A. Clinical Assessment

Patients with suspected ACS must be evaluated rapidly. Decisions made based on the initial evaluation have substantial clinical and economic consequences (11). When the patient first makes contact with the medical care system, a critical decision must be made about where the evaluation will take place. The physician then must place the evaluation

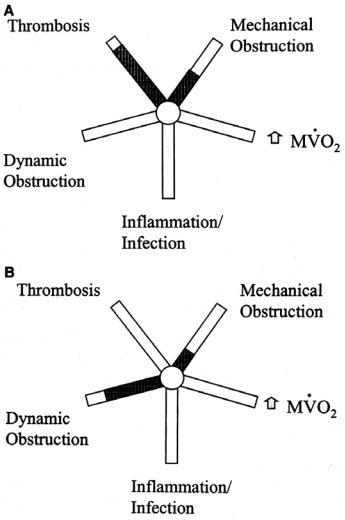


Figure 2. Schematic of the causes of UA. Each of the 5 bars (A and B) represents 1 of the etiologic mechanisms, and the filled portion of the bar represents the extent to which the mechanism is operative. A, Most common form of UA, in which atherosclerotic plaque causes moderate (60% diameter) obstruction and acute thrombus overlying plaque causes very severe (90% diameter) narrowing. B, Most common form of Prinzmetal's angina with mild (30% diameter) atherosclerotic obstruction, adjacent to intense (90% diameter) vasoconstriction. Reprinted with permission from Braunwald E. Unstable angina: an etiologic approach to management. Circulation 1998;98:2219-22.

in the context of 2 critical questions: Are the symptoms a manifestation of an ACS? If so, what is the prognosis? The answers to these 2 questions lead logically to a series of decisions about where the patient will be managed, what medications will be prescribed, and whether an angiographic evaluation will be required.

Given the large number of patients with symptoms compatible with ACS, the heterogeneity of the population, and the clustering of events shortly after the onset of symptoms

Table 4. Grading of Angina Pectoris According to CCS Classification

Class	Description of Stage
I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking >2 blocks on the level and climbing >1 flight of ordinary stairs at a normal pace and under normal conditions.
III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

Adapted with permission from Campeau L. Grading of angina pectoris (letter). Circulation 1976;54:522–3. © 1976, American Heart Association, Inc.

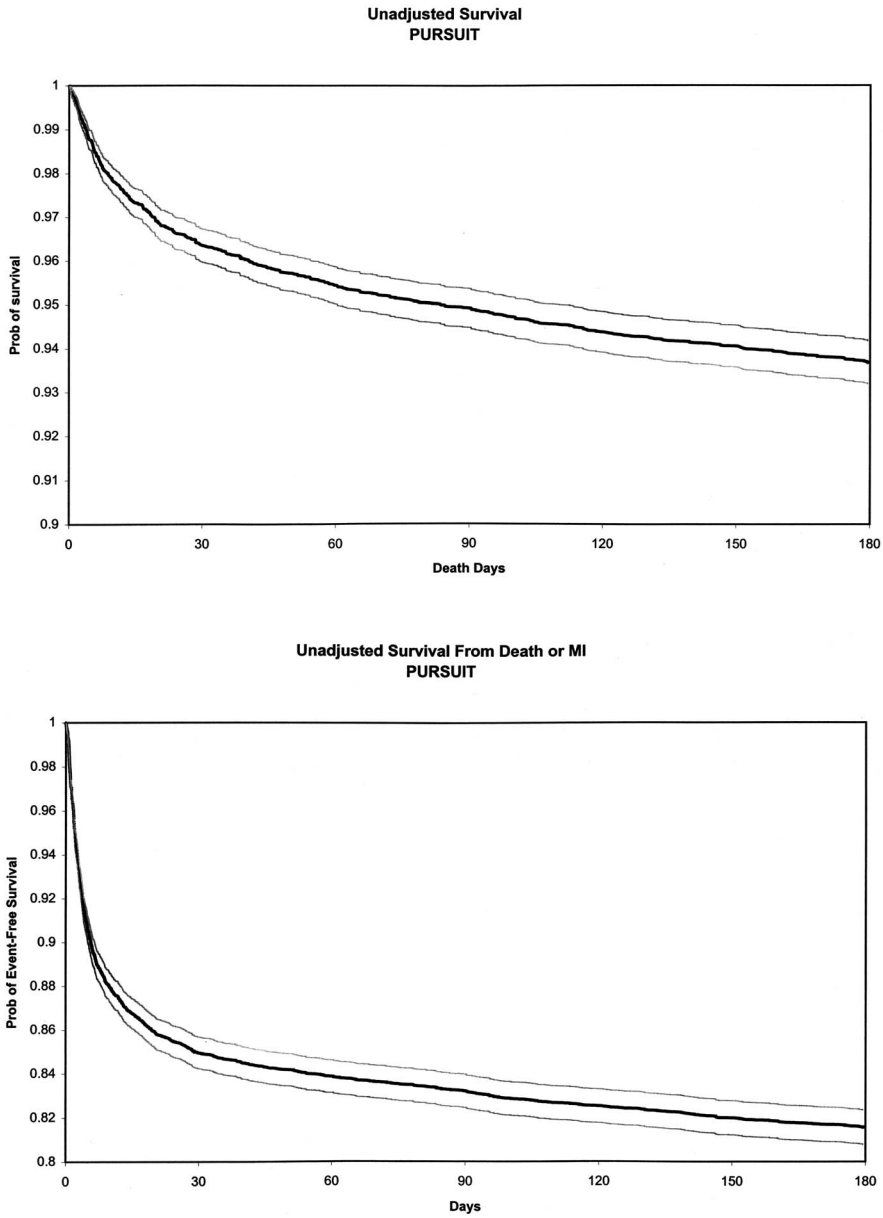


Figure 3. Top, Unadjusted survival probability (695% CI) in the PURSUIT trial of patients with ACS. Bottom, Unadjusted survival probability without death or MI in the PURSUIT trial of patients with ACS (10).

(Fig. 3), a strategy for the initial evaluation and management is essential. Healthcare providers may be informed about signs and symptoms of ACS over the telephone or in person (and perhaps in the future over the Internet). The objectives of the initial evaluation are first to identify signs of immediate life-threatening instability and then to ensure that the patient is moved rapidly to the most appropriate environment for the level of care needed based on diagnostic criteria and an estimation of the underlying risk of specific negative outcomes.

Recommendation for Telephone Triage

Class I

Patients with symptoms that suggest possible ACS 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. (Level of Evidence: C)

Health practitioners frequently receive telephone calls from patients who are concerned that their symptoms may reflect heart disease. Most such calls regarding chest discomfort of possible cardiac origin in patients without known CAD do not represent an emergency; rather these patients usually seek reassurance that they do not have heart disease or that there is little risk due to their symptoms. Despite the frequent inclination to dismiss such symptoms over the telephone, physicians should advise patients with possible accelerating angina or angina at rest that such an evaluation cannot be carried out solely via the telephone. This advice is essential because of the need for a physical examination and

an ECG and the potential importance of blood tests to measure cardiac markers.

Patients with known CAD—including those with chronic stable angina or recent MI or who have had coronary artery bypass graft surgery (CABG) or a PCI—who contact a physician because of worsening or recurrence of symptoms should be urged to go directly to an ED equipped to perform prompt reperfusion therapy. Alternatively, they may enter the emergency medical services system directly by calling 9-1-1. Patients who have recently been evaluated and who are calling for advice regarding modification of medication as part of an ongoing treatment plan represent exceptions.

Even in the most urgent subgroup of patients who present with acute-onset chest pain, there usually is adequate time for transport to an environment in which they can be evaluated and treated (12). In a large study of consecutive patients with chest pain suspected to be of cardiac etiology who were transported to the ED via ambulance, one third had a final diagnosis of AMI, one third had a final diagnosis of UA, and one third had a final diagnosis of a noncardiac cause. Only 1.5% of these patients developed cardiopulmonary arrest before arrival at the hospital or in the ED (13). These findings suggest that patients with acute chest pain might be better served by transport to an adequately staffed and equipped ED than by sending them to a less well staffed and equipped facility, thereby compromising the quality of the care environment in an attempt to shorten the initial transport time.

Patients must retain the ultimate responsibility for deciding whether to seek medical attention and, if so, in what environment. The physician cannot be expected to assume responsibility for a patient with a potentially serious acute cardiac disorder who does not present in person for urgent evaluation and declines after being advised to do so. Physicians should be cautious not to inappropriately reassure patients who are inclined not to seek further medical attention.

1. ED or Outpatient Facility Presentation

Recommendation

Class I

Patients with a suspected ACS with chest discomfort at rest for greater than 20 min, hemodynamic instability, or recent syncope or presyncope should be strongly considered for immediate referral to an ED or a specialized chest pain unit. Other patients with a suspected ACS may be seen initially in an ED, a chest pain unit, or an outpatient facility. (Level of Evidence: C)

Although no data are available that compare outcome as a function of the location of the initial assessment, this recommendation is based on evidence that symptoms and signs of an ACS may lead to a clinical decision that requires a sophisticated level of intervention. When symptoms have been unremitting for greater than 20 min, the possibility of STEMI must be considered. Given the strong evidence for a relationship between delay in treatment and death (14-16), an immediate assessment that includes a 12-lead ECG is essential. Patients who present with hemodynamic instability require an environment in which therapeutic interventions can be provided, and for those with presyncope or syncope, the major concern is the risk of sudden death. Such patients should be encouraged to seek emergency transportation when it is available. Transport as a passenger in a private vehicle is an acceptable alternative only if the wait for an emergency vehicle would impose a delay of greater than 20 to 30 min.

Patients without any of these high-risk features may be seen initially in an outpatient facility.

2. Questions to be Addressed at the Initial Evaluation

The initial evaluation should be used to provide information about the diagnosis and prognosis. The attempt should be made to simultaneously answer 2 questions:

- What is the likelihood that the signs and symptoms represent ACS secondary to obstructive CAD (Table 5)?
- What is the likelihood of an adverse clinical outcome (Table 6)? Outcomes of concern include death, MI (or recurrent MI), stroke, heart failure, recurrent symptomatic ischemia, and serious arrhythmia.

For the most part, the answers to these questions form a sequence of contingent probabilities. Thus, the likelihood that the signs and symptoms represent ACS is contingent on the likelihood that the patient has underlying CAD. Similarly, the prognosis is contingent on the likelihood that the symptoms represent acute ischemia.

B. Early Risk Stratification

Recommendations for Early Risk Stratification

Class I

1. **A determination should be made in all patients with chest discomfort of the likelihood of acute ischemia caused by CAD as high, intermediate, or low. (Level of Evidence: C)**
2. **Patients who present with chest discomfort should undergo early risk stratification that focuses on anginal symptoms, physical findings, ECG findings, and biomarkers of cardiac injury. (Level of Evidence: B)**
3. **A 12-lead ECG should be obtained immediately (within 10 min) in patients with ongoing chest discomfort and as rapidly as possible in patients who have a history of chest discomfort consistent with ACS but whose discomfort has resolved by the time of evaluation. (Level of Evidence: C)**
4. **Biomarkers of cardiac injury should be measured in**

all patients who present with chest discomfort consistent with ACS. A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients. CK-MB by mass assay is also acceptable. In patients with negative cardiac markers within 6 h of the onset of pain, another sample should be drawn in the 6- to 12-h time frame (e.g., at 9 h after the onset of symptoms). (Level of Evidence: C)

Class IIa

For patients who present within 6 h of the onset of symptoms, an early marker of cardiac injury (e.g., myoglobin or CK-MB subforms) should be considered in addition to a cardiac troponin. (Level of Evidence: C)

Class IIb

C-reactive protein (CRP) and other markers of inflammation should be measured. (Level of Evidence: B)

Class III

Total CK (without MB), aspartate aminotransferase (AST, SGOT), beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should be the markers for the detection of myocardial injury in patients with chest discomfort suggestive of ACS. (Level of Evidence: C)

1. Estimation of the Level of Risk

The medical history, physical examination, ECG, and biochemical cardiac marker measurements in patients with symptoms suggestive of ACS at the time of the initial presentation can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events. The latter include new or recurrent MI, recurrent UA, disabling angina that requires hospitalization, and/or urgent coronary revascularization. Estimation of the level of risk is a multivariable problem that cannot be accurately quantified with a simple table; therefore, Tables 5 and 6 are meant to be illustrative of the general relationships between clinical and ECG findings and the categorization of patients into those at a low, an intermediate, or a high risk of events.

2. Rationale for Risk Stratification

Because patients with ischemic discomfort at rest as a group are at an increased risk of cardiac death and nonfatal ischemic events, an assessment of the prognosis often sets the pace of the initial evaluation and treatment. An estimation of risk is useful in 1) selection of the site of care (coronary care unit, monitored step-down unit, or outpatient setting) and 2) selection of therapy, especially platelet glycoprotein (GP) IIb/IIIa inhibitors (see Section III. B) and coronary revascularization (see Section IV). For all modes of presentation of an ACS, a strong relationship exists between indicators of the likelihood of ischemia due to CAD and prognosis (Tables 5 and 6). Patients with a high likelihood of ischemia due to CAD are at a greater risk of an untoward cardiac event than are patients with a lower likelihood of CAD. Therefore, an assessment of the likelihood of CAD is the starting point for the determination of prognosis in patients who present with symptoms suggestive of an ACS. Other important elements for prognostic assessment are the tempo of the patient's clinical course, which relates to the short-term risk of future cardiac events, principally AMI, and the patient's likelihood of survival should an AMI occur.

Patients may present with ischemic discomfort but without ST-segment elevation on the 12-lead ECG in a variety of clinical scenarios, including no known prior history of CAD, a prior history of stable CAD, soon after MI, and after myocardial revascularization with CABG or PCI (7,17,18). As a clinical syndrome, ischemic discomfort without ST-seg-

Table 5. Likelihood That Signs and Symptoms Represent an ACS Secondary to CAD

Feature	High Likelihood *Any of the following:*	Intermediate Likelihood *Absence of high-likelihood features and presence of any of the following:*	Low Likelihood *Absence of high- or intermediate-likelihood features but may have:*
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age >70 years Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥0.05 mV) or T-wave inversion (≥0.2 mV) with symptoms	Fixed Q waves Abnormal ST segments or T waves not documented to be new	T-wave flattening or inversion in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services; 1994; AHCPR Publication No. 94-0602.

Table 6. Short-Term Risk of Death or Nonfatal MI in Patients With UA*

Feature	High Risk *At least 1 of the following features must be present:*	Intermediate Risk *No high-risk feature but must have 1 of the following:*	Low Risk *No high- or intermediate-risk feature but may have any of the following features:*
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 (>20 minutes) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (<20 min) or relieved with rest or sublingual NTG	New-onset or progressive CCS Class III or IV angina the past 2 weeks without prolonged (>20 min) rest pain but with moderate or high likelihood of CAD (see Table 5)
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age >75 years	Age >70 years	
ECG	Angina at rest with transient ST-segment changes >0.05 mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversions >0.2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated (e.g., TnT or TnI >0.1 ng/mL)	Slightly elevated (e.g., TnT >0.01 but <0.1 ng/mL)	Normal

*Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA 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 AHCPR Clinical Practice Guideline No. 10, Unstable Angina: Diagnosis and Management, May 1994. Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services; 1994; AHCPR Publication No. 94-0602.

ment elevation (UA and NSTEMI) shares ill-defined borders with severe chronic stable angina, a condition associated with lower risk, and with STEMI, a presentation with a higher risk of early death and cardiac ischemic events. This fact is illustrated by data from the Duke Cardiovascular Databank that describe the rate of cardiac death in 21,761 patients treated for CAD without interventional procedures at Duke University Medical Center between 1985 and 1992 and that were published in the AHCPR-NHLBI guidelines (1), now supplemented with data from large clinical trials in ACS (10) (Fig. 3). The highest risk of cardiac death was at the time of presentation, and the risk declined so that by 2 months, mortality rates for patients with ACS were at the same level as those for patients with chronic stable angina. Data from randomized controlled trials of patients with UA/NSTEMI have also shown that the rate of nonfatal cardiac ischemic events such as recurrent MI and recurrent angina is highest during the initial hospitalization and declines thereafter (4,10,19–21).

Two large clinical trials, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) (10) and Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q wave Coronary Events (ESSENCE) (22), have evaluated the clinical and ECG characteristics associated with an increased risk of death and nonfatal MI in 24 774 patients with UA/NSTEMI. The critical clinical features associated with an increased risk of death were age (greater than 65 years), presence of positive markers for myocardial necrosis on admission, lighter weight, more severe (CCS class III or IV) chronic angina before the acute admission, rales on physical examination, and ST-segment depression on the admission ECG. In the PURSUIT trial, either tachycardia or bradycardia and lower blood pressure were associated with a higher risk of death or MI. These findings allow the stratification of patients with UA/NSTEMI into those at higher risk and those at lower risk.

3. The History

Patients with suspected UA/NSTEMI may be divided into those with and those without a history of documented CAD. Particularly when the patient does not have a known history of CAD, the physician must determine whether the patient's presentation, with its constellation of specific symptoms and signs, is most consistent with chronic ischemia, with acute ischemia, or with an alternative disease process. The 5 most important factors derived from the initial history that relate to the likelihood of ischemia due to CAD, ranked in the order of importance, are 1) the nature of the anginal symptoms, 2) prior history of CAD, 3) sex, 4) age, and 5) the number of traditional risk factors present (23–25).

a. Anginal Symptoms

The characteristics of angina are described in the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina (26). Angina is characterized as a

deep, poorly localized chest or arm discomfort that is reproducibly associated with physical exertion or emotional stress and is relieved promptly (i.e., less than 5 min) with rest and/or the use of sublingual nitroglycerin (NTG) (Table 5). Patients with UA may have discomfort that has all of the qualities of typical angina except that the episodes are more severe and prolonged, may occur at rest, or may be precipitated by less exertion than previously. Some patients may have no chest discomfort but present solely with jaw, neck, ear, arm, or epigastric discomfort. If these symptoms have a clear relationship to exertion or stress or are relieved promptly with NTG, they should be considered equivalent to angina. Occasionally, such "anginal equivalents" that occur at rest are the mode of presentation of a patient with UA, but without the exertional history, it may be difficult to recognize the cardiac origin. Other difficult presentations of the patient with UA include those without any chest (or equivalent) discomfort. Isolated unexplained new-onset or worsened exertional dyspnea is the most common anginal equivalent symptom, especially in older patients; others include nausea and vomiting, diaphoresis, and unexplained fatigue. Elderly patients, especially women with ACS, often present with atypical angina.

Features that are *not* characteristic of myocardial ischemia include the following:

- Pleuritic pain (i.e., sharp or knife-like pain brought on by respiratory movements or cough)
- Primary or sole location of discomfort in the middle or lower abdominal region
- Pain that may be localized at the tip of 1 finger, particularly over the left ventricular (LV) apex
- Pain reproduced with movement or palpation of the chest wall or arms
- Constant pain that lasts for many hours
- Very brief episodes of pain that last a few seconds or less
- Pain that radiates into the lower extremities

Documentation of the evaluation of a patient with suspected UA/NSTEMI should include the physician's opinion of whether the discomfort is in 1 of 3 categories: high, intermediate, or low likelihood of acute ischemia caused by CAD (Table 5).

Although typical characteristics substantially raise the probability of CAD, features not characteristic of chest pain, such as sharp stabbing pain or reproduction of pain on palpation, *do not exclude* the possibility of ACS. In the Multicenter Chest Pain Study, acute ischemia was diagnosed in 22% of patients who presented to the ED with sharp or stabbing pain and in 13% of patients with pain with pleuritic qualities. Furthermore, 7% of patients whose pain was fully reproduced with palpation were ultimately recognized to have ACS (27). The Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) project (28,29) found that older age, male sex, the presence of chest or left arm pain, and the identification of chest pain or pressure as the most important presenting symptom all increased the likelihood that the patient was experiencing acute ischemia.

b. Demographics and History in Diagnosis and Risk Stratification

In most studies of ACS, a prior history of MI has been associated not only with a high risk of obstructive CAD (30) but also with an increased risk of multivessel CAD.

There are differences in the presentations of men and women with ACS (see Section VI. A). A smaller percentage of women than men present with STEMI, and of the patients who present without ST-segment elevation, fewer women than men have MIs (31). Women with suspected ACS are less likely to have CAD than are men with a similar clinical presentation, and when CAD is present in women, it tends to be less severe. If STEMI is present, the outcome in women tends to be worse even when adjustment is made for the older age and greater comorbidity of women. However, the outcome for women with UA is significantly better than the outcome for men, and the outcomes are similar for men and women with NSTEMI (32,33).

Older patients (see Section VI. D) have increased risks of both underlying CAD (34,35) and multivessel CAD; furthermore, they are at higher risk for an adverse outcome than are younger patients. The slope of the increased risk is steepest beyond age 70. This increased risk is related in part to the greater extent and severity of underlying CAD and the more severe LV dysfunction in older patients, but age itself appears to exert an independent prognostic risk as well, perhaps because of comorbidities. Elderly patients are also more likely to have atypical symptoms on presentation.

In patients with symptoms of possible ACS, some of the traditional risk factors for CAD (e.g., hypertension, hypercholesterolemia, cigarette smoking) are only weakly predictive of the likelihood of acute ischemia (29,36) and are far less important than are symptoms, ECG findings, and cardiac markers. *Therefore, the presence or absence of these traditional risk factors ordinarily should not be used to determine whether an individual patient should be admitted or treated for ACS.* <u>However, the presence of these risk factors does appear to relate to poor outcomes in patients with established ACS.</u> Although a family history of premature CAD raises interesting issues of the genetic contribution to the development of this syndrome, it has not been a useful indicator of diagnosis or prognosis in patients evaluated for possible symptoms of ACS. However, several of these risk factors have important prognostic and therapeutic implications. Diabetes and the presence of extracardiac (peripheral or carotid) arterial disease are major risk factors for poor outcome in patients with ACS (see Section VI. B). For both ST-segment elevation (37) and non–ST-segment elevation ACS (10), patients with these conditions have a significantly higher mortality rate and risk of acute heart failure. For the most

part, this increase in risk is due to a greater extent of underlying CAD and LV dysfunction, but in many studies, diabetes carries prognostic significance over and above these findings. Similarly, a history of hypertension is associated with an increased risk of poor outcome.

Surprisingly, current smoking is associated with a lower risk of death in the setting of ACS (38–40), predominantly because of the less severe underlying CAD. This "smokers' paradox" seems to represent a tendency for smokers to develop thrombi on less severe plaques and at an earlier age than nonsmokers.

Cocaine use has been implicated as a cause of ACS, presumably due to the ability of this drug to cause coronary vasospasm and thrombosis in addition to its direct effects on heart rate and arterial pressure and its myocardial toxic properties (see Section VI. E). It is important to inquire about the use of cocaine in patients with suspected ACS, especially younger patients (less than 40 years).

c. The Estimation of Early Risk at Presentation

Risk has been assessed using multivariable regression techniques in patients presenting with UA/NSTEMI in several large clinical trials. These have not yet been validated in large registries of such patients. Boersma et al. analyzed the relation between baseline characteristics and the incidence of death as well as the composite of death or myocardial (re)infarction at 30 days (516). The most important baseline features associated with death were age, heart rate, systolic blood pressure, ST-segment depression, signs of heart failure, and elevation of cardiac markers. From this analysis, a simple risk estimation score that should be useful in clinical decisionmaking was developed (516).

Antman et al. developed a 7-point risk score (age greater than 65 years, more than 3 coronary risk factors, prior angiographic coronary obstruction, ST-segment deviation, more than 2 angina events within 24 hours, use of aspirin within 7 days, and elevated cardiac markers) (517). The risk of developing an adverse outcome—death, (re)infarction, or recurrent severe ischemia requiring revascularization—ranged from 5% to 41% with the "TIMI (Thrombolysis In Myocardial Infarction) risk score" defined as the sum of the individual prognostic variables. The score was derived from data in the TIMI 11B trial (170) and has been validated in 3 additional trials—ESSENCE (169), TACTICS-TIMI 18 (518), and PRISM-PLUS (21). Among patients with UA/NSTEMI, there is a progressively greater benefit from newer therapies such as low-molecular-weight heparin (169,170), platelet GP IIb/IIIa inhibition (519), and an invasive strategy (518) with increasing risk score.

4. Noncardiac Causes of Exacerbation of Symptoms Secondary to Myocardial Ischemia

Recommendation

Class I

The initial evaluation of the patient with suspected ACS should include a search for noncoronary causes that could explain the development of symptoms. (Level of Evidence: C)

Information from the initial history, physical examination, and ECG (Table 5) will enable the physician to recognize and exclude from further assessment patients classified as "not having ischemic discomfort." This includes patients with noncardiac pain (e.g., musculoskeletal discomfort, esophageal discomfort) or cardiac pain not caused by myocardial ischemia (e.g., acute pericarditis). The remaining patients should undergo a more complete evaluation of secondary causes of UA that might alter management. This evaluation should include a physical examination for evidence of other cardiac disease, an ECG to screen for arrhythmias, measurement of body temperature and blood pressure, and determination of hemoglobin or hematocrit. Cardiac disorders other than CAD that may cause myocardial ischemia include aortic stenosis and hypertrophic cardiomyopathy. In secondary angina, factors that increase myocardial oxygen demand or decrease oxygen delivery to the heart may provoke or exacerbate ischemia in the presence of significant underlying CAD. Previously unrecognized gastrointestinal bleeding is a common secondary cause of worsened CAD and the development of ACS symptoms due to anemia. Acute worsening of chronic obstructive pulmonary disease (COPD) (with or without superimposed infection) may lower oxygen saturation levels sufficiently to intensify ischemic symptoms in patients with CAD. Evidence of increased cardiac oxygen demand can be judged from the presence of fever, signs of hyperthyroidism, sustained tachyarrhythmias, or markedly elevated blood pressure. Another cause of increased myocardial oxygen demand is arteriovenous (AV) fistula in patients receiving dialysis.

The majority of patients seen in the ED with symptoms of *possible* ACS will be judged after their workup to not have a cardiac problem. A recent clinical trial of a predictive instrument evaluated 10,689 patients with suspected ACS (11). To participate, patients were required to be greater than 30 years old with a chief symptom of chest, left arm, jaw, or epigastric pain or discomfort; shortness of breath; dizziness; palpitations; or other symptoms suggestive of acute ischemia. After the evaluation, 7996 patients (75%) were deemed *not* to have acute ischemia.

5. Assessment of Risk of Death in Patients With UA/NSTEMI

In patients who meet the diagnostic criteria for UA/NSTEMI, the recent tempo of ischemic symptoms is the strongest predictor of risk of death. The AHCPR guidelines "Unstable Angina: Diagnosis and Management" identified low-risk patients as those without rest or nocturnal angina and with a normal or an unchanged ECG (1). High-risk patients were identified as those with pulmonary edema; ongoing rest pain greater than 20 min in duration; angina with S_3 gallop, rales, or new or worsening mitral regurgitation (MR) murmur;

hypotension; or dynamic ST-segment change greater than or equal to 1 mm. Patients without low- or high-risk features were termed to be at "intermediate risk."

These simple clinical criteria were prospectively tested in a consecutive sample of patients who presented with symptoms suggestive of ACS (41). After prescreening was conducted to exclude patients with AMI or cardiac arrest, patients receiving thrombolytic therapy, and patients diagnosed as having noncardiac conditions, only 6% of the remaining patients diagnosed with UA were categorized as being at low risk. This low-risk population experienced no death or MI in the 30 days after the initial presentation to the ED. In contrast, the 30-day mortality rate was 1.2% for patients at intermediate risk and 1.7% for patients deemed at high risk. These observations confirmed the management recommendations made in the earlier guidelines. Patients with low-risk UA can be managed expeditiously as outpatients. Patients with high-risk UA deserve rapid clinical stabilization in an acute-care environment in the hospital. Patients at intermediate risk require individualization of management based on clinical judgment. These patients should usually be admitted to the hospital and require monitoring but do not ordinarily require an intensive care unit.

The *tempo of angina* is characterized by an assessment of changes in the duration of episodes, their frequency, and the anginal threshold. In particular, it is useful to determine whether the amount of physical or emotional stress that provokes symptoms has declined, whether symptoms are occurring at rest, and whether they awaken the patient from sleep. The integration of these factors into a score can improve the predictions of outcome (42,43). Although new-onset angina itself is associated with greater risk than is continued stable angina, most of its contribution to an adverse prognosis is determined by its severity, frequency, and tempo (42,44).

Multiple studies have demonstrated that prior MI is a major risk factor for poor outcome in both STEMI and UA/NSTEMI (10). Patients with symptoms of acute and/or chronic heart failure are also at a substantially higher risk.

a. Physical Examination

The major objectives of the physical examination are to identify potential precipitating causes of myocardial ischemia such as uncontrolled hypertension or thyrotoxicosis and comorbid conditions such as pulmonary disease and to assess the hemodynamic impact of the ischemic event. Every patient with suspected ACS should have his or her vital signs measured (blood pressure in both arms, heart rate, temperature) and undergo a thorough cardiovascular and chest examination. Patients with evidence of LV dysfunction on examination (rales, S_3 gallop) or with acute MR have a higher likelihood of severe underlying CAD and are at a high risk of a poor outcome. Just as the history of extracardiac vascular disease is important, the physical examination of the peripheral vessels can also provide important prognostic information. The presence of bruits or pulse deficits that suggest extracardiac vascular disease (carotid, aortic, peripheral) identifies patients with a higher likelihood of significant CAD.

Elements of the physical examination can be critical in making an important alternative diagnosis in patients with chest pain. In particular, several disorders carry a significant threat to life and function if not diagnosed acutely. Aortic dissection is suggested by pain in the back, unequal pulses, or a murmur of aortic regurgitation. Acute pericarditis is suggested by a pericardial friction rub, and cardiac tamponade may be evidenced by pulsus paradoxus. Pneumothorax is suspected when acute dyspnea, pleuritic chest pain, and differential breath sounds are present.

Recently, the importance of cardiogenic shock in patients with NSTEMI was emphasized. Although most literature on cardiogenic shock has focused on STEMI, the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) (45), Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-II (45a), and PURSUIT (10) trials have found that cardiogenic shock occurs in up to 5% of patients with NSTEMI and that mortality rates are greater than 60%. Thus, hypotension and evidence of organ hypoperfusion constitute a medical emergency in NSTEMI.

6. Tools for Risk Stratification

a. Electrocardiogram

The ECG is critical not only to add support to the clinical suspicion of CAD but also to provide prognostic information that is based on the pattern and magnitude of the abnormalities (46–49). *A recording made during an episode of the presenting symptoms is particularly valuable*. Importantly, transient ST-segment changes (greater than or equal to 0.05 mV) that develop during a symptomatic episode at rest and that resolve when the patient becomes asymptomatic strongly suggest acute ischemia and a very high likelihood of underlying severe CAD. Patients whose current ECG suggests acute CAD can be assessed with greater diagnostic accuracy if a prior ECG is available for comparison (Table 5) (50,51).

Although it is imperfect, the 12-lead ECG lies at the center of the decision pathway for the evaluation and management of patients with acute ischemic discomfort (Fig. 1, Table 5). The diagnosis of AMI is confirmed with serial cardiac markers in more than 90% of patients who present with ST-segment elevation of greater than or equal to 0.1 mV in greater than or equal to 2 contiguous leads, and such patients should be considered potential candidates for acute reperfusion therapy. Patients who present with ST-segment depression are initially considered to have either UA or NSTEMI; the distinction between the 2 diagnoses is based ultimately on the detection in the blood of markers of myocardial necrosis (6,18,52).

Patients with UA and reversible ST-segment depression have an increase in thrombin activity reflected in elevated levels of circulating fibrinopeptides and complex lesions that suggest thrombosis on coronary angiography (53). Up to

25% of patients with NSTEMI and elevated CK-MB go on to develop Q-wave MI, whereas the remaining 75% have non–Q-wave MI. Acute reperfusion therapy is contraindicated for ACS patients without ST-segment elevation, except for those with isolated acute posterior infarction manifested as ST-segment depressions in leads V1 to V3 and/or isolated ST-segment elevation in posterior chest leads (54). Inverted T waves may also indicate ischemia or non–Q-wave infarction. In patients suspected on clinical grounds to have ACS, marked (greater than or equal to 0.2 mV) symmetrical precordial T-wave inversion strongly suggests acute ischemia, particularly that due to a critical stenosis of the left anterior descending coronary artery (LAD) (55). Patients with this ECG finding often exhibit hypokinesis of the anterior wall and are at high risk with medical treatment (56). Revascularization will often reverse both the T-wave inversion and wall motion disorder (57). Nonspecific ST-segment and T-wave changes, usually defined as ST-segment deviation of less than 0.05 mV or T-wave inversion of less than or equal to 0.2 mV, are less helpful than the foregoing findings. Established Q waves greater than or equal to 0.04 s are also less helpful in the diagnosis of UA, although by suggesting prior MI, they do indicate a high likelihood of significant CAD. Isolated Q waves in lead III may be a normal finding, especially in the absence of repolarization abnormalities in any of the inferior leads. A completely normal ECG in a patient with chest pain does not exclude the possibility of ACS, because 1% to 6% of such patients eventually are proved to have had an AMI (by definition, an NSTEMI), and greater than or equal to 4% will be found to have UA (47,58,59).

The common alternative causes of ST-segment and T-wave changes must be considered. In patients with ST-segment elevation, the diagnoses of LV aneurysm, pericarditis, Prinzmetal's angina, early repolarization, and Wolff-Parkinson-White syndrome should be considered. Central nervous system events and drug therapy with tricyclic antidepressants or phenothiazines can cause deep T-wave inversion.

Several investigators have shown that a gradient of risk of death and cardiac ischemic events can be established based on the nature of the ECG abnormality (48,60,61). Patients with ACS and confounding ECG patterns such as bundle-branch block, paced rhythm, or LV hypertrophy are at the highest risk for death, followed by patients with ST-segment deviation (ST-segment elevation or depression); at the lowest risk are patients with isolated T-wave inversion or normal ECG patterns. Importantly, the prognostic information contained within the ECG pattern remains an independent predictor of death even after adjustment for clinical findings and cardiac marker measurements (60–63).

In addition to the presence or absence of ST-segment deviation or T-wave inversion patterns as noted earlier, there is evidence that the *magnitude* of the ECG abnormality provides important prognostic information. Thus, Lloyd-Jones et al. (64) reported that the diagnosis of acute non–Q-wave MI was 3 to 4 times more likely in patients with ischemic discomfort who had greater than or equal to 3 ECG leads that showed ST-segment depression and/or ST-segment depression of greater than or equal to 0.2 mV. Investigators from the TIMI III registry (60) reported that the 1-year incidence of death or new MI in patients with greater than or equal to 0.05-mV ST-segment deviation was 16.3% compared with 6.8% for patients with isolated T-wave changes and 8.2% for patients with no ECG changes.

Because a single 12-lead ECG recording provides only a snapshot view of a dynamic process, the usefulness of obtaining serial ECG tracings or performing continuous ST-segment monitoring was studied (46). Although serial ECGs increase the ability to diagnose AMI (65–67), the yield is higher with serial cardiac marker measurements (68). Continuous 12-lead ECG monitoring to detect ST-segment shifts, both symptomatic and asymptomatic, can be performed with microprocessor-controlled, programmable devices. Clinical experience suggests that continuous ECG monitoring identifies episodes of ischemia that are missed with standard 12-lead ECGs obtained on presentation and that such episodes of transient ischemia provide independent prognostic information that indicates an increased risk of death, nonfatal MI, and the need for urgent revascularization (69,70). However, the ultimate clinical usefulness of continuous 12-lead ECG monitoring requires additional clarification.

7. Decision Aids That Combine Clinical Features and ECG Findings

ECG findings have been incorporated into mathematics-based decision aids for the triage of patients who present with chest pain (46). The goals of these decision aids include the identification of patients at low risk of cardiac events, those with cardiac ischemia or AMI, and the estimation of prognosis (28,58,71–76).

8. Biochemical Cardiac Markers

Biochemical cardiac markers are useful for both the diagnosis of myocardial necrosis and the estimation of prognosis. The loss of membrane integrity of myocytes that undergo necrosis allows intracellular macromolecules to diffuse into the cardiac interstitium and then into the lymphatics and cardiac microvasculature (77). Eventually, these macromolecules, which are collectively referred to as *biochemical cardiac markers*, are detectable in the peripheral circulation. For optimum diagnostic usefulness, a marker of myocardial damage in the bloodstream should be present in a high concentration in the myocardium and absent from nonmyocardial tissue (52,77,78). It should be rapidly released into the blood after myocardial injury with a direct proportional relationship between the extent of myocardial injury and the measured level of the marker. Finally, the marker should persist in blood for a sufficient length of time to provide a convenient diagnostic time window with an easy, inexpensive, and rapid assay technique. Although no biochemical cardiac marker

available at the present satisfies all of these requirements, as discussed later, the cardiac-specific troponins have a number of attractive features and are gaining acceptance as the biochemical markers of choice in the evaluation of patients with ACS (6).

For patients who present without ST-segment elevation, in whom the diagnosis may be unclear, biochemical cardiac markers are useful to confirm the diagnosis of MI. In addition, they provide valuable prognostic information, because there is a quantitative relationship between the magnitude of elevation of marker levels and the risk of an adverse outcome (79).

a. Creatine Kinase

CK-MB has until recently been the principal serum cardiac marker used in the evaluation of ACS. Despite its common use, CK-MB has several limitations. Low levels of CK-MB in the blood of healthy persons limit its specificity for myocardial necrosis. CK-MB may also be elevated with severe damage of skeletal muscle (52,80,81). CK-MB isoforms exist in only 1 form in myocardial tissue (CK-MB2) but in different isoforms (or subforms) in plasma (CK-MB1). The use of an absolute level of CK-MB2 of greater than 1 U/L and a ratio of CK-MB2 to CK-MB1 of greater than 1.5 has improved sensitivity for the diagnosis of MI within the first 6 h compared with conventional assays for CK-MB, but this test has the same lack of absolute cardiac specificity as that of CK-MB itself (82). Moreover, the assay is not widely available.

b. Cardiac Troponins

The troponin complex consists of 3 subunits: TnT, TnI, and troponin C (TnC) (81). Monoclonal antibody–based immunoassays have been developed to detect cardiac-specific TnT (cTnT) and cardiac-specific TnI (cTnI), because the amino acid sequences of the skeletal and cardiac isoforms of both TnT and TnI have sufficient dissimilarity. Because cardiac and smooth muscle share isoforms for TnC, no immunoassays of TnC have been developed for clinical purposes. Therefore, in these guidelines, the term "cardiac troponins" refers to either cTnT or cTnI or to both.

Because cTnT and cTnI are not generally detected in the blood of healthy persons, the cutoff value for elevated cTnT and cTnI levels may be set to slightly above the upper limit of the assay for a normal healthy population, leading some investigators to use the term "minor myocardial damage" or "microinfarction" for patients with detectable troponin but no CK-MB in the blood (83). Case reports exist that confirm histological evidence of focal myocyte necrosis (e.g., microinfarction) in patients with elevated cardiac troponin levels and normal CK-MB values (6,84,85), indicating that myocardial necrosis can be recognized with increased sensitivity. It is estimated that approximately 30% of patients who present with rest pain without ST-segment elevation and who would otherwise be diagnosed as having UA because of a lack of CK-MB elevation actually have NSTEMI when assessed with cardiac-specific troponin assays. Although troponins are accurate in identifying myocardial necrosis (520), such necrosis is not necessarily secondary to atherosclerotic CAD. Therefore, in making the diagnosis of NSTEMI, cardiac troponins should be used in conjunction with appropriate symptoms or signs and/or ECG changes.

Elevated levels of cTnT or cTnI convey prognostic information beyond that supplied by the clinical characteristics of the patient, the ECG at presentation, and a predischarge exercise test (61,62,86–88). Furthermore, among patients without ST-segment elevation and normal CK-MB levels, elevated cTnI or cTnT concentrations identify those at an increased risk of death (61,62). Finally, there is a quantitative relationship between the quantity of cTnI or cTnT that is measured and the risk of death in patients who present with an ACS (Fig. 4). The incremental risk of death or MI in troponin-positive vs. troponin-negative patients is summarized in Tables 7 and 8. However, troponins should not be relied on as the *sole* markers for risk, because patients without troponin elevations may still exhibit a substantial risk of an adverse outcome. Neither marker is totally sensitive and specific in this regard. With currently available assays, cTnI and cTnT are of equal sensitivity and specificity in the detection of cardiac damage (90). The choice should be made on the basis of cost and the availability of instrumentation at the institution.

Patients who present without ST-segment elevation who have elevated cardiac-specific troponin levels may receive a greater treatment benefit from platelet GP IIb/IIIa inhibitors and low-molecular-weight heparin (LMWH). For example, in the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, UA patients with an elevated cTnT level at presentation had a rate of death or nonfatal MI of 23.9% when treated with placebo vs. 9.5% when treated with abciximab ($p = 0.002$) (91), whereas among patients with a normal cTnT level, the rate of death or MI was 7.5% in the placebo group vs. 9.4% in the abciximab group (p = NS). Similar results have been reported for cTnI and cTnT with use of the GP IIb/IIIa inhibitor tirofiban (92), and similar results were found in the Fragmin during Instability in Coronary Artery Disease (FRISC) trial of UA patients randomized to dalteparin or placebo. In the placebo group, the rate of death or nonfatal MI through 40 days increased progressively across the cTnT strata from 5.7% in the lowest tertile to 12.6% and 15.7% in the second and third tertiles, respectively (93). In the dalteparin groups, the rates were 4.7%, 5.7%, and 8.9% across the tertiles of cTnT levels, corresponding to a 17.5% reduction in events in the lowest tertile but 43% and 55% reductions, respectively, in events in the upper 2 tertiles of cTnT levels.

c. Myoglobin

Although myoglobin, a low-molecular-weight heme protein found in both cardiac and skeletal muscle, is not cardiac specific, it is released more rapidly from infarcted myocardium than is CK-MB or the troponins and may be detected as early as 2 h after the onset of myocardial necrosis. However, the

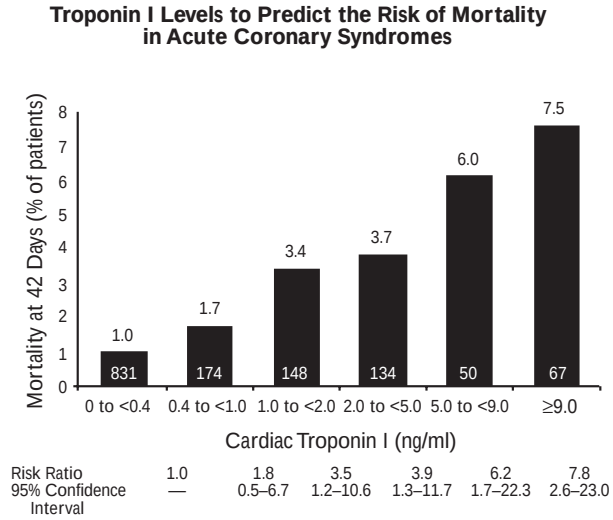


Figure 4. Relationship between cardiac troponin levels and risk of mortality in patients with ACS. Used with permission from Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342–9.

clinical value of serial determinations of myoglobin for the diagnosis of MI is limited by the brief duration of its elevation (less than 24 h) and by its lack of cardiac specificity. Thus, an isolated elevated concentration of myoglobin within the first 4 to 8 h after the onset of chest discomfort in patients with a nondiagnostic ECG should not be relied on to make the diagnosis of AMI but should be supplemented by a more cardiac-specific marker, such as CK-MB, cTnI, or cTnT (106,107). However, because of its high sensitivity, a *negative* test for myoglobin when blood is sampled within the first 4 to 8 h after onset is useful in ruling out myocardial necrosis.

d. Comparison of Cardiac Markers

The Diagnostic Marker Cooperative Study was a large, prospective, multicenter, double-blind study of patients who presented to the ED with chest pain in whom the diagnostic sensitivity and specificity for MI for total CK-MB (activity and mass), CK-MB subforms, myoglobin, and cTnI and cTnT were compared (108). CK-MB subforms and myoglobin were most efficient for the early diagnosis (within 6 h) of MI, whereas cTnI and cTnT were highly cardiac specific and were particularly efficient for the late diagnosis of MI.

Table 9 compares the advantages and disadvantages of various cardiac markers for the evaluation and management of patients with suspected ACS but without ST-segment elevation on the 12-lead ECG. The troponins offer greater diagnostic sensitivity due to their ability to identify patients with lesser amounts of myocardial damage, which has been referred to as "minor myocardial damage." Nonetheless, these lesser amounts of damage confer a high risk in patients with ACS, because they are thought to represent microinfarctions that result from microemboli from an unstable plaque; the instability of the plaque rather than the actual amount of myocardial necrosis may be what places the patient at an increased risk. In addition, analyses from clinical trials suggest that the measurement of cardiac troponin concentrations provides prognostic information above and beyond that contained in simple demographic data such as the patient's age, findings on the 12-lead ECG, and measurement of CK-MB (61,62). Thus, measurement of cardiac troponin concentrations provides an efficient method for simultaneously diagnosing MI and providing prognostic information. Although not quite as sensitive or specific as the troponins, CK-MB by mass assay remains a very useful marker for the detection of more than minor myocardial damage. A normal CK-MB, however, does not exclude the minor myocardial damage and its attendant risk of adverse outcomes detectable by cardiac-specific troponins. As noted earlier, the measurement of CK-MB isoforms is useful for the extremely early diagnosis (less than 4 h) of MI. However, to date, experience with the measurement of CK-MB isoforms has been limited predominantly to dedicated research cen-

Table 7. Risk of Death Associated With a Positive Troponin Test in Patients With Suspected ACS

Subgroup* (No. of Studies)	Troponin Test Result, Deaths/Total No. of Patients: Negative	Positive	Summary RR	95% CI	References
TnT					
Total mortality studies (4)	30/1,092	45/462	3.1	1.9-4.9	61, 94–97
Cardiac mortality studies (7)	31/1,689	52/744	3.8	2.4-6.0	83, 86, 89, 98–101
All TnT studies (11)	61/2,781	97/1,206	3.4	2.5-4.7	
TnI					
Total mortality studies (3)	34/1,451	49/815	3.1	2.0-4.9	62, 96, 102
Cardiac mortality studies (2)	3/905	26/384	25	11-56	83, 101
All TnI studies (5)	37/2,356	75/1,199	5.0	3.4-7.5	
TnT and TnI Combined					
Total mortality studies (6)	40/1,993	68/1,057	3.3	2.2-4.8	61, 94, 95, 97
Cardiac mortality studies (7)	28/1,641	55/792	5.0	3.2-7.9	83, 86, 89, 98–101
All studies (13)†	68/3,634	123/1,849	3.9	2.9-5.3	

*Trials are grouped based on how death was defined (cardiac or total).

†Three trials (4 articles) evaluated TnT and TnI in the same patients (61,83,96,101). To avoid double counting, either the TnT or TnI results were selected at random for the summary RR calculation. TnI results were used for 1 study (83), and TnT results were used for 2 studies (61,101). The TnT data from GUSTO IIA (61,96) were taken from the report by Ohman et al. (61). From P. A. Heidenreich and M. A. Hlatky for the UCSF-Stanford Evidence-based Practice Center (AHCPR).

Table 8. Risk of Death or MI Associated With a Positive Troponin Test in Patients With UA

Subgroup* (No. of Studies)	Troponin Test Result, Deaths/Total No. of Patients		Summary RR	95% CI	References
	Negative	Positive			
TnT (5)	43/667	62/301	3.7	2.5-5.6	95
TnI (2)	7/163	10/35	5.7	1.8-18.6	89, 103–105
TnT and TnI combined* (6)	47/737	67/322	3.8	2.6-5.5	87, 103

*One trial evaluated TnT and TnI in the same patients (103). To avoid double counting, 1 marker (TnT) was selected at random for summary RR calculations.
From P. A. Heidenreich and M. A. Hlatky for the UCSF-Stanford Evidence-based Practice Center (AHCPR).

ters, and its "field performance" in widespread clinical use remains to be established. Because of its poor cardiac specificity in the setting of skeletal muscle injury and its rapid clearance from the bloodstream, myoglobin should not be used as the *only* diagnostic marker for the identification of patients with NSTEMI, but its early appearance makes it quite useful for ruling out myocardial necrosis.

Cardiac-specific troponins are gaining acceptance as the primary biochemical cardiac marker in ACS. Commercially available assays are undergoing refinement, with several versions of assays in clinical use with different diagnostic cutoffs, underscoring the need for careful review of the cardiac troponin results reported in local hospital laboratories (6,109). As with any new testing procedure, there may be a period of adjustment as the laboratory introduces the troponin assays and the clinician becomes familiar with their use. Clinicians are encouraged to work closely with their colleagues in laboratory medicine to minimize the transition phase in making troponin measurements available in their institutions. The continued measurement of CK-MB mass is advisable during this transition. It should be emphasized that troponin levels may not rise for 6 h after the onset of symptoms, and in the case of a negative troponin level at less than 6 h, the measurement should be repeated 8 to 12 h after the onset of pain.

9. Integration of Clinical History With Serum Marker Measurements

Given the overlapping time frame of the release pattern of biochemical cardiac markers, it is important that clinicians incorporate the time from the onset of the patient's symptoms into their assessment of the results of biochemical marker measurements (6,110,111,111a) (Fig. 5). The earliest marker of myocardial necrosis, myoglobin, is a sensitive test but lacks cardiac specificity. Later appearing markers, such as TnT and TnI, are more specific but have a lower sensitivity for the very early detection of myocardial necrosis (e.g., less than 6 h) after the onset of symptoms, and if an early (less than 6 h) troponin test is negative, a measurement should be repeated 8 to 12 h after the onset of symptoms. Although the release kinetics of the troponins provide a wider diagnostic window for the diagnosis of MI at a time when CK-MB elevations have returned to normal, the more protracted period of elevation of troponin levels after an MI must be recognized. One possible disadvantage of the use of cardiac-specific troponins is their long (up to 10 to 14 days) persistence in the serum after release. Thus, if a patient who had an MI several days earlier presents with recurrent ischemic chest discomfort, a single, slightly elevated cardiac-specific troponin measurement may represent either old or new myocardial damage. Serum myoglobin, although less cardiac specific than the troponins, may be helpful in this situation. A negative value suggests that the elevated troponin is related to recent (less than 10 to 14 days) but not acute myocardial damage.

A promising method to both identify and exclude AMI within 6 h of symptoms is to rely on changes (Δ values) in concentrations. Because assays are becoming ever more sensitive and precise, this method permits the identification of significantly increasing values while still in the normal range of assay. Thus, by relying on Δ values, patients without ST-segment elevation can be selected for therapy with GP IIb/IIIa inhibitors, and those with negative Δ values can be considered for early stress testing (112–114).

a. Bedside Testing for Cardiac Markers

Cardiac markers can be measured in the central chemistry laboratory or with point-of-care instruments in the ED with desktop devices or hand-held bedside rapid qualitative assays (83). When a central laboratory is used, results should be available within 60 min, preferably within 30 min. Point-of-care systems, if implemented at the bedside, have the advantage of reducing delays due to transportation and processing in a central laboratory and can eliminate delays due to the lack of availability of central laboratory assays at all hours. These advantages of point-of-care systems must be weighed against the need for stringent quality control and appropriate training of ED personnel in assay performance and the higher costs of point-of-care testing devices relative to determinations in the central laboratory. In addition, these point-of-care assays at present are qualitative or, at best, semiquantitative. The evolution of technology that will provide quantitative assays of multiple markers that are simple to use will improve the diagnosis and management of patients with suspected ACS in the ED. Portable devices are becoming available that allow the simultaneous rapid measurement of myoglobin, CK-MB, and TnI at the point of care (112), and they are likely to be useful in the assessment of patients with ACS.

Table 9. Biochemical Cardiac Markers for the Evaluation and Management of Patients With Suspected ACS but Without ST-Segment Elevation on 12-Lead ECG

Marker	Advantages	Disadvantages	Point of Care Test Available?	Comment	Clinical Recommendation
CK-MB	1. Rapid, cost-efficient, accurate assays 2. Ability to detect early reinfarction	1. Loss of specificity in setting of skeletal muscle disease or injury, including surgery 2. Low sensitivity during very early MI (,6 h after symptom onset) or later after symptom onset (>36 h) and for minor myocardial damage (detectable with troponins)	Yes	Familiar to majority of clinicians	Prior standard and still acceptable diagnostic test in most clinical circumstances
CK-MB isoforms	1. Early detection of MI	1. Specificity profile similar to that of CK-MB 2. Current assays require special expertise	No	Experience to date predominantly in dedicated research centers	Useful for extremely early (3–6 h after symptom onset) detection of MI in centers with demonstrated familiarity with assay technique
Myoglobin	1. High sensitivity 2. Useful in early detection of MI 3. Detection of reperfusion 4. Most useful in ruling out MI	1. Very low specificity in setting of skeletal muscle injury or disease 2. Rapid return to normal range limits sensitivity for later presentations	Yes	More convenient early marker than CK-MB isoforms because of greater availability of assays for myoglobin Rapid-release kinetics make myoglobin useful for noninvasive monitoring of reperfusion in patients with established MI	
Cardiac troponins	1. Powerful tool for risk stratification 2. Greater sensitivity and specificity than CKMB 3. Detection of recent MI up to 2 weeks after onset 4. Useful for selection of therapy 5. Detection of reperfusion	1. Low sensitivity in very early phase of MI (<6 h after symptom onset) and requires repeat measurement at 8–12 h, if negative 2. Limited ability to detect late minor reinfarction	Yes	Data on diagnostic performance and potential therapeutic implications increasingly available from clinical trials	Useful as a single test to efficiently diagnose NSTEMI (including minor myocardial damage), with serial measurements. Clinicians should familiarize themselves with diagnostic "cutoffs" used in their local hospital laboratory

10. Other Markers

Other biochemical markers for the detection of myocardial necrosis are less well studied than those mentioned earlier. Although the available evidence does not support their routine use, these other markers are of scientific interest, and if measured in a patient with chest pain, they may provide useful supportive diagnostic information that can be incorporated into the overall assessment of the likelihood of CAD and the level of risk of the patient for death and cardiac ischemic events.

Markers of activity of the coagulation cascade, including elevated plasma levels of fibrinopeptide (115) and fibrinogen (116), appear to indicate an increased risk in ACS patients.

Given the increasing interest in the hypothesis that destabilization of atherosclerotic plaques may result from inflammatory processes, several groups have evaluated markers of the acute phase of inflammation, such as CRP, serum amyloid A (117), and interleukin-6 in patients with UA. Patients without biochemical evidence of myocardial necrosis but who have an elevated CRP level are at an increased risk of an adverse outcome, especially those whose CRP levels are markedly elevated (e.g., highest quintile in population studies) (118–121). Elevated levels of interleukin-6, the major determinant of acute phase reactant proteins in the liver, and serum amyloid A, another acute phase reactant protein, have been shown to have a similar predictive value of an adverse outcome as CRP (119,121). Increased levels of circulating soluble adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin, in patients with UA are under investigation as markers of increased risk (122).

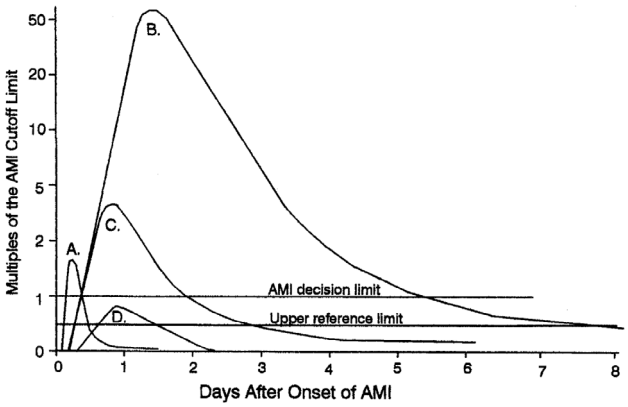


Figure 5. Plot of the appearance of cardiac markers in blood vs. time after onset of symptoms. Peak A, early release of myoglobin or CK-MB isoforms after AMI. Peak B, cardiac troponin after AMI. Peak C, CK-MB after AMI. Peak D, cardiac troponin after UA. Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration. Reprinted with permission from National Academy of Clinical Biochemistry, Washington, DC. Standards of laboratory practice: recommendations for use of cardiac markers in coronary artery disease. November 5, 1999.

C. Immediate Management

Recommendations

Class I

1. **The history, physical examination, 12-lead ECG, and initial cardiac marker 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 definite or possible ACS, but whose initial 12-lead ECG and cardiac marker levels are normal, should be observed in a facility with cardiac monitoring (e.g., chest pain unit), and a repeat ECG and cardiac marker measurement should be obtained 6 to 12 h after the onset of symptoms. (Level of Evidence: B)**
3. **<u>In patients in whom ischemic heart disease is present or suspected,</u> if the follow-up 12-lead ECG and cardiac marker measurements are normal, a stress test (exercise or pharmacological) to provoke ischemia may be performed in the ED, in a chest pain unit, or on an outpatient basis shortly after discharge. Low-risk patients with a negative stress test can be managed as outpatients. (Level of Evidence: C)**
4. **Patients with definite ACS and ongoing pain, positive cardiac markers, 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. (Level of Evidence: C)**
5. **Patients with possible ACS and negative cardiac markers who are unable to exercise or who have an abnormal resting ECG should undergo a pharmacological stress test. (Level of Evidence: B)**
6. **Patients with definite ACS and ST-segment elevation should be evaluated for immediate reperfusion therapy. (Level of Evidence: A)**

By integrating information from the history, physical examination, 12-lead ECG, and initial cardiac marker tests, clinicians can assign patients into 1 of 4 categories: noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS (Fig. 6).

Patients who arrive at a medical facility in a pain-free state, have unchanged or normal ECGs, are hemodynamically stable, and do not have elevated cardiac markers represent more of a diagnostic than an urgent therapeutic challenge. Evaluation begins in these patients by obtaining information from the history, physical examination, and ECG (see Tables 5 and 6) to be used to confirm or reject the diagnosis of UA/NSTEMI.

Patients with a low likelihood of CAD should be evaluated for other causes of the presentation, including musculoskeletal pain; gastrointestinal disorders such as esophageal spasm, gastritis, peptic ulcer disease, or cholecystitis; intrathoracic disease, such as pneumonia, pleurisy, pneumothorax, or pericarditis; and neuropsychiatric disease, such as hyperventilation or panic disorder (Fig. 6, B1). Patients who are found to have evidence of one of these alternative diagnoses should be excluded from management with these guidelines and referred for appropriate follow-up care (Fig. 6, C1). Reassurance should be balanced with instructions to return for further evaluation if symptoms worsen or if the patient fails to respond to symptomatic treatment.

Chronic stable angina may also be diagnosed in this setting (Fig. 6, B2), and patients with this diagnosis should be managed according to the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina (26).

Patients with possible ACS (Fig. 6, B3 and D1) are candidates for additional observation in a specialized facility (e.g., chest pain unit) (Fig. 6, E1). Patients with definite ACS (Fig. 6, B4) are triaged based on the pattern of the 12-lead ECG. Patients with ST-segment elevation (Fig. 6, C3) are evaluated for immediate reperfusion therapy (Fig. 6, D3) and managed according to the ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction (5), whereas those without ST-segment elevation (Fig. 6, C2) are either managed by additional observation (Fig. 6, E1) or admitted to the hospital (Fig. 6, H3). Patients with low-risk ACS (Table 5) without transient ST-segment depressions of greater than or equal to 0.05 mV and/or T-wave inversions of greater than or equal to 0.2 mV, *without* positive cardiac markers, and without a positive stress test (Fig. 6, H1) may be discharged and treated as outpatients (Fig. 6, I1).

1. Chest Pain Units

To facilitate a more definitive evaluation while avoiding the unnecessary hospital admission of patients with possible ACS (Fig. 6, B3) and low-risk ACS (Fig. 6, F1) and the inappropriate discharge of patients with active myocardial

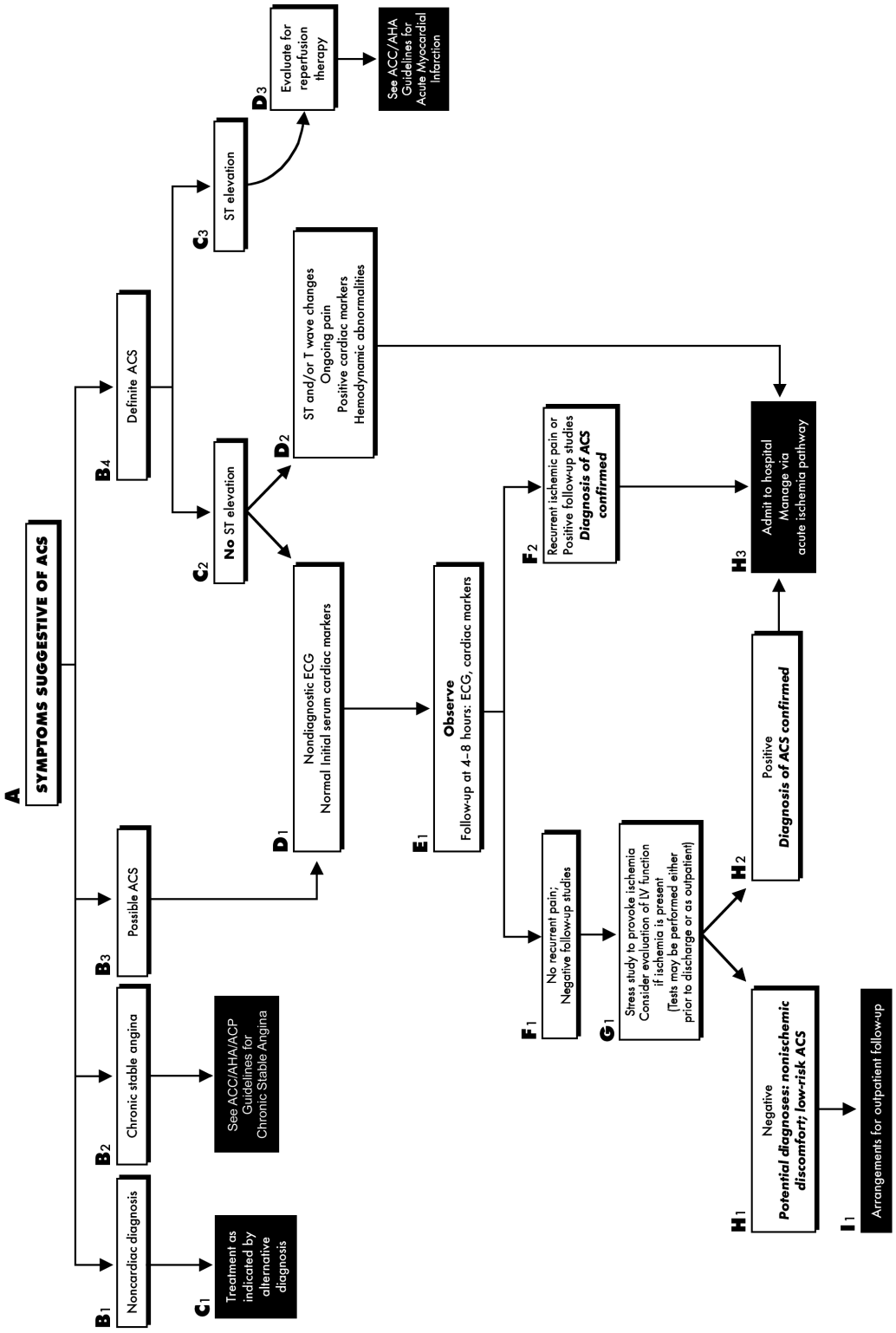


Figure 6. Algorithm for evaluation and management of patients suspected of having ACS. To facilitate interpretation of this algorithm and a more detailed discussion in the text, each box is assigned a letter code that reflects its level in the algorithm and a number that is allocated from left to right across the diagram on a given level.

ischemia without ST-segment elevation (Fig. 6, C2), special units have been devised that are variously referred to as "chest pain units" and "short-stay ED coronary care units." Personnel in these units use critical pathways or protocols designed to arrive at a decision about the presence or absence of myocardial ischemia and, if present, to characterize it further as UA or NSTEMI and to define the optimal next step in the care of the patient (e.g., admission, acute intervention) (123). The goal is to arrive at such a decision after a finite amount of time, which usually is between 6 and 12 h but may extend up to 24 h depending on the policies in individual hospitals. Although chest pain units are useful, other appropriate observation areas in which patients with chest pain can be evaluated may be used as well.

The physical location of the chest pain unit or site where patients with chest pain are observed is variable, ranging from a specifically designated area of the ED to a separate unit with the appropriate equipment (124). Similarly, the chest pain unit may be administratively a part of the ED and staffed by emergency physicians or may be administered and staffed separately. Suggestions for the design of chest pain units have been presented by several authoritative bodies and generally include provisions for continuous monitoring of the patient's ECG, ready availability of cardiac resuscitation equipment and medications, and appropriate staffing with nurses and physicians. Given the evolving nature of the field and the recent introduction of chest pain units into clinical medicine, ACEP has published guidelines that recommend a program for the continuous monitoring of outcomes of patients evaluated in such units as well as the impact on hospital resources (125). A Consensus Panel statement from ACEP emphasized that chest pain units should be considered 1 part of a multifaceted program that also includes efforts to minimize patient delays in seeking medical care and delays in the ED itself (125).

Several groups have studied the impact of chest pain units on the care of patients with chest pain who present to the ED. It has been reported, both from studies with historical controls and from randomized trials, that the use of chest pain units is cost saving compared with an in-hospital evaluation to "rule-out MI" (126,127).

A common clinical practice is to minimize the chance of "missing" an MI in a patient with chest discomfort by admitting to the hospital *all* patients with suspected ACS and by obtaining serial 12-lead ECGs and biochemical cardiac marker measurements to either exclude or confirm the diagnosis of MI. Such a practice typically results in a low percentage of admitted patients actually being confirmed to have an MI. Given the inverse relationship between the percentage of patients with a "rule-out MI evaluation" and the "MI miss rate," the potential cost savings of a chest pain unit varies depending on the practice pattern for the disposition of chest pain patients at individual hospitals (126). Hospitals with a high admission rate of low-risk patients to "rule-out MI" (70% to 80%) will experience the largest cost savings by implementing a chest pain unit approach but will have the smallest impact on the number of missed MI patients. In contrast, hospitals with relatively low admission rates of such patients (30% to 40%) will experience greater improvements in the quality of care because fewer MI patients will be missed but will have a smaller impact on costs because of the low baseline admission rate.

a. Potential Expansion of the Use of Chest Pain Units for Intermediate-Risk Patients

Farkouh et al. (128) extended the use of a chest pain unit in a separate portion of the ED to include patients at an intermediate risk of adverse clinical outcome based on the previously published AHCPR guidelines for the management of UA (1) (Table 6). They reported a 46% reduction in the ultimate need for hospital admission in intermediate-risk patients after a median stay of 9.2 h in the chest pain unit. Extension of the use of chest pain units to intermediate-risk patients in an effort to reduce inpatient costs is facilitated by making available diagnostic testing modalities such as treadmill testing and stress imaging (echocardiographic or nuclear) 7 days a week (129).

b. Triage of Patients

Patients with chest discomfort for whom a specific diagnosis cannot be made after a review of the history, physical examination, initial 12-lead ECG, and biochemical cardiac marker data should undergo a more definitive evaluation. Several categories of patients should be considered according to the algorithm shown in Fig. 6:

- Patients with *possible ACS* (Fig. 6, B3) are those who had a recent episode of chest discomfort at rest not entirely typical of ischemia but are pain free when initially evaluated, have a normal or unchanged ECG, and have no elevations of cardiac markers.
- Patients with a recent episode of typical ischemic discomfort that either is of new onset or severe or exhibits an accelerating pattern of previous stable angina (especially if it has occurred at rest or is within 2 weeks of a previously documented MI) should initially be considered to have a "definite ACS" (Fig. 6, B4). However, such patients may be at a low risk if their ECG obtained at presentation has no diagnostic abnormalities and the initial serum cardiac markers (especially cardiac-specific troponins) are normal (Fig. 6, C2 and D1). As indicated in the algorithm, patients with either "possible ACS" (Fig. 6, B3) or "definite ACS" (Fig. 6, B4) but with nondiagnostic ECG and normal initial cardiac markers (Fig. 6, D1) are candidates for additional observation in the ED or in a specialized area such as a chest pain unit (E1). In contrast, patients who present without ST-segment elevation but have features indicative of active ischemia (ongoing pain, ST-segment and/or T-wave changes, positive cardiac

markers, or hemodynamic instability) (Fig. 6, D2) should be admitted to the hospital (H3).

2. Discharge from ED or Chest Pain Unit

The initial assessment of whether a patient has UA/NSTEMI and which triage option is most suitable generally should be made immediately on the patient's arrival at a medical facility. Rapid assessment of a patient's candidacy for additional observation can be accomplished based on the status of the symptoms, ECG findings, and serum cardiac marker measurements.

Patients who experience recurrent ischemic discomfort, evolve abnormalities on a follow-up 12-lead ECG or cardiac marker measurements, or develop hemodynamic abnormalities such as new or worsening congestive heart failure (CHF) (Fig. 6, D2) should be admitted to the hospital (Fig. 6, H3) and managed as described in Section III.

Patients who are pain free, have either a normal or nondiagnostic ECG or one that is unchanged from previous tracings, and have a normal set of initial cardiac marker measurements are candidates for further evaluation to screen for nonischemic discomfort (Fig. 6, B1) vs. a low-risk ACS (Fig. 6, D1). If the patient is low risk (Table 6) and does not experience any further ischemic discomfort and a follow-up 12-lead ECG and cardiac marker measurements after 6 to 8 h of observation are normal (Fig. 6, F1), the patient may be considered for an early stress test to provoke ischemia (Fig. 6, G1). This test can be performed before the discharge and should be supervised by an experienced physician. Alternatively, the patient may be discharged and return for a stress test as an outpatient within 72 h. The exact nature of the stress test may vary depending on the patient's ability to exercise on either a treadmill or bicycle and the local expertise in a given hospital setting (e.g., availability of different testing modalities at different times of the day or different days of the week) (130). Patients who are capable of exercise and are free of confounding features on the baseline ECG, such as bundle-branch block, LV hypertrophy, or paced rhythms, can be evaluated with routine symptom-limited conventional exercise stress testing. Patients who are incapable of exercise or who have an uninterpretable baseline ECG should be considered for pharmacological stress testing with either nuclear perfusion imaging or two-dimensional echocardiography (46,131). Because LV function is so integrally related to prognosis and heavily affects therapeutic options, strong consideration should be given to the assessment of LV function with echocardiography or radionuclide ventriculography in patients with documented ischemia. In sites at which stress tests are not available, low-risk patients may be discharged and the test scheduled to be carried out within 72 h.

Patients who develop recurrent pain during observation or in whom the follow-up studies (12-lead ECG, cardiac markers) show new abnormalities (Fig. 6, F2) should be admitted to the hospital (Fig. 6, H3).

Because continuity of care is important in the overall management of patients with a chest pain syndrome, the patient's primary physician (if not involved in the care of the patient during the initial episode) should be notified of the results of the evaluation and should receive a copy of the relevant test results. Patients with a noncardiac diagnosis and those with low risk or possible ACS with a negative stress test should be counseled to make an appointment with their primary care physician as outpatients for further investigation into the cause of their symptoms (Fig. 6, I1). They should be seen by a physician within 72 h of discharge from the ED or chest pain unit.

Patients with possible ACS (Fig. 6, B3) and those with a definite ACS but a nondiagnostic ECG and normal biochemical cardiac markers when they are initially seen (Fig. 6, D1) at institutions without a chest pain unit (or equivalent facility) should be admitted to an inpatient unit. The inpatient unit to which such patients are to be admitted should have the same provisions for continuous ECG monitoring, availability of resuscitation equipment, and staffing arrangements as described earlier for the design of chest pain units.

III. HOSPITAL CARE

Patients with UA/NSTEMI, recurrent symptoms and/or ECG ST-segment deviations, or positive cardiac markers who are stable hemodynamically should be admitted to an inpatient unit with continuous rhythm monitoring and careful observation for recurrent ischemia (a step-down unit) and managed according to the acute ischemia pathway (Fig. 7). Patients with continuing discomfort and/or hemodynamic instability should be hospitalized for at least 24 h in a coronary care unit characterized by a nursing-to-patient ratio sufficient to provide 1) continuous rhythm monitoring, 2) frequent assessment of vital signs and mental status, 3) documented ability to perform defibrillation quickly after the onset of ventricular fibrillation, and 4) adequate staff to perform these functions. Patients should be maintained at that level of care until they have been observed for at least 24 h without any of the following major complications: sustained ventricular tachycardia or fibrillation, sinus tachycardia, atrial fibrillation or flutter, high-degree AV block, sustained hypotension, recurrent ischemia documented by symptoms or ST-segment change, new mechanical defect (ventricular septal defect or MR), or CHF.

Once a patient with documented high-risk ACS is admitted, standard medical therapy is indicated as discussed later. Unless a contraindication exists, these patients should be treated with aspirin (ASA), a beta-blocker, antithrombin therapy, and a GP IIb/IIIa inhibitor. Furthermore, critical decisions are required regarding the angiographic strategy. One option is a routine angiographic approach in which coronary angiography and revascularization are performed unless a contraindication exists. Within this approach, the most common strategy has called for a period of medical stabilization. Some physicians are now taking a more aggressive approach, with coronary angiography and revasculariza-

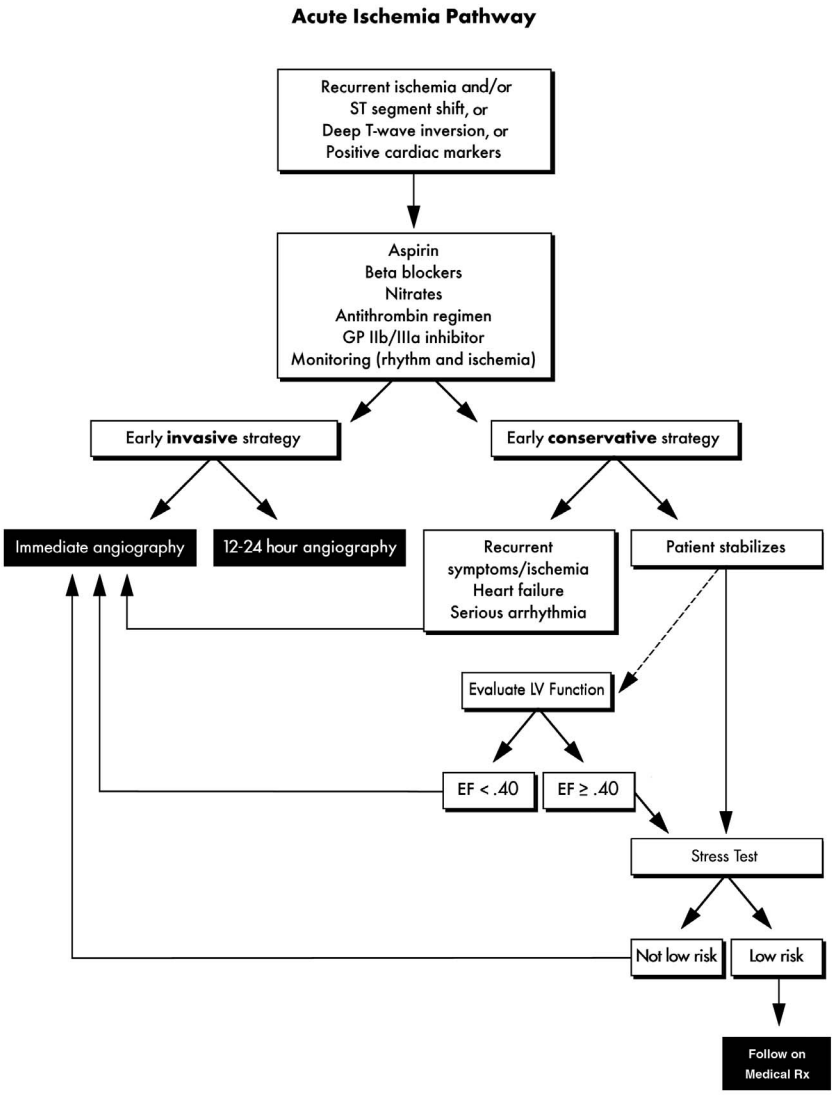


Figure 7. Acute ischemia pathway.

tion performed within 24 h of admission; the rationale for the more aggressive approach is the protective effect of carefully administered antithrombin and antiplatelet therapy on procedural outcome. The alternative approach, commonly referred to as the "initially conservative strategy" (see Section III. D), is guided by ischemia, with angiography reserved for patients with recurrent ischemia or a "high-risk" stress test despite medical therapy. Regardless of the angiographic strategy, an assessment of LV function should be strongly considered in patients with documented ischemia because of the imperative to treat patients who have impaired LV function with angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and beta-blockers and, when the coronary anatomy is appropriate (e.g., 3-vessel coronary disease), with CABG (see Section IV). When the coronary angiogram is obtained, a left ventriculogram can be obtained at the same time. When coronary angiography is not scheduled, echocardiography or nuclear ventriculography can be used to evaluate LV function.

A. Anti-Ischemic Therapy

Recommendations for Anti-Ischemic Therapy

Class I

1. **Bed rest with continuous ECG monitoring for ischemia and arrhythmia detection in patients with ongoing rest pain. (Level of Evidence: C)**
2. **NTG, sublingual tablet or spray, followed by intravenous administration, for the immediate relief of ischemia and associated symptoms. (Level of Evidence: C)**
3. **Supplemental oxygen for patients with cyanosis or respiratory distress; finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation (Sa_{O_2} greater than 90%) and continued need for supplemental oxygen in the presence of hypoxemia. (Level of Evidence: C)**
4. **Morphine sulfate intravenously when symptoms are not immediately relieved with NTG or when acute**

pulmonary congestion and/or severe agitation is present. (Level of Evidence: C)

5. **A beta-blocker, with the first dose administered intravenously if there is ongoing chest pain, followed by oral administration, in the absence of contraindications. (Level of Evidence: B)**
6. **In patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated, a nondihydropyridine calcium antagonist (e.g., verapamil or diltiazem) as initial therapy in the absence of severe LV dysfunction or other contraindications. (Level of Evidence: B)**
7. **An ACEI when hypertension persists despite treatment with NTG and a beta-blocker in patients with LV systolic dysfunction or CHF and in ACS patients with diabetes. (Level of Evidence: B)**

Class IIa

1. **Oral long-acting calcium antagonists for recurrent ischemia in the absence of contraindications and when beta-blockers and nitrates are fully used. (Level of Evidence: C)**
2. **An ACEI for all post-ACS patients. (Level of Evidence: B)**
3. **Intra-aortic balloon pump (IABP) counterpulsation for severe ischemia that is continuing or recurs frequently despite intensive medical therapy or for hemodynamic instability in patients before or after coronary angiography. (Level of Evidence: C)**

Class IIb

1. **Extended-release form of nondihydropyridine calcium antagonists instead of a beta-blocker. (Level of Evidence: B)**
2. **Immediate-release dihydropyridine calcium antagonists in the presence of a beta-blocker. (Level of Evidence: B)**

Class III

1. **NTG or other nitrate within 24 h of sildenafil (Viagra) use. (Level of Evidence: C)**
2. **Immediate-release dihydropyridine calcium antagonists in the absence of a beta-blocker. (Level of Evidence: A)**

The optimal management of UA/NSTEMI has the twin goals of the immediate relief of ischemia and the prevention of serious adverse outcomes (i.e., death or MI/[re]infarction). This is best accomplished with an approach that includes anti-ischemic therapy (Table 10), antiplatelet and antithrombotic therapy (see also Table 14), ongoing risk stratification, and the use of invasive procedures. Patients who are at intermediate or high risk for adverse outcome, including those with ongoing ischemia refractory to initial medical therapy and those with evidence of hemodynamic instability, should if possible be admitted to a critical care environment with ready access to invasive cardiovascular diagnosis and therapy procedures. Ready access is defined as ensured, timely access to a cardiac catheterization laboratory with personnel who have credentials in invasive coronary procedures, as well as to emergency or urgent cardiac surgery, vascular surgery, and cardiac anesthesia (132).

The approach to the achievement of the twin goals described here includes the initiation of pharmacological management and planning of a definitive treatment strategy for the underlying disease process. Most patients are stable at presentation or stabilize after a brief period of intensive pharmacological management and, after appropriate counseling, will be able to participate in the choice of an approach for definitive therapy. A few patients will require prompt triage to emergency or urgent cardiac catheterization and/or the placement of an IABP. Some will prefer the continuation of a medical regimen without angiography. These patients require careful monitoring of the response to initial therapy with noninvasive testing and surveillance for persistent or recurrent ischemia, hemodynamic instability, or other features that may dictate a more invasive approach. Other patients prefer a more invasive strategy that involves early coronary angiography with a view toward revascularization.

1. General Care

The severity of symptoms dictates some of the general care that should be given during the initial treatment. Patients should be placed at bed rest while ischemia is ongoing but can be mobilized to a chair and bedside commode when symptom free. Subsequent activity should not be inappropriately restrictive; instead, it should be focused on the prevention of recurrent symptoms and liberalized as judged appropriate when response to treatment occurs. Patients with cyanosis, respiratory distress, or other high-risk features

Table 10. Class I Recommendations for Anti-Ischemic Therapy in the Presence or Absence of Continuing Ischemia or High-Risk Features*

Continuing Ischemia/Other Clinical High-Risk Features*	
Present	**Absent**
Bed rest with continuous ECG monitoring	
Supplemental O_2 to maintain SaO_2 >90%	
NTG IV	
Beta-blockers, oral or IV	Beta-blockers, oral
Morphine IV for pain, anxiety, pulmonary congestion	
IABP if ischemia or hemodynamic instability persists	
ACEI for control of hypertension or LV dysfunction, after MI	ACEI for control of hypertension or LV dysfunction, after MI

*Recurrent angina and/or ischemia-related ECG changes (greater than or equal to 0.05-mV ST-segment depression or bundle-branch block) at rest or low-level activities; or ischemia associated with CHF symptoms, S_3 gallop, or new or worsening mitral regurgitation; or hemodynamic instability or depressed LV function (EF <0.40 on noninvasive study); or malignant ventricular arrhythmia.

should receive supplemental oxygen. Adequate arterial oxygen saturation should be confirmed with direct measurement or pulse oximetry. No evidence is available to support the administration of oxygen to all patients with ACS in the absence of signs of respiratory distress or arterial hypoxemia. Oxygen use during initial evaluation should be limited to patients with questionable respiratory status or those with documented hypoxemia, because it consumes resources and evidence for its routine use is lacking. Inhaled oxygen should be administered if the arterial oxygen saturation (Sa_{O_2}) declines to less than 90%. Finger pulse oximetry is useful for the continuous monitoring of Sa_{O_2} but is not mandatory in patients who do not appear to be at risk of hypoxia. Patients should undergo continuous ECG monitoring during their ED evaluation and early hospital phase, because sudden, unexpected ventricular fibrillation is the major preventable cause of death in this early period. Furthermore, monitoring for the recurrence of ST-segment shifts provides useful diagnostic and prognostic information, although the system of monitoring for ST-segment shifts must include specific methods intended to provide stable and accurate recordings.

2. Use of Anti-Ischemic Drugs

a. Nitrates

NTG reduces myocardial oxygen demand while enhancing myocardial oxygen delivery. NTG, an endothelium-independent vasodilator, has both peripheral and coronary vascular effects. By dilating the capacitance vessels (i.e., the venous bed), it increases venous pooling to decrease myocardial preload, thereby reducing ventricular wall tension, a determinant of myocardial oxygen consumption (MVO_2). More modest effects on the arterial circulation decrease systolic wall stress (afterload), contributing to further reductions in MVO_2. This decrease in myocardial oxygen demand is in part offset by reflex increases in heart rate and contractility, which counteract the reductions in MVO_2 unless a beta-blocker is concurrently administered. NTG dilates normal and atherosclerotic epicardial coronary arteries as well as smaller arteries that constrict with certain stressors (e.g., cold, mental or physical exercise). With severe atherosclerotic coronary obstruction and with less severely obstructed vessels with endothelial dysfunction, physiological responses to changes in myocardial blood flow are often impaired (i.e., loss of flow-mediated dilation), so maximal dilation does not occur unless a direct-acting vasodilator like NTG is administered. Thus, NTG promotes the dilation of large coronary arteries as well as collateral flow and redistribution of coronary blood flow to ischemic regions. Inhibition of platelet aggregation also occurs with NTG (133), but the clinical significance of this action is not well defined.

Patients whose symptoms are not relieved with three 0.4-mg sublingual NTG tablets or spray taken 5 min apart (Table 11) and the initiation of an intravenous beta-blocker (when there are no contraindications), as well as all nonhypotensive high-risk patients (Table 6), may benefit from intravenous NTG, and such therapy is recommended in the absence of contraindications (i.e., the use of sildenafil [Viagra] within the previous 24 h or hypotension). Sildenafil inhibits the phosphodiesterase (PDE5) that degrades cyclic guanosine monophosphate (cGMP), and cGMP mediates vascular smooth muscle relaxation by nitric oxide. Thus, NTG-mediated vasodilatation is markedly exaggerated and prolonged in the presence of sildenafil. Nitrate use within 24 h after sildenafil or the administration of sildenafil in a patient who has received a nitrate within 24 h has been associated with profound hypotension, MI, and even death (134).

Intravenous NTG may be initiated at a rate of 10 mcg per min through continuous infusion with nonabsorbing tubing and increased by 10 mcg per min every 3 to 5 min until some symptom or blood pressure response is noted. If no response is seen at 20 mcg per min, increments of 10 and, later, 20 mcg per min can be used. If symptoms and signs of ischemia are relieved, there is no need to continue to increase the dose to effect a blood pressure response. If symptoms and signs of ischemia are not relieved, the dose should be increased until a blood pressure response is observed. Once a partial blood pressure response is observed, the dosage increase should be reduced and the interval between increments should be lengthened. Side effects include headache and hypotension. Caution should be used when systolic blood pressure falls to less than 110 mm Hg in previously normotensive patients or to greater than 25% below the starting mean arterial blood pressure if hypertension was present. Although recommendations for a maximal dose are not available, a ceiling of 200 mcg per min is commonly used. Prolonged (2 to 4 weeks) infusion at 300 to 400 mcg per h does not increase methemoglobin levels (135).

Topical or oral nitrates are acceptable alternatives for patients without ongoing refractory symptoms. Tolerance to the hemodynamic effects of nitrates is dose and duration dependent and typically becomes important after 24 h of continuous therapy with any formulation. Patients who require continued intravenous NTG beyond 24 h may require periodic increases in infusion rate to maintain efficacy. An effort must be made to use non–tolerance-producing nitrate regimens (lower dose and intermittent dosing). When patients have been free of pain and other manifestations of ischemia for 12 to 24 h, an attempt should be made to reduce the dose of intravenous NTG and to switch to oral or topical nitrates. It is not appropriate to continue intravenous NTG in patients who remain free of signs and symptoms of ischemia. When ischemia recurs during continuous intravenous NTG therapy, responsiveness to nitrates can often be restored by increasing the dose and then, after symptoms have been controlled for several hours, attempting to add a nitrate-free interval. This strategy should be pursued as long as symptoms are not adequately controlled. In stabilized patients, intravenous NTG should generally be converted within 24 h to a nonparenteral alternative (Table 11) administered in a non–tolerance-producing regimen to avoid the potential reactivation of symptoms.

Most studies of nitrate treatment in UA have been small and uncontrolled, and there are no randomized, placebo-con-

Table 11. NTG and Nitrates in Angina

Compound	Route	Dose/Dosage	Duration of Effect
NTG	Sublingual tablets	0.3–0.6 mg up to 1.5 mg	1–7 minutes
	Spray	0.4 mg as needed	Similar to sublingual tablets
	Transdermal	0.2–0.8 mg/h every 12 h	8–12 h during intermittent therapy
	Intravenous	5–200 mcg/min	Tolerance in 7–8 h
Isosorbide dinitrate	Oral	5–80 mg, 2 or 3 times daily	Up to 8 h
	Oral, slow release	40 mg 1 or 2 times daily	Up to 8 h
Isosorbide mononitrate	Oral	20 mg twice daily	12–24 h
	Oral, slow release	60–240 mg once daily	
Pentaerythritol tetranitrate	Sublingual	10 mg as needed	Not known
Erythritol tetranitrate	Sublingual	5–10 mg as needed	Not known
	Oral	10–30 mg 3 times daily	Not known

Adapted from Table 28 in 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.

trolled trials that address either symptom relief or reduction in cardiac events. One small, randomized trial compared intravenous NTG with buccal NTG and found no significant difference in the control of ischemia (136). An overview of small studies of NTG in AMI from the prethrombolytic era suggested a 35% reduction in mortality rates (137), although both the Fourth International Study of Infarct Survival (ISIS-4) (138) and Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3) (139) trials formally tested this hypothesis in patients with suspected AMI and failed to confirm this magnitude of benefit. However, these large trials are confounded by frequent prehospital and hospital use of NTG in the "control" groups. The abrupt cessation of intravenous NTG has been associated with exacerbation of ischemic changes on the ECG (140), and a graded reduction in the dose of intravenous NTG is advisable.

Thus, the rationale for NTG use in UA is extrapolated from pathophysiological principles and extensive, although uncontrolled, clinical observations (133).

b. Morphine Sulfate

Morphine sulfate (1 to 5 mg intravenously [IV]) is recommended for patients whose symptoms are not relieved after 3 serial sublingual NTG tablets or whose symptoms recur despite adequate anti-ischemic therapy. Unless contraindicated by hypotension or intolerance, morphine may be administered along with intravenous NTG, with careful blood pressure monitoring, and may be repeated every 5 to 30 min as needed to relieve symptoms and maintain patient comfort.

Morphine sulfate has potent analgesic and anxiolytic effects, as well as hemodynamic effects that are potentially beneficial in UA/NSTEMI. No randomized trials have defined the unique contribution of morphine to the initial therapeutic regimen or its optimal administration schedule. Morphine causes venodilation and may produce modest reductions in heart rate (through increased vagal tone) and systolic blood pressure to further reduce myocardial oxygen demand. The major adverse reaction to morphine is an exaggeration of its therapeutic effect, causing hypotension, especially in the presence of volume depletion and/or vasodilator therapy. This reaction usually responds to supine or Trendelenburg positioning or intravenous saline boluses and atropine when accompanied by bradycardia; it rarely requires pressors or naloxone to restore blood pressure. Nausea and vomiting occur in approximately 20% of patients. Respiratory depression is the most serious complication of morphine; severe hypoventilation that requires intubation occurs very rarely in patients with UA/NSTEMI treated with this agent. Naloxone (0.4 to 2.0 mg IV) may be administered for morphine overdose with respiratory and/or circulatory depression. Meperidine hydrochloride can be substituted in patients who are allergic to morphine.

c. Beta-Adrenergic Blockers

Beta-blockers competitively block the effects of catecholamines on cell membrane beta-receptors. $Beta_1$-adrenergic receptors are located primarily in the myocardium; inhibition of catecholamine action at these sites reduces myocardial contractility, sinus node rate, and AV node conduction velocity. Through this action, they blunt the heart rate and contractility responses to chest pain, exertion, and other stimuli. They also decrease systolic blood pressure. All of these effects reduce MVO_2. $Beta_2$-adrenergic receptors are located primarily in vascular and bronchial smooth muscle; the inhibition of catecholamine action at these sites produces vasoconstriction and bronchoconstriction (141). In UA/NSTEMI, the primary benefits of beta-blockers are due to effects on $beta_1$-adrenergic receptors that decrease cardiac work and myocardial oxygen demand. Slowing of the heart rate also has a very favorable effect, acting not only to reduce MVO_2 but also to increase the duration of diastole and diastolic pressure-time, a determinant of coronary flow and collateral flow.

Beta-blockers should be started early in the absence of contraindications. These agents should be administered intravenously followed by oral administration in high-risk

patients as well as in patients with ongoing rest pain or orally for intermediate- and low-risk patients (Table 6).

The choice of beta-blocker for an individual patient is based primarily on pharmacokinetic and side effect criteria, as well as on physician familiarity (Table 12). There is no evidence that any member of this class of agents is more effective than another, except that beta-blockers *without* intrinsic sympathomimetic activity are preferable. The initial choice of agents includes metoprolol, propranolol, or atenolol. Esmolol can be used if an ultrashort-acting agent is required.

Patients with marked first-degree AV block (i.e., ECG PR interval [PR] of greater than 0.24 s), any form of second- or third-degree AV block in the absence of a functioning pacemaker, a history of asthma, or severe LV dysfunction with CHF should not receive beta-blockers on an acute basis (26). Patients with significant sinus bradycardia (heart rate less than 50 bpm) or hypotension (systolic blood pressure less than 90 mm Hg) generally should not receive beta-blockers until these conditions have resolved. Patients with significant COPD who may have a component of reactive airway disease should be administered beta-blockers very cautiously; initially, low doses of a $beta_1$-selective agent should be used. If there are concerns about possible intolerance to beta-blockers, initial selection should favor a short-acting $beta_1$-specific drug such as metoprolol. Mild wheezing or a history of COPD mandates a short-acting cardioselective agent at a reduced dose (e.g., 2.5 mg metoprolol IV or 12.5 mg metoprolol orally or 25 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} esmolol IV as initial doses) rather than the complete avoidance of a beta-blocker.

In the absence of these concerns, several regimens may be used. For example, intravenous metoprolol may be given in 5-mg increments by slow intravenous administration (5 mg over 1 to 2 min), repeated every 5 min for a total initial dose of 15 mg. In patients who tolerate the total 15 mg IV dose, oral therapy should be initiated 15 min after the last intravenous dose at 25 to 50 mg every 6 h for 48 h. Thereafter, patients should receive a maintenance dose of 100 mg twice daily. Alternatively, intravenous propranolol is administered as an initial dose of 0.5 to 1.0 mg, followed in 1 to 2 h by 40 to 80 mg by mouth every 6 to 8 h. Intravenous esmolol is administered as a starting dose of 0.1 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} with titration in increments of 0.05 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} every 10 to 15 min as tolerated by the patient's blood pressure until the desired therapeutic response has been obtained, limiting symptoms develop, or a dosage of 0.3 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} is reached. A loading dose of 0.5 mg per kg may be given by slow intravenous administration (2 to 5 min) for a more rapid onset of action. In patients suitable to receive a longer-acting agent, intravenous atenolol can be initiated with a 5-mg IV dose followed 5 min later by a second 5-mg IV dose and then 50 to 100 mg per day orally initiated 1 to 2 h after the intravenous dose. Monitoring during intravenous beta-blocker therapy should include frequent checks of heart rate and blood pressure and continuous ECG monitoring, as well as auscultation for rales and bronchospasm.

After the initial intravenous load, patients without limiting side effects may be converted to an oral regimen. The target resting heart rate is 50 to 60 bpm, unless a limiting side effect is reached. Selection of the oral agent should be based on the clinician's familiarity with the agent. Maintenance doses are given in Table 12.

Initial studies of beta-blocker benefits in ACS were small and uncontrolled. An overview of double-blind, randomized trials in patients with threatening or evolving MI suggests an approximately 13% reduction in the risk of progression to AMI (142). These trials lack sufficient power to assess the effects of these drugs on mortality rates for UA. However, randomized trials with other CAD patients (AMI, recent MI, stable angina with daily life ischemia, and heart failure) have all shown reductions in mortality and/or morbidity rates. Thus, the rationale for beta-blocker use in all forms of CAD, including UA, is very compelling and in the absence of contraindications is sufficient to make beta-blockers a routine part of care, especially in patients who are to undergo cardiac or noncardiac surgery.

In conclusion, evidence for the beneficial effects of the use of beta-blockers in patients with UA is based on limited randomized trial data, along with pathophysiological considerations and extrapolation from experience with CAD patients

Table 12. Properties of Beta-Blockers in Clinical Use

Drug	Selectivity	Partial Agonist Activity	Usual Dose for Angina
Propranolol	None	No	20–80 mg twice daily
Metoprolol	$Beta_1$	No	50–200 mg twice daily
Atenolol	$Beta_1$	No	50–200 mg/d
Nadolol	None	No	40–80 mg/d
Timolol	None	No	10 mg twice daily
Acebutolol	$Beta_1$	Yes	200–600 mg twice daily
Betaxolol	$Beta_1$	No	10–20 mg/d
Bisoprolol	$Beta_1$	No	10 mg/d
Esmolol (intravenous)	$Beta_1$	No	50–300 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1}
Labetalol*	None	Yes	200–600 mg twice daily
Pindolol	None	Yes	2.5–7.5 mg 3 times daily

*Labetalol is a combined alpha- and beta-blocker.
Adapted from Table 25 in 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.

who have other types of ischemic syndromes (stable angina, AMI, or heart failure). The recommendation for the use of intravenous beta-blockers in high-risk patients with evolving pain is based on the demonstrated benefit in AMI patients, as well as the hemodynamic objectives to reduce cardiac work and myocardial oxygen demand. The duration of benefit with long-term oral therapy is uncertain.

d. Calcium Antagonists

These agents reduce cell transmembrane inward calcium flux, which inhibits both myocardial and vascular smooth muscle contraction; some also slow AV conduction and depress sinus node impulse formation. Agents in this class vary in the degree to which they produce vasodilation, decreased myocardial contractility, AV block, and sinus node slowing. Nifedipine and amlodipine have the most peripheral arterial dilatory effect but little or no AV or sinus node effects, whereas verapamil and diltiazem have prominent AV and sinus node effects and some peripheral arterial dilatory effects as well. All 4 of these agents, as well as the newer agents, have coronary dilatory properties that appear to be similar. Although different members of this class of agents are structurally diverse and may have somewhat different mechanisms of action, no reliable data demonstrate the superiority of 1 agent (or groups of agents) over another in ACS, except for the risks posed by rapid-release, short-acting dihydropyridines (Table 13). Beneficial effects in ACS are believed to be due to variable combinations of decreased myocardial oxygen demand that relate to decreased afterload, contractility, and heart rate and improved myocardial flow that relates to coronary artery and arteriolar dilation (141,143). These agents also have theoretical beneficial effects on LV relaxation and arterial compliance. Major side effects include hypotension, worsening CHF, bradycardia, and AV block.

Calcium antagonists may be used to control ongoing or recurring ischemia-related symptoms in patients who are already receiving adequate doses of nitrates and beta-blockers, in patients who are unable to tolerate adequate doses of 1 or both of these agents, or in patients with variant angina (see Section VI. F). In addition, these drugs have been used for the management of hypertension in patients with recurrent UA (143). Rapid-release, short-acting dihydropyridines (e.g., nifedipine) *must be avoided* in the absence of adequate concurrent beta-blockade in ACS because controlled trials suggest increased adverse outcomes (144–146). Verapamil and diltiazem should be avoided in patients with pulmonary edema or evidence of severe LV dysfunction (147,148). Amlodipine and felodipine, however, appear to be well tolerated by patients with chronic LV dysfunction (149). The choice of an individual calcium antagonist is based primarily on the type of agent; the hemodynamic state of the patient; the risk of adverse effects on cardiac contractility, AV conduction, and sinus node function; and the physician's familiarity with the specific agent. Trials in patients with acute CAD suggest that verapamil and diltiazem are preferred if a calcium antagonist is needed (148,149).

There are several randomized trials that involve the use of calcium antagonists in ACS. Results generally confirm that these agents relieve or prevent symptoms and related ischemia to a degree similar to that of beta-blockers. The largest randomized trial is the Danish Study Group on Verapamil in Myocardial Infarction (DAVIT) (150,151), in which 3447 patients with suspected ACS were administered intravenous verapamil (0.1 mg per kg) at admission and then 120 mg 3 times daily vs. placebo. After 1 week, verapamil was discontinued in the patients (n = 2011) without con-

Table 13. Properties of Calcium Antagonists in Clinical Use

Drug	Usual Dose	Duration of Action	Side Effects
Dihydropyridines			
Nifedipine	Immediate release: 30–90 mg daily orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
	Slow release: 30–180 mg orally		
Amlodipine	5–10 mg once daily	Long	Headache, edema
Felodipine	5–10 mg once daily	Long	Headache, edema
Isradipine	2.5–10 mg twice daily	Medium	Headache, fatigue
Nicardipine	20–40 mg 3 times daily	Short	Headache, dizziness, flushing, edema
Nisoldipine	20–40 mg once daily	Short	Similar to nifedipine
Nitrendipine	20 mg once or twice daily	Medium	Similar to nifedipine
Miscellaneous			
Bepridil	200–400 mg once daily	Long	Arrhythmias, dizziness, nausea
Diltiazem	Immediate release: 30–80 mg 4 times daily	Short	Hypotension, dizziness, flushing, bradycardia, edema
	Slow release: 120–320 mg once daily	Long	
Verapamil	Immediate release: 80–160 mg 3 times daily	Short	Hypotension, myocardial depression, heart failure, edema, bradycardia
	Slow release: 120–480 mg once daily	Long	

Reprinted from Table 27 in 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.

firmed MI (presumably many of these patients had UA). Although there was no definitive evidence to suggest benefit (or harm) in this cohort, trends favored a reduction in the outcome of death or nonfatal MI. In the Holland Interuniversity Nifedipine/metoprolol Trial (HINT), nifedipine and metoprolol were tested in a 2 × 2 factorial design in 515 patients (146). Nifedipine alone *increased* the risk of MI or recurrent angina relative to placebo by 16%, metoprolol decreased it by 24%, and the combination of metoprolol and nifedipine reduced this outcome by 20%. None of these effects, however, were statistically significant because the study was stopped early because of concern for harm with the use of nifedipine alone. However, in patients already taking a beta-blocker, the addition of nifedipine appeared favorable because the event rate was reduced significantly (risk ratio [RR] 0.68) (152). Several meta-analyses that combined all of the calcium antagonists used in UA trials suggested no overall effect (142,153). However, in light of the aforementioned differences between the rapid-release dihydropyridines and the heart rate–slowing agents diltiazem and verapamil, such analyses are not appropriate. When the data for verapamil are considered alone, a beneficial effect in patients with ACS is apparent (150).

Similarly, in the Diltiazem Reinfarction Study (DRS), 576 patients were administered diltiazem or placebo 24 to 72 h after the onset of non–Q-wave MI (145). Diltiazem was associated with a reduction in CK-MB level–confirmed reinfarction and refractory angina at 14 days without a significant increase in mortality rates. Retrospective analysis of the non–Q-wave MI subset of patients in the Multicenter Diltiazem Postinfarction Trial (MDPIT) suggested similar findings without evidence of harm (154).

However, retrospective analyses of DAVIT and MDPIT suggested that the administration of verapamil and diltiazem to suspected AMI patients who have LV dysfunction (many of whom had UA/NSTEMI) may have an overall *detrimental* effect on mortality rates (145,147). Although this caution is useful for clinical practice, more recent data suggest that this issue should be readdressed. For example, in DAVIT-2, verapamil was associated with a significant reduction in diuretic use compared with placebo (155), suggesting that it did not further impair LV function. Furthermore, recent prospective trials with verapamil administered to AMI patients with heart failure who were receiving an ACEI strongly suggest benefit (147,156). The Diltiazem as Adjunctive Therapy to Activase (DATA) trial also suggests that intravenous diltiazem in AMI patients may be safe; death, MI, or recurrent ischemia decreased by 14% at 35 days and death, MI, or refractory ischemia decreased by 23% at 6 months (157). These pilot data were confirmed in 874 AMI patients without heart failure in whom long-acting diltiazem (300 mg per day) was administered 36 to 96 h after thrombolysis (158) (W.E. Boden, oral presentation, American Heart Association Scientific Sessions, Dallas, Texas, November 1998).

In conclusion, definitive evidence for benefit with all calcium antagonists in UA is predominantly limited to symptom control. For dihydropyridines, available randomized trial data are not consistent with a beneficial effect on mortality or recurrent infarction rates but in fact provide strong evidence for an increase in these serious events when they are administered early as a rapid-release, short-acting preparation without a beta-blocker. Thus, these guidelines recommend reservation of the dihydropyridine calcium antagonists as second or third choices after the initiation of nitrates and beta-blockers. For the heart rate–slowing drugs (verapamil and diltiazem), there is no controlled trial evidence for harm when they are administered early to patients with acute ischemic syndromes, and strong trends suggest a beneficial effect. Therefore, when beta-blockers cannot be used, heart rate–slowing calcium antagonists offer an alternative. When required for refractory symptom control, these agents can be used early during the hospital phase, even in patients with mild LV dysfunction, although the combination of a beta-blocker and calcium antagonist may act in synergy to depress LV function. The risks and benefits in UA of amlodipine and other newer agents relative to the older agents in this class reviewed here remain undefined.

e. Other

ACEIs have been shown to reduce mortality rates in patients with AMI or who recently had an MI and have LV systolic dysfunction (159–161,161a), in diabetic patients with LV dysfunction (162), and in a broad spectrum of patients with high-risk chronic CAD, <u>including patients with normal LV function</u> (163). Accordingly, ACEIs should be used in such patients as well as in those with hypertension that is not controlled with beta-blockers and nitrates.

Other less extensively studied techniques for the relief of ischemia, such as spinal cord stimulation (164) and prolonged external counterpulsation (165,166), are under evaluation. Most experience has been gathered with spinal cord stimulation in “intractable angina” (167), in which anginal relief has been described.

The KATP channel openers have hemodynamic and cardioprotective effects that could be useful in UA/NSTEMI. Nicorandil is such an agent that is approved in a number of countries but not yet in the United States. In a pilot double-blind, placebo-controlled study of 245 patients with UA, the addition of this drug to conventional treatment significantly reduced the number of episodes of transient myocardial ischemia (mostly silent) and of ventricular and supraventricular tachycardia (168). Further evaluation of this class of agents is under way.

B. Antiplatelet and Anticoagulation Therapy

Recommendations for Antiplatelet and Anticoagulation Therapy

~~**Class I**~~

~~**1. Antiplatelet therapy should be initiated promptly. Aspirin is the first choice and is administered as soon as possible after presentation and is continued indefi-**~~

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

~~2. A thienopyridine (clopidogrel or ticlopidine) should be administered to patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (Level of Evidence: B)~~

~~3. Parenteral anticoagulation with intravenous unfractionated heparin (UFH) or with subcutaneous LMWH should be added to antiplatelet therapy with ASA, or a thienopyridine. (Level of Evidence: B)~~

~~4. A platelet GP IIb/IIIa receptor antagonist should be administered, in addition to ASA and UFH, to patients with continuing ischemia or with other high-risk features (Table 6) and to patients in whom a PCI is planned. Eptifibatide and tirofiban are approved for this use. (Level of Evidence: A) Abciximab can also be used for 12 to 24 h in patients with UA/NSTEMI in whom a PCI is planned within the next 24 h. (Level of Evidence: A)~~

Class I

1. **Antiplatelet therapy should be initiated promptly. ASA should be administered as soon as possible after presentation and continued indefinitely. (Level of Evidence: A)**
2. **Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (Level of Evidence: A)**
3. **In hospitalized patients in whom an early noninterventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month (Level of Evidence: A) and for up to 9 months (Level of Evidence: B).**
4. **In patients for whom a PCI is planned, clopidogrel should be started and continued for at least 1 month (Level of Evidence: A) and up to 9 months in patients who are not at high risk for bleeding (Level of Evidence: B).**
5. **In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld for 5 to 7 days. (Level of Evidence: B).**
6. **Anticoagulation with subcutaneous LMWH or intravenous unfractionated heparin (UFH) should be added to antiplatelet therapy with ASA and/or clopidogrel. (Level of Evidence: A)**
7. **A platelet GP IIb/IIIa antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (Level of Evidence: A)**

Class IIa

1. **Eptifibatide or tirofiban should be administered, in addition to ASA and LMWH or UFH, to patients *with* continuing ischemia, an elevated troponin or with other high-risk features in whom an invasive management strategy is *not* planned. (Level of Evidence: A)**
2. **Enoxaparin is preferable to UFH as an anticoagulant in patients with UA/NSTEMI, unless CABG is planned within 24 h. (Level of Evidence: A)**
3. **A platelet GP IIb/IIIa antagonist should be administered to patients already receiving heparin, ASA, *and clopidogrel* in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (Level of Evidence: B)**

Class IIb

Eptifibatide or tirofiban, in addition to ASA and LMWH or UFH, to patients *without* continuing ischemia who have no other high-risk features and in whom PCI is *not* planned. (Level of Evidence: A)

~~**Class III**~~

~~**Intravenous thrombolytic therapy in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block (LBBB). (Level of Evidence: A)**~~

Class III

1. **Intravenous fibrinolytic therapy in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block (LBBB). (Level of Evidence: A)**
2. **Abciximab administration in patients in whom PCI is not planned. (Level of Evidence: A)**

Antithrombotic therapy is essential to modify the disease process and its progression to death, MI, or recurrent MI. A combination of ASA, UFH, and a platelet GP IIb/IIIa receptor antagonist represents the most effective therapy. The intensity of treatment is tailored to individual risk, and triple antithrombotic treatment is used in patients with continuing ischemia or with other high-risk features and in patients oriented to an early invasive strategy (Table 14). Table 15 shows the recommended doses of the various agents. An LMWH can be advantageously substituted for UFH, although experience with the former in PCI, in patients referred for urgent CABG, and in combination with a GP IIb/IIIa antagonist and with a thrombolytic agent is limited. In the ESSENCE (169) and TIMI 11B trials (170,171) in UA and NSTEMI, enoxa-

Table 14. Class I Recommendations for Antithrombotic Therapy*

Possible ACS	Likely/Definite ACS	Definite ACS With Continuing Ischemia or Other High-Risk Features† or Planned Intervention
Aspirin	Aspirin + Subcutaneous LMWH *or* IV heparin	Aspirin + IV heparin + IV platelet GP IIb/IIIa antagonist

*Clinical data on the combination of LMWH and platelet GP IIb/IIIa antagonists are lacking. Their combined use is not currently recommended.

†High-risk features are listed in Table 6; others include diabetes, recent MI, and elevated TnT or TnI.

Table 15. Clinical Use of Antithrombotic Therapy

Oral Antiplatelet Therapy	
Aspirin	Initial dose of 162–325 mg nonenteric formulation followed by 75–160 mg/d of an enteric or a nonenteric formulation
Clopidogrel (Plavix)	75 mg/d; a loading dose of 4–8 tablets (300–600 mg) can be used when rapid onset of action is required
Ticlopidine ((Ticlid)	250 mg twice daily; a loading dose of 500 mg can be used when rapid onset of inhibition is required; monitoring of platelet and white cell counts during treatment is required
Heparins	
Dalteparin (Fragmin)	120 IU/kg subcutaneously every 12 h (maximum 10,000 IU twice daily)
Enoxaparin (Lovenox)	1 mg/kg subcutaneously every 12 h; the first dose may be preceded by a 30-mg IV bolus
Heparin (UFH)	Bolus 60–70 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U $\cdot$ kg^{-1} $\cdot$ h^{-1} (maximum 1000 U/h) titrated to aPTT 1.5–2.5 times control
Intravenous Antiplatelet Therapy	
Abciximab (ReoPro)	0.25 mg/kg bolus followed by infusion of 0.125 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} (maximum 10 mcg/min) for 12 to 24 h
Eptifibatide (Integrilin)	180 mcg/kg bolus followed by infusion of 2.0 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} for 72 to 96 h*
Tirofiban (Aggrastat)	0.4 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} for 30 minutes followed by infusion of 0.1 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} for 48 to 96 h*

*Different dose regimens were tested in recent clinical trials before percutaneous interventions.

parin was stopped 6 to 12 h before a planned percutaneous procedure or surgery and UFH was substituted. Trials are now under way to test the safety and efficacy of enoxaparin in patients undergoing PCI and of enoxaparin and dalteparin combined with a GP IIb/IIIa antagonist and with a lytic agent. A pilot double-blind, randomized study of 55 patients compared the combination of tirofiban and enoxaparin with the combination of tirofiban and UFH. The results suggested more reproducible inhibition of platelet aggregation with enoxaparin and less prolongation in bleeding time. There was an excess of minor bleeding with enoxaparin but not of major bleeding (172). Furthermore, there may be problems in rapid reversal of the anticoagulation when required, such as before CABG.

1. Antiplatelet Therapy (Aspirin, Ticlopidine, Clopidogrel)

a. Aspirin

Some of the strongest evidence available about the long-term prognostic effects of therapy in patients with coronary disease pertains to ASA (173). By irreversibly inhibiting cyclooxygenase-1 within platelets, ASA prevents the formation of thromboxane A2, thereby diminishing platelet aggregation promoted by this pathway but not by others. This platelet inhibition is the plausible mechanism for clinical benefit of ASA because it is fully present with low doses of ASA and because platelets represent one of the principal participants in thrombus formation after plaque disruption. Alternative or additional mechanisms of action for ASA are possible, such as an anti-inflammatory effect (174), but they are unlikely at the low doses of ASA that are effective in UA/NSTEMI.

Among all clinical investigations with ASA, trials in UA/NSTEMI have most consistently documented a striking benefit of the drug independent of the differences in study design, such as time of entry after the acute phase, duration of follow-up, and doses used (175–178) (Fig. 8).

No trial has directly compared the efficacy of different doses of ASA in patients who present with UA/NSTEMI. However, trials in secondary prevention of stroke, MI, death, and graft occlusion have not shown an added benefit for ASA doses of greater than 80 and 160 mg per d but have shown a higher risk of bleeding. An overview of trials with different doses of ASA in long-term treatment of patients with CAD suggests similar efficacy for daily doses ranging from 75 to 324 mg (173). A dose of 160 mg per d was used in the Second International Study of Infarct Survival (ISIS-2) trial, which definitively established the efficacy of ASA in suspected MI (185). It therefore appears reasonable to initiate ASA treatment in patients with UA/NSTEMI at a dose of 160 mg, as used in the ISIS-2 trial, or 325 mg. In patients who present with suspected ACS who are not already receiving ASA, the first dose may be chewed to rapidly establish a high blood level. Subsequent doses may be swallowed. Thereafter, daily doses of 75 to 325 mg are prescribed.

The prompt action of ASA and its ability to reduce mortality rates in patients with suspected AMI enrolled in the ISIS-2 trial led to the recommendation that ASA be initiated immediately in the ED as soon as the diagnosis of ACS is made or suspected. In patients who are already receiving ASA, it should be continued. The protective effect of ASA has been sustained for at least 1 to 2 years in clinical trials in UA. Longer-term follow-up data in this population are lacking. Given the relatively short-term prognostic impact of UA/NSTEMI in patients with coronary disease, long-term efficacy can be extrapolated from other studies of ASA therapy in CAD. Studies in patients with prior MI, stroke, or transient ischemic attack have shown statistically significant benefit during the first 2 years and some additional but not statistically significant benefit during the third year (173). In

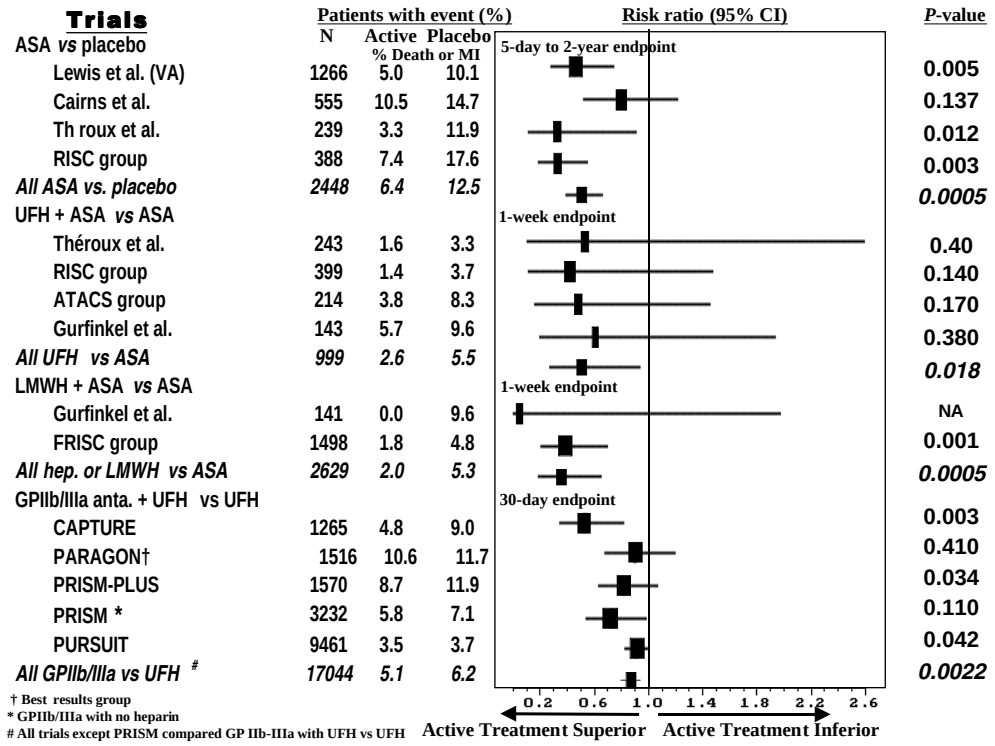


Figure 8. Summary of trials of antithrombotic therapy in UA. Meta-analysis of randomized trials in UA/NSTEMI that have compared ASA with placebo, the combination of UFH and ASA with ASA alone, the combination of an LMWH and ASA with ASA alone, and the combination of a platelet GP IIb/IIIa antagonist (anta.), UFH (hep.), and ASA with UFH plus ASA. The RR values, 95% CIs, and probability value for each trial are shown. The timing of the end point (death or MI) varied. Results with the platelet GP IIb/IIIa antagonists are reported at the 30-day time point. Incremental gain is observed from single therapy with ASA to double therapy with ASA and UFH and to triple antithrombotic therapy with ASA, UFH, and a platelet GP IIb/IIIa antagonist. In the CAPTURE trial, nearly all patients underwent PCI after 20 to 24 h per study design. From PURSUIT (10), PRISM-PLUS (21), Lewis et al. (175), Cairns et al. (176), Théroux et al. (177), RISC group (178), ATACS group (179), Gurfinkel et al. (180), FRISC group (181), CAPTURE (182), PARAGON (183), and PRISM (184).

the absence of large comparison trials of different durations of antiplatelet treatment in patients with cardiovascular disease or in primary prevention, it seems prudent to continue ASA indefinitely unless side effects are present (5,26,173). Thus, patients should be informed of the evidence that supports the use of ASA in UA/NSTEMI and CAD in general and instructed to continue the drug indefinitely, unless a contraindication develops.

Contraindications to ASA include intolerance and allergy (primarily manifested as asthma), active bleeding, hemophilia, active retinal bleeding, severe untreated hypertension, an active peptic ulcer, or another serious source of gastrointestinal or genitourinary bleeding. Gastrointestinal side effects such as dyspepsia and nausea are infrequent with the low doses. Acute gout due to impaired urate excretion is rarely precipitated. Primary prevention trials have reported a small excess in intracranial bleeding, which is offset in secondary prevention trials by the prevention of ischemic stroke. It has been proposed that there is a negative interaction between ACEIs and ASA with a reduction in the vasodilatory effects of ACEIs, presumably because ASA inhibits ACEI-induced prostaglandin synthesis. This interaction does not appear to interfere with the clinical benefits of therapy with either agent (186). Therefore, unless there are specific contraindications, ASA should be administered to all patients with UA/NSTEMI.

b. Adenosine Diphosphate Receptor Antagonists and Other Antiplatelet Agents

Two thienopyridines—ticlopidine and clopidogrel—are adenosine diphosphate (ADP) antagonists that are currently approved for antiplatelet therapy (187). The platelet effects of ticlopidine and clopidogrel are irreversible but take several days to become completely manifest. Because the mechanisms of the antiplatelet effects of ASA and ADP antagonists differ, a potential exists for additive benefit with the combination.

Ticlopidine has been used successfully for the secondary prevention of stroke and MI and for the prevention of stent closure and graft occlusion. In an open-label trial (188), 652 patients with UA were randomized to receive 250 mg of ticlopidine twice a day or standard therapy without ASA. At 6-month follow-up, ticlopidine reduced the rate of fatal and nonfatal MI by 46% (13.6% vs. 7.3%, p = 0.009). The benefit of ticlopidine in the study developed after only 2 weeks of treatment, which is consistent with the delay of the drug to achieve full effect.

The adverse effects of ticlopidine limit its usefulness: gastrointestinal problems (diarrhea, abdominal pain, nausea, vomiting), neutropenia in approximately 2.4% of patients, severe neutropenia in 0.8% of patients, and, rarely, thrombotic thrombocytopenia purpura (TTP) (189). Neutropenia

usually resolves within 1 to 3 weeks of discontinuation of therapy but very rarely may be fatal. TTP, which also is a very uncommon life-threatening complication, requires immediate plasma exchange. Monitoring of ticlopidine therapy requires a complete blood count that includes a differential count every 2 weeks for the first 3 months of therapy.

Most clinical experience with clopidogrel is derived from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial (190). A total of 19,185 patients were randomized to receive 325 mg per day ASA or 75 mg per day clopidogrel. Entry criteria consisted of atherosclerotic vascular disease manifested as recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease. Follow-up extended for 1 to 3 years. The RR of ischemic stroke, MI, or vascular death was reduced by 8.7% in favor of clopidogrel from 5.83% to 5.32% (p = 0.043). There was a slightly increased, but minimal, incidence of rash and diarrhea with clopidogrel treatment and slightly more bleeding with ASA. There was no excess neutropenia with clopidogrel, which contrasts with ticlopidine. The results provide evidence that clopidogrel is at least as effective as ASA and may be modestly more effective. In a recent report, 11 severe cases of TTP were described as occurring within 14 days after the initiation of clopidogrel; plasma exchange was required in 10 of the patients, and 1 patient died (191). These cases occurred among more than 3 million patients treated with clopidogrel.

Ticlopidine or clopidogrel is reasonable antiplatelet therapy for secondary prevention with an efficacy at least similar to that of ASA. These drugs are indicated in patients with UA/NSTEMI who are unable to tolerate ASA due to either hypersensitivity or major gastrointestinal contraindications, principally recent significant bleeding from a peptic ulcer or gastritis. Care must be taken during the acute phase with these drugs because of the delays required to achieve a full antiplatelet effect. Clopidogrel is preferred to ticlopidine because it more rapidly inhibits platelets and appears to have a more favorable safety profile. Experience is being acquired with this drug in acute situations with a loading dose (300 mg) to achieve more rapid platelet inhibition. Initial treatment with heparin (UFH or LMWH) and probably with a GP IIb/IIIa antagonist is especially important in patients with UA/NSTEMI who are treated with 1 of the thienopyridines because of their delayed onset of antiplatelet activity compared with ASA.

Two randomized trials were recently completed in which clopidogrel was compared with ticlopidine. In 1 study, 700 patients who successfully received a stent were randomized to receive 500 mg of ticlopidine or 75 mg of clopidogrel, in addition to 100 mg of ASA, for 4 weeks (192). Cardiac death, urgent target vessel revascularization, angiographically documented thrombotic stent occlusion, or nonfatal MI within 30 days occurred in 3.1% of patients who received clopidogrel and 1.7% of patients who received ticlopidine (p = 0.24), and noncardiac death, stroke, severe peripheral vascular hemorrhagic events, or any adverse event that resulted in the discontinuation of the study medication occurred in 4.5% and 9.6% of patients, respectively (p = 0.01). The CLopidogrel ASpirin Stent International Cooperative Study (CLASSICS) (P. Urban, A.H. Gershlick, H.-J. Rupprecht, M.E. Bertrands, oral presentation, American Heart Association Scientific Sessions, Atlanta, Ga, November 1999) was conducted in 1,020 patients. A loading dose of 300 mg of clopidogrel followed by 75 mg per day was compared to a daily dose of 75 mg without a loading dose and with a loading dose of 150 mg of ticlopidine followed by 150 mg twice a day (patients in each of the 3 arms also received ASA). The first dose was administered 1 to 6 h after stent implantation; the treatment duration was 28 days. The trial showed better tolerance to clopidogrel with or without a loading dose than to ticlopidine. Stent thrombosis or major complications occurred at the same frequency in the 3 groups. ~~The regimen of a loading dose (300 mg) followed by the maintenance dose (75 mg/d) is used in the ongoing large Clopidogrel in Unstable angina to Prevent ischemic Events (CURE) trial, which compares the combination of clopidogrel and ASA with ASA alone in patients with UA/NSTEMI.~~

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. All patients received aspirin. Cardiovascular death, MI, or stroke occurred in 11.5% of patients assigned to placebo and 9.3% assigned to clopidogrel (RR = 0.80, p less than 0.001). In addition, clopidogrel was associated with significant reductions in the rate of inhospital severe ischemia and revascularization, as well as the need for thrombolytic therapy or intravenous GP IIb/IIIa receptor antagonists. These results were observed across a wide variety of subgroups. A reduction in recurrent ischemia was noted within the first few hours after randomization.

There was an excess of major bleeding (2.7% in the placebo group vs. 3.7% in the clopidogrel group, p = 0.003) as well as of minor but not of life-threatening bleeding. The risk of bleeding was increased in patients undergoing CABG surgery within the first 5 days of stopping clopidogrel. CURE was conducted at centers in which there was no routine policy of early invasive procedures; revascularization was performed during the initial admission in only 23% of the patients. Although the addition of a platelet GP IIb/IIIa inhibitor in patients receiving ASA, clopidogrel, and heparin in CURE was well tolerated, fewer than 10% of patients received this combination. Therefore, additional information on the safety of the addition of heparin (LMWH or UFH) and a GP IIb/IIIa inhibitor in patients already receiving ASA and clopidogrel should be obtained. Also, it is not yet clear whether clopidogrel improved the outcome in patients who received GP IIb/IIIa antagonists.

This trial provides strong evidence for the addition of clopidogrel to ASA on admission in the management of patients with UA and NSTEMI, in whom a noninterventional approach is intended—an especially useful approach in hospitals that do not have a routine policy of early invasive pro-

cedures. The optimal duration of therapy with clopidogrel has not been determined, but the favorable results in CURE were observed over a period averaging 9 months.

In the PCI-CURE study, 2,658 patients undergoing PCI had been randomly assigned double-blind treatment with clopidogrel (n = 1,313) or placebo (n = 1,345). Patients were pretreated with aspirin and the study drug for a median of 10 days. After PCI, most patients received open-label thienopyridine for about 4 weeks, after which the study drug was restarted for a mean of 8 months. Fifty-nine patients (4.5%) in the clopidogrel group had the primary end point—a composite of cardiovascular death, MI, or urgent target-vessel revascularization—within 30 days of PCI compared with 86 (6.4%) in the placebo group (relative risk 0.70 [95% Confidence Interval {CI} 0.50-0.97], p = 0.03). Overall (including events before and after PCI), there was a 31% reduction in cardiovascular death or MI (p = 0.002). Thus, in patients with UA and NSTEMI receiving ASA and undergoing PCI, a strategy of clopidogrel pretreatment followed by at least 1 month and probably longer-term therapy is beneficial in reducing major cardiovascular events compared with placebo (522). Therefore, clopidogrel should be used routinely in patients who undergo PCI.

There now appears to be an important role for clopidogrel in patients with UA/NSTEMI, both those who are managed conservatively as well as those who undergo PCI, especially stenting. However, it is not entirely clear how long therapy should be maintained. Since clopidogrel, when added to ASA, increases the risk of bleeding during major surgery in patients who are scheduled for elective CABG, clopidogrel should be withheld for at least 5 days (521), and preferably for 7 days before surgery (523). In many hospitals in which patients with UA/NSTEMI undergo diagnostic catheterization within 24 to 36 h of admission, clopidogrel is not started until it is clear that CABG will *not* be scheduled within the next several days. A loading dose of clopidogrel can be given to a patient on the catheterization table if a PCI is to be carried out immediately. If PCI is not carried out, the clopidogrel can be begun after the catheterization.

Sulfinpyrazone, dipyridamole, prostacyclin, and prostacyclin analogs have not been associated with benefit in UA or NSTEMI and are not recommended. The thromboxane synthase blockers and thromboxane A2 receptor antagonists have been evaluated in ACS but have not shown any advantage over ASA. A number of other antiplatelet drugs are currently available, and still others are under active investigation. Oral GP IIb/IIIa receptor blockers were tested in 1 PCI trial and 3 UA/NSTEMI trials; the 4 trials failed to document a benefit and 2 showed an excess mortality rate (193,193a,193b).

~~ASA plus an intravenous GP IIb/IIIa antagonist remains the reference standard for antiplatelet therapy in patients with UA/NSTEMI who are at higher risk. Ticlopidine is not recommended during the acute phase because it takes several days to achieve its maximal antiplatelet effect.~~

Clopidogrel is the preferred thienopyridine because of its more rapid onset of action, especially after a loading dose (524,525) and better safety profile than ticlopidine (526).

2. Anticoagulants

Anticoagulants available for parenteral use include UFH, various LMWHs, and hirudin, and for oral use, the antivitamin K drugs are available. Synthetic pentasaccharides and synthetic direct thrombin inhibitors (argatroban, bivaluridine) as well as oral direct and indirect thrombin inhibitors are under clinical investigation. Hirudin is approved as an anticoagulant in patients with heparin-induced thrombocytopenia and for the prophylaxis of deep vein thrombosis after hip replacement.

Heparin exerts its anticoagulant effect by accelerating the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, and factor Xa. It prevents thrombus propagation but does not lyse existing thrombi (194). UFH is a heterogeneous mixture of chains of molecular weights that range from 5,000 to 30,000 and have varying effects on anticoagulant activity. UFH binds to a number of plasma proteins, blood cells, and endothelial cells. The LMWHs are obtained through chemical or enzymatic depolymerization of the polysaccharide chains of heparin to provide chains with different molecular weight distributions. About 25% to 50% of the pentasaccharide-containing chains of LMWH preparations contain greater than 18 saccharide units, and these are able to inactivate both thrombin and factor Xa. However, LMWH chains that are less than 18 saccharide units retain their ability to inactivate factor Xa but not thrombin. Therefore, LMWHs are relatively more potent in the catalyzation of the inhibition of factor Xa by antithrombin than in the inactivation of thrombin. Distinct advantages of LMWH over UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance with a longer half-life that results in more predictable and sustained anticoagulation with once- or twice-a-day subcutaneous administration. A major advantage of LMWHs is that they do not usually require laboratory monitoring of activity. The pharmacodynamic and pharmacokinetic profiles of the different commercial preparations of LMWHs vary, with their mean molecular weights ranging from 4,200 to 6,000. Accordingly, their ratios of anti–Xa factor to anti–IIa factor vary, ranging from 1.9 to 3.8 (195).

By contrast, the direct thrombin inhibitors very specifically block thrombin effects without the need for a cofactor such as antithrombin. Hirudin binds directly to the anion binding site and the catalytic sites of thrombin to produce potent and predictable anticoagulation (196). Several large trials (see later) that compare hirudin with UFH in UA/NSTEMI have demonstrated a modest short-term reduction in the composite end point of death or nonfatal MI with a modest increase in the risk of bleeding.

Bivalurudin (Hirulog) is a synthetic analog of hirudin that binds reversibly to thrombin. It has been compared with UFH in several small trials in UA/NSTEMI and in PCI with some

evidence of a reduction in death or MI and less bleeding than with UFH (197–199).

a. Unfractionated Heparin

Seven randomized, placebo-controlled trials with UFH have been reported (200–205). A placebo-controlled study performed by Théroux et al. (177) between 1986 and 1988 tested treatments that consisted of ASA and a 5,000-U IV bolus of UFH followed by 1,000 U per h in a 2 × 2 factorial design. UFH reduced the risk of MI by 89% and the risk of recurrent refractory angina by 63%. An extension of this study compared ASA and UFH in UA patients. MI (fatal or nonfatal) occurred in 3.7% of patients who received ASA and 0.8% of patients who received UFH ($p = 0.035$) (202).

The Research Group in Instability in Coronary Artery Disease (RISC) trial was a double-blind, placebo-controlled trial with a 2 × 2 factorial design that was conducted in men with UA or NSTEMI (178). ASA significantly reduced the risk of death or MI. UFH alone had no benefit, although the group treated with the combination of ASA and UFH had the lowest number of events during the initial 5 days. Neri-Seneri et al. (203) suggested that symptomatic and silent episodes of ischemia in UA could be prevented by an infusion of UFH but not by bolus injections or by ASA. Taken together, these trials indicate that the early administration of UFH is associated with a reduction in the incidence of AMI and ischemia in patients with UA/NSTEMI.

The results of the studies that have compared the combination of ASA and heparin with ASA alone are shown in Fig. 8. In the trials that used UFH, the reduction in the rate of death or MI during the first week was 54% ($p = 0.016$), and in the trials that used either UFH or LMWH, the reduction was 63%. Two published meta-analyses have included different studies. In 1 meta-analysis, which involved 3 randomized trials and an early end point (less than 5 days) (179), the risk of death or MI with the combination of ASA and heparin was reduced by 56% ($p = 0.03$). In the second meta-analysis, which involved 6 trials and end points that ranged from 2 to 12 weeks, the RR was reduced by 33% ($p = 0.06$) (206). Most of the benefits of the various anticoagulants are short term, however, and not maintained on a long-term basis. Reactivation of the disease process after the discontinuation of anticoagulants may contribute to this loss of early gain that has been described with UFH (207), dalteparin (181), and hirudin (208,209). The combination of UFH and ASA appears to mitigate this reactivation in part (207,210), although there is hematologic evidence of increased thrombin activity after the cessation of intravenous UFH even in the presence of ASA (211). Uncontrolled observations suggested a reduction in the "heparin rebound" by switching from intravenous to subcutaneous UFH for several days before the drug is stopped.

UFH has important pharmacokinetic limitations that are related to its nonspecific binding to proteins and cells. These pharmacokinetic limitations of UFH translate into poor bioavailability, especially at low doses, and marked variability in anticoagulant response among patients (212). As a consequence of these pharmacokinetic limitations, the anticoagulant effect of heparin requires monitoring with the activated partial thromboplastin time (aPTT), a test that is sensitive to the inhibitory effects of UFH on thrombin (factor IIa), factor Xa, and factor IXa. Many clinicians have traditionally prescribed a fixed initial dose of UFH (e.g., 5,000-U bolus, 1,000 U per h initial infusion); clinical trials have indicated that a weight-adjusted dosing regimen could provide more predictable anticoagulation than the fixed-dose regimen (213–215). The weight-adjusted regimen is recommended with an initial bolus of 60 to 70 U per kg (maximum 5,000 U) and an initial infusion of 12 to 15 $U \cdot kg^{-1} \cdot h^{-1}$·(maximum 1,000 U per h). The therapeutic range of the various nomograms differs due to variation in the laboratory methods used to determine aPTT. The American College of Chest Physicians consensus conference (212) has therefore recommended dosage adjustments of the nomograms to correspond to a therapeutic range equivalent to heparin levels of 0.3 to 0.7 U per mL by anti–factor Xa determinations, which correlates with aPTT values between 60 and 80 s. In addition to body weight, other clinical factors that affect the response to UFH include age, which is associated with higher aPTT values, and smoking history and diabetes mellitus, which are associated with lower aPTT values (212,216).

Thus, even though weight-based UFH dosing regimens are used, the aPTT should be monitored for adjustment of UFH dosing. Because of variation among hospitals in the control aPTT values, nomograms should be established at each institution that are designed to achieve aPTT values in the target range (e.g., for a control aPTT of 30 s, the target range [1.5 to 2.5 times control] would be 45 to 75 s). Measurements should be made 6 h after any dosage change and used to adjust UFH infusion until the aPTT exhibits a therapeutic level. When 2 consecutive aPTT values are therapeutic, the measurements may be made every 24 h and, if necessary, dose adjustment carried out. In addition, a significant change in the patient's clinical condition (e.g., recurrent ischemia, bleeding, hypotension) should prompt an immediate aPTT determination, followed by dose adjustment, if necessary.

Serial hemoglobin/hematocrit and platelet measurements are recommended at least daily during UFH therapy. In addition, any clinically significant bleeding, recurrent symptoms, or hemodynamic instability should prompt their immediate determination. Serial platelet counts are necessary to monitor for heparin-induced thrombocytopenia. Mild thrombocytopenia may occur in 10% to 20% of patients who are receiving heparin, whereas severe thrombocytopenia (platelet count less than 100,000) occurs in 1% to 2% of patients and typically appears after 4 to 14 days of therapy. A rare but dangerous complication (less than 0.2% incidence) is autoimmune UFH-induced thrombocytopenia with thrombosis (217). A high clinical suspicion mandates the immediate cessation of all heparin therapy (including that used to flush intravenous lines).

Most of the trials that evaluate the use of UFH in UA/NSTEMI have continued therapy for 2 to 5 days. The optimal duration of therapy remains undefined.

b. Low-Molecular-Weight Heparin

In a pilot open-label study, 219 patients with UA were randomized to receive ASA (200 mg per d), ASA plus UFH, or ASA plus nadroparin, an LMWH. The combination of ASA and LMWH significantly reduced the total ischemic event rate, the rate of recurrent angina, and the number of patients requiring interventional procedures (180).

The FRISC study (181) randomized 1,506 patients with UA or non–Q-wave MI to receive subcutaneous administration of the LMWH dalteparin (120 IU per kg twice daily) or placebo for 6 days and then once a day for the next 35 to 45 days. Dalteparin was associated with a 63% risk reduction in death or MI during the first 6 days (4.8% vs. 1.8%, p = 0.001), matching the favorable experience observed with UFH. Although an excess of events was observed after the dose reduction to once daily after 6 days, a significant decrease was observed at 40 days with dalteparin in the composite outcome of death, MI, or revascularization (23.7% vs. 18.0%, p = 0.005), and a trend was noted in a reduction in rates of death or MI (10.7% vs. 8.0%, p = 0.07).

Because the level of anticoagulant activity cannot be easily measured in patients receiving LMWH (e.g., aPTT or activated clotting time [ACT]), interventional cardiologists have expressed concern about the substitution of LMWH for UFH in patients scheduled for catheterization with possible PCI. However, Collett et al. (527) showed in a study involving 293 patients with UA/NSTEMI who received the usual dose of enoxaparin that PCI can be performed safely.

In the National Investigators Collaborating on Enoxaparin Trial (NICE-1), an observational study, intravenous enoxaparin (1.0 mg per kg) was used in 828 patients undergoing elective PCI (528) without an intravenous GP IIb/IIIa inhibitor. The rate of bleeding (1.1% for major bleeding and 6.2% for minor bleeding in 30 days) was comparable to historical controls given UFH.

An alternative approach is to use LMWH during the period of initial stabilization. The dose can be withheld on the morning of the procedure, and if an intervention is required and more than 8 hours has elapsed since the last dose of LMWH, UFH can be used for PCI according to usual practice patterns. Because the anticoagulant effect of UFH can be more readily reversed than that of LMWH, UFH is preferred in patients likely to undergo CABG within 24 h.

c. LMWH Versus UFH

Four large randomized trials have directly compared an LMWH with UFH (Fig. 9). In the FRagmin In unstable Coronary artery disease (FRIC) study, 1482 patients with UA/NSTEMI received open-label dalteparin (120 IU per kg subcutaneously twice a day) or UFH for 6 days (218). At day 6 and until day 45, patients were randomized a second time

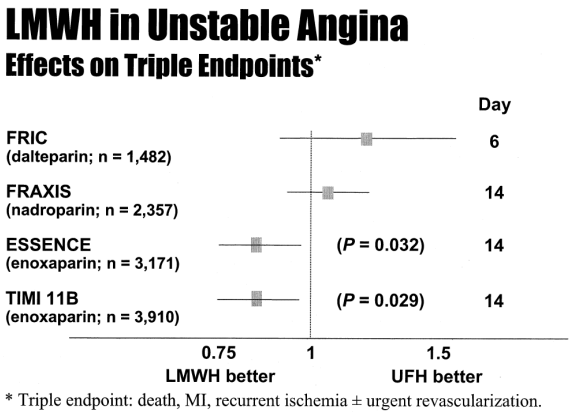


Figure 9. The use of LMWH in UA showing effects on the triple end points of death, MI, and recurrent ischemia with or without revascularization. Early (6-day) and intermediate outcomes of the 4 trials that compared LMWH and UFH: ESSENCE (169), TIMI 11B (170), FRIC (218), and FRAXIS (219). Nadroparine in FRAXIS was given for 14 days.

to double-blind administration of dalteparin (120 IU per kg once a day) or placebo. During the first part of the study, the risk of death, MI, or recurrent angina was nonsignificantly *increased* with dalteparin (9.3% vs. 7.65%, p = 0.33), and the risk of death or MI was unaffected (3.9% vs. 3.6%, p = 0.8); death also tended to occur more frequently with dalteparin (1.5% vs. 0.4% with UFH, p = 0.057). Between days 6 and 45, the rates of death, MI, and recurrence of angina were comparable between the active treatment and placebo groups.

The ESSENCE trial (169) compared enoxaparin (1 mg per kg twice daily subcutaneous administration) with standard UFH (5,000 U bolus), followed by an infusion titrated to an aPTT of 55 to 86 s, administered for 48 h to 8 days (median duration in both groups of 2.6 days) (169). With UFH, only 46% of patients reached the target aPTT within 12 to 24 h. The composite outcome of death, MI, or recurrent angina was reduced by 16.2% at 14 days with enoxaparin (19.8% UFH vs. 16.6% enoxaparin, p = 0.019) and by 19% at 30 days (23.3% vs. 19.8%, p = 0.017). The rates of death were unaffected, whereas there were trends to reductions in the rates of death and MI by 29% (p = 0.06) at 14 days and by 26% (p = 0.08) at 30 days.

The TIMI 11B trial randomized 3,910 patients with UA/NSTEMI to enoxaparin (30 mg IV initial bolus immediately followed by subcutaneous injections of 1 mg per kg every 12 h) or UFH (70 U per kg bolus followed by an infusion of 15 $U \cdot kg^{-1} \cdot h^{-1}$ titrated to a target aPTT 1.5 to 2.5 times control) (170). The acute phase therapy was followed by an outpatient phase, during which enoxaparin or placebo for patients who were initially randomized to UFH was administered in a double-blind manner twice a day. Enoxaparin was administered for a median of 4.6 days, and UFH was administered for a median of 3.0 days. The composite end point of death, MI, or need for an urgent revascularization (defined as an episode of recurrent angina prompt-

ing the performance of coronary revascularization during the index hospitalization or after discharge leading to rehospitalization and coronary revascularization) was reduced at 8 days from 14.5% to 12.4% (p = 0.048) and at 43 days from 19.6% to 17.3% (p = 0.048). The rates of death or MI were reduced from 6.9% to 5.7% (p = 0.114) at 14 days and from 8.9% to 7.9% (p = 0.276) at 43 days. No incremental benefit was observed with outpatient treatment, whereas the risk of major bleeding was significantly greater during the outpatient treatment. The risk of minor bleeding was also increased both in and out of hospital with enoxaparin.

The FRAXiparine in Ischaemic Syndrome (FRAXIS) trial had 3 parallel arms and compared the LMWH nadroparin administered for 6 or 14 days with control treatment with UFH (219). Three thousand four hundred sixty-eight patients with UA or NSTEMI were enrolled. The composite outcome of death, MI, or refractory angina occurred at 14 days in 18.1% of patients in the UFH group, 17.8% of patients treated with nadroparin for 6 days, and 20.0% of patients treated with nadroparin for 14 days; the values at 3 months were 22.2%, 22.3%, and 26.2% of patients, respectively (p less than 0.03 for the comparison of 14-day nadroparin therapy with UFH therapy). Trends to more frequent death and to more frequent death or MI were observed at all time points in nadroparin-treated patients.

Thus, 2 trials with enoxaparin have shown a moderate benefit over UFH, and 2 trials (1 with dalteparin and 1 with nadroparin) showed neutral or unfavorable trends. Whether the heterogeneous results are explained by different populations, study designs, various heparin dose regimens, properties of the various LMWHs (more specifically different molecular weights and anti–factor Xa/anti–factor IIa ratios), or other unrecognized influences is a matter of speculation. A meta-analysis of the 2 trials with enoxaparin that involved a total of 7,081 patients showed a statistically significant reduction of approximately 20% in the rate of death, MI, or urgent revascularization at 2, 8, 14, and 43 days and in the rate of death or MI at 8, 14, and 43 days. At 8, 14, and 43 days, there was a trend toward a reduction in death as well (171).

Although it is tempting to compare the relative treatment effects of the different LMWH compounds in Fig. 9, the limitations of such indirect comparisons must be recognized. The only reliable method of comparing 2 treatments is through a direct comparison in a well-designed clinical trial or series of trials. The comparison of different therapies (e.g., different LMWHs) with a common therapy (e.g., UFH) in different trials does not allow a conclusion to be made about the relative effectiveness of the different LMWHs because of the variability in both control group and experimental group event rates due to protocol differences, differences in concomitant therapies due to geographical and time variability, and the play of chance. Similar considerations apply to comparisons among platelet GP IIb/IIIa inhibitors.

<u>However, in the Enoxaparin Versus Tinzaparin (EVET) trial, 2 LMWHs, enoxaparin and tinzaparin, administered for 7 days were compared in 438 patients with UA/NSTEMI. A preliminary report stated that both the recurrence of UA and the need for revascularization were significantly lower in the enoxaparin group (529).</u> The advantages of LMWH preparations are the ease of subcutaneous administration and the absence of a need for monitoring. Furthermore, the LMWHs stimulate platelets less than UFH (220) and are less frequently associated with heparin-induced thrombocytopenia (221). They are associated with more frequent *minor, but not major,* bleeding. In the ESSENCE trial, minor bleeding occurred in 11.9% of enoxaparin patients and 7.2% of UFH patients (p less than 0.001), and major bleeding occurred in 6.5% and 7.0%, respectively. In TIMI 11B, the rates of *minor* bleeding in hospital were 9.1% and 2.5%, respectively (p less than 0.001), and the rates of *major* bleeding were 1.5% and 1.0% (p = 0.143). In the FRISC study, major bleeding occurred in 0.8% of patients with dalteparin and in 0.5% of patients with placebo, and minor bleeding occurred in 8.2% (61 of 746 patients) and 0.3% (2 of 760 patients) of patients, respectively. The anticoagulation provided with LMWH is less effectively reversed with protamine than it is with UFH. In addition, LMWH administered during PCI does not permit monitoring of the ACT to titrate the level of anticoagulation. In the ESSENCE and TIMI 11B trials, special rules were set to discontinue enoxaparin before PCI and CABG. UFH was administered during PCI to achieve ACT values of greater than 350 s. An economic analysis of the ESSENCE trial suggested cost savings with enoxaparin (222). <u>For patients who are receiving subcutaneous LMWH and in whom CABG is planned, it is recommended that LMWH be discontinued and UFH be used during the operation.</u> Additional experience with regard to the safety and efficacy of the concomitant administration of LMWHs with GP IIb/IIIa antagonists and thrombolytic agents is currently being acquired.

The FRISC, FRIC, TIMI 11B, and Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) trials evaluated the potential benefit of the prolonged administration of an LMWH after hospital discharge. The first 3 of these trials did *not* show a benefit of treatment beyond the acute phase. In the FRISC trial, doses of dalteparin were administered between 6 days and 35 to 45 days; in FRIC, patients were rerandomized after the initial 6-day treatment period to receive dalteparin for an additional 40 days; and the outpatient treatment period lasted 5 to 6 weeks in TIMI 11B and 1 week in the FRAXIS trial. The FRISC II trial used a different study design. Dalteparin was administered to all patients for a minimum of 5 days (223). Patients were subsequently randomized to receive placebo or the continued administration of dalteparin twice a day for up to 90 days. Analysis of the results from the time of randomization showed a significant reduction with dalteparin in the composite end point of death or MI at 30 days (3.1% vs. 5.9%, p = 0.002) but not at 3 months (6.7% vs. 8.0%, p = 0.17). The composite of death, MI, or revascularization during the total treatment period was reduced at 3 months (29.1% vs. 33.4%, p = 0.031). The benefits of prolonged dalteparin administration were limited to patients who were managed medically and to patients with elevated TnT levels at baseline. These

results may make a case for the prolonged use of an LMWH in selected patients who are managed medically or in whom angiography is delayed.

d. Hirudin and Other Direct Thrombin Inhibitors

Hirudin, the prototype of the direct thrombin inhibitors, has been extensively studied. The GUSTO-IIb trial randomly assigned 12,142 patients to 72 h of therapy with either intravenous hirudin or UFH (224). Patients were stratified according to the presence of ST-segment elevation on the baseline ECG (4131 patients) or its absence (8011 patients). The primary end point of death, nonfatal MI, or reinfarction at 30 days occurred in 9.8% of the UFH group vs. 8.9% of the hirudin group (odds ratio [OR] 0.89, p = 0.058). For patients without ST-segment elevation, the rates were 9.1% and 8.3%, respectively (OR 0.90, p = 0.22). At 24 h, the risk of death or MI was significantly lower in the patients who received hirudin than in those who received UFH (2.1% vs. 1.3%, p = 0.001). However, the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial of hirudin as adjunctive therapy to thrombolytic therapy in patients with STEMI showed no benefit of the drug over UFH either during study drug infusion or later (225). The GUSTO-IIb and TIMI 9B trials used hirudin doses of 0.1 mg per kg bolus and 0.1 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} infusion for 3 to 5 days after the documentation of excess bleeding with the higher doses used in the GUSTO-IIA and TIMI 9A trials (0.6 mg per kg bolus and 0.2 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} infusion) (224,226).

The Organization to Assess Strategies for Ischemic Syndromes (OASIS) program evaluated hirudin in patients with UA or non–Q-wave MI. OASIS 1 (227) was a pilot trial of 909 patients that compared the low hirudin dose of 0.1 mg per h infusion and the medium hirudin dose of 0.15 mg per h infusion with UFH. The latter dose provided the best results, with a reduction in the rate of death, MI, or refractory angina at 7 days (6.5% with UFH vs. 3.3% with hirudin, p = 0.047). This medium dose was used in the large OASIS 2 (228) trial that consisted of 10,141 patients with UA/NSTEMI who were randomized to receive UFH (5000 IU bolus plus 15 U $\cdot$ kg^{-1} $\cdot$ h^{-1}) or recombinant hirudin (0.4 mg per kg bolus and 0.15 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) infusion for 72 h. The primary end point of cardiovascular death or new MI at 7 days occurred in 4.2% in the UFH group vs. 3.6% patients in the hirudin group (RR 0.84, p = 0.064). A secondary end point of cardiovascular death, new MI, or refractory angina at 7 days was significantly reduced with hirudin (6.7% vs. 5.6%, RR 0.83, p = 0.011). There was an excess of major bleeds that required transfusion with hirudin (1.2% vs. 0.7% with heparin, p = 0.014) but no excess in life-threatening bleeds or strokes. A meta-analysis of the GUSTO-IIB, TIMI 9B, OASIS 1, and OASIS 2 trials showed risks of death or MI at 35 days relative to heparin after randomization of 0.90 (p = 0.015) with hirudin compared with UFH; RR values were 0.88 (p = 0.13) for patients receiving thrombolytic agents and 0.90 (p = 0.054) for patients not receiving thrombolytic agents (228). At 72 h, the RR values of death or MI were 0.78 (p = 0.003), 0.89 (p = 0.34), and 0.72 (p = 0.002), respectively. Additional trials of direct antithrombins in UA/NSTEMI appear warranted.

Hirudin (lepirudin) is presently indicated only for anticoagulation in patients with heparin-induced thrombocytopenia (221) and for the prophylaxis of deep vein thrombosis in patients undergoing hip replacement surgery. It should be administered as a 0.4 mg per kg IV bolus over 15 to 20 s followed by a continuous intravenous infusion of 0.15 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}, with adjustment of the infusion to a target range of 1.5 to 2.5 times the control aPTT values.

e. Long-Term Anticoagulation

The long-term administration of warfarin has been evaluated in a few pilot studies. Williams et al. (201) randomized 102 patients with UA to UFH for 48 h followed by open-label warfarin for 6 months and reported a 65% risk reduction in the rate of MI or recurrent UA. In the Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial, Cohen et al. (179) randomized 214 patients with UA/NSTEMI to ASA alone or the combination of ASA plus UFH followed by warfarin. At 14 days, there was a reduction in the composite end point of death, MI, and recurrent ischemia with the combination therapy (27.0% vs. 10.5%, p = 0.004). In a small randomized pilot study of 57 patients allocated to warfarin or placebo in addition to ASA, less evidence was noted of angiographic progression in the culprit lesion after 10 weeks of treatment with warfarin (33% for placebo vs. 4% for warfarin) and more regression was observed (229). The OASIS pilot study (230) compared a fixed dosage of 3 mg per d coumadin or a moderate dose titrated to an international normalized ratio (INR) of 2 to 2.5 in 197 patients for 7 months after the acute phase. Low-intensity warfarin had no benefit, whereas the moderate-intensity regimen reduced the risk of death, MI, or refractory angina by 58% and the need for rehospitalization for UA by 58%. However, these results were not reproduced in the larger OASIS 2 trial (228) of 3712 patients randomized to the moderate-intensity regimen of warfarin or standard therapy, with all patients receiving ASA. The rate of cardiovascular death, MI, or stroke after 5 months was 7.65% with the anticoagulant and 8.4% without (p = 0.37) (231). Thus, the role, if any, of long-term warfarin in patients with UA/NSTEMI remains to be defined.

The Coumadin Aspirin Reinfarction Study (CARS) conducted in post-MI patients was discontinued prematurely due to a lack of evidence of benefit of reduced-dose ASA (80 mg per d) with either 1 or 3 mg of warfarin daily compared with 160 mg per d ASA alone (232). The Combination Hemotherapy And Mortality Prevention (CHAMP) study found no benefit of the use of warfarin (to an INR of 1.5 to 2.5) plus 81 mg per d ASA vs. 162 mg per d ASA with respect to total mortality, cardiovascular mortality, stroke, and nonfatal MI (mean follow-up of 2.7 years) after an index AMI (Oral presentation, The Combination Hemotherapy and Mortality Prevention (CHAMP) Study: Presented at the American Heart Association Annual Scientific Sessions,

November 1999, Atlanta, GA). Low- or moderate-intensity anticoagulation with fixed-dose warfarin is not recommended for routine use after hospitalization for UA/NSTEMI. Warfarin should be prescribed, however, for UA/NSTEMI patients with established indications for warfarin, such as atrial fibrillation and mechanical prosthetic heart valves.

3. Platelet GP IIb/IIIa Receptor Antagonists

The GP IIb/IIIa receptor is abundant on the platelet surface. When platelets are activated, this receptor undergoes a change in configuration conformation that increases its affinity for binding to fibrinogen and other ligands. The binding of molecules of fibrinogen to receptors on different platelets results in platelet aggregation. This mechanism is independent of the stimulus for platelet aggregation and represents the final and obligatory pathway for platelet aggregation (234). The platelet GP IIb/IIIa receptor antagonists act by occupying the receptors, preventing fibrinogen binding, and thereby preventing platelet aggregation. Experimental and clinical studies have suggested that occupancy of greater than or equal to 80% of the receptor population and inhibition of platelet aggregation to ADP (5 to 20 micromoles per L) by greater than or equal to 80% results in potent antithrombotic effects (235). The various GP IIb/IIIa antagonists, however, possess significantly different pharmacokinetic and pharmacodynamic properties (236).

Abciximab is a Fab fragment of a humanized murine antibody that has a short plasma half-life but strong affinity for the receptor, resulting in some receptor occupancy that persists for weeks. Platelet aggregation gradually returns to normal 24 to 48 h after discontinuation of the drug. Furthermore, abciximab is not specific for GP IIb/IIIa and inhibits the vitronectin receptor ($alpha_v beta_3$) on endothelial cells and the MAC-1 receptor on leukocytes (237,238). The clinical relevance of occupancy of these receptors is not presently known.

Eptifibatide is a cyclic heptapeptide that contains the KGD (Lys-Gly-Asp) sequence; tirofiban and lamifiban (a drug that is not yet approved) are nonpeptide mimetics of the RGD (Arg-Gly-Asp) sequence of fibrinogen (236,239–241). Receptor occupancy with these 3 synthetic antagonists is in general in equilibrium with plasma levels. They have a half-life of 2 to 3 h and are highly specific for the GP IIb/IIIa receptor, with no effect on the vitronectin receptor ($alpha_v$-$beta_3$ integrin). Thus, the median percent inhibition of platelet aggregation to 5 micromoles per L ADP achieved after a loading dose of 0.4 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} of tirofiban for 30 min is 86%, and the inhibition is sustained with an infusion of 0.1 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1}. A higher dose of 10 mcg per kg over 3 min followed by an infusion of 0.15 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} achieves 90% inhibition within 5 min. Platelet aggregation returns to normal in 4 to 8 h after discontinuation of the drug, a finding that is consistent with the relatively short half-life of the drug (242). GP IIb/IIIa antagonists may bind different sites on the receptor and result in somewhat different binding properties that may modify their platelet effects and potentially, paradoxically, activate the receptor (243). Oral antagonists to the receptor are currently under investigation, although these programs have been slowed by the aforementioned negative results of 4 large trials of 3 of these compounds (193,193a,193b).

The efficacy of GP IIb/IIIa antagonists in prevention of the complications associated with percutaneous interventions has been documented in numerous trials, many of them composed totally or largely of patients with UA (182,244–246) (see Figs. 13 and 14 in Section IV). Two trials with tirofiban and 1 trial with eptifibatide have also documented their efficacy in UA/NSTEMI patients, only some of whom underwent interventions (10,21). A trial has been completed with lamifiban (183), and one is ongoing with abciximab. Because the various agents have not been compared directly with each other, their *relative* efficacy is not known.

Abciximab has been studied primarily in PCI trials, in which its administration consistently showed a significant reduction in the rate of MI and the need for urgent revascularization (Table 16). The CAPTURE trial enrolled patients with refractory UA (182). After angiographic identification of a culprit lesion suitable for angioplasty, patients were randomized to either abciximab or placebo administered for 20 to 24 h before angioplasty and for 1 h thereafter. The rate of death, MI, or urgent revascularization within 30 days (primary outcome) was reduced from 15.9% with placebo to 11.3% with abciximab (RR 0.71, $p = 0.012$). At 6 months, death or MI had occurred in 10.6% of the placebo-treated patients vs. 9.0% of the abciximab-treated patients ($p = 0.19$). The longer action of abciximab makes it less optimal in patients likely to need CABG than tirofiban or eptifibatide, whose action is shorter. Abciximab is approved for the treatment of UA/NSTEMI as an adjunct to PCI or when PCI is planned within 24 h.

<u>The GUSTO IV–ACS trial (530) enrolled 7800 patients with UA/NSTEMI who were admitted to the hospital with more than 5 min of chest pain and either ST-segment depression and/or elevated TnT or TnI concentration. All received ASA and either UFH or LMWH. They were randomized to placebo, an abciximab bolus and 24-h infusion, or an abciximab bolus and 48-h infusion. In contrast to other trials with GP IIb/IIIa antagonists, GUSTO IV–ACS enrolled patients in whom early (less than 48 h) revascularization was not intended. At 30 days, death or MI occurred in 8.0% of patients taking placebo, 8.2% of patients taking 24-h abciximab, and 9.1% of patients taking 48-h abciximab, differences that were not statistically significant. At 48 h, death occurred in 0.3%, 0.7%, and 0.9% of patients in these groups, respectively (placebo vs. abciximab 48 h, $p = 0.008$). The lack of benefit of abciximab was observed in most subgroups, including patients with elevated concentrations of troponin who were at higher risk. Although the explanation for these results is not clear, they indicate that abciximab at the dosing regimen used in GUSTO IV–ACS is *not* indicated in the management of patients with UA or NSTEMI in whom an early invasive management strategy is not planned.</u>

Table 16. Outcome of Death or MI in Clinical Trials of Platelet GP IIb/IIIa Antagonists That Involve More Than 1,000 Patients

Trial (Date)	Study Population	Drug	Results, % Placebo n	Placebo %	Platelet GP IIb/IIIa Antagonist n	Platelet GP IIb/IIIa Antagonist %	RR	95% CI	P
PCI trials									
EPIC (1994)	High-risk PTCA	Abciximab	72/696	10.3	49/708	6.9*	0.67	0.47–0.95	0.022
EPILOG (1997)	All PTCA	Abciximab	85/939	9.1	35/935	3.8*	0.41	0.28–0.61	<0.001
CAPTURE (1997)	UA	Abciximab	57/635	9.0	30/630	4.8	0.53	0.35–0.81	0.003
IMPACT II (1997)	All PTCA	Eptifibatide	112/1,328	8.4	93/1,349	6.9*	0.82	0.63–1.06	0.134
RESTORE (1997)	UA	Tirofiban	69/1,070	6.4	54/1,071	5.0	0.78	0.55–1.10	0.162
EPISTENT (1998)	Elective stenting	Abciximab	83/809	10.2	38/794	4.8*	0.47	0.32–0.68	<0.000
ACS trials									
PRISM-PLUS (1998)	UA/NQWMI	Tirofiban	95/797	11.9	67/733	8.7*	0.70	0.51–0.96	0.03
PRISM (1998)	UA/NQWMI	Tirofiban	115/1,616	7.1	94/1,616	5.8	0.80	0.61–1.05	0.11
PURSUIT (1998)	UA/NQWMI	Eptifibatide	744/4,739	15.7	67/4,722	14.2*	0.91	0.82–1.00	0.042
PARAGON A (1998)	UA/NQWMI	Lamifiban	89/758	11.7	80/755	10.6*†	0.9	0.68–1.20	0.48
GUSTO IV ACS (2001)	UA/NQWMI	Abciximab	209/2,598	8.0	450/5,202‡	8.7	1.1	0.92-1.26	0.82
All PCI trials			482/5,477	8.8	299/5,487	5.4	0.62	~~0.62–0.71~~ 0.54-0.71	<0.001
All ACS trials			~~1,043/7,910~~	~~13.2~~	~~912/7,826~~	~~11.7~~	~~0.81~~	~~0.81–0.96~~	~~0.004~~
			1,252/10,508	11.9	1,362/13,028	10.5	0.88	0.82-0.94	<0.001
All PCI and ACS trials			~~1,525/13,387~~	~~11.4~~	~~1,211/13,313~~	~~9.1~~	~~0.80~~	~~0.74–0.86~~	~~<0.001~~
			1,734/15,985	10.9	1,661/18,515	9.0	0.83	0.78-0.88	<0.001

ACS, indicates acute coronary syndrome; CI, confidence index; NQWMI, non-Q-wave MI; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RR, risk ratio; UA; unstable angina.
*Best treatment group selected for analysis.
†Platelet GP IIb/IIIa antagonist without heparin.
‡Pooled results for 24 and 48 h infusion arms.

Tirofiban was studied in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) (184) and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) (21) trials. The former trial directly compared tirofiban with heparin in 3232 patients with accelerating angina or angina at rest and ST-segment or T-wave changes and with enzyme elevation, a previous MI, or a positive stress test or angiographically documented coronary disease. The primary composite outcome (death, MI, or refractory ischemia at the end of a 48-h infusion period) was reduced from 5.6% with UFH to 3.8% with tirofiban (RR 0.67, p = 0.01). At 30 days, the frequency of the composite outcome was similar in the 2 groups (17.1% for UFH vs. 15.9% for tirofiban, p = 0.34), but a trend toward reduction in the rate of death or MI was present with tirofiban (7.1% vs. 5.8%, p = 0.11), and a significant reduction in mortality rates was observed (3.6% vs. 2.3%, p = 0.02). The benefit of tirofiban was mainly present in patients with an elevated TnI or TnT concentration at baseline (90).

The PRISM-PLUS trial enrolled 1915 patients with clinical features of UA within the previous 12 h and the presence of ischemic ST-T changes or CK and CK-MB elevation. Patients were randomized to tirofiban alone, UFH alone, or the combination for a period varying from 48 to 108 h. The tirofiban-alone arm was dropped during the trial because of an excess mortality rate. The combination of tirofiban and UFH compared with UFH alone reduced the primary composite end point of death, MI, or refractory ischemia at 7 days from 17.9% to 12.9% (RR 0.68, p = 0.004). This composite outcome was also significantly reduced by 22% at 30 days (p = 0.03) and by 19% at 6 months (p = 0.02). The end point of death or nonfatal MI was reduced by 43% at 7 days (p = 0.006), 30% at 30 days (p = 0.03), and 22% at 6 months (p = 0.06).

Computer-assisted analysis of coronary angiograms obtained after 48 h of treatment in 1491 patients in the PRISM-PLUS trial showed a significant reduction in the thrombus load at the site of the culprit lesion and improved coronary flow as assessed according to the TIMI criteria in patients who received the combination of tirofiban and UFH (247). Tirofiban, in combination with heparin, has been approved for the treatment of patients with ACS, including patients who are managed medically as well as those undergoing PCI.

Eptifibatide was studied in the PURSUIT trial, which enrolled 10,948 patients who had chest pain at rest within the previous 24 h and ST-T changes or CK-MB elevation (10). The study drug was added to standard management until hospital discharge or for 72 h, although patients with normal coronary arteries or other mitigating circumstances had shorter infusions. The infusion could be continued for an additional 24 h if an intervention was performed near the end of the 72-h infusion period. The primary outcome rate of

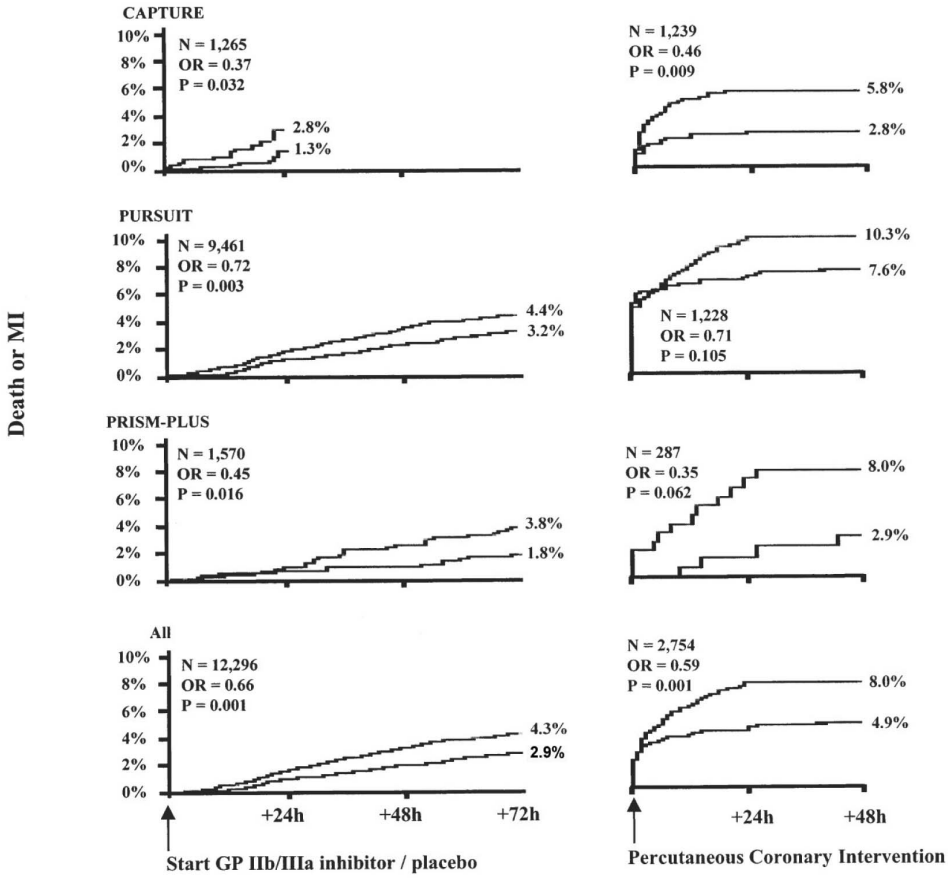


Figure 10. Kaplan-Meier curves showing cumulative incidence of death or MI in patients randomly assigned to platelet GP IIb/IIIa receptor antagonist (bold line) or placebo. Data are derived from the CAPTURE, PURSUIT, and PRISM-PLUS trials (248). Left, Events during the initial period of medical treatment until the moment of PCI or CABG. In the CAPTURE trial, abciximab was administered for 18 to 24 h before the PCI was performed in almost all patients as per study design; abciximab was discontinued 1 h after the intervention. In PURSUIT, a PCI was performed in 11.2% of patients during a period of medical therapy with eptifibatide that lasted 72 h and for 24 h after the intervention. In PRISM-PLUS, an intervention was performed in 30.2% of patients after a 48-h period of medical therapy with tirofiban, and the drug infusion was maintained for 12 to 24 h after an intervention. Right, Events occurring at the time of PCI and the next 48 h, with the event rates reset to 0% before the intervention. CK or CK-MB elevations exceeding 2 times the upper limit of normal were considered as infarction during medical management and exceeding 3 times the upper limit of normal for PCI-related events. Adapted from Boersma et al. (248), CAPTURE (182), PURSUIT (10), and PRISM-PLUS (21).

death or nonfatal MI at 30 days was reduced from 15.7% to 14.2% with eptifibatide (RR 0.91, p = 0.042). Within the first 96 h, a substantial treatment effect was seen (9.1% vs. 7.6%, p = 0.01). The benefits were maintained at 6-month follow-up. Eptifibatide has been approved for the treatment of patients with ACS (UA/NSTEMI) who are treated medically or with PCI. It is usually administered with ASA and heparin.

The cumulative event rates observed during the phase of medical management and at the time of PCI in the CAPTURE, PRISM-PLUS, and PURSUIT trials are shown in Figure 10 (248). By protocol design, almost all patients underwent PCI in CAPTURE. In PRISM-PLUS, angiography was recommended. A percutaneous revascularization was performed in 30.5% of patients in PRISM-PLUS and in 13.0% of patients in PURSUIT. Each trial has shown a statistically significant reduction in the rate of death or MI during the phase of medical management; the reduction in event rates was magnified at the time of the intervention.

Although it is tempting to evaluate the drug effect by comparing patients who had intervention with those who did not, such an analysis is inappropriate. Patients who do not undergo intervention include many low-risk patients, patients who died before having the opportunity for intervention, patients with contraindications, and patients with uncomplicated courses in countries and practices that use the ischemia-guided approach; there is no way to adjust for these imbalances. Accordingly, the analysis in Figure 10 includes the event rates for all patients during the time when they were treated medically. It then begins the analysis anew in patients who underwent PCI at the time of angiography while on drug or placebo. In the PRISM-PLUS trial, 1069 patients did not undergo early PCI. Although tirofiban treatment was associated with a lower incidence of death, MI or death, or of MI or refractory ischemia at 30 days, these reductions were not statistically significant (531). In a high-risk subgroup of these patients not undergoing PCI (TIMI risk score greater than or equal to 4) (517) tirofiban appeared to be beneficial whether they underwent PCI (OR 0.60, 95% CI 0.35–1.01) or not (OR 0.69, 95% CI 0.49–0.99). However, no benefit was observed in patients at lower risk (519,532). In the PUR-

SUIT trial eptifibatide reduced the incidence of death or MI from 15.7% to 14.2% (RR 0.91, 95% CI = 0.79–1.00, p = 0.032) (534).

Boersma et al. carried out a meta-analysis of GP IIb/IIIa antagonists of all six large randomized placebo-controlled trials (including GUSTO IV [530] involving 31,402 patients with UA/NSTEMI not routinely scheduled to undergo coronary revascularization [535]). A small reduction in the odds of death or MI in the active treatment arm (11.8% vs 10.8%, OR = 0.91, 95% CI 0.84–0.98, p = 0.015) was observed. Unexpectedly, no benefit was observed in women (test for interaction between treatment assignment and gender, p less than 0.0001). In the meta-analysis, reductions in the end points of death or nonfatal MI considered individually did *not* achieve statistical significance.

Although not scheduled for coronary revascularization procedures, 11,965 of the 31,402 patients (38%) actually underwent PCI or CABG within 30 days, and in this subgroup the OR for death or MI in the patients assigned to GP IIb/IIIa antagonists was 0.89 (95% CI 0.80–0.98). In the other 19,416 patients who did not undergo coronary revascularization, the OR for death or MI in the GP IIb/IIIa group was 0.95 (0.86–1.05, NS). Major bleeding complications were increased in the GP IIb/IIIa antagonist-treated group compared to those who received placebo (2.4% vs. 1.4%, p less than 0.0001). The authors concluded that in patients with UA/NSTEMI not routinely scheduled for early revascularization and at high risk of thrombotic complications, "treatment with a GP IIb/IIIa inhibitor might therefore be considered" (535). Thus, GP IIb/IIIa inhibitors are of substantial benefit in patients with UA/NSTEMI who undergo PCI; they are of modest benefit in patients who are not routinely scheduled to undergo PCI (but who may do so), and they are of questionable benefit in patients who do not undergo PCI. ~~When the trials are combined, the message is compelling: the GP IIb/IIIa inhibitors are effective in reducing event rates in the acute phase of medical management of UA/NSTEMI, and this effect is magnified if a PCI is performed. Therefore, it is recommended that a GP IIb/IIIa inhibitor be administered, along with ASA and UFH, to patients with UA/NSTEMI with active ischemia or with any of the high-risk features shown in Table 6.~~

Although there is a temptation to use the comparison of each of these GP IIb/IIIa inhibitors with placebo to draw conclusions about relative efficacy, such an exercise could be misleading. Each trial had different entry criteria, different approaches to angiographic evaluation, and different criteria for end point measurement and took place in different locations in different time periods. The effects of these differences cannot be accounted for in an indirect comparison. Head-to-head (direct) comparisons will be required to draw reliable conclusions about the relative efficacy of these different molecules.

Treatment with a GP IIb/IIIa antagonist increases the risk of bleeding, which is typically mucocutaneous or involves the access site of vascular intervention. Unfortunately, each trial also used a different definition of bleeding and reported differently with regard to bleeding related to CABG. In the PRISM trial with no interventions on treatment, major bleeding (excluding CABG) occurred in 0.4% of patients who received tirofiban and 0.4% of patients who received UFH. In the PRISM-PLUS trial, major bleeding according to the TIMI criteria was reported in 1.4% of patients who received tirofiban and 0.8% of patients who received placebo (p = 0.23), whereas PURSUIT reported major bleeding in 10.6% of patients who received eptifibatide and 9.1% of patients who received placebo (p = 0.02). In the PURSUIT trial, with the exclusion of patients who underwent CABG, the rates were 3.0% with eptifibatide and 1.3% with placebo (p less than 0.001). No trials have shown an excess of intracranial bleeding with a GP IIb/IIIa inhibitor. As with the efficacy data, the temptation to make indirect comparisons should be tempered by the variability in protocol, circumstances, and definitions of the trial.

ASA has been used with the intravenous GP IIb/IIIa receptor blockers in all trials. A strong case can also be made for the concomitant use of heparin with GP IIb/IIIa receptor blockers. The tirofiban arm without UFH in the PRISM-PLUS trial was discontinued early because of an excess of deaths. In addition, the PURSUIT trial reported a higher event rate in the 11% of patients who were not treated with concomitant heparin (10). Current recommendations call for the concomitant use of heparin with GP IIb/IIIa inhibitors. It should be noted that an interaction exists between heparin and GP IIb/IIIa inhibitors with a higher ACT for the combination and a need for lower doses of heparin than usually recommended to achieve the best outcomes in the setting of PCI. Information is currently being gained concerning the safety and efficacy of the combination of LMWH and GP IIb/IIIa inhibitors.

Blood hemoglobin and platelet counts should be monitored and patient surveillance for bleeding should be carried out daily during the administration of GP IIb/IIIa receptor blockers. Thrombocytopenia is an unusual complication of this class of agents. Severe thrombocytopenia defined by nadir platelet counts of less than 50,000 mL^{-1} is observed in 0.5% of patients, and profound thrombocytopenia defined by nadir platelet counts of less than 20,000 mL^{-1} is observed in 0.2% of patients. Although reversible, thrombocytopenia is associated with an increased risk of bleeding (249,250).

Although the data are not definitive, it does appear that GP IIb/IIIa inhibitors can be used with LMWH. In the Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE II) study (536), UFH and enoxaparin were compared in patients with UA/NSTEMI receiving tirofiban. The incidence of major and minor bleeding was similar, and there was a trend to fewer adverse events in the patients receiving enoxaparin. A number of other open-label studies have examined the safety of combining enoxaparin with abciximab, eptifibatide, or tirofiban in patients with UA/NSTEMI being treated with PCI or conservatively (536); of combining enoxaparin with abciximab in patients undergoing elective PCI (537); of combining dalteparin with abciximab during PCI (538) (J.J. Ferguson, oral presentation,

ACC Annual Scientific Sessions, Orlando, Florida, March 2001); and of administering dalteparin to patients with UA/NSTEMI receiving abciximab who were treated conservatively (L.C. Wallentin, oral presentation, Congress of the European Society of Cardiology, Amsterdam, The Netherlands, August 2000). Although the majority of these studies relied on historical controls, none suggested that the combination of LMWH and a GP IIb/IIIa inhibitor was associated with excess bleeding, whether or not the patient also underwent PCI.

a. Thrombolysis

The failure of intravenous thrombolytic therapy to improve clinical outcomes in the absence of AMI with ST-segment elevation or bundle-branch block was clearly demonstrated in the TIMI IIIB, ISIS-2, and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 (GISSI) 1 trials (19,251,252). A meta-analysis of thrombolytic therapy in UA patients showed no benefit of thrombolysis vs. standard therapy for the reduction of AMI (19). Thrombolytic agents had no significant beneficial effect and actually increased the risk of MI (19). Consequently, such therapy is not recommended for the management of patients with an ACS without ST-segment elevation, a posterior wall MI, or a presumably new LBBB (see ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction [5]).

C. Risk Stratification

Recommendations

Class I

1. **Noninvasive stress testing in low-risk patients (Table 6) who have been free of ischemia at rest or with low-level activity and of CHF for a minimum of 12 to 24 h. (Level of Evidence: C)**
2. **Noninvasive stress testing in patients at intermediate risk (Table 6) who have been free of ischemia at rest or with low-level activity and of CHF for a minimum of 2 or 3 days. (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 suitable 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, preexcitation, and digoxin effect. (Level of Evidence: C)**
4. **An imaging modality is 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, imaging modality may add sensitivity. (Level of Evidence: B~~C~~)**
5. **Pharmacological stress testing with imaging when physical limitations (e.g., arthritis, amputation, severe peripheral vascular disease, severe COPD, general debility) preclude adequate exercise stress. (Level of Evidence: B)**
6. **Prompt angiography without noninvasive risk stratification for failure of stabilization with intensive medical treatment. (Level of Evidence: B)**

Class IIa

A noninvasive test (echocardiogram or radionuclide angiogram) to evaluate LV function in patients with definite ACS who are not scheduled for coronary arteriography and left ventriculography. (Level of Evidence: C)

The management of ACS patients requires continuous risk stratification. Important prognostic information is derived from careful initial assessment, the patient's course during the first few days of management, and the patient's response to anti-ischemic and antithrombotic therapy. The Braunwald classification (8,111a) has been validated prospectively and represents an appropriate clinical instrument to help predict outcome (253). Angina at rest, within 48 h in the absence of an extracardiac condition (primary UA) (Braunwald Class III), and UA in the early postinfarction period (Braunwald Class C), along with age, male sex, hypertension, and maximal intravenous antianginal/anti-ischemic therapy, were independent predictors for death or nonfatal MI. The baseline ECG on presentation was also found to be extremely useful for risk stratification in the TIMI III registry (60). For example, patients with ST-segment depression of greater than or equal to 0.1 mV had an 11% rate of death or nonfatal MI at 1 year. Those with LBBB had rates of 22.9%. The majority of patients had no ECG change or only isolated T-wave changes, with 6.8% to 8.2% rates of death or MI, respectively, at 1 year. In another study, the rates of death or MI associated with these initial ECG findings in ACS patients were even higher (254) (Fig. 11). In many cases, noninvasive stress testing provides a very useful supplement

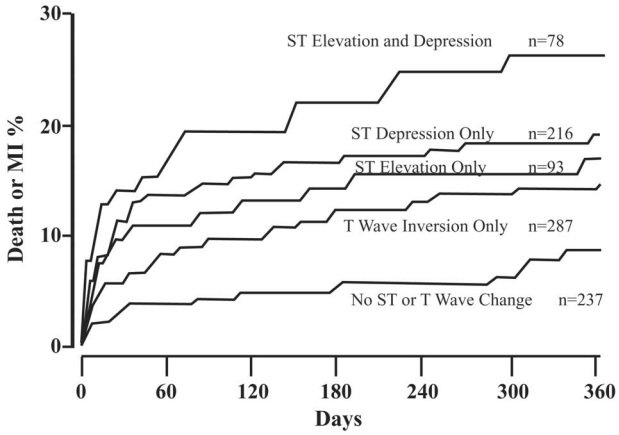


Figure 11. Adverse outcome by initial ECG in ACS. Adapted from Nyman I, Areskog M, Areskog NH, Swahn E, Wallentin L. Very early risk stratification by electrocardiogram at rest in men with suspected unstable coronary heart disease. The RISC Study Group. J Intern Med 1993;234:293–301.

to such clinically based risk assessment. In addition, as pointed out previously, troponins are very helpful in risk assessment.

Some patients, however, are at such high risk for an adverse outcome that noninvasive risk stratification would not be likely to identify a subgroup with sufficiently low risk to avoid coronary angiography to determine whether revascularization is possible. These patients include those who manifest, despite intensive medical therapy, recurrent rest angina, hemodynamic compromise, or severe LV dysfunction. Such patients should be considered directly for early coronary angiography without noninvasive stress testing. However, referral for coronary angiography is not reasonable if they are unwilling to consider revascularization or have severe complicating illnesses that preclude revascularization. Other patients may have a very low likelihood of CAD after the initial clinical evaluation with the risk of an adverse outcome so low that no abnormal test finding would be likely to prompt therapy that would further reduce the already very low risk for adverse outcomes (e.g., a 35-year-old woman without CAD risk factors). Such patients would ordinarily not be considered for coronary angiography and revascularization unless the diagnosis is unclear. Patients who do not fall into these categories are reasonable candidates for risk stratification with noninvasive testing.

1. Care Objectives

The goals of noninvasive testing are to 1) determine the presence or absence of ischemia in patients with a low likelihood of CAD and 2) estimate prognosis. This information is key for the development of further diagnostic steps and therapeutic measures.

A detailed discussion of noninvasive stress testing in CAD is presented in the ACC/AHA Guidelines for Exercise Testing, ACC/AHA Guidelines for the Clinical Use of Cardiac Radionuclide Imaging, and ACC/AHA Guidelines for the Clinical Application of Echocardiography (255–257) (Tables 17 to 19). Briefly, the provocation of ischemia at a low workload, such as less than or equal to 6.5 metabolic equivalents (METs), a high-risk treadmill score (greater than or equal to 11) (258), implies severe limitation in the ability to increase coronary blood flow. This is usually the result of severe coronary artery obstruction and is associated with a high risk for adverse outcome and/or severe angina after discharge. Unless there are contraindications to revascularization, such patients generally merit referral for early coronary angiography to direct a revascularization procedure, if possible. On the other hand, the attainment of a higher workload (e.g., greater than 6.5 METs) without evidence of ischemia (low-risk treadmill score greater than or equal to 5) (258) is associated with functionally less severe coronary artery obstruction. Such patients have a better prognosis and can often be safely managed conservatively. Ischemia that develops at greater than 6.5 METs may be associated with severe coronary artery obstruction, but unless other high-risk markers are present (greater than 0.2-mV ST-segment depression or elevation, fall in blood pressure, ST-segment shifts in multiple leads reflecting multiple coronary regions, or prolonged [greater than 6 min of ST-segment shifts] recovery), these patients may also be safely managed conservatively (Table 17).

Table 17. Noninvasive Risk Stratification

High risk (>3% annual mortality rate)
1. Severe resting LV dysfunction (LVEF <0.35)
2. High-risk treadmill score (score ≤−11)
3. Severe exercise LV dysfunction (exercise LVEF <0.35)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving >2 segments) developing at a low dose of dobutamine (≤10 mg · kg^{-1} · min^{-1}) or at a low heart rate (<120 bpm)
9. Stress echocardiographic evidence of extensive ischemia

Intermediate risk (1–3% annual mortality rate)
1. Mild/moderate resting LV dysfunction (LVEF 0.35–0.49)
2. Intermediate-risk treadmill score (−11 < score <5)
3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤2 segments

Low risk (<1% annual mortality rate)
1. Low-risk treadmill score (score ≥5)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

From Table 23 in 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.

Stress radionuclide ventriculography or stress echocardiography (Table 18) provides an important alternative. Myocardial perfusion imaging with pharmacological stress (Table 19) is particularly useful in patients unable to exercise. The prognostic value of pharmacological stress testing appears similar to that of exercise testing with imaging, although there are few direct comparisons.

2. Noninvasive Test Selection

There are no conclusive data that either LV function or myocardial perfusion at rest and during exercise or pharma-

Table 18. Noninvasive Test Results That Predict High Risk for Adverse Outcome (LV Imaging)

Stress radionuclide ventriculography	Stress echocardiography
Exercise EF ≤0.50	Rest EF ≤0.35
Rest EF ≤0.35	Wall motion score index >1
Fall in EF ≥0.10	

Adapted from O'Rourke RA, Chatterjee K, Dodge HT, et al. Guidelines for clinical use of cardiac radionuclide imaging, December 1986: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Nuclear Imaging). J Am Coll Cardiol 1986;8:1471–83; and Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA guidelines for the clinical application of echocardiography. Circulation 1997;95: 1686–744.

Table 19. Noninvasive Test Results That Predict High Risk for Adverse Outcome on Stress Radionuclide Myocardial Perfusion Imaging

- Abnormal myocardial tracer distribution in >1 coronary artery region at rest or with stress or a large anterior defect that reperfuses
- Abnormal myocardial distribution with increased lung uptake
- Cardiac enlargement

Adapted from O'Rourke RA, Chatterjee K, Dodge HT, et al. Guidelines for clinical use of cardiac radionuclide imaging, December 1986: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Nuclear Imaging). J Am Coll Cardiol 1986;8:1471– 83.

cological stress is superior in the assessment of prognosis. Both the extent of CAD and the degree of LV dysfunction are important in the selection of the appropriate therapy. Studies that directly compare prognostic information from multiple noninvasive tests for ischemia in patients after the stabilization of UA are hampered by small sample size. An exception may be the initial improved LV function, as seen with dobutamine stress echocardiography, which then deteriorates with increasing dobutamine doses (256). This test is particularly useful in patients with good acoustical windows because both resting LV function and the functional consequences of a coronary stenosis can be assessed.

The RISC study evaluated predischarge symptom-limited bicycle exercise testing in 740 men with UA/NSTEMI (259). Multivariate analysis showed that the extent of ST-segment depression expressed as the number of leads that showed ischemia at a low maximal workload was independently negatively correlated with infarct-free survival rates at 1 year. This and other smaller studies permit a comparison of the effectiveness of exercise ECG with exercise or dipyridamole thallium-201 study for risk stratification. All of these noninvasive tests show similar accuracy in dichotomization of the total population into low- and high-risk subgroups.

Selection of the noninvasive stress test should be based primarily on patient characteristics, local availability, and expertise in interpretation (260). Because of simplicity, lower cost, and widespread familiarity with performance and interpretation, the standard low-level exercise ECG stress test remains the most reasonable test in patients who are able to exercise and have a resting ECG that is interpretable for ST-segment shifts. Patients with an ECG pattern that would interfere with interpretation of the ST segment should have an exercise test with imaging. Patients who are unable to exercise should have a pharmacological stress test with imaging. A low-level exercise test (e.g., to completion of Bruce Stage II) may be carried out in low-risk patients (Table 6) who have been asymptomatic for 12 to 24 h. A symptom-limited test can be conducted in patients without evidence of ischemia for 7 to 10 days.

The optimal testing strategy in women remains less well defined than that in men (see Section VI. A), but there is evidence that imaging studies are superior to exercise ECG in women (260,261). Exercise testing has been reported to be less accurate for diagnosis in women. At least a portion of the lower reported accuracy derives from a lower pretest likelihood of CAD in women compared with men.

Results of a symptom-limited exercise test performed 3 to 7 days after UA/NSTEMI were compared with results of a test conducted 1 month later in 189 patients (262). The diagnostic and prognostic values of the tests were similar, but the earlier test identified patients who developed adverse events during the first month, and this represented about one half of all events that occurred during the first year. These data illustrate the importance of *early* noninvasive testing for risk stratification.

The Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial used symptom-limited thallium exercise treadmill testing at 3 to 5 days to direct the need for angiography in the 442 non–Q-wave MI patients randomized to an early conservative strategy (263). This strategy included an effort to detect ischemia with noninvasive testing that would be associated with a high risk for adverse outcome. Cumulative death rates in the 238 conservative strategy patients directed to angiography on the basis of recurrent ischemia or high-risk stress test results were 3%, 10%, and 13% at 1, 6, and 12 months, respectively, whereas the rates were 1%, 3%, and 6% in the patients who were not directed to angiography (no recurrent ischemia or high-risk test). These findings support the concept that noninvasive stress testing can be used successfully to identify a high-risk subset of patients who could be directed to coronary angiography. It is unlikely that any angiographically directed early revascularization strategy could alter the very low early event rates observed in patients without a high-risk stress test.

Noninvasive tests are most useful for management decisions when risk can be stated in terms of events over time. A large population of patients must be studied to derive and test equations needed to accurately predict individual patient risk. No noninvasive study has been reported in a sufficient number of patients after the stabilization of UA to develop and test the accuracy of a multivariable equation to report test results in terms of absolute risk. Therefore, data from studies of stable angina patients must be used for risk reported as events over time. Although the pathological process that evokes ischemia may be different in the 2 forms of angina, it is likely that the use of prognostic nomograms derived from patients with stable angina are also predictive of risk in patients with recent UA after stabilization. With this untested assumption, the much larger literature derived from populations that include patients with both stable angina and UA provides equations for risk stratification that convert physiological changes observed during noninvasive testing into statements of risk expressed as events over time.

3. Selection for Coronary Angiography

In contrast to the noninvasive tests, coronary angiography provides detailed structural information to allow an assessment of prognosis and to provide direction for appropriate management. When combined with LV angiography, it also allows 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. The recently revised ACC/AHA Guidelines for Coronary Angiography present greater details on this subject (264).

Coronary angiography is usually indicated in patients with UA/NSTEMI who either have recurrent symptoms or ischemia despite adequate medical therapy or are at high risk categorized by clinical findings (CHF, malignant ventricular arrhythmias) or noninvasive test findings (significant LV dysfunction: ejection fraction [EF] less than 0.35, large anterior or multiple perfusion defects) (Tables 17 to 19), as discussed in Section III. B. Patients with UA who have had previous PCI or CABG should also in general be considered for early coronary angiography, unless prior coronary angiography data indicate that no further revascularization is likely to be possible. The placement of an IABP may be useful in patients with recurrent ischemia despite maximal medical management as well as in those with hemodynamic instability until coronary angiography and revascularization can be completed. Patients with suspected Prinzmetal's variant angina are also candidates for coronary angiography (see Section VI. F).

In all cases, the general indications for coronary angiography and revascularization are tempered by individual patient characteristics and preferences. Patient and physician judgments regarding risks and benefits are particularly important for patients who may not be candidates for coronary revascularization, such as very frail elderly persons and those with serious comorbid conditions (i.e., severe hepatic, pulmonary, or renal failure; active or inoperable cancer).

4. Patient Counseling

Results of testing should be discussed with the patient, his or her family, and/or his or her advocate in language that is understood. Test results should be used to help determine the advisability of coronary angiography, the need for adjustments in the medical regimen, and the need for secondary prevention measures (see Section V).

D. Early Conservative Versus Invasive Strategies

1. General Principles

Two different treatment strategies, termed "early conservative" and "early invasive," have evolved for patients with UA/NSTEMI. In the *early conservative strategy*, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest or with minimal activity or dynamic ST-segment changes) or a strongly positive stress test, despite vigorous medical therapy. In the *early invasive strategy*, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and angiographically directed revascularization if possible.

Recommendations

~~**Class I**~~

~~**1. An early invasive strategy in patients with UA/NSTEMI and any of the following high-risk indicators. (Level of Evidence: B):**~~

~~**a) Patients with recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy**~~

Class I

1. An early invasive strategy in patients with UA/NSTEMI and any of the following high-risk indicators. (Level of Evidence: A).
   - **a) Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy**
   - **b) Elevated TnT or TnI**
   - **c) New or presumably new ST-segment depression**
   - **~~b~~d) Recurrent angina/ischemia with CHF symptoms, an S_3 gallop, pulmonary edema, worsening rales, or new or worsening MR**
   - **~~c~~e) High-risk findings on noninvasive stress testing**
   - **~~d~~f) Depressed LV systolic function (e.g., EF less than 0.40 on noninvasive study)**
   - **~~e~~g) Hemodynamic instability**
   - **~~f~~h) Sustained ventricular tachycardia**
   - **~~g~~i) PCI within 6 months**
   - **~~h~~j) Prior CABG**

2. In the absence of these findings, either an early conservative or an early invasive strategy in hospitalized patients without contraindications for revascularization. (Level of Evidence: B)

Class IIa

1. An early invasive strategy in patients with repeated presentations for ACS despite therapy and without evidence for ongoing ischemia or high risk. (Level of Evidence: C)

~~**2. An early invasive strategy in patients greater than 65 years old or patients who present with ST-segment depression or elevated cardiac markers and no contraindications to revascularization. (Level of Evidence: C)**~~

Class III

1. Coronary angiography in patients with extensive comorbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization are not likely to outweigh the benefits. (Level of Evidence: C)

2. Coronary angiography in patients with acute chest pain and a low likelihood of ACS. (Level of Evidence: C)

3. Coronary angiography in patients who will not consent to revascularization regardless of the findings. (Level of Evidence: C)

a. Rationale for the Early Conservative Strategy

Three multicenter trials have shown similar outcomes with early conservative and early invasive therapeutic strategies (19,265,266). The conservative strategy spares the use of invasive procedures with their risks and costs in all patients. Recent trials (266,267) have emphasized the early risk associated with revascularization procedures. When the early conservative strategy is chosen, a plan for noninvasive evaluation is required to detect severe ischemia that occurs spontaneously or at a low threshold of stress and to promptly refer these patients for coronary angiography and revascularization when possible. In addition, as in STEMI (268), an early echocardiogram should be considered to identify patients with significant LV dysfunction (e.g., EF less than 0.40). Such a finding prompts consideration for angiography to identify left main or multivessel CAD, because patients with multivessel disease and LV dysfunction are at high risk and may accrue a survival benefit from bypass surgery (269,270). In addition, a stress test (e.g., exercise or pharmacological stress) for the assessment of ischemia is recommended before discharge or shortly thereafter to identify patients who may also benefit from revascularization. The use of either LMWH or platelet GP IIb/IIIa receptor blockers has reduced the incidence of adverse outcomes in patients managed conservatively (see Section III. B) (10,169–171,182,184, 247,248), suggesting that the early conservative strategy may be advantageous because costly invasive procedures may be avoided in even more patients.

b. Rationale for the Early Invasive Strategy

In patients with UA/NSTEMI without recurrent ischemia in the first 24 h, the use of early angiography provides an invasive approach to risk stratification. It can identify the 10% to 15% of patients with no significant coronary stenoses and the approximately 20% with 3-vessel disease with LV dysfunction or left main CAD. This latter group may derive a survival benefit from bypass surgery (see Section IV). In addition, early percutaneous revascularization of the culprit lesion has the potential to reduce the risk for subsequent hospitalization and the need for multiple antianginal drugs compared with the early conservative strategy (TIMI IIIB) (19). Just as the use of improved antithrombotic therapy with LMWH and/or a platelet GP IIb/IIIa receptor blocker has improved the outcome in patients managed according to the early conservative strategy, the availability of these agents also makes the early invasive approach more attractive, because the early hazard of percutaneous intervention is lessened. The availability of GP IIb/IIIa receptor blockers has led to 2 alternatives for the invasive approach: immediate angiography or deferred angiography.

c. Immediate Angiography

Some believe that proceeding immediately to angiography is an efficient approach for the ACS patient. Patients found not to have CAD may be discharged rapidly or shifted to a different management strategy. Patients with obvious culprit lesions amenable to percutaneous intervention could have a procedure performed immediately, thus hastening discharge. Patients with left main CAD and patients with multivessel disease and LV dysfunction could be sent expeditiously to undergo bypass surgery, thereby avoiding a risky waiting period. However, only 1 observational study (271) has addressed this approach directly, and the results are not definitive.

d. Deferred Angiography

In most reports that involve use of the early invasive strategy, angiography has been deferred for 12 to 48 h while antithrombotic and anti-ischemic therapies are intensified. Several observational studies (~~272~~552) have found a lower rate of complications in patients undergoing percutaneous intervention more than 48 h after admission, during which heparin and ASA were administered, compared with early intervention. However, it should be noted that the value of medical stabilization before angiography has never been assessed formally.

2. Care Objectives

The objective is to provide a strategy that has the most potential to yield the best clinical outcome. The purpose of coronary angiography is to provide detailed information about the size and distribution of coronary vessels, the location and extent of atherosclerotic obstruction, and the suitability for revascularization. The LV angiogram, which is usually carried out along with coronary arteriogram, provides an assessment of the extent of focal and global LV dysfunction and of the presence and severity of coexisting disorders (e.g., valvular or congenital lesions). A detailed discussion of revascularization is presented in Section IV of these guidelines, as well as in the ACC/AHA Guidelines for Percutaneous Transluminal Coronary Angioplasty (552) and ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery (274). Although general guidelines can be offered, the selection of appropriate procedures and the decision to refer patients for revascularization require both clinical judgment and counseling with the patient and his or her family regarding expected risks and benefits. In this counseling, it is important to consider that large registry and controlled clinical trial data generally show no or limited evidence of reduced death or MI rates when early coronary angiography followed by revascularization is used in a routine and unselected manner in patients with UA/NSTEMI.

Because the basis for acute ischemia is plaque rupture/erosion and/or severe obstructive CAD, it has been postulated that early revascularization would improve prognosis. This notion led to considerable investigation in patients with stable coronary syndromes as well as AMI in the 1970s. In selected circumstances, revascularization with CABG seems to be associated with lower morbidity and mortality rates compared with a more conservative strategy. These circumstances center around the documentation of severe ischemia

(resting ECG and on noninvasive testing) or potential for severe ischemia (left main stenosis or severe multivessel CAD with impaired LV function). These data, however, are limited because both medical and surgical treatments have been markedly improved in the past 2 decades and the population of patients who present with CAD today has changed (e.g., a higher proportion of women, elderly persons, minorities, and diabetics).

Although 2 recent studies were not conducted in patients with UA/NSTEMI, they have addressed the value of stress testing in guiding therapy. The DANish trial in Acute Myocardial Infarction (DANAMI) studied 503 patients with inducible ischemia (i.e., a positive exercise stress test) after thrombolytic therapy for first MI and compared an ischemia-guided invasive strategy with a conservative strategy (275). The invasive strategy in the post-AMI patients with inducible ischemia resulted in a reduction in the incidence of reinfarction, hospitalizations for UA, and stable angina. Similarly, in the Asymptomatic Cardiac Ischemia Pilot (ACIP) (276,277), 558 clinically stable patients with ischemia on stress testing and during daily life (ST-segment depression on exercise treadmill testing or perfusion abnormality on radionuclide pharmacological stress test if unable to exercise, in addition to ST-segment depression on ambulatory ECG monitoring), of whom most had angina in the previous 6 weeks, were randomized to 1 of 3 initial treatment strategies: symptom-guided medical care, ischemia-guided medical care, and revascularization. More than one third of these patients had "complex" stenoses on angiography. Those randomized to early revascularization experienced less ambulatory ischemia at 12 weeks than did those randomized to initial medical care in whom revascularization was delayed and symptom driven.

In ACS patients with UA/NSTEMI, the purpose of noninvasive testing is to identify ischemia as well as to identify candidates at high risk for adverse outcome and to direct them to coronary angiography and revascularization when possible. However, both randomized trials (19,265,266,278) and observational data (279–281) do not uniformly support an inherent superiority for the routine use of early coronary angiography and revascularization. In fact, the VANQWISH trial suggests that an early conservative strategy, in which candidates for coronary angiography and revascularization are selected from the results of ischemia-guided noninvasive testing, may be associated with fewer deaths. Accordingly, the decision regarding which strategy to pursue for a given patient should be based on the patient's estimated outcome risk assisted by clinical and noninvasive test results, available facilities, previous outcome of revascularization by the team available and in the institution in which the patient is hospitalized, and patient preference.

Early coronary angiography may enhance prognostic stratification. This information may be used to guide medical therapy as well as to plan revascularization therapy, but it is important to emphasize that adverse outcome in ACS is very time dependent and that after 1 to 2 months, the risk for adverse outcome is essentially the same as that for low-risk chronic stable angina (Fig. 3). Furthermore, numerous studies in patients with stable angina, including Research Group in Instability in Coronary Artery Disease (RITA)-2 (267), have documented the significant early risk of death or MI with an interventional strategy compared with medical management alone. Thus, the timing of coronary angiography and revascularization is critically important if patients at high risk are to benefit. Unfortunately, the total number of operative complications is increased when revascularization procedures are performed *routinely*, because some patients who are not in need of revascularization will be exposed to its hazards.

The population of patients with UA/NSTEMI includes a subgroup (i.e., those with left main coronary stenosis or multivessel stenoses with reduced LV function) at high risk for adverse outcome and therefore highly likely to benefit from revascularization. Clinical evaluation and noninvasive testing will aid in the identification of most of these high-risk patients who have markers of high risk such as advanced age (greater than 70 years), prior MI, revascularization, ST-segment deviation, CHF or depressed resting LV function (i.e., EF less than 0.40) on noninvasive study, or noninvasive stress test findings that suggest severe ischemia (see Section III. C). The remaining larger subgroup of patients, however, do not have the findings that portend a high risk for adverse outcomes. Accordingly, they are not likely to receive such benefit from routine revascularization, and invasive study is optional for them. It can be safely deferred pending further clinical developments. Decisions regarding coronary angiography in patients who are *not* high risk according to findings on clinical examination and noninvasive testing can be individualized on the basis of patient preferences.

The data on which these recommendations are based are from 4 randomized trials, TIMI IIIB (19), VANQWISH (266), Medicine versus Angiography in Thrombolytic Exclusion (MATE) (265), and FRISC II (278); a large prospective multinational registry, the OASIS registry (279); and 2 retrospective analyses (280,281).

In TIMI IIIB, 1473 patients with UA (67%) or NSTEMI (33%) with chest pain of less than 24-h duration were randomized to either an invasive or early conservative strategy. At 42 days, 16.2% of the early invasive patients had died, had experienced a nonfatal MI, or had a strongly positive exercise test vs. 18.1% of early conservative patients ($p = 0.33$). Similarly, there was no difference in the outcome of death or MI in a comparison of treatment strategies (4,282). An analysis of factors associated with the failure of medical therapy in TIMI IIIB predicted patients who could be directed to a more invasive strategy in a cost-efficient manner. Among the 733 patients randomized to the conservative strategy, the factors that independently predicted failure of medical therapy included ST-segment depression on the qualifying ECG, prior ASA use, and older age. For most patients with 3 or more such risk factors, medical therapy had failed, defined as death, MI, rest angina, or markedly abnormal stress test results at 6 weeks. A combination of factors should be considered in the selection of patients for expedited angiography and revascularization (282).

NSTEMI represents a high-risk acute ischemic syndrome. The VANQWISH Investigators randomly assigned 920 patients with NSTEMI defined on the basis of CK-MB to either early invasive (462 patients) or conservative (458 patients) management within 72 h of the onset of an NSTEMI (266). The number of patients with either death or recurrent nonfatal MI and the number who died were higher in the invasive strategy group at hospital discharge (36 vs. 15 patients, p = 0.004 for death or nonfatal MI; 21 vs. 6, p = 0.007 for death), and these differences persisted at 1 month and at 1 year. Mortality rates during the almost 2-year follow-up also showed a strong trend toward reduction in patients assigned to the conservative strategy compared with those assigned to the invasive strategy (hazard ratio, 0.72; 95% CI, 0.51 to 1.01). The investigators concluded that most patients with NSTEMI do *not* benefit from routine, early invasive management and that a conservative, ischemia-guided initial approach is both safe and effective even in the predominantly high-risk male population of the VANQWISH.

The MATE trial (265) enrolled 201 patients with a variety of ACSs who were ineligible for thrombolytic therapy and were assigned to an early invasive or early conservative strategy. Although the incidence of total ischemic in-hospital events was lower in the early invasive strategy group, there were no differences between the groups in the incidence of death and reinfarction. Follow-up at a median of 21 months showed no significant differences in the cumulative incidences of death, MI, rehospitalization, or revascularization.

Most recently, in the FRISC II study, 3048 ACS patients were treated with dalteparin for 5 to 7 days (278). Of these patients, 2457 without acute problems who were not at high risk of a revascularization procedure (e.g., their age was not greater than 75 years, and they did not have prior CABG) were randomized (2 × 2 factorial design) to continue to receive either dalteparin or placebo (double blind) and either an invasive or a noninvasive treatment strategy. The latter patients were revascularized only for refractory or recurrent symptoms despite maximum medical therapy or severe ischemia (ST-segment depression greater than or equal to 0.3 mV) on symptom-limited exercise testing or AMI. At 6 months, there were no differences between continued dalteparin compared with placebo. However, death or MI occurred in 9.4% of patients assigned to the invasive strategy and in 12.1% of those assigned the noninvasive strategy (p less than 0.031). At 1 year the mortality rate in the invasive strategy group was 2.2% compared with 3.9% in the noninvasive strategy group (p = 0.016) (278a). It may be concluded from FRISC II that patients with UA/NSTEMI who are not at very high risk for revascularization and who first receive an average of 6 days of treatment with LMWH, ASA, nitrates, and beta-blockers have a better outcome at 6 months with a (delayed) routine invasive approach than with a routine conservative approach.

In the TACTICS-TIMI 18 trial (518), 2220 patients with UA or NSTEMI were treated with ASA, heparin, and the GP IIb/IIIa inhibitor tirofiban. They were randomized to an early invasive strategy with routine coronary angiography within 48 h followed by revascularization if the coronary anatomy was deemed suitable, or to a more conservative strategy. In the latter, catheterization was performed only if the patient had recurrent ischemia or a positive stress test. Death, MI, or rehospitalization for ACS at 6 months occurred in 15.9% of patients assigned to the invasive strategy vs. 19.4% assigned to the more conservative strategy (p = 0.025). Death or MI (539) was also reduced at 6 months (7.3% vs 9.5%, p less than 0.05). The beneficial effects on the outcome were observed in medium- and high-risk patients, as defined by an elevation of TnT greater than 0.01 ng per mL, the presence of ST-segment deviation, or a TIMI risk score of greater than 3 (517). In the absence of these high-risk features, outcomes in patients assigned to the 2 strategies were similar. Rates of major bleeding were similar, and lengths of hospital stay were reduced in patients assigned to the invasive strategy. The benefits of the invasive strategy were achieved at no significant increase in the costs of care over the 6-month follow-up period.

Thus, both the FRISC II (278) and TACTICS-TIMI 18 (518) trials, the 2 most recent trials comparing invasive vs. conservative strategies in patients with UA/NSTEMI, showed a benefit in patients assigned to the invasive strategy. In contrast to earlier trials, a large majority of patients undergoing PCI in these 2 trials received coronary stenting as opposed to balloon angioplasty alone. In FRISC II, the invasive strategy involved treatment for an average of 6 days in the hospital with LMWH, ASA, nitrates, and beta blockers prior to coronary angiography, an approach that would be difficult to adopt in US hospitals. In TACTICS-TIMI 18, treatment included the GP IIb/IIIa antagonist tirofiban, which was administered for an average of 22 h *prior to* coronary angiography. The routine use of the GP IIb/IIIa inhibitor in this trial may have eliminated the excess risk of early (within 7 days) acute MI in the invasive arm, an excess risk that was observed in FRISC II and other trials in which there was no routine "upstream" use of a GP IIb/IIIa blocker. Therefore, an invasive strategy is associated with a better outcome in UA/NSTEMI patients at high risk as defined in Table 6 and in TACTICS-TIMI 18 and who receive a GP IIb/IIIa inhibitor (518). Although the benefit of intravenous GP IIb/IIIa inhibitors is established for UA/NSTEMI patients undergoing PCI, the optimum time to commence these drugs before the procedure has not been established. In the PURSUIT trial (10), in patients with UA/NSTEMI who were admitted to community hospitals, the administration of eptifibatide was associated with a reduced need for transfer to tertiary referral centers and improved outcomes (541).

~~Retrospective analysis of these trials identified 2 subgroups of patients who appear to benefit from an early invasive strategy: patients who presented with ST-segment depression and those greater than 65 years old. When these 2 subgroups of patients were assigned to the conservative arm of TIMI IIIB, they were at a higher risk of failing medical therapy (282), and they displayed a particularly strong benefit from the invasive therapy in FRISC II (278).~~

~~It is important to note the differences between these randomized trials. Baseline patient characteristics indicate that risk was highest in VANQWISH, which enrolled only NSTEMI patients, and lowest in FRISC II, which had fewer smokers, patients with previous MIs or hypertension, diabetics, and patients with NSTEMI (as opposed to UA). FRISC II excluded patients greater than 75 years old and with prior CABG and treated all patients with LMWH for a median of 6 days before deployment of the invasive strategy. FRISC II also had the most restrictive criteria for the use of revascularization in patients randomized to a conservative strategy, requiring greater than 0.3 mV ST-segment depression on stress testing. TIMI IIIB patients seem to be intermediate in risk, but again, the subgroup with NSTEMI had a higher risk for death or reinfarction. Other differences may be related to the lower mortality rates with surgical revascularization in FRISC II compared with VANQWISH. Thus, in VANQWISH, the poor outcome in the invasive arm was observed in high-risk patients with early intervention, whereas the favorable effect with the invasive arm in FRISC II was seen in patients at lower risk in whom intervention was carried out after 5 to 7 days. FRISC II also used centers of excellence for CABG and had a very low peri-CABG mortality rate.~~

~~Data from recent observational studies support the conclusion that an early invasive strategy does not reduce the "hard" end points of death and MI but does reduce recurrent stable angina or UA. The OASIS Registry Investigators (279) prospectively studied the relation between rates of angiography and revascularization and rates of cardiovascular death, nonfatal MI, stroke, refractory angina, and major bleeding in a prospective registry-based study in 6 countries with widely varying intervention rates. A total of 7987 patients who presented with UA/NSTEMI were recruited from 95 hospitals and followed for up to 6 months. Rates of procedure use were highest in patients in the United States and Brazil, intermediate in Canada and Australia, and lowest in Hungary and Poland. There were no significant differences in death or MI among these countries. There were no differences in the rates of death or MI in countries with the highest rates of invasive procedures (59%) vs. the remaining countries (21%). Higher rates of invasive and revascularization procedures were associated with lower rates of angina and readmission for UA but a higher incidence of stroke.~~

~~Although PCI has advanced with the development of stents and platelet GP IIb/IIIa receptor blockers, the use of the latter has also been associated with a reduced need for revascularization in non–ST-segment elevation ACS (10,21). In this regard, an analysis from the GUSTO-IIb and PURSUIT trials of patients who underwent coronary angiography during initial hospitalization for non–ST-segment elevation ACS found that a conservative, ischemia-guided strategy was associated with improved outcome compared with a routine invasive strategy (adjusted OR for death or MI, invasive vs. conservative: 6.61 at 30 days and 1.98 at 6 months) (281). At 1 year, however, the outcomes were similar.~~

~~Although data are not available to permit a formal cost-effectiveness analysis of these alternate strategies, any savings realized initially in the group not receiving coronary angiography and revascularization has the potential to be offset by the need for initial longer hospitalization and for subsequent care, as was observed in TIMI IIIB (4,19,282). However, the VANQWISH results showed a significantly longer duration of hospitalization for the invasive strategy (266).~~

~~Based on these data, a *routine early* invasive strategy with angiography and revascularization is difficult to justify. The FRISC II data suggest that a *delayed* invasive strategy after 5 to 7 days of LMWH and beta-blocker therapy in selected patients (<75 years old and no prior CABG) could be a useful approach, but the delay of angiography by 6 days mitigates one of the advantages of the invasive strategy. The early use of angiography in patients deemed at high risk on the basis of clinical and noninvasive test findings would appear to be an acceptable approach.~~

Some selected areas require additional comment. In a patient with UA, a history of *prior PCI* within the past 6 months suggests the presence of restenosis, which often can be effectively treated with repeat PCI. Coronary angiography without preceding functional testing is generally indicated. Patients with *prior CABG* represent another subgroup for whom a strategy of early coronary angiography is usually indicated. The complex interplay between the progression of native coronary disease and the development of graft atherosclerosis with ulceration and embolization is difficult to untangle noninvasively; all argue for early coronary angiography. In addition, patients with known or suspected *reduced LV systolic function*, including patients with prior anterior Q-wave MIs, those with prior measurements that show depressed LV function, and those who present with CHF, have sufficient risk that the possibility of benefit from revascularization procedures merits early coronary angiography without preceding functional testing.

In patients with UA/NSTEMI, coronary angiography typically shows the following profile: 1) no severe epicardial stenosis in 10% to 20%, 2) 1-vessel stenosis in 30% to 35%, 3) multivessel stenosis in 40% to 50%, and 4) significant (greater than 50%) left main stenosis in 4% to 10%. In the early invasive strategy in TIMI IIIB, no critical obstruction (less than 60% diameter stenosis) was found in 19% of patients, 1-vessel stenosis in 38%, 2-vessel stenosis in 29%, 3-vessel stenosis in 15%, and left main stenosis (greater than 50%) in 4%. Complex plaques are usually believed to be responsible for the culprit lesions. These usually are eccentric and sometimes have irregular borders, and correlate with intracoronary thrombi and an increased risk of recurrent ischemia at rest, MI, and cardiac death (283). Similar findings were noted in more than 80% of the patients in the VANQWISH trial, and more than 1 complex lesion was found in most patients (284). Interestingly, in TIMI IIIB, many of the patients without severe stenosis had reduced contrast clearance, which suggests microvascular dysfunction (285), which may contribute to impaired myocardial perfusion.

Patients with severe 3-vessel stenosis and reduced LV function and those with left main stenosis should be considered

for early CABG (see Section IV). In low-risk patients, quality of life and patient preferences should be given considerable weight in the selection of a treatment strategy. Low-risk patients whose symptoms do not respond well to maximal medical therapy and who experience poor quality of life and functional status and are prepared to accept the risks of revascularization should be considered for revascularization.

The discovery that a patient does not have significant obstructive CAD can help avert improper "labeling" and prompt a search for the true cause of symptoms. Unfortunately, many such patients continue to have recurrent symptoms, become disabled, are readmitted to the hospital, and continue to consume healthcare resources even with repeated coronary angiography (286,287).

It is not presently possible to define the extent of comorbidity that would, in every case, make referral for coronary angiography and revascularization inappropriate. The high-risk patient with significant comorbidities requires thoughtful discussion among the physician, patient, and family and/or patient advocate. A decision for or against revascularization must be made on a case-by-case basis.

Examples of extensive comorbidity that usually preclude revascularization include 1) advanced or metastatic malignancy with a projected life expectancy of less than or equal to 1 year, 2) intracranial pathology that contraindicates the use of systemic anticoagulation or causes severe cognitive disturbance (e.g., Alzheimer's disease) or advanced physical limitations, 3) end-stage cirrhosis with symptomatic portal hypertension (e.g., encephalopathy, visceral bleeding), and 4) CAD that is known from previous angiography not to be amenable to revascularization. This list is not meant to be all inclusive. More difficult decisions involve patients with comorbidities not as serious as those listed here; examples include patients who have moderate or severe renal failure but are stable on dialysis.

Consultation with an interventional cardiologist and cardiac surgeon before coronary angiography is advised to define technical options and likely risks and benefits. The operators who perform coronary angiography and revascularization and the facility in which these procedures are carried out are important considerations because the availability of interventional cardiologists and cardiac surgeons who are experienced in high-risk and complex patients is essential. As a general principle, the potential benefits of coronary angiography and revascularization must be carefully weighed against the risks and the conflicting results of the clinical trials and registries.

IV. CORONARY REVASCULARIZATION

A. General Principles

As discussed in Section III, coronary angiography is useful for defining the coronary artery anatomy in patients with UA/NSTEMI and for identifying subsets of high-risk patients who may benefit from early revascularization. Coronary revascularization (PCI or CABG) is carried out to improve prognosis, relieve symptoms, prevent ischemic complications, and improve functional capacity. The decision to proceed from diagnostic angiography to revascularization is influenced not only by the coronary anatomy but also by a number of additional factors, including anticipated life expectancy, ventricular function, comorbidity, functional capacity, severity of symptoms, and quantity of viable myocardium at risk. These are all important variables that must be considered before revascularization is recommended. For example, patients with distal obstructive coronary lesions or those who have large quantities of irreversibly damaged myocardium are unlikely to benefit from revascularization, particularly if they can be stabilized with medical therapy. Patients with high-risk coronary anatomy are likely to benefit from revascularization in terms of both symptom improvement and long-term survival (Fig. 12). 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/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina (26), as well as in the ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery (274).

Plaque rupture with subsequent platelet aggregation and thrombus formation is most often the underlying pathophysiological cause of UA (1,18). The management of many patients with UA/NSTEMI often involves revascularization of the underlying CAD with either PCI or CABG. Selection of the appropriate revascularization strategy often depends on clinical factors, operator experience, and extent of the underlying CAD. Many patients with UA/NSTEMI have coronary disease that is amenable to either form of therapy. However, some patients have high-risk features, such as reduced LV function, that places them in a group of patients who experience improved long-term survival rates with CABG. In other patients, adequate revascularization with PCI may not be optimal or even possible, and CABG may be the better revascularization choice.

Findings in large registries of patients with CAD suggest that the mode of clinical presentation should have little bearing on the subsequent revascularization strategy. In a series of 9263 patients with CAD, an admission diagnosis of UA (vs. chronic stable angina) had no influence on 5-year survival rates after CABG, percutaneous transluminal coronary angioplasty (PTCA), or medical treatment (288). An initial diagnosis of UA also did not influence survival 3 years after either CABG or PTCA in 59,576 patients treated in the state of New York (289). Moreover, long-term survival rates after CABG are similar for UA patients who present with rest angina, increasing angina, new-onset angina, or post-MI angina (290). These observations suggest that published data that compare definitive treatments for patients who initially present with multiple clinical manifestations of CAD can be used to guide management decisions for patients who present with UA/NSTEMI. Consequently, the indications for coronary revascularization in patients with UA/NSTEMI are, in general, similar to those for patients with stable angina.

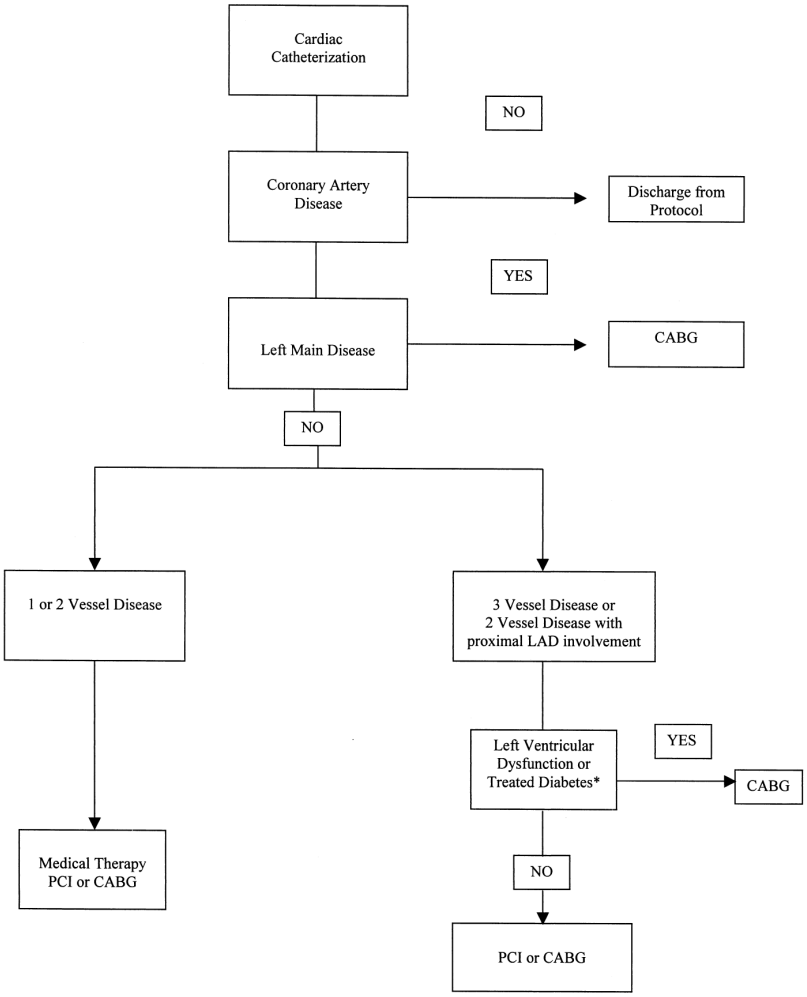


Figure 12. Revascularization strategy in UA/NSTEMI. *There is conflicting information about these patients. Most consider CABG to be preferable to PCI.

The principal difference is that the impetus for some form of revascularization is stronger in patients with UA/NSTEMI by the very nature of the presenting symptoms (290).

Recommendations for Revascularization with PCI and CABG in Patients with UA/NSTEMI (see Table 20)

Class I

1. **CABG for patients with significant left main CAD. (Level of Evidence: A)**
2. **CABG for patients with 3-vessel disease; the survival benefit is greater in patients with abnormal LV function (EF less than 0.50). (Level of Evidence: A)**
3. **CABG for patients with 2-vessel disease with significant proximal left anterior descending CAD and either abnormal LV function (EF less than 0.50) or demonstrable ischemia on noninvasive testing. (Level of Evidence: A)**
4. **PCI or CABG for patients with 1- or 2-vessel CAD 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)**
5. **PCI for patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function and without diabetes. (Level of Evidence: A)**
6. **Intravenous platelet GP IIb/IIIa inhibitor in UA/NSTEMI patients undergoing PCI. (Level of Evidence: A)**

Class IIa

1. **Repeat CABG for patients with multiple saphenous vein graft (SVG) stenoses, especially when there is significant stenosis of a graft that supplies the LAD. (Level of Evidence: C)**
2. **PCI for focal SVG lesions or multiple stenoses in poor candidates for reoperative surgery. (Level of Evidence: C)**
3. **PCI or CABG for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. (Level of Evidence: B)**
4. **PCI or CABG for patients with 1-vessel disease with significant proximal left anterior descending CAD. (Level of Evidence: B)**

Table 20. Mode of Coronary Revascularization for UA/NSTEMI

Extent of Disease	Treatment	Class/Level of Evidence
Left main disease,* candidate for CABG	CABG	I/A
	PCI	III/C
Left main disease, not candidate for CABG	PCI	IIb/C
Three-vessel disease with EF <0.50	CABG	I/A
Multivessel disease including proximal LAD with EF <0.50 or treated diabetes	CABG or PCI	I/A IIb/B
Multivessel disease with EF >0.50 and without diabetes	PCI	I/A
One- or 2-vessel disease without proximal LAD but with large areas of myocardial ischemia or high-risk criteria on noninvasive testing (see Table 17)	CABG or PCI	I/B
One-vessel disease with proximal LAD	CABG or PCI	IIa/B†
One- or 2-vessel disease without proximal LAD with small area of ischemia or no ischemia on noninvasive testing	CABG or PCI	III/C†
Insignificant coronary stenosis	CABG or PCI	III/C

*≥50% diameter stenosis.
†Class/level of evidence I/A if severe angina persists despite medical therapy.

5. **CABG with the internal mammary artery for patients with multivessel disease and treated diabetes mellitus. (Level of Evidence: B)**

Class IIb

PCI for patients with 2- or 3-vessel disease with significant proximal left anterior descending CAD, with treated diabetes or abnormal LV function, and with anatomy suitable for catheter-based therapy. (Level of Evidence: B)

Class III

1. **PCI or CABG for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD or with mild symptoms or symptoms that are unlikely due to myocardial ischemia or who have not received an adequate trial of medical therapy and who have no demonstrable ischemia on noninvasive testing. (Level of Evidence: C)**
2. **PCI or CABG for patients with insignificant coronary stenosis (less than 50% diameter). (Level of Evidence: C)**
3. **PCI in patients with significant left main coronary artery disease who are candidates for CABG. (Level of Evidence: B)**

B. Percutaneous Coronary Intervention

In recent years, technological advances coupled with high acute success rates and low complication rates have increased the use of percutaneous catheter procedures in patients with UA/NSTEMI. Stenting and the use of adjunctive platelet GP IIb/IIIa inhibitors have further broadened the use of PCI by improving both the safety and durability of these procedures.

Percutaneous coronary revascularization (intervention) strategies are referred to in these guidelines as "PCI." This term refers to a family of percutaneous techniques, including standard balloon angioplasty (PTCA*), intracoronary stenting, and atheroablative technologies (e.g., atherectomy, thrombectomy, laser). The majority of current PCIs involve balloon dilatation and coronary stenting. Stenting has contributed greatly to catheter-based revascularization by reducing the risks of both acute vessel closure and late restenosis. Although stenting has become the most widely used percutaneous technique, and in 1998 it was used in approximately 525,000 of 750,000 PCIs, other devices continue to be used for specific lesions and patient subsets. Although the safety and efficacy of atheroablative and thrombectomy devices have been demonstrated, limited outcome data are available that describe the use of these new strategies specifically in patients with UA/NSTEMI (291).

In the absence of active thrombus, rotational atherectomy is useful to debulk arteries that contain large atheromatous burdens and to modify plaques in preparation for more definitive treatment with adjunctive balloon angioplasty or stenting. This approach is particularly well suited for use in hard, calcific lesions, in which it preferentially ablates inelastic tissue. Rotational atherectomy, even in patients with stable angina, may result in the release of CK-MB isoenzymes after seemingly uncomplicated procedures. This often reflects distal embolization of microparticulate matter and platelet activation, and the clinical outcome has been correlated with the magnitude of the enzyme elevation (292). The magnitude and frequency of postprocedural myocardial necrosis reflected in CK-MB enzyme rises can be reduced with concomitant treatment with a platelet GP IIb/IIIa inhibitor (293,294).

Other new techniques and devices, such as the use of Angiojet thrombectomy and extraction atherectomy (translu-

*PTCA is used to refer to studies in which this was the dominant form of PCI, before the widespread use of stenting.

minal extraction catheter), are being tested for the treatment of thrombi that are visible within a coronary artery (295). In addition, there is some evidence that extraction atherectomy can be used to treat SVG disease through the removal of degenerated graft material and thrombus (296). In this situation, it often is used as an adjunct to more definitive therapy with balloon angioplasty and stents.

The reported clinical efficacy of PCI in UA/NSTEMI has varied. This is likely attributable to differences in study design, treatment strategies, patient selection, and operator experience. Nevertheless, the success rate of PCI in patients with UA/NSTEMI is often quite high. In TIMI IIIB, for example, angiographic success was achieved in 96% of patients with UA/NSTEMI who underwent balloon angioplasty. With clinical criteria, periprocedural MI occurred in 2.7%, emergency bypass surgery was required in 1.4%, and the death rate from the procedure was 0.5% (4,19,297).

The use of balloon angioplasty has been evaluated in several other trials of patients with UA vs. stable angina (298–303). A large retrospective study compared the results of angioplasty in patients with stable angina with that in patients with UA (299). After an effort to control patients with UA with medical therapy, PTCA was carried out an average of 15 days after hospital admission. In comparison with patients with stable angina, UA patients showed no significant differences with respect to primary clinical success (92% for UA vs. 94% for stable angina), in-hospital mortality rates (0.3% vs. 0.1%), or the number of adverse events at 6-month follow-up (299). These findings suggest that PTCA results in immediate and 6-month outcomes that are comparable in patients with stable angina and UA. In addition, in a retrospective analysis, the results in UA patients were similar regardless of whether the procedure was performed early (less than 48 h) or late (greater than 48 h) after hospital presentation (298).

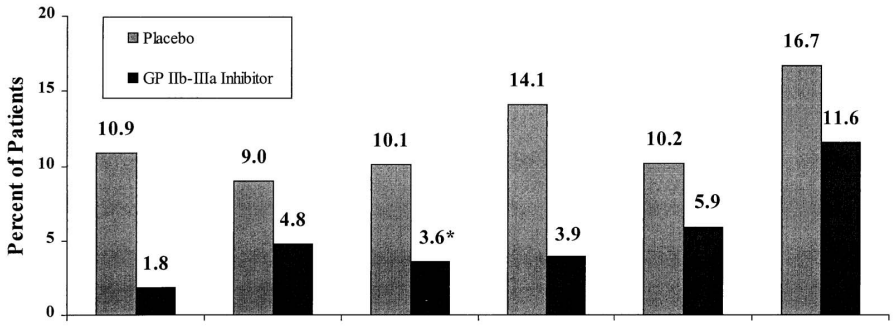
Although other earlier studies (predominantly from the 1980s) have suggested that patients with UA who undergo balloon PTCA have higher rates of MI and restenosis compared with patients with stable angina (300–304), contemporary catheter revascularization often involves coronary stenting and adjunctive use of platelet GP IIb/IIIa receptor inhibitors, which are likely to affect not only immediate- but also long-term outcome (246). Historically, PTCA has been limited by acute vessel closure, which occurs in approximately 5% of patients, and by coronary restenosis, which occurs in approximately 35% to 45% of treated lesions during a 6-month period. Coronary stenting offers an important alternative to PTCA because of its association with both a marked reduction in acute closure and lower rates of restenosis. By preventing acute or threatened closure, stenting reduces the incidence of procedure-related STEMI and need for emergency bypass surgery and may also prevent other ischemic complications.

In a comparison of the use of the Palmaz-Schatz coronary stent in patients with stable angina and patients with UA, no significant differences were found with respect to in-hospital outcome or restenosis rates (305). Another study found similar rates of initial angiographic success and in-hospital major complications in stented patients with UA compared with those with stable angina (306). Major adverse cardiac events at 6 months were also similar between the 2 groups, whereas the need for repeat PCI and target vessel revascularization was actually less in the UA group. On the other hand, other recent data have suggested that UA increases the incidence of adverse ischemic outcomes in patients undergoing coronary stent deployment despite therapy with ticlopidine and ASA, which suggests the need for more potent antiplatelet therapy in this patient population (307,308).

1. Platelet Inhibitors and Percutaneous Revascularization

An important advance in the treatment of patients with UA/NSTEMI who are undergoing PCI has been the introduction of platelet GP IIb/IIIa receptor inhibitors (see Section III. B) (10,18,21,244–246,309–311). This therapy takes advantage of the fact that platelets play an important role in the development of ischemic complications that may occur in patients with UA/NSTEMI or during coronary revascularization procedures. Currently, 3 platelet GP IIb/IIIa inhibitors are approved by the Food and Drug Administration based on the outcome of a variety of clinical trials: abciximab (ReoPro), tirofiban (Aggrastat), and eptifibatide (Integrilin). The Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of PTCA and Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade (EPILOG), CAPTURE, and Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT) trials investigated the use of abciximab; the PRISM, PRISM-PLUS, and Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE) trials evaluated tirofiban; and the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) and PURSUIT trials studied the use of eptifibatide (Figs. 13 and 14). All 3 of these agents interfere with the final common pathway for platelet aggregation. All have shown efficacy in reducing the incidence of ischemic complications in patients with UA (Fig. 10, Table 16).

In the EPIC trial, high-risk patients who were undergoing balloon angioplasty or directional atherectomy were randomly assigned to 1 of 3 treatment regimens: placebo bolus followed by placebo infusion for 12 h; weight-adjusted abciximab bolus (0.25 mg per kg) and 12-h placebo infusion; or weight-adjusted abciximab bolus and 12-h infusion (10 mcg per min) (244,309). In this trial, high risk was defined as severe UA, evolving MI, or high-risk coronary anatomy defined at cardiac catheterization. The administration of bolus and continuous infusion of abciximab reduced the rate of ischemic complications (death, MI, revascularization) by 35% at 30 days (12.8 vs. 8.3%, $p = 0.0008$), by 23% at 6 months, and by 13% at 3 years (244,309,310). The favorable long-term effect was mainly due to a reduction in the need for bypass surgery or repeat PCI in patients with an initially successful procedure.



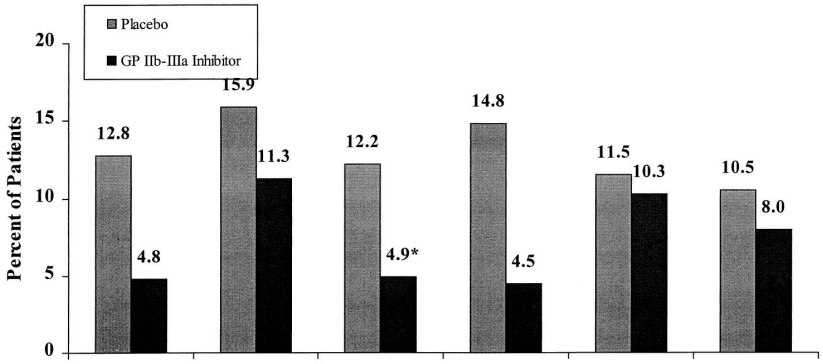
	EPIC	CAPTURE	EPILOG	EPISTENT*	PRISM-PLUS^	PURSUIT^
	P=0.001	*P*=0.003	*P*<0.001	*P*=0.001	*P*=N/A **	*P*=0.01
Relative Reduction	83	47 %	64%	72%	42%	31%
Absolute Reduction	9.1%	4.2%	6.5%	10.2%	4.3%	5.1%
Sample Size N	321	1265	1328	335	475	1228
Rx Duration (hrs)	12	18-25	12	12	57-95	72-96
GP IIb-IIIa Inhibitor	Abciximab	Abciximab	Abciximab	Abciximab	Tirofiban	Eptifibatide

* Combined Abciximab Arms ~ Stent +/- Abciximab ** Confidence Interval (0.29-1.09) ^ Patients that went on to PCI

Figure 13. Death and MI at 30 days after PCI in patients with ACS: GP IIb/IIIa trials. EPIC (315), CAPTURE (182), EPILOG (internal data, Centocor), and EPISTENT (internal data, Centocor) trials were intervention trials in PRISM-PLUS (21) and PURSUIT (10); PCI was performed at the physician's discretion.

The administration of abciximab in the EPIC trial was associated with an increased bleeding risk and transfusion requirement. In the subsequent EPILOG trial, which used weight-adjusted dosing of concomitant heparin, the incidence of major bleeding and transfusion associated with abciximab and low-dose weight-adjusted heparin (70 U per kg) was similar to that seen with placebo (245). The cohort of patients with UA undergoing PCI in the EPILOG trial demonstrated a 64% reduction (10.1% to 3.6%, p = 0.001) in the composite occurrence of death, MI, or urgent revascularization to 30 days with abciximab therapy compared with placebo (standard-dose weight-adjusted heparin).

The RESTORE trial was a randomized double-blind study that evaluated the use of tirofiban vs. placebo in 2139 patients with UA or AMI, including patients with non–Q-wave MI who underwent PCI (balloon PTCA or directional atherectomy) within 72 h of hospitalization (312). The trial was designed to evaluate both clinical outcomes and resteno-



	EPIC	CAPTURE	EPILOG	EPISTENT~	IMPACT II**	RESTORE
	P=0.012	*P*=0.012	*P*<0.001	*P*=0.003	*P*=NS †	*P*=0.052 ‡
Relative Reduction	63%	28.9%	60 %	70%	10.4%	24%
Absolute Reduction	8.0%	4.6%	7.3%	10.3%	1.2%	2.5%
Sample Size N	321	1265	1328	335	1653	2141
Rx Duration (hrs)	12	18-24	12	12	20-24	36
GP IIb-IIIa Inhibitor	Abciximab	Abciximab	Abciximab	Abciximab	Eptifibatide	Tirofiban

* Combined Abciximab Arms ~ Stent +/- Abciximab ** Combined Eptifibatide Arms

† IMPACT II 92% UA, 8% AMI

‡ RESTORE 67% UA, 26% AMI (non-primary intervention), 7% AMI (primary PTCA)

Figure 14. Death, MI, and urgent intervention at 30 days after PCI in patients with ACS: GP IIb/IIIa trials. Data are from EPIC (315), CAPTURE (182), EPILOG (internal data, Centocor), EPISTENT (246), IMPACT II (316), and RESTORE (312).

sis. Although the infusion of tirofiban (bolus of 10 mcg per kg followed by a 36-h infusion at 0.15 mcg · kg^{-1} · min^{-1}) had no significant effect on the reduction in restenosis at 6 months, a trend was observed for a reduction in the combined clinical end point of death/MI, emergency CABG, unplanned stent placement for acute or threatened vessel closure, and recurrent ischemia compared with placebo at 6 months (27.1% vs. 24.1%, p = 0.11).

The clinical efficacy of tirofiban was further evaluated in the PRISM-PLUS trial, which enrolled patients with UA/NSTEMI within 12 h of presentation (21) (see Section III). Among patients who underwent PCI, the 30-day incidence of death, MI, refractory ischemia, or rehospitalization for UA was 15.3% in the group that received heparin alone compared with 8.8% in the tirofiban/heparin group. After PCI, death or nonfatal MI occurred in 10.2% of those receiving heparin vs. 5.9% of tirofiban-treated patients.

Eptifibatide, a cyclic heptapeptide GP IIb/IIIa inhibitor, has also been administered to patients with ACS. In the PURSUIT trial, nearly 11,000 patients who presented with an ACS were randomized to receive either UFH and ASA or eptifibatide, UFH, and ASA (10). In patients undergoing PCI within 72 h of randomization, eptifibatide administration resulted in a 31% reduction in the combined end point of nonfatal MI or death at 30 days (17.7 vs. 11.6%, p = 0.01).

The EPISTENT trial was designed to evaluate the efficacy of abciximab as an adjunct to elective coronary stenting (246,313). Of the nearly 2,400 patients who were randomized, 20% of the stented patients had UA within 48 h of the procedure. Patients were randomly assigned to either stent deployment with placebo, stent plus abciximab, or PTCA plus abciximab. Nineteen percent of the PTCA group had provisional coronary stent deployment for a suboptimal angioplasty result. All stented patients in this trial received oral ASA (325 mg) and oral ticlopidine (250 mg twice daily for 1 month). The adjunctive use of abciximab was associated with a significant reduction in the composite clinical end point of death, MI, or urgent revascularization. The 30-day primary end point occurred in 10.8% of the stent-plus-placebo group, 5.3% of the stent-plus-abciximab group, and 6.9% of the PTCA-plus-abciximab group. Most of the benefit from abciximab were related to a reduction in the incidence of moderate to large MI (CK greater than 5 times the upper limit of normal or Q-wave MI); these reductions occurred in 5.8% of the stent-plus-placebo group, 2.6% of the balloon-plus-abciximab group, and 2.0% of the stent-plus-abciximab group.

At 1 year of follow-up, stented patients who received bolus and infusion abciximab had reduced mortality rates compared with patients who received stents without abciximab (1.0% vs. 2.4%, representing a 57% risk reduction; p = 0.037) (314). In diabetics, target vessel revascularization at 6 months was markedly and significantly reduced (51%, p = 0.02) in stented patients who received abciximab compared with those who did not. Although a similar trend was also observed in nondiabetic patients, it did not reach statistical significance.

The Enhanced Suppression of Platelet Receptor GP IIb/IIIa Using Integrilin Therapy (ESPRIT) trial was a placebo-controlled trial designed to assess whether eptifibatide improved the outcome of patients undergoing stenting (542). Fourteen percent of the 2064 patients enrolled in ESPRIT had UA/NSTEMI. The primary end point (the composite of death, MI, target-vessel revascularization, and "bailout" GP IIb/IIIa inhibitor therapy) was reduced from 10.5% to 6.6% with treatment (p = 0.0015). There was consistency in the reduction of events in all components of the composite end points and in all major subgroups, including patients with UA/NSTEMI. Major bleeding occurred more frequently in patients who received eptifibatide (1.3%) than in those who received placebo (0.4%; p = 0.027). However, no significant difference in transfusion occurred. At 1-year follow-up, death or MI occurred in 12.4% of placebo-track patients and 8.0% of eptifibatide-treated patients (p = 0.001) (543).

In the only head-to-head comparison of 2 GP IIb/IIIa inhibitors, the Tirofiban and Reopro Give Similar Efficacy Outcomes Trial (TARGET) randomized 5308 patients to tirofiban or abciximab before undergoing PCI with the intent to perform stenting (544). The primary end point, a composite of death, nonfatal MI, or urgent target-vessel revascularization at 30 days, occurred less frequently in those receiving abciximab than tirofiban (6.0% vs. 7.6%, p = 0.038). There was a similar direction and magnitude for each component of the end point. The difference in outcome between the 2 treatment groups may be related to a suboptimal dose of tirofiban resulting in inadequate platelet inhibition.

Eptifibatide has not been compared directly to either abciximab or tirofiban.

In summary, data from both retrospective observations and randomized clinical trials indicate that PCI can lead to angiographic success in most patients with UA/NSTEMI (Figs. 13 and 14). The safety of these procedures in these patients is enhanced by the addition of intravenous platelet GP IIb/IIIa receptor inhibitors to the standard regimen of ASA, heparin, and anti-ischemic medications.

C. Surgical Revascularization

Two randomized trials conducted in the early years of CABG compared medical and surgical therapy in UA. The National Cooperative Study Group randomized 288 patients at 9 centers between 1972 and 1976 (317). The Veterans Administration (VA) Cooperative Study randomized 468 patients between 1976 and 1982 at 12 hospitals (269,319–321). Both trials included patients with progressive or rest angina accompanied by ST-T–wave changes. Patients greater than 70 years old or with a recent MI were excluded; the VA study included only men. In the National Cooperative Study, the hospital mortality rate was 3% for patients undergoing medical therapy and 5% after CABG (p = NS). Follow-up to 30 months showed no differences in survival rates between the treatment groups. In the VA Cooperative Study, survival rates to 2 years were similar after medical therapy and CABG overall and in subgroups

defined by the number of diseased vessels. A post hoc analysis of patients with depressed LV function, however, showed a significant survival advantage with CABG regardless of the number of bypassed vessels (321).

All randomized trials of CABG vs. medical therapy (including those in stable angina) have reported improved symptom relief and functional capacity with CABG. However, long-term follow-up in these trials has suggested that by 10 years, there is a significant attenuation of both the symptom relief and survival benefits previously conferred by CABG, although these randomized trials reflect an earlier era for both surgical and medical treatment. Improvements in anesthesia and surgical techniques, including internal thoracic artery grafting to the LAD, and improved intraoperative myocardial protection with cold potassium cardioplegia, are not reflected in these trials. In addition, the routine use of heparin and ASA in the acute phase of medical therapy and the range of additional therapeutic agents that are now available (e.g., LMWH, GP IIb/IIIa inhibitors) represent significant differences in current practice from the era in which these trials were performed.

A meta-analysis was performed on the results of 6 trials conducted between 1972 and 1978 to compare long-term survival in CAD patients treated medically or with CABG (142). A clear survival advantage was documented for CABG in patients with left main and 3-vessel coronary disease that was independent of LV function. No survival difference was documented between the 2 therapies for patients with 1- or 2-vessel coronary disease.

Pocock et al. (322) performed a meta-analysis on the results of 8 randomized trials completed between 1986 and 1993 and compared the outcomes of CABG and PTCA in 3,371 patients with multivessel CAD before widespread stent use. Many of these patients presented with UA. At 1-year follow-up, no difference was documented between the 2 therapies in cardiac death or MI, but a lower incidence of angina and need for revascularization was associated with CABG.

The Bypass Angioplasty Revascularization Investigation (BARI) trial is the largest randomized comparison of CABG and PTCA in 1829 patients with 2- or 3-vessel CAD (323,324). UA was the admitting diagnosis in 64% of these patients, and 19% had treated diabetes. A statistically significant advantage in survival without MI independent of the severity of presenting symptoms was observed in the entire group for CABG over PCI 7 years after study entry (84.4% vs. 80.9%, $p = 0.04$) (325). However, subgroup analysis demonstrated that the survival benefit seen with CABG was confined to diabetic patients treated with insulin or oral hypoglycemic agents. At 7 years, the survival rate for diabetics was 76.4% with CABG compared with 55.7% among patients treated with PTCA ($p = 0.001$). In patients without diabetes, survival rates were virtually identical (CABG vs. PTCA, 86.4% vs. 86.8%, $p = 0.71$). Subsequent analysis of the Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI) trial results also showed a survival benefit for the use of CABG in comparison with PTCA in diabetic patients with multivessel CAD (326). These observations have been confirmed in a study from Emory University, which showed that with correction for baseline differences, there were improved survival rates for insulin-requiring patients with multivessel disease who were revascularized with CABG rather than with PTCA (327) (see Section VI. C).

Other nonrandomized analyses have compared CABG, PTCA, and medical therapy. With statistical adjustment for differences in baseline characteristics of 9,263 consecutive CAD patients entered into a large registry, the 5-year survival rates were compared for patients who were treated medically and those who underwent PTCA and CABG between 1984 and 1990 (288). Patients with 3- or 2-vessel disease with a proximal severe (greater than or equal to 95%) LAD stenosis treated with CABG had significantly better 5-year survival rates than did those who received medical treatment or PTCA. In patients with less severe 2-vessel CAD or with 1-vessel CAD, either form of revascularization improved survival relative to medical therapy. The 2 revascularization treatments were equivalent for patients with nonsevere 2-vessel disease. PTCA provided better survival rates than CABG in patients with 1-vessel disease except for those with severe proximal LAD stenosis, for whom the 2 revascularization strategies were equivalent. However, in patients with 1-vessel disease, all therapies were associated with high 5-year survival rates, and the differences among the treatment groups were very small.

Hannan et al. (289) compared 3-year risk-adjusted survival rates in patients undergoing revascularization in the state of New York in 1993. The 29,646 CABG patients and 29,930 PTCA patients had different baseline and angiographic characteristics evaluated with Cox multivariable models. The anatomic extent of disease was the only variable that interacted with the specific revascularization therapy that influenced long-term survival. Although the limitations of such observational studies must be recognized, it is of interest that UA or diabetes did not result in treatment-related differences in long-term survival rates. Patients with 1-vessel disease not involving the LAD or with less than 70% LAD stenosis had statistically significant higher adjusted 3-year survival rates with PTCA (95.3%) than with CABG (92.4%). Patients with proximal LAD stenosis of greater than or equal to 70% had statistically significant higher adjusted 3-year survival rates with CABG than with PTCA regardless of the number of diseased coronary vessels. Patients with 3-vessel disease had statistically significant higher adjusted 3-year survival rates with CABG regardless of proximal LAD disease. Patients with other 1- or 2-vessel disease had no treatment-related difference in survival rates.

Thus, large cohort trials with statistical adjustment showed that survival differences between CABG and PTCA were related to the anatomic extent of disease, in contrast to the randomized trials of multivessel disease that showed no differences. This difference may be due to the smaller numbers of patients in the randomized trials and, hence, their lower power and to the fact that a broad range of angiographic characteristics were not included in the randomized trials in

comparison with the patient cohort studies. The location of a coronary stenosis in the LAD, especially if it is severe and proximal, appears to be a characteristic associated with higher mortality rates and, therefore, with a more favorable outcome with CABG. As already noted, the finding in the BARI and CABRI randomized trials that diabetes appeared to identify a subset of patients who had a better outcome with CABG than with PTCA was not confirmed in the 2 cohort studies (323,324,326). Analysis of the diabetic subgroup was not proposed at the time of trial design in either the BARI or CABRI trial. Moreover, this treatment-related effect was not reproduced in the BARI registry population (328). A reasonable explanation is that in the cohort studies, physicians may be able to recognize characteristics of coronary arteries of diabetic patients that will permit them to more safely undergo one or another of the revascularization therapies. However, when all diabetic patients are randomly assigned to therapies without the added insight of clinical judgment, a treatment advantage is apparent for CABG. Until further studies that compare newer percutaneous devices (in particular, stents) and surgical techniques can more clearly resolve these differences, it is reasonable to consider CABG as the preferred revascularization strategy for most patients with 3-vessel disease, especially if it involves the proximal LAD and patients with multivessel disease and treated diabetes or LV dysfunction. Alternatively, it would be unwise to deny the advantages of PCI to a patient with diabetes and less severe coronary disease on the basis of the current information.

An important consideration in a comparison of different revascularization strategies is that none of the large randomized trials reflect the current practice of interventional cardiology that includes the routine use of stents and the increasing use of platelet receptor inhibitors. Coronary stenting improves procedural safety and reduces restenosis in comparison with PTCA. The adjuvant use of platelet inhibitors, particularly in high-risk patients, is also associated with improved short- and intermediate-term outcomes. Although the effects of coronary stenting and platelet GP IIb/IIIa inhibitors would have likely improved the PCI results observed, their added benefit relative to CABG cannot be assessed on the basis of the previously reported randomized trials or large registries. Refinement of surgical management with right internal mammary artery grafts, radial artery grafts, retroperfusion, and less invasive methodology may reduce the morbidity rates for CABG, but no recent advance has been shown to influence long-term survival more favorably than the current standard operative technique. Therefore, decisions regarding appropriate revascularization strategies in the future will have to be made on the basis of information that compares long-term outcome for these 2 techniques and the effects of adjunctive pharmacotherapy.

D. Conclusions

In general, the indications for PCI and CABG in UA/NSTEMI are similar to those for stable angina (324,329–333). High-risk patients with LV systolic dysfunction, patients with diabetes mellitus, and those with 2-vessel disease with severe proximal LAD involvement or severe 3-vessel or left main disease should be considered for CABG (Fig. 12). Many other patients will have less-severe CAD that does not put them at high risk for cardiac death. However, even less-severe disease can have a substantial negative impact on the quality of life. Compared with high-risk patients, low-risk patients will receive negligibly or very modestly increased chances of long-term survival with CABG. Therefore, in low-risk patients, quality of life and patient preferences are given more weight than are strict clinical outcomes in the selection of a treatment strategy. Low-risk patients whose symptoms do not respond well to maximal medical therapy and who experience a significant negative impact on their quality of life and functional status should be considered for revascularization. Patients in this group who are unwilling to accept the increased short-term procedural risks to gain long-term benefits or who are satisfied with their existing capabilities should be managed medically at first and followed carefully as outpatients. Other patients who are willing to accept the risks of revascularization and who want to improve their functional status or to decrease symptoms may be considered appropriate candidates for early revascularization.

V. HOSPITAL DISCHARGE AND POST–HOSPITAL DISCHARGE CARE

The acute phase of UA/NSTEMI is usually over within 2 months. The risk of progression to MI or the development of recurrent MI or death is highest during that period. At 1 to 3 months after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease (Fig. 3).

The broad goals during the hospital discharge phase, as described in this section, are 2-fold: 1) to prepare the patient for normal activities to the extent possible and 2) to use the acute event as an opportunity to reevaluate long-term care, particularly lifestyle and risk factor modification. Aggressive risk factor modification is the mainstay of the long-term management of stable CAD. Patients who have undergone successful PCI with an uncomplicated course are usually discharged the next day, and patients who undergo uncomplicated CABG are generally discharged 4 to 7 days after CABG. Medical management of low-risk patients after noninvasive stress testing and coronary arteriography can typically be accomplished rapidly with discharge on the day of or the day after testing. Medical management of a high-risk group of patients who are unsuitable for or unwilling to undergo revascularization may require a prolonged hospitalization period to achieve the goals of adequate symptom control and minimization of the risk of subsequent cardiac events.

A. Medical Regimen

In most cases, the inpatient anti-ischemic medical regimen used in the nonintensive phase (other than intravenous NTG)

should be continued after discharge and the antiplatelet/anticoagulant medications should be changed to an outpatient regimen. The goals for continued medical therapy after discharge relate to potential prognostic benefits (primarily shown for ASA, beta-blockers, cholesterol-lowering agents, and ACEIs, especially for EF less than 0.40), control of ischemic symptoms (nitrates, beta-blockers, and calcium antagonists), and treatment of major risk factors such as hypertension, smoking, hyperlipidemia, and diabetes mellitus (see later). Thus, the selection of a medical regimen is individualized to the specific needs of each patient based on the in-hospital findings and events, the risk factors for CAD, drug tolerability, or the type of recent procedure. The mnemonic *ABCDE* (**A**spirin and antianginals; **B**eta-blockers and blood pressure; **C**holesterol and cigarettes; **D**iet and diabetes; **E**ducation and exercise) has been found to be useful in guiding treatment (26).

An effort by the entire staff (physicians, nurses, dietitians, pharmacists, rehabilitation specialists, and physical and occupational therapists) is often necessary to prepare the patient for discharge. Both the patient and family should receive instructions about what to do if symptoms occur in the future (333a). Direct patient instruction is important and should be reinforced and documented with written instruction sheets. Enrollment in a cardiac rehabilitation program after discharge may enhance patient education and enhance compliance with the medical regimen.

Recommendations

Class I

1. **Drugs required in the hospital to control ischemia should be continued after hospital discharge in patients who do not undergo coronary revascularization, patients with unsuccessful revascularization, or patients with recurrent symptoms after revascularization. Upward or downward titration of the doses may be required. (Level of Evidence: C)**
2. **All patients should be given sublingual or spray NTG and instructed in its use. (Level of Evidence: C)**
3. **Before discharge, patients should be informed about symptoms of AMI and should be instructed in how to seek help if symptoms occur. (Level of Evidence: C)**

1. Long-Term Medical Therapy

Many patients with UA/NSTEMI have chronic stable angina at hospital discharge. The management of the patient with stable CAD is detailed in the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina (26). The following are recommendations for pharmacotherapy to prevent death and MI.

Recommendations

Class I

1. **Aspirin 75 to 325 mg per d in the absence of contraindications. (Level of Evidence: A)**
2. **Clopidogrel 75 mg daily (in the absence of contraindications) ~~for patients with a contraindication to ASA~~. when ASA is not tolerated because of hypersensitivity or gastrointestinal intolerance. (Level of Evidence: A~~B~~)**
3. **The combination of ASA and clopidogrel for 9 months after UA/NSTEMI. (Level of Evidence: B)**
4~~3~~. **Beta-blockers in the absence of contraindications. (Level of Evidence: B)**
5~~4~~. **Lipid-lowering agents and diet in post-ACS patients, including postrevascularization patients, with low-density lipoprotein (LDL) cholesterol of greater than 130 mg per dL. (Level of Evidence: A)**
6~~5~~. **Lipid-lowering agents if LDL cholesterol level after diet is greater than 100 mg per dL. (Level of Evidence: B)**
7~~6~~. **ACEIs for patients with CHF, LV dysfunction (EF less than 0.40), hypertension, or diabetes. (Level of Evidence: A)**

A reduction in the rates of mortality and vascular events was reported in the Heart Outcomes Prevention Evaluation (HOPE) Study (163) with the long-term use of an ACEI in moderate-risk patients with CAD, many of whom had preserved LV function, as well as patients at high risk of developing CAD. Other agents that may be used in patients with chronic CAD are listed in Table 21 and are discussed in detail in the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina (26).

Although observational data suggest a protective effect of hormone replacement therapy (HRT) for coronary events, the only randomized trial of HRT for secondary prevention of death and MI that has been completed (Heart and Estrogen/progestin Replacement Study [HERS]) failed to demonstrate a beneficial effect (334). Disturbingly, there was an excess risk for death and MI early after HRT initiation. It is recommended that postmenopausal women who receive HRT may continue but that HRT should *not* be initiated for the secondary prevention of coronary events. There may, however, be other indications for HRT in postmenopausal women (e.g., prevention of flushing, osteoporosis).

B. Postdischarge Follow-Up

Recommendations

Class I

1. **Discharge instructions should include a follow-up appointment. Low-risk medically treated patients and revascularized patients should return in 2 to 6 weeks, and higher-risk patients should return in 1 to 2 weeks. (Level of Evidence: C)**
2. **Patients managed initially with a conservative strategy who experience recurrent unstable angina or severe (CCS Class III) chronic stable angina despite medical management who are suitable for revascularization should undergo coronary arteriography. (Level of Evidence: B)**

Table 21. Medications Used for Stabilized UA/NSTEMI

Anti-Ischemic and Antithrombotic/ Antiplatelet Agent	Drug Action	Class/Level of Evidence
Aspirin	Antiplatelet	I/A
Clopidogrel* or ticlopidine	Antiplatelet when aspirin is contraindicated	I/A
Beta-blockers	Anti-ischemic	I/A
ACEI	EF less than 0.40 or CHF EF greater than 0.40	I/A IIa/A~~B~~
Nitrates	Antianginal	I/C For ischemic symptoms
Calcium antagonists (short-acting dihydropyridine antagonists should be avoided)	Antianginal	I For ischemic symptoms When beta-blockers are not successful (level of evidence: B) or contraindicated Or cause unacceptable side effects (level of evidence: C)
Warfarin low intensity with or without aspirin	Antithrombotic	IIb/B
Dipyridamole	Antiplatelet	III/A

Agent	Risk Factor	Class/Level of Evidence
HMG-CoA reductase inhibitors	LDL cholesterol greater than 130 mg/dL	I/A
HMG-CoA reductase inhibitors	LDL cholesterol 100–130 mg/dL	IIa/B~~C~~
Gemfibrozil	HDL cholesterol less than 40 mg/dL	IIa/B
Niacin	HDL cholesterol less than 40 mg/dL	IIa/B
Niacin or gemfibrozil	Triglycerides greater than 200 mg/dL	IIa/B
Folate	Elevated homocysteine	IIb/C
Antidepressant	Treatment of depression	IIb/C
Treatment of hypertension	Blood pressure greater than 135/85 mm Hg	I/A
HRT (initiation)†	Postmenopausal state	III/B
HRT (continuation)†	Postmenopausal state	IIa/C

ACEI indicates angiotensin-converting enzyme inhibitor; CHF, congestive heart failure; EF, ejection fraction; HDL, high-density lipoprotein; HRT, hormone replacement therapy; LDL, low-density lipoprotein; NSTEMI, non–ST-segment elevation myocardial infarction; UA, unstable angina.
*Preferred to ticlopidine.
†For risk reduction of coronary artery disease.

3. Patients 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)

The risk of death within 1 year can be predicted on the basis of clinical information and the ECG. For 515 survivors of hospitalization for NSTEMI, risk factors include persistent ST-segment depression, CHF, advanced age, and ST-segment elevation at discharge (335). Patients with all high-risk markers present had a 14-fold greater mortality rate than did patients with all markers absent. Elevated cardiac TnT levels have also been demonstrated to provide independent prognostic information for cardiac events at 1 to 2 years. For patients with all ACS in a GUSTO-IIa substudy, age, ST-segment elevation on admission, prior CABG, TnT, renal insufficiency, and severe COPD were independently associated with risk of death at 1 year (100,336). For UA/NSTEMI patients, prior MI, TnT positivity, accelerated angina before admission, and recurrent pain or ECG changes were independently associated with risk of death at 2 years. Patients managed with an initial conservative strategy (see Section III) should be reassessed at the time of return visits for the need for cardiac catheterization and revascularization. Specifically, the presence and severity of angina should be ascertained. Rates of revascularization during the first year have been reported to be high (337). Long-term (7 years) follow-up of 282 patients with UA demonstrated high event rates during the first year (MI 11%, death 6%, PTCA 30%, CABG 27%). However, after the first year, event rates were low (337). Independent risk factors for death/MI were age greater than 70 years, diabetes, and male sex. Mental depression has also been reported to be an independent risk factor for cardiac events after MI and occurs in up to 25% of such patients (338). Patients recognized to be at high risk for a cardiac event after discharge deserve earlier and more frequent follow-up than low-risk patients.

The overall long-term risk for death or MI 2 months after an episode of UA/NSTEMI is similar to that of other CAD patients with similar characteristics. van Domburg et al. (337) reported low rates of admission for recurrent chest pain (5%, 4%, 3%, and 2% at 1, 3, 5, and 7 years, respectively). When the patient has returned to the baseline level, typically 6 to 8 weeks after hospitalization, arrangements should be made for long-term regular follow-up visits, as for stable CAD. Cardiac catheterization with coronary angiography is recommended for any of the following situations: 1) significant increase in anginal symptoms, including recurrent UA;

2) high-risk pattern (e.g., greater than or equal to 2-mm ST-segment depression, systolic blood pressure decline of greater than or equal to 10 mm Hg) on exercise test; 3) CHF; 4) angina with mild exertion (inability to complete Stage 2 of the Bruce protocol for angina); and 5) survivors of sudden cardiac death. Revascularization is recommended based on the coronary anatomy and ventricular function (see Section IV and ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina [26]).

C. Use of Medications

Recommendations

Class I

1. **Before hospital discharge, patients and/or designated responsible caregivers should be provided with well-understood instructions with respect to medication type, purpose, dose, frequency, and pertinent side effects. (Level of Evidence: C)**
2. **Anginal discomfort lasting greater than 2 or 3 min should prompt the patient to discontinue the activity or remove himself or herself from the stressful event. If pain does not subside immediately, the patient should be instructed to take NTG. If the first tablet or spray does not provide relief within 5 min, then a second and third dose, at 5-min intervals, should be taken. Pain that lasts greater than 15 to 20 min or persistent pain despite 3 NTG doses should prompt the patient to seek immediate medical attention by calling 9-1-1 and going to the nearest hospital ED, preferably via ambulance or the quickest available alternative. (Level of Evidence: C)**
3. **If the pattern of anginal symptoms change (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 to determine the need for additional treatment or testing. (Level of Evidence: C)**

Either formal or informal telephone follow-up can serve to reinforce in-hospital instruction, provide reassurance, and answer the patient's questions (339). If personnel and budget resources are available, the healthcare team may consider establishing a follow-up system in which nurses call patients on the telephone approximately once a week for the first 4 weeks after discharge. This structured program can gauge the progress of the patient's recovery, reinforce the CAD education taught in the hospital, address patient questions and concerns, and monitor progress in meeting risk factor modification goals.

D. Risk Factor Modification

Recommendations

Class I

1. **Specific instructions should be given on the following:**
   - **a) Smoking cessation and achievement or maintenance of optimal weight, daily exercise, and diet. (Level of Evidence: B)**
   - **b) HMG-CoA reductase inhibitors for LDL cholesterol greater than 130 mg per dL. (Level of Evidence: A)**
   - **c) Lipid-lowering agent if LDL cholesterol after diet is greater than 100 mg per dL. (Level of Evidence: B)**
   - **d) A fibrate or niacin if high-density lipoprotein (HDL) cholesterol is less than 40 mg per dL, occurring as an isolated finding or in combination with other lipid abnormalities. (Level of Evidence: B)**
   - **~~d~~e) Hypertension control to a blood pressure of less than 130 per 85 mm Hg. (Level of Evidence: A)**
   - **~~e~~f) Tight control of hyperglycemia in diabetes. (Level of Evidence: B)**
2. **Consider the referral of patients who are smokers to a smoking cessation program or clinic and/or an outpatient cardiac rehabilitation program. (Level of Evidence: B)**

Class IIa

1. **HMG-CoA reductase inhibitors and diet for LDL cholesterol greater than 100 mg per dL begun 24 to 96 h after admission and continued at hospital discharge. *(Level of Evidence: B)***
2. **~~1~~. Gemfibrozil or niacin for patients with HDL cholesterol of less than 40 mg per dL and triglycerides of greater than 200 mg per dL. (Level of Evidence: B)**

The healthcare team should work with patients and their families to educate them regarding specific targets for LDL cholesterol, blood pressure, weight, and exercise. The family may be able to further support the patient by making changes in risk behavior (e.g., cooking low-fat meals for the entire family, exercising together). This is particularly important when a screening of the family members reveals common risk factors, such as hyperlipidemia, hypertension, and obesity.

There is a wealth of evidence that cholesterol-lowering therapy for patients with CAD and hypercholesterolemia (340) and for patients with mild cholesterol elevation (mean 209 to 218 mg per dL) after MI and UA reduces vascular events and death (341,342). Patients should be educated regarding cholesterol reduction and their current and target cholesterol levels. Patients who have undergone PTCA or CABG derive benefit from cholesterol lowering (343) and deserve special counseling lest they mistakenly believe that revascularization obviates the need for change. The National Cholesterol Education Program 2 recommends a target LDL cholesterol level less than 100 mg per dL, a low-saturated-fat diet for persons with an LDL cholesterol level greater than 100 mg per dL, and the addition of medication for persons with an LDL cholesterol level greater than 130 mg per dL (343a,343b). The treatment of hypertriglyceridemia and low HDL cholesterol (less than 35 mg per dL) with gemfibrozil has resulted in reduced cardiovascular events in men with

coronary heart disease (217). Either niacin or gemfibrozil may be added to the diet when fasting triglycerides are greater than 200 mg per dL (5).

The National Cholesterol Education Program III has raised the target for HDL cholesterol to 40 mg per dL (545). In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, 3086 patients were randomized to treatment with an aggressive lipid-lowering regimen of atorvastatin 80 mg per d or placebo 24 to 96 h after an ACS (546). At 16 weeks of follow-up, the primary end point of death, nonfatal MI, resuscitated cardiac arrest, or recurrent severe myocardial ischemia was reduced from 17.4% in the placebo group to 14.8% in the atorvastatin group (p = 0.048). There were *no* significant differences in the risk of death, nonfatal MI, cardiac arrest, or worsening heart failure in the 2 groups, but there were fewer strokes and a lower risk of severe recurrent ischemia. The Lipid-Coronary Artery Disease (L-CAD) study was a small trial that randomized 126 patients with an ACS to early treatment with pravastatin, alone or in combination with cholestyramine or niacin, or to usual care. At 24 months, the patients who received early aggressive treatment had a lower incidence of clinical events (23%) than the usual-care group (52%; p = 0.005) (547).

Although the evidence from clinical trials that predischarge initiation of lipid-lowering therapy [the MIRACL (546) and L-CAD studies (547)] is not yet robust or definitive, observational studies support this policy. In the Swedish Registry of Cardiac Intensive Care of almost 20,000 patients, the adjusted relative risk of mortality was 25% lower in patients in whom statin therapy was initiated before hospital discharge (548).

Patients in whom lipid-lowering therapy was begun in the hospital were much more likely to be on such therapy at a later time. In one demonstration project, the Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP), the inhospital initiation of lipid-lowering therapy increased the percentage of patients treated with statins 1 year later from 10% to 91% and of those with an LDL cholesterol less than 100 mg per dL from 6% to 58% (549).

Although additional trials are ongoing, there appear to be no adverse effects and substantial advantages to the initiation of lipid-lowering therapy before hospital discharge (550,551). Such early initiation of therapy has also been recommended in the third report of the National Cholesterol Education Program (NCEP) (545).

~~Despite the overwhelming evidence for the benefits of statin therapy in patients with elevated LDL cholesterol levels, almost no data exist about the timing of the initiation of therapy in ACS. Fewer than 300 patients have been entered into the currently completed trials within 4 months of ACS. These trials excluded ACS patients in the acute phase because of several concerns. In the acute setting, the LDL cholesterol level drops, so the implications of further acute depression of levels are unclear. A theoretical argument can be made that the inhibition of vascular smooth muscle cell proliferation with statins could prevent plaque stabilization, and the beneficial effects of statin therapy have not been observed in the first several months of therapy in long-term trials. These theoretical concerns must be weighed against substantial evidence that if lipid-lowering therapy is not instituted in the acute setting, it often is forgotten. Another potential benefit of early treatment with statins is the rapid improvement in endothelial function they induce. Before pharmacological LDL-lowering therapy is begun, a baseline of 2 or 3 fasting lipoprotein measurements should be obtained; metabolic stability should be attained before such therapy is begun (343c).~~

Blood pressure control is an important goal, and hypertensive patients should be educated regarding this goal (344). Systolic and diastolic blood pressures should be in the normal range (systolic less than 135 mm Hg, diastolic less than 85 mm Hg). Particular attention should be paid to smoking cessation. Daly et al. (345) quantified the long-term effects of smoking on patients with ACS. Men less than 60 years old who continued to smoke had a risk of death from all causes 5.4 times that of men who stopped smoking (p less than 0.05). Referral to a smoking cessation program and the use of nicotine patches or gum are recommended (346). Bupropion, an anxiolytic agent and weak inhibitor of neuronal uptake of neurotransmitters, has been effective when added to brief regular counseling sessions in helping patients to quit smoking. The treatment of 615 study subjects for 7 weeks resulted in smoking cessation rates of 28.8% for the 100 mg per d dosage and 44.2% for 300 mg per d dosage compared with 19.6% for placebo-assigned patients (p less than 0.001) The abstinence rate at 1 year was 23.0% for those treated with 300 mg per d bupropion vs. 12.4% for those receiving placebo (346). Family members who live in the same household should also be encouraged to quit smoking to help reinforce the patient's effort and to decrease the risk of second-hand smoke for everyone.

Tight glucose control in diabetics during and after MI (DIGAMI study) has been shown to lower acute and 1-year mortality rates in ACS (347). Tight glucose control (HbA1c less than 7.0%) reduces microvascular disease (348,349) and is strongly recommended. The recently published UK Prospective Diabetes Study (UKPDS) (349–351) demonstrated that the control of glycemia reduced diabetes-related events, including MI (16% reduction, p = 0.052), for newly detected type 2 diabetics aged 25 to 65 years without symptomatic macrovascular disease.

Overweight patients should be instructed in a weight loss regimen, with emphasis on the importance of regular exercise and a life-long prudent diet to maintain ideal weight.

Although there is an association of elevated homocysteine blood levels and CAD, a reduction in homocysteine levels with folate has not yet been demonstrated to reduce the risk of CAD events (352,353).

Very often, patients will not ask their physicians or other healthcare providers about the resumption of sexual activity after hospital discharge. When appropriate, patients need to be reassured that sexual activity is still possible. The resumption of sexual activity can typically occur within 7 to 10 days

in stable patients. Nitrates and sildenafil should not be used together within 24 h of each other.

Recommendation

Class I

Beyond the instructions for daily exercise, patients require specific instruction on activities (e.g., heavy lifting, climbing stairs, yard work, household activities) that are permissible and those that should be avoided. Specific mention should be made regarding resumption of driving and return to work. (Level of Evidence: C)

Daily walking can be encouraged immediately after discharge. Driving regulations vary among states. Typically, patients may begin driving 1 week after discharge, but they must comply with all state department of motor vehicle restrictions, which may include the need to be accompanied and to avoid stressful circumstances such as rush hours, inclement weather, night driving, heavy traffic, and high speeds. Commercial air travel may be undertaken by *stable* patients (without fear of flying) within the first 2 weeks of discharge if they travel with a companion, carry sublingual NTG, and request airport transportation to avoid rushing.

E. Medical Record

The patient's medical record from the time of hospital discharge should indicate the discharge medical regimen, the major instructions about postdischarge activities and rehabilitation, and the patient's understanding and plan for adherence to the recommendations. After resolution of the acute phase of UA/NSTEMI, the medical record should summarize cardiac events, current symptoms, and medication changes since hospital discharge or the last outpatient visit and should document the plan for future care.

VI. SPECIAL GROUPS

A. Women

Recommendation

Class I

Women with UA/NSTEMI should be managed in a manner similar to men. Specifically, women, like men with UA/NSTEMI, should receive ASA and clopidogrel. Indications for noninvasive and invasive testing are similar in women and men. (Level of Evidence: B)

Although at any age women have a lower incidence of CAD than men, they account for a considerable proportion of UA/NSTEMI patients, and UA/NSTEMI is a serious and common condition among women. It is important to overcome long-held notions that severe coronary manifestations are uncommon in this population; however, women may manifest CAD somewhat differently than men. Women who present with chest discomfort are more likely than men to have noncardiac causes, as well as nonatherosclerotic cardiac causes, such as coronary vasospasm (354–356). Women with CAD are, on average, older than men and are more likely to have comorbidities such as hypertension, diabetes, and CHF (32,357–359); to manifest angina rather than AMI; and, among angina and MI patients, to have atypical symptoms.

1. Stress Testing

In general, ECG exercise testing is less predictive in women than in men (261,360–362), primarily because of the lower pretest probability of CAD. Breast attenuation may be a problem with thallium-201 stress testing but not with dobutamine echocardiography. Stress echocardiography (dobutamine or exercise) is therefore an accurate and cost-effective technique for CAD detection in women (261). Recommendations for noninvasive testing in women are the same as in men (see Section III) (26,363). A report of 976 women who underwent treadmill exercise suggests that the Duke Treadmill Score (DTS) provides accurate diagnostic and prognostic estimates in women as well as in men (364). The DTS actually performed better for women than for men in the exclusion of CAD. There were fewer low-risk women than men with any significant CAD (greater than 1 vessel with greater than 75% stenosis: 20% in women vs. 47% in men, p less than 0.001).

Regarding dobutamine stress echocardiography, pilot phase data from the Women's Ischemia Syndrome Evaluation (WISE) study (365) indicated that in women, the test reliably detects multivessel disease (sensitivity 81.8%, similar to that in men) but not 1-vessel disease. Several studies have indicated that women with positive stress tests tend not to be evaluated as aggressively as men (366).

2. Management

In studies that span the spectrum of CAD, women tend to receive less intensive pharmacological treatment than men (357), which is perhaps related in part to a less serious view of the impact of CAD in women. Although the specifics vary regarding beta-blockers and other drugs (32,357,366), a consistent (and disturbing) pattern is that women are prescribed ASA as well as other antithrombotic agents less frequently than men (32).

Although it has been widely believed that women fare worse with PCI and CABG than do men because of technical factors (e.g., smaller artery size, greater age, and more comorbidities) (367–371), recent studies cast doubt on this (32,358). In the case of PCI, it has been suggested that angiographic success and late outcomes are similar in women and men, although in some series, early complications occur more frequently in women (367,368,372–375). However, the outlook for women undergoing PTCA appears to have improved as evidenced by the NHLBI registry (376). Earlier studies of women undergoing CABG showed that women were less likely to receive internal mammary arteries or complete revascularization and had a higher mortality rate (RRs

1.4 to 4.4) than men (367,368,372–380). However, more recent studies in CABG patients with ACS show a more favorable outlook for women (see later) (32,358) than previously thought.

3. Data on UA/NSTEMI

Considerable clinical information about UA/NSTEMI in women has emerged from the TIMI III trial (32) (which examined the use of tissue plasminogen activator and invasive strategies in ACS) and the TIMI III registry (357). There were 497 women in the former population and 1,640 in the latter. As in other forms of CAD, women were older and had more comorbidities (diabetes and hypertension), as well as stronger family histories (32,357–359). Women were less likely to have had a previous MI or cardiac procedures (Fig. 15) (357) and had less LV dysfunction. However, they presented with symptoms of similar frequency, duration, pattern, and ST-segment changes to those of the men. As in other studies, medication use, most particularly ASA, was less in women than in men in the week before the event, during hospitalization, and at discharge. However, no differences between men and women were evident in the results of medical therapy. In the registry, women underwent exercise testing in a similar proportion to that of men. The frequencies of stress test positivity were also similar, although women were less likely to have a high-risk stress test result. However, women were less likely to undergo angiography (RR 0.71, p less than 0.001), perhaps related to the lower percentage with high- risk test results on noninvasive testing (357).

Coronary angiograms in both the TIMI III trial and registry, as well as in other studies (285,381), revealed less extensive CAD in women, of whom a higher proportion had no CAD. In the registry, women were also less likely than men to undergo revascularization (RR 0.66, p less than 0.001) (357); in the TIMI III trial (in which angiography was mandated), there was no gender difference in the percent of patients undergoing PTCA, but less CABG was performed in women, presumably because of a lower incidence of multivessel disease. Importantly, gender was not an independent predictor of the outcome of revascularization. Thus, a key observation in the TIMI III trial and registry (32,357) was that gender was *not* an independent prognostic factor, with outcomes of death, MI, and recurrent ischemia similar in women and men.

Two additional studies were consistent with the TIMI data on interventions in ACS. A Mayo Clinic review of 3014 patients (941 women) with UA who underwent PCI reported that women had similar early and late results to men (358).

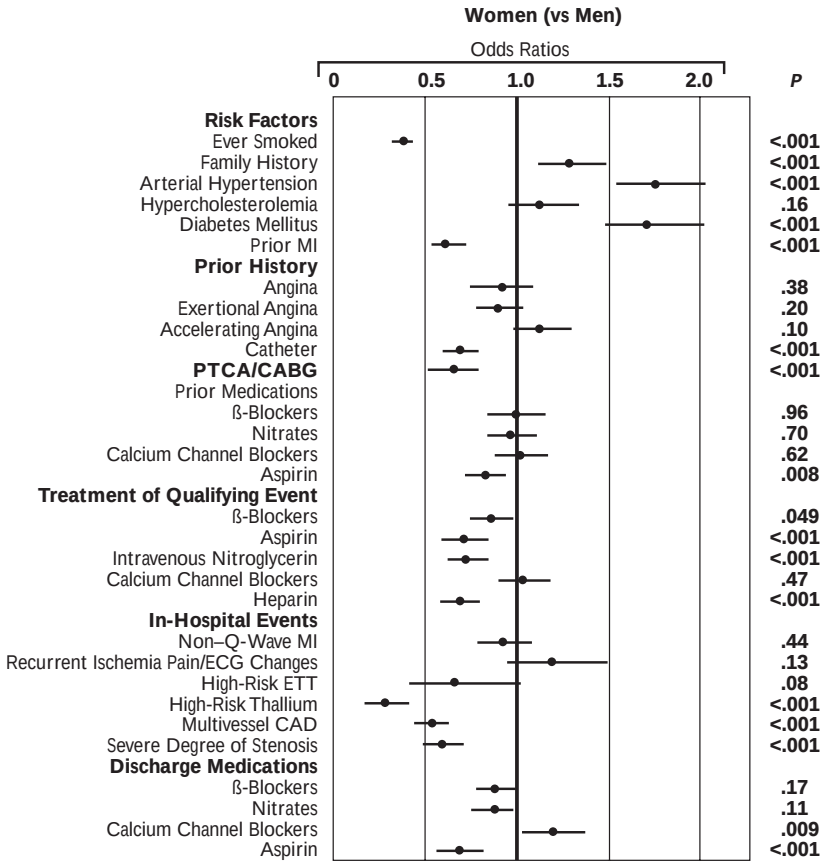


Figure 15. OR of selected characteristics, treatment, outcome, and discharge medication in women with unstable angina and non–ST-segment elevation MI versus men in the TIMI III registry. Horizontal bars represent 95% CIs. ETT indicates exercise treadmill test; PA, PTCA. Reprinted with permission from 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.

The BARI trial of 1829 patients compared PTCA and CABG, primarily in patients with UA, and showed that the results of revascularization were, if anything, better in women than men, when corrected for other factors. At an average 5.4-year follow-up, mortality rates for men and women were 12% and 13%, respectively, but when adjusted for baseline differences (e.g., age, diabetes, and other comorbidities), there was a lower risk of death (RR 0.60, p = 0.003) but a similar risk of death or MI (RR 0.84, p = NS) in women compared with men (382).

In a more recent review of patients with ACS from GUSTO-IIb, an extensive prospective study of anticoagulation in 12,142 patients (3662 women and 8480 men) with ACS, the differences in profile between men and women were similar to those previously reported (31). As in other studies, women were more likely to have UA than MI (adjusted OR 1.51, 95% CI 1.34 to 1.69, p less than 0.001) and were older and had a higher incidence of CHF (10.2% vs. 6.1%, p less than 0.001) and a different risk factor profile (increased hypertension, diabetes, and cholesterol; less smoking, previous MI, and coronary surgery and procedures). On coronary angiography, women with UA also had fewer diseased arteries than did men, and more had no significant coronary stenosis (30.5% vs. 13.9%, p less than 0.001). The 30-day event rate (death/MI) was significantly lower in women than in men with UA (events OR 0.65, p = 0.003).

The use of HRT in postmenopausal women is discussed in Section V.A.

4. Conclusions

Women with ACS are older and more frequently have comorbidities than men but have more atypical presentations and appear to have less severe and extensive obstructive CAD. Women receive ASA less frequently than do men, but patients with UA/NSTEMI of either sex should receive this agent. Women undergo angiography less frequently, and they have similar use of exercise testing and the same prognostic factors on exercise tests as men. Outcomes of revascularization are similar in women and men, whereas overall outcomes in UA may be similar to that in men or more favorable in women.

B. Diabetes Mellitus

Recommendations

Class I

1. **Diabetes is an independent risk factor in patients with UA/NSTEMI. (Level of Evidence: A)**
2. **Medical treatment in the acute phase and decisions on whether to perform stress testing and angiography and revascularization should be similar in diabetic and nondiabetic patients. (Level of Evidence: C)**
3. **Attention should be directed toward tight glucose control. (Level of Evidence: B)**
4. **For patients with multivessel disease, CABG with use of the internal mammary arteries is preferred over PCI in patients being treated for diabetes. (Level of Evidence: B)**

Class IIa

1. **PCI for diabetic patients with 1-vessel disease and inducible ischemia. (Level of Evidence: B)**
2. **Abciximab for diabetics treated with coronary stenting. (Level of Evidence: B)**

CAD accounts for 75% of all deaths in diabetics (32–34), and approximately 20% to 25% of all patients with UA/NSTEMI are diabetic (197,324,357,383–385). Among patients with UA/NSTEMI, diabetics have more severe CAD (383,386,387), and diabetes is an important independent predictor for adverse outcomes (death, MI, or readmission with UA at 1 year) (RR 4.9) (388–391). Also, many diabetics who present with UA/NSTEMI are post-CABG (392).

Diabetics tend to have more extensive noncoronary vascular comorbidities, hypertension, LV hypertrophy, cardiomyopathy, and CHF. In addition, autonomic dysfunction, which occurs in approximately one third of diabetics, influences heart rate and blood pressure, raises the threshold for the perception of angina, and may be accompanied by LV dysfunction (393–395). On coronary angioscopy, diabetic patients with UA have a greater proportion of ulcerated plaques (94% vs. 60%, p = 0.01) and intracoronary thrombi (94% vs. 55%, p = 0.004) than nondiabetics. These findings suggest a higher risk of instability (396).

Although beta-blockers may mask the symptoms of hypoglycemia or lead to it by blunting the hyperglycemic response, they should nevertheless be used with appropriate caution in diabetics with ACS. Diuretics that cause hypokalemia may inhibit insulin release and thereby worsen glucose intolerance.

1. Coronary Revascularization

Approximately 20% of all patients who undergo CABG (397) and PCI (368,369,372,373,386,387) have diabetes. Data regarding outcomes are complex. In the Coronary Artery Surgery Study (CASS) of CABG, diabetics had a 57% higher mortality rate than nondiabetics. A striking advantage for CABG over PTCA was found in treated diabetics in the BARI trial (383), a randomized trial of PTCA vs. CABG in 1829 stable patients with multivessel disease, of whom 19% were diabetics (see Section IV). Diabetics, as in other studies, had increased comorbidity rates. Five years after randomization, patients who required treatment for diabetes had a lower survival rate than nondiabetics (73.1% vs. 91.3%, p less than 0.0001), whereas survival rates in nondiabetics and diabetics who did not require hypoglycemic treatment were similar (93.3% vs. 91.1%, p = NS). Outcomes for CABG in treated diabetics were far better than those for PTCA (80.6% vs. 65.5% survival, p = 0.0003). An interesting finding was that the mortality rate during the 5.4 years of

the study in diabetics who received SVGs (18.2%) was similar to that of patients who underwent PTCA (20.6%), whereas the mortality rate in patients who received internal mammary arteries was much lower (2.9%). Results of the Emory Angioplasty versus Surgery Trial (EAST) at 8 years showed a similar trend but were less conclusive (398). The increased mortality rate noted in randomized trials in PTCA-treated diabetics has been confirmed in a registry study from Emory University (327). Uncorrected, there was little difference in long-term mortality rates. The CABG patients had more severe disease, and with correction for baseline differences, there was an improved survival rate in insulin-requiring patients with multivessel disease who were revascularized with CABG rather than with PTCA. That the more severely diseased patients, in a nonrandomized registry, were selectively sent more often for CABG than for PTCA probably represents good clinical decision making.

A 9-year follow-up of the NHLBI registry showed a similar disturbing pattern for diabetics undergoing PTCA. Immediate angiographic success and completeness of revascularization were similar, but compared with nondiabetics, diabetics (who, again, had more severe CAD and comorbidities) had increased rates of hospital mortality (3.2% vs. 0.5%), nonfatal MI (7.0% vs. 4.1%), death and MI (10.0% vs. 4.5%), and the combined end point of death, MI, and CABG (11% vs. 6.7%, p less than 0.01 for all). At 9 years, rates of mortality (35.9% vs. 17.9%), MI (29% vs. 18.5%), repeat PTCA (43.0% vs. 36.5%), and CABG (37.6% vs. 27.4%) were all higher in diabetics than in nondiabetics (386).

However, as pointed out in Section IV, other data point to less of a differential effect of PCI in diabetics. For example, data from the BARI registry varied from those of the trial. In the registry, there was no significant difference in cardiac survival for diabetics undergoing PTCA (92.5%) and CABG (94%) (NS) (328,399). In the Duke University registry, patients with diabetes and PTCA or CABG were matched with the BARI population. The outcome in diabetics was worse than that in nondiabetics with either CABG or PTCA, but there was no differential effect. The 5-year survival rate for PTCA and CABG adjusted for baseline characteristics was 86% and 89% in diabetics and 92% and 93% in nondiabetics, respectively (400).

Stents may offer diabetics a much improved outcome for PCI. In a recent study with historical controls, the outcome after coronary stenting was superior to that after PTCA in diabetics, and the restenosis rate after stenting was reduced (63% vs. 36%, diabetics vs. nondiabetics with balloon PTCA at 6 months, p = 0.0002) compared with 25% and 27% with stents (p = NS) (398). On the other hand, diabetics who underwent atherectomy had a substantial restenosis rate (60% over 6 months) (401).

Finally, 3 recent trials have shown that abciximab considerably improved the outcome of PCI in diabetics. In the EPILOG trial, abciximab resulted in a greater decline in death/MI over 6 months after PTCA in diabetics (hazard ratio 0.36, 95% CI 0.21 to 0.61) than in nondiabetics (0.60, 95% CI 0.44 to 0.829) (402). Similar results have been reported for tirofiban in the PRISM-PLUS trial (314). EPISTENT was a randomized trial that compared stent plus placebo with stent plus abciximab and balloon plus abciximab in 2399 patients, of whom 20.5% had diabetes and 20.3% had UA (246). The 30-day event rate (death, MI, urgent revascularization) in diabetics declined from 12.1% (stent plus placebo) to 5.6% (stent plus abciximab) (p = 0.040). At 6 months, the drug reduced revascularization of target arteries in diabetics (16.6% vs. 8.1%, p = 0.02). Death or MI was reduced to a similar degree in diabetics as that of nondiabetics (313). These benefits were maintained at 1 year (403). Thus, in the 6-month data, the drug, as well as stents, considerably improved the safety of PCI in diabetics.

2. Conclusions

Diabetes occurs in about one fifth of patients with UA/NSTEMI and is an independent predictor of adverse outcomes. It is associated with more extensive CAD, unstable lesions, frequent comorbidities, and less favorable long-term outcomes with coronary revascularization, especially with PTCA. It is unclear whether these differences are due to more frequent restenosis and/or severe progression of the underlying disease (386). The use of stents, particularly with abciximab, appears to provide more favorable results in diabetics, although more data are needed. Clinical outcomes with CABG, especially with the use of 1 or both internal mammary arteries, are better than those with PTCA but are still less favorable than in nondiabetics.

C. Post-CABG Patients

Recommendations

Class I

1. **Medical treatment for post-CABG patients 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: B)**

Class IIa

1. **Repeat CABG is recommended for multiple SVG stenoses, especially when there is significant stenosis of a graft that supplies the LAD. PCI is recommended for focal saphenous vein stenosis. (Level of Evidence: C)**
2. **Stress testing should generally involve imaging in post-CABG patients. (Level of Evidence: C)**

Overall, up to 20% of patients presenting with UA/NSTEMI have previously undergone CABG (392). Conversely, approximately 20% of post-CABG patients develop UA/NSTEMI during an interval of 7.5 years (404), with a

highly variable postoperative time of occurrence (405). Post-CABG patients who present with UA/NSTEMI are at higher risk, with more extensive CAD and LV dysfunction than those patients who have not previously undergone surgery.

1. Pathological Findings

Pathologically, intimal hyperplasia or atherosclerosis may develop in SVGs, and there is a particular tendency for thrombotic lesions to develop in these vessels (in 72% of grafts resected in 1 study) (406–409). In addition, post-CABG patients may develop atherosclerosis in their native vessels and this may also lead to UA/ NSTEMI (409,410). However, obstructive lesions are more likely to occur in SVGs (53% within 5 years, 76% at 5 to 10 years, 92% at greater than 10 years) (411). Spasm in grafts or native vessels (412,413) and technical complications may also play a role in the development of UA/NSTEMI during the early postoperative period (404,414). Both angioscopic and angiographic findings indicate that SVG disease is a serious and unstable process. Angioscopically, friable plaques occur uniquely in SVGs (44% vs. 0% in native coronary arteries), whereas rough and white plaques occur in both SVGs and native coronary arteries (415). Angiographically, the SVGs more frequently have complex lesions (i.e., overhanging edges, irregular borders, ulcerations, or thrombosis), thrombi (37% vs. 12%, p = 0.04), and total occlusions (49% vs. 24%, p = 0.02) (411).

2. Clinical Findings and Approach

Compared with UA/NSTEMI patients without prior CABG, post-CABG patients are more often male (presumably because more men than women have undergone CABG), older, and diabetic. They have more extensive native vessel CAD and more previous MIs and LV dysfunction. Symptomatically, these patients have more prolonged chest pain than ACS patients without prior CABG. More than 30% of post-CABG patients have resting ECG abnormalities, and ECG stress tests are therefore less conclusive (416). However, a test that becomes positive after having been negative is helpful in the diagnosis of ischemia. Myocardial stress perfusion imaging and dobutamine echocardiography are often helpful diagnostically (417).

The outcomes of UA/NSTEMI in post-CABG patients are less favorable than those in patients who have not undergone CABG. There is a high rate of embolization of atherosclerotic material from friable grafts at the time of intervention, making these procedures more difficult and associated with higher rates of complications (418). In 1 matched-control study of UA, the initial course was similar, but post-CABG patients had twice the incidence of adverse events (death, MI, recurrent UA) during the first year. This was attributed to a lower rate of complete revascularization, which was possible in only 9 of 42 post-CABG patients compared with 39 of 52 patients who had not previously undergone CABG (p = 0.001) (405). Results were directionally similar in the TIMI III registry of ACS, in which 16% of patients were post-CABG. Here again, early outcomes in post-CABG patients and others were equivalent, but at 1 year, 39.3% vs. 30.2% experienced adverse events (death, MI, recurrent ischemia) (p = 0.002) (419).

Revascularization with either PCI or reoperation is often indicated and possible in post-CABG patients with UA/NSTEMI. In a randomized control trial that compared stents with PTCA of obstructed SVGs, there was no statistically significant difference in restenosis during 6 months, although a trend favored stents: 34% vs. 46%. Although hemorrhagic complications were higher in the stent group, clinical outcomes (freedom from MI or repeat revascularization) were better (73% vs. 58%, p = 0.03) (420). Reoperation of patients with stenotic SVGs has been successful in reducing symptoms of recurrent ischemia, and it appears to improve survival rates in patients greater than 5 years after surgery, especially with disease in the LAD, for which survival rates were 74% vs. 53% (p = 0.004) (reoperated vs. nonreoperated post-CABG patients) (421,422).

3. Conclusions

Post-CABG patients, especially those with only SVGs, are at high risk of UA/NSTEMI. There is a higher likelihood of disease in SVGs than in native arteries and this difference increases with postoperative time. Pathologically and angiographically, disease in SVGs has characteristics associated with instability. There also are difficulties with treadmill ECG testing and less favorable outcomes with repeat revascularization than in patients who have not undergone previous CABG.

D. Elderly Patients

Recommendations

Class I

1. **Decisions on management should reflect considerations of general health, comorbidities, cognitive status, and life expectancy. (Level of Evidence: C)**
2. **Attention should be paid to altered pharmacokinetics and sensitivity to hypotensive drugs. (Level of Evidence: B)**
3. **Intensive medical and interventional management of ACS may be undertaken but with close observation for adverse effects of these therapies. (Level of Evidence: B)**

In this discussion, patients greater than 75 years are considered to be “elderly,” although a number of studies have used other cutoff ages, such as 65 or 70 years. Elderly persons constitute about one tenth of ACS patients (357) and present with a number of special problems. They are more likely to have cardiac and noncardiac comorbidities; these include a diminished beta-sympathetic response, increased cardiac afterload due to decreased arterial compliance and arterial hypertension, cardiac hypertrophy, and ventricular

dysfunction, especially diastolic dysfunction (423).

CAD is more common and more severe in elderly persons, who, when they develop UA/NSTEMI, are also more likely to present with atypical symptoms, including dyspnea and confusion, rather than with the ischemic chest pain that is typical for younger patients. There also is a higher incidence of unrecognized prior MI than in younger patients (424). Conversely, comorbid conditions such as hiatus hernia are also more frequent and may be associated with chest pain at rest and may mimic UA. The greater likelihood of comorbidity in elderly persons (e.g., COPD, renal failure, and cerebral disease) also increases the morbidity and mortality rates for cardiac events and interventions in this population.

It may be difficult for elderly persons to perform exercise tests because of muscle weakness and orthopedic problems. In such patients, a pharmacological stress test may be performed (see Section III). The higher prevalence of preexisting resting ECG abnormalities (389), arrhythmias (425,426), and cardiac hypertrophy complicates the interpretation of stress ECG and may require the use of imaging.

1. Pharmacological Management

Reductions in cardiac output and in renal and hepatic perfusion and function reduce the elimination of drugs in elderly persons. Drugs such as propranolol that undergo first-pass hepatic metabolism exhibit increased bioavailability (427). Pharmacodynamic responses to drugs are influenced by the lower cardiac output, plasma volume, and vasomotor tone and the blunted baroreceptor and beta-adrenergic responses.

Elderly persons are particularly vulnerable to drugs with hypotensive actions (e.g., nitrates and calcium antagonists) and cerebral effects (e.g., beta-blockers). Responses to beta-blockers are influenced by 2 competing factors. There may be a blunted response to beta-blockers because of decreased adrenergic activity in elderly persons. On the other hand, baseline sympathetic tone may be decreased. Thus, the magnitude of response to beta-blockers is not entirely predictable. Clearance of warfarin may be reduced, and sensitivity to it may be increased with age (428); heparin dosage requirements also appear to be reduced (210). Overall, however, it should be emphasized that all of the drugs commonly used in the management of younger patients with UA/NSTEMI are useful in elderly patients, provided these differences are recognized and proper precautions are taken (i.e., beginning with lower doses than in younger patients and, in particular, careful observation for toxicity).

2. Observations in UA/NSTEMI

The TIMI III registry (357) provided data on elderly patients (greater than 75 years old), who (by design) composed 25% of the 3,318 patients. This group had fewer atherosclerotic risk factors (smoking, hypercholesterolemia, family history), more previous angina, and fewer previous procedures (Fig. 16) (357), and in other studies, they had more CHF (429,430). They were less likely to receive beta-blockers and heparin in the hospital and far less likely to undergo angiography (RR 0.65, p less than 0.001 at 6 weeks) and coronary revascularization (RR 0.79, p = 0.002 at 6 weeks) than younger patients, although when this procedure was carried out, they were found to have more extensive disease. The 6-week mortality (RR 3.76, p less than 0.001) and MI (RR 2.05, p less than 0.001) rates were elevated. Overall, elderly patients were treated less aggressively with both medical therapy and procedures than were their younger counterparts, despite a higher-risk profile.

3. Interventions and Surgery

A high prevalence of cerebral and peripheral vascular comorbidity influences the results of coronary revascularization in elderly persons. However, results of revascularization in elderly persons are improving. A Medicare review of both PCI and CABG (225,915 PCI and 357,885 CABG patients greater than 65 years old) between 1987 and 1990 revealed that revascularization is commonly carried out in patients in this age group and that outcomes have improved compared with earlier periods. The 30-day and 1-year mortality rates during this time period were 3.3% and 8.0% for PCI and 5.8% and 11.0% for CABG, respectively, with lower mortality rates for patients who received internal mammary artery implants. Estimated 30-day and 1-year mortality rates for PCI rose from 2.1% and 5.2% in patients 65 to 69 years old to 7.8% and 17.3% in patients greater than 80 years old, and respective rates for CABG rose from 4.3% and 8.0% to 10.6% and 19.5%. As expected, comorbidities were associated with increased mortality rates (431).

A smaller but more closely observed matched comparison of CABG vs. PCI in patients greater than 70 years old (a majority of whom had UA) in which the CABG group had more extensive CAD reported that rates for in-hospital mortality (9% vs. 2%), cerebrovascular accidents (5% vs. 0%), and STEMI (6% vs. 1%) were all significantly higher with CABG (432). However, there was more relief of angina with surgery, and 5-year survival rates were similar between the 2 groups (65% CABG vs. 63% PCI) (p = NS).

Some studies of PCI in patients aged 65 to 75 years have shown that success rates with experienced medical professionals are similar to those in younger patients (429,433–435), but with even older patients, success rates decline and complications rates rise. In a recent VA study, in patients greater than 70 years old, the angiographic success rate was 86%, the clinical success rate was 79%, and the in-hospital mortality rate was 11% (all rates were less favorable than those for younger patients), and the urgent CABG rate was less than 1% (436). In 1 report of 26 patients greater than 90 years old, of whom 20 had UA, the procedural success rate for PTCA was 92%, whereas the acute clinical success rate was only 65%, with an in-hospital mortality rate of 23% (437).

On the other hand, a Mayo Clinic review of PCI in patients greater than 65 years old (of whom 75% had UA) revealed an overall success rate of 93.5%, an immediate in-hospital mor-

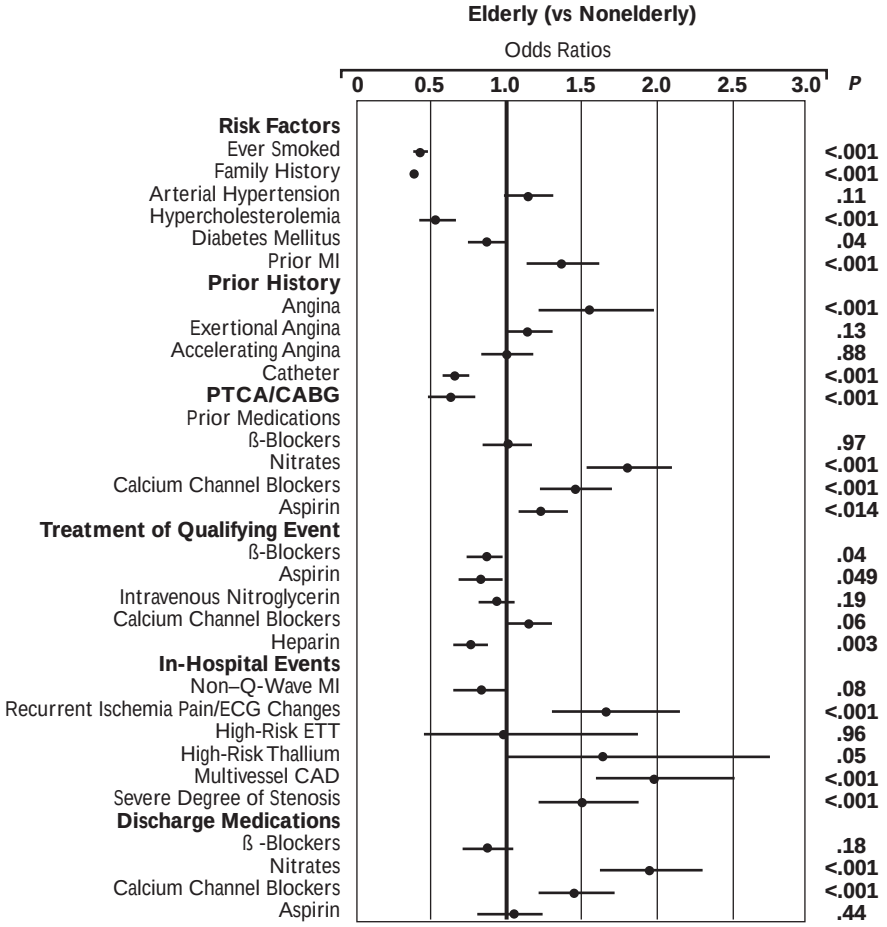


Figure 16. ORs of selected characteristics, treatment, outcome, and discharge medications in elderly patients (aged more than 75 years) vs younger patients with unstable angina and non–ST-segment elevation MI in the TIMI III registry. Horizontal bars represent 95% confidence intervals. PA indicates PTCA; and ETT, exercise treadmill test. Reprinted with permission from 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. *PTCA is used to refer to studies in which this was the dominant form of PCI, before the widespread use of stenting.

tality rate of 1.4%, and a need for emergency CABG rate of only 0.7%. Angiographic outcome changed little between the 65- to 69-year-old group and the greater than 75-year-old group, and the 1-year event rate (death, MI, CABG, repeat PCI, or severe angina) was 45.1% in all patients greater than 65 years old (429). Predictors of outcomes (i.e., extent and severity of CAD and comorbidities) after PCI in the elderly were the same as those in younger patients (435). Similarly, a review of coronary stenting in the elderly reported that procedural success rates were high (95% to 98%) and periprocedural complication rates were low (MI 1.2% to 2.8%, urgent CABG 0.9% to 1.8%, repeat PCI 0% to 0.6%) in the elderly with little difference between those greater than 75 years old and those less than 65 years old (430). Subgroup analyses in both TIMI IIIB (19) and FRISC II (278) showed a greater advantage of the invasive strategy in patients greater than 65 years old.

A review of 15,679 CABG procedures carried out in patients greater than 70 years old from The Toronto Hospital (438) reported encouraging results. Operative mortality rates declined from 7.2% in 1982 to 1986 to 4.4% in 1987 to 1991 (from 17.2% to 9.1% for high-risk patients) but showed little further change in the period of 1992 to 1996. Predictors of operative death (LV dysfunction, previous CABG, peripheral vascular disease, and diabetes) were similar to those in younger patients. When adjusted for these risk factors, age (i.e., a comparison of patients greater than 75 years old with those 70 to 74 years old) was not a significant risk factor.

In octogenarians, early mortality rates with CABG were found to be approximately 2.5 times those in patients 65 to 70 years old (431); stroke occurred in approximately 8% (439), and less serious cerebral complications were even more common (433,440). However, in a review of patients studied between 1985 and 1989, the 3-year survival rate for octogenarian CABG patients was better than that in comparably aged patients with CAD who did not undergo surgery (77% vs. 55%, p = 0.0294) (440), and in another study, the quality of life of patients 80 to 93 years old was improved with CABG (441).

4. Conclusions

Elderly patients with UA/NSTEMI tend to have atypical presentations of disease, substantial comorbidity, ECG stress tests that are more difficult to interpret, and different

responses to pharmacological agents compared with younger patients. Their outcomes with interventions and surgery are not as favorable as those of younger patients, in part because of greater comorbidities. However, coronary revascularization can be performed when the same group of prognostic risk factors that play a role in the younger age group are taken into account. The approach to these patients also must consider general medical and mental status and anticipated life expectancy. Very frail elderly patients represent a high-risk group and should be evaluated for revascularization on a case-by-case basis. In many of these patients, even those with diffuse coronary arterial disease, PCI, with its lower morbidity rates, may be preferable to CABG. In ESSENCE (169) and TIMI 11B (170), the benefits or LMWH in patients greater than 65 years old were particularly impressive. In the case of platelet GP IIb/IIIa inhibitors, the relative benefits for older patients were similar to those of younger patients, but with the higher event rate in elderly patients, this translated into a greater *absolute* benefit.

E. Cocaine

Recommendations for Patients With Chest Pain After Cocaine Use

Class I

1. **NTG and oral calcium antagonists for patients with ST-segment elevation or depression that accompanies ischemic chest discomfort. (Level of Evidence: C)**
2. **Immediate coronary arteriography, if possible, in patients whose ST segments remain elevated after NTG and calcium antagonists; thrombolysis (with or without PCI) if thrombus is detected. (Level of Evidence: C)**

Class IIa

1. **Intravenous calcium antagonists for patients with ST-segment deviation suggestive of ischemia. (Level of Evidence: C)**
2. **Beta-blockers for hypertensive patients (systolic blood pressure greater than 150 mm Hg) or those with sinus tachycardia (pulse greater than 100 min-1). (Level of Evidence: C)**
3. **Thrombolytic therapy if ST segments remain elevated despite NTG and calcium antagonists and coronary arteriography is not possible. (Level of Evidence: C)**
4. **Coronary arteriography, if available, for patients with ST-segment depression or isolated T-wave changes not known to be old and who are unresponsive to NTG and calcium antagonists. (Level of Evidence: C)**

Class III

Coronary arteriography in patients with chest pain without ST-T-wave changes. (Level of Evidence: C)

The use of cocaine is associated with a number of cardiac complications that can produce myocardial ischemia and can cause and present as UA/NSTEMI (442–445). The widespread use of cocaine makes it mandatory to consider this cause, because its recognition mandates special management.

The action of cocaine is to block presynaptic reuptake of neurotransmitters such as norepinephrine and dopamine, producing excess concentrations at the postsynaptic receptors that lead to sympathetic activation and the stimulation of dopaminergic neurons (446). There may also be a direct contractile effect on vascular smooth muscle (443). Detoxification occurs with plasma and liver cholinesterases, which form metabolic products that are excreted in the urine. Infants, elderly patients, and patients with hepatic dysfunction lack sufficient plasma cholinesterase to metabolize the drug (447) and therefore are at high risk of adverse effects with cocaine use.

1. Coronary Artery Spasm

The basis for coronary spasm has been demonstrated in both in vitro (447) and in vivo (443,448–452) experiments in animals and humans. Reversible vasoconstriction of rabbit aortic rings has been demonstrated with cocaine in concentrations of 10^{-3} to 10^{-8} mol per L. Pretreatment with calcium antagonists markedly inhibits the cocaine-induced vasoconstriction. Coronary injection of cocaine produces vasoconstriction in miniswine with experimentally induced nonocclusive atherosclerotic lesions (453).

Nademanee et al. (454) performed 24-h ECG monitoring in 21 male cocaine users after admission to a substance abuse treatment center and found that 8 had frequent episodes of ST-segment elevation, most during the first 2 weeks of withdrawal. In cocaine users with prolonged myocardial ischemia, coronary arteriography may reveal coronary artery spasm with otherwise normal appearing coronary arteries or with underlying minimally obstructive coronary atherosclerosis (443,445,448). The cocaine-induced increase in coronary vascular resistance is reversed with calcium antagonists (449,455). Cocaine increases the response of platelets to arachidonic acid, thus increasing thromboxane A2 production and platelet aggregation (456). In addition, reversible combined reduction in protein C and antithrombin III has been observed in patients with cocaine-related arterial thrombosis (457). All of these effects favor coronary thrombosis (443,450,458). Coronary thrombus may also develop as a consequence of coronary spasm.

Cocaine users may develop ischemic chest discomfort that is indistinguishable from the UA/NSTEMI secondary to coronary atherosclerosis. The patient who presents with prolonged myocardial ischemia should be questioned about the use of cocaine. In a study by Hollander et al., the presence or absence of cocaine use was assessed in only 13% of patients who presented to the ED with chest pain (458). Table 22 lists the clinical characteristics of a typical patient with cocaine-related chest pain or MI (445).

Most patients who present to the ED with cocaine-associated chest pain do not develop MI (460); MI development has been reported to occur in 6% of such patients (445).

Table 22. Clinical Characteristics in the Typical Patient With Cocaine-Related Chest Pain, UA, or MI

Young age, usually <40 years
Male gender
Cigarette smokers, but no other risk factors for atherosclerosis
Chronic or first-time cocaine user
Symptom onset minutes or even several hours after cocaine use
Associated with all routes of administration
May occur with small or large doses
Often associated with concomitant use of cigarettes and/or alcohol

Reprinted with permission from 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.

Accelerated coronary atherosclerosis has been reported in chronic users of cocaine (461,462); coronary artery spasm is more readily precipitated at sites of atherosclerotic plaques (448). Cocaine causes sinus tachycardia, an increase in blood pressure, and myocardial contractility, thereby increasing myocardial oxygen demand (449). These increases may precipitate myocardial ischemia and UA/NSTEMI in both the presence and absence of obstructive coronary atherosclerosis and coronary spasm.

Aortic dissection (463) and coronary artery dissection (443,463) have been reported as consequences of cocaine use. Other reported cardiac complications are myocarditis (462) and cardiomyopathy (464,465).

2. Treatment

When a patient with or suspected of cocaine use is seen in the ED with chest pain compatible with myocardial ischemia and ST-segment elevation, NTG and a calcium antagonist (e.g., 20 mg diltiazem) should be administered intravenously (443,452). If there is no response, immediate coronary arteriography should be performed, if possible. If thrombus is present, thrombolytic agents are administered if there are no contraindications (466,467). If catheterization is not available, thrombolytic agents may be considered.

If the ECG is normal or shows only minimal T-wave changes and there is a history of chest pain compatible with acute myocardial ischemia, the patient should receive NTG and an oral calcium antagonist and be observed. After cocaine use, increased motor activity, skeletal muscle injury, and rhabdomyolysis can occur, causing CK and even CK-MB elevation in the absence of MI (468). TnI or TnT is more specific for myocardial injury and therefore is preferred. Blood should be drawn twice for serum markers of myocardial necrosis at 6-h intervals. If the ECG shows ST-segment changes and the biochemical markers are normal, the patient should be observed in the hospital in a monitored bed for 24 h; most complications will occur within 24 h (459). If the patient's clinical condition is unchanged and the ECG remains unchanged after 24 h, the patient can be discharged (469).

Many observers believe that beta-blockers are contraindicated in cocaine-induced coronary spasm, because there is evidence from a single double-blind, randomized, placebo-controlled trial that beta-adrenergic blockade augments cocaine-induced coronary artery vasoconstriction (470). Others believe that if the patient has a high sympathetic state with sinus tachycardia and hypertension, then beta-blockers should be used (443). Labetalol, an alpha/beta-blocker, has been advocated, but in the doses commonly used, its beta-adrenergic–blocking action predominates over its alpha-adrenergic–blocking activity (471). Therefore, in cocaine-induced myocardial ischemia and vasoconstriction, NTG and calcium antagonists are the preferred drugs. Both NTG and verapamil have been shown to reverse cocaine-induced hypertension and coronary arterial vasoconstriction (452,470) and tachycardia (verapamil).

F. Variant (Prinzmetal's) Angina

Class I

1. **Coronary arteriography in patients with episodic chest pain and ST-segment elevation that resolves with NTG and/or calcium antagonists. (Level of Evidence: B)**
2. **Treatment with nitrates and calcium antagonists in patients whose coronary arteriogram is normal or shows only nonobstructive lesions. (Level of Evidence: B)**

Class IIa

Provocative testing in patients with a nonobstructive lesion on coronary arteriography, the clinical picture of coronary spasm, and transient ST-segment elevation. (Level of Evidence: B)

Class IIb

1. **Provocative testing without coronary arteriography. (Level of Evidence: C)**
2. **In the absence of significant CAD on coronary arteriography, provocative testing with methylergonovine, acetylcholine, or methacholine when coronary spasm is suspected but there is no ECG evidence of transient ST-segment elevation. (Level of Evidence: C)**

Class III

Provocative testing in patients with high-grade obstructive lesions on coronary arteriography. (Level of Evidence: B)

Variant angina (Prinzmetal's angina) is a form of UA that usually occurs spontaneously, is characterized by transient ST-segment elevation, and most commonly resolves *without progression to MI* (472). The earliest stages of AMI may also be associated with cyclic ST-segment elevations. Although Prinzmetal was not the first to describe this condition (473), he was the first to offer the hypothesis that it is caused by transient coronary artery spasm; this was subsequently proved with coronary arteriography (474). The spasm is most commonly focal and can occur simultaneously at greater than 1 site (475). Even coronary segments that are apparently normal on coronary angiography often have evidence of

mural atherosclerosis on intravascular ultrasonography (476). This can result in localized endothelial dysfunction and coronary spasm.

Patients with Prinzmetal's angina frequently have coronary artery plaques that can be nonobstructive or produce significant stenosis (477). Walling et al. (478) reported in 217 patients that coronary arteriography showed 1-vessel disease in 81 (39%) patients and multivessel disease in 40 (19%) patients. Rovai et al. (479) found a similar high prevalence of obstructive disease in 162 patients with variant angina.

1. Clinical Picture

Although chest discomfort in the patient with variant angina can be precipitated by exercise, it usually occurs without any preceding increase in myocardial oxygen demand; the majority of patients have normal exercise tolerance, and stress testing may be negative. Because the anginal discomfort usually occurs at rest without precipitating cause, it simulates UA/NSTEMI secondary to coronary atherosclerosis. Episodes of Prinzmetal's angina often occur in clusters with prolonged weeks to months of asymptomatic periods. However, attacks can be precipitated by hyperventilation (480), exercise (481), and exposure to cold (482). There tends to be a circadian variation in the episodes of angina, with most attacks occurring in the early morning (483). Compared with patients with chronic stable angina, patients with variant angina are younger and, except for smoking, have fewer coronary risk factors (484,485). Some studies have shown an association of variant angina with other vasospastic disorders such as migraine headache and Raynaud's phenomenon (486).

Most often, the attacks resolve spontaneously without evidence of MI. However, if the coronary vasospasm is prolonged, MI, a high degree of AV block, life-threatening ventricular tachycardia, or sudden death may occur (487,488).

2. Pathogenesis

The pathogenesis of focal coronary spasm in this condition is not well understood. The probable underlying defect is the presence of dysfunctional endothelium that exposes the medial smooth muscle to vasoconstrictors such as catecholamines, thromboxane A2, serotonin, histamine, and endothelin (489). Endothelial dysfunction may also impair coronary flow-dependent vasodilatation due to the decreased production and release of nitric oxide (490) and enhance phosphorylation of myosin light chains, an important step for smooth muscle contraction (491). There may be an imbalance between endothelium-produced vasodilator factors (i.e., prostacylin, nitric oxide) and vasoconstrictor factors (i.e., endothelin, angiotensin II), to favor the latter (492). There also is evidence for involvement of the autonomic nervous system with reduced parasympathetic tone and enhanced reactivity of the alpha-adrenergic vascular receptors (490,493,494). Regardless of the mechanism, the risk for focal spasm is transient but recurrent.

3. Diagnosis

The diagnosis of variant angina is made by demonstrating ST-segment elevation in a patient during transient chest discomfort (which usually occurs at rest) that resolves when the chest discomfort abates. On coronary arteriography, if the artery is found to be angiographically normal or exhibits only nonobstructive plaques, then coronary artery spasm is the most likely explanation. If the patient has a spontaneous episode of pain and ST-segment elevation in the course of coronary arteriography, severe focal spasm of an epicardial coronary artery may be visualized. If the spasm is persistent, MI can occur; this is a rare complication in patients with variant angina who have normal or near-normal coronary arteries on arteriography. However, MI is common when coronary spasm complicates multivessel obstructive CAD (478). Coronary arteriography can show obstructive lesions, and increased arterial tone at a site of stenosis can precipitate total occlusion and the picture of impending infarction that is reversed on resolution of the increased vasomotor tone.

When the coronary arteriogram is normal or shows only nonobstructive plaques and if transient ST-segment elevation can be demonstrated at the time at which the patient has the discomfort, the presumptive diagnosis of Prinzmetal's angina can be made and no further tests are necessary. The key is to observe the ECG at the time of the attacks. If attacks occur frequently, a 24-h ambulatory ECG may be helpful in establishing the diagnosis.

In the *absence* of ST-segment elevation that accompanies chest discomfort, a number of provocative tests (methylergonovine, acetylcholine, and methacholine) can precipitate coronary artery spasm that can be visualized angiographically and is accompanied by ST-segment elevation in patients with Prinzmetal's variant angina (495). The patients should be withdrawn from nitrates and calcium antagonists before provocative testing. Hyperventilation performed for 6 min in the morning alone or after exercise is another test for coronary artery spasm (496). Patients with a positive hyperventilation test are more likely to have a higher frequency of attacks, multivessel spasm, and a high degree of AV block or ventricular tachycardia than are patients with a negative hyperventilation test (496). Because these provocative tests can occasionally cause prolonged intense and even multivessel spasm that requires intracoronary NTG or calcium antagonists for relief, the tests that require intravenous injections should be conducted in a catheterization laboratory with the catheter positioned in the coronary artery to deliver these drugs (497). The aforementioned drugs that are used to precipitate coronary artery spasm are not always readily available, so hyperventilation may be used.

4. Treatment

Coronary spasm is usually very responsive to NTG, long-acting nitrates, and calcium antagonists (498–500). Smoking should be discontinued. Usually, a calcium antagonist at a high dose (e.g., 240 to 480 mg per d verapamil, 120 to 360

mg per d diltiazem, 60 to 120 mg per d nifedipine) is started. If the episodes are not completely eliminated, a second calcium antagonist from another class or a long-acting nitrate should be added. Alpha-receptor blockers have been reported to be of benefit, especially in patients who are not responding completely to calcium antagonists and nitrates (491). In patients who develop coronary spasm (with or without provocation) during coronary angiography, 0.3 mg of NTG should be infused directly into the coronary artery that is involved.

5. Prognosis

The prognosis is usually excellent in patients with variant angina who receive medical therapy. Yasue et al. (501) reported an 89% to 97% overall 5-year survival rate. The prognosis is especially favorable in patients with normal or near-normal coronary arteries on arteriography. In a 7-year follow-up in approximately 300 patients, the incidence of sudden death was 3.6%, and the incidence of MI was 6.5% (501). Patients with coronary artery vasospasm superimposed on a fixed obstructive CAD have a worse prognosis. In a study of 162 patients with variant angina by Rovai et al. (479), the patients with normal coronary arteries and 1-vessel disease had a 5-year survival rate of 95% compared with a rate of 80% for those with multivessel disease. Almost identical survival rates were reported in an earlier study by Walling et al. (478).

G. Syndrome X

Recommendations

Class I

1. **Reassurance and medical therapy with nitrates, beta-blockers, and calcium antagonists alone or in combination. (Level of Evidence: B)**
2. **Risk factor reduction. (Level of Evidence: C)**

Class IIb

1. **Intracoronary ultrasound to rule out missed obstructive lesions. (Level of Evidence: B)**
2. **If no ECGs are available during chest pain and coronary spasm cannot be ruled out, coronary arteriography and provocative testing with methylergonovine, acetylcholine, or methacholine. (Level of Evidence: C)**
3. **HRT in postmenopausal women unless there is a contraindication. (Level of Evidence: C)**
4. **Imipramine for continued pain despite Class I measures. (Level of Evidence: C)**

Class III

Medical therapy with nitrates, beta-blockers, and calcium antagonists for patients with noncardiac chest pain. (Level of Evidence: C)

1. Definition and Clinical Picture

The term "syndrome X" is used to describe patients with angina or angina-like discomfort with exercise, ST-segment depression on treadmill testing, and normal or nonobstructed coronary arteries on arteriography. This entity should be differentiated from the "metabolic syndrome X," which describes patients with insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and abdominal obesity. It should also be differentiated from noncardiac chest pain. Syndrome X is more common in women than in men (354,502). Chest pain can vary from that of typical angina pectoris to chest pain with atypical features to chest pain that simulates UA, secondary to CAD (502). Other atypical features can be prolonged chest pain at rest and chest pain that is unresponsive to NTG (503). Most often, the chest pain occurs with activity and simulates angina pectoris due to stable CAD. However, because chest pain may accelerate in frequency or intensity or occur at rest, the patient may present with the clinical picture of UA. Therefore, this syndrome is discussed in this guideline.

The cause of the discomfort and ST-segment depression in patients with syndrome X is not well understood. The most frequently proposed causes are impaired endothelium-dependent arterial vasodilatation with decreased nitric oxide production, increased sensitivity to sympathetic stimulation, or coronary vasoconstriction in response to exercise (355,504,505). There is increasing evidence that these patients frequently also have an increased responsiveness to pain and an abnormality in pain perception.

The diagnosis of syndrome X is one of the exclusion of critical obstruction of an epicardial coronary artery in patients with exertional chest discomfort who have ST-segment depression on treadmill exercise. Other causes of angina-like chest discomfort not associated with cardiac disease, such as esophageal dysmotility, fibromyalgia, and costochondritis, must also be eliminated. In addition, in patients with a clinical presentation consistent with variant angina, coronary spasm must be ruled out by the absence of ST-segment elevation with the anginal discomfort or by provocative testing. Myocardial perfusion scanning may be abnormal due to a patchy abnormal response to exercise of the microvasculature that may lead to reduced coronary flow to different regions of the myocardium (355).

The intermediate-term prognosis of patients with syndrome X is excellent (502,503,506). The CASS registry reported a 96% 7-year survival rate in patients with anginal chest pain, normal coronary arteriograms, and an LV EF of greater than 0.50 (507). Long-term follow-up shows that ventricular function usually remains normal (503), although there have been reports of progressive LV dysfunction, and many patients continue to have chest pain that requires medication (508).

2. Treatment

Because the long-term prognosis is excellent, the most important therapy consists of reassurance and symptom relief. However, persistence of symptoms is common, and many patients do not return to work (503). The demonstration of normal coronary arteries on angiography can be reassuring. In 1 study, after a normal coronary arteriogram, there

was a reduced need for hospitalization as well as a reduced number of hospital days for cardiac reasons (286).

Both beta-blockers and calcium antagonists have been found to be effective in reducing the number of episodes of chest discomfort (509,510). Beneficial effects with nitrates are seen in about one half of patients (511). The use of alpha-adrenergic blockers would appear to be a rational therapy, but the results of small trials are inconsistent (512). Imipramine 50 mg daily has been successful in some chronic pain syndromes, including syndrome X, reducing the frequency of chest pain by 50% (513). Estrogen replacement in postmenopausal women with angina and normal coronary arteriograms has been shown to reverse the acetylcholine-induced coronary arterial vasoconstriction, presumably by improving endothelium-dependent coronary vasomotion (514). In a double-blind, placebo-controlled study, Rosano et al. (515) found that cutaneous estrogen patches in 25 postmenopausal women with syndrome X reduced the frequency of chest pain episodes by 50%.

It is recommended that patients be reassured of the excellent intermediate-term prognosis and treated with long-acting nitrates. If the patient continues to have episodes of chest pain, a calcium antagonist or beta-blocker can be started (510). Finally, 50 mg of imipramine daily has been successful in reducing the frequency of chest pain episodes. If symptoms persist, other causes of chest pain, especially esophageal dysmotility, should be ruled out (9,95,97–99,102,104,105,318).

APPENDIX 1

Acute coronary syndrome—any constellation of clinical signs or symptoms suggestive of AMI or UA. This syndrome includes patients with AMI, STEMI, NSTEMI, enzyme-diagnosed MI, biomarker-diagnosed MI, late ECG-diagnosed MI, and UA. This term is useful to generically refer to patients who ultimately prove to have 1 of these diagnoses to describe management alternatives at a time before the diagnosis is ultimately confirmed. This term is also used prospectively to identify those patients at a time of initial presentation who should be considered for treatment of AMI or UA. **Probable acute coronary syndrome** is a term that is commonly used, and this represents the primary consideration of patients on initial presentation. **Possible acute coronary syndrome** is useful as a secondary diagnosis when an alternate diagnosis seems more likely but an acute ischemic process has not been excluded as a possible cause of the presenting symptoms.

Acute myocardial infarction—an acute process of myocardial ischemia with sufficient severity and duration to result in permanent myocardial damage. Clinically, the diagnosis of permanent myocardial damage is typically made when there is a characteristic rise and fall in cardiac biomarkers indicative of myocardial necrosis that may or may not be accompanied by the development of Q waves on the ECG. Permanent myocardial damage may also be diagnosed when histological evidence of myocardial necrosis is observed on pathological examination.

Angina pectoris—a clinical syndrome typically characterized by a deep, poorly localized chest or arm discomfort that is reproducibly associated with physical exertion or emotional stress and relieved promptly (i.e., less than 5 min) with rest or sublingual NTG. The discomfort of angina is often hard for patients to describe, and many patients do not consider it to be "pain." Patients with UA may have discomfort with all the qualities of typical angina except that episodes are more severe and prolonged and may occur at rest with an unknown relationship to exertion or stress. In most, but not all, patients, these symptoms reflect myocardial ischemia that results from significant underlying CAD.

Angiographically significant coronary artery disease—CAD is typically judged "significant" at coronary angiography if there is greater than 70% diameter stenosis, assessed visually, of greater than 1 major epicardial coronary segments or greater than 50% diameter stenosis of the left main coronary artery. The term "significant CAD" used in these guidelines does not imply *clinical* significance but refers only to an *angiographically* significant stenosis.

Coronary artery disease—although a number of disease processes other than atherosclerosis can involve coronary arteries, in these guidelines, the term "CAD" refers to the atherosclerotic narrowing of the major epicardial coronary arteries.

Enzyme- or biomarker-diagnosed acute myocardial infarction—diagnostic elevation of cardiac enzymes or biomarkers (e.g., troponin) that indicates definite myocardial injury in the absence of diagnostic ECG changes (Q waves or ST-segment deviation).

Ischemic heart disease—a form of heart disease with primary manifestations that result from myocardial ischemia due to atherosclerotic CAD. This term encompasses a spectrum of conditions, ranging from the asymptomatic preclinical phase to AMI and sudden cardiac death.

Likelihood—used in these guidelines to refer to the probability of an underlying diagnosis, particularly significant CAD.

Myocardial ischemia—a condition in which oxygen delivery to and metabolite removal from the myocardium fall below normal levels, with oxygen demand exceeding supply. As a consequence, the metabolic machinery of myocardial cells is impaired, leading to various degrees of systolic (contractile) and diastolic (relaxation) dysfunction. Ischemia is usually diagnosed indirectly through techniques that demonstrate reduced myocardial blood flow or its consequences on contracting myocardium.

Non–Q-wave myocardial infarction—an AMI that is not associated with the evolution of new Q waves on the ECG. The diagnosis of non–Q-wave MI is often difficult to make

soon after the event and is commonly made only retrospectively on the basis of elevated cardiac enzyme levels.

Non–ST-segment elevation myocardial infarction—NSTEMI is an acute process of myocardial ischemia with sufficient severity and duration to result in myocardial necrosis (see Acute Myocardial Infarction). The initial ECG in patients with NSTEMI does not show ST-segment elevation; the majority of patients who present with NSTEMI do not develop new Q waves on the ECG and are ultimately diagnosed as having had a non–Q-wave MI. NSTEMI is distinguished from UA by the detection of cardiac markers indicative of myocardial necrosis in NSTEMI and the absence of abnormal elevation of such biomarkers in patients with UA.

Post–myocardial infarction angina—UA occurring from 1 to 60 days after an AMI.

Reperfusion-eligible acute myocardial infarction—a condition characterized by a clinical presentation compatible with AMI accompanied by ST-segment elevation or new LBBB or anterior ST-segment depression with upright T waves on ECG.

Unstable angina—an acute process of myocardial ischemia that is not of sufficient severity and duration to result in myocardial necrosis. Patients with UA typically do not present with ST-segment elevation on the ECG and do not release biomarkers indicative of myocardial necrosis into the blood.

Variant angina—a clinical syndrome of rest pain and reversible ST-segment elevation without subsequent enzyme evidence of AMI. In some patients, the cause of this syndrome appears to be coronary vasospasm alone, often at the site of an insignificant coronary plaque, but a majority of patients with variant angina have angiographically significant CAD.

APPENDIX 2. ABBREVIATIONS

AAFP = American Academy of Family Physicians
ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
ACEI = angiotensin-converting enzyme inhibitor
ACEP = American College of Emergency Physicians
ACIP = Asymptomatic Cardiac Ischemia Pilot
ACP-ASIM = American College of Physicians–American Society of Internal Medicine
ACS = acute coronary syndrome
ACT = activated clotting time
ADP = adenosine diphosphate
AHA = American Heart Association
AHCPR = Agency for Health Care Policy and Research
AMI = acute myocardial infarction
aPTT = activated partial thromboplastin time
ASA = aspirin
ATACS = Antithrombotic Therapy in Acute Coronary Syndromes
AV = atrioventricular
BARI = Bypass Angioplasty Revascularization Investigation
CABG = coronary artery bypass graft surgery
CABRI = Coronary Angioplasty versus Bypass Revascularisation Investigation
CAD = coronary artery disease
CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CAPTURE = c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina
CARS = Coumadin Aspirin Reinfarction Study
CASS = Coronary Artery Surgery Study
CCS = Canadian Cardiovascular Society
CHAMP = Combination Hemotherapy And Mortality Prevention
cGMP = cyclic guanosine monophosphate
CHF = congestive heart failure
CI = confidence interval
CK = creatine kinase
CLASSICS = CLopidogrel ASpirin Stent International Cooperative Study
COPD = chronic obstructive pulmonary disease
CRP = C-reactive protein
cTnI = cardiac-specific TnI
cTnT = cardiac-specific TnT
CURE = Clopidogrel in Unstable angina to Prevent ischemicEvents
DANAMI = DANish trial in Acute Myocardial Infarction
DATA = Diltiazem as Adjunctive Therapy to Activase
DAVIT = Danish Study Group on Verapamil in Myocardial Infarction
DRS = Diltiazem Reinfarction Study
DTS = Duke Treadmill Score
EAST = Emory Angioplasty versus Surgery Trial
ECG = 12-lead electrocardiogram, electrocardiographic
ED = emergency department
EF = ejection fraction (left ventricle)
EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications
EPILOG = Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIA receptor blockade
EPISTENT =Evaluation of Platelet IIb/IIIa Inhibitor for STENTing
ESSENCE = Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q wave Coronary Events
FRAXIS = FRAxiparine in Ischaemic Syndrome

FRIC = FRagmin In unstable Coronary artery disease study
FRISC = Fragmin during Instability in Coronary Artery Disease
FRISC II = Fast Revascularization During Instability in Coronary Artery Disease
GABI = German Angioplasty Bypass Surgery Investigation
GISSI-1 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1
GISSI-3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico
GP = glycoprotein
GUSTO-II = Global Use of Strategies to Open Occluded Coronary Arteries-II
GUSTO-III = Global Use of Strategies to Open Occluded Coronary Arteries-III
HDL = high-density lipoprotein
HERS = Heart and Estrogen/progestin Replacement Study
HINT = Holland Interuniversity Nifedipine/metoprolol Trial
HOPE = Heart Outcomes Prevention Evaluation
HRT = hormone replacement therapy
IABP = intra-aortic balloon pump
IMPACT = Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis
INR = international normalized ratio
IV = intravenous
ISIS = International Study of Infarct Survival
LAD = left anterior descending coronary artery
LBBB = left bundle-branch block
L-CAD = Lipid Coronary Artery Disease Study
LDL = low-density lipoprotein
LMWH = low-molecular-weight heparin
LV = left ventricular, left ventricle
MATE = Medicine versus Angiography in Thrombolytic Exclusion
MB = cardiac muscle isoenzyme of creatine kinase
MDPIT = Multicenter Diltiazem Postinfarction Trial
MET = metabolic equivalent
MI = myocardial infarction
MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
MM = skeletal muscle isoenzyme of creatine kinase
MR = mitral regurgitation
MVO_2 = myocardial oxygen consumption
NCEP = National Cholesterol Education Program
NHAAP = National Heart Attack Alert Program
NHLBI = National Heart, Lung, and Blood Institute
NSTEMI = non–ST-segment elevation myocardial infarction
NTG = nitroglycerin
OASIS = Organization to Assess Strategies for Ischemic Syndromes
OR = odds ratio
PCI = percutaneous coronary intervention
PR ECG = PR segment
PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management
PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
PTCA = percutaneous transluminal coronary angioplasty
PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis
RISC = Research Group in Instability in Coronary Artery Disease
RITA = Randomized Intervention Treatment of Angina
RR = relative risk
SHEP =S ystolic Hypertension in the Elderly Program
SHOCK = SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK
STEMI = ST-segment elevation myocardial infarction
STS = Society of Thoracic Surgeons
SVG = saphenous vein graft
TIMI = Thrombolysis In Myocardial Infarction
TIMI 9A and 9B = Thrombolysis and Thrombin Inhibition in Myocardial Infarction
TnC = troponin C
TnI = troponin I
TnT = troponin T
TTP = thrombotic thrombocytopenia purpura
UA = unstable angina
UFH = unfractionated heparin
UKPDS = UK Prospective Diabetes Study
VA = Veterans Administration
VANQWISH = Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital
WISE = Women's Ischemia Syndrome Evaluation

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