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Unstable angina and non-ST-segment elevation myocardial infarction

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Abstract

Coronary artery disease remains the most common cause of death in the world. Acute coronary syndromes, including unstable angina and non-ST-elevation myocardial infarction are commonly seen by critical care specialists. This article reviews up-to-date information on the diagnosis and state-of-the-art treatment of this condition.

Keywords: Acute coronary syndromes, myocardial infarction, angioplasty, thrombolysis, antiplatelet agents, aspirin

Introduction

Unstable angina (UA) and non-ST-segment–elevation myocardial infarction (NSTEMI) are common heterogeneous disorders that involve widely different risks but have similar clinical presentations. Unstable angina was first named and defined in 1971 [1]. Patients with an acute coronary syndrome (ACS) have a high risk of myocardial infarction (MI) and death (**Figure 1**). The last few years has seen several advances in the evaluation and management of these patients, including medical therapies and interventional procedures. Today, selection of noninvasive or invasive evaluation and optimal management can be tailored for each patient, to achieve the best results [2].

Epidemiology

In the United States, UA/NSTEMI is an important reason for emergency department visits, accounting for approximately 5.3 million such visits per year. It accounts for more than 1 million hospital admissions annually in the United States and about 2.5 million admissions worldwide. More than half of the patients admitted to the hospital for UA/NSTEMI are over 65 years old, and almost half of them are women [3]. The prevalence of UA/NSTEMI in men aged 40 to 59 years is 2.5 % to 5.0%, around 80 new cases per 100,000 patients being diagnosed each year [4]. A significant percentage of patients with an acute myocardial infarction develop unstable angina in the early postinfarction period. In recent years, the number of hospital admissions for patients with UA/NSTEMI has been increasing, while the number of patients with an ST-segment–elevation myocardial infarction (STEMI) has been decreasing [2].

Pathophysiology

Myocardial ischemia occurs when the blood supply is insufficient to meet the demands of the myocardium. This deficiency results in chest pain and/or dyspnea. An acute coronary syndrome is initiated by an atherosclerotic plaque rupture or erosion that leads to intracoronary thrombus formation an platelet activation. The plaque invades the coronary lumen. If the plaque causes more then 70% luminal narrowing, blood flow is reduced and the myocardial oxygen demand is increased [5].

The causes of unstable angina (**Table 1**) include:

- nonocclusive stenosis: a coronary artery narrowing produced by a nonocclusive clot, causing a decrease in myocardial perfusion.
- an active obstruction: severe spasm of part of an epicardial coronary artery that has only mild atherosclerosis.
- increasing mechanical obstruction: narrowing without the presence of thrombus or vasoconstriction.

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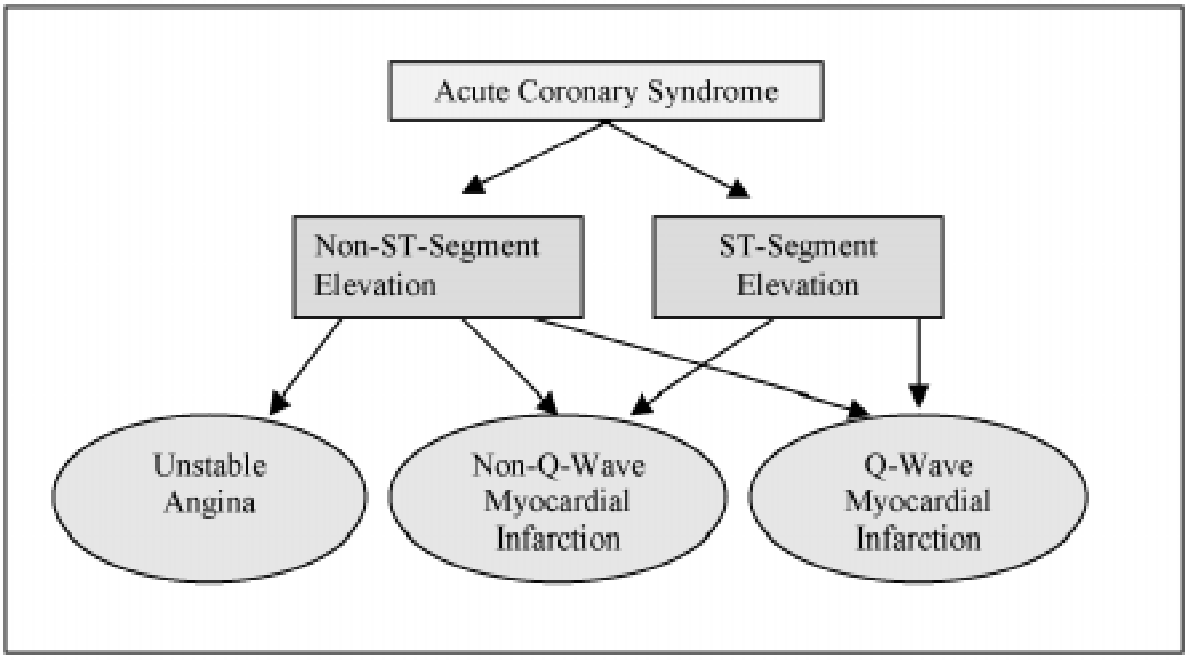

FIGURE 1. ALGORITHM: ACUTE CORONARY SYNDROME.

- infection: activated factors in the plaque that may produce narrowing and collapse of the plaque.
- secondary causes of unstable angina: anemia or tachycardia can produce an inflammation of the coronary arteries and can also increase the oxygen demand when myocardial blood flow is affected by atherosclerotic coronary stenosis [6].

TABLE 1. CAUSES OF UNSTABLE ANGINA

Nonocclusive clot on preexisting plaque
Active obstruction
Increasing mechanical obstruction
Infection
Consequential unstable angina (fever, tachycardia, thyrotoxicosis, hypotension, anemia, and hypoxemia)

Diagnosis

Presentation of Unstable Angina

Patients with unstable angina may present in one of three different ways (**Table 2**). Diagnosis is based on the prolongation, intensity, and grade of angina, as classified by the Canadian Cardiovascular Society. The purpose of this classification is to simplify communication about these patients and to help determine the appropriate diagnosis and therapy in each case [7].

The typical angina patient presents with substernal chest pain that may affect both sides of the chest and radiate to shoulder, arm, jaw, neck, and back. The pain is often described as tight, squeezing, aching, crushing, or burning. It increases with physical activity and is relieved by rest or nitroglycerin. Canto and coworkers [8] reported that among patients with confirmed unstable angina, 51.7% had atypical presentations that included dyspnea, nausea, diaphoresis, syncope, or pain in the arms, epigastrium, shoulders, or neck. These symptoms occur in as many as half of patients ≥ 65 years of age [8]. These patients usually have symptoms at rest, while sleeping at night, or during minimal physical exertion; the pain occurs unpredict-

TABLE 2. THREE MAIN PRESENTATIONS OF UNSTABLE ANGINA

Rest angina	Angina presenting at rest and commonly lasting for >20 minutes.
New-onset angina	New-onset angina of at least CCS Class III severity.
Advancing angina	Antecedently diagnosed angina that has become more frequent, longer-lasting, or smaller in threshold (progressing or equal to 1 CCS class, to at least CCS Class III severity)

CCS, Canadian Cardiovascular Society

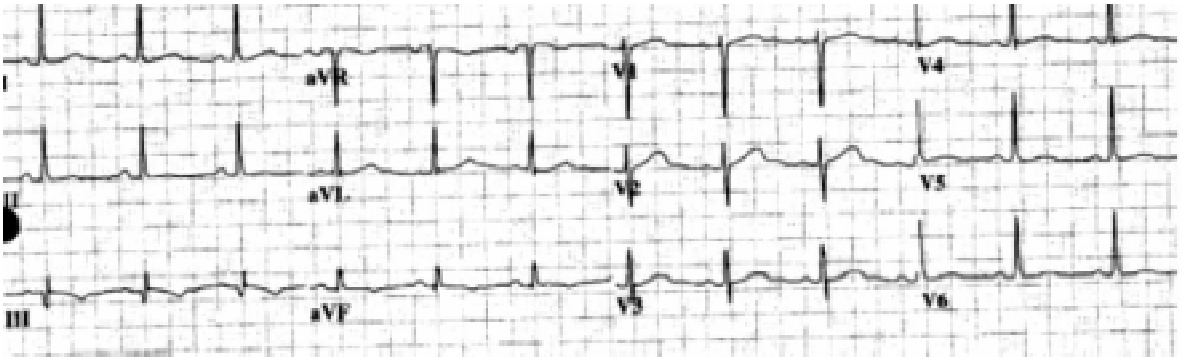

FIGURE 2. ELECTROCARDIOGRAM. NORMAL SINUS RHYTHM AND NONSPECIFIC T-WAVE ABNORMALITIES IN INFERIOR LEADS (II, III, AVF).

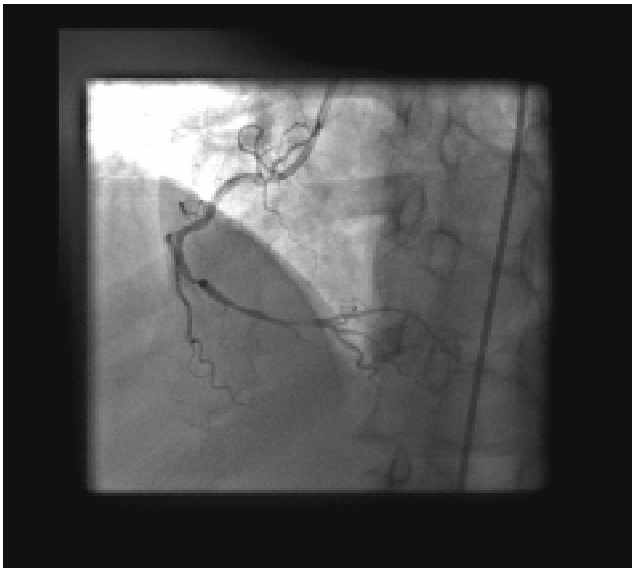

FIGURE 3. (DIAGNOSTIC ANGIOGRAM): CORONARY ANGIOGRAM, SHOWING A STENOSIS OF THE RIGHT CORONARY ARTERY.

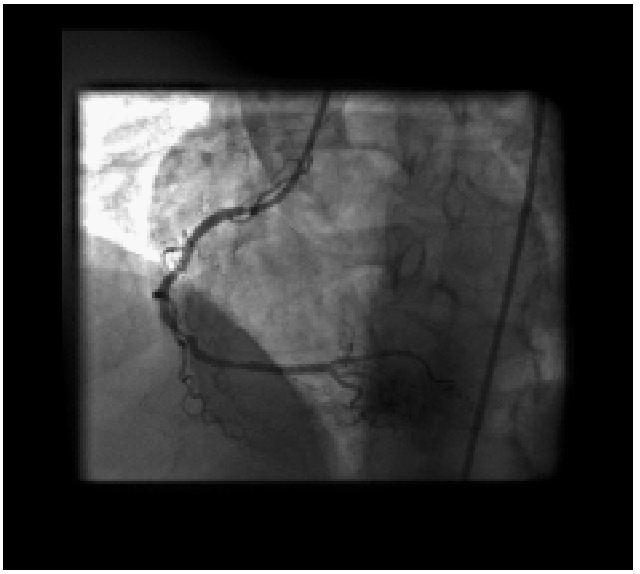

FIGURE 4. (POST-STENT ANGIOGRAM): CORONARY ANGIOGRAM, OBTAINED AFTER STENT PLACEMENT.

ably and is severe, persistent (>30 minutes), seldom relieved by rest, and less responsive to medications than is typical angina. In patients with unstable angina, the risk of death related to complications is lower than in patients with MI but is higher than in those with stable angina. Around 5% to 10% of patients with unstable angina progress to have a MI, which will be fatal in 1% of the cases [9].

Differential Diagnosis

Because of the many possible etiologies involved, the differential diagnosis of chest pain can be most challenging. Because chest pain can be the first symptom of a life-threatening condition such as acute MI, prompt and correct assessment of the likely etiology is essential. Whereas acute coronary artery disease may be the reason for many emergency room admissions, chest pain does not always signify coronary artery disease. Noncardiac causes of chest pain include musculoskeletal, esophageal, neurologic, and psychiatric etiologies. Another common cause of chest pain is panic disorder, which accounts for 25% of emergency department admissions for chest pain (**Table 3**) [10].

Risk Stratification

Patient stratification according to the risk of unstable angina and NSTEMI should be based on the clinical history, physical examination, electrocardiographic findings, and cardiac biomarker levels [11]. The timing of the clinical course and the quality of the chest pain should be also considered [8]. Five important factors from the initial history may indicate that the patient is experiencing an ischemic episode related to coronary artery disease. These factors are age, gender, nature of the symptoms, a previous history of coronary artery disease, and the number of traditional risk factors for coronary artery disease. If the

TABLE 3. DIFFERENTIAL DIAGNOSIS

Chest Pain Diagnosis	Etiology
Nonischemic cardiovascular	Acute pericarditis, aortic dissection, myocarditis
Pulmonary	Pulmonary embolism, pneumonia, severe pulmonary hypertension, pneumothorax, pleuritis
Gastrointestinal:	
Esophageal	Reflux, spasm, esophagitis
Biliary	Colic, cholecystitis, choledocholithiasis, cholangitis
Gastric	Peptic ulcer
Pancreas	Pancreatitis
Chest wall	Fibrositis, costochondritis, rib fracture, sternoclavicular arthritis, herpes zoster
Psychiatric:	
Anxiety disorders	Hyperventilation, panic disorder, primary anxiety
Affective disorders	
Somatiform disorders	
Thought disorders	Fixed delusions

patient history and risk factors suggest an ACS, therapy should be initiated immediately [2]. The initial information should be used to differentiate an acute coronary syndrome related to coronary artery disease from an adverse outcome including MI, stroke, heart failure, recurrent symptomatic ischemia, and serious arrhythmia. Stratification into high-, intermediate-, and low-risk groups is useful to estimate the risk of death or recurrent nonfatal cardiac ischemic events (**Table 4**) [12].

TIMI Risk Score

The Thrombolysis in Myocardial Infarction (TIMI) risk score is a simple, convenient method of risk stratification based on the number of independent risk factors at presentation (**Table 5**). The incidence of an adverse outcome (death, myocardial reinfarction, or recurrent severe is-

TABLE 4. SHORT-TERM RISK OF DEATH OR NONFATAL MYOCARDIAL INFARCTION IN PATIENTS WITH UNSTABLE ANGINA

Feature	High Risk (At least 1 of the following conditions)	Intermediate Risk (No high-risk features and at least 1 of the following conditions)	Low Risk (No high- or intermediate-risk features but at least 1 of the following conditions)
Clinical history	Accelerating tempo of ischemic symptoms in the previous 48 h	Previous MI, PVD, CVD, CABG, or aspirin use	———————
Pain characteristics	Ongoing pain for >20 min	Prolonged for >20 min; rest angina now resolved; moderate to high likelihood of CAD. Rest angina or relieved with rest or sublingual NTG	New-onset CCS class III or IV angina in the past 2 wks without >20-min rest pain but with high or moderate likelihood of CAD
Clinical signs	Pulmonary edema, likely related to ischemia. New or worsening MR murmur S_3 or new/worsening rales; hypotension, bradycardia, tachycardia; age >75 y	Age >75 y	———————
ECG	Angina at rest with transient ST-segment changes of >0.05 mV; bundle-branch block, new or presumed new; sustained VT	T-wave inversions of >0.2 mV; pathologic Q waves	Normal or without changes during chest pain
Cardiac markers	Marked troponin elevation (>0.1 ng/ml)	Slightly elevated troponin levels (>0.01 ng/ml but <0.1 ng/ml	Normal

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CVD, cerebrovascular disease; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; PVD, peripheral vascular disease; VT, ventricular tachycardia

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chemia) at 14 days ranges from 5% (for patients with a risk score of 0-1) to 41% (for those with a risk score of 6-7) (**Figure 5**). This risk score was derived from an analysis of patients in the TIMI 11B trial and validated by four additional trials and one registry [13]. As the risk score increased, progressively greater benefits were observed for treatment with low-molecular-weight heparin (LMWH) versus unfractionated heparin (UFH), with the platelet glycoprotein (GP) IIb/IIIa receptor blocker tirofiban versus a placebo, and with an invasive versus a conservative strategy. However, patients across all levels of the TIMI risk score showed similar relative reductions in adverse outcomes with clopidogrel. The risk score was also effective in predicting postdischarge adverse outcomes. This ability of a risk assessment scheme to detect differences in treatment benefits specific to particular therapies greatly supports the imperative to use the score in practice [14].

TABLE 5. VARIABLES FOR THE THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI) RISK SCORE

Characteristics	Points
History	
Age ≥65 years	1
≥3 risk factors for coronary artery disease	1
History of coronary artery disease	
Hypertension	
Hypercholesterolemia	
Diabetes	
Current smoker	
Use of aspirin in 7 days before presentation	
≥50% coronary stenosis on angiography	1
ST-segment change of >0.5 mm	1
Presentation	
Severe anginal symptoms (≥2 anginal episodes in 24 hours before presentation)	1
Elevated serum concentration of cardiac markers	1
Total score	0–7

Assessment of Cardiac Biomarkers

Cardiac biomarkers are used to diagnose myocardial necrosis and predict its outcome. The myocardial cell-wall damage that takes place during an ischemic event allows intracellular macromolecules to be released into the lymphatic system and the bloodstream. The level of these biomarkers should reflect the extent of the myocardial damage [15]. For a cardiac biomarker to be useful for diagnosis, it should be rapidly released into the bloodstream after myocardial cell injury; should have a high concentration in the myocardium and be absent from nonmyocardial tissue; and should persist in the bloodstream long enough to permit a diagnostic assay. Unfortunately, no biomarker has all of these characteristics. Nevertheless, in patients with electrocardiographic non-ST-segment elevation, biomarkers can help establish the diagnosis of MI and can predict a possible adverse outcome [16]. Biomarkers may suggest different pathophysiologic events. For instance, UA/NSTEMI involves three pathophysiologic factors: plaque instability and the myonecrosis resulting from microembolization; vascular inflammation; and left ventricular damage. These factors are indicated by elevated cardiac-specific troponin, C-reactive protein, and brain

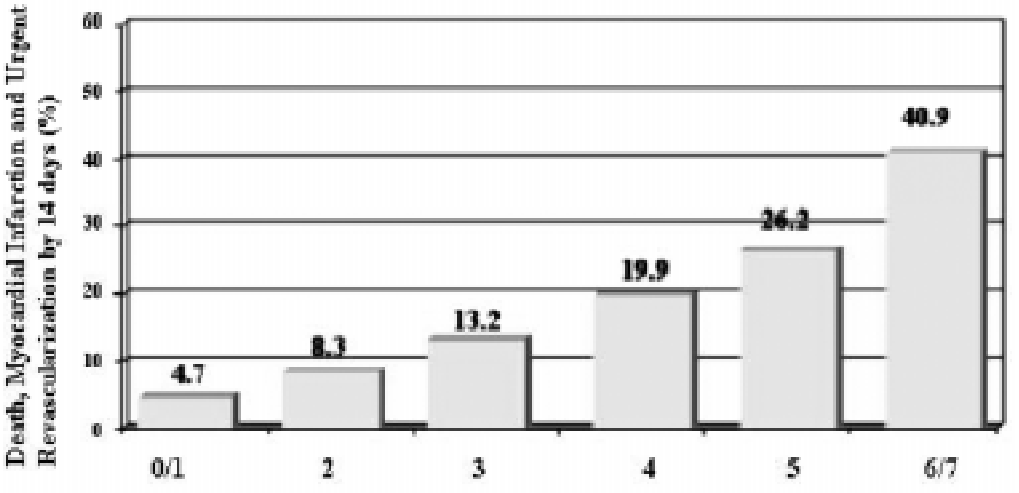

FIGURE 5. THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI) RISK SCORE FOR UNSTABLE ANGINA AND NON-ST-SEGMENT–ELEVATION MYOCARDIAL INFARCTION.

natriuretic peptide levels, respectively (**Figure 6**).

Assessment of three biomarkers (i.e., myoglobin, creatine kinase-MB, and troponin I) allows more accurate risk stratification than assessment of a single marker alone.

Myoglobin

Measurement of the myoglobin level is a basic step in the early detection or exclusion of myocardial cell damage. Myoglobin is a low-molecular-weight protein that is abundant in cardiac and skeletal muscle and that transports oxygen from the sarcolemma to the mitochondria. When released into the serum, this protein suggests cell injury.

Myoglobin levels are elevated as early as 1 to 3 hours after myocardial injury. (In comparison, creatinine and troponin levels are not elevated until 6 to 7 hours after the onset of symptoms). Therefore, myoglobin assessment is a useful test for rapid triage in the emergency room. When Polanczyk and coworkers [17] measured myoglobin levels at the time of patient arrival and again 1 to 2 hours later, they found that doubling of the level was diagnostic of myocardial injury. Measurement performed within 4 hours of the onset of chest pain was as helpful as serial measurement.

Although myoglobin is a sensitive (95%) marker of MI with a high negative predictive value, it lacks specificity [11]. Whereas it is released rapidly after an acute coronary event, it is also cleared rapidly by the kidneys, so that abnormal renal function is one of the differential diagnoses for patients with elevated myoglobin levels.

Creatinine Kinase

In the 1960s, creatinine kinase (CK) was identified as a biomarker that became elevated in the bloodstream after an MI. Creatinine kinase is an enzyme that catalyzes the reaction of creatinine and adenosine triphosphate (ATP), adding a high-energy phosphate to creatinine and resulting in creatinine phosphate and adenosine diphosphate. Creatinine phosphate is transported from the mitochondria to the cytoplasm, where it is stored. During muscle contraction, the cytoplasmatic isoenzymes catalyze the reverse reaction of creatinine kinase for the regeneration of ATP to support muscle metabolism. Creatinine kinase is present in most tissues. Its presence in striated muscle and the brain makes it a relatively nonspecific marker for myocardial injury.

Creatine kinase has three isoenzymes: MM, MB, and BB. The MM isoenzyme predominates in most tissues, the BB isoenzyme being found mainly in the brain and gastrointestinal tract. The amount of CK present as the MB isoenzyme is approximately 15% to 30% in the myocardium versus 1% to 3% in striated muscle. Because of the quantity of CK-MB present in the myocardium, it is the marker of choice for identifying myocardial injury [18]. However, the fact that increased serum levels of CK-MB can result from other conditions besides myo-

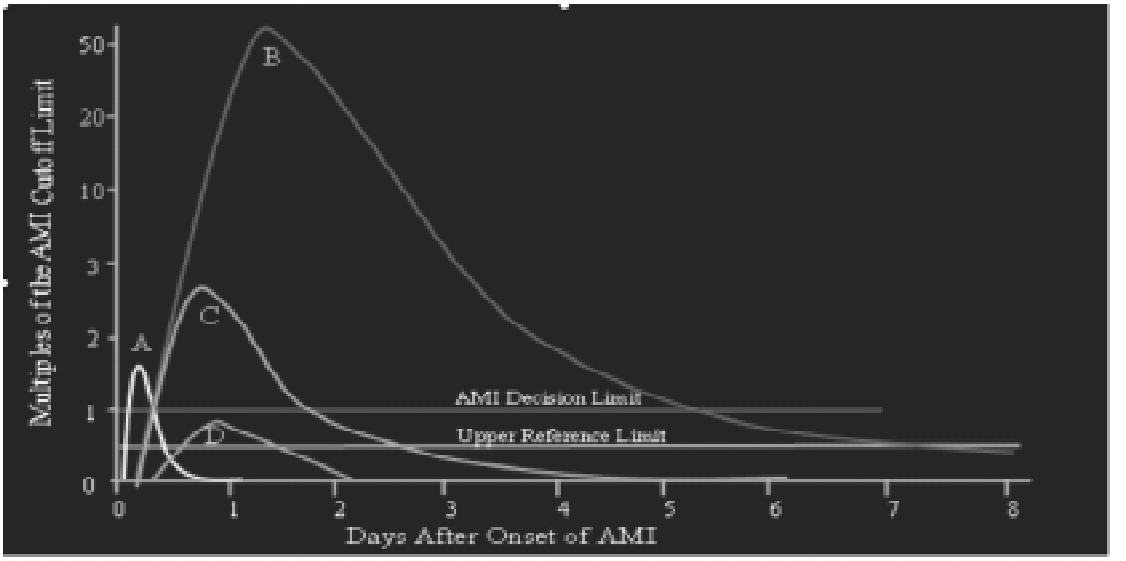

FIGURE 6. ELEVATION OF BIOMARKERS IN ORDER OF APPEARANCE AND DURATION IN THE BLOOD STREAM. **(A)** MYOGLOBIN EARLY RELEASE. **(B)** CARDIAC TROPONIN. **(C)** CREATINE KINASE-MB LEVEL ELEVATION AFTER MYOCARDIAL INFARCTION. **(D)** CARDIAC TROPONIN ELEVATION AFTER UNSTABLE ANGINA. AMI, ACUTE MYOCARDIAL INFARCTION

WITH PERMISSION NATIONAL ACADEMY OF CLINICAL BIOCHEMISTRY, WASHINGTON, DC. STANDARDS OF LABORATORY PRACTICE RECOMMENDATION FOR USE OF CARDIAC MARKERS IN CORONARY ARTERY DISEASE. NOVEMBER 5, 1999.

cardial injury decreases the specificity of this assay [28]. In the presence of an MI, there are differences in the relative ratios identified by the initial CK-MB assays.

CK-MB is most commonly measured according to its activity or mass. An activity assay measures the degree in which creatinine is converted to creatinine phosphokinase. Assay of the mass is more sensitive, reliable, and specific. Increased isoform shifting in the plasma usually occurs early (6 to 12 hours after the onset of infarction), peaks at 24 hours, and returns to baseline after 36 to 72 hours, having a sensitivity of 92%.Traditionally, a CK-MB mass limit of >7 ng/mL has been considered the initial level for diagnosing an acute MI [19].

Troponin

Troponin is a complex globular protein that acts on tropomyosin. Tropomyosin is an elongated protein that, in combination with actin, is responsible for contraction of skeletal and cardiac muscle. The troponin complex consists of three subunits: C, which binds calcium ions; I, which inhibits bonding between subunit T and tropomyosin; and T, which forms a bond with tropomyosin [20].

The codification of troponin involves three different genes that are expressed to different degrees in different types of muscle. Cardiac troponin I is highly specific for myocardial tissue. Troponin I is not expressed in human skeletal muscle even during development, damage, or regeneration and is not detectable in the blood of healthy persons. During an ischemic event, the muscle contraction complex, including the troponin complex, is degraded or modified. Troponin I degradation is a progressive process. The serum level increases in proportion to the severity of the ischemic insult. Calpain, a calcium-dependent protease, is probably responsible for the degradation of troponin I.

Troponin levels begin to rise 3 to 12 hours after injury and peak at 12 to 24 hours, providing high sensitivity and specificity in detecting recent myocardial necrosis. Troponin T levels remain elevated for 8 to 21 days, and troponin I levels remain elevated for 7 to 14 days. The enzyme-linked immunosorbent assay (ELISA) is the mainstay of troponin testing. In the emergency room, measuring the troponin levels can predict the course of patients with an ACS: patients with elevated troponin T levels on arrival in the emergency room have a three- to fourfold higher mortality than do patients with normal troponin T levels. Therefore, troponin T assessment may be an excellent means of predicting the short-term outcome of an ACS, and continued screening of this variable may predict adverse cardiac events.

Cardiac troponin I levels of at least 0.4 ng/ml in a single plasma specimen at presentation are associated with an increased risk of mortality, even when the CK-MB level is not abnormally elevated. Troponin I assays with levels of >0.4 ng/ml have a sensitivity of 47% and a specificity of 80% for major cardiac events during the 72 hours after the arrival in the emergency room. However, because of their long half life, troponin levels are not accurate for diagnosing new-onset MI. Because the presence of cardiac troponin has been associated with myocardial stunning, measuring the serum level of this biomarker has become the most important step in diagnosing a myocardial injury [21].

Patients with unstable angina may have normal CK, MB, and troponin levels; normal CK but elevated MB levels; or normal CK and MB but elevated troponin levels [22]. Histologic evidence of focal myocyte necrosis in patients with elevated troponin levels and normal CK-MB values has been reported [18]. It is estimated that around 30% of patients who have rest pain without ST-segment elevation, unstable angina, or CK-MB elevation will actually have NSTEMI when assessed with cardiac-specific troponin assays. The TIMI IIIB trial revealed a 3.7% mortality for patients with troponin I levels of $\geq$0.4 ng/mL versus only a 1% mortality for patients with troponin I levels of <0.4 ng/mL. The TACTICS-TIMI 18 trial showed that patients with elevated troponin levels had a significantly higher risk of death, recurrent ischemia, or new MI at both 30 days and 6 months [22]. In patients with an intermediate or higher risk of coronary ischemia, serial testing of CK-MB and troponin levels is recommended, with at least one repeat value obtained 6 to 8 hours after the initial value. Two negative values mean that the patient has not had an MI and is at relatively low risk for an adverse event. However, these results do not imply the absence of coronary disease or myocardial ischemia. A test that is positive for either MB or troponin elevation should result in aggressive risk-reduction therapy including aspirin, beta-blockers, LMWH, and possibly GP Ilb/IIIa antagonists or early angiography [18].

Novel Biomarkers

The role of inflammation in the formation and development of atherosclerotic plaque is well accepted. Detection of lymphocyte and macrophage infiltration of the vascular endothelial wall around an atherosclerotic lesion supports the presence of an inflammatory process. Once macrophages are activated, they secrete proteolytic enzymes that weaken the plaque, making it susceptible to fracture and the production of a further ischemic event [23]. Half of patients with an ACS have normal lipid levels. Because of the role of in-

flammation in coronary artery disease, serum inflammatory markers have been proposed as predictors of cardiovascular events. These markers include C-reactive protein (CRP), interleukin-6 (IL-6), and serum amyloid A.

C-reactive protein has emerged as the most important inflammatory marker for cardiovascular disease [24]. CRP is synthesized by hepatocytes in response to IL-6, IL-1, and TNF-α, which are synthesized by adipose cells and inflammatory cells in the atherosclerotic lesion. CRP is a member of the family of pentraxin proteins involved with innate immunity and is considered an "acute-phase protein" because of its early increase in human serum in response to tissue injury and infection. CRP was discovered by Tillet and Frances in 1930, in patients infected by *Streptococcus pneumoniae*, in whom CRP reacts to the polysaccharide C of the bacterial cell wall. Levels of CRP are increased early during an infection and stay elevated for a week or more. Normal persons have a CRP level of 2 mg/L or less. In the presence of an inflammatory process, this value may increase 1000-fold.

In conventional CRP assays, the lowest level that could be detected was 3 to 8 mg/L. In newer tests, however, lower levels can be detected, permitting discovery of an inflammatory process in its early stages. The American Heart Association and the Centers for Disease Control and Prevention (AHA/CDC) classify the results of the new sensitivity assays as low risk (<1 mg/L), average risk (1-3 mg/L), and high risk (>3 mg/L), recommending that two measurements be obtained, one at baseline and the second 2 weeks later [25].

In patients with unstable angina, traditional troponin assessment may show no evidence of myocardial necrosis, but a CRP concentration of >3 mg/L on emergency room admission is associated with an increased incidence of recurrent cardiovascular events [26]. In patients with non-ST-segment–elevation ACS, a CRP concentration of >5 mg/L predicts a major incidence of ischemic events in the ensuing 6 months regardless of troponin levels.

The Physicians Health Study demonstrated that CRP levels were higher in the individuals who had a stroke or MI; the benefit of aspirin was increased in patients with elevated CRP levels, but aspirin had no benefits in patients with lower CRP levels. The Women 's Health Study showed that, compared with a control group, patients with the highest CRP levels had a relative risk of 4.4 for any kind of cardiovascular event; even in women with low-density lipoprotein cholesterol (LDLC) levels of <130 mg/dL (who are normally considered at low risk), elevated CRP levels predicted a higher risk of future ischemic events [28].

For all of these reasons, the CRP level may be useful for predicting the short- and long-term prognosis and may identify patients at increased risk of cardiovascular ischemic events even if these patients would otherwise have been considered at low risk. A FRISC II substudy suggested that an elevated serum level of IL-6, the major determinant of acute-phase reactant proteins in the liver, and of serum amyloid A, another acute-phase reactant protein, has a predictive value similar to that of CRP in identifying a "high-risk" subgroup that would particularly benefit from early coronary angiography.

Increased levels of circulating soluble adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin in patients with unstable angina are under investigation as markers of increased risk [29].

Electrocardiographic Changes

In emergency room patients with acute chest pain, electrocardiography is one of the most basic techniques for diagnosing the problem, determining the prognosis, and choosing an appropriate treatment, based on the magnitude and pattern of the abnormalities present [30]. In patients with suspected coronary artery disease, electrocardiography complements the clinical examination. A 12-lead electrocardiogram (EKG) should be obtained within 10 minutes after the admission of patients with ongoing chest pain and as soon as possible after the admission of patients with a history of chest discomfort, even if it has resolved by the time of evaluation. If the EKG shows important ST-segment changes (>0.05 mV) with symptoms of unstable angina, followed by a normal EKG and resolution of the symptoms, acute ischemia and severe underlying coronary artery disease should be strongly suspected [11]. For these reasons, follow-up serial EKGs are crucial to decision-making in the evaluation and management of patients with an ACS. In the TIMI III study, ST-segment deviation was the most important EKG feature for predicting an adverse outcome.

The presentation of patients with an ACS is highly variable. The EKG may show T-wave inversion, bundle-branch block, transient ST-segment changes, or nonspecific changes; it may even be normal in symptomatic patients [31]. However, in the presence of normal electrocardiographic findings, other etiologies should be considered and ruled out.

Unstable angina and NSTEMI are two life-threatening conditions that cannot be differentiated at the beginning of the acute ischemic event. There is a direct relationship between the severity of ST-segment depression and the probability of an adverse outcome. Therefore, in addition to complete 12-lead electrocardiography and evaluation of biomarkers, ST-segment monitoring is fun-

damental for risk stratification and prognosis assessment. If a patient who complained of chest pain on arrival has a normal EKG within 12 or 24 hours after arrival and has no elevated biomarkers, he or she may be considered at relatively low risk [32].

Medical Treatment

Antiplatelet Therapy

Aspirin

In recent years, aspirin has become a cornerstone in the management of UA/NSTEMI. According to the ACC/AHA, aspirin is a class I recommended medication (**Table 6**). The Veterans Administration Cooperative Study and the Canadian Multicenter Trial showed that aspirin therapy decreases the risk of sudden cardiac death, reducing the incidence of myocardial infarction by 51% to 72% in patients with unstable angina [33-35]. Aspirin prevents the creation of thromboxane A_2 by irreversibly inhibiting cycloxygenase-1 within platelets. An initial dose of 160 mg, followed by 80 to 325 mg per day for an indefinite period, is currently recommended [9]. The first dose should be given as soon as an acute coronary syndrome is suspected or confirmed, and the aspirin may be chewed to rapidly produce a high blood level. In higher doses, aspirin can cause gastrointestinal side effects [36].

Despite the demonstrated benefits of aspirin use, several studies have indicated that 8% to 45% of patients are aspirin resistant and, therefore, unable to achieve an adequate antiplatelet effect. The reasons are unclear, but there are several possible explanations for aspirin's poor efficacy of action [37]. These are the three main causes of aspirin failure, denominated aspirin resistance. The first explanation is that platelets can be activated for other pathways that aspirin is unable to block [38]. Another possible explanation is that some patients need higher doses of aspirin (75 to 325 mg/d) to achieve the best antithrombotic effect [39]. However, there is currently no clear evidence of a relationship between a high dose and efficacy [40]. The third possible explanation is that, despite the receipt of a therapeutic aspirin dose, some patients are still able to produce thromboxane A_2 [41].

TABLE 6. ACC/AHA CLASSIFICATIONS

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 divergence of opinion about the usefulness/efficacy of a procedure or treatment.

- **IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.
- **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.

ACC, American College of Cardiology; AHA, American Heart Association

Thienopyridines (Clopidogrel and Ticlopidine)

Clopidogrel is an oral antiplatelet agent of the thienopyridine family, which irreversibly inhibits the platelet ADP P2Y receptor and has synergistic effects with aspirin. The CAPRIE trial indicated that clopidogrel is better than aspirin at decreasing the combined risk of ischemic stroke, MI, or death resulting from vascular disease. At a dosage of 75 mg/d, a loading dose of 300 to 400 mg can be used when rapid onset of action is necessary [42].

Another thienopyridine, ticlopidine, which can be used for the therapy of unstable angina, is effective in reducing the risk of death, stroke, and MI. The current recommended dosage is 250 mg twice daily; a loading dose of 500 mg can be used when rapid onset of action is necessary [43]. Side effects of ticlopidine include diarrhea, abdominal pain, nausea, vomiting, and neutropenia. Clopidogrel has fewer side effects, provides faster platelet inhibition, and is more potent [44]. When combined with aspirin, clopidogrel may be safer than ticlopidine, so it is recommended as first-line drug for patients with UA/NSTEMI.

Thienopyridines, given in combination with aspirin for 4 weeks, have been shown to reduce adverse events in patients undergoing percutaneous coronary intervention with stent placement [45].

Clopidogrel has also been shown to improve the outcomes of patients with non-ST-segment-elevation ACS (NSTEACS). The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial randomized 12,562 patients with UA/NSTEMI, all of whom were receiving aspirin, to take either clopidogrel (a 300-mg loading dose, followed by 75 mg daily) or a placebo. After a follow-up period that averaged 9 months, the primary prespecified "hard" endpoints of cardiovascular death, MI, and stroke

were significantly reduced by 20%, from 11.5% in the placebo group to 9.3% in the clopidogrel group ($P<0.001$). A reduction of recurrent ischemia was documented within 6 hours after randomization. The salutary effects were noted across all of the subgroups, including those without ST-segment deviation or troponin release and those with a low TIMI risk score. The major benefit was a reduction in the incidence of MI. Although clopidogrel tended to surpass the placebo at reducing death and stroke, this difference did not achieve statistical significance. However, the rate of major bleeding was significantly higher in the clopidogrel arm than in the placebo arm (3.7% vs. 2.7%; $P<0.001$). After undergoing coronary artery bypass grafting, the clopidogrel-treated patients had no significant excess of major bleeding; most of them had discontinued the drug within a median of 5 days before surgery. However, in the 912 patients who stopped the medication ≤ 5 days before surgery, the risk of major bleeding was 9.6% in the clopidogrel group and 6.3% in the placebo group ($p=0.06$) [46].

In an observational substudy in CURE, involving 2658 patients undergoing percutaneous coronary intervention (PCI) a median of 10 days after randomization (the PCI-CURE Study), all of whom received 30 days of clopidogrel after intervention, pretreatment with clopidogrel was associated with a significant (30%) reduction in the incidence of cardiovascular death, MI, or urgent target-vessel revascularization at 30 days (4.5% vs. 6.4 %; $p=0.03$) [47]. When blinded study medication (placebo vs. clopidogrel) was resumed 1 month after PCI, a continuing benefit of clopidogrel was observed during the 8 months. These results were confirmed in CREDO (Clopidogrel for Reduction of Events During Observation), a trial involving 2116 patients, which showed that clopidogrel pretreatment for at least 6 hours before elective PCI reduced the 28-day incidence of death, MI, or urgent target-vessel revascularization from 9.4% to 5.8% ($p=0.05$) [48].

When coronary angiography is deemed emergent, a larger loading dose of clopidogrel may be required for more rapid platelet inhibition. Pharmacokinetic studies have shown that clopidogrel doses in the range of 450 to 600 mg may achieve maximal antiplatelet effects more rapidly than 300-mg doses [49], but the effect of the higher loading doses on clinical outcomes needs to be studied in a randomized, prospective fashion.

The benefit observed with clopidogrel pretreatment in the PCI cohort from CURE, compared with the increased risk of bleeding if coronary artery bypass grafting is performed within 5 days of drug discontinuation, has sparked much debate regarding whether this medication ought to be started before coronary angiography in patients with NSTEACS. Because the benefits of clopidogrel pretreatment outweigh the surgical bleeding risks, up-front treatment of patients before coronary angiography is a reasonable strategy based on the apparently synergistic effect of clopidogrel in combination with GP IIb/IIIa inhibitors [50]. **Table 7** shows recommendations for antiplatelet therapy.

Platelet Glycoprotein IIb/IIIa inhibitors

Platelets play an important role in the development of any ischemic complications that may occur in patients with UA/NSTEMI during coronary revascularization procedures. Therefore, the introduction of platelet glycoprotein IIb/IIIa antagonists was an important advance in the treatment of UA/NSTEMI patients undergoing PCI (**Table 8**).

Three new GP IIb/IIIa-inhibiting agents are tirofiban, eptifibatide, and abciximab. These agents proliferate on the platelet surface and are limited to that area. They should be included as antiplatelet therapy mainly in high-risk patients or those planning to undergo a PCI. When

TABLE 7. CLASS I ANTIPLATELET THERAPY

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 hyper sensitivity 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 and who are not at high risk for bleeding, clopidogrel should be started and continued for at least 1 month (level of evidence: A) and for up to 9 months (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 before surgery (level of evidence: B).

*New indication in the guidelines. ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

TABLE 8. CLASS I GP IIB/IIIA ANTAGONISTS

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).

1. Eptifibatide or tirofiban should be administered, in addition to ASA and LMWH or UFH, to patients with continuing ischemia, an elevated troponin level, or other high-risk features in whom an invasive management strategy is not planned (level of evidence: A).

2. A platelet GP IIb/IlIa antagonist should be administered to patients already receiving heparin, ASA, and clopidogrel in whom catheterization and PCI are planned. The GP IIb/IlIa antagonist may also be administered just prior to PCI (level of evidence: B). Abciximab should not be administrated to patients for whom PCI is not planned (level of evidence: A).

*These are all new indications, not included in the September 2000 guidelines. ASA, acetylsalicylic acid; GP, glycoprotein; LMWH, low-molecular-weight hepatin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin

platelets are active, the GP IIb/IIIa receptors increase the platelets' ability to attach to fibrinogen. When one molecule of fibrinogen sticks to receptors on two platelets, platelet aggregation begins. This is the final pathway required for platelet aggregation. The GP IIb/IIIa inhibitors act by sitting on the receptor, thereby preventing fibrinogen and von Willebrand factor from binding, and inhibiting platelet aggregation.

Multiple randomized, placebo-controlled clinical trials have shown that inhibition of the platelet GP IIb/IIIa receptor reduces the incidence of adverse cardiac events in high-risk patients with NSTEACS and those undergoing PCI [51]. Because contemporary trials favor an early invasive strategy in the management of NSTEACS, controversy has arisen regarding whether GP IIb/IIIa inhibitor therapy should be started upstream in all patients or should be reserved only for patients selected to undergo PCI. Closer inspection of the outcomes in patients treated early with GP IIb/IIIa inhibitors in large clinical trials favors early aggressive inhibition of platelet aggregation in this population, regardless of the subsequent revascularization strategy. Early invasive therapy, coupled with upstream blockade of the GP IIb/IIIa receptor, appears to offer a complementary benefit, as demonstrated in PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms), PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy), and PARAGON-B (Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network-B). Compared with the overall treatment effect seen in these trials, performance of PCI within 72 hours of admission enhanced the reduction of 30-day mortality or MI rates with upstream GP IIb/IIIIa inhibition.

In an analysis of patients treated with early PCI in the PURSUIT trial of eptifibatide for NSTEACS, greater absolute and relative reductions in death or MI at 30 days were observed with GP IIb/IIIa blockade (11.6% in the eptifibatide group vs. 16.7% in the placebo group) than in the overall PURSUIT cohort (14.2% vs. 15.7%, respectively).

Multiple trials have shown that the benefit of upstream GP IIb/IIIa inhibitor therapy in NSTEACS is derived early, during the period of medical management that precedes revascularization procedures. This finding is important to physicians considering strategies for optimizing procedural outcomes in this high-risk patient population. In the PRISM-PLUS trial of tirofiban in unstable coronary syndromes, patients treated with tirofiban plus heparin compared to heparin only had a significantly reduced death or MI rate during the protocol-mandated 48-hour waiting period before coronary angiography (2.6% vs. 0.9%; p=0.01). Similarly, patients with refractory unstable angina enrolled in the CAPTURE (C7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina) trial had a significant reduction in death or MI with abciximab and heparin compared with heparin only (2.8% vs. 1.3 %; p=0.032) during the 18-24–hour pretreatment period between diagnostic catheterization and planned PCI .

A meta-analysis of the PRISM-PLUS, PURSUIT, and CAPTURE trials demonstrated a 34% reduction in the rate of death or MI with GP IIb/llla inhibition during the period of initial medical stabilization that preceded revascularization (2.5% vs. 3.8%; p=0.001), with further benefit seen after PCI (**Figure 7**) [52].

However, few data are available from trials in which the strategy of purposefully refraining from performing PCI was employed. One notable exception is the GUSTO IV-ACS trial, which was designed to examine the potential benefit of abciximab in patients with UA/NSTEMI for whom PCI was not intended. No benefit was observed: indeed, a secondary endpoint, i.e., death within 48 hours, favored the placebo [53]. A retrospective analysis of the PRISM-PLUS trial showed that tirofiban reduced the incidence of adverse outcomes in patients at high risk (TIMI risk score $\geq$ 4) who did not undergo PCI.

Perhaps the most light that has been shed on this question comes from a meta-analysis of GP IIb/IIIa antago-

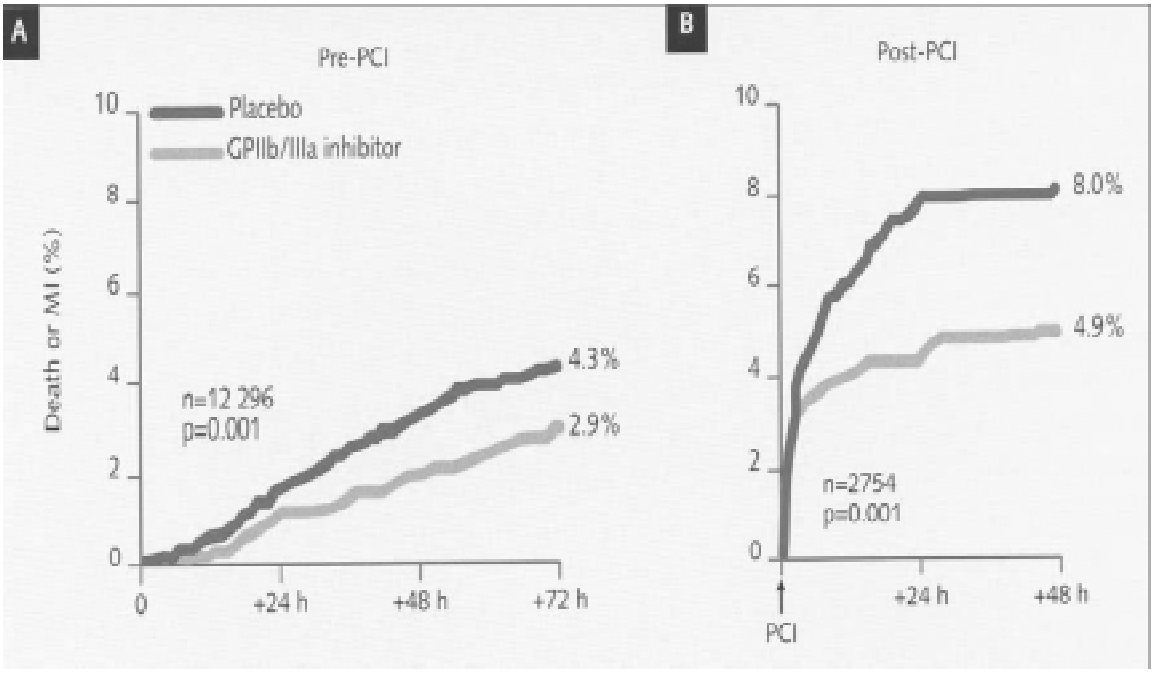

FIGURE 7. KAPLAN-MEIER ESTIMATES OF THE CENSORED OCCURRENCE OF DEATH OR MYOCARDIAL INFARCTION (MI) IN DATA DERIVED FROM CAPTURE, PURSUIT, AND PRISM-PLUS, SHOWING SIGNIFICANT CURVE DIVERGENCE BEFORE PERCUTANEOUS CORONARY INTERVENTION (PCI), WITH FURTHER BENEFIT AFTER PCI. **(A)** EVENT RATES DURING THE INITIAL PERIOD OF MEDICAL MANAGEMENT BEFORE PCI. **(B)** EVENT RATES AFTER PCI. CAPTURE, C7E3 FAB ANTIPLATELET THERAPY IN UNSTABLE REFRACTORY ANGINA; GP, GLYCOPROTEIN; PRISM-PLUS, PLATELET RECEPTOR INHIBITION FOR ISCHEMIC SYNDROME MANAGEMENT IN PATIENTS LIMITED BY UNSTABLE SIGNS AND SYMPTOMS; PURSUIT, PLATELET GLYCOPROTEIN IIB/IIIA IN UNSTABLE ANGINA: RECEPTOR SUPPRESSION USING INTEGRILIN THERAPY.[52]

nists that comprised six large trials involving 31,402 UA/NSTEMI patients who were not scheduled to undergo PCI. A significant but small (-9% relative; 1% absolute) reduction in the odds for the combined endpoint of death or MI was observed in the GP IIb/IIIa antagonist group, and bleeding was increased significantly (from 1.4% in the placebo group to 2.4% in the GP IIb/IIIa antagonist group). Only 19% of the patients underwent early (within 5 days) revascularization, and the observed benefit of GP IIb/IIIa antagonists, i.e., reduction of death or MI, was largely confined to the subgroup with elevated troponin levels (-21%). On the other hand, in the majority of patients (81%), who did not undergo early revascularization, the reduction in death or MI (-3%) was not significant.

In accordance with the findings of the Global Utilization of Strategies to Open Occluded Arteries study (GUSTO-IV ACS), abciximab is not indicated in patients for whom PCI is not planned. None of the GP IIb/IIIa inhibitors appears to be effective or indicated in the routine management of low-risk, patients without increased troponin levels for in whom early angiography is not intended. In PCI-CURE and CREDO, clopidogrel did not appear to add to the bleeding risk posed by GP IIb/IIIa inhibitors [47]; however, additional observation of the interaction between GP IIb/IIIa inhibitors and thienopyridines is warranted. The efficacies of thienopyridine and GP IIb/IIIa inhibitors appears to be additive, and triple antiplatelet therapy (with aspirin, clopidrogel, and a GP IIb/IIIa inhibitor) is indicated in high-risk patients who are planning to undergo PCI and who do not have an excessive risk of bleeding [48].

Anticoagulant Therapy

Unfractionated Heparin

Unfractionated heparin exerts its anticoagulant effect by binding antithrombin III by means of a pentasaccharide sequence. This causes a conformational change in the antithrombin III, increasing its ability to inhibit coagulation factors Ia (thrombin) and Xa. The use of UFH for the treatment of ACS was first suggested in 1912. This therapy, combined with aspirin, has been utilized in the treatment of UA/NSTEMI for more than a decade. There are two reasons for combining these two agents. Heparin and aspirin interfere with thrombus formation at different sites. Heparin therapy, when

discontinued, is associated with a return of unstable angina symptoms, and aspirin can minimize this phenomenon. Despite these benefits, UFH has many disadvantages [54]. It has nonspecific binding and is inactivated by platelets, vascular endothelium, fibrin, platelet factor 4, and circulating proteins. It also produces antiheparin antibodies and causes heparin-induced thrombocytopenia. The ACC and the AHA task force and the Sixth American College of Chest Physicians Consensus Conference recommended that UFH be given by means of a continuous infusion in patients with NSTEACS. The appropriate dosage consists of an 80 U/kg intravenous bolus and initial maintenance therapy at 1250 U/h; this dosage should be adjusted to maintain the activated partial thromboplastin time between 50 and 70 seconds [55].

Table 9. Recommendations for the Use of Low-Molecular-Weight Heparin and Unfractionated Heparin

Class I

1. Anticoagulation with subcutaneous LMWH or intrave nous UFH should be added to antiplatelet therapy with ASA and/or clopidogrel (level of evidence: A)

Class IIa

1. Enoxaparin is preferable to UFH as an anticoagulant in UA/NSTEMI patients without renal failure unless CABG is scheduled within 24 h (level of evidence: A).

*These are all new indications, not included in the September 2000 guidelines. ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; LMWH, low-molecular-weight hepatin; UA/NSTEMI, unstable angina/non-ST-segment–elevation myocardial infarction; UFH, unfractionated heparin

Low-Molecular-Weight Heparin

Because of the disadvantages of UFH, the use of LMWH has become more widespread. This agent has two main advantages over UFH: it entails a lower incidence of heparin-induced thrombocytopenia, and it can be administered without monitoring (owing to its rapid and predictable absorption after subcutaneous administration and its prolonged elimination). LMWH restricts the formation of thrombin by means of the anti-factor Xa effect and inhibits the circulation of thrombin by means of the anti-factor IIa effect (**Table 9**).

Two large, randomized, controlled trials have compared UFH with enoxaparin in NSTEACS patients. In the Efficacy and Safety of Subcutaneous Enoxaparin versus Intravenous Unfractionated Heparin in Non-Q-wave Coronary Events (ESSENCE) trial, enoxaparin was associated with a significantly lower incidence of death, MI, or recurrent ischemia at 30 days compared with UFH (19.8% vs. 23.3%; p=0.016). The TIMI 11B trial reproduced these findings, reducing the primary composite endpoint of death, MI, or urgent revascularization at 8 days from 14.5% with UFH to 12.4% with enoxaparin (p=0.048). In a meta-analysis of the ESSENCE and TIMI 11B trials, enoxaparin was associated with a significant reduction in the incidence of death, MI, or urgent revascularization at 43 days when compared with UFH (7.1 % vs. 8.6%; p=0.02) [56]; this treatment effect was maintained at 1 year (23.3% for enoxaparin vs. 25.8% with UFH; p=0.008) [57]. On the basis of these results, enoxaparin therapy in NSTEACS patients is now a class Ia recommendation in the ACC/AHA guidelines, whereas UFH is a class IIa recommendation. In both trials, however, enoxaparin was discontinued before revascularization, and PCI was done with UFH, even in the enoxaparin group. This fact, coupled with the recent adoption of an early invasive approach to managing NSTEACS, may explain why, despite proven superiority, enoxaparin has had limited acceptance in clinical practice. A growing body of evidence, however, confirms the safety and efficacy of enoxaparin when used as an adjunct to PCI [58]. Because the level of anticoagulant activity (e.g., activated partial thromboplastin time or activated clotting time) cannot be easily measured in patients given LMWH, interventional cardiologists have expressed concern about the substitution of LMWH for UFH in patients scheduled for catheterization with possible PCI and about the safety of LMWH in patients receiving GP IIa/IIIB inhibitors.

In a small, nonrandomized observational study involving 293 patients, Collet and associates showed that PCI can be performed safely in UA/NSTEMI patients who have received the usual dose of enoxaparin. In NICE-1 (National Investigators Collaborating on Enoxaparin), an observational study, intravenous enoxaparin (1 mg/kg) was used in 828 patients undergoing elective PCI without an intravenous GP IIb/IIIa antagonist. The 30-day rates of bleeding (1.1% major; 6.2% minor) were comparable to those observed in historical control patients receiving UFH.

An alternative approach is to use LMWH during the period of initial stabilization and to withhold the dose on the morning of the procedure. If an intervention is required and more than 8 hours have elapsed since the last dose of LMWH, UFH can be used for PCI according to the 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 coronary artery bypass grafting (CABG) within 24 hours.

Although the data are not definitive, it now appears

that GP IIb/IIIa antagonists can be used with LMWH. In the ACUTE II (Anti-thrombotic Combination Using Tirofiban and Enoxaparin II) study, UFH and enoxaparin were compared in UA/NSTEMI patients given tirofiban. The frequencies of both major and minor bleeding were similar, and there was a trend toward fewer adverse events in the enoxaparin recipients. A number of other open-label studies have examined the safety of combining enoxaparin with abciximab, eptifibatide, or tirofiban in UA/NSTEMI patients who are treated with PCI or conservative therapy; combining enoxaparin with abciximab in patients undergoing elective PCI; and combining dalteparin with abciximab in UA/NSTEMI patients receiving conservative treatment and during PCI. Although the majority of these studies relied on historical controls, none suggested that the combination of enoxaparin and a GP IIb/IlIa antagonist was associated with excess bleeding, regardless of whether the patient underwent PCI [59].

In the Integrelin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT), enoxaparin was compared with UFH in 746 UA/NSTEMI patients receiving aspirin and eptifibatide. The primary endpoint, non-CABG-associated major bleeding, was significantly lower in the enoxaparin group than in the UFH group (1.8 % vs 4.6%), although this finding was reversed with respect to minor bleeding. Also, the rates of death or nonfatal MI at 30 days and of ischemia on continuous Holter monitoring were each reduced by almost half in the enoxaparin group.

At the 2003 ACC Scientific Sessions, the results of the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) [60] trial were presented. This study involved 8000 high risk-patients with at least two of the following conditions: age ≥60 years, ST-segment elevation (transient) or depression, and elevated CK-MB or troponin levels. The randomized trial was designed to compare enoxaparin with UFH in NSTEACS patients treated with an early invasive management strategy. The endpoint of death or MI at 30 days was the same in both groups. Enoxaparin was not superior to UFH but was at least as effective as UFH in the overall population, although enoxaparin was associated with more frequent bleeding events. The authors concluded that enoxaparin is an effective and a safe alternative to UFH for the early invasive management of high-risk ACS patients.

Another trial investigating the use of enoxaparin in NSTEACS patients is the A-to-Z trial (Aggrastat phase of the Aggrastat to Zocor study), which is divided into two sequential parts. In the first phase, NSTEACS patients treated with aspirin and tirofiban are randomized to receive enoxaparin or UFH. The choice of antithrombotic agent for patients undergoing PCI is left to the discretion of the investigator [61]. The results have shown no superiority for either drug at 7 days with respect to the primary composite endpoint of death, MI, and refractory ischemia (enoxaparin 8.4% versus UFH 9.4%; *p*=NS).

The available information concerning the relative efficacies of different LMWHs is relatively scant. In the EVET trial (Enoxaparin VErsus Tinzaparin in the management of unstable coronary artery disease), 2 LMWHs, enoxaparin and tinzaparin, administered for 7 days, were compared in 438 UA/NSTEMI patients. Enoxaparin was superior to tinzaparin in reducing the recurrence of unstable angina and the need for revascularization.

Antianginal Therapy

Beta Blockers

In UA/NSTEMI, the primary benefits of beta blockers are due to effects on β1-adrenergic receptors that decrease cardiac work and myocardial oxygen demand. Slowing of the heart rate also has a favorable effect, not only reducing myocardial oxygen consumption but also increasing the duration of diastole and the diastolic pressure-time, a determinant of coronary and collateral flow. In the absence of contraindications, beta-blocker therapy should be started early. Because beta blockers improve the survival of patients with an acute MI, these agents are principally indicated for patients with a history of a previous MI. Yusuf and coworkers demonstrated that beta blockers decrease the risk of myocardial infarction by 13% [62]. Severe bradycardia, sick sinus syndrome, and high-degree atrioventricular block are contraindications to treatment with beta blockers. The most frequent side effects of these agents are fatigue, weakness, insomnia, depression, and gastrointestinal problems.

Nitrates

Routine medical management should include nitrates despite the fact that these agents have not shown a mortality benefit in patients with a suspected acute MI. Nevertheless, nitroglycerin decreases the incidence and severity of angina and increases clinical stability. The nitrates' mechanisms of action include venous dilatation and coronary vasodilation, which decrease myocardial wall stress and myocardial oxygen consumption. In turn, the decreased the left ventricular end-diastolic pressure augments blood flow to ischemic areas of the myocardium. The principal effect is improved subendocardial

oxygenation secondary to coronary artery dilatation. After 24 hours of receiving nitrates, patients can develop a tolerance for these agents through a mechanism that is not yet clear. If such tolerance occurs, either the dose should be increased or another method of administration should be chosen. Potential adverse effects include headache, hypotension, presyncope, and syncope [63].

Cholesterol-Lowering Therapy

Statins

Beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase (statin) therapy, has shown benefits in patients with elevated LDLC levels (>125 mg/dL). Patients with lower serum LDLC levels can also benefit from statins after an MI [64]. The early use of statins after an ACS augments the long-term compliance of patients. Acute coronary syndromes are caused by rupture of an unstable coronary plaque. Recent data have shown that statin therapy has an antiinflammatory effect, as reflected by CRP levels early after administration. This effect appears to be independent of the drug's cholesterol-lowering effects. Statins elevate endothelial-cell nitric-oxide synthase expression, which is an important antiinflammatory mediator [65]. These medications are considered to be in ACC/AHA class IIa. Statin therapy and a diet containing >100 mg/dL of LDLC should be instituted 24 to 96 hours after admission and continued after hospital discharge.

The optimal timing and intensity of statin therapy is unclear. Observational studies of early (predischarge) commencement of statin therapy has yielded mixed results. In the only large double-blind, placebo-controlled trial-the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial [66]-3086 patients were randomized to receive an aggressive lipid-lowering regimen of atorvastatin (80 mg per day) or a placebo 24 to 96 hours after an ACS. After 16 weeks of follow-up, the primary endpoint 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 intergroup differences with regard to the following individual endpoints: death, nonfatal MI, cardiac arrest, or worsening heart failure; however, there were fewer strokes and a lower risk of severe recurrent ischemia in the atorvastatin group. Although the MIRACL trial showed a benefit for early statin use, it achieved just nominal significance (p=0.048) without having any benefit against the "hard" prespecified endpoints of death or MI. Two large, prospective statin trials in post-ACS patients are now in the follow-up phase, and their results will be reported within the next year.

In the ongoing A to Z Trial [61], patients with ACS are assigned to commence simvastatin therapy (40 mg/d) or placebo therapy before hospital discharge. At 4 months, these two arms treatment arms begin to receive simvastatin 80 mg/d and 20 mg/d, respectively.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)- TIMI 22 is assessing marked cholesterol-lowering therapy, using atorvastatin 80 mg/d, thereby addressing the question of " how low is low enough?" with respect to LDLC. In a second randomization, this trial is also comparing gatofloxacin, an oral fluoroquinolone that has potent antichlamydial properties, with a placebo (**Figure 8**) [67]. In patients hospitalized within the preceding 10 days for an ACS, an "intensive" high-dose LDLC-lowering regimen (median LDLC, 62 mg/dL) reduced the risk of all-cause mortality or major cardiac events by 16% compared to "moderate" standard-dose lipid-lowering therapy (median LDLC, 95 mg/dL) (p=0.005). Benefits emerged within 30 days after ACS and continued throughout the 2.5 years of follow-up. Moreover, the benefits were consistent across all the cardiovascular endpoints except stroke and across most clinical subgroups**.** The study indicated that patients recently hospitalized for an ACS benefit from early, continued reduction of LDLC to levels substantially below current target levels.

There is general agreement about the following points. First, patients with UA/NSTEMI should be treated, at the very least, in accordance with the third report of the National Cholesterol Education Program (NCEP III) [68], and these patients' LDLC concentrations should be reduced to <100 mg/dL. The Heart Protection Study [64] indicates that for patients in stable condition with even lower baseline levels, the outcome can be improved with a statin. Second, early (i.e., predischarge) commencement of statin therapy is well tolerated. Third, observational studies have shown that patients who commence statin therapy before hospital discharge are much more likely to be compliant and to achieve NCEP III established target LDLC levels (<100 mg/dL) than are patients not treated in this manner. Fourth, in UA/NSTEMI patients who are already receiving a statin at the time of presentation, the drug should not be withdrawn [69]. Fifth, in the Lescol Intervention Prevention Study (LIPS) [70], 1669 patients were randomized to receive 80 mg of fluvastatin or a placebo, beginning 2 days after PCI. After a follow-up period of 3.9 years, the statin-treated group had a lower incidence of clinical events (21.4%) than the placebo group (26.7%) (p=0.01). The clinical event rate in the

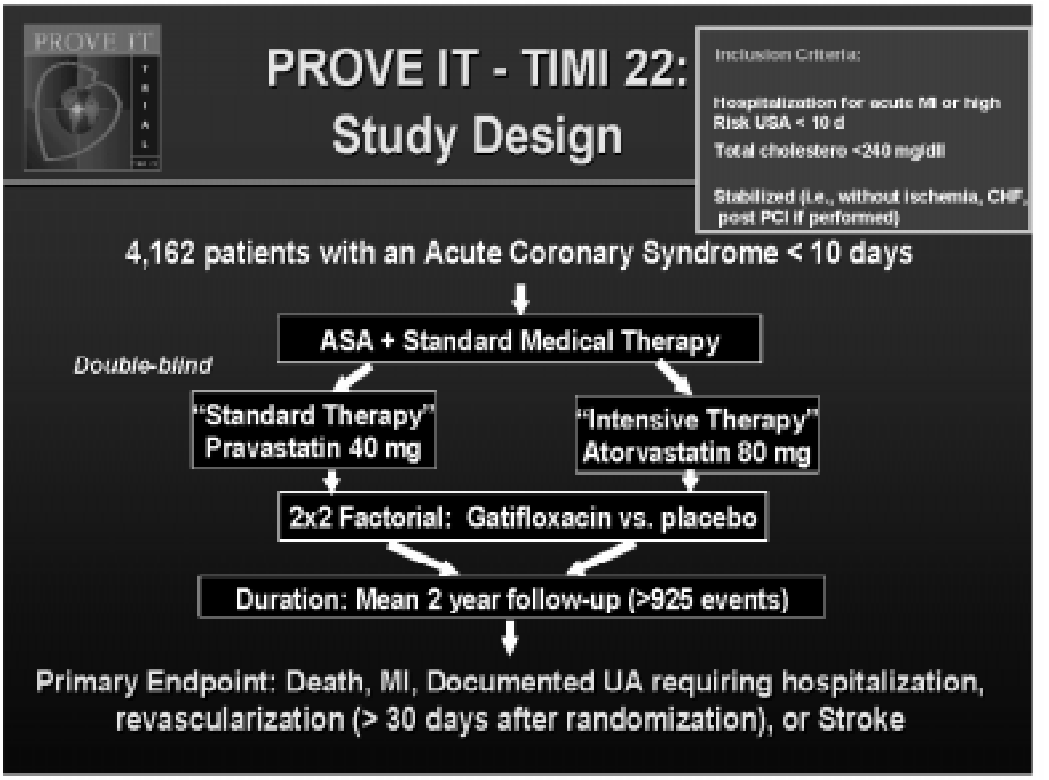

FIGURE 8. PROVE IT – TIMI 22 STUDY DESIGN. ASA, ACETYLSALICYLIC ACID; CHF, CONGESTIVE HEART FAILURE; MI, MYOCARDIAL INFARCTION; PCI, PERCUTANEOUS CORONARY INTERVENTION; PROVE IT, PRAVASTATIN OR ATORVASTATIN EVALUATION AND INFECTION THERAPY; TIMI, THROMBOLYSIS IN MYOCARDIAL INFARCTION; UA, UNSTABLE ANGINA

CANNON CP, MCCABE CH, BELDER R, ET AL. PRAVASTATIN OR ATORVASTATIN EVALUATION AND INFECTION THERAPY (PROVE-IT)-TIMI 22 TRIAL: RATIONALE AND DESIGN. REPRODUCED WITH PERMISSION *AM J CARDIOL* 2002;**89**:860-1.

statin-treated group was reduced significantly (by 20%). Therefore, it is logical to include UA/NSTEMI patients who have undergone PCI in an early cholesterol-reduction program. Furthermore, patients with low HDLC (<40 mg/dL) should be considered for additional therapy with fibrate or niacin.

Early Pharmacologic Management of NSTEACS

The average timing of cardiac catheterization in the interventional arms of the aforementioned trials has varied from 22 hours after hospital admission in TACTICS-TIMI 18 to 4 days in FRISC II. Therefore, even in the most aggressive treatment scenario, a critical window of at least several hours exists when upstream pharmacologic "passivation" of unstable plaque is pivotal before more definitive revascularization efforts are undertaken. In addition to aspirin, which should be universally used for unstable ACS, antithrombin and antiplatelet therapies ought to be considered for this patient population.

Invasive Versus Conservative Treatment and Long-Term Management

Evaluation of UA/NSTEMI patients begins with the clinical history, electrocardiography, and measurement of cardiac biomarkers to assess the likelihood of coronary artery disease and the patient's risk of death or recurrent cardiac events. Patients with a *low* likelihood of having UA/NSTEMI should undergo a "diagnostic pathway" evaluation involving serial EKGs and measurement of cardiac markers in an emergency department observation/chest pain unit [11].

Patients who have a clinical history that is strongly consistent with UA/NSTEMI should undergo antithrombotic therapy with aspirin, clopidogrel, heparin, or LMWH. Beta blockers and nitrates are recommended for the initial management of all patients.

For patients deemed at low risk, an early conservative strategy is adequate, although an invasive strategy offers an equal clinical benefit. For intermediate- and high-risk patients (with ST-segment changes, elevated troponin levels, and a TIMI risk score of $\geq$3), the above-men-

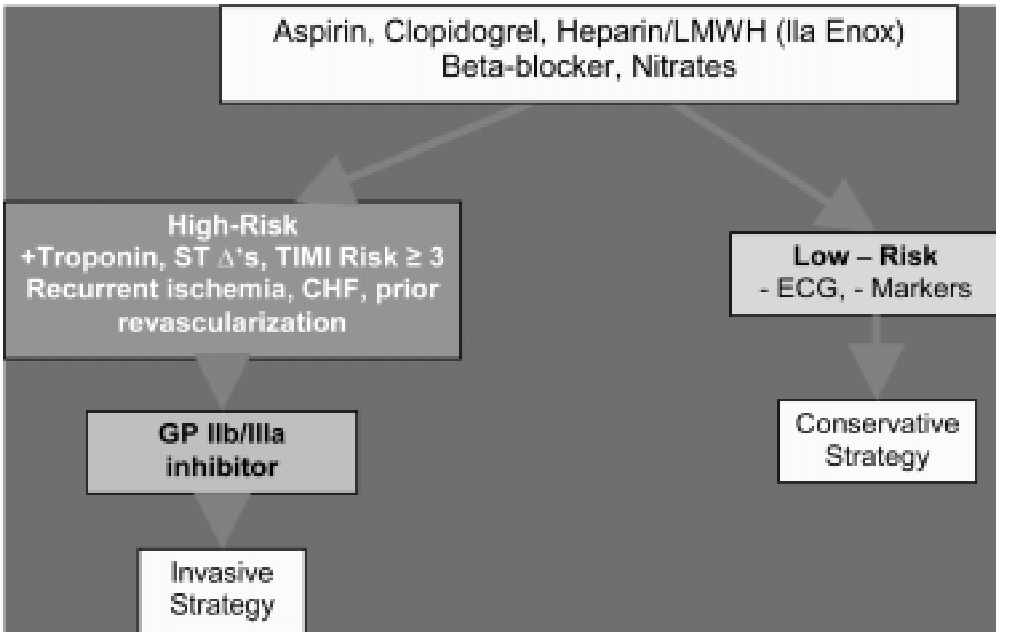

FIGURE 9. RISK STRATIFICATION TO TARGET THERAPIES IN UNSTABLE ANGINA WITH NON-ST-SEGMENT–ELEVATION MYOCARDIAL INFARCTION (UA/NSTEMI). THE "WEIGHT OF EVIDENCE" SHOWS A BENEFIT FOR INVASIVE VS. CONSERVATIVE STRATEGY IN PATIENTS WITH UA/NSTEMI. CHF, CONGESTIVE HEART FAILURE; ECG, ELECTROCARDIOGRAM; GP, GLYCOPROTEIN; LMWH, LOW-MOLECULAR-WEIGHT HEPARIN; TIMI, THROMBOLYSIS IN MYOCARDIAL INFARCTION.

tioned medications are beneficial; GP IIb/IIIa inhibition is also recommended, and an early invasive strategy is preferred (**Figure 9**). Additional studies of the various combinations of treatments are ongoing to further define the safety of these regimens.

Nine randomized trials have assessed the merits of an invasive strategy involving routine cardiac catheterization and revascularization, if feasible, versus a conservative strategy in which angiography and revascularization are reserved for patients who have evidence of recurrent ischemia either at rest or on provocative testing. The first three trials (VANQWISH, MATE, TIMI IIIB) failed to reveal a significant benefit, but the following three trials all found that an invasive strategy offers a significant benefit (**Figure 10**) [72, 73]:

- FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC) II.
- Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)-TIMI 18 trials.
- Randomized Intervention Trial of unstable Angina (RITA).

The VANQWISH (Veterans Affairs Non-Q Wave Infarction Strategies in Hospital) trial randomized NSTEMI patients to receive either invasive or conservative management [74]. During an average follow-up period of 23 months, the cumulative rates of death or MI did not differ significantly between both treatment arms (the hazard ratio [HR] for the conservative versus the invasive group was 0.87, with a 95% confidence interval [CI] of 0.68-1.10). There were, however, alarming differences between the two cohorts in the incidence of early clinical events. The rate of death or MI was significantly higher in the invasive group than in the conservative group before hospital discharge (p=0.004), at 1 month (p=0.012), and at 1 year (p=0.05). The mortality was also higher in the invasive arm than in the conservative arm at 1 year (12.6% vs. 7.7%; p=0.025). During long-term follow-up observation, however, the cumulative all-cause mortality did not differ significantly between the two treatment arms (HR, 0.72; 95% CI, 0.51-1.01).

The median time to coronary angiography was 2 days for the early invasive group and 14 days for the conservative group; 44% of the former group and 33% of the latter group underwent revascularization within 30 days [75].

In the TIMI IIIB trial, patients presenting with NSTEACS were randomized to receive either a) early invasive treatment, with planned cardiac catheterization within 18 to 48 hours after admission and revascularization soon thereafter when appropriate or b)

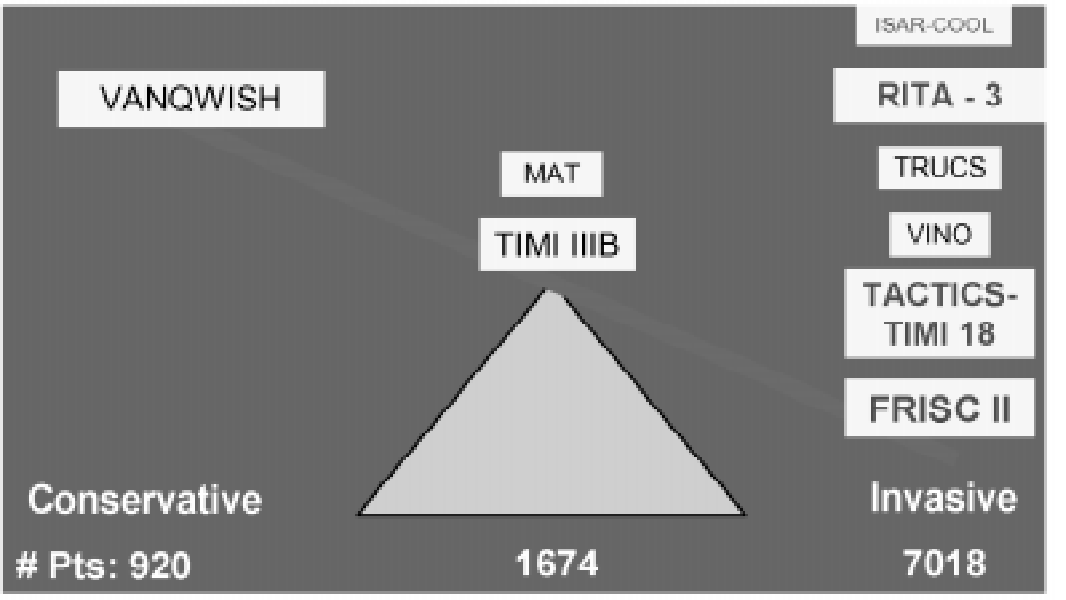

FIGURE 10. FRISC, FRAGMIN AND FAST REVASCULARISATION DURING INSTABILITY IN CORONARY ARTERY DISEASE; ISAR-COOL, INTRACORONARY STENTING WITH ANTITHROMBOTIC REGIMEN COOLING-OFF; RITA, RANDOMIZED INTERVENTION TRIAL OF UNSTABLE ANGINA; TACTICS, TREAT ANGINA WITH AGGRASTAT AND DETERMINE COST OF THERAPY WITH INVASIVE OR CONSERVATIVE STRATEGY; TIMI, THROMBOLYSIS IN MYOCARDIAL INFARCTION; TRUCS, TREATMENT OF REFRACTORY UNSTABLE ANGINA IN GEOGRAPHICALLY ISOLATED AREAS WITHOUT CARDIAC SURGERY; VANQWISH, VETERANS AFFAIRS NON-Q WAVE INFARCTION STRATEGIES IN HOSPITAL; VINO, VALUE OF FIRST DAY ANGIOGRAPHY/ANGIOPLASTY IN EVOLVING NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION.

a conservative approach in which coronary angiography was reserved for patients who had recurrent ischemia despite medical therapy [71]. There was no significant intergroup difference with respect to the primary endpoint of death, MI, or failed exercise treadmill test at 6 weeks (16.2 % in the invasive group vs. 18.1 % in the conservative group; *P* = not significant [NS]) [71]. There were no intergroup differences in the 6-month mortality rate (2.4% in the invasive arm vs. 2.5% in the conservative arm; *p*=NS). The mean time to catheterization was 1.5 days from admission among patients in the early invasive arm (98% of whom underwent catheterization) and 7.1 days in the conservative arm (64% of whom underwent catheterization). Percutaneous transluminal coronary angioplasty (PTCA) was undertaken in 38% of the invasive cohort and 26% of the early conservative cohort. The surgical revascularization rates for the two groups were 25% and 24%, respectively [71].

The FRISC II trial conducted in the late 1990s, when stents were available and used in 90% of PCIs was the first study to find a significant *benefit* for an invasive strategy [72]. The primary endpoint, death or MI at 6 months, was significantly lower in the invasive group than in the conservative group (9.4% vs. 12.1%; *p*=0.03l). At 1 year, the *mortality* was significantly reduced in the invasive vs. the conservative group (2.2% vs. 3.9%, respectively; *p*=0.0l6) (**Figure 11**).

In the TACTICS-TIMI 18 trial, in which both stents and GP IIb/IIIa inhibition (tirofiban) were used, early invasive treatment (within 4 to 48 hours after presentation; average, 23 hours) reduced by 22% the rate of death, MI, or rehospitalization at 6 months (9.4% for the conservative group vs. 15.9% for the early invasive group; *p*=0.025). The rate of death or MI at 6 months was also reduced by 26% with the routine invasive approach (7.3% vs. 9.5% for conservatively treated patients; *P*< 0.05). Similarly, death or nonfatal MI was significantly reduced at 30 days (7.0% vs. 4.7%, respectively; *p*=0.02) and at 6 months (*p*=0.0498). Similarly, RITA 3 found a 34% reduction in death, MI, or refractory angina at 4 months (14.5% vs. 9.6%; *p*= 0.001) [73].

The benefits of an early invasive strategy were seen in intermediate- and high-risk patients, especially those with ST-segment changes and elevated troponin levels on admission (**Figure 12** and **Table 10**) or a TIMI risk score of =3 [73]. In TACTICS TIMI 18, which used the TIMI risk score, patients at intermediate risk (score of 3 to 4) or at high risk (score of 5 to 7) derived the greatest benefit from an invasive approach (25% and 45% risk reduction, respectively), whereas low-risk patients (score

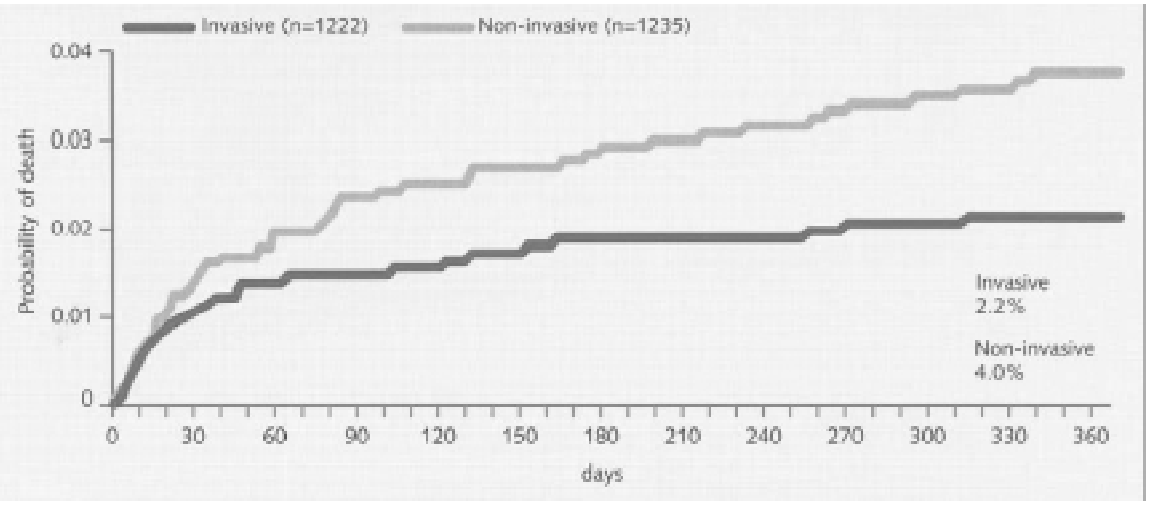

FIGURE 11. KAPLAN-MEIER ESTIMATES OF ALL-CAUSE MORTALITY AT 1 YEAR IN THE INVASIVE AND NONINVASIVE ARMS OF THE FRISC II TRIAL, SHOWING A SIGNIFICANT REDUCTION IN MORTALITY AT 1 YEAR IN THE INVASIVE GROUP, WITH A RELATIVE RISK OF 0.56 (95% CONFIDENCE INTERVAL [CI], 0.35-0.89; *P*=0.018). FRISC II: FRAGMIN AND FAST REVASCULARIZATION DURING INSTABILITY IN CORONARY ARTERY DISEASE II.[75]

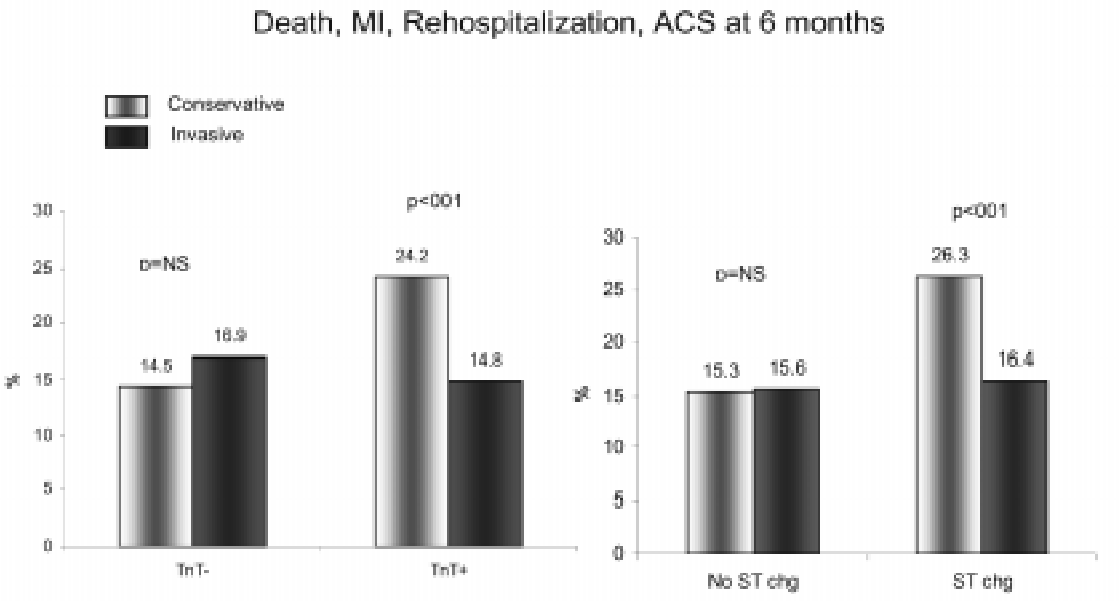

FIGURE 12. BENEFIT OF INVASIVE STRATEGY BY TROPONIN AND ST-SEGMENT CHANGES, SHOWING DEATH, MYOCARDIAL INFARCTION, REHOSPITALIZATION, AND ACUTE CORONARY SYNDROME AT 6 MONTHS. ACCORDINGLY, THE 2002 THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION GUIDELINES ADDED ST-SEGMENT CHANGES AND ELEVATED TROPONIN LEVELS TO THE LIST OF HIGH-RISK INDICATORS THAT WOULD LEAD TO A CLASS I RECOMMENDATION FOR AN EARLY INVASIVE STRATEGY FOR ANY OF THESE HIGH-RISK INDICATORS (LEVEL OF EVIDENCE: A). CHG, CHANGE; TNT, TROPONIN T.

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of 0 to 2) appeared to receive no benefit from an invasive approach (**Table 10**) [73].

Interestingly, an early invasive strategy is very cost-effective (approximately $12,739 per life-year saved). In FRISC II, after 1 year, an invasive strategy had saved 1.7 out of 100 lives, prevented 2 nonfatal infarctions and 20 readmissions, and provided earlier and better symptom relief at the cost of 15 more CABG operations and 21 more PCIs [75].

Long-Term Secondary Prevention

The time of hospital discharge is a "teachable moment" for the patient, when the physician can review and optimize the medical regimen. Risk-factor modification (**Table 11**) is a key to success and should include discussions relevant to the patient's specific risk factors.

For medical treatment, five classes of drugs are categorized in class I by the 2002 ACC/AHA guidelines for long-term medical therapy (**Table 12**).

TABLE 10. CLASS I RECOMMENDATIONS FOR AN EARLY INVASIVE STRATEGY

Any of these high-risk indicators:
Level of evidence: A
Recurrent angina at rest and during low-level activity despite medical therapy
Elevated troponinT or troponin I
New ST-segment depression
Recurrent angina/ischemia with CHF symptoms, rales, mitral regurgitation
Positive stress-test result
Ejection fraction of <0.40
Decreased blood pressure
Sustained ventricular tachycardia
Percutaneous coronary intervention within the previous 6 months; previous CABG

CABG, coronary artery bypass grafting; CHF, congestive heart failure

TABLE 11. CLASS I RECOMMENDATIONS FOR RISK-FACTOR MODIFICATION

Smoking cessation
Achieve optimal weight
Daily exercise
AHA diet
Hypertension control for target BP of <130/85 mmHg
Tight control of hyperglycemia in patients with diabetes mellitus
HMG-CoA reductase inhibitor for LDLC of >130 mg/dl
Lipid-lowering agent if LDLC after diet is >100 mg/dl
Fibrate or niacin if HDLC is <40 mg/dl

AHA, American Heart Association; BP, blood pressure; HDLC, high-density-lipoprotein cholesterol; HMG, 3-hydroxy-3-methyl-glutaryl; LDLC, low-density-lipoprotein cholesterol

Establishing the optimal secondary prevention regimen is a key function not only of the cardiologist or internist who discharges the patient but also of the primary care physician who follows up that patient. This is partly because early initiation of medical therapy is associated with better long-term compliance. Indeed, the ACC/AHA Guidelines state that, hospital discharge instructions should include a follow-up appointment and that before discharge, patients and/or designated responsible caregivers should be given easily understandable instructions regarding the medication type, purpose, dosage, frequency, and pertinent side effects. The transition from the hospital phase to the outpatient phase is a critical period.

(**Figure 13**) shows a proposed algorithm for aggressive medical stabilization and early invasive management in patients with NSTEACS .

The goal is for the patient to follow the ACC/AHA guidelines, which recommend five drug classes for long-term secondary prevention, as noted above. Thus, the cardiologist or internist should try to send the patient home on a regimen that includes all of these medications.

Conclusion

The past decade has seen many advances in UA/NSTEMI management. Risk stratification and the use of troponin levels and risk scores to target appropriate therapies are critical. In addition, outcomes have been improved by

TABLE 12. LONG-TERM MEDICAL THERAPY: CLASS I RECOMMENDATIONS

ASA, 75–325 mg/d
Clopidogrel, 75 mg daily, when ASA is not tolerated
Combined ASA and clopidogrel for 9 months after UA/NSTEMI
ß-blocker
Lipid-lowering agent and diet in patients with LDLC of >130 mg/dl
Lipid-lowering therapy if LDLC is >100 mg/dl after diet
ACE inhibitor for patients with CHF, LV dysfunction (EF <0.40), hypertension, or diabetes mellitus

ACE, angiotensin-converting enzyme; ASA, acetylsalisylic acid; CHF, congestive heart failure; EF, ejection fraction; LDLC, low-density-lipoprotein cholesterol; UA/NSTEMI, unstable angina/non-ST-segment–elevation myocardial infarction

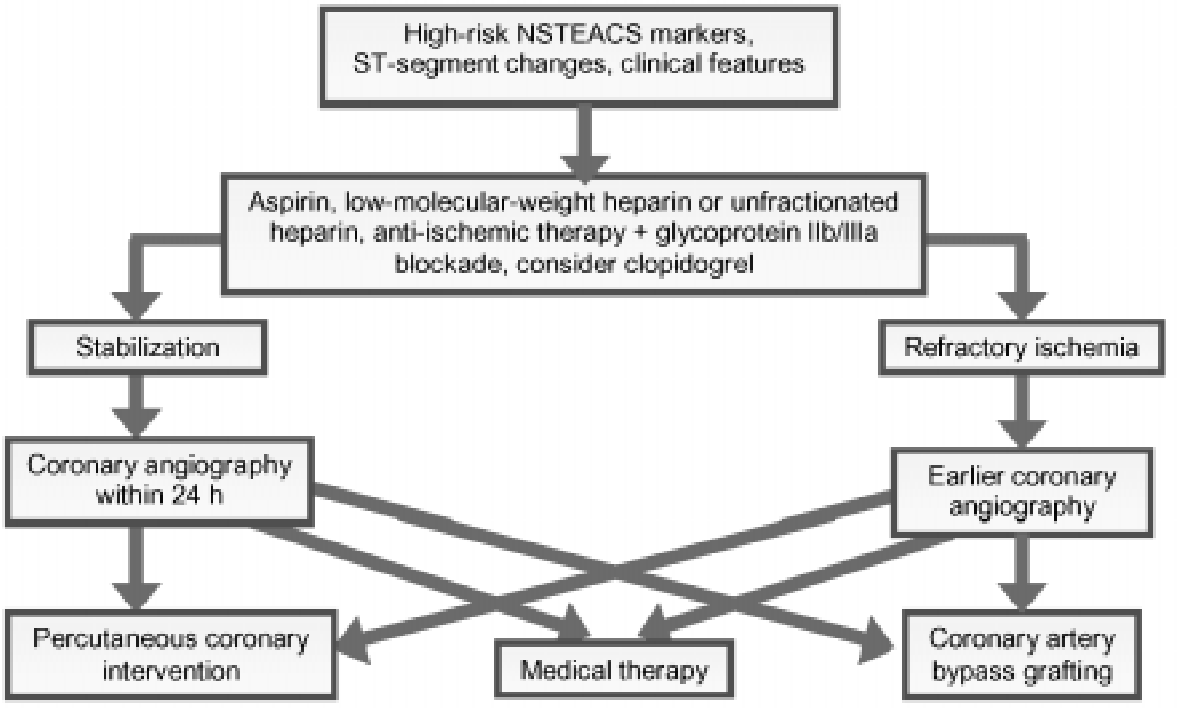

FIGURE 13. HIGH-RISK MARKERS, ST-SEGMENT CHANGES, AND CLINICAL FEATURES ASSOCIATED WITH NON-ST-SEGMENT–ELEVATION ACUTE CORONARY SYNDROME (NSTEACS).
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many advances in antithrombotic therapy, e.g., clopidogrel, LMWH, and selective use of GP IIb/IIIa inhibitors. An early invasive approach is clearly beneficial for intermediate- and high-risk patients and is relatively cost-effective. UA/NSTEMI patients should be reevaluated at the time of hospital discharge to ensure that they are receiving the five classes of drugs recommended by the ACC/AHA guidelines for secondary prevention and are enrolled in a comprehensive risk-factor modification program.

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