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

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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I. Introduction

The American College of Cardiology (ACC)/American Heart Association (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. These life-threatening disorders are a major cause of emergency medical care and hospitalizations in the United States. In 1996, the National Center for Health Statistics reported 1 433 000 hospitalizations for UA or NSTEMI. 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 in 1994 was evident. This Task Force therefore formed the current committee to develop guidelines for the management of UA and NSTEMI. The present guidelines supersede the 1994 guidelines.

"ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction: Executive Summary and Recommendations: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Unstable Angina)" was approved by the American College of Cardiology Board of Trustees in June 2000 and by the American Heart Association Science Advisory and Coordinating Committee in June 2000.

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The customary ACC/AHA classifications I, II, and III 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.**

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 low rank (C) was given when expert consensus was the primary basis for the recommendation.

The full text of the guidelines is published in the September 2000 issue of the *Journal of the American College of Cardiology*. This document was approved for publication by the governing bodies of the American College of Cardiology and the American Heart Association.

UA and NSTEMI are acute coronary syndromes (ACSs) that are characterized by an imbalance between myocardial oxygen supply and demand. The most common cause is reduced myocardial perfusion that results from coronary artery narrowing caused by a nonocclusive thrombus that has developed on a disrupted atherosclerotic plaque. Abnormal constriction of the coronary arteries may also be responsible. In the guidelines, UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar but of differing severity (ie, 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 the MB isoenzyme of creatine phosphokinase [CK-MB]). Once it has been established that no biochemical marker of myocardial necrosis has been released, the patient with an ACS may be considered to have experienced UA, whereas the diagnosis of NSTEMI is established if a marker of myocardial injury has been released.

II. Initial Evaluation and Management

A. Clinical Assessment

Recommendations for Initial Triage

Class I

1. **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 electrocardiogram (ECG). (Level of Evidence: C)**
2. **Patients with a suspected ACS with chest discomfort at rest for >20 minutes, hemodynamic instability, or recent syncope or presyncope should be strongly considered for immediate referral to an emergency department (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)**

When symptoms have been unremitting for >20 minutes, the possibility of ST-segment elevation myocardial infarction (STEMI) must be considered. Given the strong evidence for a relationship between a delay in treatment and death for patients with STEMI, an immediate assessment that includes a 12-lead ECG is essential. Patients who are diagnosed as having an acute myocardial infarction (AMI) that is suitable for reperfusion should be managed as indicated according to the ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction.

B. Early Risk Stratification

Recommendations

Class I

1. **A determination of the likelihood (high, intermediate, or low) of acute ischemia caused by CAD should be made in all patients with chest discomfort. (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 minutes) 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 hours of the onset of pain, another sample should be drawn in the 6- to 12-hour time frame (eg, at 9 hours after the onset of symptoms). (Level of Evidence: C)**

Class IIa

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

Class IIb

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

TABLE 1. 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 features)	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 hrs	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD	New-onset CCS Class III or IV angina in the past 2 wk with moderate or high likelihood of CAD
		Rest angina (<20 min or relieved with rest or sublingual NTG)	
Clinical findings	Pulmonary edema, most likely related to ischemia	Age >70 y	
	New or worsening MR murmur		
	S_3 or new/worsening rales		
	Hypotension, bradycardia, tachycardia		
	Age >75 y		
ECG findings	Angina at rest with transient ST-segment changes >0.05 mV	T-wave inversions >0.2 mV	Normal or unchanged ECG during an episode of chest discomfort
	Bundle-branch block, new or presumed new	Pathological Q waves	
	Sustained ventricular tachycardia		
Cardiac markers	Markedly elevated (eg, TnT or TnI >0.1 ng/mL)	Slightly elevated (eg, TnT >0.01 but <0.1 ng/mL)	Normal

An 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, the table is meant to offer general guidance and illustration rather than rigid algorithms.

Adapted with permission from 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. AHCPR Clinical Practice Guideline No. 10, Unstable Angina: Diagnosis and Management, May 1994.

Class III

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

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 initial presentation can be integrated into an estimate of the risk of death and nonfatal cardiac ischemic events. An estimation of the level of risk is a multivariable problem that cannot be simply quantified. Table 1 is 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 level of risk of events.

Because patients with new or severe ischemic discomfort are at an increased risk of cardiac death and nonfatal ischemic events, an assessment of the prognosis should set the pace of 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. Therefore, an assessment of the likelihood of CAD is the starting point for determination of the prognosis of patients who present with symptoms that are 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 acute ischemic event occur.

The 5 most important factors from the initial history that relate to the likelihood that the patient is experiencing an episode of ischemia due to CAD are (1) the nature of the symptoms, (2) a prior history of CAD, (3) age, (4) sex, and (5) the number of traditional risk factors that are present for CAD. 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 was previously necessary.

Recommendation for the Diagnosis of Noncardiac Causes of Symptoms

Class I

1. **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 will enable the physician to recognize and exclude from further assessment patients classified as "not having ischemic discomfort." This includes patients with noncardiac pain and patients with cardiac pain that is not caused by myocardial ischemia. The remaining patients should undergo a more complete evaluation of secondary causes of UA that might alter management. In patients with 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.

The major objectives of the physical examination are to identify potential precipitating causes of myocardial ischemia (eg, uncontrolled hypertension or thyrotoxicosis) and evidence of other cardiac disease (eg, aortic stenosis or hypertrophic cardiomyopathy), and comorbid conditions (eg, pulmonary disease) and to assess the hemodynamic impact of the ischemic event.

Assessment of Risk of Death in Patients With UA/NSTEMI

The AHCPR guidelines "Unstable Angina: Diagnosis and Management" identified low-risk UA patients as those *without* rest or nocturnal angina and with normal or unchanged ECGs. High-risk patients were identified as those with pulmonary edema; ongoing rest pain for >20 minutes; angina with S_3 gallop, rales, or new or worsening mitral regurgitation murmur; hypotension; or dynamic ST-segment change of ≥1 mm. Patients without low- or high-risk features were termed to be at intermediate risk. The present guidelines endorse these principles (Table 1) but indicate that a rapid tempo of angina, a prior MI, and elevation of the cardiac-specific troponin level are also strong predictors of the risk of an adverse outcome. The *tempo of angina* is characterized by an assessment of changes in the duration of episodes, their frequency, and the anginal threshold.

Tools for Risk Stratification

Although imperfect, the 12-lead ECG lies at the center of the decision pathway for the evaluation and management of patients with ischemic discomfort. A recording made during an episode of the presenting symptoms is particularly valuable. Importantly, transient ST-segment changes (≥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.

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 (Table 2). Low levels of CK-MB in the blood of healthy individuals limit its specificity for myocardial necrosis. CK-MB levels may also be elevated with severe damage of skeletal muscle.

Monoclonal antibody–based immunoassays have been developed to detect cardiac-specific TnT (cTnT) and cardiac-specific TnI (cTnI). Because cTnT and cTnI are not detected in the blood of healthy individuals, the cutoff value for elevated cTnT and cTnI levels may be set to slightly above the upper limit of the assay of a normal healthy population, leading to the terms "minor myocardial damage" or "microinfarction" for patients with detectable troponin but no CK-MB in the blood. It is estimated that ≈30% of patients who present with rest pain without ST-segment elevation and 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.

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. 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. 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 UA/NSTEMI (Figure 1). Patients who present without ST-segment elevation and have elevated cardiac-specific troponin levels may receive a greater treatment benefit from platelet GP IIb/IIIa inhibitors and low-molecular-weight heparin (LMWH).

Table 2 provides a comparison of the advantages and disadvantages of various cardiac markers for the evaluation and management of patients with suspected ACS but without ECG ST-segment elevation. The troponins offer greater diagnostic sensitivity due to their ability to identify patients with lesser amounts of myocardial damage. Nevertheless, these lesser amounts of damage are associated with a high risk in patients with ACSs, because they are thought to represent microinfarctions that result from microemboli from an unstable plaque. Cardiac-specific troponins are gaining acceptance as the primary biochemical cardiac marker in ACS. 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 level, however, does not exclude the minor myocardial damage and its attendant risk of adverse outcomes detectable with cardiac-specific troponins. 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 with myocardial injury makes its absence quite useful in ruling out myocardial necrosis.

When a central laboratory is used to measure biochemical cardiac markers, results should be available within 60 minutes and preferably within 30 minutes. 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.

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 in patients with UA. Patients who do not have biochemical evidence of

TABLE 2. Biochemical Cardiac Markers for the Evaluation and Management of Patients Suspected of Having an 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 by troponins)	Yes	Familiar to majority of clinicians	Prior standard and still acceptable diagnostic test in most clinical circumstances
CK-MB isoforms	Early detection of MI	1. Specificity profile similar to 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	Should not be used as only diagnostic marker because of lack of cardiac specificity
Cardiac troponins	1. Powerful tool for risk stratification 2. Greater sensitivity and specificity than CK-MB 3. Detection of recent MI up to 2 wk 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

myocardial necrosis but have an elevated CRP level appear to be at increased risk of an adverse outcome, especially those whose CRP levels are markedly elevated.

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 to 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 (eg, chest pain unit), and a repeat ECG and cardiac marker measurement should be obtained 6 to 12 hours after the onset of symptoms. (Level of Evidence: B)**
3. **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 have 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)**

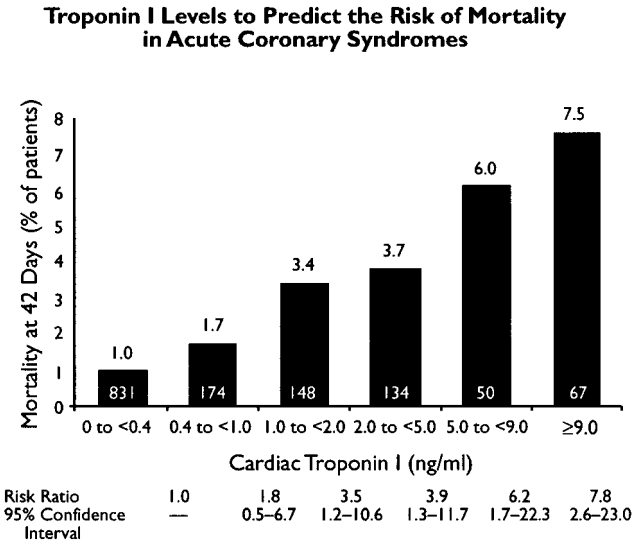

Figure 1. Relationship between cardiac troponin levels and risk of death in patients with ACS. Used with permission from Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342–1349.

Through the integration of information from the history, physical examination, 12-lead ECG, and initial biochemical cardiac marker tests, clinicians can assign patients to 1 of 4 categories: noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS (Figure 2). Patients with *possible ACS* are those who had a recent episode of chest discomfort at rest that was 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 is either 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 *definite ACS*. However, such patients may be at low risk if the ECG obtained at presentation has no diagnostic abnormalities and the initial cardiac markers (especially a cardiac-specific troponin) are normal.

To facilitate a more definitive evaluation while avoiding the unnecessary hospital admission of patients with possible ACS and low-risk ACS and the inappropriate discharge of patients with active myocardial ischemia without ST elevation, special units have been devised that are variously referred to as "chest pain units" and "short-stay ED coronary care units." 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 as UA or NSTEMI and to define the optimal next step in the care of the patient (eg, discharge, admission, acute intervention). The goal is to arrive at such a decision after a finite amount of time, usually between 6 and 12 hours.

Patients who arrive at a medical facility in a pain-free state, have unchanged or normal ECGs, are hemodynamically

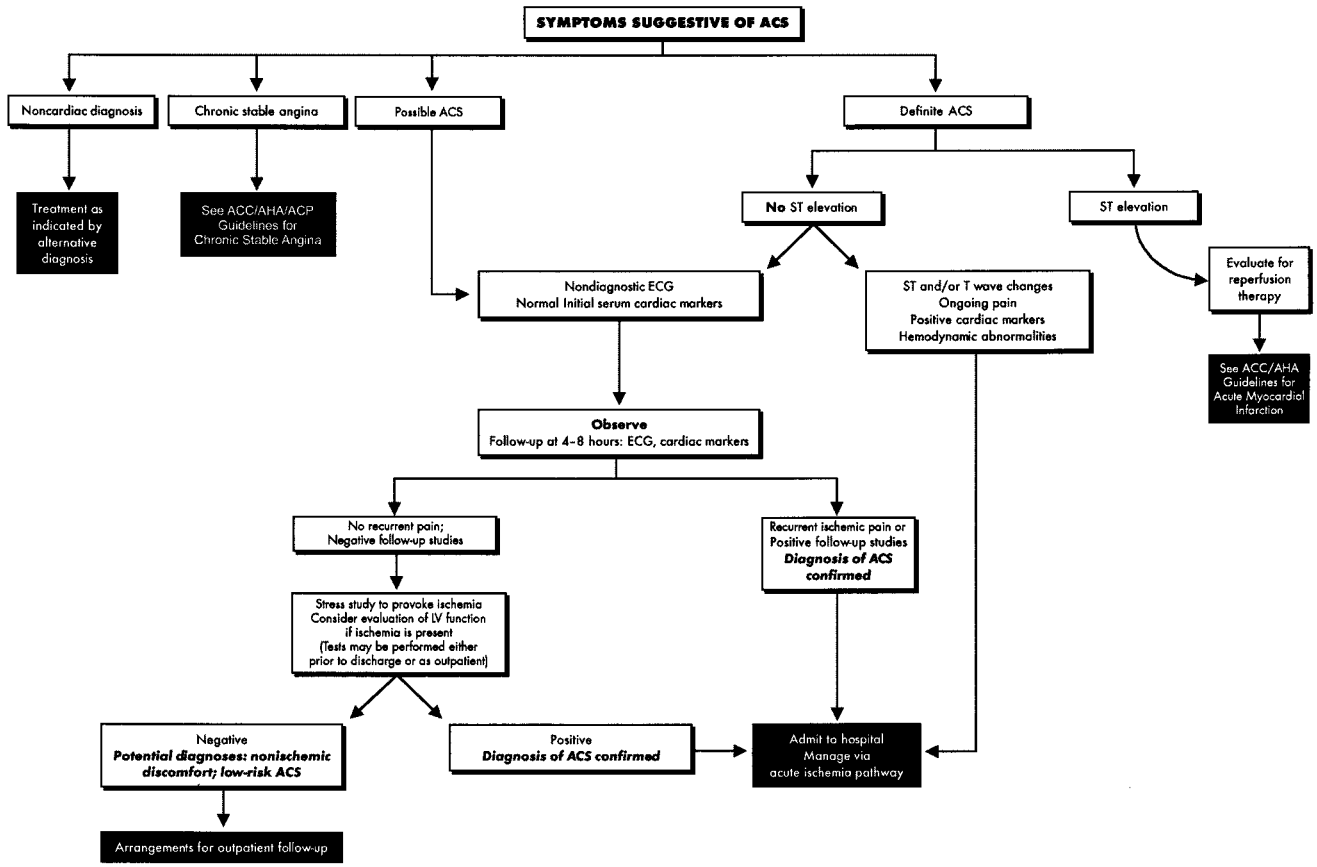

Figure 2. Algorithm for the evaluation and management of patients suspected of having an ACS.

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 (Table 1) to be used to confirm or reject the diagnosis of UA/NSTEMI. Patients with possible ACS are candidates for additional observation in a specialized facility (eg, chest pain unit). Patients with definite ACS are triaged based on the pattern of the 12-lead ECG. Patients with ST-segment elevation are evaluated for immediate reperfusion therapy and managed according to the ACC/AHA Guidelines for Management of Patients with Acute Myocardial Infarction, whereas those without ST-segment elevation are managed with either admission to the hospital or additional observation. During such observation, patients who experience recurrent ischemic discomfort, evolve abnormalities on a follow-up 12-lead ECG or cardiac marker measurement, or develop hemodynamic abnormalities such as new or worsening congestive heart failure (CHF) should be admitted to the hospital and managed as described in Section III. If the patient is at low risk (Table 1) and does not experience any further ischemic discomfort and his or her follow-up 12-lead ECG and cardiac marker measurements after 6 to 8 hours of observation remain normal, the patient may be considered for an early stress test to provoke ischemia. Patients discharged from the chest pain unit or ED should be counseled to make an appointment with their primary care physician as outpatients for further investigation into the cause of their symptoms. They should be seen by a physician within 72 hours of discharge from the ED or chest pain unit.

III. Hospital Care

The hospital care of patients with UA/NSTMEI is outlined in Figure 3.

A. Anti-Ischemic Therapy

Recommendations

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. **Nitroglycerin (NTG), sublingual tablet or spray, followed by intravenous administration, for 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 (Sao_2 >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 β-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 β-blockers are contraindicated, a nondihydropyridine calcium antagonist (eg, verapamil or diltiazem), followed by oral therapy, 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 β-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 β-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 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 β-blocker. (Level of Evidence: B)**
2. **Immediate-release dihydropyridine calcium antagonists in the presence of a β-blocker. (Level of Evidence: B)**

Class III

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

Patients should be placed at bed rest while ischemia is ongoing but can be mobilized to a chair and bedside commode when symptom free. Patients with cyanosis, respiratory distress, or other high-risk features should receive supplemental oxygen. Adequate arterial oxygen saturation should be confirmed with direct measurement or pulse oximetry. Inhaled oxygen should be administered if the arterial oxygen saturation (Sao_2) declines to <90%. Finger pulse oximetry is useful for continuous monitoring of Sao_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 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.

Patients whose symptoms are not relieved with three 0.4-mg sublingual nitroglycerin (NTG) tablets or spray taken 5 minutes apart and initiation of an intravenous β-blocker (when there are no contraindications), as well as all nonhypotensive high-risk patients (Table 1), may benefit from

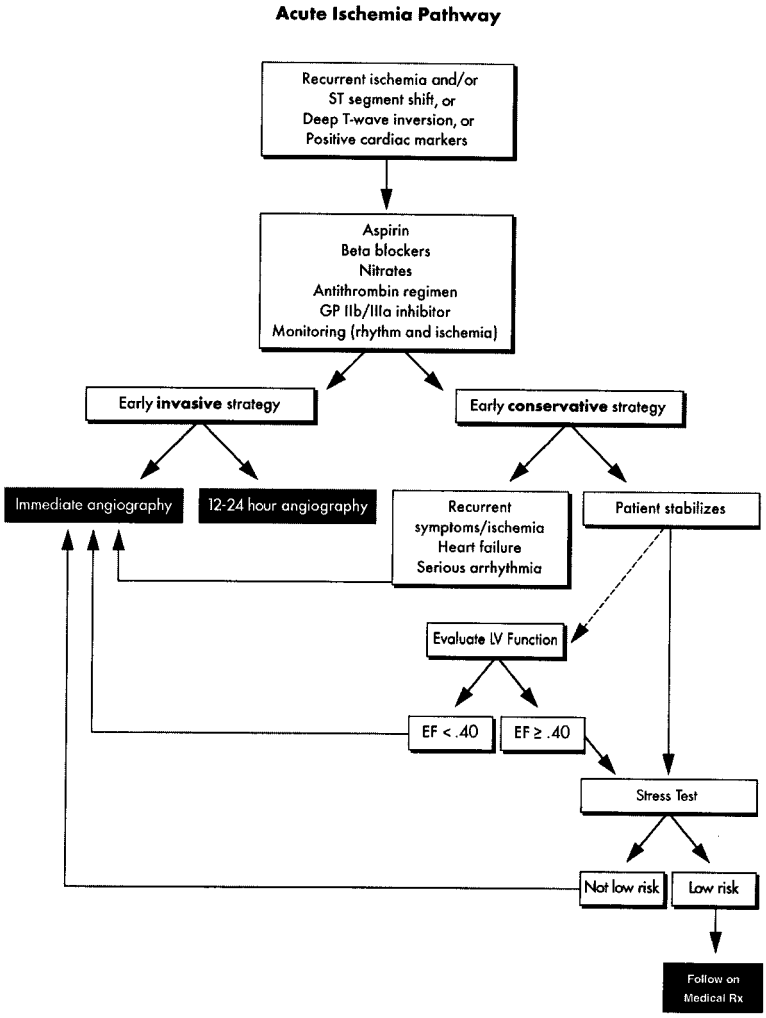

Figure 3. Acute ischemia pathway. Rx indicates therapy.

intravenous NTG, and such therapy is recommended in the absence of contraindications (ie, the use of sildenafil within the previous 24 hours or hypotension). Intravenous NTG may be initiated at a rate of 10 μg/min via continuous infusion with nonabsorbing tubing and increased by 10 μg/min every 3 to 5 minutes until some symptomatic or blood pressure response is noted.

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 hours of continuous therapy with any formulation. Patients who require continued intravenous NTG beyond 24 hours may require periodic increases in the infusion rate to maintain efficacy. An effort must be made to use non–tolerance-producing nitrate regimens (lower dose and intermittent dosing).

Morphine sulfate at a rate of 1 to 5 mg 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 minutes as needed to relieve symptoms and maintain patient comfort.

β-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. Several regimens may be used. For example, intravenous metoprolol may be administered in 5-mg increments via slow intravenous administration (5 mg every 1 to 2 minutes) and repeated every 5 minutes for a total initial dose of 15 mg. In patients who tolerate the total 15-mg intravenous dose, oral therapy should be initiated 15 minutes after the last intravenous dose at 25 to 50 mg every 6 hours for 48 hours. Thereafter, patients should receive a maintenance dose of 100 mg twice daily. Monitoring during intravenous β-blocker therapy should include frequent checks of heart rate and blood pressure and continuous ECG monitoring, as well as auscultation for rales and bronchospasm.

Calcium antagonists may be used to control ongoing or recurring ischemia-related symptoms in patients who are already receiving adequate doses of nitrates and β-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. Rapid-release, short-acting dihydropyridines (eg, nifedipine)

must be avoided in the absence of adequate concurrent β-blockade in ACS, because controlled trials suggest increased adverse outcomes. When β-blockers cannot be used, heart rate–slowing calcium antagonists (eg, verapamil or diltiazem) offer an alternative. When required for the control of refractory symptoms, these agents can be used early during the hospital phase even in patients with mild left ventricular (LV) dysfunction, although the combination of a β-blocker and calcium antagonist may act in synergy to depress LV function.

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce mortality rates in patients with AMI and in patients with recent MI or with LV systolic dysfunction, in diabetic patients with LV dysfunction, and in a broad spectrum of patients with high-risk chronic CAD. Accordingly, ACEIs should be used in such patients as well as in those with hypertension that is not controlled with β-blockers and nitrates.

B. Antiplatelet and Anticoagulation Therapy

Recommendations

Class I

1. **Antiplatelet therapy should be initiated promptly. Aspirin (ASA) is the first choice and is administered as soon as possible after presentation and continued indefinitely. (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 (see Table 2) and to patients in whom a percutaneous coronary intervention (PCI) is planned. Eptifibatide and tirofiban are approved for this use. (Level of Evidence: A) Abciximab can also be used for 12 to 24 hours in patients with UA/NSTEMI in whom a PCI is planned within the next 24 hours. (Level of Evidence: A)**

Class III

1. **Intravenous thrombolytic therapy in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block. (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 should be used in patients with continuing ischemia or with other high-risk features and in patients in whom an early invasive strategy is planned.

Some of the strongest evidence available about the long-term prognostic effects of therapy in CAD patients pertains to ASA. Among all clinical investigations with ASA, trials in UA/NSTEMI have most consistently documented a striking benefit of the drug despite differences in study design, such as time of entry after the acute phase, duration of follow-up, and doses. ASA should be initiated at a daily dose of 160 or 325 mg in patients with UA/NSTEMI. In patients who present with suspected ACS who are not already receiving ASA, the first dose may be chewed to establish a high blood level rapidly. Subsequent doses may be swallowed. Thereafter, daily doses of 75 to 325 mg are prescribed.

Few contraindications to ASA exist; these are 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.

Two thienopyridines, ticlopidine and clopidogrel, are adenosine diphosphate (ADP) antagonists that are currently approved for antiplatelet therapy. The platelet effects of ticlopidine and clopidogrel are irreversible but take several days to become completely manifest. The adverse effects of ticlopidine limit its usefulness and include gastrointestinal problems (eg, diarrhea, abdominal pain, nausea, vomiting), neutropenia in ≈2.4% of patients, severe neutropenia in 0.8% of patients, and, rarely, thrombotic thrombocytopenia purpura (TTP). Neutropenia usually resolves within 1 to 3 weeks of the discontinuation of therapy but very rarely may be fatal.

Ticlopidine and clopidogrel are useful antiplatelet drugs 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 has a more favorable safety profile.

Heparin is a key component in the antithrombotic management of UA/NSTEMI. The results of the studies that have compared the combination of ASA and either UFH or LMWH with the use of ASA alone have shown reductions in the rate of death or MI during the first week of 50% to 60%.

UFH has important pharmacokinetic limitations that are related to its nonspecific binding to proteins and cells. These limitations translate into poor bioavailability, especially at low doses, and marked variability in anticoagulant response among patients. As a consequence, the anticoagulant effect of UFH requires monitoring according to the activated partial thromboplastin time. The dose of UFH should be titrated to an activated partial thromboplastin time that is 1.5 to 2.5 times control. Serial hemoglobin/hematocrit and platelet measurements should be taken at least daily during UFH therapy. 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 does UFH and are less frequently associated with heparin-

induced thrombocytopenia. However, they appear to be associated with significantly more frequent *minor, but not major,* bleeding.

Two trials with enoxaparin, an LMWH, have shown a moderate benefit over UFH, and 2 trials, 1 with dalteparin and 1 with nadroparin, have shown neutral or unfavorable trends. A meta-analysis of the 2 trials with enoxaparin that involves a total of 7081 patients showed a statistically significant reduction of ≈20% in the rate of death, MI, or urgent revascularization and in the rate of death or MI at 8, 14, and 43 days. There was a trend toward a reduction in death as well.

Platelet GP IIb/IIIa Receptor Antagonists

The GP IIb/IIIa receptor ($\alpha_{IIb}\beta_3$ integrin) is abundant on the platelet surface. When platelets are activated, this receptor undergoes a change in configuration that increases its affinity for binding to fibrinogen and other ligands. 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. The platelet GP IIb/IIIa receptor antagonists act by preventing fibrinogen binding and thereby preventing platelet aggregation.

The various GP IIb/IIIa antagonists, however, possess significantly different pharmacokinetic and pharmacodynamic properties. 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 hours after the discontinuation of the drug. 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 as well. Eptifibatide is a cyclic heptapeptide that contains the KGD (Lys-Gly-Asp) sequence; tirofiban is a nonpeptide mimetic of the RGD (Arg-Gly-Asp) sequence of fibrinogen. Receptor occupancy with these 2 synthetic antagonists is in general in equilibrium with plasma levels. They have a half-life of 2 to 3 hours and are highly specific for the GP IIb/IIIa receptor, with no effect on the vitronectin receptor ($\alpha_v\beta_3$ integrin).

The efficacy of GP IIb/IIIa antagonists in prevention of the complications associated with percutaneous interventions has been documented in numerous trials, many of which are composed entirely or in large part of patients with UA. Two trials with tirofiban and 1 trial with eptifibatide have also documented their efficacy in UA/NSTEMI patients, of whom only some underwent interventions. 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. Because the various agents have not been compared directly with each other, their *relative* efficacy is not known.

The cumulative event rates observed during the phase of medical management and at the time of PCI in the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) (abciximab), Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) (tirofiban), and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) (eptifibatide) trials are shown in Figure 4. 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.

Treatment with a GP IIb/IIIa antagonist increases the risk of bleeding, which is typically mucocutaneous or involves the access site of vascular intervention. No trials have shown an excess of intracranial bleeding with a GP IIb/IIIa inhibitor. 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. 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. Information is currently being gained concerning the safety and efficacy of the combination of LMWH and GP IIb/IIIa inhibitors.

The failure of intravenous thrombolytic therapy to improve clinical outcomes in UA/NSTEMI has been clearly demonstrated in several trials.

C. Risk Stratification

Recommendations

Class I

1. **Noninvasive stress testing in low-risk patients (Table 1) who have been free of ischemia at rest or with low-level activity and of CHF for a minimum of 12 to 24 hours. (Level of Evidence: C)**
2. **Noninvasive stress testing in patients at intermediate risk (Table 1) 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, or digoxin effect. (Level of Evidence: C)**
4. **An imaging modality is added in patients with resting ST-segment depression (≥0.10 mV), LV hypertrophy, bundle-branch block, intraventricular conduction defect, preexcitation, or digoxin who are able to exercise. In patients undergoing a low-level exercise test, an imaging modality may add sensitivity. (Level of Evidence: C)**
5. **Pharmacological stress testing with imaging when physical limitations (eg, arthritis, amputation, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, 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)**

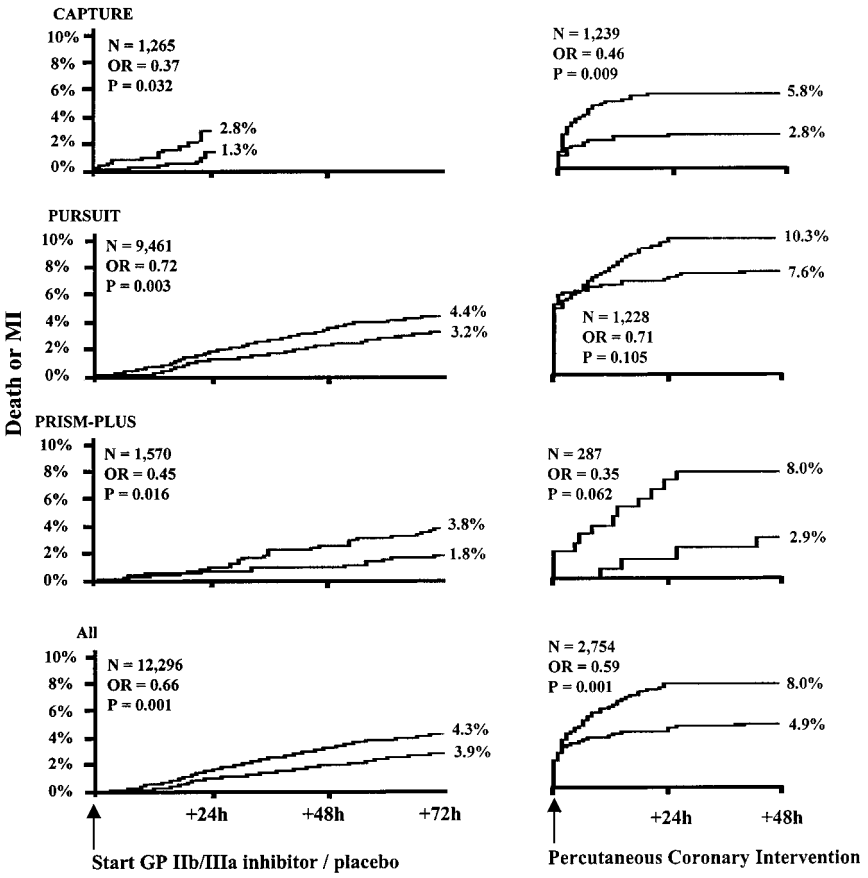

Figure 4. Kaplan-Meier curves showing cumulative incidence of death or MI in patients randomly assigned to platelet GP IIb/IIIa receptor antagonist (bold line) or placebo. Data are derived from the CAPTURE, PURSUIT, and PRISM-PLUS trials. Left, Events during the initial period of medical treatment until the moment of PCI or CABG. In the CAPTURE trial, abciximab was administered for 18 to 24 hours before the PCI was performed in almost all patients as per study design; abciximab was discontinued 1 hour 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 hours and for 24 hours after the intervention. In PRISM-PLUS, an intervention was performed in 30.2% of patients after a 48-hour period of medical therapy with tirofiban, and the drug infusion was maintained for 12 to 24 hours after an intervention. Right, Events occurring at the time of PCI and the next 48 hours, 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. OR indicates odds ratio. Adapted with permission from Boersma E, Akkerhuis KM, Theroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non–ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation*. 1999;100:2045–2048.

Class IIa

1. **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 patients with an ACS requires continuous risk stratification. Important prognostic information is derived from a careful initial assessment and the patient's course over the first few days of management and the response to anti-ischemic and antithrombotic therapy. The goals of noninvasive testing are to (1) determine the presence or absence of ischemia in patients at low likelihood of CAD and (2) estimate prognosis.

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 able to exercise who 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 (eg, to completion of Bruce Stage II) may be carried out in low-risk patients (Table 1) who have been asymptomatic for 12 to 24 hours. A symptom-limited test can be conducted in patients without evidence of ischemia for 7 to 10 days.

In contrast to the noninvasive tests, coronary angiography provides detailed structural information to allow an assessment of the prognosis and to provide direction for appropriate management. When combined with LV angiography, it also allows an assessment of global and regional LV function. In patients with UA/NSTEMI, coronary angiography typically shows the following profile: (1) no severe epicardial stenosis in 10% to 20% of patients, (2) significant (>50%) left main stenosis in 5% to 10% of patients, (3) multivessel stenosis in 40% to 50% of patients, and (4) 1-vessel stenosis in 30% to 35% of patients.

D. Early Conservative Versus Invasive Strategies

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 or ST-segment changes at rest or with minimal activity) 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**
b) **Recurrent angina/ischemia with CHF symptoms, an S_3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation**
c) **High-risk findings on noninvasive stress testing**
d) **Depressed LV systolic function (eg, EF <0.40 on noninvasive study)**
e) **Hemodynamic instability or angina at rest accompanied by hypotension**
f) **Sustained ventricular tachycardia**
g) **PCI within 6 months**
h) **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 of ongoing ischemia or high risk. (Level of Evidence: C)**
2. **An early invasive strategy in patients >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 (eg, liver or pulmonary failure, cancer), in whom 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)**

Rationale for the Early Invasive Strategy

In patients with UA/NSTEMI without recurrent ischemia in the first 24 hours, the use of early angiography provides a convenient approach to risk stratification. It can identify the patients with no significant coronary stenoses and those with 3-vessel disease with LV dysfunction or left main disease. The former group has an excellent prognosis, whereas the latter group may derive a survival benefit from coronary artery bypass graft surgery (CABG) (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. Some believe that proceeding immediately to angiography is an efficient approach for the ACS patient. Others believe that 12 to 48 hours of anti-ischemic or antithrombotic therapy is preferable.

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 generally indicated. 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, or those who present with CHF, have sufficient risk that the possibility of benefit from revascularization procedures merits early coronary angiography without preceding functional testing.

Rationale for the Early Conservative Strategy

Clinical evaluation and noninvasive testing aid in the identification of most patients who require revascularization, because they have markers of high risk, such as advanced age (>70 years), prior MI, revascularization, ST-segment deviation, CHF, or depressed resting LV function (ie, EF <0.40) on noninvasive study or noninvasive stress test findings that suggest severe ischemia. 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 coronary arteriography is optional in 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 based on patient preferences.

IV. Coronary 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 on medical therapy. Patients with high-risk coronary anatomy are likely to benefit from revascularization in terms of both symptom improvement and long-term survival. The indications for coronary revascularization in patients with UA/NSTEMI are similar to those for patients with chronic stable angina (see the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina and the ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery).

Recommendations for Revascularization With PCI and CABG in Patients With UA/NSTEMI

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

Class IIb

1. **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 to be 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 (<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)**

Percutaneous coronary revascularization (intervention) strategies are referred to in the guidelines as "PCI." The majority of current PCIs involve balloon dilatation and coronary stenting. Stenting has contributed greatly to catheter-based revascularization by reducing the risk of both acute vessel closure and late restenosis.

Platelet Inhibitors and Percutaneous Revascularization

Data from both retrospective observations and randomized clinical trials indicate that PCI can lead to angiographic success in most patients with UA/NSTEMI. An important advance in the treatment of patients with UA/NSTEMI undergoing PCI has been the introduction of platelet GP IIb/IIIa receptor inhibitors (see Section III). 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. 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.

Percutaneous Transluminal Coronary Angioplasty Versus CABG

A meta-analysis of 8 randomized trials completed between 1986 and 1993 has been carried out that compared the outcomes of CABG and percutaneous transluminal coronary angioplasty (PTCA) in 3371 patients with multivessel CAD (many of whom 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. Subsequently, the results were reported of the Bypass Angioplasty Revascularization Investigation (BARI) trial, the largest randomized comparison of CABG and PTCA, which was conducted in 1829 patients with 2- or 3-vessel CAD; UA was the admitting diagnosis in 64% of these patients. A statistically significant advantage in survival without MI independent of the severity of presenting symptoms was observed in the entire group for CABG compared with PCI at 7 years after study entry (84.4% versus 80.9%, $P=0.04$). However, subgroup analysis demonstrated that the survival benefit seen with CABG was confined to diabetic patients treated with insulin or oral hypoglycemic agents.

Conclusions

In general, the indications for PCI and CABG in UA/NSTEMI are similar to those in stable angina. High-risk patients with LV systolic dysfunction, 2-vessel disease with severe proximal LAD involvement, severe 3-vessel disease, or left main disease should be considered for CABG. 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 affect on the quality of life. Compared with high-risk patients, low-risk patients receive negligible 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 affect on their quality of life and functional status should be considered for 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 of patients with chronic stable coronary disease.

A. Medical Regimen

An effort of the entire staff (physicians, nurses, dietitians, pharmacists, rehabilitation specialists, and physical and occupational therapists) is often necessary to prepare the patient for discharge. 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 for Postdischarge Therapy

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. **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)**
3. **Before hospital discharge, patients should be informed about symptoms of acute myocardial infarction and should be instructed in how to seek help if they occur. (Level of Evidence: C)**
4. **All patients should be given sublingual or spray NTG and instructed in its use. (Level of Evidence: C)**
5. **Anginal discomfort that lasts >2 or 3 minutes 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 minutes, then a second and third dose, at 5-minute intervals, should be taken. Pain that lasts >15 to 20 minutes 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 by ambulance or the quickest available alternative. (Level of Evidence: C)**
6. **If the pattern of anginal symptoms changes (eg, pain that is more frequent or severe, 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)**
7. **ASA 75 to 325 mg/d in the absence of contraindications. (Level of Evidence: A)**
8. **Clopidogrel 75 mg/d in patients with a contraindication to ASA. (Level of Evidence: B)**
9. **β-Blockers in the absence of contraindications. (Level of Evidence: B)**
10. **Lipid-lowering agents and diet in post ACS patients including patients who are post revascularization with low-density lipoprotein (LDL) cholesterol of >125 mg/dL, including after revascularization. (Level of Evidence: A)**
11. **Lipid-lowering agents if LDL cholesterol level after diet is >100 mg/dL. (Level of Evidence: C)**
12. **ACEIs for patients with CHF, LV dysfunction (EF <0.40), hypertension, or diabetes. (Level of Evidence: A)**

A reduction in the mortality and vascular event rates was reported in 1 large trial, the Heart Outcomes Prevention Evaluation (HOPE) Study, with the long-term use of an ACEI in moderate-risk patients with CAD, many of whom had preserved LV function, as well as in patients at a high risk of developing CAD. 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. It is recommended that postmenopausal women on HRT continue but that HRT *not* be initiated for the secondary prevention of coronary events.

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 (Canadian Cardiovascular Society [CCS] Class III) chronic stable angina despite medical management and who are suitable for revascularization should undergo coronary arteriography. (Level of Evidence: B)**
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)**

C. Risk Factor Modification

Recommendations

Class I

1. **Specific instructions should be given regarding the following:**

a) **Smoking cessation and achievement or maintenance of optimal weight, daily exercise, and diet (Level of Evidence: B)**
b) **Hypertension control to a blood pressure of <130/85 mm Hg (Level of Evidence: A)**
c) **Tight control of hyperglycemia in diabetes (Level of Evidence: B)**
d) **HMG-CoA reductase inhibitors for LDL cholesterol of >130 mg/dL. (Level of Evidence: C)**
e) **Lipid-lowering agent if LDL >100 mg/dL after diet. (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. **Gemfibrozil or niacin in patients with a high-density lipoprotein (HDL) cholesterol level of <40 mg/dL and a triglyceride level of >200 mg/dL. (Level of Evidence: B)**

There is a wealth of evidence that cholesterol-lowering therapy for patients with CAD and hypercholesterolemia and for patients with mild cholesterol elevation (mean 209 to 218 mg/dL) after MI and UA reduces vascular event and death rates.

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

Recommendation

Class I

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

VI. Special Groups

A. Women

Recommendation

Class I

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

B. Diabetes Mellitus

Recommendations

Class I

1. **Diabetes is an independent prognostic factor for increased risk, and this should be taken into account in the initial evaluation. (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 who are receiving treatment 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)**

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. The use of stents, particularly with abciximab, appears to provide more favorable results in diabetics, although more data are needed. Clinical outcome with CABG, especially using 1 or both internal mammary arteries, is better than that with PTCA but is still less favorable than in nondiabetics.

C. Post-CABG Patients

Recommendations

Class I

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

Overall, up to 20% of UA/NSTEMI patients are status post CABG. Conversely, ≈20% of post-CABG patients develop UA/NSTEMI over 7.5 years, with a highly variable postoperative time of occurrence. Post-CABG patients who present with UA/NSTEMI are at a higher risk with more extensive CAD and LV dysfunction than previously unoperated patients.

Post-CABG patients, especially those with only SVGs, are at a high risk of ACS and other adverse cardiac outcomes, including UA/NSTEMI. There is a high likelihood of disease in SVGs versus native arteries that increases with postoperative time. There are also difficulties with treadmill ECG testing and less favorable outcomes with repeat revascular-

ization 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)**

Elderly persons 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, but 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 include consideration of the general medical and mental status and the 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.

E. Cocaine

Recommendations

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. **β-Blockers for hypertensive patients (systolic blood pressure >150 mm Hg) or those with sinus tachycardia (pulse >100 bpm). (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 who have 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

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

The basis for cocaine-induced coronary spasm has been demonstrated in both in vitro and in vivo experiments in animals and humans. The use of cocaine is associated with a number of cardiac complications that can produce myocardial ischemia, and cocaine users may develop ischemic chest discomfort that is indistinguishable from UA/NSTEMI. The widespread use of cocaine makes it mandatory to consider this cause, because its recognition mandates special management.

F. Variant (Prinzmetal's) Angina

Recommendations

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

1. **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

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

Variant (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. The earliest stages of AMI may also be associated with cyclic ST-segment elevations. It is caused by coronary spasm that is most commonly focal and can occur simultaneously at >1 site.

Coronary spasm is usually very responsive to NTG, long-acting nitrates, and calcium antagonists. Smoking should be

discontinued. Usually, a calcium antagonist at a high dose (verapamil 240 to 480 mg/d, diltiazem 120 to 360 mg/d, nifedipine 60 to 120 mg/d) is started. If the episodes are not completely eliminated, a second calcium antagonist from another class or a long-acting nitrate should be added. α-Receptor blockers have also been reported to be of benefit, especially in patients who are not responding completely to calcium antagonists and nitrates.

Recommendations for Patients With Syndrome X

Class I

1. **Reassurance and medical therapy with nitrates, β-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

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

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. Syndrome X is more common in women than in men. 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. The intermediate-term prognosis of patients with syndrome X is excellent.

It is recommended that patients be reassured of the excellent intermediate-term prognosis and be treated with long-acting nitrates. If the patient continues to have episodes of chest pain, a calcium antagonist or β-blocker can be started. Imipramine at 50 mg HS has been successful in reducing the frequency of chest pain episodes.

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