Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction:
Part I. Initial Evaluation and Management, and Hospital Care

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Each year, more than 1 million patients are admitted to U.S. hospitals because of unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI). To help standardize the assessment and treatment of these patients, the American College of Cardiology and the American Heart Association convened a task force to formulate a management guideline. This guideline, which was published in 2000 and updated in 2002, highlights recent medical advances and is a practical tool to help physicians provide medical care for patients with UA/NSTEMI. Management of suspected UA/NSTEMI has four components: initial evaluation and management; hospital care; coronary revascularization; and hospital discharge and post-hospital care. Part I of this two-part article discusses the first two components of management. During the initial evaluation, the history, physical examination, electrocardiogram, and cardiac biomarkers are used to determine the likelihood that the patient has UA/NSTEMI and to aid in risk assessment when the diagnosis is established. Hospital care consists of appropriate initial triage and monitoring. Medical treatment includes anti-ischemic therapy (oxygen, nitroglycerin, beta blocker), antiplatelet therapy (aspirin, clopidogrel, platelet glycoprotein IIb/IIIa inhibitor), and antithrombotic therapy (heparin, low-molecular-weight heparin). (Am Fam Physician 2004;70:525-32 Copyright© 2004 American Academy of Family Physicians.)

This is part I of a two-part article on unstable angina and non–ST-segment elevation myocardial infarction. Part II, "Coronary Revascularization, Hospital Discharge, and Post-Hospital Care," appears on page 535 in this issue.

ACF This article exemplifies the AAFP 2004 Annual Clinical Focus on caring for America's aging population.

See page 425 for definitions of strength-of-recommendation labels.

The term "acute coronary syndrome" encompasses unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI) and ST-segment elevation myocardial infarction (STEMI). UA/NSTEMI is the combination of two closely related clinical entities (i.e., a syndrome), whereas STEMI is a distinct clinical entity. UA/NSTEMI is characterized by an imbalance between myocardial oxygen supply and demand. Most often, the syndrome develops because of decreased myocardial perfusion resulting from coronary narrowing caused by nonocclusive thrombus formation subsequent to disruption of an atherosclerotic plaque. In contrast, STEMI results from an occlusive thrombus.

Each year, more than 5 million patients present to U.S. emergency departments with chest pain and related symptoms.[1] Approximately 1.4 million of these patients are admitted for management of UA/NSTEMI.[1] Because of the scope of the problem, it is important for family physicians to understand the diagnosis, risk assessment, and treatment of this syndrome.

To help standardize the assessment and treatment of patients with UA/NSTEMI, the American College of Cardiology (ACC) and the American Heart Association (AHA) convened a task force to produce a management guideline. The ACC/AHA guideline, which was published in 2000[1] and updated in 2002,[2,3] divides the management of suspected UA/NSTEMI into four components: initial evaluation and management; hospital care; coronary revascularization; and hospital discharge and post-hospital care. This two-part article focuses on the major management recommendations in the guideline, using the ACC/AHA classification of recommendations *(Table 1)*.[3] Recent advances in management are highlighted. Part I reviews the first two components of management, and part II[4] reviews the other two components.

Initial Evaluation and Management

Two important issues arise in the initial evaluation of the patient with a suspected acute coronary syndrome: the likelihood that the clinical presentation represents an acute coronary syndrome *(Table 2)*[3,5] and the risk of adverse outcomes *(Table 3)*.[3,5] The initial clinical evaluation to address both issues should include a history, a physical examination, an electrocardiogram, and a cardiac biomarker measurement (a cardiac-specific troponin level [preferred in the ACC/AHA guideline[2,3]] or an MB isoenzyme of creatine kinase level). Data from this evaluation aid in the assessment of risk and in decisions about the required intensity of monitoring (intensive care unit versus "step-down" unit), choice of therapeutic agents, and use of cardiac catheterization and revascularization.

RISK PREDICTION RULE

The 2002 ACC/AHA guideline[2,3] includes the use of a risk prediction rule for early assessment. Multiple risk scores have been developed to predict the likelihood of adverse outcomes in patients presenting with UA/NSTEMI.[6-8] One example is the seven-point Thrombolysis in Myo-

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TABLE 2

Likelihood of Acute Coronary Syndrome Secondary to Coronary Artery Disease Based on Clinical Features

Area of assessment	Likelihood of acute coronary syndrome based on clinical features		
	High	*Intermediate*	*Low*
Symptoms	Chest or left arm pain or discomfort reproducing previously documented angina	Chest or left arm pain or discomfort	Symptoms with features other than those indicating intermediate or high likelihood
History	Known history of coronary artery disease or myocardial infarction	Patient age > 70 years, male sex, diabetes mellitus	Recent cocaine use
Physical examination	Transient mitral regurgitation, hypotension, diaphoresis, rales	Manifestations of extracardiac vascular disease	Chest pain reproduced by palpation
ECG	New transient ST-segment deviation or T-wave inversions with symptoms	Q waves; abnormal ST segments or T waves not documented to be new	Normal ECG
Cardiac biomarkers	Elevated cardiac-specific troponin level or elevated MB isoenzyme of creatine kinase level	Cardiac biomarker levels not elevated	Cardiac biomarker levels not elevated

ECG = electrocardiogram.

Adapted with permission from ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Accessed online May 11, 2004, at: http://www.americanheart.org/presenter.jhtml?identifier=300 1260, and Braunwald E. Unstable angina: diagnosis and management. Rockville, Md.: U.S. Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, National Heart, Lung, and Blood Institute, 1994; clinical practice guideline no. 10; AHCPR publication no. 94-0602.

TABLE 3

Clinical Features Associated with Risk of Death or Nonfatal Myocardial Infarction in Patients with Unstable Angina

Area of assessment	Risk of death or nonfatal myocardial infarction based on clinical features		
	High*	Intermediate†	Low
History	Accelerating tempo of ischemic symptoms in preceding 48 hours	Previous myocardial infarction, peripheral vascular disease, cerebrovascular disease, coronary artery bypass grafting, or aspirin use	—
Character of pain	Prolonged, ongoing (> 20 minutes) angina at rest	Prolonged angina at rest (> 20 minutes), now resolved Angina at rest (< 20 minutes) or relieved with rest or sublingual nitroglycerin	New-onset or progressive anginal symptoms, not occurring at rest
Clinical findings	Ischemic pulmonary edema, new or worsening mitral regurgitation, S_3 gallop, hypotension, bradycardia, tachycardia, patient age > 75 years	Patient age > 70 years	—
ECG	Angina at rest, with new transient ST-segment deviation; bundle-branch block or sustained ventricular tachycardia	T-wave inversions, Q waves	Normal ECG, or no changes in ECG during pain episode
Cardiac biomarker	Cardiac-specific troponin level elevated above "necrosis limit"	Cardiac-specific troponin level elevated but below "necrosis limit"	Cardiac-specific troponin level not elevated

ECG = electrocardiogram.

*—Risk is high if at least one clinical feature is present

†—Risk is intermediate if at least one clinical feature in the column is present and no high-risk clinical features are present.

Adapted with permission from ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Accessed online May 11, 2004, at: http://www.americanheart.org/presenter.jhtml?identifier=300 1260, and Braunwald E. Unstable angina: diagnosis and management. Rockville, Md.: U.S. Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, National Heart, Lung, and Blood Institute, 1994; clinical practice guideline no. 10; AHCPR publication no. 94-0602.

cardial Infarction (TIMI) risk score for UA/NSTEMI *(Figure 1)*.[6]

The TIMI risk score integrates historical factors, frequency of symptoms, electrocardiographic findings, and cardiac biomarker levels.[6] Higher scores are associated with an increased risk of adverse outcomes such as death, (re)infarction, or recurrent ischemia requiring revascularization. The risk of these outcomes ranges from approximately 5 percent with a TIMI risk score of zero or one point to approximately 41 percent with a risk score of six or seven points. The risk score may be used to help guide therapeutic decisions. Patients with

higher risk scores have been shown to derive greater benefit from specific pharmacologic therapies (enoxaparin [Lovenox],[6] platelet glycoprotein IIb/IIIa inhibitor[9]) and an early cardiac catheterization (invasive) strategy.[10]

BIOMARKERS

Recent studies have examined the role of nontraditional biomarkers in the risk stratification of patients with acute coronary syndrome. High-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, has been shown to provide prognostic information in patients with acute coronary syndromes, independent of clinical factors and

TIMI Risk Score for UA/NSTEMI

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Figure 1.

High-Risk Indicators Favoring an Early Invasive Strategy in Patients with UA/NSTEMI

Recurrent angina or ischemia at rest or with low-level activity, despite intensive anti-ischemic therapy

Elevated cardiac-specific troponin level (troponin I or T)

New or presumably new ST-segment depression

Recurrent angina or ischemia with symptoms of congestive heart failure, an S_3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation

High-risk findings on noninvasive stress testing

Depressed left ventricular function (e.g., ejection fraction < 40% on noninvasive study)

Hemodynamic instability

Sustained ventricular tachycardia

Percutaneous coronary intervention within previous six months

Previous coronary artery bypass grafting

UA/NSTEMI = unstable angina and non–ST-segment elevation myocardial infarction.

Information from reference 3.

traditional markers of necrosis.[11-13] B-type natriuretic peptide (BNP) has been associated with heart failure, as well as adverse clinical outcomes (predominantly mortality), in patients with acute coronary syndromes.[14] The study findings[11-14] suggest that future risk stratification in patients with acute coronary syndrome may involve a panel of biomarkers.

One investigative team[15] has proposed a simplified method of combining the information provided by biomarkers. From zero to three points are assigned, depending on the number of elevated biomarkers (cardiac-specific troponin, hs-CRP, BNP). The risk of death, recurrent myocardial infarction, or congestive heart failure has been found to be 4.5 times higher when all three biomarkers are elevated than when no biomarker is elevated.[15] However, more data are needed before use of hs-CRP and BNP can be recommended for risk stratification in UA/NSTEMI.
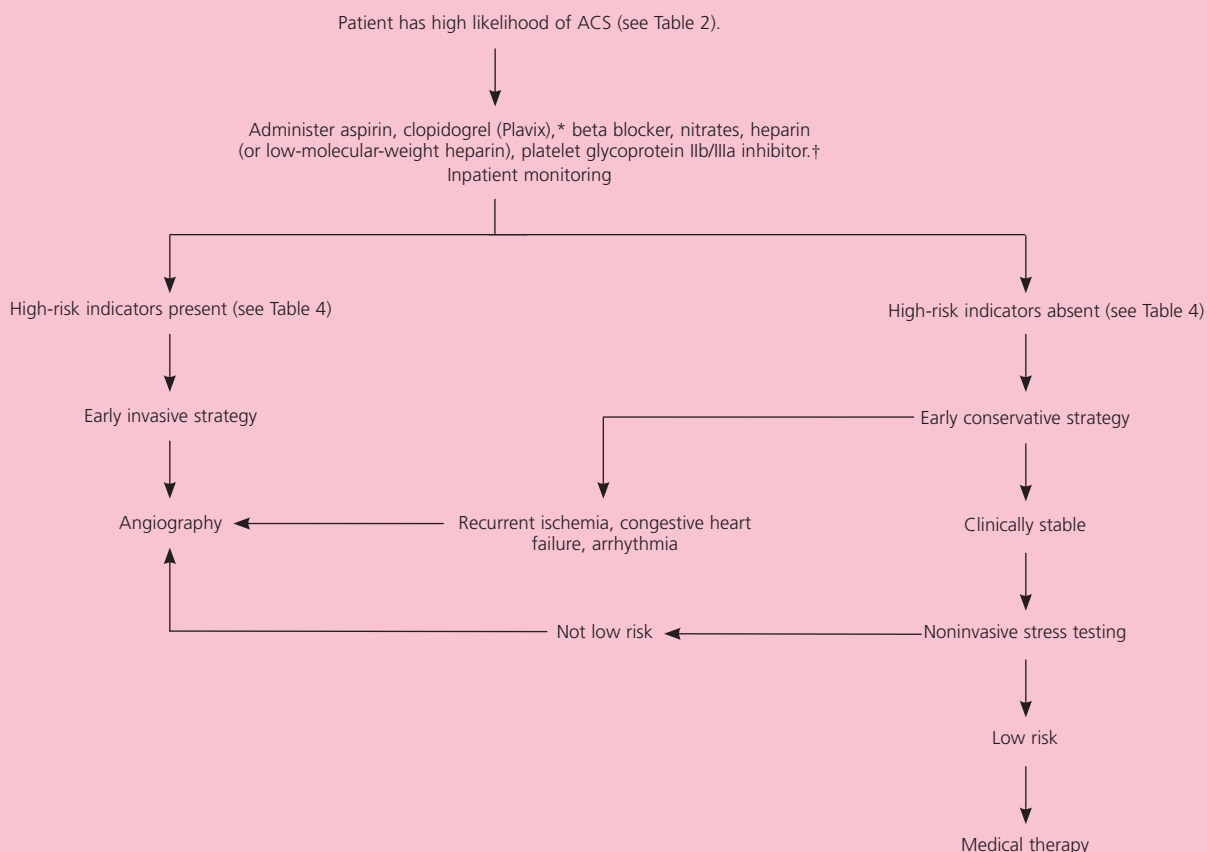
Hospital Care

Patients with UA/NSTEMI should be admitted to an inpatient unit, where they should undergo continuous monitoring for arrhythmias and recurrent ischemia. Patients with high-risk indicators, such as recurrent pain or hemodynamic disturbance *(Table 4)*,[3] should be admitted to a coronary care or intensive care unit capable of more extensive monitoring. Therapy should include anti-ischemic, antiplatelet, and antithrombotic agents, as well as a care plan that includes consideration of an early invasive strategy *(Figure 2)*.[3]

ANTI-ISCHEMIC THERAPY

ACC/AHA class I anti-ischemic interventions include supplemental oxygen, sublingually or intravenously administered nitroglycerin for relief of recurrent ischemia and associated symptoms and, in the absence of contraindications, an intravenously administered beta blocker for management of ongoing chest pain followed by an orally administered beta blocker.[2,3] Beta blockers should be used cautiously in patients with marked first-degree atrioventricular block, second- and third-degree atrioventricular block without a pacemaker, asthma, severe left ventricular dysfunction with congestive heart failure, significant chronic obstructive pulmonary disease, and significant sinus bradycardia or hypotension.[2,3]

Evaluation and Management of a Patient with Probable ACS

Patient has high likelihood of ACS (see Table 2).

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Administer aspirin, clopidogrel (Plavix),* beta blocker, nitrates, heparin (or low-molecular-weight heparin), platelet glycoprotein IIb/IIIa inhibitor.†
Inpatient monitoring

High-risk indicators present (see Table 4) → Early invasive strategy → Angiography

High-risk indicators absent (see Table 4) → Early conservative strategy → Clinically stable → Noninvasive stress testing → Low risk → Medical therapy

Recurrent ischemia, congestive heart failure, arrhythmia → Angiography

Not low risk → Angiography

Noninvasive stress testing → Not low risk

*—Clopidogrel may be administered at the time of angiography in patients with a planned early invasive strategy.

†—Platelet glycoprotein IIb/IIIa inhibitors are given an ACC/AHA class I indication (see Table 1) in patients for whom catheterization is planned, and an ACC/AHA class IIa indication in patients who have high-risk indicators, such as an elevated cardiac-specific troponin level or ST-segment deviation (see Table 4), and in whom a conservative strategy is planned.

Figure 2. Evaluation and management of the patient with a high likelihood of having an acute coronary syndrome (ACS). (ACC = American College of Cardiology; AHA = American Heart Association)

Adapted with permission from ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Accessed online May 11, 2004, at: http://www.americanheart.org/presenter.jhtml?identifier=3001260.

ANTIPLATELET THERAPY

Three classes of antiplatelet agents have important roles in the management of UA/NSTEMI: aspirin, thienopyridines, and platelet glycoprotein IIb/IIIa inhibitors.

Aspirin. A cornerstone of management in acute coronary syndromes, aspirin has been shown to reduce cardiovascular events by 50 to 70 percent.[16] In the absence of known contraindications, aspirin therapy should be used in all patients with suspected, probable, or definite acute coronary syndrome.

Clopidogrel. The updated ACC/AHA guideline[2,3] recommends use of the thienopyridine clopidogrel (Plavix) in patients who cannot tolerate aspirin[17] (ACC/AHA class I). Because of its safety profile (compared with ticlopidine [Ticlid]), clopidogrel currently is the preferred thienopyridine.[1] Clopidogrel is a potent antiplatelet agent that acts by irreversibly blocking the P2Y12 adenosine diphosphate receptor on the platelet surface, thereby interrupting platelet activation and aggregation.

One of the major changes in the care of patients with

UA/NSTEMI has been the ACC/AHA class I indication for use of clopidogrel in addition to aspirin in patients with acute coronary syndromes.[2,3] This change occurred because of the findings of recent major clinical trials. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial[18] randomized more than 12,000 patients with UA/NSTEMI to receive clopidogrel or placebo in addition to aspirin. Patients were followed for three to 12 months. In the CURE trial, death, myocardial infarction, or stroke occurred in 9.3 percent of the patients treated with clopidogrel, compared with 11.5 percent of those who received placebo. The improvement occurred at the cost of a small, but significant increase in bleeding (relative risk: 27 percent), especially in patients who underwent coronary artery bypass grafting within five days of discontinuing clopidogrel therapy.

In an analysis of patients undergoing percutaneous coronary intervention (PCI-CURE study),[19] patients were treated with clopidogrel or placebo for a median of 10 days before the intervention (all patients also received aspirin). After the intervention, patients in the PCI-CURE study received open-label clopidogrel or ticlopidine for four weeks, followed by the initial study drug (clopidogrel or placebo) for an average of eight months. The clopidogrel-treated patients had fewer early (30-day) and long-term cardiovascular events.

As a result of the study findings, the 2002 ACC/AHA guideline[2,3] considers the use of clopidogrel in addition to aspirin to have a class I indication in patients with UA/NSTEMI who are undergoing an early noninterven-

tional or interventional approach and are not at high risk for bleeding. Clopidogrel therapy is recommended for at least one month and may be continued for up to nine months. Aspirin, unless contraindicaetd, should be continued for life. When elective coronary artery bypass grafting is planned, clopidogrel should be withheld for five to seven days.

Platelet Glycoprotein IIb/IIIa Inhibitors. These agents constitute a third class of antiplatelet agents that may be used in patients hospitalized with UA/NSTEMI. Three agents in this class currently are available for clinical use: abciximab (ReoPro), which is a monoclonal antibody; and eptifibatide (Integrelin) and tirofiban (Aggrastat), which are "small molecule" glycoprotein IIb/IIIa inhibitors. These potent inhibitors of platelet aggregation are administered intravenously.

Clinical trials have shown that platelet glycoprotein IIb/IIIa inhibitor therapy is beneficial in selected patients with UA/NSTEMI.[20] However, benefit appears to be greater in patients for whom an early invasive strategy is planned (i.e., cardiac catheterization and percutaneous coronary intervention)[20,21] and patients who have elevated cardiac-specific troponin levels[22] or other high-risk indicators such as an elevated TIMI risk score[9] or diabetes mellitus.[23] In patients for whom an early invasive strategy is not planned, the Global Utilization of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndromes (GUSTO IV-ACS) randomized trial[24] showed no benefit for abciximab compared with placebo. As a result of the GUSTO IV-ACS study findings, use of abciximab is contraindicated in patients for whom an early invasive strategy is not planned (ACC/AHA class III).

Based on the combined study findings,[20-23,25] platelet glycoprotein IIb/IIIa inhibitors have an ACC/AHA class I indication in patients for whom catheterization and percutaneous coronary intervention are planned. These agents should be administered in addition to aspirin and heparin. An ACC/AHA class IIa recommendation is given to the use of eptifibatide or tirofiban in addition to aspirin and heparin in patients with continuing ischemia, elevated cardiac-specific troponin levels, or other high-risk features for whom an invasive strategy is not planned.

ANTITHROMBOTIC THERAPY

The final component of medical therapy to consider in patients with UA/NSTEMI is antithrombotic/anticoagulant therapy. Unfractionated heparin results in anticoagulation by facilitating the action of antithrombin which, in turn, inactivates factor IIa (thrombin), factor

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Strength of Recommendations

Key clinical recommendation	SOR labels	References
The updated ACC/AHA guideline recommends use of the thienopyridine clopidogrel (Plavix) in patients who cannot tolerate aspirin (ACC/AHA class I).	A	2, 3, 17
The updated ACC/AHA guideline considers the use of clopidogrel in addition to aspirin to have a class I indication in patients with UA/NSTEMI who are undergoing an early noninterventional or interventional approach and are not at high risk for bleeding.	A	2, 3, 18,19
When elective coronary artery bypass grafting is planned, clopidogrel should be withheld for five to seven days.	C	2, 3
Platelet glycoprotein IIb/IIIa inhibitors have an ACC/AHA class I indication in patients for whom catheterization and percutaneous coronary intervention are planned. These agents should be administered in addition to aspirin and heparin.	A	20-23, 25
Anticoagulation with unfractionated heparin or low-molecular-weight heparin for patients with UA/NSTEMI has an ACC/AHA class I indication. The heparin is to be used in addition to aspirin or clopidogrel.	A	27

ACC = American College of Cardiology; AHA = American Heart Association; UA/NSTEMI = unstable angina and non–ST-segment elevation myocardial infarction.

IXa, and factor Xa. Treatment with unfractionated heparin has been shown to be superior to aspirin therapy alone in patients with UA/NSTEMI.[26] Low-molecular-weight (LMW) heparin (e.g., enoxaparin) is obtained through cleavage of heparin to provide chains with different molecular weights. Compared with unfractionated heparin, the LMW heparins are relatively more potent inhibitors of factor Xa. LMW heparins also have a more predictable pharmacology, which means that laboratory monitoring of anticoagulation status is not needed.[26] Anticoagulation with unfractionated heparin or LMW heparin has an ACC/AHA class I indication.[27] One of these agents is to be used in addition to aspirin or clopidogrel.

Recent trial data[28] have shown superior results with the use of enoxaparin compared with unfractionated heparin in patients with UA/NSTEMI. Consequently, the guideline[2,3] indicates a ACC/AHA class IIa recommendation for the use of enoxaparin, rather than unfractionated heparin, in patients with UA/NSTEMI. Although data are not conclusive, recent trials have shown that LMW heparin is safe to use in combination with glycoprotein IIb/IIIa inhibitors[29,30] and in percutaneous coronary intervention.[31-33]

Despite the role of thrombosis in UA/NSTEMI, thrombolytic agents have not been shown to provide benefit in patients with UA/NSTEMI; in fact, there is a trend toward worse outcomes.[34-36] Consequently, thrombolytic agents are contraindicated for use in the treatment of patients who have UA/NSTEMI.

REFERENCES

1. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina) [published correction appears in J Am Coll Cardiol 2001;38:294-5]. J Am Coll Cardiol 2000;36:970-1062.

2. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Circulation 2002;106:1893-1900.

3. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Accessed online May 11, 2004, at: http://www.americanheart.org/presenter.jhtml?identifier=3001260.

4. Wiviott SD, Braunwald E. Unstable angina and non-ST-segment-elevation myocardial infarction: part II. Coronary revascularization, hospital discharge, and post-hospital care. Am Fam Physician 2004;70:535-8.

5. Braunwald E. Unstable angina: diagnosis and management. Rockville, Md.: U.S. Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, National Heart, Lung, and Blood Institute, 1994; clinical practice guideline no. 10; AHCPR publication no. 94-0602.

6. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835-42.

7. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000;101:2557-67.

8. Jacobs DR Jr, Kroenke C, Crow R, Deshpande M, Gu DF, Gatewood L, et al. PREDICT: a simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota heart survey. Circulation 1999;100:599-607.

9. Morrow DA, Antman EM, Snapinn SM, McCabe CH, Theroux P, Braunwald E. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes. Application of the TIMI Risk Score for UA/NSTEMI in PRISM-PLUS. Eur Heart J 2002;23:223-9.

10. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-87.

11. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;331:417-24.

12. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1998;31:1460-5.

13. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;343:1139-47.

14. De Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014-21.

15. Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation 2002;105:1760-3.

16. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105-11.

17. Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. Cochrane Database Syst Rev 2004;(2):CD001246.

18. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation [published corrections appear in N Engl J Med 2001;345:1716 and N Engl J Med 2001;345:1506]. N Engl J Med 2001;345:494-502.

19. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.

20. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials [published correction appears in Lancet 2002;359:2120]. Lancet 2002;359:189-98.

21. ESPRIT Investigators. Enchanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial [published correction appears in Lancet 2001;357:1370]. Lancet 2000;356:2037-44.

22. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. Lancet 1999;354:1757-62.

23. Cannon CP, Weintraub WS, Demopoulos LA, Robertson DH, Gormley GJ, Braunwald E. Invasive versus conservative strategies in unstable angina and non-Q-wave myocardial infarction following treatment with tirofiban: rationale and study design of the international TACTICS-TIMI 18 Trial. Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy. Thrombolysis In Myocardial Infarction. Am J Cardiol 1998;82:731-6.

24. Simoons ML; GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001;357:1915-24.

25. Bosch X, Marrugat J. Platelet glycoprotein IIb/IIIa blockers for percutaneous coronary revascularization and unstable angina and non-ST-segment elevation myocardial infarction. Cochrane Database Syst Rev 2004;(2):CD002130.

26. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA 1996;276:811-5.

27. Magee KD, Sevcik W, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. Cochrane Database Syst Rev 2004;(2):CD002132.

28. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. Circulation 1999;100:1602-8.

29. Cohen M, Theroux P, Weber S, Laramee P, Huynh T, Borzak S, et al. Combination therapy with tirofiban and enoxaparin in acute coronary syndromes. Int J Cardiol 1999;71:273-81.

30. SoRelle R. QTc interval and B-type natriuretic peptide levels predict death in patients with advanced heart failure. Circulation 2003;107:e9024-32.

31. Collet JP, Montalescot G, Lison L, Choussat R, Ankri A, Drobinski G, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. Circulation 2001;103:658-63.

32. Kereiakes DJ, Grines C, Fry E, Esente P, Hoppensteadt D, Midei M, et al. Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. J Invasive Cardiol 2001;13:272-8.

33. Fry ET. Glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparins: a combined role in coronary interventions? Clin Cardiol 2001;24(3 suppl):I8-11.

34. Bar FW, Verheugt FW, Col J, Materne P, Monassier JP, Geslin PG, et al. Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome. Results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. Circulation 1992;86:131-7.

35. Schreiber TL, Rizik D, White C, Sharma GV, Cowley M, Macina G, et al. Randomized trial of thrombolysis versus heparin in unstable angina. Circulation 1992;86:1407-14.

36. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994;89:1545-56.