Management of Unstable Angina: Integrating the New Approaches

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Great strides have been made in the understanding of unstable angina and its relationship to the acute coronary syndromes and myocardial infarction during the last decade of the 20th century. Detailed information about ECG changes and serum cardiac markers, as well as the conclusions drawn from numerous large, randomized interventional trials can now be integrated into the traditional clinical picture. Clinicians can now classify patients into diagnostic and prognostic categories and can perform risk stratification with unprecedented precision. With this information, the decision to hospitalize patients and the selection of noninvasive or invasive evaluation and management strategies can be individualized for optimal outcomes. [Rev Cardiovasc Med. *2000;1(2):104-119*]

Key words: Angina, unstable • Anticoagulation therapy • Antiplatelet therapy • Glycoprotein receptor antagonists • Myocardial ischemia • Revascularization

Unstable angina (UA), a major reason for emergency department visits, is responsible for more than 1 million hospital admissions annually in this country.[1] It is, therefore, imperative that health care providers be familiar with recent developments in the diagnosis and management of this condition.

Acute coronary syndrome (ACS) refers to a constellation of clinical signs and symptoms produced by acute myocardial ischemia. It comprises UA and acute myocardial infarction (MI) associated with ST-segment elevation or depression. Patients with angina and no ST-segment elevation have either UA or non–ST-segment elevation MI (NSTEMI). The 2 conditions can be differentiated by the presence or absence of the circulating markers of myocardial necrosis.

Braunwald and colleagues[2,3] have described 3 principal presentations of UA, which include rest angina, new-onset angina, and increasing angina. Rest angina is angina occurring at rest, usually lasting longer than 20 minutes and occurring within a week of presentation. New-onset angina is angina of at least Canadian Cardiovascular Society Classification III severity, with onset within 2 months of initial presentation. Increasing angina is previously diagnosed angina that is distinctly more frequent, is longer in duration, or occurs at a lower threshold.

Pathogenesis

ACS is produced by an imbalance between myocardial oxygen supply and demand. The most common cause of UA/NSTEMI is reduced myocardial blood flow from a nonocclusive thrombus that has formed over a disrupted atherosclerotic plaque. Factors that induce and promote inflammation or atherogenesis, thus giving rise to an atherosclerotic lesion, include hypercholesterolemia and other lipid-related abnormalities; hypertension; high plasma homocysteine concentrations; endothelial insult secondary to smoking; and, possibly, certain infections, such as those caused by herpesviruses or *Chlamydia pneumoniae*.[4]

In the advanced lesion, a fibrous cap separates the lesion from the arterial lumen. The cap covers a mixture of leukocytes, macrophages, foam cells, lipids, and debris, which may form a necrotic core (Figure 1).[4] A typical vulnerable lesion consists of an eccentric plaque, rich in extracellular lipids within a large lipid pool, and has a thin, fibrous cap. Degradation, followed by cap rupture, may result from expression of matrix metalloproteinases (collagenases, elastases, and stromelysins) by macrophages. Cap rupture exposes the lipid core, the most potent substrate for platelet-rich thrombus formation, to flowing blood.

Plaque disruption leads to platelet activation, adhesion, and aggregation. Platelet activation causes changes in the shape of platelets and conformational alterations in glycoprotein (GP) IIb/IIIa receptors, allowing them to bind to fibrinogen. By forming bridges between platelets, fibrinogen facilitates platelet aggregation.[5]

Plaque disruption also leads to the release of tissue factor, which is expressed by smooth muscle and foam cells in unstable plaques. Tissue factor interacts with factor VIIa to initiate the coagulation cascade. This causes local thrombin generation, fibrin deposition and, ultimately, platelet-rich thrombus formation.

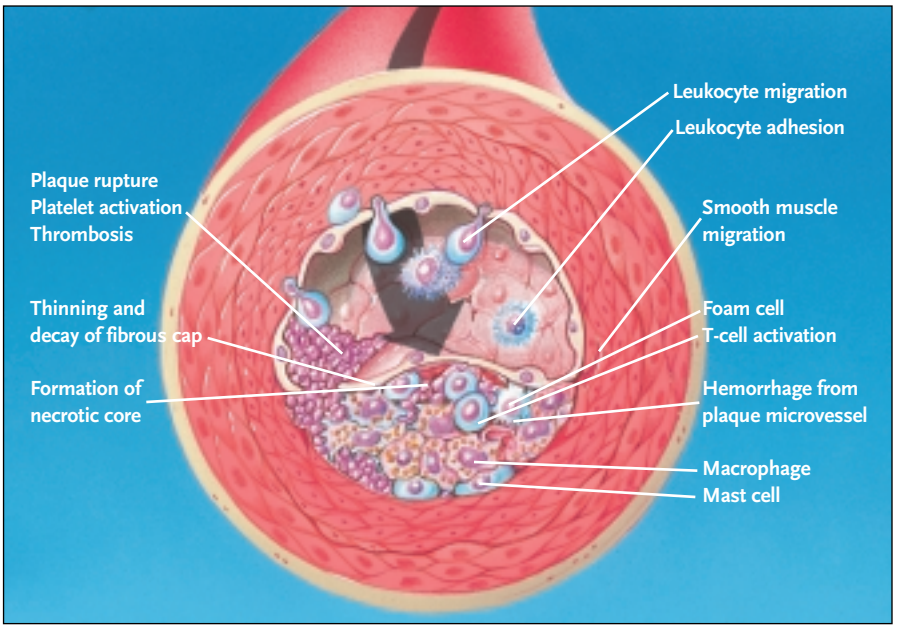


Figure 1. Pathogenesis of the acute coronary syndrome. Vulnerable atherosclerotic plaques (those with a large lipid core, a thin fibrous cap, and inflammatory cells) can rupture. Should the cap rupture, the highly thrombogenic lipid core may become the substrate for thrombus formation that can lead to partial or complete occlusion of the vessel.

The less common causes of UA/NSTEMI include severe spasm of a segment of epicardial artery with only mild coronary atherosclerosis (Prinzmetal angina), severe narrowing of an epicardial coronary artery without thrombus or spasm, and different types of infections resulting in inflammation of the coronary arteries. Severe anemia, fever, tachycardia, and thyrotoxicosis can cause UA/NSTEMI by increasing oxygen demand when myocardial blood flow is compromised by atherosclerotic coronary stenosis.

Initial Evaluation and Risk Stratification

When patients have symptoms that suggest ACS, the likelihood of coronary artery disease (CAD) can be estimated from the medical history, physical examination findings, ECG data, and serum marker measurements. In particular, the diagnostic and prognostic roles of the ECG and serum markers have become better characterized during the past several years. If the likelihood of CAD is intermediate or high, the clinical presentation is used to categorize patients into a low, intermediate, or high level of short-term risk of ischemic events, such as death or nonfatal MI.[3]

ECG. The 12-lead ECG is critical not only for adding support to the clinical suspicion of CAD but also for providing prognostic information (Table 1). Transient ST-segment or T-wave changes that develop during a symptomatic episode at rest and resolve when the patient becomes asymptomatic strongly suggest acute ischemia and a very high likelihood of underlying severe CAD.[6] Inverted

Table 1
ECG Evidence of Unstable Angina

ECG pattern in a patient with possible ACS	Interpretation
Established Q waves ≥ 0.04 s	Suggest high probability of CAD but not strongly diagnostic for UA
Inverted T waves (especially of ≥ 0.1 mV in leads with dominant R waves)	Ischemia or non–Q wave infarction
Normal ECG with chest pain	UA, acute MI, and CAD cannot be ruled out
ST-segment deviation ≤ 0.5 mm	Not strongly diagnostic for UA
Symmetric precordial T-wave inversion ≥ 0.3 mV	Acute ischemia, probably from critical LAD coronary artery stenosis
Transient ST-segment or T-wave changes associated with symptom	Probable acute ischemia; high likelihood of severe underlying CAD
T-wave inversion ≤ 0.1 mV	Not strongly diagnostic for UA

ACS, acute coronary syndrome; CAD, coronary artery disease; UA, unstable angina; MI, myocardial infarction; LAD, left anterior descending.

T waves may indicate ischemia or non–Q wave infarction, especially with T-wave inversion of at least 0.1 mV in leads with dominant R waves. In patients with ACS, symmetric precordial T-wave inversion of at least 0.3 mV strongly suggests acute ischemia—caused, most likely, by a critical stenosis of the left anterior descending coronary artery.[7]

Nonspecific ST-segment and T-wave changes, usually defined as ST-segment deviation no greater than 0.5 mm or T-wave inversion of 0.1 mV or less, are less strongly diagnostic for UA. Established Q waves lasting at least 0.04 second are also less helpful in the diagnosis of UA, although they indicate a high likelihood of significant CAD. A completely normal ECG in a patient with chest pain does not exclude the possibility of ACS, since 1% to 6% of such patients eventually prove to have had an acute MI and since 4% or more will be found to have UA.[8]

The risk of death, based on admission ECG data, is highest when there is a left bundle branch block (LBBB) pattern, paced rhythm, and left ventricular hypertrophy. Risk of death is intermediate with ST-segment deviations and lowest with isolated T-wave changes. In the Thrombolysis in Myocardial Infarction (TIMI)-III Registry, patients with ST-segment depression of 1 mm or greater had an 11% rate of death or nonfatal MI at 1 year, and those with LBBB had rates of 22.9%.[9] In the majority of patients, there were no ECG changes or only isolated T-wave changes; in these patients, the rates of death or MI at 1 year were 6.8% and 8.2%, respectively.

Serum cardiac markers. For patients presenting without ST-segment elevation, serum cardiac markers provide valuable diagnostic and prognostic information. Until recently, CK-MB, the MB isoenzyme of creatine kinase (CK), has been the principal serum cardiac marker used to evaluate patients with ACS. Despite its widespread acceptance, however, CK-MB measurement has several limitations. First, a low level of CK-MB in the blood of healthy individuals limits sensitivity and specificity for detecting myocardial necrosis. Second, CK-MB may be elevated in severe damage of skeletal muscle.[10]

Immunoassays have been developed to detect cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI). Both are sensitive and specific markers of myocyte damage. For the clinical management of patients with ACS, cTnT and cTnI assays are of comparable diagnostic and prognostic efficacy (Table 2). In patients with renal insufficiency, however, cTnI is superior to cTnT.[11] Approximately 30% of patients who present with rest pain but no ST-segment elevation and in whom a misdiagnosis of UA would be made because they do not have elevated CK-MB levels are actually found to have NSTEMI when assessed using cardiac-specific troponin assays.[12]

Elevated levels of cTnI or cTnT convey prognostic information beyond that supplied by the clinical characteristics of the patient, the ECG at presentation, and the predischarge exercise test.[13,14] In patients without ST-segment elevation and normal CK-MB levels, elevated cTnI or cTnT concentrations identify those at an increased

risk for death.[13,15] In addition, there is an almost linear relationship between the cTnI or cTnT level and the risk of mortality in patients presenting with ACS (Figure 2).[13,15,16] Moreover, patients presenting without ST-segment elevation but with elevated cardiac-specific troponin levels may receive a greater benefit from treatment with GP IIb/IIIa inhibitors or low molecular weight heparin (LMWH).[17,18]

The clinical value of serial determinations of myoglobin levels for diagnosing MI is limited by the brief duration of myoglobin level elevation (less than 24 hours) and by lack of cardiac specificity. A negative myoglobin test is extremely useful in ruling out myocardial necrosis, however.

Elevated plasma fibrinogen levels indicate increased risk in patients with ACS.[19] Patients with elevated levels of high-sensitivity C-reactive protein (a marker for acute phase of inflammation) and with no elevation of troponin levels on admission are at increased risk for an adverse outcome.[20] Elevated levels of interleukin-6 and serum amyloid-A also imply an adverse outcome in patients with ACS.[21,22]

Early Hospital Care

Early inhospital care of patients with UA or ACS comprises therapy with antiplatelet agents, anticoagulants, GP IIb/IIIa receptor antagonists, and antiischemic drugs. Effective antiplatelet agents include aspirin (acetylsalicylic acid [ASA]) and the thienopyridines, ticlopidine and clopidogrel. Sulfinpyrazone, dipyridamole, prostacyclin, and prostacyclin analogs have not been associated with benefit in UA. Recommended anticoagulation therapy includes LMWH and direct thrombin inhibitors as well as unfractionated heparin (UFH). Available GP IIb/IIIa receptor antagonists are abciximab, eptifibatide, and tirofiban. Anti-ischemic drugs are nitrates, ß-blockers, and calcium channel blockers and are frequently used in conjunction with angiotensin-converting enzyme inhibitors (ACEIs).

Thrombolytic therapy does not improve clinical outcomes in the absence of acute MI with ST-segment elevation or LBBB.[23,24] A meta-analysis of thrombolytic therapy in patients with UA does not support its use.[2]

Antiplatelet therapy. ASA prevents the formation of thromboxane A_2 by irreversibly inhibiting cyclooxygenase-1 within platelets, thereby diminishing platelet aggregation. Various studies have shown that ASA reduces the risk of death or MI by 51% to 72% in patients presenting with UA.[25-27] In no trial, however, has the efficacy of different doses of ASA been compared. Usually, a dosage of 160 or 325 mg is given to patients with UA. The first dose should be given as soon as the diagnosis of ACS is suspected, and it may be chewed so that a high blood level of ASA is established rapidly.

The thienopyridine drugs inhibit adenosine diphosphate receptors and prevent transformation of GP IIb/IIIa receptors into the high-affinity stage. Two agents—ticlopidine and clopidogrel—are currently approved for antiplatelet therapy. Both are reasonable antiplatelet therapies for secondary prevention and have an efficacy similar to that of ASA.

Ticlopidine is effective for the secondary prevention of stroke and MI. It has also been used for the prevention of stent closure and graft occlusion. In a trial involving 652 patients with UA, ticlopidine reduced the rate of fatal and nonfatal MI at 6 months by 46% (13.6% in patients not taking ticlopi-

Table 2
Using Serum Cardiac Markers in UA/NSTEMI and ACS

- cTnT and cTnI assays have comparable diagnostic and prognostic value when renal function is normal.
- cTnI is superior to cTnT in patients with renal insufficiency.
- Elevated cTnI or cTnT levels predict increased risk of death in patients with normal CK-MB levels and no ST-segment elevation.
- Elevations in cTnI or cTnT levels may allow diagnosis of NSTEMI rather than UA in patients with rest angina, no ST-segment elevation, and normal CK-MB levels.
- Elevations in hs-CRP imply increased risk of poor outcome when troponin levels are normal.
- Elevations in levels of interleukin-6 and serum amyloid-A imply adverse outcome in ACS.
- Elevations in plasma fibrinogen levels suggest increased risk in patients with ACS.

UA, unstable angina; NSTEMI, non–ST-segment elevation myocardial infarction; ACS, acute coronary syndrome; cTnT, cardiac-specific troponin T; cTnI, cardiac-specific troponin I; CK-MB, MB isoenzyme of creatine kinase; hs-CRP, high-sensitivity C-reactive protein.

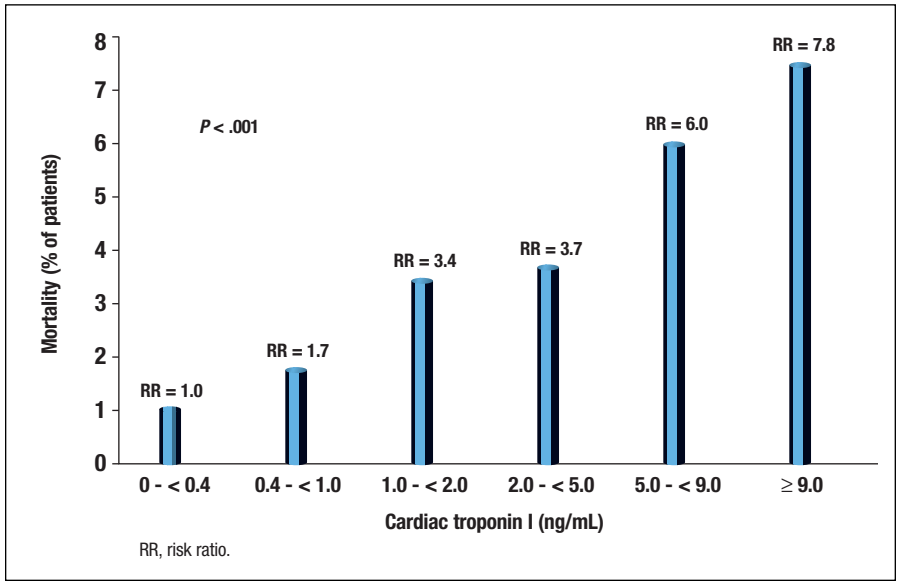


Figure 2. Mortality at 42 days in patients with unstable angina according to baseline levels of troponin I.[15]

dine versus 7.3% in patients taking it, $P = .009$).[28] The benefit of ticlopidine was apparent only after 2 weeks of treatment.

Adverse effects of ticlopidine include GI problems (such as diarrhea, abdominal pain, nausea, and vomiting), mild to moderate neutropenia (in approximately 2.4% of patients), severe neutropenia (in 0.8% of patients), and thrombotic thrombocytopenic purpura (TTP). Neutropenia usually resolves within 1 to 3 weeks after discontinuing therapy but may be fatal (although this is rare). TTP—an uncommon, life-threatening complication—requires immediate plasmapheresis. Patients taking ticlopidine need to be monitored with a complete blood cell count, including a differential count, every 2 weeks for the first 3 months of therapy.

Clopidogrel is at least as effective as ASA and may be slightly more so. In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, 19,185 patients with recent ischemic stroke, recent MI, or symptomatic atherosclerotic peripheral vascular disease were randomized to receive treatment with ASA, 325 mg/d, or clopidogrel, 75 mg/d.[29] The relative annual risk of ischemic stroke, MI, or vascular death was reduced by 8.7% in favor of clopidogrel, from 5.83% to 5.32% ($P = .043$).

A randomized, multicenter trial comparing clopidogrel with ticlopidine, the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), enrolled 1020 patients undergoing coronary stenting.[30] The trial showed better tolerance of clopidogrel, with or without a loading dose, than of ticlopidine. Stent thrombosis and other major complications occurred at the same frequency in all of the groups in the study.

Both clopidogrel and ticlopidine are indicated for patients who have UA but who are unable to tolerate ASA because of hypersensitivity or major GI contraindications, especially gastritis or recent bleeding from a peptic ulcer. Clopidogrel is preferred over ticlopidine because it is more potent, inhibits platelets more rapidly, possesses a longer half-life (making it suitable for once-daily administration), and is safer. Clopidogrel was associated with a very low incidence of neutropenia in the CAPRIE trial, but active surveillance of patients (not necessarily in randomized trials) taking clopidogrel identified 11 instances of TTP over a 2-year period.[31]

For patients with UA who are treated with ticlopidine or clopidogrel, initial treatment with UFH or LMWH is especially important, because the onset of antiplatelet activity is delayed relative to ASA. With ticlopidine, care needs to be taken during the acute phase of illness, because there is a 2-week delay before the full antiplatelet effect is reached.

Anticoagulation therapy. Heparin prevents thrombus propagation but does not lyse existing thrombi.[32] In 2 meta-analyses, 1 involving 3 randomized trials[33] and the other involving 6 trials,[27] the relative risk of death or MI with the combination of ASA and heparin was reduced by 56% ($P = .03$) and by 33% ($P = .06$), respectively.

UFH is a glycosaminoglycan made up of polysaccharide chains ranging in molecular weight from 5000 to 30,000 daltons. It exhibits both anti-Xa and anti-IIa activity, is sensitive to inactivation by platelet factor 4, and binds nonspecifically to plasma proteins and endothelial cells, which compromises its ability to interact with antithrombin. It also has a variable dose-response curve and is relatively inefficient at inhibiting the generation of thrombin because of the length of its polysaccharide chains. It exerts its anticoagulant effect by accelerating the action of circulating antithrombin III, a proteo-

lytic enzyme that inhibits thrombin (factor IIa), factor IXa, and factor Xa.

Most of the benefit of anticoagulants is short-term. Clinical trials have indicated that a weight-adjusted dosing regimen could provide more predictable anticoagulation than the fixed-dose regimen. The weight-adjusted regimen is recommended; a bolus of 60 to 80 U/kg of heparin is given, followed by an initial infusion rate of 12 to 18 U/kg/h, to achieve a target activated partial thromboplastin time (aPTT) in the range of 1.5 to 2.0 times control.

The optimal duration of therapy remains undefined. In most of the trials evaluating the use of UFH in UA, anticoagulation therapy lasted for 2 to 5 days. Mild thrombocytopenia may occur in 10% to 20% of patients receiving heparin and usually appears in the first days of therapy. Severe thrombocytopenia (platelet count lower than 100,000/mL) occurs in 1% to 2% of patients and typically appears after 3 to 5 days of therapy.

A dangerous but rare complication, with an incidence of less than 0.2%, is autoimmune UFH-induced thrombocytopenia with thrombosis (also known as heparin-induced thrombocytopenia [HIT]). Serial platelet counts are necessary to monitor for HIT, and a high clinical suspicion of HIT mandates immediate cessation of all heparin therapy (including that used to flush intravenous lines).

LMWHs are obtained by chemical or enzymatic depolymerization of the polysaccharide chains of heparin to provide smaller chains, with molecular weights ranging from 1000 to 10,000 daltons. LMWHs are more selective in catalyzing the inhibition of factor Xa by antithrombin III and are less selective in inactivating thrombin. The anti-Xa to anti-IIa ratios of different LMWHs vary, ranging from 1.9 to 3.8.[32]

LMWH has distinct clinical advantages over UFH (Table 3). These include less binding to plasma proteins and endothelial cells; dose-independent clearance; and a longer half-life, which results in more reproducible and sustained anticoagulation. As a result, certain LMWHs can be administered subcutaneously twice daily. LMWHs stimulate platelets less than UFH does and are less frequently associated with HIT. Furthermore, monitoring of aPTT is not required with LMWH use.

A disadvantage of LMWH use is that anticoagulation is less effectively reversed with protamine, compared with UFH. As a result, planning is required when coronary artery bypass graft (CABG) surgery is anticipated. In addition, administration of LMWH during percutaneous catheter interventions (PCIs) precludes monitoring of activated clotting time for titrating the dosage of anticoagulant.

In a pilot open-label study by Gurfinkel and colleagues,[34] the combination of ASA and the LMWH nadroparin significantly reduced the total ischemic event rate, the rate of recurrent angina, and the number of intervention procedures. The Fragmin During Instability in Coronary Artery Disease (FRISC) study randomized 1506 patients with UA or non–Q wave MI to receive either the LMWH dalteparin subcutaneously or placebo.[35]

Table 3
Advantages and Disadvantages of LMWHs

Advantages
Administration is subcutaneously, once or twice daily (some LMWHs)
No need for aPTT testing q6h
Incidence of HIT is lower than with UFH
Less binding to plasma proteins and endothelial cells than is UFH
Less stimulation of platelets than is produced by UFH
Longer half-life than has UFH
More reproducible and sustained anticoagulation than with UFH
Superior efficacy in reducing cardiac events and revascularization in UA/NSTEMI
Disadvantages
Anticoagulation more difficult to reverse with protamine, compared with UFH
Planning required when CABG surgery may be necessary
Use during PCI does not permit monitoring of ACT

LMWH, low molecular weight heparin; aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; UFH, unfractionated heparin; UA, unstable angina; NSTEMI, non–ST-segment elevation myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous catheter intervention; ACT, activated clotting time.

Dalteparin was associated with a 63% risk reduction in death or MI during the first 6 days (4.8% versus 1.8%, $P < .001$). At 40 days, a significant decrease was observed in the composite outcome of death, MI, or revascularization (23.7% versus 18%, $P = .005$). There was no difference in the rates of end points after 150 days.

The safety and efficacy of LMWH and UFH in patients with UA have been compared in 4 large randomized trials. These include the Fragmin in Unstable Coronary Artery Disease (FRIC) study,[36] the Fraxiparine in Ischaemic Syndrome (FRAXIS) study,[37] the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) study,[38] and the TIMI-11B trial.[34] Two trials documented a moderate benefit of the LMWH enoxaparin over UFH, and 2 trials, 1 with nadroparin and 1 with dalteparin, reported neutral or unfavorable trends associated with LMWH use (Table 4).

The ESSENCE trial showed that enoxaparin was more effective than UFH in reducing rates of death, MI, or recurrent angina. TIMI-11B confirmed that outcomes with enoxaparin were better than with UFH but also showed that prolonged enoxaparin therapy increased major bleeding without providing additional risk reduction. The conclusion of the FRIC study was that dalteparin may be an alternative to UFH for patients with UA/NSTEMI but that prolonged therapy with dalteparin provided no benefit over ASA and heparin. In the FRAXIS study, outcomes with nadroparin were equivalent to outcomes with UFH, but no additional benefit accrued from the use of nadroparin for longer than 14 days.

The inconsistent outcomes may reflect the fact that the studies used several LMWHs, with different molecular weights and anti-Xa/anti-IIa ratios (3.8, 2.7, and 3.6 for enoxaparin, dalteparin, and nadroparin, respectively). The 2 trials with positive results (ESSENCE and TIMI-11B) used enoxaparin, suggesting that differences among LMWHs may exist. A meta-analysis of these 2 trials, involving a total of 7081 patients, showed a statistically significant reduction of approximately 20% in the rate of death, MI, or refractory ischemia at 2, 8, 14, and 43 days and in the rate of death or MI at 8, 14, and 43 days.[38]

LMWHs are associated with significantly more frequent minor—but not major—bleeding, according to the ESSENCE and TIMI-11B trials. Additional experience with regard to safety and efficacy of concomitant administration of LMWHs with GP IIb/IIIa antagonists and thrombolytic agents is currently being acquired. The FRISC, FRIC, TIMI-11B, and Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC-II) trials evaluated the potential benefit of prolonged administration of LMWH therapy after hospital discharge. The

Table 4
Conclusions From 4 Randomized Trials Comparing Low Molecular Weight Heparin and Unfractionated Heparin in Patients With Unstable Angina

Trial	Regimen	Conclusion
FRIC	Acute phase: dalteparin, 120 IU/kg SC bid; prolonged phase: dalteparin, 7500 IU qd	Dalteparin may be an alternative to UFH for patients with UA/NSTEMI; prolonged therapy with dalteparin at a lower dose qd did not confer any benefit over ASA + heparin
ESSENCE	Enoxaparin, 1 mg/kg SC bid vs IV UFH for 2 - 8 d	Combination enoxaparin + ASA was more effective than UFH + ASA in reducing death, MI, or recurrent angina
TIMI-11B	IV UFH vs enoxaparin for 2 - 8 d; following discharge, UFH group received placebo while enoxaparin group continued therapy for 43 d	Enoxaparin produced better 14-d outcome, compared with UFH; prolonged therapy with enoxaparin provided no additional benefit and was associated with more major bleeding
FRAXIS	IV UFH vs nadroparin for 6 ± 2 d vs nadroparin for 14 d	Nadroparin for 14 d was associated with worse outcome at 90 d, compared with UFH

FRIC, Fragmin in Unstable Coronary Artery Disease; UFH, unfractionated heparin; UA, unstable angina; NSTEMI, non–ST-segment elevation myocardial infarction; ASA, acetylsalicylic acid (aspirin); ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events; MI, myocardial infarction; TIMI-11B, Thrombolysis in Myocardial Infarction; FRAXIS, Fraxiparin in Ischaemic Syndrome.

first 3 of these trials did not show a benefit of treatment beyond the acute phase. In FRISC-II, the composite primary end point of death or MI, or of revascularization was reduced at 3 months ($P = .03$), but the benefits were not sustained at 6 months.[39]

Hirudin is a potent direct thrombin inhibitor that binds the anion binding site and the catalytic site of thrombin without the need for a cofactor. Several large trials comparing hirudin with UFH in patients with UA/NSTEMI have demonstrated a modest reduction in the composite end point of death or nonfatal MI and a modest increase in the risk of bleeding. Hirudin possesses no circulating inhibitor and produces highly reproducible anticoagulation. A long-acting preparation of hirudin (PEG-hirudin) suitable for once-daily subcutaneous administration is currently being investigated.

Based on an analysis that included the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb), the TIMI-9B, the Organisation to Assess Strategies for Ischaemic Syndromes (OASIS)-1, and the OASIS-2 trials, further study of the use of hirudin in the management of UA/NSTEMI seems warranted. According to this analysis, the relative risks of death or MI 35 days after randomization were 0.90 with hirudin, compared with UFH ($P = .15$), 0.88 for patients receiving thrombolytics ($P = .13$), and 0.90 for patients not receiving thrombolytics ($P = .54$).[40]

GP IIb/IIIa receptor antagonists. The GP IIb/IIIa receptor is specific to and abundant on the platelet surface. When platelets are activated, this receptor undergoes a conformational change that increases its affinity for binding fibrinogen and other ligands. Binding of 1 molecule of fibrinogen to receptors on 2 platelets results in platelet aggregation. This mechanism is independent of the stimulus for platelet aggregation and represents the final and obligatory pathway to it.[5] The platelet GP IIb/IIIa receptor antagonists act by occupying the receptor, preventing fibrinogen binding and, thereby, platelet aggregation.

Three GP IIb/IIIa receptor antagonists are currently available—abciximab, eptifibatide, and tirofiban. Abciximab is 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 12 to 24 hours following discontinuation of the drug. Abciximab is not specific for GP IIb/IIIa, however, inhibiting the vitronectin receptor as well.

Eptifibatide is a cyclic heptapeptide, and tirofiban is a nonpeptide. They have half-lives of 2 to 3 hours and are highly specific for the GP IIb/IIIa integrin, with no effect on the vitronectin receptor. Platelet aggregation rapidly returns to normal in the hours that follow the discontinuation of the drug.

These 3 GP IIb/IIIa receptor antagonists have been compared with placebo in 10 large trials involving more than 32,000 patients who had ACS and who underwent PCI.[41] In a meta-analysis incorporating all 10 trials, and for which the end point was risk of death or MI at 30 days, the GP IIb/IIIa was found to be uniformly better than placebo. For the GP IIb/IIIa receptor antagonists, the relative risk of death or MI at 30 days was 0.79 (Figure 3), and this result was highly statistically significant ($P < 10^{-9}$).[41] These studies suggest that GP IIb/IIIa receptor antagonists are useful in the treatment of patients with UA, particularly those at high risk.

Tirofiban as primary medical therapy was studied in the Platelet Receptor Inhibition in Ischemic Syndromes Management (PRISM)[42] and Platelet Receptor Inhibition in Ischemic Syndromes Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS)[43] trials. The PRISM trial compared tirofiban with heparin in 3232 patients with UA/NSTEMI. All patients received ASA. Although the primary composite outcome (rate of death, MI, or refractory ischemia) was reduced from 5.6% with UFH to 3.8% with tirofiban (relative risk, 0.67; $P = .01$) at the end of a 48-hour infusion period, the benefit did not persist at 30 days.

The PRISM-PLUS trial enrolled 1915 patients with UA/NSTEMI. Patients were randomized to receive tirofiban alone, UFH alone, or the combination for 48 to 108 hours. All patients received ASA. The tirofiban-alone arm was dropped during the trial because of excess mortality. The conclusion was that the clinical outcome was better for patients who received tirofiban and heparin than for patients treated with heparin alone.

The incidence of the primary composite end point (death, MI, or refractory ischemia at 7 days) was lower in patients receiving tirofiban and heparin (12.9%) than in patients receiving heparin alone (17.9%; relative risk, 0.68; $P = .004$). This benefit persisted at 30 days ($P = .03$) and at 6 months ($P = .02$). In addition, the end point reflecting incidence of death or nonfatal MI was reduced by 43% at 7 days ($P = .006$), 30% at 30 days ($P = .03$), and 22% at 6 months ($P = .06$).

Eptifibatide as a primary medical therapy was studied in the Platelet

IIb/IIIa Inhibitors in PCI and ACS
Death/MI at 30 days

Trial	Agent	# Patients	% Placebo	% IIb/IIIa
PCI Trials				
EPIC	Abciximab	2099	10.1	7.0
IMPACT II	Eptifibatide	4010	8.4	7.1
EPILOG	Abciximab	2792	9.1	4.0
CAPTURE	Abciximab	1265	9.0	4.8
EPISTENT	Abciximab	2399	10.2	5.2
RESTORE	Tirofiban	2139	6.3	5.1
Unstable Angina/Non–Q wave MI Trials				
PRISM	Tirofiban	3231	7.0	5.7
PRISM Plus	Tirofiban	1570	11.9	8.7
PARAGON	Lamifiban	2282	11.7	11.3
PURSUIT	Eptifibatide	10,948	15.7	14.2
Overall		**32,735**	**11.1**	**9.0**

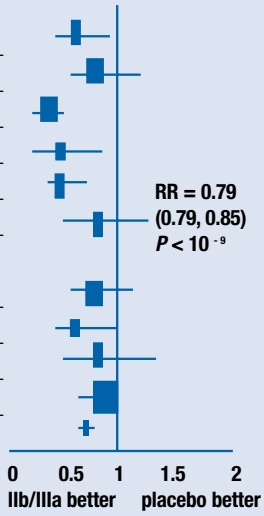


Figure 3. Meta-analysis of 10 randomized, placebo-controlled trials showing benefits of glycoprotein IIb/IIIa inhibitors in patients with unstable angina and percutaneous catheter interventions.[45] (PCI, percutaneous catheter intervention; ACS, acute coronary syndrome; MI, myocardial infarction.)

Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT)[44] trial, which enrolled 10,948 patients with ACS (without persistent ST-segment elevation). All patients could receive ASA and heparin. The primary outcome of death or nonfatal MI at 30 days was reduced from 15.7% to 14.2% with eptifibatide (relative risk, 0.91; P = .042). Within the first 96 hours, a substantial treatment effect was seen (9.1% versus 7.6%, P = .01), and this effect was sustained at 1 week (11.6% versus 10.1%, P = .02). The high event rate reported in this trial was due primarily to small elevations in CK-MB concentration.

Abciximab has been studied mainly in trials of percutaneous coronary revascularization. These are the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC),[45] Evaluation of PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa Receptor Blockade (EPILOG),[46] c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE),[47] and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT)[48] trials. Its use has consistently been associated with significant reductions in both the rate of MI and the need for urgent revascularization. PRISM, PRISM-PLUS, and the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE)[49] evaluated tirofiban. The Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT)[50] and PURSUIT trials studied the use of eptifibatide. Overall, these trials showed a relative risk of 0.79, compared with placebo (an incidence of death or MI at 30 days of 9% with a GP IIb/IIIa receptor antagonist versus 11.1% for placebo, $P < 10^{-9}$).[41]

Unlike trials involving balloon angioplasty, the EPISTENT trial was designed to evaluate the efficacy of abciximab as an adjunct to elective coronary stenting. The adjunctive use of abciximab was associated with a significant reduction in the composite clinical end point of death, MI, or urgent revascularization. The 30-day primary end point occurred in 10.8% of the patients who received a stent and placebo, in 5.3% of the patients who received a stent and abciximab, and in 6.9% of patients who underwent balloon angioplasty (without stent placement) and received abciximab ($P < .001$).[48] Most of the benefit from abciximab was related to a reduction in the incidence of moderate to large MI (defined by the presence of CK levels exceeding 5 times the upper limit of normal or a Q wave MI). At 1 year,

stented patients who received abciximab had a lower mortality than did patients who received stents without abciximab (0.8% versus 2.4%, representing a 67% risk reduction; $P = .01$).

Treatment with a GP IIb/IIIa receptor antagonist increases the risk of bleeding. Typically, such bleeding is mucocutaneous or involves the access site of vascular intervention. No trial has shown an excess of intracranial bleeding with a GP IIb/IIIa inhibitor. ASA and heparin have been used with the intravenous GP IIb/IIIa receptor antagonists in all trials.

Throughout the period of use of a GP IIb/IIIa receptor antagonist, hemoglobin concentration and platelet count should be monitored and surveillance of patients for bleeding should be carried out daily. Thrombocytopenia is an unusual complication with these agents. Severe thrombocytopenia (platelet counts lower then 50,000/mL) and profound thrombocytopenia (platelet counts lower than 20,000/mL) are seen in 0.2% and 0.5% of patients, respectively.

Long-term anticoagulation with warfarin. The long-term administration of warfarin has been evaluated in only a few studies. Based on them, the evidence supporting the use of long-term anticoagulation combined with standard ASA therapy in patients with ACS is inconclusive.

The Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial[33] showed that there was a reduction in the composite end point of death, MI, and recurrent ischemia rates at 14 days with combination therapy that included ASA and warfarin compared with ASA alone (27% versus 10.5%, $P = .04$). The difference was not significant after 12 weeks, however.

The OASIS pilot study[51] showed that low-intensity warfarin (fixed-dose therapy at a dosage of 3 mg/d) had no benefit, whereas the moderate-intensity regimen (with warfarin dosage adjusted to achieve an international normalized ratio of 2.0 to 2.5) reduced the risk of death, MI, or refractory angina by 58% at 3 months (12.1% in the standard-therapy group and 5.1% in the warfarin-treated group, $P = .08$). A larger OASIS trial,[52] in which patients were randomized either to a moderate-intensity regimen of warfarin or to standard therapy (with ASA given to both groups), did not show differences in the rate of cardiovascular death, MI, or stroke after 5 months.

Use of anti-ischemic drugs. Routine medical management should include the use of nitrates, ß-blockers, and calcium channel blockers. Both the Fourth International Study of Infarct Survival (ISIS-4)[53] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3)[54] trials, involving patients with suspected acute MI, failed to show a significant mortality benefit associated with nitrates. Use of nitroglycerin in UA, however, has been shown to reduce incidence and severity of angina and improve clinical stability. An overview of double-blinded, randomized trials in which ß-blockers were used in patients with threatening or evolving MI suggests that the risk of progression to acute MI is reduced by approximately 13% with appropriate ß-blockade.[55]

Calcium channel blockers may be used to control ongoing or recurring ischemia-related symptoms in patients already receiving adequate doses of ni-

Main Points

- Assays of cardiac-specific troponin T and cardiac-specific troponin I (cTnI) provide equivalent diagnostic and prognostic information in most patients with acute coronary syndrome. Measurement of cTnI levels is more reliable in patients with renal insufficiency.
- Patients with unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI) and high short-term risk of death or nonfatal MI are candidates for aggressive therapy with ß-blockade, antithrombins, glycoprotein (GP) IIb/IIIa receptor antagonists, and aspirin.
- GP IIb/IIIa receptor antagonists are effective in reducing cardiac event rates in the acute phase of medical management of UA/NSTEMI; this benefit is magnified in patients who undergo percutaneous catheter interventions.
- Low molecular weight heparin may offer significant advantages over unfractionated heparin (UFH); however, if immediate revascularization is anticipated, the use of UFH may be preferable.
- Following acute MI, angiotensin-converting enzyme inhibitors reduce mortality in patients with left ventricular dysfunction and are recommended in patients with hypertension not controlled by ß-blockers and nitrates and in patients with diabetes.
- Consider coronary artery bypass graft surgery specifically for the patient with significant left main coronary artery disease (CAD) or for the patient with multivessel CAD and depressed left ventricular function.

Table 5
Noninvasive Test Results Indicating High-Risk Coronary Artery Disease[62,63]

Consider coronary angiography and possible revascularization when patients have any of these findings on noninvasive tests:

Exercise ECG testing
Angina during exercise
Duration of symptom-limited exercise < 6 METS
Exercise-induced ST-segment elevation except in lead aVR
Flat SBP response ≤ 130 mm Hg with progressive exercise
Horizontal or downsloping ST-segment depression (any of the following situations):
Involving multiple (≥ 5) leads
Lasting ≥ 6 min into recovery
Onset at heart rate ≤ 120 bpm
Onset at ≤ 6.5 METS
ST-segment depression ≥ 2 mm
Sustained decrease in SBP ≥ 10 mm Hg with progressive exercise
Sustained or symptomatic VT with exercise
Stress radionuclide myocardial perfusion imaging
Increased pulmonary radiotracer uptake after exercise
Large reversible anterior wall defect
Multiple reversible defects in 2 or more coronary artery regions
Transient LV dilatation immediately after exercise
Left ventricular imaging (stress radionuclide ventriculography)
Decrease in EF ≥ 10%
Exercise EF ≤ 50%
Resting EF ≤ 35%

METS, metabolic equivalents of tasks; SBP, systolic blood pressure; bpm, beats per minute; VT, ventricular tachycardia; LV, left ventricular; EF, ejection fraction.

trates and ß-blockers and in patients with variant angina. Several meta-analyses incorporating data for all of the calcium channel blockers reportedly used in ACS, however, have indicated that there is no overall benefit in mortality reduction or MI prevention associated with these agents.[55,56] Moreover, controlled trials suggest that adverse outcomes in patients with ACS are more frequent with the use of rapid-release, short-acting dihydropyrimidines when concurrent ß-blockade is inadequate.[57,58]

ACEIs have been shown to reduce mortality in patients with acute MI with left ventricular dysfunction,[59] in diabetic patients with left ventricular dysfunction following recent MI, and in a broad spectrum of patients with chronic CAD. Accordingly, ACEIs should be used in such patients as well as in patients with hypertension not controlled with ß-blockers and nitrates. There is a trend toward the use of ACEIs and away from the use of calcium channel blockers in patients discharged from hospitals following MI. Postdischarge ASA use has increased to 88%; ß-blocker use, to 65%; and ACEI use, to 33%.[60] Calcium channel blocker use has decreased to 18%.[52]

Risk Stratification After Initial Stabilization

It is important to differentiate between patients who need prompt angiography without noninvasive testing and those who can safely undergo further noninvasive testing for risk stratification. Prompt angiography without noninvasive risk stratification is required when medical treatment has failed to stabilize a patient's condition. In general, noninvasive stress testing should be done in patients who have been free of angina at rest, of angina during low-level activity, and of congestive heart failure for a minimum of 24 to 48 hours and who are not otherwise considered to be at high risk.

Noninvasive test selection. The choice of stress test should be based on the resting ECG, the ability to perform exercise, and the local expertise and technologies available.[61] Exercise stress testing without imaging is appropriate for the patient who is able to exercise and whose resting ECG is normal. For the patient who is able to exercise and whose resting ECG shows LBBB, left

ventricular hypertrophy, an intraventricular conduction delay, a preexcitation pattern, or a digoxin effect, consider exercise stress testing with imaging. Patients unable to exercise are candidates for pharmacologic stress testing with imaging.

Patients with definite ACS should undergo echocardiography or radionuclide angiography to evaluate left ventricular function. Those whose noninvasive test results predict a high risk for adverse outcome should be referred for coronary angiography and revascularization (Table 5).[62,63]

It is important to perform stress tests at the appropriate time following diagnosis of UA/NSTEMI. Stress testing using a standard protocol can be performed as soon as the patient's clinical condition has stabilized and the patient has been free of ischemic symptoms for 24 to 48 hours. In a study of 189 patients, symptom-limited exercise testing performed 3 to 7 days after an episode of UA or non–Q wave MI correctly predicted those who would develop adverse events during the first month.[64] This illustrates the importance of early noninvasive testing for risk stratification.

Selection of early management strategies. Several randomized trials and observational studies have been carried out to resolve the question of whether an early conservative approach or an invasive approach is preferred. The TIMI-IIIB,[23] the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH),[65] and FRISC-II[66] trials were randomized.

In the TIMI-IIIB trial, 15.5% of patients who underwent an early invasive approach and 17.7% of those treated with an early conservative approach reached the primary composite end point of death, MI, or a positive symptom-limited exercise test at 6 weeks (P = .26). There was no difference in the rate of death or MI between the 2 treatment groups.

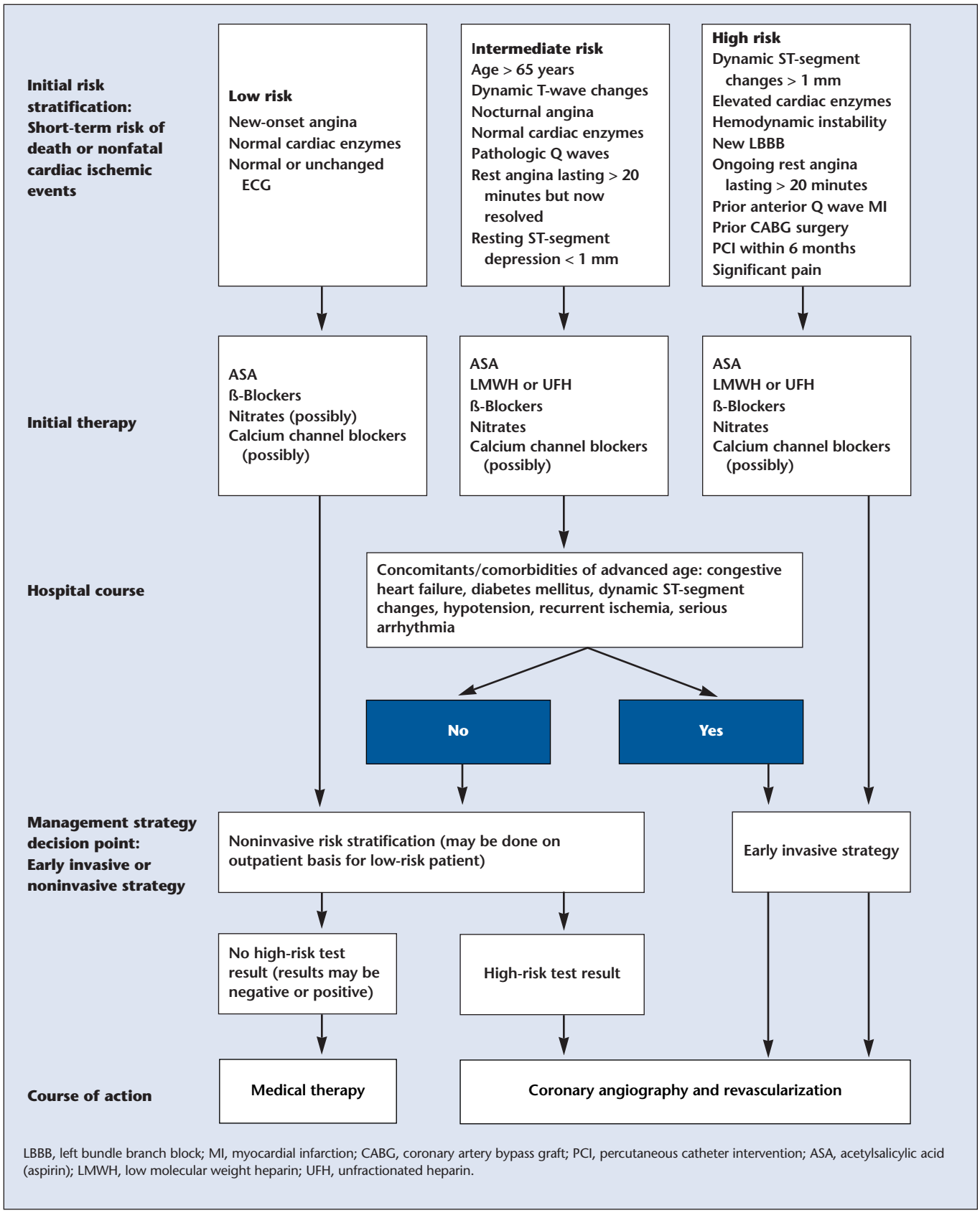
In the VANQWISH trial,[65] the number of patients who died or sustained nonfatal MI and the number who died were consistently higher in the group managed with the invasive strategy than in the group managed conservatively. At hospital discharge, 36 patients in the invasive-assessment group died or sustained nonfatal MI, compared with 15 patients in the conservative-care group (P = .004); 21 patients in the invasively managed group died, compared with 6 in the conservatively managed group (P = .007). At 1 month, 48 patients died or had nonfatal MI with invasive management and 26 did so with conservative care (P = .012); there were 23 deaths in the invasively managed group and 9 in the conservatively managed group (P = .021). At 1 year, 111 patients evaluated invasively and 85 evaluated conservatively died or had nonfatal MI (P = .05); 58 invasively managed and 36 conservatively managed patients died (P = .025). These results could be explained by the fact that the mortality was higher (11.6%) among patients undergoing CABG surgery in the early invasive approach group than among the early conservative approach group (3.4%).

In the FRISC II trial,[66] at 6 months, death or MI occurred in 9.4% of patients assigned to the invasive strategy and in 12.1% of those assigned to the noninvasive strategy (P = 0.03).[58] The mortality associated with the invasive strategy was 1.9%, compared with 2.9% for the noninvasive strategy (P = .10). This showed that patients who are not at high risk for revascularization and who receive 5 to 10 days of treatment with dalteparin, ASA, nitrates, and ß-blockers have a lower likelihood of MI or death with an early invasive approach than with the standard conservative approach.

The TIMI-IIIB, VANQWISH, and FRISC-II trials were performed before stents and GP IIb/IIIa receptor antagonists were used. These data, therefore, need to be applied with caution today, when stents and GP IIb/IIIa receptor antagonists are available. In the OASIS Registry,[67] there were no differences in the rates of death or MI between countries with the highest rates of invasive procedures (59%) and countries with lower rates (21%).

Among the patients randomized to the conservative strategy in the TIMI-IIIB trial, factors independently predicting failure of medical therapy were the presence of reversible ST-segment deviation, a history of angina, prior use of ASA or heparin, a family history of premature CAD, and older age.[68] As the number of risk factors increased, so did the incidence of failure of medical therapy (from 32% in patients with 1 risk factor to 88% in patients with 6 risk factors). Such factors should be considered when selecting patients for expedited angiography and revascularization.

To evaluate for revascularization, an early invasive strategy involving prompt coronary angiography is recommended for patients who have specific signs and symptoms despite intensive anti-ischemic therapy. Such signs and symptoms include recurrent anginal ischemia, at rest or with low-level activities, and angina accompanied by evidence of congestive heart failure, an S_3 gallop, or new or worsening mitral regurgitation.[69] In addition, an early invasive strategy is advised in the patient with high-risk findings on



LBBB, left bundle branch block; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous catheter intervention; ASA, acetylsalicylic acid (aspirin); LMWH, low molecular weight heparin; UFH, unfractionated heparin.

Figure 4. Approach to the management of patients with unstable angina based on short-term risk of death or nonfatal cardiac ischemic events and on decision to pursue early invasive or noninvasive strategy.

noninvasive stress testing, depressed left ventricular systolic function, hemodynamic instability, or sustained ventricular tachycardia. In the absence of such findings, an early conservative approach appears acceptable.

Coronary Revascularization

PCI or CABG surgery is done to improve prognosis, relieve symptoms, prevent ischemic complications, and improve functional capacity. Patients with UA/NSTEMI and high-risk features will benefit from coronary revascularization. Such high-risk anatomic or disease-related features include left main CAD with greater than 50% stenosis, left main equivalent CAD, 3-vessel disease, CAD involving the proximal left anterior descending (LAD) coronary artery with 1- or 2-vessel disease, and 1- or 2-vessel disease without proximal LAD disease but with a large area of ischemia.

The indications for PCI and CABG surgery in UA/NSTEMI are similar to those in stable angina. In general, CABG surgery is clearly recommended in patients with significant left main CAD and in patients with multivessel CAD and depressed left ventricular function.[70]

Postdischarge Care

The acute phase of UA/NSTEMI is usually over within 2 months, after which time most patients resume a clinical course similar to that of patients with chronic stable CAD. Medical therapy after discharge from the hospital should include medications to prevent future coronary events (ranging from ischemia to MI and death), control ischemic symptoms, and modify major risk factors to the extent possible and practical.

Pharmacotherapy. Medications to prevent premature death and MI in the patient who has had UA/NSTEMI are ASA, ß-blockers, ACEIs, and lipid-lowering agents, which should be used in conjunction with dietary and lifestyle modifications. The ASA dosage is 75 to 160 mg/d. ß-Blockade is indicated whether or not the patient has had an MI. Lipid-lowering agents and dietary modification are appropriate for any patient whose serum low-density lipoprotein (LDL) cholesterol level exceeds 100 mg/dL. In particular, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are recommended. ACEIs are especially important if there is left ventricular dysfunction, the ejection fraction in less than 40%, or the patient is diabetic.

Patient education and support. It is necessary to educate the patient regarding the importance of lifestyle changes and awareness of general cardiac-related health issues. Such education is as much a part of comprehensive care as is pharmacotherapy.

Key risk-reduction measures are smoking cessation, achievement or maintenance of optimal weight (with a low-fat diet), aerobic exercise, and control of hypertension and diabetes mellitus. Secondary prevention trials with simvastatin and pravastatin have amply demonstrated the profound impact of lowered LDL cholesterol levels on event-rate reduction, underscoring the need to reach LDL cholesterol levels of less than 100 mg/dL.

The optimal time to initiate lipid-lowering measures after an episode of ACS is unclear. A practical approach would involve initiating lipid-lowering efforts as soon as possible, or they may be forgotten completely.

UA/NSTEMI Management: Overview and Summary

The history, physical examination findings, 12-lead ECG, and initial serum marker assays help differentiate patients with UA into those with low, intermediate, or high short-term risk of death or nonfatal ischemic events (Figure 4).[71] Patients with a low short-term risk may be observed in a facility where cardiac monitoring is available, such as a chest pain unit. Subsequent ECG and serum marker measurements should be obtained 4 to 8 hours after the first battery.

If the results of follow-up 12-lead ECG and serum marker measurements are normal, an exercise stress test or stress myocardial perfusion imaging may be performed to provoke ischemia. Patients with a negative stress test result can be managed as outpatients. Patients with a high-risk stress test result should be referred for coronary angiography and for revascularization.

Patients with UA/NSTEMI and high-risk features should be admitted to a coronary care unit and aggressively treated with standard medical therapy. This includes ASA, ß-blocker, antithrombin therapy, and a GP IIb/IIIa inhibitor. After initial stabilization, such patients should undergo early coronary angiography and revascularization.

Patients with intermediate-risk features should be hospitalized and carefully observed for complications, such as sustained ventricular tachycardia or fibrillation, sinus tachycardia, atrial fibrillation or flutter, high-degree atrio-

ventricular block, sustained hypotension, recurrent ischemia (documented by symptoms or ST-segment change), any new mechanical defect (such as a ventricular septal defect or mitral regurgitation), or pulmonary edema. If such complications develop, initial stabilization with aggressive medical therapy, followed by an early invasive strategy, should be carried out.

Other intermediate-risk patients may undergo the initially conservative strategy, which includes early, noninvasive risk stratification. Further decision making must be based on the results of noninvasive testing. The early use of a reliable risk stratification strategy may help provide both medically optimal and economically acceptable care for patients. ■

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