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Medical Treatment of Unstable Angina, Acute Non–ST-Elevation Myocardial Infarction, and Coronary Artery Spasm

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Key Points

- Unstable angina and non–ST-elevation myocardial infarction (NSTEMI) are usually caused by coronary artery atherosclerotic plaque fissuring or ulceration with subsequent transient and repetitive thrombosis and vasoconstriction with unstable angina, and slightly more prolonged but still transient or subtotal coronary artery occlusion and vasoconstriction in the patient with NSTEMI.
- Patients with increased serum levels of C-reactive protein (CRP) or of a troponin should be referred for coronary arteriography and percutaneous coronary intervention (PCI) or surgical revascularization when their coronary artery anatomy is appropriate. Recent data suggest referral for PCI or coronary artery bypass graft (CABG) is also appropriate for patients with elevations of multiple serum biomarkers, for example, CRP, troponin, and brain naturetic peptide (BNP) and for those with elevated Thrombosis in Myocardial Infarction (TIMI) risk scores (three or more of the following: age of 65 years or older, at least three risk factors for coronary heart disease, prior coronary artery stenosis of 50% or greater, ST segment deviation on the electrocardiogram (ECG) on presentation, at least two anginal events in prior 24 hours, use of aspirin in prior 7 days, and elevated serum cardiac markers).
- Recent studies have suggested that many patients with these coronary artery syndromes have coronary arterial plaque inflammation and a vulnerable atherosclerotic plaque(s).
- Initial medical treatment of these acute coronary syndromes includes aspirin, heparin (either low molecular weight or unfractionated), clopidogrel (Plavix), and a beta-blocker if blood pressure or heart rate are elevated. A platelet glycoprotein IIb/IIIa inhibitor is added in those with continuing angina at rest or in those with known or suspected complex coronary anatomy and in the diabetic patient undergoing PCI. Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are added to the acute and chronic medical management regimen when there are no contraindications.

The development of unstable angina with a crescendo or a rest angina pattern, or both (Braunwald classification IIIB and C, Table 39.1), should be considered a relative medical emergency and warrant hospitalization to rule out myocardial infarction (MI) and to initiate therapy that might prevent MI.[1–28] Patients presenting with sustained and more severe chest pain; electrocardiographic changes of ST deviation, usually depression and T-wave flattening or inversion; elevated serum creatine kinase, the MB isoenzyme of creatine

TABLE 39.1. Braunwald's classification of unstable angina

	Clinical circumstances		
Severity	*A. Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)*	*B. Develops in absence of extracardiac condition (primary UA)*	*C. Develops within 2 weeks after AMI (postinfarction UA)*
I. New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II. Angina at rest within past month but not within preceding 48 hours (angina at rest, subacute)	IIA	IIB	IIC
III. Angina at rest within 48 hours (angina at rest, acute)	IIIA	IIIB	IIIC

AMI, acute myocardial infarction; UA, unstable angina.

Patients with UA may also be divided into three groups depending on whether UA occurs (1) in the absence of treatment for chronic stable angina, (2) during treatment for chronic stable angina, or (3) despite maximal antiischemic drug therapy. These three groups may be designated by subscripts 1, 2 or 3, respectively.

kinase; and either troponin I or T concentrations have non–ST-elevation myocardial infarction (NSTEMI) (non–Q-wave MI) and are treated in the same manner as patients with unstable angina (Fig. 39.1). The medical treatment regimen attempts to prevent persistent thrombus formation at the site of the unstable plaque(s) and to relieve the associated vasoconstriction. Aspirin is begun immediately in patients without contraindication. Intravenous nitroglycerin is initiated beginning at doses of 1 to 2 μg/min with increases in dosage in increments of 5 μg/min to reduce systolic blood pressure to the 100 to 120 mm Hg range while avoiding systemic arterial hypotension or increases in heart rate above 100 beats/min. Pain relief often occurs after complete bed rest and the institution of intravenous nitroglycerin and aspirin. Elevated blood pressure should be controlled with nitrates, an angiotensin-converting enzyme (ACE) inhibitor, and/or a beta-blocker. Patients with rest angina should be given heparin, unless it is contraindicated. This may be unfractionated heparin given intravenously,[1] typically beginning with a bolus dose of approximately 3000 to 5000 units and followed by a sustained infusion of 900 to 1000 U/h. The partial thromboplastin time (PTT) [or activated coagulation time (ACT)] is followed at 8- to 12-hour intervals, and the heparin infusion rate is adjusted usually on a weight-based regimen to maintain the PTT in the 60- to 80-second range or the ACT in the 250- to 350-second range. Alternatively, low molecular weight heparin may be given in appropriate dosage subcutaneously.[10–12] Clopidogrel is an adenosine diphosphate (ADP) antagonist, and it is additive to aspirin in preventing thrombosis and protective in patients with acute coronary syndromes (ACS).[12,14,25,28] It is given to patients initially with a loading dose of 300 mg orally followed by 75 mg per day. Angiotensin-converting enzyme (ACE) inhibitors should be considered in the acute and chronic medical management of these patients when blood pressure and renal function allow. Angiotensin II promotes inflammation in addition to its vasoconstrictor effects, and ACE inhibitors are likely to decrease inflammation as they protect coronary arteries.[29] However, elevated serum blood urea nitrogen (BUN) and creatinine may increase further with ACE therapy, especially in the patient with unilateral or bilateral renal artery stenoses, limiting their utility. Angiotensin-converting enzyme inhibitors may promote potassium retention and should be avoided in the patient with hyperkalemia. Immediate serum cholesterol and low-density lipoprotein (LDL) lowering with a statin is also desirable; prompt rapid lowering of total serum cholesterol and LDL with a statin, such as atorvastatin (Lipitor) has been shown to reduce the risk of future events in patients with ACS.[30–32] Beta-blockers should be added to this therapy in the patient without contraindications who has elevated blood pressure, increased heart rate due to pain or anxiety, or complex ventricular ectopy.

Evidence-Based Overview of Specific Therapies

Aspirin and Heparin

One to four aspirin per day reduces the risk of death and MI in the patient with unstable angina (Fig. 39.2).[1–3] However, recent studies suggest that acetylsalicylic acid (ASA) may not reduce the risk of MI in healthy postmenopausal women.[33] Aspirin diminishes platelet aggregation and thromboxane A_2 synthesis and diminishes inflammation and platelet-white blood cell interactions. The combination of aspirin and heparin inhibits the effects of thromboxane A_2 and thrombin as potentiators of platelet aggregation, leading to thrombosis and dynamic vasoconstriction. Their inhibition of thromboxane A_2 and thrombin improves regional myocardial blood flow and helps prevent thrombosis. Heparin (either unfractionated or low molecular weight heparin) should be given to the patient with rest angina in whom there is no contraindication. Théroux and associates[1] have shown that the administration of heparin often relieves angina and reduces the risk for subsequent MI and death (Fig. 39.2). In their study, aspirin was also effective in reducing fatal and nonfa-

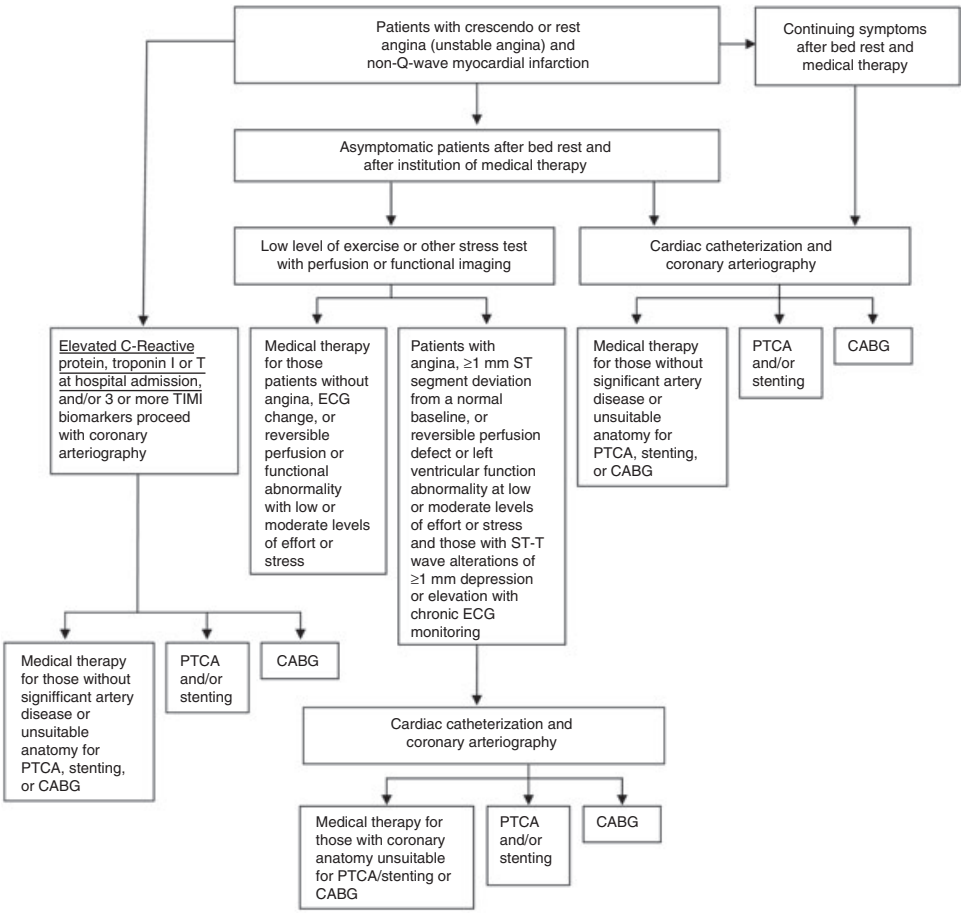


FIGURE 39.1. Schematic diagram demonstrates therapeutic alternatives for the treatment of patients with unstable angina pectoris and NSTEMI. ADP, adenosine diphosphate; CABG, coronary artery bypass grafting; ECG, electrocardiogram; PTCA, percutaneous transluminal coronary angioplasty.

tal MIs. Others have shown similar protective effects from aspirin therapy in these patients.[2–4] The combination of aspirin and heparin increases the risk of bleeding.[1] Abrupt withdrawal of heparin in the patient with unstable angina or MI may be associated with a heparin "rebound," with abrupt worsening of angina, the development of MI, or both.[5–7] When heparin and other thrombin inhibitors are discontinued in these patients, it should be done slowly over a period of several hours and with concomitant administration of aspirin and usually other antiplatelet therapy, including clopidogrel.

More specific thrombin inhibitors are being developed, and there are other pharmacologic inhibitors of thrombus available. Low molecular weight heparins are useful alternatives to unfractionated heparin in the patient with unstable angina or NSTEMI.[8–13] The use of low molecular weight inhibitors of heparin is discussed later in this chapter.

The direct thrombin antagonists are useful alternatives to heparins in patients who develop thrombocytopenia or vascular thrombosis, or bleeding as an allergic response to heparin administration—heparin-induced thrombocytopenia (HIT) and heparin-induced thrombosis syndrome (HITS) (see Chapter 113: Hematologic Disease and Heart Disease). The direct inhibitors of thrombin have more reliable and consistent effects on PTT than does heparin, allowing much less frequent measurement of PTT or ACT. Indeed, patients given direct thrombin antagonists may be managed without follow-up measurements of their PTT or ACT.

Clopidogrel and Platelet IIb/IIIa Receptor Antagonists

Other mediators that promote thrombosis and are present at the site(s) of a fissured or ulcerated plaque(s) are not inhibited by this regimen, including ADP, serotonin, platelet-activating factor (PAF), oxygen-derived free radicals, tissue factor, and endothelin (Fig. 39.2B). If pain relief does not occur with bed rest and the use of intravenous nitrates, aspirin, and a heparin, the risk for subsequent MI, sudden death, and ventricular arrhythmias is increased. More comprehensive inhibitors of platelet aggregation than aspirin and heparin, inhibiting platelet aggregation in response to most or all of these mediators, can be useful in the treatment of these patients, including the addition of an ADP antagonist, such as clopidogrel,[14] or an inhibitor of platelet glycoprotein (GP) IIb/IIIa receptors, including the monoclonal antibody abciximab (ReoPro), the synthetic peptide inhibitor eptifibatide (Integrilin), or a low molecular weight inhibitor, such as

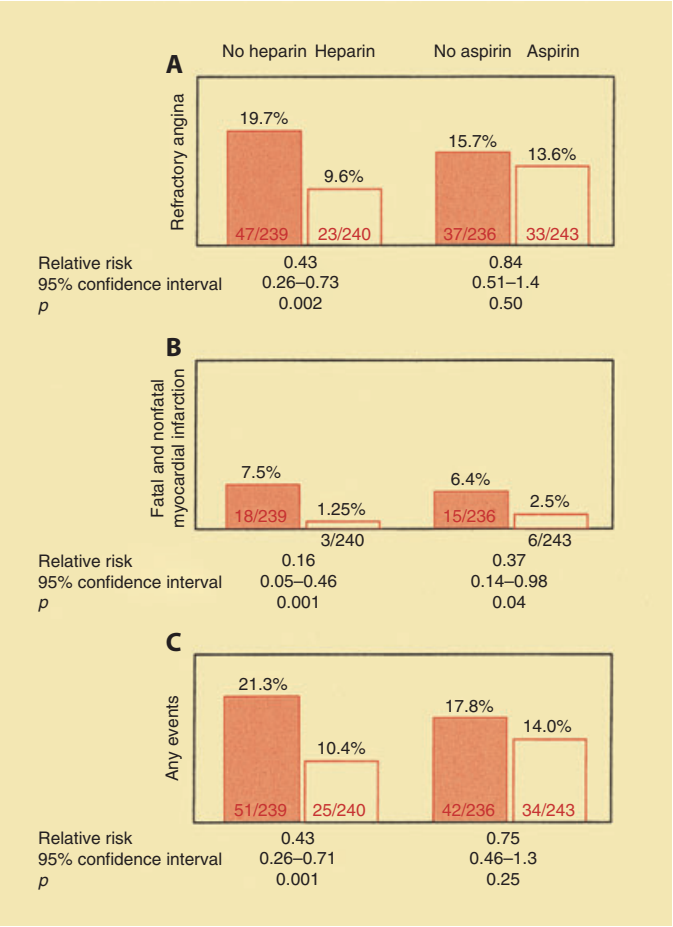


FIGURE 39.2. (A–C) The influence of aspirin and heparin in the treatment of patients with unstable angina pectoris. Both aspirin and heparin (B) reduce the risk for fatal and nonfatal myocardial infarction (MI). Heparin also reduces the frequency of important coronary events, including death, fatal and nonfatal MI, and continuing angina. The combination of heparin and aspirin was no more successful than heparin alone in this study.

tirofiban.[15–18] These therapies are discussed in detail later in this chapter.

If rest angina persists or blood pressure or heart rate are elevated, the addition of a beta-blocker is recommended. A platelet GP IIb/IIIa receptor antagonist may be added to this therapeutic regimen in the patient who continues to have rest angina despite this medical regimen, and who will undergo interventional therapy, such as percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA), or stenting. The platelet GP IIb/IIIa inhibitors seem especially useful in the diabetic patient[18] and in those patients with elevations of a serum troponin who will undergo PCI.[15–17] One should consider the addition of intraaortic balloon counterpulsation if rest angina persists despite the medical therapy outlined above (Fig. 39.3). Intraaortic balloon counterpulsation almost always relieves rest pain in the patient with unstable angina or NSTEMI. In patients with continuing rest angina requiring such intensive combined therapy, proceeding to coronary arteriography and PCI, or coronary artery bypass graft surgery (CABG) is urgently needed.

Low Molecular Weight Heparin

The disruption of an atherosclerotic plaque causes platelet activation, adhesion, and aggregation at the site of the injured plaque and activates the coagulation cascade through tissue factor release and the accumulation of multiple platelet and other cell-derived mediators of thrombosis. Tissue factor complexes with factor VIIa activate factor Xa, thereby catalyzing formation of thrombin (Fig. 39.4). Thrombin promotes further platelet aggregation, vasoconstriction at the site(s) of vascular injury, and mediates the conversion of fibrinogen to fibrin. Since both platelet activation and thrombin generation are involved in the thrombotic process, there is an obvious rationale for the use of inhibitors of both platelet aggregation and coagulation in the treatment of the patient with unstable angina or NSTEMI (and patients with STEMI). Low molecular weight heparins act primarily through antithrombin III–mediated inhibition of factor Xa, but there is also some direct thrombin inhibition. There is evidence that anti-Xa activity relates to survival and efficacy in ACS patients treated with enoxaparin.[19] Patients with low anti-Xa activity on enoxaparin treatment have a lower mortality rate at 30 days when anti-Xa activity was <0.5IU/mL.[19] As is true of conventional heparin, low molecular weight heparin promotes the release of tissue factor pathway inhibitor (TFPI), which may contribute to its antithrombotic effects.[20–22]

Low molecular weight heparin is administered subcutaneously. It has a low degree of protein binding and a predictable anticoagulant response for a given dose without the need for laboratory monitoring of PTT or ACT values.[20,21] Therefore, one can provide a consistent anticoagulant and antithrombin effect by subcutaneous injections of fixed doses of low molecular weight heparin, generally on a two-times-per-day basis.[20–22] It is usually avoided in patients with elevated serum creatinine values of ≥2.5 mg/dL because renal insufficiency potentiates the effect of any particular dose. Instead, unfractionated heparin is given to these patients. In patients with HIT or HITS, low molecular weight heparin may still not be safe, as there is some cross-reactivity between the heparin antibody and low molecular weight heparin. Here, a direct acting thrombin inhibitor is needed if an inhibitor of thrombin is to be used.

Frisc Study

The influence of low molecular weight heparin in patients with unstable angina pectoris or non-STEMI was evaluated in the Fragmin During Instability in Coronary Artery Disease (FRISC) study.[20] In this double-blind trial, 1506 patients were randomly assigned to receive a low molecular weight heparin, subcutaneous dalteparin (Fragmin), 120IU/kg body weight with a maximal dose of 10,000IU given twice daily for 6 days and then 7500IU once daily for the next 35 to 45 days, or placebo. The primary end point was the rate of new MI and death during the first 6 days after beginning treatment. Secondary end points were rates of death and new MI after 40 and 150 days, respectively;

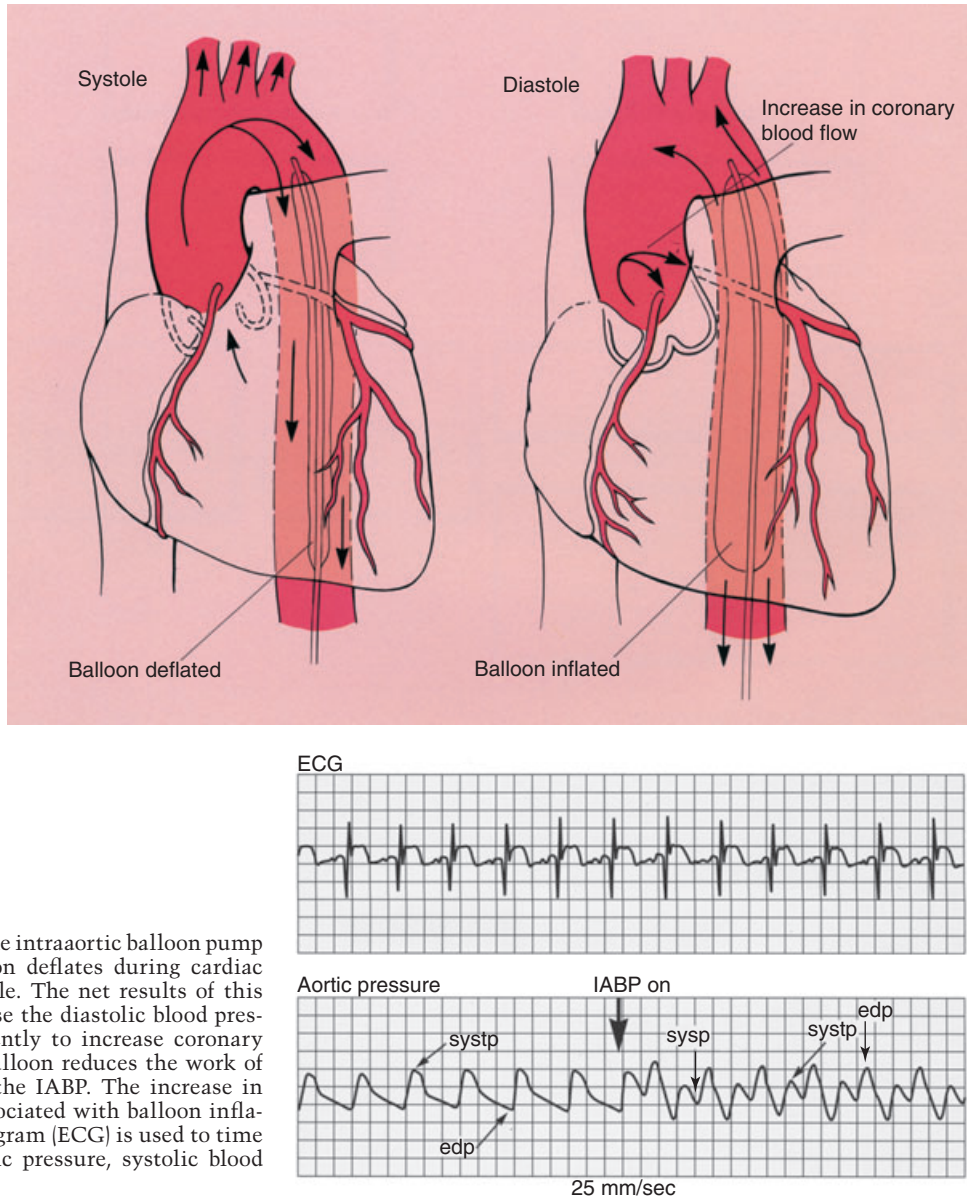


FIGURE 39.3. (A) The position in which the intraaortic balloon pump (IABP) is placed in the aorta. The balloon deflates during cardiac systole and inflates during cardiac diastole. The net results of this filling and collapsing action are to increase the diastolic blood pressure in the proximal aorta and consequently to increase coronary blood flow. The systolic collapse of the balloon reduces the work of the heart. (B) The physiologic effects of the IABP. The increase in aortic diastolic blood pressure (diastp) associated with balloon inflation (IABP on) is shown. The electrocardiogram (ECG) is used to time cardiac systole and diastole. edp, diastolic pressure, systolic blood pressure.

the frequency of revascularization procedures; the need for heparin-infusion; and a composite end point.

Patients were recruited at 23 Swedish hospitals. Eligible patients were men older than 40 years and women more than 1 year after menopause admitted to the hospital with chest pain in the previous 72 hours. Eligibility for treatment required the patient to have newly developed or increased angina pectoris or angina at rest in the previous 2 months or persisting chest pain with the suspicion of MI and at least one of the following electrocardiographic criteria: transient or persistent ST depression of 0.1 mV or more and T-wave inversion of 0.1 mV or more in at least two adjacent leads without significant Q waves in these same leads. All patients without contraindications received aspirin, 75 mg daily after an initial dose of 300 mg, beta-blockers, and calcium antagonists and nitrates as needed. At the discretion of the attending physician, nitroglycerin was given intravenously.

The findings of the study are shown in Table 39.2 and Figure 39.5. Within the first 6 days, the rates of new MI and death were lower in the dalteparin group than in the placebo group [13 (1.8%) vs. 36 (4.8%); risk ratio, 0.37] (Fig. 39.5). The frequency of the need for intravenous heparin and revascularization was also reduced by dalteparin treatment. The composite end point of death, MI, revascularization, and need for intravenous heparin was also significantly reduced in favor of dalteparin [40 patients (4.5%) vs. 78 patients (10.3%); risk ratio, 0.52]. At 40 days, the differences in rates of MI and death and in the composite end point persisted, although subgroup analyses showed that the effect was confined to nonsmokers at this time. Survival analysis showed a risk of reactivation and reinfarction when the dose of

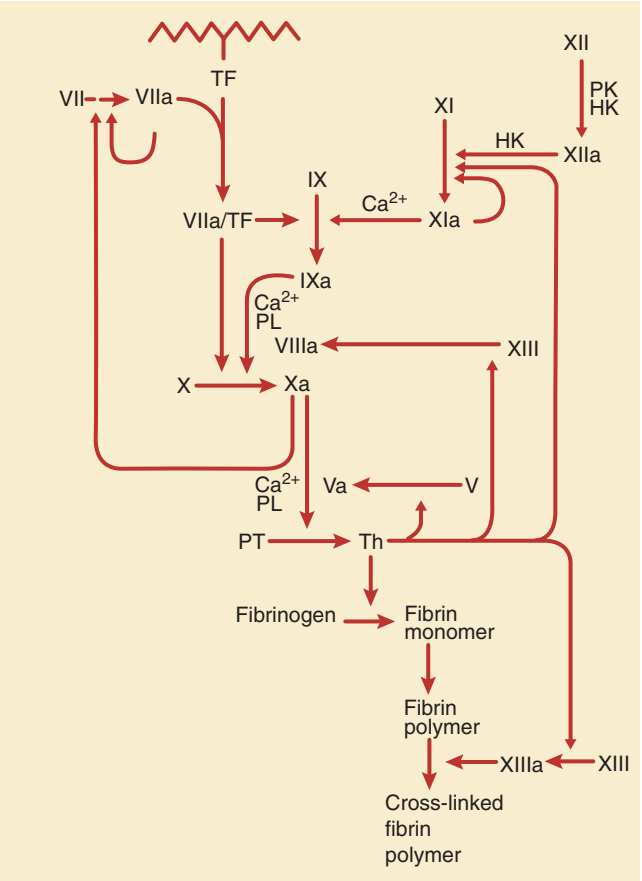


FIGURE 39.4. The scheme involved in tissue factor's (TF) participation in the coagulation cascade in the generation of thrombin (Th) and the role that thrombin plays in the development of fibrin cross-linking and platelet aggregation. HK, high molecular weight kininogen; PK, prekallikrein; PL, phospholipid; PT, prothrombin.

dalteparin was decreased; this was especially pronounced in nonsmokers. By 4 to 5 months after treatment, there were no significant differences in the rates of death, new MI, or revascularization. This regimen was safe, and patient compliance was good among the treated patients.

This study demonstrated the benefits of thrombin inhibition with low molecular weight heparin in the treatment of patients with unstable angina pectoris and NSTEMI. However, a potential advantage of low molecular weight heparin therapy is the ability to continue it after hospital discharge with continued suppression of thrombin's effects. In this study, the effects of long-term treatment with low molecular weight heparin appeared to be primarily confined to the nonsmokers, which included 80% of the patient population. Efforts at reducing the dose of the low molecular weight inhibitor resulted in a risk of reinfarction that was most pronounced in nonsmokers.

Low molecular weight heparin is a very good and possibly preferred alternative to unfractionated heparin in the patient with unstable angina and NSTEMI.[8–13,23,24] There may be real advantages in continuing low molecular weight heparin after hospital discharge in some patients, particularly in those who do not receive an interventional procedure, such as angioplasty or stenting, atherectomy, or surgical revascularization. There is an ongoing risk of MI or reinfarction in the subsequent 4 to 6 weeks in patients with unstable angina pectoris and NSTEMI, probably related to the persistent presence of endothelial injury after plaque ulceration and fissuring and the time required for its repair. The authors believe that as long as the endothelium remains anatomically disrupted or dysfunctional, the patient has a continuing risk of unstable angina and MI and that these clinical entities represent aborted STEMI with transient rather than permanent thrombosis. One limitation, however, of the low molecular weight heparins is their relatively long duration of effect after their discontinuation (up to 24 hours) and the absence of an effective inhibitor of their effects. In patients with

TABLE 39.2. Absolute frequency of primary and separate end points for patients in the Fragmin During Instability in Coronary Artery Disease (FRISC) study

	Placebo (n = 749)	*Dalteparin (n = 726)*	*Risk ratio (95% CI)*	*p value*
Primary end points				
Death or MI	116 (15.5%)	102 (14.0%)	0.90 (0.71–1.15)	.41
Death, MI, or revascularization	326 (43.5%)	296 (40.8%)	0.92 (0.82–1.04)	.18
Death, MI, revascularization or intravenous heparin	337 (45.0%)	312 (43.0%)	0.94 (0.84–1.05)	.28
Exclusion of revascularization for ischemia				
Death, MI, revascularization because of angina	214 (28.6%)	175 (24.1%)	0.84 (0.70–0.99)	.039
Death, MI, revascularization because of angina, or intravenous heparin	241 (32.2%)	204 (28.1%)	0.87 (0.74–1.01)	.066
Separate end points				
Death*	41 (5.5%)	39 (5.4%)	0.98 (0.64–1.50)	
MI*	98 (13.1%)	83 (11.4%)	0.86 (0.66–1.14)	.30
Revascularization	254 (33.9%)	229 (31.5%)	0.92 (0.79–1.06)	.23
Revascularization because of angina	131 (17.5%)	87 (12.0%)	0.68 (0.53–0.86)	.002
Heparin infusion	121 (16.2%)	83 (11.4%)	0.71 (0.55–0.91)	.008

CI, confidence interval; MI, myocardial infarction.

*Separate statistical analyses of death and MI not planned in protocol.

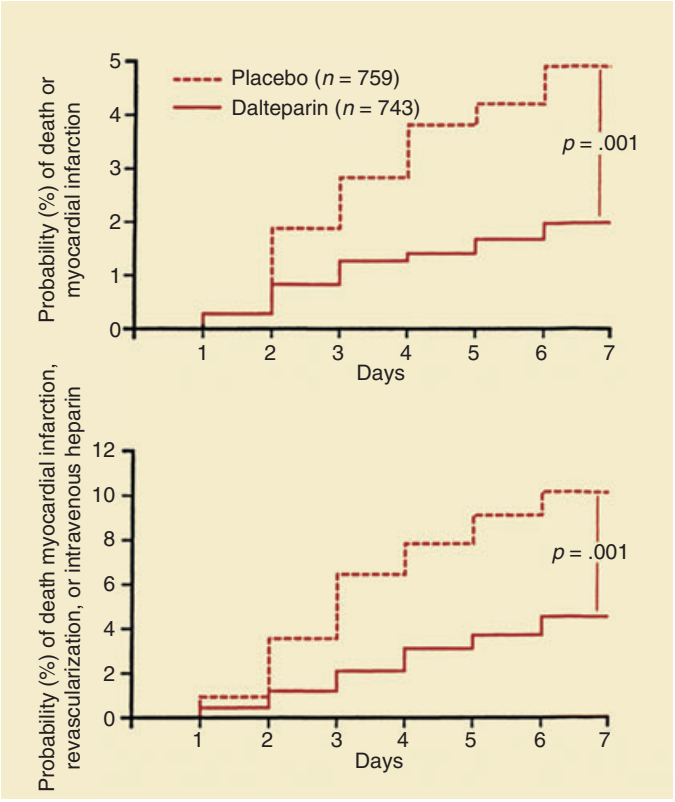


FIGURE 39.5. The protective effect of low molecular weight heparin in the form of dalteparin in the Fragmin During Instability in Coronary Artery Disease (FRISC) study. The administration of dalteparin to patients with unstable angina and non–Q-wave myocardial infarction (MI) reduced their risk of MI (top) and of death, MI, revascularization, or need for intravenous heparin (bottom) (see Table 39.2).

bleeding problems and those requiring emergent surgery, these are important limitations.

Thrombosis in Myocardial Infarction 11 Study

In the Thrombosis in Myocardial Infarction (TIMI) 11 study,[23] patients with unstable angina and NSTEMI were randomized to receive either (1) unfractionated heparin for approximately 3 days followed by placebo injections subcutaneously or (2) uninterrupted antithrombin therapy with enoxaparin during the acute phase (initial 30-mg intravenous bolus) followed by subcutaneous injections of 1.0 mg/kg every 12 hours. Outpatient injections were given every 12 hours of 40 mg subcutaneously for patients less than 65 kg and 60 mg for those equal to or greater than 65 kg in weight.[23] A total of 3910 patients were randomized in this study, and the primary end point was death, MI, or urgent revascularization. The primary end point occurred by 8 days in 14.5% of patients in the unfractionated heparin group and in 12.4% in the enoxaparin group (p = .048) and by 43 days in 19.7% of patients receiving unfractionated heparin and 17% of those received enoxaparin (p = .048) (Fig. 39.6). Throughout the initial hospitalization, there were no differences in major hemorrhage in the treatment groups. In the hospital, all patients received aspirin (100 to 325 mg daily). During the outpatient phase, major hemorrhage occurred in 1.5% of the group treated with placebo and 2.9% of the patients treated with enoxaparin (p = .02). The TIMI 11 data suggest that enoxaparin is superior to unfractionated heparin for reducing a composite end point of death and serious cardiac ischemic events during the acute management of patients with unstable angina and NSTEMI without a significant increase in the rate of major hemorrhage. There was no further relative decrease in events with continuing treatment during the outpatient enoxaparin therapy, but there was an increase in the rate of major hemorrhage.

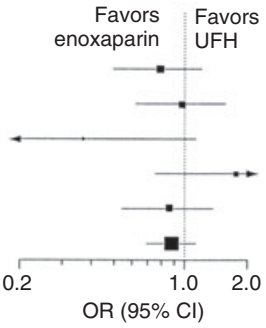
Essence Trial

The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trial[24] randomly assigned 3171 patients with angina at rest or non–Q-wave MI to receive either 1 mg/kg of low molecular weight heparin in the form of enoxaparin administered subcutaneously twice daily or continuous intravenous unfractionated heparin. Therapy was continued for a minimum of 48 hours to a maximum of 8 days. At 14 days, the risks of death, MI, and recurrent angina were significantly lower in patients assigned to enoxaparin therapy (16.6% vs. 19.8%, p = .019). At 30 days, the risk of this composite end point remained significantly lower in the enoxaparin group (19.8% versus 23%, p = .016). The need for revascularization procedures at 30 days was also significantly less frequent in patients assigned to enoxaparin (27% vs. 32%, p = .001). The incidence of major bleeding complications at 30 days was 6.5% in the enoxaparin group and 7% in the unfractionated heparin group, but the incidence of bleeding overall was significantly higher in the enoxaparin group (18% vs. 14%, p = .001), primarily in the form of ecchymoses at injection sites. The data obtained in the ESSENCE trial suggest that antithrombotic therapy with enoxaparin and aspirin was more effective than unfractionated heparin and aspirin in reducing the incidence of ischemic events in patients with unstable angina and NSTEMI in the early phase of therapy. This benefit was achieved with an increase in minor but not major bleeding.

The FRISC, TIMI 11, and ESSENCE trials demonstrated the utility of low molecular weight heparin in the treatment of patients with unstable angina and NSTEMI. These trials suggest that low molecular weight heparin may be clinically superior to unfractionated heparin in reducing the risk of MI and death and the need for revascularization in patients with unstable angina and NSTEMI. This benefit is achieved at some increase in risk of minor bleeding and, when continued in the outpatient phase, in minor-major bleeding. Thus, one should seriously consider the use of low molecular weight heparin in the treatment of these patients who are not allergic to heparin during the inpatient phase of therapy. Figure 39.6 shows the data from five trials using low molecular weight heparins, including 21,946 patients with unstable angina (UA) and NSTEMI.[8] The ESSENCE and TIMI 11B trials were conducted in an era when clopidogrel and platelet GP IIb/IIIa antagonists were not available. Glycoprotein IIb/IIIa antagonists were protocol driven in the Acute II, Interact, and A to Z trials, and the use of clopidogrel was encouraged in accordance with the

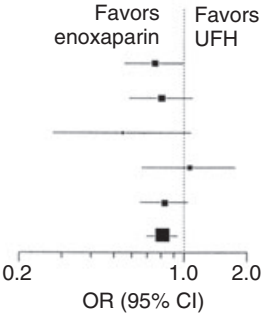
A Death at 30 days

Trial	Events, No./total (%) Enoxaparin	UFH	OR (95% CI)
ESSENCE[7]	39/1607 (2.4)	49/1564 (3.1)	0.77 (0.51–1.18)
TIMI 11B[8]	41/1257(3.3)	42/1242 (3.4)	0.96 (0.62–1.49)
INTERACT[17]	4/304 (1.3)	11/295 (3.7)	0.37 (0.12–1.12)
A to Z[15]	18/587 (3.1)	10/539 (1.9)	1.64 (0.76–3.52)
SYNERGY[16]	37/1211 (3.1)	44/1222 (3.6)	0.85 (0.55–1.32)
Overall	139/4966 (2.8)	156/4867 (3.2)	0.88 (0.69–1.11)



B Death or myocardial infarction at 30 days

Trial	Events, No./total (%) Enoxaparin	UFH	OR (95% CI)
ESSENCE[7]	94/1607 (5.8)	118/1564 (7.5)	0.76 (0.58–1.01)
TIMI 11B[8]	81/1257 (6.4)	97/1242 (7.8)	0.81 (0.60–1.10)
INTERACT[17]	14/304 (4.6)	24/295 (8.1)	0.55 (0.28–1.08)
A to Z[15]	43/589 (7.3)	37/537 (6.9)	1.06 (0.68–1.67)
SYNERGY[16]	165/1212 (12.6)	44/1228 (14.8)	0.84 (0.68–1.05)
Overall	139/4969 (8.0)	458/4866 (9.4)	0.81 (0.70–0.94)



Test for heterogeneity: $\chi^2_4 = 5.46$, $p = .24$ (A); $\chi^2_4 = 2.86$, $p = .58$ (B).

FIGURE 39.6. Summary of five trials of low molecular weight heparin. ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events; INTERACT, A to Z; SYNERGY, and TIMI, Thrombosis in Myocardial Infarction; UFH, unfractionated heparin.[8]

American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for UA/NSTEMI (Figs. 39.6 and 39.7).[25] The noninferiority of low molecular weight heparin as compared to unfractionated heparin in the treatment of patients with unstable angina and NSTEMI has been shown in these studies.

Clopidogrel as Inhibitor of Platelet Aggregation and Treatment of UA/NSTEMI Patients

As noted earlier, clopidogrel (Plavix) blocks ADP receptors inhibiting platelet aggregation. Less well recognized is the fact that clopidogrel also reduces platelet aggregation to thromboxane A_2 and serotonin.[26] Thus, clopidogrel exerts a powerful inhibitory effect on platelet aggregation at sites of atherosclerotic plaque fissuring and ulceration.

Yusuf and his colleagues[27] studied the early and late effects of adding clopidogrel in the treatment of patients with ACS. A total of 12,562 patients with ACS were randomized to receive clopidogrel (300 mg initially followed by 75 mg per day orally) or placebo for 3 to 12 months. Clopidogrel and placebo were added to aspirin therapy in these patients. The proportion of patients experiencing cardiovascular death, MI, or strokes at 30 days was 5.4% in the placebo group and 4.3% in the actively treated group [relative risk (RR), 0.79]. Beyond 36 days, the corresponding rates were 6.3% versus 5.2% (RR, 0.82) (Fig. 39.7). There was no significant increase in life-threatening bleeding either to 30 days or 12 months, but clopidogrel-treated patients did have increased minor and major bleeding and required more blood transfusions. Careful evaluation of the early treatment data showed benefit within 24 hours of treatment with consistently lower rates of adverse outcomes. Thus, clopidogrel should be added to aspirin and nitrates and a thrombin inhibitor (a heparin) in the immediate and long-term therapy of ACS patients. In patients who are selected for CABG, clopidogrel should be discontinued for at least 5 days in advance of the surgery, with the demonstration of a return to relatively normal platelet aggregation in response to ADP prior to elective or semielective CABG. Otherwise, there is a major risk of bleeding intra- and postoperatively. Major bleeding associated with clopidogrel treatment is treated with multiple infusions of fresh platelets from untreated patients.

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, there was an approximately 20% reduction in the risk of vascular death, MI, and stroke after 9 months of therapy with both aspirin and clopidogrel (Fig. 39.8).[27,28] There were 2658 patients (21%) who underwent PCI in the CURE trial, a median of 10 days after enrollment. This was decided by physician preference rather than trial design. Among these patients, there was a relative reduction in cardiovascular death, MI, or urgent revascularization from the PCI procedure through 30 days of 30% ($p = .03$).[27,28,34] From the time of the PCI procedure through the remainder of the

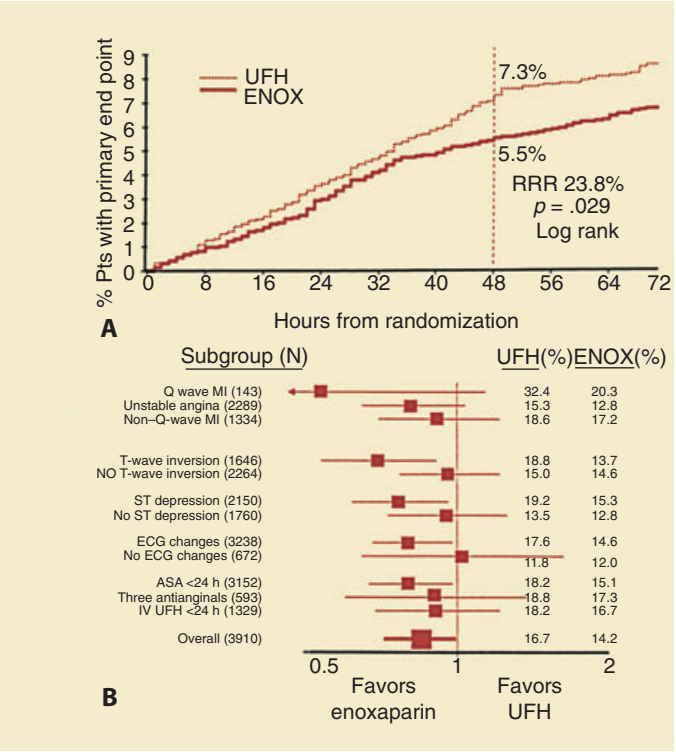


FIGURE 39.7. (A) The reduction in primary end point (death, MI, or urgent revascularization) in patients treated with low molecular weight heparin (ENOX, enoxaparin) in the TIMI 11 study. RRR, relative risk reduction; UFH, unfractionated heparin. (B) Subgroup analysis of patients in the TIMI 11 study shows that low molecular weight heparin reduces the primary end point better than unfractionated heparin in most patient subgroups with unstable angina and non–Q-wave infarcts. ASA, acetylsalicylic acid; ECG, electrocardiogram; MI, myocardial infarction.

12-month follow-up, there was a relative risk reduction of 25% ($p = .047$).[27,28,34]

Other clinical trials that have evaluated the effects of clopidogrel in patients with ACS are summarized in Table 39.3. One issue that is not yet completely resolved is how effective and safe clopidogrel is when added to the treatment of ACS patients who are already receiving aspirin, a heparin, and a GP IIb/IIIa receptor antagonist. Similarly, how much additional protective benefit versus risk there is from a GP IIb/IIIa antagonist in patients who are already receiving clopidogrel, aspirin, and heparin is not clear. These issues may be answered in future clinical trials, but at this time ACS patients receiving aspirin, clopidogrel, heparin, and nitrates should probably have a GP IIb/IIIa antagonist added only if they continue to have rest angina and will have a PCI procedure or if they have complex coronary artery anatomy or diabetes and they are undergoing PCI. Both clopidogrel and GP IIb/IIIa antagonists need to be withdrawn prior to CABG if at all possible; otherwise, there will be a very substantial intra- and postoperative bleeding risk that usually requires many units of platelets to overcome, if it can be overcome.

Clopidogrel/Atorvastatin Interactions

Some authors have reported that the combined administration of atorvastatin (Lipitor) and clopidogrel reduces clopidogrel's ability to inhibit platelet aggregation in response to ADP, as a result of its being metabolized by the cytochrome P4503A4 system, which might then competitively inhibit the metabolic activation of clopidogrel in the liver.[30] However, investigators in the CREDO trial were unable to show an inhibiting effect of atorvastatin in a placebo-controlled post hoc analysis.[32] If there is an important clinical interaction between these drugs in vivo, it is probably limited to a relatively small number of genetically susceptible individuals.

Platelet Glycoprotein IIb/IIIa Antagonists

Figure 39.9 identifies the processes of platelet activation and aggregation and the inhibition of platelet aggregation by inhibitors of platelet GP IIb/IIIa receptors. Platelet

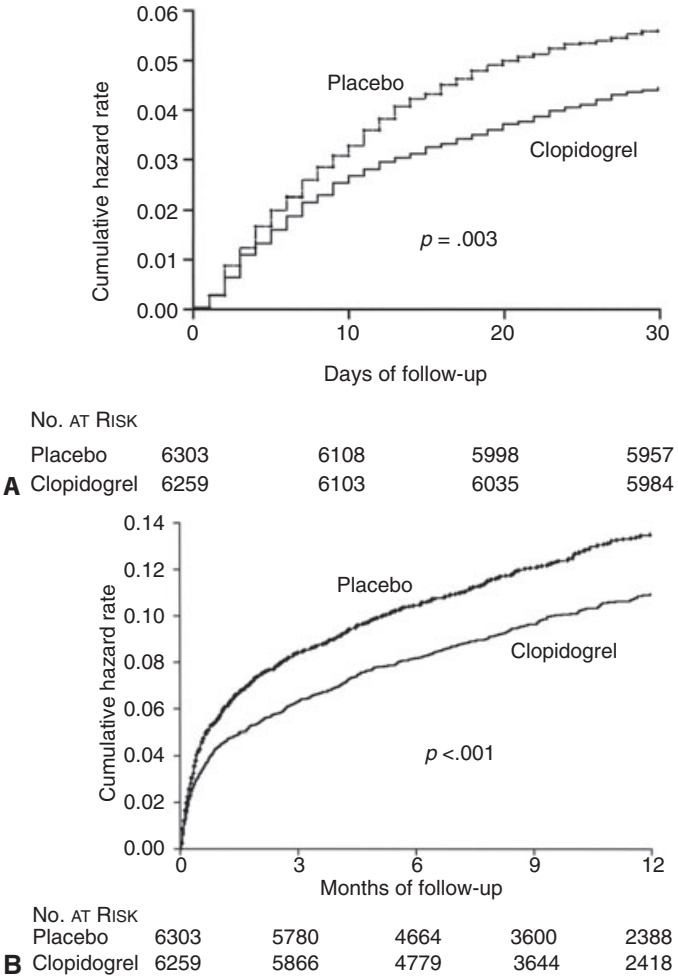


FIGURE 39.8. Cumulative hazard rates for cardiovascular death, MI, and stroke, in patients presenting with acute coronary syndromes without ST-T segment elevation in the CURE trial. (A) Days of follow-up. (B) Months of follow-up.

TABLE 39.3. Clinical trials with clopidogrel in patients with acute coronary syndrome (ACS) and those with elective percutaneous coronary intervention (PCI)

Trial	*No. of patients*	*Primary outcome*	*Duration of follow-up (months)*	*Results*
1. CURE (Circulation 2003; 107:966–972 and N Engl J Med 2001;345:494–502)	12,562	Cardiovascular death, myocardial infarction, or stroke	12	30% relative risk reduction; 25% relative risk reduction for those receiving PCI
2. CREDO* (JAMA 2002;288:2411–2420)	2,116 patients.with PCI, with or without a stent.	Cardiovascular death, myocardial infarction, or stroke	12	27% reduction in the composite end point

* Patients undergoing elective PCI or at high likelihood of undergoing PCI.

activation causes changes in the shape of platelets and conformational changes in the GP IIb/IIIa receptors, transforming the receptors from ligand-unreceptive to a ligand-receptive state. Ligand-receptive GP IIb/IIIa receptors bind fibrinogen molecules, which form bridges between adjacent platelets and facilitate platelet aggregation. Inhibitors of GP IIb/IIIa receptors bind to the GP IIb/IIIa receptors blocking the binding of fibrinogen, thereby preventing platelet aggregation.

The GP IIb/IIIa receptor belongs to the integrin family of heterodimeric adhesion molecules formed by the noncovalent interaction of a series of α and β subunits.[35] Integrins are found in almost all cell types and mediate a diversity of physiologic responses. Multiple integrins, including Ia/IIa, Ic, and IIa, are present on the surface of platelets and play a role in platelet adhesion. The GP IIb/IIIa receptors are the most abundant on the platelet surface with approximately 50,000 copies per platelet.[36] The most important clinical interaction of the GP IIb/IIIa receptors is with fibrinogen, but this receptor has also been shown to bind other adhesive proteins involved in platelet aggregation, including fibronectin, vitronectin, and von Willebrand factor.[35]

The recognition specificity of the GP IIb/IIIa receptor is defined by two peptide sequences: the Arg-Gly-Asp (RGD) sequence and the Lys-Gln-Ala-Gly-Asp-Val sequence.[36] Previous studies have suggested that the second sequence is a predominant site for fibrinogen-GP IIb/IIIa binding.

Resting platelets do not express GP IIb/IIIa receptors in a configuration suitable for ligand binding, but with platelet activation this complex undergoes conformational change that allows it to bind avidly to fibrinogen (see Fig. 39.7).[37] Once activated, the original platelet monolayer recruits additional platelets, eventually forming a platelet thrombus through GP IIb/IIIa-fibrinogen-GP IIb/IIIa bridging (Fig. 39.9). This process continues as new platelets enter the injured vascular bed, become activated by local mediators, express GP IIb/IIIa receptors in the appropriate conformation, and become incorporated into the growing thrombus. An area of previously denuded endothelium resulting from fissuring or ulceration of an atherosclerotic plaque is covered by the growing platelet thrombus. If the neighboring endothelium is relatively normal, protection against thrombus development is exerted by the more normal endothelial cells secreting substances that prevent thrombus formation, including prostacyclin, nitric oxide, and tissue plasminogen activator.[38,39]

Since there is a large number of mediators of platelet aggregation within the area of endothelial injury, platelet GP IIb/IIIa receptor inhibitors are particularly attractive as interventions to prevent thrombus formation by antagonizing the multiple mediators because they interfere with platelet aggregation in the final common pathway. The clinical utility of inhibitors of GP IIb/IIIa receptors in the treatment of patients with ACS, unstable angina pectoris, and NSTEMI has been demonstrated, most especially in patients who have PCI procedures.[15–18] Reviews of the approved GP IIb/IIIa receptor antagonists and representative examples of the protection afforded by inhibitors of GP IIb/IIIa receptors are presented below.

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

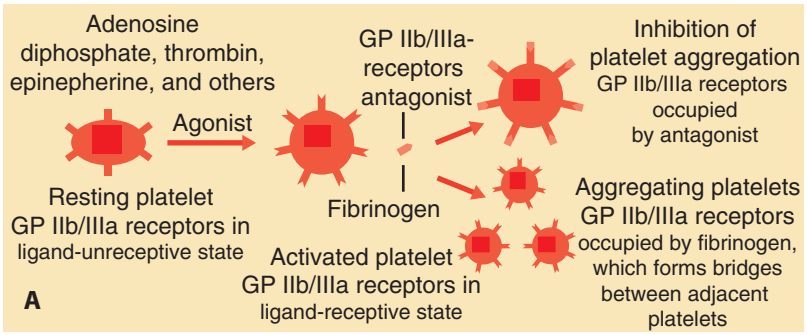
There are three available platelet glycoprotein IIb/IIIa receptor antagonists: abciximab (ReoPro), tirofiban (Aggrastat), and eptifibatide (Integrilin). Abciximab is a recombinant human-murine chimeric Fab fragment that binds irreversibly to the platelet GP IIb/IIIa receptor with a short plasma half-life of 10 minutes. ReoPro also binds to the $\alpha_2\beta_3$ (vitronectin) receptor and the leukocyte receptor MAC-1.

Tirofiban is a low molecular weight nonpeptide GP IIb/IIIa receptor antagonist that has a plasma half-life of 1.3 hours and reversible binding to the GP IIb/IIIa receptors. It has no interaction with vitronectin or MAC-1 receptors.

Eptifibatide (Integrilin) is a peptide that competitively inhibits the RGD sequence of GP IIb/IIIa receptors with a long plasma half-life of 150 minutes. Both eptifibatide and tirofiban are cleared by the kidneys and require dose adjustments in patients with renal failure. Eptifibatide, like tirofiban, does not inhibit the vitronectin or MAC-1 receptors. In fact, both tirofiban and eptifibatide in vitro appear to enhance leukocyte–platelet aggregation in whole blood.[40]

c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina Study

In the c7E3 Antiplatelet Therapy in Unstable Refractory Angina Study (CAPTURE), patients with refractory unstable angina (defined as recurrent myocardial ischemia while the patient was under medical treatment, including heparin and nitrates) were randomized to receive a monoclonal antibody to the platelet GP IIb/IIIa receptors (abciximab) or placebo for 18 to 24 hours before PTCA and continuing for 1 hour



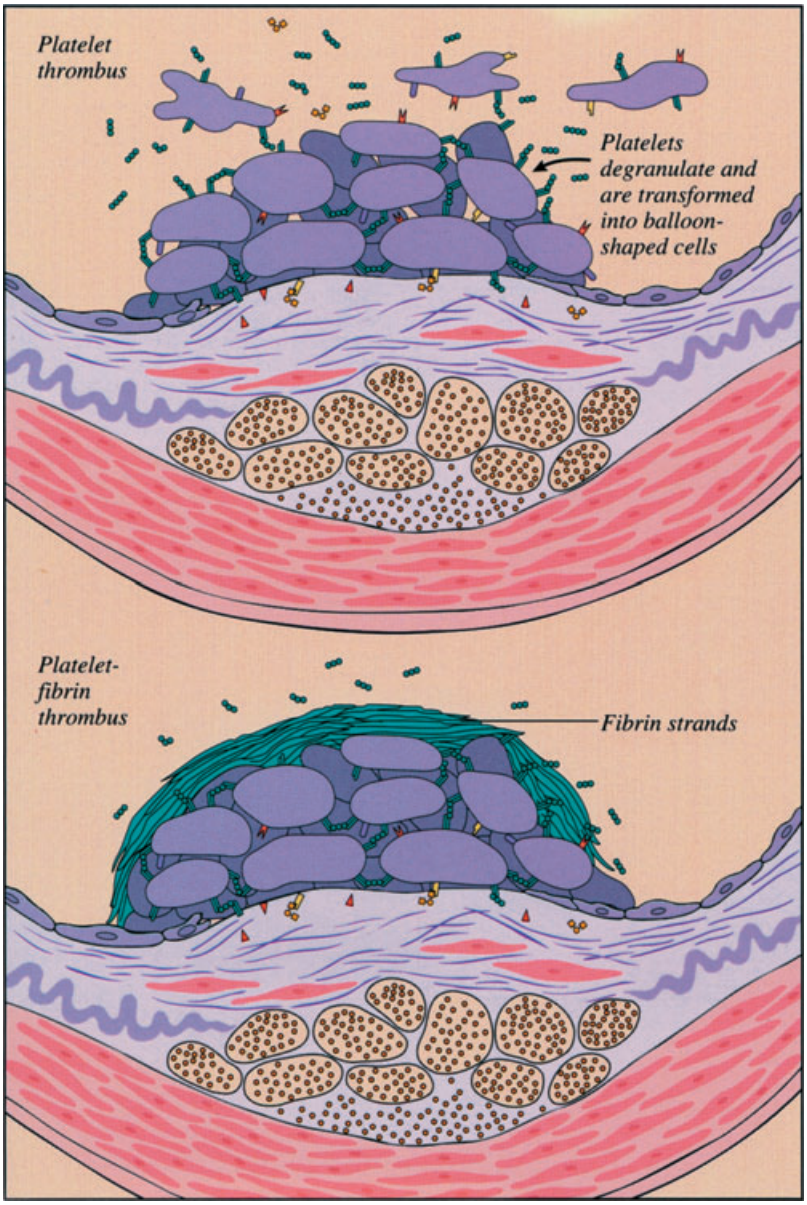


FIGURE 39.9. (A) The activation of platelets, the expression of glycoprotein (GP) IIb/IIIa receptors in a ligand-receptive state, and the protective role played by GP IIb/IIIa receptor antagonists are demonstrated. Platelets aggregate by binding to one another through fibrinogen, which occupies the GP IIb/IIIa receptors, allowing platelets to aggregate in a fibrin mesh. (B) Aggregating platelets develop thrombi at sites of endothelial injury. Top: As they aggregate, they degranulate and are transformed into balloon-shaped cells binding to one another through their GP IIb/IIIa-fibrinogen-binding sites. Bottom: A stable thrombus is formed.

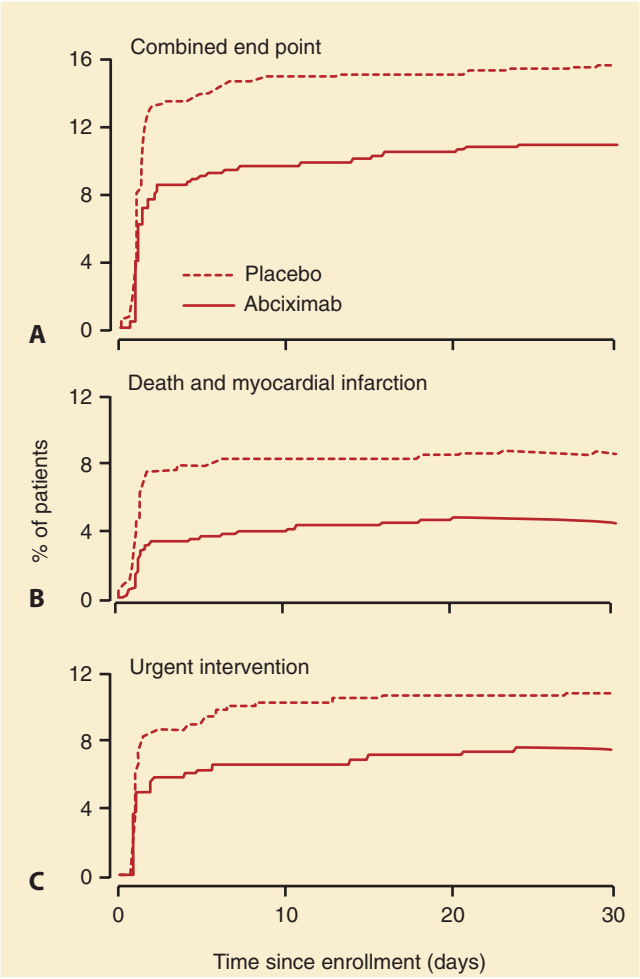


FIGURE 39.10. The protective effect of the monoclonal antibody directed against platelet GP IIb/IIIa receptors, abciximab, in reducing the composite end point (A), death and myocardial infarction (B), and the need for urgent intervention (C) in patients with unstable angina pectoris who were medically unstable.

afterward.[41,42] The primary end point was the occurrence within 30 days after PTCA of death, MI, or urgent intervention for recurrent ischemia. By 30 days, the primary end point had occurred in 71 (11%) of 630 patients who received abciximab compared with 101 (16%) of 635 placebo recipients (p = .01) (Fig. 39.10). The frequency of MI was lower in the abciximab-treated patients than in the placebo-treated patients before PTCA [four patients (0.6%) compared with 13 patients (2.1%), p = .029] and during PTCA [16 patients (2.6%) vs. 34 patients (5.5%), p = .009]. Major bleeding was infrequent, but it occurred more often with abciximab than with placebo [24 patients (3.8%) vs. 12 patients (1.9%), p = .04]. The protective effect of abciximab was not sustained after therapy, and at 6 months follow-up, death, MI, or repeat intervention had occurred in 193 patients in each group. Thus, this study demonstrated that in patients with refractory unstable angina, abciximab reduces the rate of thrombotic complications, especially MI before, during, and after PTCA, even in patients receiving nitrates and heparin. There was no evidence that this regimen influenced the rate of MI or the need for subsequent revascularization in the days following discontinuation of therapy.

Pursuit Trial

The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial was the largest done to date involving a GP IIb/IIIa receptor antagonist in patients with unstable angina.[43] Between November 1995 and January 1997, 10,948 patients in 28 countries were randomized to one of two doses of eptifibatide (Integrilin) or placebo. All patients randomized to eptifibatide received a 180 µg/kg bolus and either a 1.3 µg/kg/min or a 2.0 µg/kg/min infusion for 72 hours. After 1487 patients received a moderate-dose infusion of 1.3 µg/kg/min of eptifibatide, this arm was discontinued because the higher-dose arm had a similarly acceptable safety profile. The primary end point of the trial was a composite all-cause mortality and nonfatal MI or reinfarction at 30 days after therapy. Secondary end points included death and MI or reinfarction at 30 days, the composite at 96 hours and 7 days, and safety and efficacy outcome in patients undergoing percutaneous coronary interventions. At the time of enrollment, 45% of the patients had NSTEMIs. Aspirin was administered to 93% and heparin to 90% of the patients in the study. Figure 39.11 shows the effect of eptifibatide on the cumulative incidence of death or nonfatal MI at 30 days. Eptifibatide reduced the composite end point from 15.7 to 14.2%, p = .03, a 10% relative reduction in death and nonfatal MI.

Prism Study

In the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study, 3232 patients with unstable angina were randomized to receive either intravenous tirofiban (a low molecular weight, nonpeptide, nonantibody inhibitor of the GP IIb/IIIa receptor) or heparin for 48 hours.[44] The primary end point was a composite of death, MI, or refractory ischemia. The incidence of the composite end point was 32% lower at 48 hours in patients who received tirofiban (3.8%

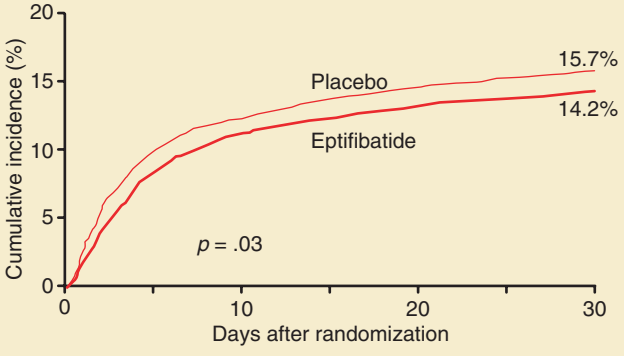


FIGURE 39.11. Eptifibatide, a synthetic peptide competing for the GP IIb/IIIa receptor site, reduced the cumulative incidence of death, MI, and need for second intervention in patients with unstable angina and non–Q-wave MI in the PURSUIT Trial.

vs. 5.6% with heparin). Percutaneous revascularization was performed in 1.9% of the patients during the first 48 hours. At 30 days, the frequency of the composite end point with the addition of readmission for unstable angina was similar in the two groups (15.9% in the tirofiban group vs. 17% in the heparin group). There was a trend toward a reduction in the rate of death or MI with tirofiban, 5.8% compared with 7% in the heparin group, but this did not reach statistical significance. Mortality was 2.3% in the tirofiban group compared with 3.6% in the heparin group ($p = .02$). Major bleeding occurred in 0.4% of the patients in both groups. Reversible thrombocytopenia occurred more frequently in tirofiban-treated patients than in heparin-treated patients (1.1% vs. 0.4%, $p = .04$).

Prism-Plus Study

In the Platelet Receptor in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study, tirofiban was given to patients with unstable angina and non–Q-wave MI in 1915 patients randomly assigned in a double-blind manner to receive tirofiban, heparin, or tirofiban and heparin.[45] Patients received aspirin if its use was not contraindicated. The study drugs were infused for a mean of 71 ± 20 hours, during which time coronary angiography and angioplasty were performed after 48 hours when clinically indicated. The composite primary end point consisted of death, MI, and refractory ischemia within 7 days after randomization.

The study was stopped prematurely for the group receiving tirofiban alone because of an excess mortality at 7 days, 4.6% compared with 1.1% for the patients treated with heparin alone. The frequency of the composite primary end point at 7 days was lower among the patients who received tirofiban and heparin than among those who received heparin alone (12.9% vs. 17.9%, risk ratio 0.68, $p = .004$) (Fig. 39.12). The composite end point for the tirofiban plus heparin group was also reduced compared with that in the heparin-only group at 30 days (18.5% vs. 22%, $p = .03$) and at 6 months (27.7% vs. 32%, $p = .02$). At 7 days, the frequency of death or MI was 4.9% in the tirofiban and heparin group as contrasted with 8% in the heparin-only group ($p = .006$). Comparable data at 30 days were 8.7% and 11.9% ($p = .03$), respectively, and at 6 months, 12% and 15% ($p = .06$). The protection from tirofiban and heparin was consistent in the various subgroups of patients, both in those treated medically and in those treated with PTCA. Major bleeding occurred in 3% of the patients receiving heparin alone and 4% of the patients receiving combination therapy.

The conclusion of this study is that when administered with heparin and aspirin, the platelet GP IIb/IIIa receptor inhibitor tirofiban reduces the risk of death or MI in patients with unstable angina and NSTEMI.[45]

The GP IIb/IIIa receptor antagonists, including the monoclonal antibody (abciximab), synthetic peptide (eptifibatide), and nonpeptide low molecular weight inhibitor (tirofiban), when added to aspirin and heparin in patients with unstable angina pectoris and NSTEMI, reduce the risks of MI and death and the need for interventional therapy during their administration and sometimes in the short time period thereafter (Fig. 39.13). However, this benefit is particularly apparent in patients who have PCI. Tables 39.4 and 39.5 provide a representative listing of clinical trials done with GP IIb/IIIa receptor antagonists in patients with unstable angina and acute MI, demonstrating the generally protective effect found in these trials. More recent studies also suggest that the platelet glycoprotein IIb/IIIa receptor inhibitors may exert their greatest efficacy in patients with UA and NSTEMI

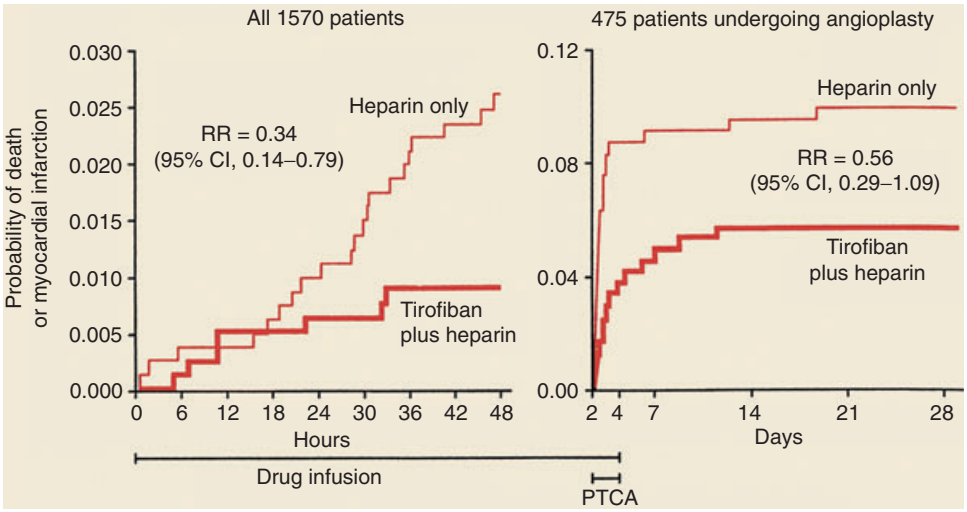


FIGURE 39.12. Left: The beneficial effect of a nonpeptide, nonantibody, low molecular weight inhibitor of GP IIb/IIIA receptors, tirofiban, and heparin compared with heparin alone in reducing the probability of death or MI during the period of drug infusion. Right: The same protective effect of tirofiban and heparin is demonstrated in the patients admitted with unstable angina and non–Q-wave infarction who subsequently had angioplasty. CI, confidence interval; PTCA, percutaneous transluminal coronary angioplasty; RR, risk ratio.

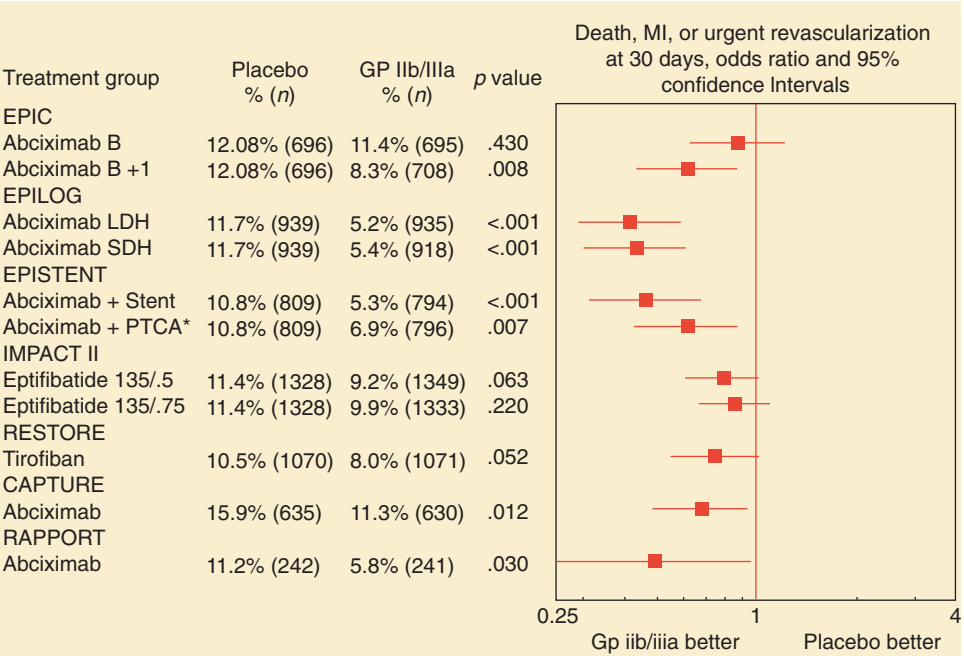


FIGURE 39.13. The results of randomized interventional trials in patients with unstable angina or non–Q-wave MI and other patients with limiting angina and complex coronary artery lesions who underwent an interventional procedure and were treated by GP IIb/IIIa antagonists. Composite end point data in each of these trials are shown (see Table 39.5). B, bolus; B + I, bolus and infusion; LDH, low-dose heparin; SHD, standard-dose heparin.

with elevated serum troponin I or T values who have PCI (Fig. 39.14).[15–18]

Whereas there is additive protection provided by the GP IIb/IIIa receptor inhibitors, especially in patients with elevated troponins that proceed to have PCI, it is also clear that protection is not complete. There are still patients who have MIs, recurrent unstable angina, and the need for additional intervention. Thus, available antithrombotic therapy still needs to be improved. Probable reasons for lack of complete protection from the GP IIb/IIIa antagonists include that these agents do not inhibit (1) platelet adhesion at sites of vascular injury and (2) platelet activation or secretion, and (3) probably they do not effectively inhibit thrombin bound to thrombus or tissue factor that is inaccessible within the thrombotic plaque.

Glycoprotein IIb/IIIa Receptor Antagonists Used with Interventional Therapies

Figure 39.13 and Tables 39.4 and 39.5 demonstrate the effect of the GP IIb/IIIa inhibitors in patients requiring interventional procedures, including angioplasty and stents. These patients had compelling medical reasons for PCI, and many received PCI after being hospitalized with unstable angina or NSTEMI. As the figures demonstrate, abciximab, eptifibatide, and low molecular weight inhibitors of GP IIb/IIIa receptors, as represented by tirofiban, exert beneficial effects and reduce composite end points of death, MI, or need for urgent revascularization at 30 days in these patients. Thus, the benefit of these interventions in patients treated medically for unstable angina and NSTEMI occurs primarily in patients who subsequently have PCI (Fig. 39.13), and these patients, and patients with elevated serum troponin levels, probably derive the most benefit from the GP IIb/IIIa inhibitors.[15–18]

In the Evaluation of Platelet IIb/IIIa Inhibitors for Stenting (EPISTENT) study, abciximab therapy reduced the risk of MI, death, and need for subsequent intervention in patients with diabetes mellitus to levels comparable to those found in nondiabetic patients.[46] Previously, it had been shown that PCI in patients with diabetes mellitus often fails to provide important long-term beneficial results. Earlier studies have suggested the superiority of CABG over PCI in these patients. Thus, this is an important finding of the EPISTENT study; however, not all subsequent studies have confirmed this protective effect in patients with diabetes.

The Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa Receptor Blockade (EPILOG) study[47] demonstrated that the benefits of abciximab therapy in patients with coronary heart disease undergoing angioplasty extends to both low-risk and high-risk patients. The earlier Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) study[48] had shown that abciximab therapy reduced the risk of subsequent MI, death, and need for a second intervention in high-risk patients undergoing PTCA. In the EPIC study, high-risk patients were those with unstable angina, recent NSTEMI, and complicated coronary arterial lesions.[48]

In several of the previously mentioned interventional studies using abciximab, composite end points were favorably influenced through 6 months and longer, especially when initial treatment was followed by PCI.

TABLE 39.4. Clinical outcomes of the PARAGON, PRISM, PRISM-PLUS, and PURSUIT trials in which GP IIb/IIIA antagonists were used to treat patients with unstable angina pectoris and non–Q-wave myocardial infarction

	PARAGON			*PRISM*		*PRISM-PLUS*			*PURSUIT*		
Characteristic	*Placebo*	*Lamifiban 1 μg/min ± heparin*	*Lamifiban 5 μg/min ± heparin*	*Heparin*	*Tirofiban 0.15 μg/kg-min*	*Heparin*	*Heparin + Tirofiban 0.10 μg/kg-min*	*Tirofiban 0.15 μg/kg-min*	*Placebo*	*Eptifibatide 1.3 μg/kg-min*	*Eptifibatide 20 μg/kg-min*
n	758	755	769	1616	1616	797	773	345	4739	1487	4722
30-day outcome											
Death (%)	2.9	3.0	3.6	3.6	2.3	4.5	3.6	(6.1)	3.7	(3.4)	3.5
Nonfatal MI (%)	10.6	9.4	10.9	4.3	4.1	9.2	6.6	(9.0)	13.5	(12.0)	12.6
Death or MI (%)											
Overall	11.7	10.6	12.0	7.1	5.8	11.9	8.7	(13.6)	15.7	(13.4)	14.2
Relative reduction (%)		9	−6		18		27				10
PTCA patients				9.1	7.2	10.2	5.9		16.8		11.8
Non-PTCA patients				6.2	3.6	7.8	3.6		15.7		14.6
6-month outcome											
Death (%)	6.6	5.2	6.8			7.0	6.9	(7.2)	6.2		6.4
Nonfatal MI (%)	14.3	10.8	12.9			10.5	8.3	(10.1)	15.7		14.7
Death or MI (%)	17.9	13.7	16.4			15.3	12.3	(15.9)	19.0		17.8
Relative reduction (%)		23	8				20				8
Major bleeding (%)*	3.0	3.0	6.0	0.4	0.4	0.8	1.4		1.3		3.0
Intracranial hemorrhage (%)	0	0	0.1	0.1	0.1	0	0		0.1		0.1
RBC transfusion (%)†	4.4	4.4	8l7	1.4	2.4	2.8	4.0		1.8		4.4
Thrombocytopenia (%)‡	1.1	1.5	1.3	0.1	0.4	0.3	0.5		0.4		0.6

MI, myocardial infarction; PARAGON, Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; PRISM, Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PTCA, percutaneous transluminal coronary angioplasty; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina; Receptor Suppression Using Integrilin Therapy; RBC, red blood cell.

Numbers in parentheses are from discontinued treatment arms and are not contemporaneous; these are listed only for completeness, not direct comparisons.

*Major bleeding as defined by intracranial hemorrhage or decrease in hemoglobin ≥5 g/dL not associated with CABG.

†Transfusions reported are not associated with CABG, except for PARAGON.

‡Thrombocytopenia defined as platelet count ≤50,000 mm.

TABLE 39.5. Summary of results of randomized interventional trials in patients with unstable angina/non–Q-wave myocardial infarction and other patients with limiting angina and complex coronary artery lesions who underwent an interventional procedure and were treated by glycoprotein IIb/IIIa antagonists: 30-day efficacy end point figures

	Death (%)	*MI (%)*	*Urgent PCI (%)*	*Urgent CABG (%)*
EPIC trial				
Placebo	1.7	8.6	4.5	3.6
Abciximab bolus	1.3	6.2	3.6	2.3
Abciximab bolus + infusion	1.7	5.2	0.8	2.4
EPILOG trial				
Placebo	0.8	8.7	3.8	1.7
Abciximab + reduced heparin	0.3	3.7	1.2	0.4
Abciximab + standard heparin	0.4	3.8	1.5	0.9
EPISTENT trial				
Placebo + stent	0.6	9.6	1.2	1.1
Abciximab + stent	0.3	4.5	0.6	
Abciximab + PTCA	0.8	5.3	1.3	0.6
IMPACT II trial				
Placebo	1.1	8.1	2.8	2.8
Eptifibatide 135/0.5 dose	0.5	6.6	2.6	1.6
Eptifibatide 135/0.75 dose	0.8	6.9	2.9	2.0
RESTORE trial*				
Placebo	0.7	5.7	4.0	1.4
Tirofiban	0.8	4.2	2.3	1.1
CAPTURE trial				
Placebo	1.3	8.2	4.4	1.7
Abciximab	1.0	4.1	3.1	1.0
RAPPORT trial†				
Placebo	2.1	4.1	5.4	1.2
Abciximab	2.5	3.3	1.7	0
TARGET trial				
Tirofiban				
Abciximab				

CABG, coronary artery bypass graft surgery; CAPTURE, c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina; EPIC, Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications; EPILOG, Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa Receptor Blockade; EPISTENT, Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; IMPACT, Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis; MI, myocardial infarction; PCI, percutaneous coronary intervention; RAPPORT, ReoPro and Primary PTCA Organization and Randomized Trial; RESTORE, Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis.

* RESTORE trial end points listed here are for published post hoc analysis including only urgent repeat revascularization for consistency with the other trials. The primary composite end point of RESTORE included urgent or elective repeat revascularization. RESTORE trial end points listed here differ from those of the other trials in that only patients in whom the lesion was successfully crossed with the guidewire were included in the efficacy analysis of RESTORE, providing a "treated patient" analysis rather than the "intention-to-treat" analysis utilized in the other studies.

† RAPPORT end points listed here are for the secondary composite of death, myocardial reinfarction, and urgent target vessel revascularization. This end point differs from those of the other trials in that it does not include urgent nontarget vessel revascularization procedures.

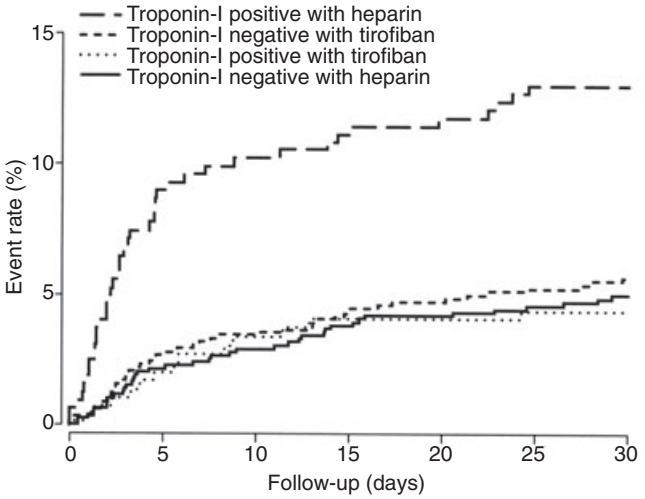


FIGURE 39.14. Event rate curves (mortality, MI) for 30-day follow-up for patients with troponin I concentrations higher and lower than threshold of 1.0μg/L.

Interventional Therapy

The TIMI 18 study suggests that patients with UA/NSTEMI who have elevation in serum CRP or troponin levels on admission and those with a TIMI risk factor score of 3 or greater (Figs. 39.15 and 39.16)[49–51] have reductions in subsequent risk of death, MI, or need for future intervention when treated by PCI or CABG.[51] Women with ACS seem particularly likely to benefit from interventional therapy when admitted with elevated serum CRP and troponin I.[33] The TIMI 18 study compared an early invasive (within 48 hours) with a conservative approach in patients with ACS, all of whom received aspirin, heparin, and tirofiban. The 30-day and 6-month outcome data in the invasive group were significantly better than in the conservative group largely driven by a 33% reduction in MI. By contrast with the FRISC II trial,[52] there was no early hazard possibly as a result of the "upstream" use of tirofiban in all patients and early intervention with a high rate of stenting and PCI (86%).[50,53]

In the TIMI risk score for patients with UA/NSTEMI,[49–51] patients are risk stratified on the basis of seven baseline characteristics: age ≥65 years, ≥3 risk factors for coronary artery disease, known coronary artery disease, use of aspirin in the preceding 7 days, ≥2 episodes of angina in the previous 24 hours, ST segment deviation ≥0.5 mm, and elevated cardiac biomarkers of necrosis. Patients are assigned 1 point for each risk factor that is present. On the basis of their TIMI risk scores, they are then categorized as low risk (0 to 2 points), intermediate risk (3 or 4 points), or high risk (5 to 7 points). These categories have been shown to have prognostic predictive ability.[49–51] One recent study has shown that upstream platelet GP IIb/IIIa inhibition and coronary artery stenting is useful in the invasive management of patients with UA/NSTEMI in the patients with intermediate- or high-risk TIMI scores [odds ratio (OR), 1.39 in low-risk, 0.80 in intermediate-risk, and 0.57 in high-risk patients].[54] The TACTICS-TIMI 18 trial was the second TIMI trial to compare an early invasive with conservative management of patients with UA/NSTEMI.[49] An earlier TIMI IIIB trial had not shown benefit of relatively early invasive management of these patients.[55] The TACTICS 18 trial[49] had the benefit of using GP IIb/IIIa antagonists, stents, and separation of patients into various risk profiles while demonstrating the greatest outcome benefit from the invasive strategy in patients with increasing baseline risk, that is, intermediate- and high-risk TIMI scores and patients with elevated biomarkers of CRP and a troponin (Fig. 39.16).[49–51]

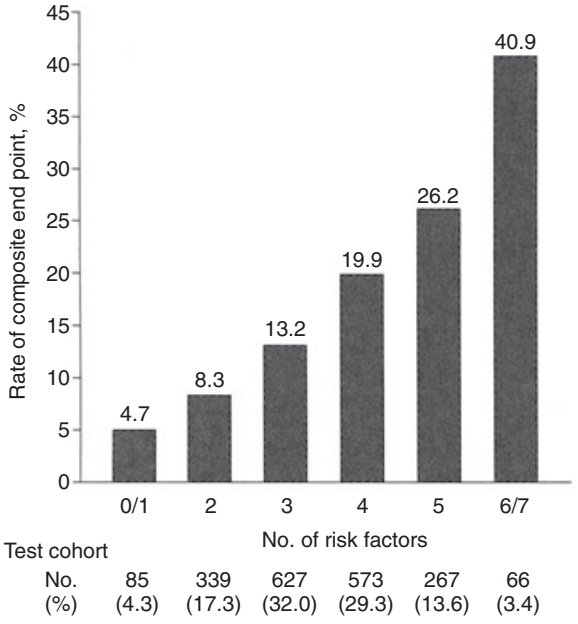


FIGURE 39.15. Rates of all-cause mortality, MI, and severe recurrent ischemia prompting urgent revascularization through 14 days after randomization were calculated for various subgroups based on the number of risk factors in the test cohort (the unfractionated heparin group in the TIMI 11 trial). Event rates increased significantly as the TIMI risk scores increased.

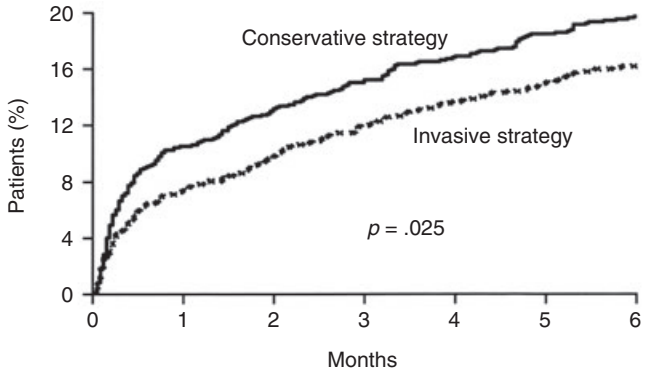


FIGURE 39.16. Cumulative incidence of the primary end point of death, nonfatal MI, or rehospitalization for an acute coronary syndrome during the six-month follow-up. The rate of the primary end point was lower in the invasive-strategy group than in the conservative-strategy group (15.9% vs. 19.4%, $p = .025$).

Angiotensin-Converting Enzyme Inhibitors

Several large scale clinical trials have demonstrated improved survival with ACE inhibitor therapy begun during acute MI.[29] There are data available for 98,496 patients from four clinical trials involving more than 1000 patients in whom ACE inhibitor therapy was begun in the acute phase (0 to 36 hours) of MI and continued for 4 to 6 weeks.[29] Thirty-day mortality was 7.1% among patients treated with ACE inhibitors and 7.6% among control patients, that is, 7% proportional reduction [standard deviation (SD), 2%; 95% confidence interval (CI), 2% to 11%; $p < .004$]. This represents reduction in deaths of about 5 per 1000 patients.[29] Most of this benefit occurred in the first week. The absolute benefit was more marked in selected high-risk groups, including patients with Killip class 2 or 3, heart rate >100 bpm at entry and in patients with anterior MIs.[29] Angiotensin-converting enzyme (ACE) inhibitor therapy also reduced the incidence of nonfatal congestive heart failure (CHF) (14.6% vs. 15.2%, $p = .01$), but it was also associated with an excess of persistent hypotension (17.6% vs. 9.3%, $p < .01$) and renal dysfunction (1.3% vs. 0.6%, $p < .01$).[29] These data suggest the potential benefit of ACE inhibitors in the early treatment of MIs in patients with anterior MI, those with CHF, and those at increased risk of MI and death in whom there is no contraindication (Fig. 39.17). It should be emphasized, however, that these trials were not conducted exclusively in NSTEMI and UA patients;

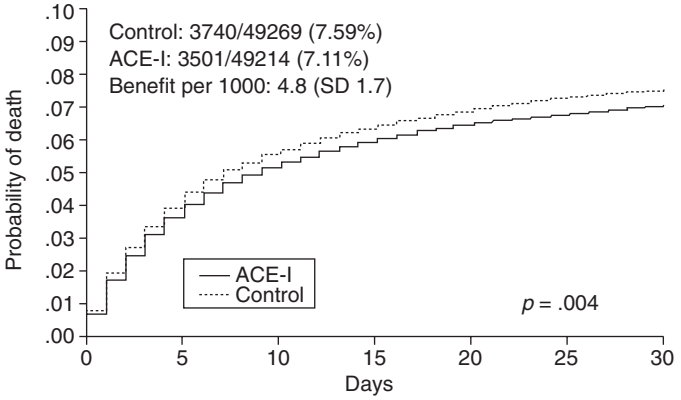


FIGURE 39.17. Effect of angiotensin-converting enzyme (ACE) inhibitor therapy on cumulative mortality during days 0 to 30 in all trials combined.

therefore, the application of the data to these select patient groups needs to be done with caution.

Acute Lipid Lowering with a Statin

Schwartz et al.[30] evaluated the effects of atorvastatin given in high dose to patients with UA and NSTEMI on the incidence of death, nonfatal MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia (with objective evidence requiring emergency rehospitalization). The primary end point was reduced from 17.4% in the placebo group to 14.8% in the atorvastatin group in the 16 weeks of the trial (P = .048) [Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study] (Fig. 39.18). This same therapy reduced the overall cerebrovascular accident rate by half and did not cause hemorrhagic stroke (Fig. 39.18).[56] The therapy was particularly effective in patients with elevated CD40L levels (Fig. 39.18). This approach is being further evaluated in additional clinical trials, but the authors believe that statin therapy should be initiated in these patients beginning on admission to the hospital in a dose sufficient to markedly lower serum LDL concentrations rapidly.

General Considerations

Coronary arteriography is often recommended for the high- and medium-risk patient with unstable angina and NSTEMI without other severe and life-threatening medical disease or very advanced age after the angina is controlled medically with ASA, a heparin, and clopidogrel (in patients not likely to need urgent CABG) (see Fig. 39.1). A platelet GP IIb/IIIa antagonist may be started prior to PCI in patients with an elevated serum troponin and in patients with a complex culprit coronary lesion, and in the diabetic undergoing PCI. Abciximab should probably be the platelet GP IIb/IIIa inhibitor one uses in the diabetic patient having PCI, as the evidence that a GP IIb/IIIa inhibitor might be protective in the diabetic is strongest for abciximab.

Coronary arteriography is absolutely indicated in patients with continuing rest angina in whom medical therapy does not prevent pain. However, medical therapy initially, in patients without the indications mentioned above for interventional therapy, with subsequent referral for coronary arteriography and PCI or CABG of patients with continuing myocardial ischemia at low-level effort despite medical therapy, is a reasonable alternative (see Fig. 39.1). In the patient in whom rest angina recurs despite an appropriate medical regimen, coronary arteriography becomes mandatory; 10% to 15% of patients with unstable angina have significant left main coronary artery stenoses, including 50% or greater luminal diameter narrowing of the main left coronary artery.[57–59] Coronary artery bypass graft surgery (CABG) prolongs the lives of these patients.[55–63] Approximately 10% of patients with unstable angina have no angiographic evidence of significant coronary disease.[57,59] Therefore, in 25% of these patients, the angiographic findings help select an appropriate therapeutic approach. In the remaining patients, identifying the location and extent of coronary artery disease (CAD) is useful prognostically. In

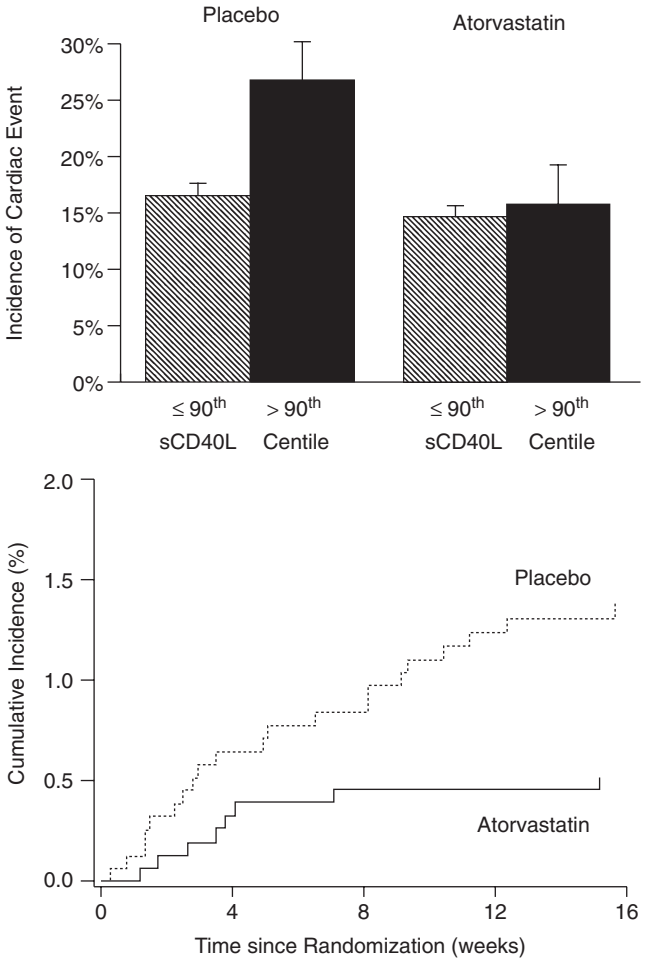


FIGURE 39.18. (A) Incidence of recurrent events over 16 weeks in placebo and atorvastatin groups according to sCD40L above or below 90th percentile. Error bars indicate 95% CI. High vs. low sCD40L significant only for placebo (p >.01). (B) Kaplan-Meier estimates for nonfatal stroke. The relative risk of nonfatal stroke in the atorvastatin group compared with the placebo group was 0.40 (95% confidence interval, 0.19 to 0.88; P = .02), as based on a Cox proportional hazards analysis.[56]

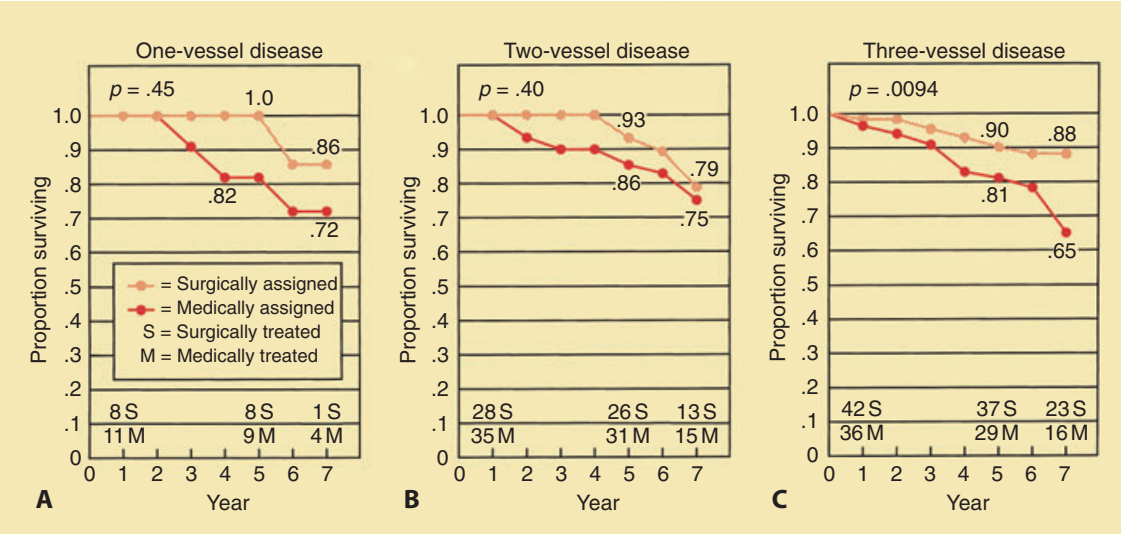


FIGURE 39.19. The influence of coronary artery bypass surgery compared with medical therapy in patients with significant one-vessel disease (A), two-vessel disease (B), and three-vessel disease (C). As demonstrated, survival is better in patients with triple-vessel coronary disease who undergo coronary artery surgery (C).

the patient with continuing angina at rest, the arteriographic findings lead the physician to consider PCI or CABG (see Fig. 39.1).

In patients in whom angina is medically controlled and a conservative regimen is chosen, and in those in whom coronary arteriographic findings do not suggest a need for immediate coronary artery revascularization, exercise (or some other form of stress) testing should be obtained (see Fig. 39.1). Submaximal exercise tests can usually be safely done days after the relief of chest pain, followed several weeks later by maximal exercise tests. The addition of some form of nuclear, echocardiographic, or magnetic resonance perfusion or functional imaging testing with exercise or other stress improves its sensitivity and specificity for identification of patients with physiologically important CAD.[64–68] Patients with continuing angina or objective evidence of myocardial ischemia at rest or at low levels of activity despite a good medical regimen, and those with significant left main or three-vessel coronary stenoses and depressed left ventricular function, should undergo coronary artery revascularization (Fig. 39.19).[60–63] Coronary artery revascularization relieves or markedly reduces the frequency of angina in the patient with continuing myocardial ischemia despite a good medical regimen, and CABG prolongs the lives of patients with significant left main or three-vessel coronary stenoses[69] and depressed left ventricular function (Fig. 39.19). In patients with unstable angina, PCI or CABG usually relieves angina; CABG is also associated with a reduced risk for recurrent unstable angina compared with continuing medical therapy.[60–63] Diabetic patients with multivessel CAD and need for coronary revascularization appear to benefit more from CABG than PCI with the possible exception that future studies will confirm that PCI with abciximab infusion or one of the drug-eluting stents will be successful in making stent results comparable to those with CABG in these patients, including diabetes and those with multivessel CAD.

However, there is no persuasive evidence that coronary artery revascularization reduces the risk of MI or prolongs the lives of patients with unstable angina who do not have significant left main coronary artery stenosis, three-vessel CAD, or severe two-vessel CAD, including 90% or greater proximal left anterior descending (LAD) artery stenosis above the first septal perforator artery, and reduced left ventricular function. A general scheme for the management of patients with unstable angina and NSTEMI is shown in Figure 39.20.

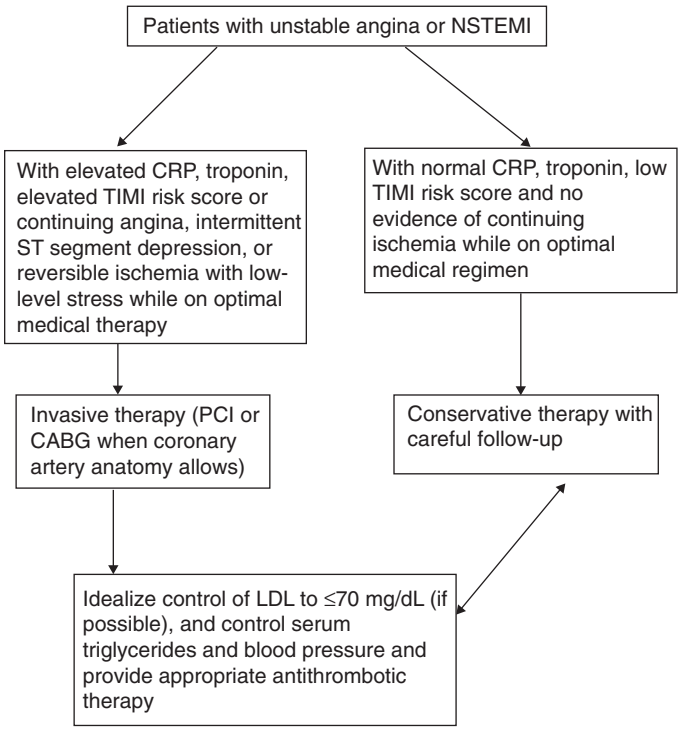


FIGURE 39.20. Treatment of patients with unstable angina and NSTEMI.

Coronary Arterial Spasm: Variant Angina, Prinzmetal's Angina

The initial treatment of coronary artery spasm should utilize nitrates, a selected calcium antagonist, or both.[70–72] Beta-blockers are contraindicated in patients with suspected or documented coronary artery spasm because they may cause more frequent and severe episodes of coronary artery spasm. Patients with variant angina usually respond well to medical therapy with nitrates or one of the selected calcium antagonists (Fig. 39.21).[73–83] Episodes of coronary artery spasm tend to be intermittent, occurring for a few days or weeks and then disappearing, sometimes to recur months or years later. In general, coronary artery revascularization and PTCA are not as useful in these patients as in those with other CAD syndromes. In patients with coronary artery spasm, PTCA itself may cause immediate and recurrent coronary artery spasm. The exceptions are patients with extensive coronary stenoses and superimposed coronary artery spasm in whom it may be necessary to treat both pathophysiologic mechanisms of CAD. Coronary artery revascularization may be necessary in the patient who has angina associated with low-level exercise or stress, an increased myocardial oxygen demand, and relative inability of the stenotic artery to delivery oxygen.[84] A calcium antagonist or nitrates are used to treat primary decreases in coronary blood flow caused by coronary artery spasm, even when they have been provoked by exercise or by cocaine.[74–83,85]

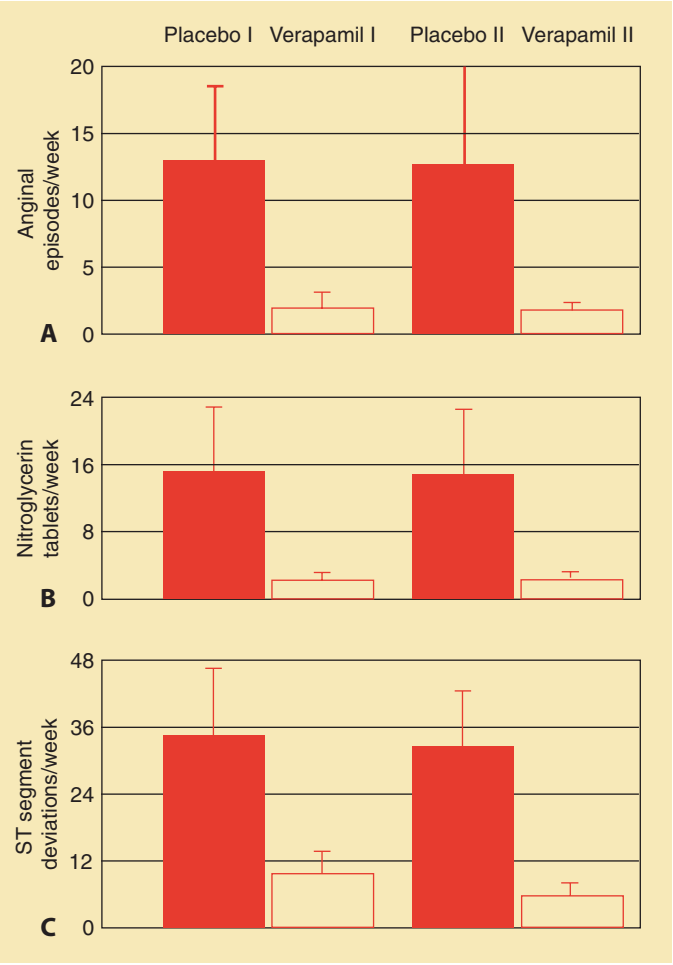


FIGURE 39.21. The beneficial effect of the slow channel calcium antagonist verapamil in patients with Prinzmetal's angina. In this study, verapamil reduced the number of anginal episodes per week (A), the number of nitroglycerin tablets consumed per week (B), and the electrocardiographic alterations detected by continuous 24-hour Holter monitoring (C).

Evidence-Based Medicine Related to the Treatment of Patients with Unstable Angina and NSTEMI

The ACC/AHA guidelines for patients with unstable angina stress that "patients who are at intermediate or high risk for adverse outcomes should, if possible, be admitted to a critical care environment with ready access to invasive cardiovascular diagnosis and therapy procedures."[25] Class I recommendations for an early invasive strategy include patients with any of the following high-risk indicators[25]:

1. Patients with recurrent angina at rest or with low-level activity despite intensive anti-ischemic therapy
2. Elevated serum troponin T (TnT) or troponin I (TnI) value
3. New or presumably new ST-segment depression
4. Recurrent angina with symptoms of CHF, S3 gallop, or new or worsening mitral insufficiency
5. High-risk findings on noninvasive stress testing (left ventricular ejection fraction <0.35, large stress perfusion defect or multiple moderate-sized defects, stress-induced moderate-sized perfusion defects with left ventricular dilation
6. Hemodynamic instability
7. Sustained ventricular tachycardia
8. PCI within the previous 6 months
9. Prior coronary artery bypass surgery

Class IIa recommendations suggest an early invasive strategy in patients with repeated ACS presentations despite therapy and without evidence for ongoing ischemia.[25]

Glycoprotein IIb/IIIa inhibitors received a class I recommendation for patients receiving aspirin and heparin in whom cardiac catheterization and PCI are planned, and they may be administered immediately before PCI.[25] The complete ACC/AHA guidelines for treating patients with unstable angina and NSTEMI are available via the following Web site on http://www.americanheart.org/presenter.jhtml?identifier=3004542.

Future Lifestyle Modifications

Patients with ACS should undergo lifestyle modification following their initial treatment. They should follow a low-cholesterol, low-fat diet and receive appropriate medication to lower serum LDL concentration to below 100 mg/dL, preferably to 70 mg/dL or lower. This often requires therapy

with a statin or Ezetimide (see Chapter 128). Weight loss, smoking cessation, avoidance of "recreational drugs" (e.g., cocaine), control of blood pressure, and an appropriate regular exercise program should be followed. Post-ACS treatment includes the use of long-term ASA and, in patients with PCI and stents, clopidogrel. Beta-blockers are protective against future MI, and angiotensin receptor antagonists help to protect injured arteries, control blood pressure, and provide additive benefit in patients with left ventricular dysfunction, most especially those patients with left ventricular ejection fractions (LVEFs) <40%.

Patients' resumption of their usual physical activities, including sex, driving a car, and returning to work, should be determined individually. However, in general, resumption of sex with one's usual partner may begin 2 to 3 weeks post-ACS and driving a car within 4 weeks. Returning to work is often delayed for at least 2 to 3 weeks, with a gradual resumption of perhaps one-half day initially.

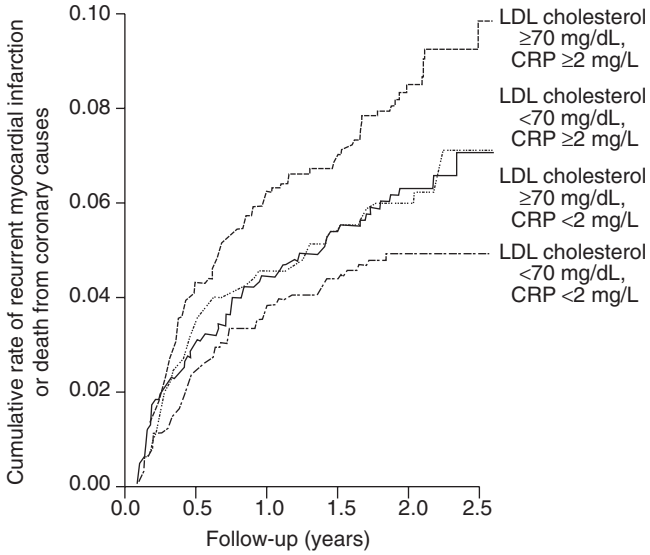
Summary

In the management of patients with unstable angina and NSTEMI, several points are of critical importance. First, one should recognize that these two acute coronary syndromes are closely related one to another and generally occur as a result of atherosclerotic plaque fissuring or ulceration allowing platelet aggregation, thrombosis, and dynamic vasoconstriction to occur at the site of the plaque injury. Unstable angina generally occurs when the periods of severe reduction in coronary blood flow persist for less than 20 minutes and NSTEMI when the period of coronary occlusion lasts between 30 minutes and 2 hours. In both instances, the occlusive thrombus and dynamic vasoconstriction are transient and a STEMI is prevented by the failure of the thrombus to remain permanently occlusive for longer periods of time. Patients with unstable angina and NSTEMI have a substantial risk of future coronary events within the subsequent 6 weeks as a result of persistent endothelial injury and recurrence of thrombosis and vasoconstriction in the absence of PCI or CABG treatment. The object of therapy in treating these syndromes acutely is to prevent the persistence of a thrombus with its associated vasoconstriction. Thus, initial therapy depends on (1) the administration of nitrates, usually in the form of intravenous nitroglycerin; (2) antithrombotic therapies, most especially aspirin, which is an inhibitor of thromboxane A_2, of platelet-white blood cell complexes, and of inflammation; and (3) an inhibitor of thrombin, either unfractionated or low molecular weight heparin. In patients who continue to have rest angina or angina at mild-to-moderate effort, one may prescribe additional antithrombotic medication, including clopidogrel or platelet glycoprotein IIb/IIIa antagonists when subsequent PCI is planned. Clopidogrel is continued long term in patients who have PCI. Beta-blockers should be added for patients with angina at limited effort, as well as those with elevated blood pressures or heart rates or considerable anxiety. They may also be useful in the treatment of complex ventricular ectopy. Angiotensin-converting enzyme inhibitors should be started early in the patient with an anterior MI, in patients with CHF, and in those with elevated blood pressures in whom there is no contraindication. When blood pressure and renal function allow, however, the ACE inhibitor potentially decreases coronary artery inflammation and may be useful in preventing ACS in the future.

In patients who continue to have rest angina or angina at mild-to-moderate effort despite a good medical regimen and in those with elevated serum CRP, or a troponin and in those with increased TIMI risk scores (3 or more), we recommend that the patient be taken to the cardiac catheterization laboratory for coronary arteriography to define the location and extent of the coronary disease and, ideally, the culprit lesion for coronary artery revascularization, PCI, or, when the coronary stenoses are diffuse and severe, CABG. In patients who are to receive PCI, the administration of a platelet GP IIb/IIIa receptor antagonist provides protection against the composite risks of MI, need for a second intervention, and death.

One of the major needs in contemporary cardiovascular medicine is to be able to identify those patients at risk for unstable angina/MI and their consequences in advance of their occurrence. Although it seems likely that one may need to evaluate coronary atherosclerotic plaques directly for characteristics that identify their instability (see Chapter 27A), presently one may use one of the following variables to identify patients at increased risk. Patients with increases in their troponin I or T with unstable angina/NSTEMI on admission are, in general, at increased risk for future unstable angina and MI. Similarly, patients with increases in their serum CRP on admission or at hospital discharge are also at increased risk for future unstable angina, MI, and their consequences. Patients with recurring ST-T wave changes consistent with recurrent myocardial ischemia are also at increased risk. Thus, one should plan a more aggressive management program for these patients, including earlier coronary arteriography and PCI or CABG. One may also identify patients at increased risk by using low-level stress perfusion or functional evaluations within a few days after presentation of the patient with unstable angina or NSTEMI and at a time that the patient has become angina free. Reversible stress perfusion or function alterations identify patients at increased risk for ACS in the subsequent weeks to months and should lead to further evaluation of these patients with coronary arteriography and either intensified medical therapy or PCI or CABG when their coronary artery anatomy is suitable.

Intensive LDL-lowering therapy early in the patient's course with a statin may also have subsequent beneficial results in reducing the risk of recurrent nonfatal MI and cardiovascular accident (CVA), especially in those with increased serum CD40l levels. There appears to be additional benefit in lowering both LDL and CRP levels with a potent statin acutely in patients with acute coronary syndromes (Fig. 39.22).[86] Indeed, de Winter et al.[87] were unable to show a benefit of early invasive (PCI or CABG) therapy in patients with unstable angina and NSTEMI who were treated by maximal medical therapy, including intensive lipid-lowering therapy, aspirin, enoxaparin for 48 hours, and abciximab at the time of percutaneous intervention.



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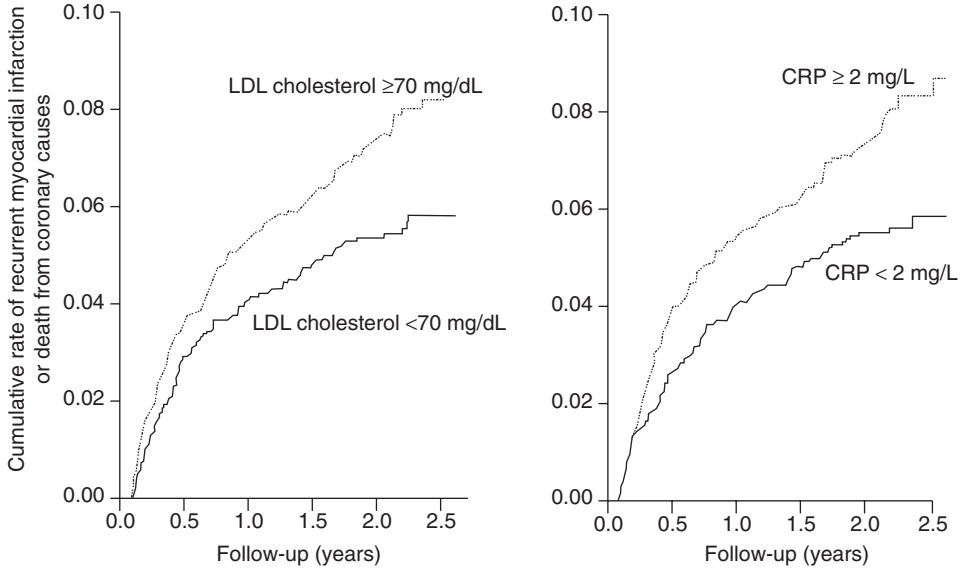

B

FIGURE 39.22. (A) Cumulative incidence of recurrent MI or death from coronary causes, according to whether the achieved LDL cholesterol or CRP levels are above or below the median. The approximate median value of LDL cholesterol was 70 mg/dL (1.8 mmol/L), and the median value of CRP was 2 mg/L. The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker. (B) Cumulative incidence of recurrent MI or death from coronary causes, according to the achieved levels of both LDL cholesterol and CRP. The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker.[86]

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