

PHARMACOLOGICAL TREATMENT OF UNSTABLE ANGINA (UA) AND NON ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (NSTEMI)

The optimal management of UA/NSTEMI has the twin goals of the immediate relief of ischemia and the prevention of serious adverse outcomes, such as death, infarction, or reinfarction. This is best accomplished with an approach that includes *anti-ischemic therapy*, *antiplatelet* and *antithrombotic therapy*.

CONVENTIONAL ANTI-ISCHEMIC THERAPY

Nitrates

Patients whose symptoms are not relieved with three 0.4-mg sublingual nitroglycerine (NTG) tablets or spray taken 5 min apart and the initiation of an intravenous β -blocker (when there are no contraindications), as well as all non-hypotensive high-risk patients, may benefit from intravenous NTG, and such therapy is recommended in the absence of contraindications (i.e., the use of sildenafil [Viagra] within the previous 24 h or hypotension). Sildenafil inhibits the phosphodiesterase (PDE5) that degrades cyclic guanosine monophosphate (cGMP), and cGMP mediates vascular smooth muscle relaxation by nitric oxide. Thus, NTG-mediated vasodilatation is markedly exaggerated and prolonged in the presence of sildenafil. Nitrate use within 24 h after sildenafil or the administration of sildenafil in a patient who has received a nitrate within 24 h has been associated with profound hypotension, MI, and even death¹.

Intravenous NTG may be initiated at a rate of 10 mg/min through continuous infusion with non-absorbing tubing and increased by 10 mg/min every 3 to 5 min until some symptom or blood pressure response is noted. If no response is seen at 20 mg/min, increments of 10 and, later, 20 mg/min can be used.

If symptoms and signs of ischemia are relieved, there is no need to continue to increase the dose to effect a blood pressure response.

If symptoms and signs of ischemia are not relieved, the dose should be increased until a blood pressure response is observed. Once a partial blood pressure response is observed, the dosage increase should be reduced and the interval between increments should be lengthened.

Side effects include headache and hypotension. Caution should be used when systolic blood pressure falls to <110 mm Hg in previously normotensive patients or to <25% below the starting mean arterial blood pressure if hypertension was present.

¹ Cheitlin MD, Hutter AMJ, Brindis RG, et al. ACC/AHA expert consensus document: use of sildenafil (Viagra) in patients with cardiovascular disease: American College of Cardiology/American Heart Association. J Am Coll Cardiol 1999;33:273– 82.

Although recommendations for a maximal dose are not available, a ceiling of 200 mg/min is commonly used. Prolonged (2 to 4 weeks) infusion at 300 to 400 mg/h does not increase methemoglobin levels.

Tolerance to nitrates is dose and duration dependent and typically becomes important after 24 h of continuous therapy with any formulation. Patients who require continued intravenous NTG beyond 24 h may require periodic increases in infusion rate to maintain efficacy.

An effort must be made to use non-tolerance-producing nitrate regimens, resorting to lower and intermittent dosing. For example, when patients have been free of pain and other manifestations of ischemia for 12 to 24 h, an attempt should be made to reduce the dose of intravenous NTG and to switch to oral or topical nitrates, with introduction of a nitrate-free window.

When ischemia recurs during continuous intravenous NTG therapy, responsiveness to nitrates can often be restored by increasing the dose and then, after symptoms have been controlled for several hours, attempting to add a nitrate-free interval.

Recent studies have also demonstrated that the supplemental use of antioxidants, especially vitamin C, appears to prevent nitrate tolerance².

β-Blockers

β-blockers provide convincing benefits with respect to mortality for patients with acute myocardial infarction, and much of this beneficial effect is thought to be mediated through the ability of these agents to decrease myocardial oxygen demand. Evidence supporting the use of beta-blockers in unstable angina, however, is based on limited data from randomized trials. A meta-analysis of these studies involving 4700 patients with unstable angina documented a 13% reduction in the risk of myocardial infarction among patients treated with β-blockers³.

The strong pathogenic link existing between unstable angina and acute myocardial infarction has led to the uniform recommendation that these medications be used as first-line agents in all acute coronary syndromes⁴. β-blockers should be started early in the absence of contraindications.

These agents should be administered intravenously followed by oral administration in high-risk patients, as well as in patients with ongoing rest pain or orally for intermediate-

² Bassenge E, Fink N, Skatchkov M, Fink B. Dietary supplement with vitamin C prevents nitrate tolerance. *J Clin Invest* 1998;102:67-71.

³ Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;260:2259-63.

⁴ Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Clinical practice guideline. No. 10. Rockville, Md.: Department of Health and Human Services, 1994.

and low-risk patients. The choice of β -blocker for an individual patient is based primarily on pharmacokinetic and side effect criteria, as well as on physician familiarity. There is no evidence that any member of this class of agents is more effective than another, except that β -blockers *without* intrinsic sympathomimetic activity are preferable. The initial choice of agents includes metoprolol, propranolol, or atenolol. Esmolol can be used if an ultrashort-acting agent is required.

Patients with marked first-degree AV block (i.e., PR interval of >0.24 s), any form of second- or third-degree AV block in the absence of a functioning pacemaker, a history of asthma, or severe LV dysfunction with congestive heart failure (CHF) **should not** receive β -blockers on an acute basis⁵.

Patients with significant sinus bradycardia (heart rate <50 bpm) or hypotension (systolic blood pressure <90 mm Hg) generally should not receive β -blockers until these conditions have resolved. Patients with COPD or mild wheezing should be administered β -blockers very cautiously; initially, low doses of a short-acting β_1 -selective agent, such as **metoprolol**, should be used (e.g., 2.5 mg metoprolol IV or 12.5 mg metoprolol orally), rather than avoidance of β -blockers administration.

In the absence of these concerns, several regimens may be used. For example, intravenous **metoprolol** may be given in 5-mg increments by slow intravenous administration (5 mg over 1 to 2 min), repeated every 5 min for a total initial dose of 15 mg. In patients who tolerate the total 15 mg IV dose, oral therapy should be initiated 15 min after the last intravenous dose at 25 to 50 mg every 6 h for 48 h. Thereafter, patients should receive a maintenance dose of 100 mg twice daily.

Alternatively, intravenous **propranolol** is administered as an initial dose of 0.5 to 1.0 mg, followed in 1 to 2 h by 40 to 80 mg by mouth every 6 to 8 h.

Intravenous **esmolol** is administered as a starting dose of 0.5 mg/Kg in 1 min followed by 50 mcg/kg for 4 min and eventually by a maintenance dose of 100-300 mcg/kg.

In patients suitable to receive a longer-acting agent, intravenous **atenolol** can be initiated with a 5-mg IV dose followed 5 min later by a second 5-mg IV dose and then 50 to 100 mg/d orally initiated 1 to 2 h after the intravenous dose.

Monitoring during intravenous β -blockers therapy should include frequent checks of heart rate and blood pressure and continuous ECG monitoring, as well as auscultation for rales and bronchospasm. After the initial intravenous load, patients without limiting side effects may be converted to an oral regimen. The target resting heart rate is 50 to 60 bpm, unless a limiting side effect is reached.

Morphine Sulfate

⁵ Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. J Am Coll Cardiol 1999;33:2092-197.

Morphine sulfate (1 to 5 mg IV) is recommended for patients whose symptoms are not relieved after 3 serial sublingual NTG tablets or whose symptoms recur despite adequate anti-ischemic therapy. Unless contraindicated by hypotension or intolerance, morphine may be administered along with intravenous NTG, with careful blood pressure monitoring, and may be repeated every 5 to 30 min as needed to relieve symptoms and maintain patient comfort.

Although morphine sulfate has potent analgesic and anxiolytic effects, as well as hemodynamic effects that are potentially beneficial in UA/NSTEMI, no randomized trials have defined the unique contribution of morphine to the initial therapeutic regimen or its optimal administration schedule.

Morphine causes venodilation and may produce modest reductions in heart rate (through increased vagal tone) and systolic blood pressure to further reduce myocardial oxygen demand.

The major adverse reaction to morphine is an exaggeration of its therapeutic effect, causing hypotension, especially in the presence of volume depletion and/or vasodilator therapy.

This reaction usually responds to supine or Trendelenburg positioning or intravenous saline boluses and atropine when accompanied by bradycardia.

Nausea and vomiting occur in <20% of patients. Respiratory depression is the most serious complication of morphine; severe hypoventilation that requires intubation occurs very rarely in patients with UA/NSTEMI treated with this agent. In those cases, naloxone (0.4 to 2.0 mg IV) may be administered for morphine overdose with respiratory and/or circulatory depression. Meperidine hydrochloride can be substituted in patients who are allergic to morphine.

Calcium-Channel Blockers

There are two main categories of calcium-channel blockers — the dihydropyridines (including nifedipine) and the non-dihydropyridines (including verapamil and diltiazem).

Both types cause coronary vasodilatation and reduce blood pressure. As compared with the non-dihydropyridines, the dihydropyridines exert a greater effect on vascular vasodilatation, have a smaller inhibitory effect on both the sinus and atrioventricular nodes, and have a smaller negative inotropic effect.

A meta-analysis of studies in which patients with unstable angina were treated with calcium-channel blockers found no effect of the drugs on the incidence of death or

myocardial infarction⁶. In patients who were not previously receiving beta-blockers, conventional nifedipine was associated with a 16 percent higher risk of myocardial infarction or recurrent angina than was placebo, whereas the combination of metoprolol and nifedipine was associated with a 20 percent lower incidence of these events (neither effect reached statistical significance)⁷. Rapid-release, short-acting dihydropyridines (e.g., nifedipine) *must be avoided* in the absence of adequate concurrent b-blockade in ACS. The probable explanation for the increased mortality among patients treated with nifedipine alone is that such therapy leads to reflex tachycardia and an increase in oxygen demand⁸.

In contrast with monotherapy with nifedipine, treatment with diltiazem and verapamil may impart advantages in terms of survival and reduced rates of reinfarction to patients with the acute coronary syndromes who have a normal ejection fraction and no evidence of pulmonary congestion on x-ray films (30% lower rates of mortality and reinfarction among patients treated with diltiazem than among those who received placebo after a mean follow-up period of 25 months)⁹.

Lowered heart rate, reduced myocardial contractility, and reduced afterload may be responsible for some of the observed benefits seen with the non-dihydropyridine agents in patients without impaired systolic function.

The use of calcium-channel blockers, especially the non-dihydropyridines, should be used in patients with ongoing or recurring ischemia-related symptoms despite adequate doses of nitrates and b-blockers, in patients who are unable to tolerate adequate doses of 1 or both of these agents, or in patients with variant angina. In addition, these drugs have been used for the management of hypertension in patients with recurrent UA.

Verapamil and diltiazem should be avoided in patients with pulmonary edema or evidence of severe LV dysfunction¹⁰. Amlodipine and felodipine, however, appear to be well tolerated by patients with chronic LV dysfunction¹¹.

⁶ Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;260:2259-63.

⁷ Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol* 1987;60:18A-25A.

⁸ Ferrari R. Prognosis of patients with unstable angina or acute myocardial infarction treated with calcium channel antagonists. *Am J Cardiol* 1996;77:22D-25D.

⁹ Théroux P, Taeymans Y, Morissette D, Bosch X, Pelletier GB, Waters DD. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol* 1985;5:717-22.

¹⁰ Hansen JF, Hagerup L, Sigurd B, et al. Cardiac event rates after acute myocardial infarction in patients treated with verapamil and trandolapril versus trandolapril alone. Danish Verapamil Infarction Trial (DAVIT) Study Group. *Am J Cardiol* 1997;79:738-41.

¹¹ Beevers DG, Sleight P. Short acting dihydropyridine (vasodilating) calcium channel blockers for hypertension: is there a risk? *BMJ* 1996;312:1143-5.

Thrombolytic Therapy

Despite the fact that initial small studies suggested that there is a benefit associated with thrombolysis in patients with unstable angina, more recent and larger clinical trials have clearly demonstrated that this therapy should be avoided. The TIMI IIIB trial demonstrated an actual increase in the rates of death, myocardial infarction, and bleeding in patients categorized as having unstable angina or non-Q-wave myocardial infarction^{12,13}. Other trials have confirmed the lack of benefit from the use of thrombolytic therapy in the acute coronary syndromes that are not associated with ST-segment elevation¹⁴.

Anti-Ischemic Therapy

The AHA/ACC recommendations for anti-ischemic therapy in patients with unstable angina or non ST-segment elevation myocardial infarction are summarized as followed:

Class I recommendations

Bed rest with continuous ECG monitoring for ischemia and arrhythmia detection in patients with ongoing rest pain. (*Level of Evidence: C*)

NTG, sublingual tablet or spray, followed by intravenous administration, for the immediate relief of ischemia and associated symptoms. (*Level of Evidence: C*)

Supplemental oxygen for patients with cyanosis or respiratory distress; finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation (SaO₂ >90%) and continued need for supplemental oxygen in the presence of hypoxemia. (*Level of Evidence: C*)

Morphine sulfate intravenously when symptoms are not immediately relieved with NTG or when acute pulmonary congestion and/or severe agitation is present. (*Level of Evidence: C*)

A β -blocker, with the first dose administered intravenously if there is ongoing chest pain, followed by oral administration, in the absence of contraindications. (*Level of Evidence: B*)

¹² Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. *Circulation* 1994;89:1545-56.

¹³ Bovill EG, Tracy RP, Knatterud GL, et al. Hemorrhagic events during therapy with recombinant tissue plasminogen activator, heparin, and aspirin for unstable angina (Thrombolysis in Myocardial Ischemia, phase IIIB trial). *Am J Cardiol* 1997;79:391-6.

¹⁴ Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1 000 patients. *Lancet* 1994;343:311-22.

In patients with continuing or frequently recurring ischemia when β -blockers are contraindicated, a nondihydropyridine calcium antagonist (e.g., verapamil or diltiazem) as initial therapy in the absence of severe LV dysfunction or other contraindications. (*Level of Evidence: B*)

An ACE inhibitor when hypertension persists despite treatment with NTG and a β -blocker in patients with LV systolic dysfunction or congestive heart failure and in patients with diabetes. (*Level of Evidence: B*)

ANTIPLATELET THERAPY

Antiplatelet therapy is a cornerstone in the management of UA/NSTEMI. Three classes of antiplatelet drugs (ASA, thienopyridines, and GP IIb/IIIa antagonists) have been found useful in the management of these patients and are the subject of continued intensive investigation and analysis.

Aspirin

Aspirin blocks platelet cyclooxygenase by irreversible acetylation, thus preventing the formation of thromboxane A₂. The Veterans Administration Cooperative Study¹⁵, the Canadian Multicenter Trial¹⁶, and the Montreal Heart Institute Study¹⁷ confirmed that aspirin reduces the risk of death from cardiac causes and fatal and nonfatal myocardial infarction by 51 to 72 percent in patients presenting with unstable angina.

Although no trial has directly compared the efficacy of different doses of ASA in patients who present with UA/NSTEMI, an overview of trials with different doses of ASA in long-term treatment of patients with CAD suggests similar efficacy for daily doses ranging from 75 to 324 mg¹⁸. It appears reasonable to initiate ASA treatment in patients with UA/NSTEMI at a dose of 160 mg, as used in the ISIS-2 trial¹⁹, or 325 mg. In patients who present with suspected ACS who are not already receiving ASA, the first dose may be chewed to rapidly establish a high blood level. Subsequent doses may be swallowed. Thereafter, daily doses of 75 to 325 mg are prescribed.

¹⁵ Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration cooperative study. *N Engl J Med* 1983;309:396-403.

¹⁶ Cairns JA, Gent M, Singer J, et al. Aspirin, sulfipyrazone, or both in unstable angina: results of a Canadian multicenter trial. *N Engl J Med* 1985;313:1369-75.

¹⁷ Th  roux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.

¹⁸ Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients.

¹⁹ ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet* 1988;2:349-60.

Contraindications to ASA include intolerance and allergy (primarily manifested as asthma), active bleeding, hemophilia, active retinal bleeding, severe untreated hypertension, an active peptic ulcer, or another serious source of gastrointestinal or genitourinary bleeding. Gastrointestinal side effects such as dyspepsia and nausea are infrequent with the low doses.

Adenosine Diphosphate Receptor Antagonists and Other Antiplatelet Agents

Two thienopyridines, ticlopidine and clopidogrel, are adenosine diphosphate (ADP) antagonists that are currently approved for antiplatelet therapy.

Since the mechanisms of the antiplatelet effects of aspirin and ADP antagonists differ, a potential exists for additive benefit with a combination therapy.

The platelet effects of ticlopidine and clopidogrel are irreversible. However, since the anti-platelet effects, unlike those of aspirin, take several days to become completely manifest, it ensues that in patients with UA/NSTEMI treated with either thienopyridines initial treatment with heparin (UFH or LMWH) and probably with a GP IIb/IIIa antagonist is especially important.

Ticlopidine

Ticlopidine has been used successfully for the secondary prevention of stroke and MI and for the prevention of stent closure and graft occlusion. In an open-label trial²⁰, 652 patients with UA were randomized to receive 250 mg ticlopidine twice a day or standard therapy without ASA. At 6-month follow-up, ticlopidine reduced the rate of fatal and nonfatal MI by 46% (13.6% vs. 7.3%). The benefit of ticlopidine in the study developed after only 2 weeks of treatment, which is consistent with the delay of the drug to achieve full effect. Unfortunately, the adverse effects of ticlopidine, including gastrointestinal problems, neutropenia (2.4% of patients), severe neutropenia (0.8% of patients), and, rarely, thrombotic thrombocytopenia purpura (TTP) limit its usefulness. Neutropenia usually resolves within 1 to 3 weeks of discontinuation of therapy, but very rarely may be fatal. TTP, which also is a very uncommon life-threatening complication, requires immediate plasma exchange. Hence, since monitoring of ticlopidine therapy requires a complete blood count including a differential count every 2 weeks for the first 3 months of therapy, clopidogrel is preferred to ticlopidine because it more rapidly inhibits platelets and appears to have a more favorable safety profile.

Clopidogrel

²⁰ Balsano F, Rizzon P, Violi F, et al. Antiplatelet treatment with ticlopidine in unstable angina: a controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990;82:17–26.

As stated above, given its more rapid onset of action and better safety profile compared with ticlopidine, clopidogrel is now the preferred thienopyridine.

The CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial²¹ randomized 12,562 patients with UA/STEMI who presented within 24 h to placebo or clopidogrel (loading dose of 300 mg followed by 75 mg daily) and followed them for 3 to 12 months; all patients were given aspirin.

Cardiovascular death, myocardial infarction (MI), or stroke occurred in 11.5% of patients assigned to placebo and 9.3% of those assigned to clopidogrel.

However, there was a significant increase in major and minor bleeding, as well as a non-significant trend for an increase in life-threatening bleeding. The risk of bleeding was increased in patients who underwent coronary artery bypass grafting (CABG) within the first 5 days after clopidogrel was discontinued.

Since the CURE trial was performed in hospitals in which there was *no* routine policy of early invasive procedures, Clopidogrel appears to be especially useful in hospitals without early PCI availability, and in patients who are not candidates or do not wish to be considered for revascularization. The optimal duration of therapy with clopidogrel has not been determined. However, the major benefits in CURE were observed at 30 days, with small additional benefits observed over the subsequent treatment period.

In PCI-CURE, a substudy of CURE, in 2,658 patients with UA and NSTEMI who were given ASA and underwent PCI, a strategy of clopidogrel pretreatment followed by at least 1 month and probably longer-term therapy proved to be beneficial in reducing major cardiovascular events.

There now appears to be an important role for clopidogrel in patients with UA/NSTEMI, both those who are managed conservatively and those who undergo PCI, especially stenting.

However, since clopidogrel, when added to ASA, increases the risk of bleeding during major surgery in patients who are scheduled for CABG, if possible, clopidogrel should be withheld for at least 5 days and preferably for 7 days before surgery.

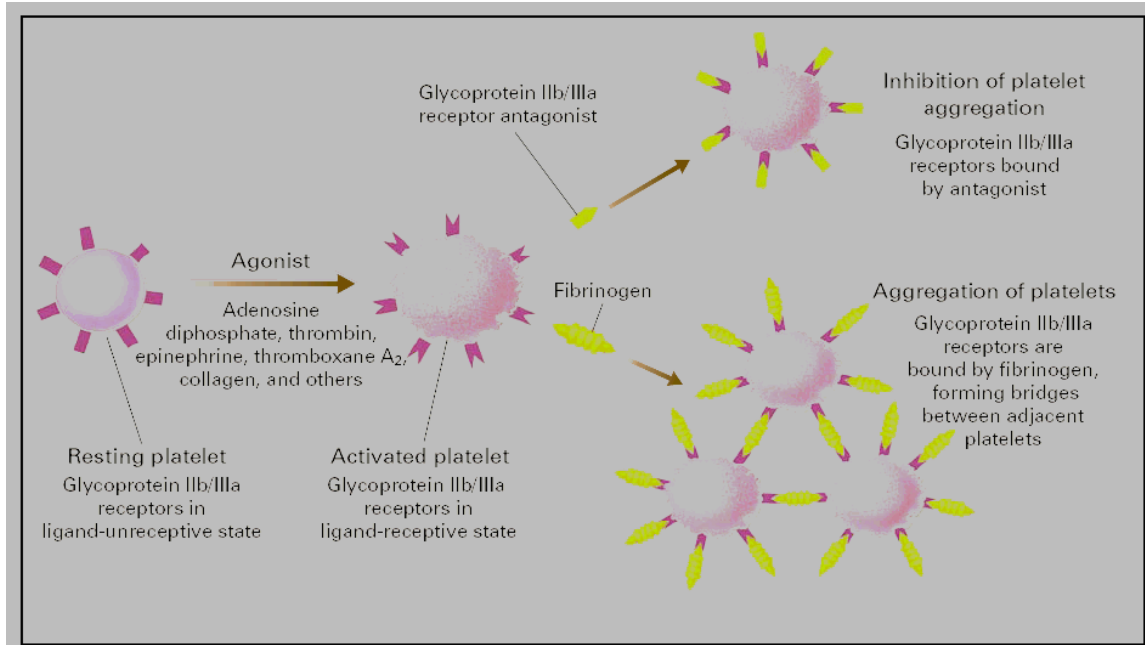
Glycoprotein IIb/IIIa antagonists in PCI.

Unlike antiplatelet agents that target only one of many individual pathways involved in platelet aggregation, antagonists of glycoprotein IIb/IIIa, a receptor on the platelet for adhesive proteins such as fibrogen and von Willebrand factor, maximally inhibit the final common pathway involved in platelet adhesion, activation, and aggregation. The

²¹ Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.

processes of platelet activation/aggregation and inhibition of platelet aggregation by inhibitors of glycoprotein IIb/IIIa receptors are depicted in the figure below.

Three classes of glycoprotein IIb/IIIa inhibitors have been developed: murine–human chimeric antibodies (e.g., abciximab), synthetic peptide forms (e.g., eptifibatide), and synthetic nonpeptide forms (e.g., tirofiban and lamifiban)²².



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

Glycoprotein IIb/IIIa antagonists in PCI

The introduction of platelet GP IIb/IIIa antagonists represents an important advance in the treatment of patients with UA/ NSTEMI who are undergoing PCI. These drugs take advantage of the fact that platelets play an important role in the development of ischemic complications that may occur in patients with UA/NSTEMI during coronary revascularization procedures.

The glycoprotein IIb/IIIa antagonists consistently reduce the 30-day relative risk of the composite end point of death, myocardial infarction, or the need for repeated

²² Madan M, Berkowitz SD, Tchong JE. Glycoprotein IIb/IIIa integrin blockade. *Circulation* 1998;98:2629-35.

revascularization by 22 to 56% when they are administered with unfractionated heparin and aspirin, but they have no effect on mortality alone. The magnitude of benefit varied among the trials.

In one of the first trials (Evaluation of 7E3 for the Prevention of Ischemic Complications trial)²³, patients at high risk for abrupt vessel closure were randomly assigned to receive a bolus of abciximab alone, a bolus of abciximab followed by a 12-hour infusion, or placebo. As compared with placebo, treatment with the abciximab bolus plus infusion resulted in a 35% reduction in the incidence of the composite end point at 30 days (8.3% vs. 12.8%), a 23% reduction at 6 months (27% vs. 35.1%), and a 13% reduction at 3 years (41.1% vs. 47.2%), although the rate of major bleeding was twice as high in this group as in the placebo group. Mortality at 30 days was similarly low (1.7%) in each group, but at 3 years, evolving myocardial infarction or unstable angina was 60% less common (5.1% vs. 12.7%) among the high-risk patients who received the abciximab bolus plus infusion than among those who received placebo.

In the TARGET trial (Do Tirofiban and ReoPro Give similar Efficacy? Trial) the only head-to-head comparison of GP IIb/IIIa antagonists, over 5000 patients were randomized to tirofiban or abciximab before PCI with the intent to perform stenting²⁴. The primary end point, a composite of death, nonfatal MI, and urgent target-vessel revascularization at 30 days, occurred less frequently in those given abciximab than in those given tirofiban (6.0% vs. 7.6%). There was a similar direction and magnitude for each component of the end point. The difference in outcome between the 2 treatment groups may be related to a suboptimal dose of tirofiban, resulting in inadequate platelet inhibition. However, by six months, the primary end point occurred in a similar percentage of patients in each group (14.9% tirofiban vs. 14.3% abciximab). Mortality was also similar (1.9% vs. 1.7%)²⁵.

Glycoprotein IIb/IIIa antagonists without scheduled PCI.

A meta-analysis of GP IIb/IIIa antagonists in 6 large, randomized, placebo-controlled trials (involving 31,402 patients with UA/NSTEMI who were not routinely scheduled to undergo coronary revascularization) was recently performed²⁶.

A small reduction in the odds of death or MI in the active treatment arm (11.8% vs 10.8%) was observed.

²³ The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956-61.

²⁴ Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;344:1888-94.

²⁵ Roffi M, Moliterno DJ, Meier B, et al. Impact of different platelet glycoprotein IIb/IIIa receptor inhibitors among diabetic patients undergoing percutaneous coronary intervention: do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial (TARGET) 1-year follow-up. *Circulation* 2002;105:2730-6.

²⁶ Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189-98.

Unexpectedly, no benefit was observed in women, with the exception of women at higher risk (positive troponins), who derived a treatment benefit similar to men.

Although not scheduled for coronary revascularization procedures, 11,965 of the 31,402 patients (38%) actually underwent PCI or CABG within 30 days, and in this subgroup, death or MI in patients assigned to GP IIb/IIIa antagonists were significantly reduced.

On the contrary, in the other 19,416 patients who did not undergo coronary revascularization, the odds of death or MI in the GP IIb/IIIa group were not different from those of the untreated group.

Major bleeding complications were increased in the GP IIb/IIIa antagonist-treated group as compared to the placebo group (2.4 vs. 1.4%, $p < 0.0001$).

Hence, GP IIb/IIIa inhibitors are of benefit in high-risk patients with UA/NSTEMI who are not routinely scheduled for early revascularization, while their use in patients who do not undergo PCI is questionable.

Anticoagulant Therapy

Anticoagulation therapy can be achieved by means of indirect (unfractionated heparin, and low molecular weight heparin) or direct

Unfractionated heparin is a glycosaminoglycan made up of polysaccharide chains ranging in molecular weight from 3000 to 30,000. These polysaccharide chains bind to antithrombin III and cause a conformational change that accelerates the inhibition of thrombin and factor Xa by antithrombin III. A meta-analysis showed a 33% lower incidence of myocardial infarction or death among patients who received combination therapy with aspirin and unfractionated heparin than among those who received aspirin alone²⁷.

Current practice guidelines support the use of the combination of unfractionated heparin and aspirin for the treatment of unstable angina. The maximal duration of continuous infusion in patients without symptoms is 48 hours after admission, since longer treatment may result in a higher incidence of death or myocardial infarction than shorter treatment²⁸; if symptoms persist, however, the infusion is continued until an invasive intervention can be performed. Despite its extensive use in treating the acute coronary syndromes, unfractionated heparin has the disadvantage of variability in its dose–response curve. This variability is due to the fact that unfractionated heparin binds competitively to plasma proteins other than antithrombin.

²⁷ Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. *JAMA* 1996;276:811-5.

²⁸ Klein LW, Wahid F, VandenBerg BJ, Parrillo JE, Calvin JE. Comparison of heparin therapy for < or = 48 hours to > 48 hours in unstable angina pectoris. *Am J Cardiol* 1997;79:259-63.

Other disadvantages contributing to a further reduction in the heparin-mediated antithrombotic activity include: the resistance of clot-bound thrombin to inhibition by heparin, and the sensitivity of heparin to platelet factor 4. In addition, the potential occurrence of the idiosyncratic and unpredictable serious side effect of heparin-induced thrombocytopenia creates a compelling need for other antithrombin agents²⁹.

Low-Molecular-Weight Heparins

Unlike unfractionated heparin, preparations of low-molecular-weight heparin have in common a predictable pharmacokinetic profile, high bioavailability, a long plasma half-life, and an easy means of administration (subcutaneous injection), without the need to monitor activated partial-thromboplastin time³⁰.

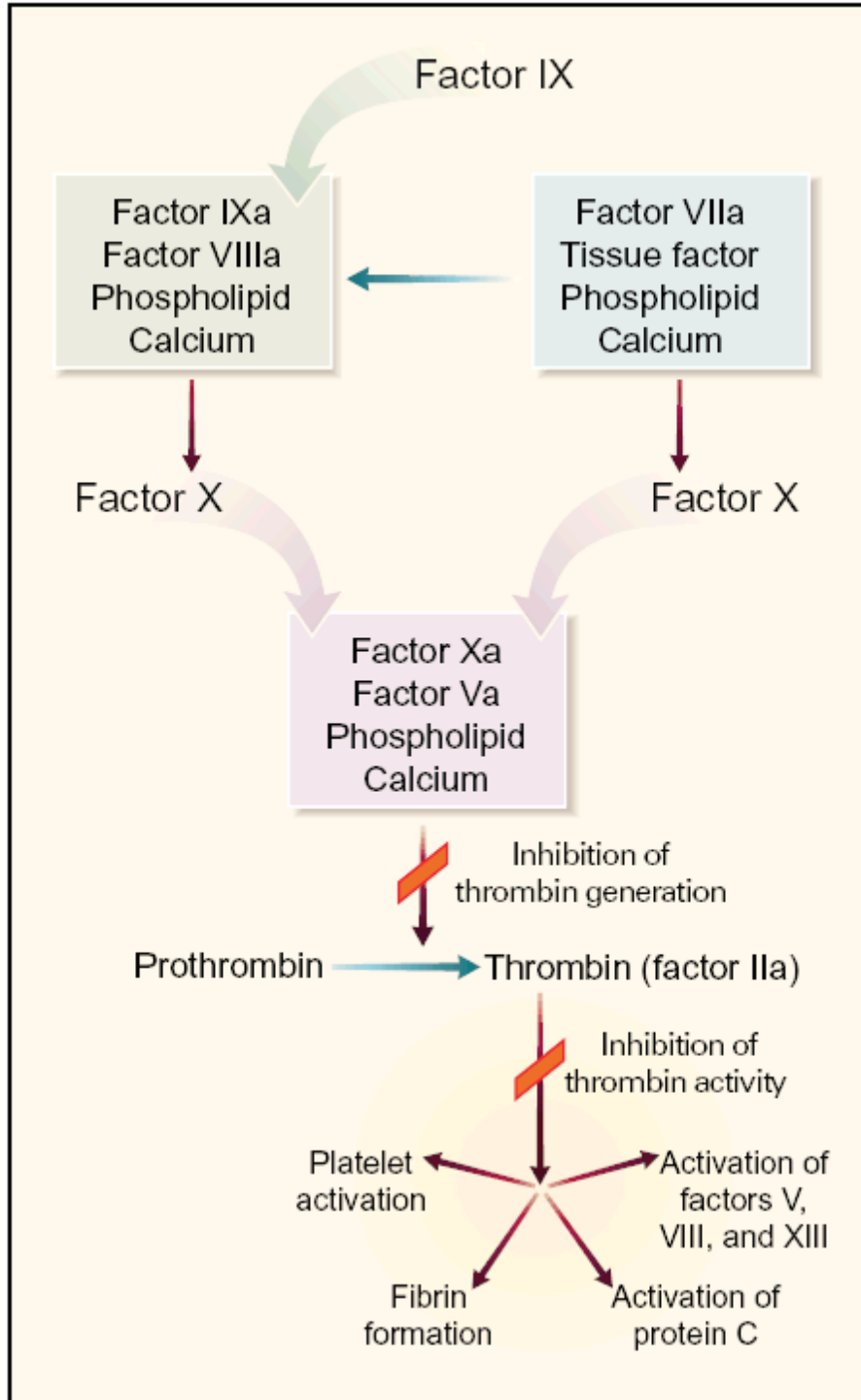
Preparations of low molecular-weight heparin and their anti-factor Xa:anti-factor IIa ratios.

PREPARATION	MEAN MOLECULAR WEIGHT	ANTI-FACTOR Xa: ANTI-FACTOR IIa RATIO
Ardeparin	6000	1.9
Dalteparin	6000	2.7
Enoxaparin	4200	3.8
Nadroparin	4500	3.6
Reviparin	4000	3.5
Tinzaparin	4500	1.9

Short-chain (<18 saccharides) fragments of low-molecular-weight heparin have been formulated, with varying anti-factor Xa:anti-factor IIa ratios (Table 1). Higher ratios of anti-factor Xa to anti-factor IIa activity provide for potent inhibition of thrombin generation as well as inhibition of thrombin activity (See figure below).

²⁹ Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-5.

³⁰ Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997;337:688-98.



Role of Factors Xa and IIa (Thrombin) in Coagulation

Indirect antithrombins, such as low-molecular-weight heparins, bind both factors IIa and Xa, thus reducing both thrombin activity and thrombin generation. In contrast, direct thrombin inhibitors are less efficacious clinically, because they inhibit the action of thrombin (factor IIa) only.

The efficacy of low-molecular-weight heparins in the treatment of unstable angina has been variable, depending on the particular preparation used, which seems to reflect differences in the anti-factor Xa:anti-IIa ratios.

Low-ratio preparations are associated with outcome data that are similar to those of unfractionated heparin, whereas high-ratio preparations produce superior results.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events study demonstrated that the incidence of the composite end point of death, myocardial infarction, or recurrent angina was lower with enoxaparin than with unfractionated heparin, at 14 days (incidence, 16.6% vs. 19.8%) and at 30 days (19.8% vs. 23.3%), although there was no significant difference in the rate of death alone³¹.

The recent Thrombolysis in Myocardial Infarction (TIMI) 11B study confirmed that enoxaparin is superior to unfractionated heparin in reducing the composite end point of myocardial infarction and emergency revascularization without causing a significant increase in the rate of major bleeding. There was, however, no significant difference in mortality³².

Because the level of anticoagulant activity cannot be easily measured in patients given LMWH (e.g., activated partial thromboplastin time or activated clotting time), interventional cardiologists have expressed concern about the substitution of LMWH for UFH in patients scheduled for catheterization with possible PCI. However, a small nonrandomized observational study carried out in 293 patients showed that PCI can be performed safely with UA/NSTEMI patients who received the usual dose of enoxaparin³³.

In addition, since the anticoagulant effect of UFH can be more readily reversed than that of LMWH, UFH is preferred in patients likely to undergo CABG within 24 hour.

Direct Antithrombins

Unlike indirect thrombin inhibitors (e.g., unfractionated heparin or low-molecular-weight heparins), which bind both factor IIa and factor Xa, the direct antithrombins inhibit thrombin formation in a manner that is independent of antithrombin III activity and primarily decrease thrombin activity.

Direct antithrombins, which include hirudin, hirulog, argatroban, efegatran, and inogatran, may inhibit clot-bound thrombin more effectively than indirect thrombin

³¹ Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447-52.

³² Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-601.

³³ Collet JP, Montalescot G, Lison L, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. *Circulation* 2001;103:658-63.

inhibitors. Hirudin, the prototype of the direct thrombin inhibitors, has been extensively studied.

In the recent Organization to Assess Strategies for Ischemic Syndromes trial³⁴, therapy with recombinant hirudin in patients with acute myocardial ischemia without ST-segment elevation seemed to be superior to therapy with unfractionated heparin in preventing death, myocardial infarction, and refractory angina, both at 72 hours and at 7 days, although a higher rate of major bleeding was observed in the hirudin group (1.2% vs. 0.7%).

In contrast, the effect of inogatran on the composite end point of death, myocardial infarction, or refractory angina was not significantly different from that of unfractionated heparin³⁵.

To date, the efficacy and safety of direct antithrombins as primary antithrombotic therapy in patients with unstable angina have not been widely accepted and additional trials testing safety and efficacy of direct antithrombins in UA/NSTEMI appear warranted.

Hirudin (lepirudin) is presently indicated only for anticoagulation in patients with heparin-induced thrombocytopenia³⁶ and for the prophylaxis of deep vein thrombosis in patients undergoing hip replacement surgery. It should be administered as a 0.4 mg/kg IV bolus over 15 to 20 seconds followed by a continuous intravenous infusion of 0.15 mg·kg⁻¹·h⁻¹, with adjustment of the infusion to a target range of 1.5 to 2.5 times the control aPTT values.

Warfarin

Warfarin monotherapy appears to be at least as effective after myocardial infarction as aspirin in preventing death or recurrent myocardial infarction, but whether warfarin and aspirin as combination therapy for the acute coronary syndromes actually improve prognosis remains unclear.

The Antithrombotic Therapy in Acute Coronary Syndromes study showed that combination therapy with aspirin and anticoagulants (heparin followed by warfarin, with a target *international normalized ratio* [INR] of 2.0 to 3.0) for 12 weeks resulted in a reduction of approximately 60% in the primary end points of recurrent angina with electrocardiographic changes, myocardial infarction, death, or all three at 14 days, as

³⁴ Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularization procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999;353:429-38.

³⁵ Thrombin Inhibition in Myocardial Ischaemia (TRIM) Study Group. A low molecular weight, selective thrombin inhibitor, inogatran, vs heparin, in unstable coronary artery disease in 1209 patients: a double-blind, randomized, dose-finding study. *Eur Heart J* 1997;18:1416-25.

³⁶ Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-5.

compared with aspirin alone³⁷. A nearly 50% reduction in ischemic events continued to be observed at three months, and the rate of bleeding complications was only slightly higher in the combination-therapy group than in the aspirin-alone group.

Conversely, The Coumadin Aspirin Reinfarction Study (CARS) conducted in post MI patients was discontinued prematurely due to a lack of evidence of benefit of reduced-dose ASA (80 mg/d) with either 1 or 3 mg warfarin daily, as compared with 160 mg/d ASA alone³⁸.

More recently, attention has turned to moderate-intensity warfarin therapy plus aspirin as treatment for the acute coronary syndromes. Combination therapy with a target INR of 2.0 to 2.5 for 10 weeks after the initial presentation of unstable angina produced a significantly better clinical and angiographic outcome than aspirin monotherapy, without any difference in the frequency of bleeding³⁹

A more recent report from the Organization to Assess Strategies for Ischemic Syndromes pilot study⁴⁰ suggested that aspirin combined with long-term, moderate-intensity warfarin therapy (with a target INR of 2.0 to 2.5), rather than with low-intensity warfarin therapy (with an INR of 1.5), produced lower rates of death, new myocardial infarction, and stroke than aspirin alone at three months. However, this benefit occurred at the expense of an appreciable increase in bleeding in the group receiving moderate-intensity warfarin therapy.

Hence, low- or moderate-intensity anticoagulation with fixed-dose warfarin is not recommended for routine use after hospitalization for UA/NSTEMI.

Warfarin should be prescribed, however, for UA/NSTEMI patients with established indications for warfarin, such as atrial fibrillation and mechanical prosthetic heart valves.

Thrombolytic Therapy

Despite the fact that initial small studies suggested that there is a benefit associated with thrombolysis in patients with unstable angina, more recent and larger clinical trials have clearly demonstrated that this therapy should be avoided. The TIMI IIIB trial demonstrated an actual increase in the rates of death, myocardial infarction, and bleeding

³⁷ Cohen MC, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users: primary end points analysis from the ATACS Trial. *Circulation* 1994;89:81-8.

³⁸ Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet* 1997;350:389-96.

³⁹ Williams MJA, Morison IM, Parker JH, Stewart RAH. Progression of the culprit lesion in unstable coronary artery disease with warfarin and aspirin versus aspirin alone: preliminary study. *J Am Coll Cardiol* 1997;30:364-9.

⁴⁰ Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study results. *Circulation* 1998;98:1064-70.

in patients categorized as having unstable angina or non-Q-wave myocardial infarction⁴¹ Other trials have confirmed the lack of benefit from the use of thrombolytic therapy in the acute coronary syndromes that are not associated with ST-segment elevation⁴²

In conclusion, clopidogrel (in addition to aspirin and heparin or low molecular weight heparin) is recommended for patients with UA/NSTEMI in whom a non-interventional approach is planned (Class I recommendation).

In patients in whom an interventional approach is planned, a GP IIb/IIIa inhibitor (in addition to aspirin and heparin or low molecular weight heparin) is recommended (Class I recommendation).

No head-to-head comparison of clopidogrel, a GP IIb/IIIa inhibitor, and their combination has been reported. The addition of a GP IIb/IIIa inhibitor to a subset of patients in the CURE trial who were receiving aspirin, clopidogrel, and heparin appeared to be well tolerated, and current practice frequently involves the use of this combination of drugs. However, until further information on the safety and efficacy of such quadruple therapy becomes available, a Class IIa recommendation is made for the addition of a GP IIb/IIIa inhibitor for patients with UA/NSTEMI who are receiving aspirin, clopidogrel, and unfractionated or low molecular weight heparin and who are referred for an invasive strategy.

A Class I recommendation is made for a GP IIb/IIIa inhibitor at the time of PCI in patients receiving heparin and aspirin.

The AHA/ACC recommendations for the use of antiplatelet/anticoagulant regimens in UA/NSTEMI patients are as follows:

Class I recommendations

Antiplatelet therapy should be initiated promptly. ASA should be administered as soon as possible after presentation and continued indefinitely. (*Level of Evidence: A*)

Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (*Level of Evidence: A*)

⁴¹ Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. *Circulation* 1994;89:1545-56.

⁴² Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1 000 patients. *Lancet* 1994;343:311-22.

In hospitalized patients in whom an early non-interventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month (*Level of Evidence: A*), and for up to 9 months. (*Level of Evidence: B*)

Parenteral anticoagulation with intravenous unfractionated heparin (UFH) or with subcutaneous LMWH should be added to antiplatelet therapy with ASA, or a thienopyridine. (*Level of Evidence: A*)

A platelet GP IIb/IIIa receptor antagonist should be administered, in addition to ASA and UFH, to patients with continuing ischemia or with other high-risk features (Table 6) and to patients in whom a PCI is planned. Eptifibatid and tirofiban are approved for this use. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (*Level of Evidence: A*)

In patients for whom a PCI is planned and who are not at high risk for bleeding, clopidogrel should be started and continued for at least 1 month (*Level of Evidence: A*) and for up to 9 months. (*Level of Evidence: B*)

In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld for 5 to 7 days. (*Level of Evidence: B*)

EARLY CONSERVATIVE VS. EARLY INVASIVE STRATEGIES: WHICH ONE IS BETTER?

The September 2000 AHA/ACC guidelines indicated that 2 different treatment strategies, termed “early conservative” and “early invasive,” may be used in patients with UA/NSTEMI⁴³.

In the *early conservative strategy*, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest or with minimal activity or dynamic STsegment changes) or a strongly positive stress test despite vigorous medical therapy.

In the *early invasive strategy*, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and angiographically directed revascularization, if possible.

Several trials comparing these 2 strategies were reviewed, but greatest attention was paid to the FRISC II (Fragmin and Fast Revascularization during InStability in Coronary artery disease II) trial⁴⁴.

⁴³ Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-STsegment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970–1062.

At 1 year, the mortality rate in the invasive strategy group was 2.2% compared with 3.9% in the noninvasive strategy group. However, in FRISC II, the invasive strategy involved treatment for an average of 6 days in the hospital with LMWH, ASA, nitrates, and beta-blockers before coronary angiography, an approach that would be difficult to adopt in U.S. hospitals.

In the interim, the TACTICS-TIMI 18 trial was reported⁴⁵. In this trial, 2,220 patients with UA or NSTEMI were treated with ASA, heparin, and the GP IIb/IIIa antagonist tirofiban. They were then randomized to an early invasive strategy with routine coronary angiography within 48 hours followed by revascularization if the coronary anatomy was deemed suitable, or to a more conservative strategy. In the latter, catheterization was performed only if the patient had recurrent ischemia or a strongly positive stress test. Death, myocardial (re)infarction, or rehospitalization for an acute coronary syndrome at 6 months occurred in 19.4% of patients assigned to the conservative strategy vs. 15.9% assigned to the invasive strategy. Occurrence of death or MI was also reduced at 6 months.

The beneficial effects on outcome were particularly evident in medium- and high-risk patients, as defined by an elevation of troponin T greater than 0.01 ng/ml or of troponin I greater than 0.1 ng/ml, the presence of ST segment deviation, or a TIMI risk score greater than or equal to 3.

In the absence of these high-risk features, outcomes in patients assigned to the 2 strategies were similar. Rates of major bleeding were similar, and lengths of hospital stay were reduced in patients assigned to the invasive strategy.

The benefits of the invasive strategy were achieved at no significant increase in the cost of care over the 6-month follow-up period. Thus, both the FRISC II and TACTICS-TIMI 18 trials, the 2 most recent trials comparing invasive vs. conservative strategies in patients with UA/NSTEMI, showed a benefit in patients assigned to the invasive strategy.

Class I recommendations

An early invasive strategy in patients with UA/NSTEMI without serious comorbidity and who have any of the following high-risk indicators: (*Level of Evidence: A*)

⁴⁴ Pozen MW, D'Agostino RB, Selker HP, Sytkowski PA, Hood WBJ. A predictive instrument to improve coronary-care-unit admission practices in acute ischemic heart disease: a prospective multicenter clinical trial. *N Engl J Med* 1984;310:1273–8.

⁴⁵ Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879–87.

In the absence of any of these findings, either an early conservative or an early invasive strategy may be offered in hospitalized patients without contraindications for revascularization. (*Level of Evidence: B*)

RISK FACTOR MODIFICATION

The September 2000 guidelines pointed out that despite the overwhelming evidence for the benefits of beta-hydroxybeta-methylglutaryl-coenzyme A (HMG-CoA) reductase (statin) therapy in patients with elevated low-density lipoprotein (LDL) cholesterol levels, almost no data existed about the timing of initiation of therapy in patients with acute coronary syndromes.

Although several trials are ongoing, there appear to be no adverse effects and substantial advantages to the initiation of lipid-lowering therapy before hospital discharge.

Such early initiation of therapy has also been recommended in the third report of the National Cholesterol Education Program (NCEP III), which also raised the threshold of high-density lipoprotein cholesterol concentration that required therapy.

Similar considerations apply to the early initiation of statin therapy following PCI.

In addition to maintaining the original Class I recommendations for LDL cholesterol reduction, specific additional recommendations for the use of lipid-lowering therapy in UA/NSTEMI in the revised guidelines are as follows:

Class I recommendations

A fibrate or niacin if high-density lipoprotein cholesterol is less than 40 mg per dl, occurring as an isolated finding or in combination with other lipid abnormalities. (*Level of Evidence: B*)

Class IIa recommendations

HMG-CoA reductase inhibitors and diet for LDL cholesterol greater than 100 mg per dl begun 24 to 96 h after admission and continued at hospital discharge. (*Level of Evidence: B*)