Subject Review

Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

Perspectives on Combination Therapy

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We reviewed recent clinical data on the management of unstable angina and non-ST-segment elevation myocardial infarction. We concentrated on the use of new therapies, particularly in combination with both older agents and other new methods, in order to present health care providers with an overview of available treatment options.

The clinical trials reviewed herein provide strong evidence and proof of principle that combination therapies targeting 1) platelet function (aspirin, thienopyridines, and GP IIb/IIIa antagonists), 2) the coagulation cascade (unfractionated heparin and low-molecular-weight heparin), and 3) the physical characteristics of the active lesion (percutaneous intervention) reduce the risk of death or ischemic complications after thrombotic progression of coronary atherosclerosis. ***(Tex Heart Inst J 2001;28:276-87)***

Unstable angina and non-ST elevation myocardial infarction (NSTEMI) are responsible for approximately 5.3 million emergency-room visits and 1.4 million hospitalizations per year in the United States alone.[1,2] Such illnesses present a tremendous burden both to individual patients and to the health care system in general. It is therefore essential that health care providers become familiar with recent clinical data concerning the management of these conditions and the use of new therapies, particularly in combination with both older agents and other new methods.

In most instances, the precipitating event for rapid progression of atherosclerotic disease is rupture or erosion of an advanced atherosclerotic plaque. Platelet attachment, activation, accumulation, and fibrin deposition at the site of rupture effect a drastic change in vessel lumen characteristics, the severity of which can vary from moment to moment. This sequence of events and the resultant interruption of myocardial blood supply can result in new or rapidly worsening symptoms of coronary artery disease, such as unstable angina or myocardial infarction (MI). Evidence from autopsy studies suggests that such rapid disease progression is also responsible for a substantial proportion of sudden cardiac deaths.[3,4] The platelet and blood coagulation mechanisms at work in this situation have provided the rationale for a large number of clinical trials, which have examined the impact of antiplatelet and anticoagulant therapy on the natural progression of unstable atherosclerotic disease. We briefly review the currently available antiplatelet and anticoagulant agents and the clinical trials that have evaluated their combined use in patients with unstable angina and NSTEMI.

Key words: *Angina, unstable; angioplasty, transluminal, percutaneous coronary; anticoagulants; antithrombotics; aspirin; atherosclerosis; clinical trials; drug therapy, combination; heparin; heparin, low-molecular-weight; myocardial infarction; platelet aggregation inhibitors; platelet glycoprotein IIb/IIIa complex*

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Pharmacologic Agents and Clinical Trial Results

Antiplatelet Therapy

Aspirin (ASA) exerts its antiplatelet effect by acetylating a key serine moiety (serine 530) of cyclooxygenase-1. Irreversible inhibition of cyclooxygenase-1 prevents the transformation of arachidonic acid to thromboxane A_2, impairing thromboxane-dependent platelet aggregation (although not aggregation in response to other agonists). The use of ASA as part of routine therapy for unstable angina is supported by the results of 4 randomized clinical trials and 1 meta-analysis (Table I[5-11]). The

TABLE I. Summary of Selected Clinical Trials Using Aspirin and Unfractionated Heparin

Trials (Year)	No. Patients	Treatment Regimen	Death or MI Event Rates at 5 Days–2 Years (%)			
			Plac/Ctrl	Active	*P*	NNT
ASA vs Placebo						
VA Cooperative (1983)[5]	1,266	ASA 324 mg/d vs placebo for 12 wk	10.1	5	0.0005	20
Canadian Multicenter Trial (1985)[6]	555	ASA 1300 mg/d vs sulfinpyrazone 800 mg/d vs both vs placebo for up to 2 y	38.1	12.2	0.008	4
Theroux P, et al. (1988)[7]	479	2 × 2 factorial design; ASA 650 mg/d vs placebo for 6 ± 3 d; UFH 5000 U bolus, then 1000 U/h vs placebo	13.6	3.3	0.012	10
RISC Group (1990)[8]	388	ASA 75 mg/d vs placebo for 1 y	17.6	7.4	0.003	10
ACC/AHA Meta-Analysis (2000)[9]	2,448	ASA vs placebo	12.5	6.4	0.0005	16
UFH + ASA vs ASA						
Theroux P, et al. (1988)[7]	479	ASA 650 mg/d vs ASA + UFH 5000-U bolus, then 1000 U/hr for 6 ± 3 d	3.3	1.6	0.4	—
RISC Group (1990)[8]	796	ASA 75 mg/d with or without intermittent IV UFH for 5 d	3.7	1.4	0.14	—
ATACS Group (1994)[10]	214	ASA 162.5 mg/d vs ASA + UFH 100 U/kg, then infusion + warfarin INR 2.0–3.0 for 12 wk	8.3	3.8	0.17	—
Gurfinkel EP, et al. (1995)[11]	219	ASA 200 mg/d vs ASA + UFH 5000-IU bolus, then 400 IU/kg body weight per day for 5–7 d	9.6	5.7	0.38	—
ACC/AHA Meta-Analysis (2000)[9]	999	UFH + ASA vs ASA	5.5	2.6	0.018	34

ASA = aspirin; Ctrl = control; INR = international normalized ratio; MI = myocardial infarction; NNT = number needed to treat; Plac = placebo; UFH = unfractionated heparin

Veterans Administration Cooperative Study[5] randomized 1,266 men with unstable angina to 3 months of treatment with ASA or placebo. In patients treated with ASA, the overall relative risk reduction (RRR) for the incidence of death or any MI was 50% (10.1% vs 5% with ASA, *P*=0.0005). A Canadian Multicenter Trial[6] was a placebo-controlled trial that compared the efficacy of ASA, sulfinpyrazone, both, or placebo in 555 patients with unstable angina. After a mean follow-up of 18 months, there was a striking RRR of 70.6% in subjects treated with ASA (from 12.9% to 6% with ASA, *P*=0.004) for the endpoint of cardiac death or death from any cause. The Antiplatelet Trialists' Collaboration meta-analysis[12] combined the results of 145 randomized clinical trials of prolonged antiplatelet therapy in 70,000 high-risk patients and 30,000 low-risk patients from the general population. Of these, 7 trials comprised a total of 4,018 patients with unstable angina. The vascular event rate at 6 months was reduced from 14% to 9% with ASA therapy (RRR, 35%; 95% CI, 21%–49%).

Summary. Data for the use of ASA are compelling. A useful way to view these data is in terms of the number needed to treat (NNT), defined as the number of patients who need to receive the intervention to prevent 1 bad outcome. The NNT for aspirin is very low (Table I). Therefore, the use of ASA is strongly advocated as 1st-line therapy in all patients with an acute coronary syndrome (ACS) who can tolerate ASA.

Anticoagulation Therapy

Unfractionated Heparin. Unfractionated heparin is a heterogeneous mixture of varying-length polysaccharide chains (molecular weights, 5,000–30,000 daltons). Heparin exerts its anticoagulant effect by binding to antithrombin III through a specific pentasaccharide sequence. This process results in a conformational change in the antithrombin III molecule and increases its ability to inhibit coagulation factors IIa (thrombin) and Xa. Anticoagulation therapy for ACS was first suggested in 1912.[13] While the pathogenesis of unstable syndromes was debated, the pro-

totype anticoagulant drug—unfractionated heparin (UFH)—was used inconsistently in clinical practice.

After DeWood's group[14] demonstrated angiographically the importance of thrombus in acute MI, 3 randomized trials[7,15,16] pursued UFH as an essential part of the management of all unstable coronary syndromes. In the 1st modern, double-blind, placebo-controlled trial of UFH, Telford and colleagues[15] randomized 400 patients who had ACS to treatment with UFH, atenolol, both, or placebo. At 1 week, there was an 80% RRR in the occurrence of MI in the 2 groups of patients treated with UFH compared with those undergoing no anticoagulation. In 1986, Williams and associates[16] randomized 102 patients who had ACS to 1) UFH administration for 48 hours followed by warfarin for 6 months or 2) no anticoagulation. They reported a 65% RRR in the occurrence of death, MI, or recurrent unstable angina at 6 months in the group treated with anticoagulants. However, problems with study design, recruitment, and patient withdrawal limited the impact of these trials. In 1988, Theroux and coworkers[7] randomly allocated 479 patients to treatment with ASA, UFH, or placebo. They reported a 94% reduction in fatal and nonfatal MI (12% vs 0.85%, $P < 0.001$) and a 69% reduction in refractory angina (23% vs 8.5%, $P = 0.002$) in the UFH group compared with those in the placebo group. The risk reductions with UFH were greater than those with ASA alone. Results of 2 additional trials, the RISC and ATACS studies (discussed below), have further supported the use of UFH for the treatment of unstable coronary syndromes.

Summary. These studies strongly suggested a benefit for UFH but could not be considered decisive, given their limited statistical power.

Aspirin and Heparin

With the apparent benefit of both UFH and ASA established in randomized trials, a separate question arose: Will combined antiplatelet therapy with ASA and anticoagulant therapy with UFH provide additive benefits or merely increase the risk of bleeding side effects?

Theroux and co-authors[7,17] were the 1st group to study the question, randomizing 479 patients with unstable angina to treatment with ASA, UFH, both, or placebo. After 1 week, the incidence of MI was 12% for those in the placebo group, 3% for the ASA group, 1.6% for the ASA plus UFH group, and 0.8% for the UFH group. These results further supported the value of antithrombotic therapy but did not permit researchers to draw any meaningful conclusions about combination therapy. The Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC)[8] examined the effects of ASA, UFH, both, or placebo in 796 men who had either unstable angina or NSTEMI. With follow-up extending to 90 days, the endpoint of death or MI occurred in 17.6% of the placebo group, 16.6% of the UFH group, 7.4% of the ASA group, and 5.7% of the combined treatment group. The size of this trial, as with the study by Theroux and co-authors,[7] precluded any meaningful conclusions regarding ASA therapy versus combination therapy.[8] The Antithrombotic Therapy in Acute Coronary Syndromes (ATACS)[10] trial was designed to investigate the use of long-term anticoagulant therapy in addition to ASA. In 214 patients with unstable angina and NSTEMI, the study compared treatment with ASA alone as opposed to treatment with ASA and UFH that was followed by ASA and warfarin. At 14 days, total ischemic events were significantly lower in the combination group than in the ASA group (10.5% vs 27%, respectively; $P = 0.004$). However, at later time-points, withdrawal of patients from the study due to side effects made interpretation of outcomes more difficult.

With time and the introduction of low-molecular-weight heparins (LMWHs), additional data were accumulated, although never sufficient to provide a definitive answer regarding the value of combined antiplatelet and anticoagulant therapy. Therefore, Eikelboom's group[18] performed a meta-analysis of 12 trials comprising a total of 17,157 patients with unstable coronary syndromes. Patients were given ASA alone or in combination either with UFH that was administered as a bolus followed by continuous infusion guided by the activated partial thromboplastin time (aPTT) or with LMWH. In this large population, the combination of ASA and short-term anticoagulation with either type of heparin appeared to lower the incidence of death and MI. These findings are proof of principle that inhibiting both platelet function and thrombin generation reduces the risk of events (death or MI). However, this benefit was accrued only when combination therapy was used early after the diagnosis of an unstable coronary syndrome. Beyond the 1st week of therapy, the addition of anticoagulant therapy provided no additional benefit and increased the risk of bleeding side effects.

Low-Molecular-Weight Heparins. Low-molecular-weight heparins are derived from the chemical cleavage of the larger heparin molecules typically found in UFH. This process produces shorter saccharide chains (molecular weights, 4,000–6,000 daltons) that retain their ability to augment the activity of antithrombin III. Because the inhibition of thrombin (but not factor Xa) by the heparin–antithrombin complex is chain-length dependent, shorter chains result in a greater degree of factor Xa inhibition relative to factor IIa inhibition. Although some have speculated that this caused a more potent, predictable, and sustained anticoagulation,[19] others have suggested that

the relative factor Xa:IIa activity may simply be a laboratory phenomenon that has little impact on the antithrombotic effects of these agents.[20] Results from the FRISC, FRIC, FRAXIS, ESSENCE, and TIMI 11B studies have supported the safety and efficacy of LMWHs in patients with ACS (see Table II[9,21-26]). The FRISC-II and NICE study groups have evaluated the use of LMWHs with invasive management strategies. It is important to note that all of these trials have used combination antiplatelet and anticoagulant strategies (LMWH combined with ASA) with or without percutaneous intervention (PCI).

The FRISC (Fragmin During Instability in Coronary Artery Disease) trial[21] randomized 1,506 patients with unstable angina to treatment with placebo or with dalteparin administered subcutaneously twice daily for 6 days (acute phase), then once daily for the next 35 to 45 days (chronic phase). All patients received ASA. The 6-day relative reduction of death or MI was 63% in the dalteparin group (4.8% vs 1.8% with dalteparin, P=0.001), as was the need for revascularization (1.2% vs 0.4% with dalteparin, P=0.07). Continuation of lower-dose dalteparin for 40 days produced a sustained benefit in nonsmokers and high-risk patients.

The FRIC (Fragmin in Unstable Coronary Artery Disease) study[22] randomized 1,482 patients who had unstable angina or NSTEMI to treatment with dalteparin or UFH, and later to dalteparin or placebo. All patients received ASA. As in FRISC, dalteparin was administered subcutaneously twice daily during the acute (6-day) phase and once daily during the prolonged (6–45 day) phase; UFH was administered during the first 6 days and then switched to placebo. There was no significant difference in the outcomes between the dalteparin group and the UFH-placebo group at 6 days or at 45 days.

The FRAXIS (Fraxiparine in Ischaemic Syndrome) study[23] enrolled 3,468 patients with unstable angina or NSTEMI and compared nadroparin (administered for 6 or 14 days) and UFH (for 6 days). All patients received ASA. At day 14, there were no differences in the primary efficacy measures of death, MI, and refractory or recurrent angina.

The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events)

TABLE II. Summary of Selected Clinical Trials Using Low-Molecular-Weight Heparin

Trials (Year)	No. Patients	Treatment Regimen	Event Rates at 1–2 Weeks* (%)			
			Placebo	Active	*P*	NNT
FRISC Group (1996)[21]	1,506	Dalteparin 120 IU/kg body weight SQ twice daily vs placebo for 6 days, then once daily for 35–45 d vs placebo. All pts, ASA.	4.8	1.8	0.001	33
FRIC Group (1997)[22]	1,482	Dalteparin 120 IU/kg body weight SQ twice daily vs UFH (target aPTT 2×) for 6 d, then dalteparin once daily vs placebo for 39 d. All pts, ASA.	7.6	9.3	0.33	—
FRAXIS (1999)[23]	3,468	Nadroparin 86 anti-Xa IU/kg bolus + SQ injections twice daily for 6 or 14 d vs UFH 5000-U bolus, infusion 1250 IU/h for 6 ± 2 d. All pts, ASA.	20	18	0.03	50
ESSENCE (1997)[24]	3,171	Enoxaparin 1 mg/kg SQ twice daily vs UFH 5000-U bolus, infusion (aPTT 55–86 s) for 2–8 d. All pts, ASA.	19.8	16.6	0.019	31
TIMI 11B (1999)[25]	3,910	Enoxaparin 30-mg IV bolus, then SQ injection 1 mg/kg twice daily for ≤8 d vs UFH 70-U/kg bolus, infusion 15 U/kg per h (aPTT 1.5–2.5×) for 3–8 d. Outpatient phase, enoxaparin vs placebo for 35 d. All pts, ASA.	14.5	12.4	0.048	48
FRISC-II (1999)[26]	3,048	Dalteparin 120 IU/kg twice daily for 5–7 d, 2 × 2 factorial design invasive vs noninvasive and dalteparin vs placebo for 3 mo.	12.1	9.4	0.031	37
ACC/AHA Meta-Analysis (2000)[9]	2,629	All UFH or LMWH vs ASA (for death/MI only)	5.3	2	0.0005	30

aPTT = activated partial thromboplastin time; ASA = aspirin; LMWH = low-molecular-weight heparin; NNT = number needed to treat; pts = patients; SQ = subcutaneous; UFH = unfractionated heparin

*Percentages depict rates of triple endpoints (death, MI, and recurrent ischemia with or without urgent revascularization).

trial[24] randomized 3,171 patients with unstable angina or NSTEMI to treatment with enoxaparin and ASA or UFH and ASA for 2 to 8 days. The risk of the composite endpoint of death, MI, or recurrent angina was significantly reduced in the enoxaparin group at 14 days (19.8% vs 16.6% with enoxaparin, P=0.019) and at 30 days (23.3% vs 19.8% with enoxaparin, P=0.016).

In TIMI 11B,[25] 3,910 patients with unstable angina or NSTEMI were randomized to treatment with either enoxaparin or UFH for up to 8 days. Those receiving enoxaparin stayed on that medication for the next 35 days (outpatient phase), while patients in the UFH group were switched to placebo. All patients received ASA. The composite endpoint of death, MI, and urgent revascularization was lower in enoxaparin-treated patients as early as 48 hours into the study and was maintained at 8 and 14 days, with a positive trend at 43 days. In a prespecified meta-analysis of TIMI 11B and ESSENCE,[27] a significant 20% RRR was demonstrated in the composite endpoint of death, MI, and urgent revascularization at 2, 8, 14, and 43 days, and in death or MI alone at 8, 14, and 43 days with use of enoxaparin as opposed to UFH.

Low-Molecular-Weight Heparin and Percutaneous Intervention. Antiplatelet agents are a mandatory part of the pharmacologic regimen of patients who undergo PCI. In addition, during the performance of the procedure, intense anticoagulation is administered, typically with UFH. Low-molecular-weight heparins have been slow to gain popularity, due to the difficulty in monitoring the intensity of therapy and also to concerns about their use with potent antiplatelet agents such as clopidogrel and the glycoprotein (GP) IIb/IIIa antagonists. The FRISC and NICE studies have shown that in addition to being safe, LMWHs used adjunctively in the setting of PCI are at least as good as UFH and may confer some added benefit.

In the FRISC-II (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease) study,[26,28] 3,048 patients who had unstable angina or NSTEMI received dalteparin for 5 to 7 days. Of these, 2,457 were randomized in a 2 × 2 factorial design to receive either dalteparin or placebo and either an early invasive (angiographic investigation) or early noninvasive (angiography for recurrent symptoms or a treadmill test revealing ≥3-mm ST-segment depression) treatment strategy. After 5 to 7 days of medical therapy (noninvasive group) or after completion of procedures (invasive group), 2,289 patients were randomized to continue dalteparin or placebo for another 3 months. At 6 months, there was a reduction in the composite endpoint of death or reinfarction in the patients treated with an early invasive approach (12.1% vs 9.4% invasive, P=0.031).

The NICE (National Investigators on the Collaborative Study of Enoxaparin) group has begun a series of studies evaluating the use of enoxaparin during PCI. The NICE-1 trial[29] was an open-label study of 812 patients given a single intravenous bolus of enoxaparin before elective PCI or coronary artery bypass grafting (CABG). The NICE-4 study[30] enrolled 857 patients to receive a lower dose of enoxaparin and the standard abciximab bolus and infusion before PCI. In both trials, the 30-day event rates for death, Q-wave MI, and urgent revascularization, as well as bleeding complications, were low and compared favorably with outcome data from the other trials that have used UFH. The NICE-3 trial* was an open-label, nonrandomized safety study of a combination of LMWH and clinically available GP IIb/IIIa inhibitors in 661 patients who had unstable angina or NSTEMI. The incidence of major and minor bleeding was low and comparable to that of historical controls, as were the measures of clinical efficacy (death, MI, or ischemia-driven target-vessel revascularization). The study was not designed with the statistical power to detect differences among the GP IIb/IIIa inhibitors.

Summary. Unfractionated heparin is effective as an addition to ASA during periods of intense disease activity. Treatment beyond the 1st week provides no added benefit. The LMWHs are at least as effective as UFH. Although some of the trials suggest the superiority of LMWH over UFH, the NNT to obtain any measurable clinical benefit is comparable, if not higher, for LMWH. Furthermore, an important consideration is that almost one half of the UFH-treated patients in these trials were outside the therapeutic range. Thus, LMWH may be superior simply because a greater number of patients are therapeutically anticoagulated due to ease of administration. The safety data for use of LMWH during PCI are encouraging as they accumulate.

Adenosine Diphosphate Receptor Antagonists

Ticlopidine and clopidogrel are thienopyridines that inhibit adenosine diphosphate (ADP)-induced platelet activation. When compared with ticlopidine, clopidogrel has a greater molar potency, a faster onset of action, and a superior side-effect profile. The importance of this pathway in platelet function is demonstrated by the capability of these agents to inhibit platelet aggregation in response to a variety of stimuli.

One study has evaluated ticlopidine use in patients with unstable angina.[31] In an open-label trial, 652 patients were randomized to treatment with conventional therapy (excluding ASA) with or without ticlopidine. At 6 months, there was a 46% RRR in the ticlopidine group for the endpoints of death or non-

*Oral presentation by J.J. Ferguson at the Congress of the European Society of Cardiology; Amsterdam, Netherlands; August 2000.

fatal MI (from 13.6% to 7.3% with ticlopidine, *P*=0.009). No study to date has compared ticlopidine with ASA in patients who have ACS, nor has its performance in combination therapy been studied.

The clinical experience with clopidogrel is derived mostly from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,[32] which randomized 19,185 patients with atherosclerotic vascular disease (recent ischemic stroke, MI, or symptomatic peripheral arterial disease) to treatment with either clopidogrel 75 mg/day or ASA 325 mg/day with a 1- to 3-year follow-up. At a mean follow-up of 1.9 years, clopidogrel was associated with an 8.7% RRR (from 5.83% to 5.32% with clopidogrel, *P*=0.043) in the annual risk of fatal or nonfatal ischemic stroke, MI, or other vascular death. For the endpoint of MI alone, there was a 19.2% RRR with clopidogrel therapy. The results of this trial provided strong evidence that clopidogrel is at least as effective as ASA and may be slightly more effective in certain patient subsets.

Two recent randomized studies have compared clopidogrel with ticlopidine as adjunctive therapy in patients undergoing coronary stenting. An initial trial[33] comprised 700 patients who were given ticlopidine 500 mg/day or clopidogrel 75 mg/day for 4 weeks. All patients were given aspirin 100 mg/day. The 2nd trial, Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS),[34] randomized 1,020 patients to a 28-day treatment with either clopidogrel (a 300-mg loading dose, then 75 mg/day) or ticlopidine (250 mg twice daily). All patients were given aspirin. Neither trial showed a difference in the incidence of stent thrombosis or any vascular events, although the overall tolerance was better for clopidogrel than for ticlopidine.

Two trials evaluating the efficacy of combination therapy with clopidogrel and ASA in patients with ACS have been undertaken. The Clopidogrel in Unstable Angina to Prevent Ischemic Events (CURE) trial[35] randomized 12,562 patients with unstable angina or NSTEMI either to combination therapy with clopidogrel (300-mg loading dose then 75 mg/day) and ASA or to ASA alone. Treatment with clopidogrel and ASA was associated with a 20% RRR in the primary endpoint of death, MI, or stroke (11.4% vs 9.3%, *P* <0.001), driven by a 23% RRR in the incidence of MI (6.68% vs 5.19%, *P*=0.001). The coprimary endpoint of death, MI, stroke, or refractory ischemia was reduced by 14% (18.8% vs 16.5% with clopidogrel and ASA, *P* <0.001), driven mainly by a 31% RRR in in-hospital refractory ischemia (from 2.09% to 1.42%, *P*=0.001) and a 25% RRR in severe ischemia (from 5.03% to 3.83%, *P*=0.001). The benefits of clopidogrel were noted very early and were present across all major subgroups in the subset analyses: in patients with and without major ST-segment deviation, enzyme or troponin elevation, and prior or subsequent revascularization. A similar study, under way in the People's Republic of China, is evaluating combination therapy versus ASA alone in 30,000 patients with ACS.

Summary. Clopidogrel may be used as a substitute in ASA-allergic patients, as an addition to therapy briefly after PCI, and in combination with ASA in patients with ACS. We await results from the People's Republic of China study. Meanwhile, the results of the CURE trial are compelling and proof of principle that combination antiplatelet therapy (as has been shown in glycoprotein IIb/IIIa trials with concomitant ASA therapy, see below), added to anticoagulant therapy strategies, reduces events and improves outcomes. The use of clopidogrel in various patient subsets, such as those with an increased risk of bleeding or a high likelihood of referral for CABG, needs to be further defined.

Glycoprotein IIb/IIIa Antagonists

The GP IIb/IIIa receptor serves as the final common pathway for platelet aggregation and is a principal determinant of arterial thrombus volume and strength. Inhibition of GP IIb/IIIa function cripples platelet hemostatic function, prevents thrombus growth, and favors thrombus dissolution. There are currently 3 commercially available GP IIb/IIIa inhibitors. Abciximab (Reopro®, Eli Lilly and Company; Indianapolis, Ind) is a chimeric monoclonal antibody that binds nonspecifically to the GP IIb/IIIa receptor. Eptifibatide (Integrilin®, Cor Therapeutics, Inc.; South San Francisco, Calif) is a cyclic heptapeptide that competitively and selectively binds the GP IIb/IIIa receptor. Tirofiban (Aggrastat®, Merck & Co., Inc.; Whitehouse Station, NJ) is a nonpeptide derivative of tyrosine that also binds the GP IIb/IIIa receptor in a selective and competitive fashion. The use of GP IIb/IIIa antagonists in combination with standard medical therapy (ASA and UFH) for unstable angina and NSTEMI was first evaluated in patients undergoing PCI (Table III[9,36-48]). Early data regarding the adjunctive use of abciximab with PCI from the EPIC, EPILOG, and CAPTURE trials showed significant reductions in the endpoints of death or MI at 30 days, with NNT ranging from 19 to 30. Similar relative reductions were reported with tirofiban and eptifibatide in the RESTORE and IMPACT-II trials, but these failed to reach statistical significance.

Glycoprotein IIb/IIIa Antagonists: Percutaneous Intervention Trials. The EPIC (Evaluation of 7E3 in Preventing Ischemic Complications) trial[45,49] enrolled 2,099 patients undergoing high-risk angioplasty or atherectomy in 1 of 3 treatment arms: a bolus followed by a 12-hour infusion of abciximab; a bolus of

TABLE III. Summary of Selected Clinical Trials Using GP IIb-IIIa Antagonists

Trials (Year)	No. Patients	Treatment Regimen	Death or MI Event Rates at 30 days (%) Placebo	Active	*P*	NNT
GP IIb/IIIa Antagonists + UFH vs UFH (Medical Therapy Trials)						
PURSUIT (1998)[36]	10,948	UFH 5000-U bolus, infusion vs eptifibatide 180-µg/kg bolus, infusion 2 µg/kg per min + UFH for 72–96 h. All pts, ASA.	3.7	3.5	0.042	500
PRISM (1998)[37]	3,232	UFH 5000-U bolus, 1000 U/h (target 2× aPTT) vs tirofiban 0.6-µg/kg body weight bolus, infusion 0.15 µg/kg per min for 48–96 h. All pts, ASA.	7.1	5.8	0.11	—
PRISM-PLUS (1998)[38]	1,915	UFH 5000-U bolus, 1000 U/h (target 2× aPTT) + placebo vs UFH + tirofiban 0.4-µg/kg bolus, infusion 0.1 µg/kg per min for 3–5 d. All pts, ASA unless contra-indicated.	11.9	8.7	0.034	31
PARAGON A (1998)[39]	2,282	2 × 2 Factorial design, lamifiban 1- or 5-µg/min infusion, with or without UFH vs standard therapy (ASA + UFH) for 3–5 d. All pts, ASA.	11.7	10.6	0.41	—
PARAGON B (2000)[40]	5,228	Same as in PARAGON-A, with lamifiban doses adjusted to renal function.	12.8	11.8	0.329	—
GUSTO-IV ACS (2001)[41]	7,800	Abciximab 0.25 mg/kg bolus, 0.125 µg/kg per min infusion for 24 or 48 h vs placebo for 48 h. All pts, ASA. All pts, UFH except for LMWH subset.	8.0	8.2	NS	—
ACC/AHA Meta-analysis (2000)[9]	17,044	All GP IIb/IIIa + UFH vs UFH	6.2	5.1	0.0022	91
PCI + GP IIb/IIIa Antagonists + UFH (PCI Trials)						
CAPTURE (1997)[42]	1,265	Abciximab 0.25-mg/kg bolus + 10-µg per min infusion vs placebo for 18–24 h before PCI and 1 h afterwards. All pts, ASA and UFH.	9	4.8	0.003	24
RESTORE (1997)[43]	2,141	Tirofiban 10-µg/kg bolus + 0.15-µg/kg per min infusion vs placebo for 36 h. All pts, ASA and UFH (target ACT 300–400 s).	6.4	5.0	0.162	—
TACTICS-TIMI 18 (2001)[44]	2,220	ASA + UFH 5000-U bolus, then 1000 U/h + tirofiban 0.4 µg/kg per min, then 0.1 µg/kg per min for 48 h or until intervention. Then early invasive or selectively invasive approach.	9.5	7.3	<0.05	45
EPIC (1997)[45]	2,099 (43% ACS)	Abciximab 0.25-mg/kg bolus, 10-µg/min infusion vs abciximab bolus + placebo infusion, vs placebo for 12 h. All pts, ASA and UFH.	10.3	6.9	0.022	29
EPILOG (1997)[46]	2,792 (68% ACS)	Abciximab 0.25-mg/kg bolus, 0.125-µg/kg per min infusion + UFH (standard dose) vs abciximab + UFH (reduced dose) vs UFH alone for 12 h. All pts, ASA.	9.1	3.8	<0.001	19
EPISTENT (1998)[47]	2,399 (33% ACS)	Stenting + abciximab vs stenting + placebo vs balloon angioplasty + abciximab. All pts, ASA and UFH. Both stent arms, ticlopidine.	10.2	4.8	<0.0001	19
IMPACT-II (1997)[48]	4,010 (41% ACS)	Eptifibatide 135-µg/kg bolus + either 0.5- or 0.75-µg/kg per min infusion vs placebo for 20–24 hours. Procedure preceded by ASA and followed by UFH in all pts.	8.4	6.9	0.134	—
ACC/AHA Meta-analysis (2000)[9]	10,964	All PCI trials	8.8	5.4	<0.001	29
ACC/AHA Meta-analysis (2000)[9]	26,700	All PCI + medical therapy trials	11.4	9.1	<0.001	43

ACS = acute coronary syndrome; ACT = activated clotting time; aPTT = activated partial thromboplastin time; ASA = aspirin; MI = myocardial infarction; NNT = number needed to treat; PCI = percutaneous intervention; pts = patients; UFH = unfractionated heparin

abciximab followed by a placebo infusion; or a placebo bolus and a placebo infusion. All patients received ASA and UFH. In the patients with unstable angina (n=489),[45] the 30-day composite endpoint of death, MI, or urgent intervention was reduced from 12.8% to 4.8% in the arm given the bolus plus infusion of

abciximab. At 6 months, there was an even more dramatic effect of the bolus–infusion regimen on the incidence of death (from 6.6% to 1.8%) and MI (from 11.1% to 2.4%). In the NSTEMI cohort (n=64) that had angioplasty performed within 12 hours, treatment with the bolus–infusion was associated with a 91% decrease in the composite endpoints at 6 months (from 47.8% to 4.5%, *P*=0.002).

The EPILOG (Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade) trial[46] randomized 2,792 patients (68% with ACS) who were undergoing urgent or elective PCI to 1 of 3 arms: 1) a bolus–infusion regimen of abciximab (as in EPIC) with standard UFH dosing, 2) the same abciximab dosage with low-dose UFH, and 3) placebo with standard UFH dosing. All patients were given aspirin. Abciximab therapy was associated with a reduction in the 30-day risk of death, MI, or urgent revascularization (11.7% vs 5.2% with abciximab, *P* <0.001).

CAPTURE (C7E3 Antiplatelet Therapy in Unstable Refractory Angina)[42] randomized 1,265 patients with refractory unstable angina to treatment with abciximab (administered as an infusion 18–24 hours before a planned PCI and continued for 1 hour afterward) or placebo. There was a significant reduction in the primary endpoint of 30-day death, MI, or urgent intervention in patients who received abciximab (15.9% vs 11.3% with abciximab, *P*=0.012), with similar reductions in all of the events that constituted the primary endpoint.

The RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) trial[43] enrolled 2,141 patients with unstable angina and NSTEMI and randomized them to treatment with either tirofiban (bolus, then infusion) or placebo for 36 hours preceding a planned PCI. Two days after PCI, a 3.3% absolute reduction in the primary endpoint of death, MI, stent placement for actual or threatened abrupt closure, coronary bypass surgery, or repeat PCI for recurrent ischemia was noted (from 8.7% to 5.4% with tirofiban, *P* ≤0.005). This benefit did not persist at 30 days (12.2% with placebo vs 10.3% with tirofiban, *P*=0.16).

Glycoprotein IIb/IIIa Antagonists: Medical Therapy with Percutaneous Intervention Trials. On the basis of efficacy shown in the early PCI trials, the use of GP IIb/IIIa antagonists was evaluated as part of standard medical therapy (in combination with ASA, with or without UFH) for patients with unstable coronary syndromes in these studies: PURSUIT, PRISM, PRISM-PLUS, PARAGON, and GUSTO-IV ACS (Table III[9,36-48]).

The PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial[36] randomized 10,948 patients with unstable angina and NSTEMI to standard therapy (UFH and ASA) with or without eptifibatide. At 30 days, treatment with eptifibatide reduced the risk of death or MI from 15.7% to 14.2% (*P*=0.04). Those who received eptifibatide (n=1,228) and underwent early PCI (within 72 hours) showed a 31% RRR in the incidence of death or MI (from 16.7% to 11.6%, *P*=0.01).

The PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management) trial[37] randomized 3,232 patients with unstable angina to a 48-hour infusion of either heparin or tirofiban. All patients were given ASA. The composite endpoint of death, MI, or refractory ischemia was reduced at 48 hours with tirofiban (5.6% vs 3.8%, *P*=0.01) but not at 30 days. However, for the endpoint of death alone, there was a 32% RRR at 30 days with tirofiban.

The PRISM-PLUS (PRISM in Patients Limited by Unstable Signs and Symptoms) trial[38] enrolled 1,915 patients with unstable angina or NSTEMI and randomized them to an infusion of UFH, tirofiban, or both, for 48 to 96 hours. When indicated, PCI was performed after 48 hours of treatment. Patients received ASA unless contraindicated. The tirofiban-only arm was terminated prematurely because of mortality. The combination of tirofiban and UFH reduced the composite endpoint of death, MI, and refractory ischemia by 32% at 7 days (from 17.9% [UFH alone] to 12.9% [tirofiban and UFH], *P*=0.004), 30 days (22% RRR, *P*=0.03), and 6 months (19% RRR, *P*=0.02). In patients undergoing PCI between 48 and 72 hours after beginning therapy, tirofiban substantially reduced ischemic events.

The PARAGON-A (Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network) trial[39] randomized 2,282 patients with unstable angina or NSTEMI to 2 different dosages of lamifiban, with or without UFH, versus standard therapy (placebo and UFH). All patients received aspirin. There was no difference in the endpoint of death or MI at 30 days. At 6 months, death or MI had occurred in 13.7% of the low-dose lamifiban participants and in 17.9% of the placebo group (*P*=0.03). The higher dose of lamifiban added no benefit. The follow-up study, PARAGON-B,[40] randomized 5,228 patients with unstable angina or NSTEMI to lamifiban therapy (dosed according to the creatinine clearance) or placebo. All patients received UFH and ASA. There was no significant difference in the primary endpoint of death, MI, or urgent revascularization at 30 days or 6 months. Subset analyses, however, revealed that lamifiban reduced the 30-day composite endpoint in patients who underwent early PCI (from 18.5% to 11.6%) and in those with elevated troponin levels (from 19% to 11%, *P*=0.018).

The GUSTO IV-ACS (Global Use of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndrome) trial[41] enrolled 7,800 patients with unstable angina or NSTEMI and randomized them to placebo or to 24- or 48-hour infusions of abciximab. All patients received ASA and heparin (either dalteparin or UFH). Unexpectedly, abciximab failed to show any benefit with regard to the primary endpoint of death or MI at 30 days. Outcomes in terms of all other endpoints were neutral. Subset analyses similarly failed to demonstrate any benefit with the use of abciximab. The main conclusion was that treatment with the GP IIb/IIIa blocker abciximab for 24 or 48 hours—in addition to ASA and heparin but without early intervention—does not reduce the incidence of death or MI.

Summary and Comments. Results from the medical therapy trials, particularly from GUSTO-IV ACS,[41] are sobering. Which patients really stand to benefit from GP IIb/IIIa blockade? Early studies show clearly that in combination with PCI, GP IIb/IIIa antagonists reduce events with the relatively low combined NNT of 29 (as low as 19 in EPILOG[46]). Such a benefit is not as evident from results of the medical therapy trials, in which the *P* values indicate statistical significance but the combined NNT is significantly higher at 91 (up to 500 in PURSUIT[36]). In fact, closer analysis reveals that the only patients who gained any significant clinical benefit from therapy were those who underwent PCI (Fig. 1[50] and Table IV[36-38,42,45-47]). An analysis by Boersma and colleagues[50] of patients from the CAPTURE, PURSUIT, and PRISM-PLUS trials showed that the greatest reduction in the clinical endpoint of death or MI occurred within 48 hours after the performance of PCI (Fig. 1). The incremental benefit of GP IIb/IIIa antagonism during the 24 hours preceding PCI, although present, was extremely small (NNT was 71). Subset analyses of the patients who were treated with PCI in the EPIC, EPILOG, CAPTURE, PRISM-PLUS, and PURSUIT trials and of those who received medical therapy alone (available only from PRISM, PRISM-PLUS, and PURSUIT patients) yielded similar trends (Table IV). With the exception of the PRISM trial (in which the comparison was between tirofiban and UFH), only those patients who underwent PCI received clinical benefit; GP IIb/IIIa antagonists as an adjunct to medical therapy alone provided no benefit.

The most recent GP IIb/IIIa trial in patients with ACS, TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction)-18,[44] supports this concept of combined GP IIb/IIIa antagonism and PCI. In this trial, 2,220 patients with unstable angina or NSTEMI received upstream ASA, UFH, and tirofiban. They were then

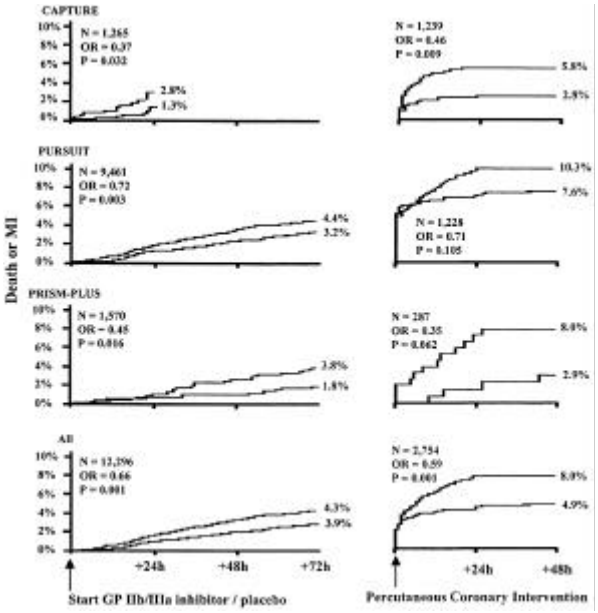

Fig. 1 *Kaplan-Meier curves depicting the cumulative incidence of death or myocardial infarction in patients randomized to GP IIb/IIIa antagonism (bold line) or placebo. Data were derived from CAPTURE, PURSUIT, and PRISM-PLUS. Left: Event rates during the initial period of medical treatment until the moment of percutaneous coronary intervention (PCI) or coronary artery bypass grafting, if any. Right: Event rates among PCI patients during 48-hour period after the procedure. At the beginning of each period, event rates were reset to 0.*

(Adapted from Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. Circulation 1999;100:2045-8.[50] Published with permission from Lippincott Williams & Wilkins and from the author.)

randomized either to an early invasive approach (angiography within 4–48 hours, then revascularization) or to a conservative approach (medical stabilization, and then risk stratification with a functional study). There was a significant reduction in the primary endpoint of death, MI, or rehospitalization for unstable angina at 30 days with the early invasive approach (10.5% vs 7.4% with PCI, *P*=0.009) and at 6 months (19.4% vs 15.9% with PCI, *P*=0.025). Whether this reduction was due to the early invasive strategy, to the upstream use of a GP IIb/IIIa antagonist, or to a higher proportion of stent use (compared with that in the TIMI-IIb study) is unknown.

There is very little evidence that GP IIb/IIIa inhibitors are useful as medical therapy unless a revascularization procedure is performed. With the proof of principle from the PCI trials that these agents are effective, the most probable cause of their failure as medical therapy is that their incremental benefit is very small in the population of patients who can be

TABLE IV. Glycoprotein IIb/IIIa Trials: Medical-Therapy-Only and PCI-Treated Patients

	Event Rates for Death or MI at 30 days (%)							
	Medical Therapy and PCI				Medical Therapy Only			
Trial	Active	Placebo	*P*	NNT	Active	Placebo	*P*	NNT
PRISM-PLUS[38]	5.9	10.2	NS	23	7.8	10.1	NS	44
PURSUIT[36]	11.6	16. 4	0.01	20	14.5	15.6	NS	91
PRISM[37]	7.2	9.1	NS	53	3.6	6.2	<0.01	38
EPIC[45]	1.8	10.9	0.001	11	NA	NA	NA	NA
CAPTURE[42]	4.8	9	0.003	24	NA	NA	NA	NA
EPILOG[46]	3.6	10.1	<0.001	15	NA	NA	NA	NA
EPISTENT[47]	3.9	14.1	0.001	10	NA	NA	NA	NA

MI = myocardial infarction; NNT = number needed to treat; PCI = percutaneous intervention

treated medically. Conversely, GP IIb/IIIa inhibitors may be of use in high-risk populations, such as patients awaiting transfer for revascularization, those receiving thrombolytic therapy for MI, and those showing evidence of ongoing disease progression (for example, recurrent pain or ST-segment deviation). These populations have a very high event rate; therefore, even a small incremental gain can be clinically important.

Summary and Conclusions

The clinical syndromes of NSTEMI and unstable angina are the result of a complex pathophysiology involving platelets, thrombus, and the vessel wall, all of which provide the basis for combining strategies targeting each of these factors. The clinical trials reviewed herein provide strong evidence and proof of principle that combination therapies targeting 1) platelet function (ASA, the thienopyridines, and GP IIb/IIIa antagonists), 2) the coagulation cascade (UFH and LMWH), and 3) physical characteristics of the active lesion (PCI) reduce the risk of death or ischemic complications after thrombotic progression of coronary atherosclerosis.

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