Antithrombotic Therapy in Patients Undergoing Percutaneous Coronary Intervention

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**Abbreviations:** ACT = activated clotting time; APTT = activated partial thromboplastin time; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; EPIC trial = Evaluation of 7E3 for the Prevention of Ischemic Complications; GP = glycoprotein; LMWH = low-molecular-weight heparin; NS = not significant; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RR = relative risk; TIMI = Thrombolysis in Myocardial Infarction

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Coronary angioplasty was performed in >700,000 patients in the United States in 1999, exceeding the number of patients undergoing coronary artery bypass graft (CABG) surgery. The expanded growth of coronary angioplasty in patients with coronary artery disease (CAD) is attributable to major advances in interventional technology over the past several years, the most notable of which are the availability of coronary stents and the adjunct use of potent antithrombotic agents during percutaneous coronary intervention (PCI), including the use of platelet glycoprotein (GP)-IIb/IIIa inhibitors. It is now well-recognized that balloon angioplasty enlarges the coronary lumen by dilatation, by tearing the atherosclerotic plaque and vessel wall, and, to a lesser extent, by longitudinal redistribution of the atherosclerotic plaque.1 The use of balloon angioplasty is limited in many patients by early complications (eg, abrupt closure) and late restenosis. New coronary devices were developed to improve on the procedural outcomes achieved with conventional balloon angioplasty. These new revascularization devices were designed to remove (eg, directional, rotational, or extraction atherectomy), ablate (eg, excimer laser angioplasty), or scaffold (eg, stents) atherosclerotic plaque. The term PCI refers to all forms of percutaneous mechanical revascularization and may involve the use of a single device or multiple new devices and balloons. Importantly, it is estimated that 60 to 80% of patients undergoing PCIs have one or more coronary stents placed,2 based on the ability of stents to prevent acute complications3 and to reduce late restenosis.4

Periprocedural use of conventional platelet inhibitors (eg, aspirin) and anticoagulants (eg, unfractionated heparin) reduces the frequency of early ischemic complications after PCI.6–8 A number of antiplatelet and antithrombolytic agents also have been developed to further improve clinical outcomes in patients undergoing mechanical revascularization. This chapter will review the current recommendations for antithrombotic therapy during PCI based on the available clinical evidence. The clinician is encouraged to consider these recommendations when selecting antithrombotic therapy in patients undergoing PCIs, understanding that the ultimate decision will require careful balancing of the risks and benefits of these therapies as applied to the individual patient.

**Oral Antiplatelet Agents**

Aspirin

Aspirin is the most commonly used antiplatelet agent and reduces the frequency of ischemic complications after balloon angioplasty (Table 1). In a study of 376 patients randomly assigned to receive either aspirin (990 mg daily) plus dipyridamole (225 mg daily) or placebo starting 24 h before angioplasty and continuing for 4 to 7 months thereafter,4 the frequency of periprocedural Q-wave myocardial infarction was significantly reduced in the patients given the combination of aspirin plus dipyridamole (1.6% vs 6.9% in placebo-treated patients; p = 0.011). A second study randomly assigned 333 patients to treatment with placebo, the combination of aspirin (650 mg daily) plus dipyridamole (225 mg daily), or ticlopidine (750 mg daily) before coronary angioplasty.9 Immediate procedure-related complications (eg, abrupt occlusion, thrombosis, or major dissection) occurred in 23 of the 333 patients (7%); complications were less frequent in patients treated with aspirin plus dipyridamole (5%) and with ticlopidine (2%) than in those receiving placebo (14%) (p < 0.005).9 The beneficial effect of antiplatelet agents in reducing ischemic complications also was documented in a retrospective study that included 300 patients undergoing coronary angioplasty.10 Patients were classified into three groups in this study, based on their medication use at the time of coronary angioplasty. Stepwise logistic regression demonstrated that the lack of antiplatelet therapy at the time of coronary angioplasty was the most important predictor for the development of angiographically and clinically significant periprocedural thrombus.10

The minimum effective aspirin dosage in the setting of PCI has not been established. In a study that randomized 495 patients to treatment with low-dose aspirin (80 mg daily) or to high-dose aspirin (1,500 mg daily) starting 24 h before balloon angioplasty,11 there was no difference in the incidence of myocardial infarction (3.6% vs 3.9%, respectively) or in the need for coronary bypass surgery (3.6% vs 3.7%, respectively). Given that GI side effects can occur up to 35% of patients given high doses of aspirin (990 mg daily),6 an empiric dose of aspirin (80 to 325 mg) given at least 2 h before the angioplasty procedure is recommended.12 Longer pretreatment durations (up to 24 h) should be considered if lower dosages of aspirin (80 to 100 mg) are used due to a potential delay in bioavailability and attainment of adequate plasma levels.

**Thienopyridine Derivatives**

In patients undergoing balloon angioplasty, ticlopidine or clopidogrel may be used as alternatives in aspirin-
A study in a group of patients with subacute stent thrombosis (575 mg daily) or the combination of aspirin (650 mg daily) and dipyridamole (75 mg daily) to placebo, the frequency of immediate complications after coronary angioplasty was similar in the patients treated with ticlopidine and with aspirin plus dipyridamole (2% and 5%, respectively), and both treatment regimens were significantly better (p < 0.05) than placebo for patients in whom the frequency of complications was 14%. Whenever possible, ticlopidine should be given for at least 24 h prior to the procedure to achieve maximum platelet inhibition.

More potent antithrombotic therapy is needed to prevent the occurrence of ischemic complications after stent implantation. In prior years, the enthusiasm for stent use was tempered by the sudden, and often unpredictable, occurrence of subacute stent thrombosis, which developed in 3.5 to 8.6% of stent-treated patients. The occurrence of subacute stent thrombosis was often delayed, occurring, on average, 6 days (range, 2 to 14 days) after stent placement; it occurred after hospital discharge in 60% of patients in one study. Subacute stent thrombosis often resulted in major cardiac events, including myocardial infarction and death.

Early studies used an aggressive anticoagulation regimen to reduce the risk of subacute thrombosis after stent placement, including aspirin (325 mg daily), dipyridamole (75 mg daily), IV low-molecular-weight dextran-40, and IV heparin (10,000 to 15,000 IU during the procedure and 1,000 IU/h after sheath removal) until systemic anticoagulation was achieved with warfarin (international normalized ratio, 2.0 to 3.5). It is not surprising that bleeding and vascular complications occurred more often in stent-treated patients than in balloon-treated patients (13.5% vs 3.1%, respectively; p < 0.001); accordingly, hospital stays were also longer in stent-treated patients (8.5 vs 3.1 days, respectively; p < 0.001).

Anatomic factors after stent deployment (eg, underdilatation of the stent, proximal and distal dissections, poor inflow or outflow obstruction, or < 3 mm vessel diameter) rather than suboptimal anticoagulation regimens now appear to have contributed to the development of subacute thrombosis in the early stent experience. Sequential intravascular ultrasound studies have since shown that earlier stent deployment methods often resulted in incomplete apposition of the stent struts against the vessel wall, asymmetric expansion, and incomplete stent dilatation in comparison to the proximal and distal reference segment.

### Table 1—Effect of Antiplatelet Agents on Procedural Outcome After Coronary Angioplasty

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Type of Study</th>
<th>Treatment</th>
<th>Procedural Outcome, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Death</td>
<td>MI</td>
</tr>
<tr>
<td>Schwartz et al/1988</td>
<td>Elective</td>
<td>157 RCT</td>
<td>Aspirin, 330 mg tid</td>
</tr>
<tr>
<td>White et al/1987</td>
<td>Elective</td>
<td>111 RCT</td>
<td>Aspirin, 325 mg tid</td>
</tr>
<tr>
<td>Barnathan et al/1987</td>
<td>All patients</td>
<td>Observational</td>
<td>Aspirin and DP</td>
</tr>
<tr>
<td>Mufson et al/1988</td>
<td>Elective</td>
<td>253 RCT</td>
<td>Aspirin, 80 mg daily</td>
</tr>
<tr>
<td>Lembo et al/1990</td>
<td>Elective</td>
<td>117 RCT</td>
<td>Aspirin, 325 mg tid</td>
</tr>
<tr>
<td>Knudtson et al/1990</td>
<td>Elective</td>
<td>134 RCT</td>
<td>Prostacyclin × 48 h</td>
</tr>
</tbody>
</table>

*Compls = complications; DP = dipyridamole; MI = myocardial infarction; NR = not reported; RCT = randomized controlled trial.

†p < 0.05 compared with placebo.

‡p < 0.01 compared with placebo.

50% of patients in one study. Sensitivity to aspirin (650 mg daily) and dipyridamole (75 mg daily) to placebo, the frequency of immediate complications after coronary angioplasty was similar in the patients treated with ticlopidine and with aspirin plus dipyridamole (2% and 5%, respectively), and both treatment regimens were significantly better (p < 0.05) than placebo for patients in whom the frequency of complications was 14%. Whenever possible, ticlopidine should be given for at least 24 h prior to the procedure to achieve maximum platelet inhibition.

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Incompletely deployed stent struts may have triggered platelet deposition and subsequent thrombosis. By correcting these technical factors using high-pressure postdeployment stent dilatation techniques, often with intravascular ultrasound guidance, lower frequencies of subacute stent thrombosis have been achieved.

Ticlopidine, as an adjunct to aspirin, has been shown to reduce the frequency of subacute thrombosis in patients after stent placement. In a study of high-risk patients treated with Palmaz-Schatz stents for acute myocardial infarction, suboptimal angioplasty, or other high-risk clinical and anatomic features, 517 patients were randomly assigned to antplatelet therapy (aspirin plus ticlopidine; N = 257) or to anticoagulant therapy (aspirin, IV heparin, and phenprocoumon; N = 260) after successful stent placement. The primary cardiac end point, a composite of cardiac death, myocardial infarction, coronary bypass surgery, or repeat angioplasty, occurred in 1.6% of patients assigned to antplatelet therapy and in 6.2% of those assigned to anticoagulant therapy (relative risk [RR], 0.25; 95% confidence interval [CI], 0.06 to 0.77). Compared with patients receiving anticoagulation therapy, patients receiving antplatelet therapy had an 82% lower risk of myocardial infarction and a 78% lower need for repeat surgery.
angioplasty.\textsuperscript{20} Occlusion of the stented vessel occurred in 0.8% of the group receiving antiplatelet therapy and in 5.4% of the group receiving anticoagulant therapy (RR, 0.14; 95% CI, 0.02 to 0.62).\textsuperscript{20} Hemorrhagic complications and peripheral vascular events were also lower in patients treated with antiplatelet therapy.\textsuperscript{20}

The Stent Antithrombotic Regimen Study compared the effect of aspirin (325 mg daily), the combination of aspirin (325 mg daily) plus ticlopidine (500 mg daily for 1 month), and aspirin (325 mg daily) plus warfarin on early (<30 days) ischemic complications in 1,653 low-risk patients after successful Palmaz-Schatz stent placement.\textsuperscript{21} The primary 30-day composite end point of death, target lesion revascularization, angiographic thrombosis, or myocardial infarction occurred in 3.6% of patients assigned to aspirin only therapy, in 2.7% of patients assigned to aspirin plus ticlopidine therapy, and in 0.5% of patients assigned to aspirin plus ticlopidine therapy.\textsuperscript{21} The RR for aspirin plus ticlopidine vs aspirin alone was 0.15 (95% CI, 0.05 to 0.43; p < 0.001), and that for aspirin plus ticlopidine vs aspirin plus warfarin was 0.20 (95% CI, 0.07 to 0.61; p = 0.014).\textsuperscript{21}

Although ticlopidine was given after successful stent deployment in the Stent Antithrombotic Regimen Study, pretreatment with ticlopidine for \( \text{24 h} \) may allow more effective inhibition of platelet activation than shorter durations of therapy.\textsuperscript{13} One study also has shown a lower frequency of non-Q-wave myocardial infarction in patients treated with ticlopidine for \( \text{24 h} \) before stent placement compared with those treated with ticlopidine on the day of the procedure; the lowest incidence of non-Q-wave myocardial infarction was seen in patients treated with ticlopidine for \( \text{72 h} \) prior to the stent procedure.\textsuperscript{22}

While GI symptoms (20%),\textsuperscript{23} cutaneous rashes (4.8 to 15%),\textsuperscript{23} and biochemical abnormalities in liver function tests\textsuperscript{23} may occur with ticlopidine, the major side effect is severe leukopenia (granulocyte count, <450/\text{mL}), which can occur in up to 1% of patients.\textsuperscript{21,24} In most cases, the neutropenia is reversible after the discontinuation of ticlopidine therapy,\textsuperscript{25} but episodes of sepsis and death have occurred. Serious and fatal episodes of thrombotic thrombocytopenic purpura also have been reported.\textsuperscript{26–28} A shorter duration (10 to 14 days) of ticlopidine therapy may reduce the risk of these side effects.\textsuperscript{29}

Clopidogrel is a new thienopyridine derivative that inhibits platelet aggregation induced by adenosine diphosphate.\textsuperscript{30} In a study of 19,185 patients with atherosclerotic cerebrovascular disease, peripheral vascular disease, or CAD, clopidogrel (75 mg daily) was more effective than aspirin (325 mg daily) in reducing the combined incidence of ischemic stroke, myocardial infarction, or vascular death (5.32% vs 5.83%; p = 0.043).\textsuperscript{30} Thrombocytopenia occurred in 0.26% of both clopidogrel-treated patients and aspirin-treated patients; low neutrophil counts were seen in 0.10% of clopidogrel-treated patients and in 0.17% of aspirin-treated patients.\textsuperscript{30}

Data from three single-center registries also have suggested that clopidogrel may be used as an alternative to ticlopidine for the prevention of ischemic complications after stent implantation\textsuperscript{31–33} (Table 2). In the largest of these registries, the clinical outcomes of 500 patients receiving aspirin and clopidogrel (300 mg loading dose followed by 75 mg daily for 14 days) after stent placement were compared with the clinical outcomes of 827 patients receiving aspirin and ticlopidine (500 mg loading dose and 250 mg twice daily for 14 days).\textsuperscript{32} No differences in the frequency of subacute stent thrombosis rate or in the 30-day major adverse cardiac event rate were found between the two groups.\textsuperscript{30} Another study demonstrated

### Table 2—Comparison of Ticlopidine and Clopidogrel After Coronary Stent Placement

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Type of Study</th>
<th>Patients, No.</th>
<th>Treatment</th>
<th>Stent Thrombosis, %</th>
<th>Side Effects, %</th>
<th>Any Event</th>
<th>Death</th>
<th>MI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moussa et al\textsuperscript{31/1999}</td>
<td>Observational registry</td>
<td>1406</td>
<td>Aspirin, 325 mg qd Ticlopidine, 250 mg bid</td>
<td>1.5</td>
<td>10.6</td>
<td>3.1</td>
<td>0.9</td>
<td>1.8</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspirin, 330 mg tid Ticlopidine, 250 mg bid</td>
<td>1.4</td>
<td>5.3^</td>
<td>2.4</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Berger et al\textsuperscript{32/1999}</td>
<td>Observational registry</td>
<td>827</td>
<td>Aspirin, 325 mg qd Ticlopidine, 75 mg qd</td>
<td>0.7</td>
<td>NR</td>
<td>1.6</td>
<td>1.1</td>
<td>0.5</td>
<td>0.5^</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspirin, 330 mg tid Ticlopidine, 75 mg bid</td>
<td>0.2</td>
<td>NR</td>
<td>0.8</td>
<td>0.4</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Mishkel et al\textsuperscript{33/1999}</td>
<td>Observational registry</td>
<td>361</td>
<td>Aspirin, 325 mg qd Ticlopidine, 250 mg bid</td>
<td>0.3</td>
<td>NR</td>
<td>1.4</td>
<td>0.6</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspirin, 330 mg tid Ticlopidine, 75 mg qd</td>
<td>0.2</td>
<td>NR</td>
<td>2.1</td>
<td>0.9</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Muller et al\textsuperscript{34/2000}</td>
<td>RCT</td>
<td>345</td>
<td>Aspirin, 325 mg qd Ticlopidine, 75 mg qd</td>
<td>9.6</td>
<td>3.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspirin, 330 mg tid Ticlopidine, 75 mg bid</td>
<td>4.5^</td>
<td>1.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\textsuperscript{*}See Table 1 for abbreviations not used in text.
\textsuperscript{\^}p = 0.006 compared with ticlopidine.
\textsuperscript{\P}PTCA or CABG.
\textsuperscript{\*$p* = 0.01 compared with ticlopidine.
equal safety with use of the two drugs, but significantly fewer side effects associated with clopidogrel use.31

Two large randomized trials showed no difference in clinical efficacy between clopidogrel and ticlopidine in patients undergoing stent placement, with fewer side effects in patients treated with clopidogrel.34,35 In one of these studies, 700 patients were assigned to treatment with ticlopidine (500 mg daily) or clopidogrel (75 mg daily) for 30 days after stent placement in addition to aspirin (100 mg daily).34 Cardiac events occurred in 3.1% of patients treated with clopidogrel and in 1.7% of those treated with ticlopidine (p = 0.24). Important side effects were lower in those patients treated with clopidogrel than in those treated with ticlopidine (4.5% vs 9.6%, respectively; p = 0.01).34

Based on this information, clopidogrel (300-mg loading dose followed by 75 mg daily) may be used as an alternative to ticlopidine in patients undergoing stent implantation. Clopidogrel therapy should be started as soon as possible after stent placement; whether pretreatment with clopidogrel provides any additional advantage over clopidogrel given at the time of the procedure is not known. Clopidogrel therapy should be continued for 14 to 30 days after the stent procedure. Whether long-term treatment with clopidogrel imparts further benefits over aspirin alone on secondary prevention is currently under evaluation in the Clopidogrel for Reduction of Events During Observation trial. Rare hemotologic complications, including hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura, also have been reported with clopidogrel use.

Other Agents

The results of early studies with cilostazol, a phosphodiesterase inhibitor, also suggest that this agent may be used as an alternative to ticlopidine in patients undergoing stent implantation.36–40 The addition of dipyridamole to aspirin provides little incremental value over the use of aspirin alone for the prevention of early complications after coronary angioplasty. In a study of 232 patients randomly assigned to treatment with aspirin alone (975 mg/d) or to the combination of aspirin (975 mg/d) plus dipyridamole (225 mg/d) before coronary angioplasty, there were no differences in the frequency of Q-wave myocardial infarction (1.7% vs 4.3%, respectively; p = 0.008). In contrast, the bolus of abciximab alone did not produce a significant reduction in ischemic events. The beneficial effect for patients receiving bolus abciximab plus infusion abciximab compared to those receiving placebo (8.3% vs 12.5%, respectively; p = 0.008).12 In contrast, the bolus of abciximab alone did not produce a significant reduction in ischemic events. The beneficial effect for patients receiving bolus abciximab plus infusion abciximab was primarily attributable to a reduction in the incidence of nonfatal myocardial infarction compared to those receiving placebo (5.2% vs 8.6%, respectively; p = 0.013) and in the need for repeat coronary angioplasty compared to that in placebo-treated patients (0.8% vs 4.5%, respectively; p < 0.001). These effects were maintained for at least 3 years after the procedure.50 Of the patients given bolus plus infusion abciximab, those with unstable clinical syndromes (ie, acute myocardial infarction and refractory unstable angina) derived a greater treatment benefit (hazard ratio, 0.5; 95% CI, 0.3 to 0.9) than patients with high-risk anatomy alone (hazard ratio, 0.7; 95% CI, 0.5 to 1.1).51

**Platelet GPIIb/IIIa Antagonists**

Despite pretreatment with aspirin, early ischemic events still occur in 3.0 to 12.8% of patients after coronary angioplasty. Aspirin is only a partial inhibitor of platelet function, as demonstrated by the persistence of platelet aggregation, platelet thrombus formation, and postangioplasty cyclic flow variations during coronary intervention in aspirin-treated patients. Continued platelet reactivity, despite aspirin-induced cyclooxygenase inhibition, reflects platelet activation through thromboxane A2-independent pathways. Potent platelet agonists, such as thrombin and collagen, can cause adenosine diphosphate and serotonin release and can induce the functional expression of GPIIb/IIIa receptors on the platelet surface, even in the presence of aspirin. Functionally active GPIIb/IIIa receptors, binding fibrinogen and other adhesive proteins that bridge adjacent platelets, serve as the final common pathway of platelet thrombus formation. Accordingly, the GPIIb/IIIa receptors have become a prime target for inhibition. GPIIb/IIIa antagonists include a monoclonal antibody against the GPIIb/IIIa receptor, naturally occurring Arg-Gly-Asp-containing peptides from various snake venoms, synthetic Arg-Gly-Asp-containing peptides, and nonpeptidyl mimetics (—fibatides), and nonpeptidyl mimetics (—fibans) (see page 39S in this supplement).

**Abciximab**

The clinical safety and efficacy of abciximab (ReoPro; Eli Lilly; Indianapolis, IN) were evaluated in the Evaluation of TE3 for the Prevention of Ischemic Complications (EPIC) Trial, a clinical study of 2,099 patients at high risk for complications after coronary angioplasty (Table 3). High-risk patients were defined as those with acute myocardial infarction, refractory unstable angina, and high-risk clinical and angiographic features. All patients enrolled in the EPIC study received aspirin (325 mg) and heparin (10,000- to 12,000-IU bolus) prior to coronary angioplasty. Patients were randomly assigned to treatment with placebo, a bolus of abciximab (0.25 mg/kg), or a bolus of abciximab (0.25 mg/kg) followed by a 12-h abciximab infusion (10 g/min). All patients received a 12-h infusion of heparin (1,000 IU/h heparin to maintain the activated partial thromboplastin time [APTT] at 1.5 to 2 times control). There was a 35% reduction in the frequency of the composite clinical end point, which was defined as death, nonfatal myocardial infarction, repeat revascularization, and procedural failure resulting in stent or intra-aortic balloon pump placement, in patients given both the bolus of abciximab plus infusion abciximab compared to those receiving placebo (8.3% vs 12.5%, respectively; p = 0.008). In contrast, the bolus of abciximab alone did not produce a significant reduction in ischemic events. The beneficial effect for patients receiving bolus abciximab plus infusion abciximab was primarily attributable to a reduction in the incidence of nonfatal myocardial infarction compared to those receiving placebo (5.2% vs 8.6%, respectively; p = 0.008). In the need for repeat coronary angioplasty compared to that in placebo-treated patients (0.8% vs 4.5%, respectively; p < 0.001). These effects were maintained for at least 3 years after the procedure. Of the patients given bolus plus infusion abciximab, those with unstable clinical syndromes (ie, acute myocardial infarction and refractory unstable angina) derived a greater treatment benefit (hazard ratio, 0.5; 95% CI, 0.3 to 0.9) than patients with high-risk anatomy alone (hazard ratio, 0.7; 95% CI, 0.5 to 1.1). Two randomized trials have shown that abciximab reduces early ischemia in patients with acute myocardial infarction undergoing primary angioplasty. In the first trial of 429 patients with acute myocardial infarction assigned to treatment with abciximab or placebo, a signifi-
significant (\(p = 0.03\)) reduction in the incidence of death, reinfarction, or urgent target vessel revascularization at 30 days was found in patients treated with abciximab (4.9%) compared with those treated with placebo (10.3%).54 The second study randomly assigned 401 patients with acute myocardial infarction to treatment with abciximab or placebo. The 30-day composite end point of death, reinfarction, and target lesion revascularization occurred significantly (\(p = 0.038\)) less often in abciximab-treated patients (5.0%) than in placebo-treated patients (10.5%).52 Neither of these two studies showed a reduction in restenosis with abciximab.52,53 The administration of abciximab in the emergency department resulted in a Thrombolysis in Myocardial Infarction (TIMI) flow of grade 2 or 3 in 40% of patients and TIMI flow grade 3 in approximately 20% of patients.54 The need for the use of a bailout stent during primary angioplasty also was reduced in patients receiving abciximab compared with those not receiving abciximab (11.5% vs 18.3%, respectively; \(p = 0.031\)).52,54

The Evaluation of Percutaneous Transluminal Coronary Angioplasty (PTCA) to Improve Long-term (EPILOG) Outcome by Abciximab GPIIb/IIa Receptor Blockade study was designed to evaluate the strategy of low-dose heparin and early sheath removal in conjunction with abciximab therapy in 4,800 low-risk patients undergoing coronary angioplasty.57 Patients undergoing coronary angioplasty procedures were randomly assigned to therapy with the following agents: abciximab with standard-dose, weight-adjusted heparin (initial dose, 100 U/kg; minimum target activated clotting time [ACT], 300 s); abciximab with low-dose, weight-adjusted heparin (initial dose, 70 U/kg; minimum target ACT, 200 s); or placebo with standard-dose, weight-adjusted heparin (100 U/kg; minimum target ACT, 300 s).57 At 30 days, the composite event rate (ie, death from any cause, myocardial infarction, or urgent revascularization) was 11.7% in the group assigned to placebo with standard-dose heparin, 5.2% in the group assigned to abciximab with low-dose heparin (hazard ratio, 0.43; 95% CI, 0.30 to 0.60; \(p < 0.001\)); and 5.4% in the group assigned to abciximab with standard-dose heparin (hazard ratio, 0.45; 95% CI, 0.32 to 0.63; \(p < 0.001\)).57 The need for RBC transfusion was 3.9% in the placebo plus standard-dose heparin group; 1.9% in the abciximab plus low-dose heparin group; and 3.3% in the abciximab plus standard-dose heparin group.57 Although use of low-dose, weight-adjusted heparin has reduced the number of overall bleeding complications, abciximab use in combination with thrombolytic therapy still may be associated with a slightly higher risk of bleeding complications.58 Patients undergoing directional coronary atherectomy also may derive benefit from abciximab. In a subset of 199 patients who underwent directional atherectomy in the EPIC study, an abciximab bolus plus infusion produced a 70% reduction in the incidence of non-Q-wave myocardial
infarction compared with placebo from 15.2 to 4.5% (p < 0.001). Similar reductions in creatine phosphokinase-MB elevations were also shown in a registry after rotational atherectomy. Bolus and infusion abciximab therapy also was shown to reduce the occurrence of distal embolization in 101 patients undergoing saphenous vein graft angioplasty compared to those patients receiving placebo in the EPIC study (2% vs 18%, respectively; p = 0.017), although composite 30-days event rates were not lower in patients treated with abciximab. A larger study has questioned the incremental benefit of abciximab in the setting of saphenous vein graft angioplasty.

One limitation of abciximab use is the development of human antichimeric antibodies in 3 to 5% of patients, which may potentially preclude readministration. In the ReoPro Readministration Registry, 92 patients with prior exposure to abciximab were retreated with abciximab. Acute thrombocytopenia (platelet count, < 100,000/mL) occurred in 6.5% of patients, and severe thrombocytopenia (platelet count, < 50,000/mL) developed in 2.2% of patients. No patient developed profound thrombocytopenia (platelet count, < 20,000/mL), and there were no episodes of death, intracranial bleeding, or allergic reactions with abciximab readministration.

The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting trial randomly assigned 2,399 patients with ischemic CAD to treatment with stenting plus placebo, stenting plus abciximab, or balloon PTCA plus abciximab. The primary 30-day composite end point (death, myocardial infarction, or need for urgent revascularization) occurred in 10.9% of patients in the stent-plus-placebo group, in 5.3% of patients in the stent-plus-abciximab group (hazard ratio, 0.48; p < 0.001), and in 6.9% of patients in the balloon-plus-abciximab group (hazard ratio, 0.63; p = 0.007). There were no significant differences in bleeding complications among the groups. Although the need for late revascularization was not significantly (p = 0.22) lower in patients receiving stenting plus abciximab (8.7%) compared with patients receiving stenting plus placebo (10.6%), there was a significant (p = 0.02) reduction in revascularization in diabetic patients assigned to treatment with stenting plus abciximab (8.1%) compared with patients receiving stenting plus placebo (16.6%). A pooled analysis also suggests that abciximab may reduce mortality in diabetic patients.

Eptifibatide

The Integritin to Manage Platelet Aggregation to Prevent Coronary Thrombosis-II trial was a double-blind, placebo-controlled trial at 82 centers in the United States that enrolled 4,010 patients undergoing elective, urgent, or emergency coronary angioplasty. Patients were assigned to one of the three following treatments: placebo (n = 1,328); eptifibatide (Integrilin) bolus (135 μg/kg) followed by a low-dose eptifibatide infusion (0.5 μg/kg/min for 20 to 24 h; n = 1,349); or an eptifibatide bolus (135 μg/kg) and a higher-dose infusion (0.75 μg/kg/min for 20 to 24 h; n = 1,333). The primary end point, a 30-day composite occurrence of death, myocardial infarction, unplanned surgical or repeat percutaneous revascu-
The PRISM–PLUS trial randomly assigned 1,570 patients with unstable angina or non-Q-wave myocardial infarction to 48 to 108 h of treatment with heparin plus tirofiban or heparin alone.72 Coronary angioplasty was performed in 30.5% of patients between 49 and 96 h after enrollment.72 A composite end point, which included death, myocardial infarction, or repeat coronary angioplasty, was significantly reduced in patients treated with heparin plus tirofiban compared to patients treated with heparin alone (10.0% vs 15.7%, respectively; p < 0.01).73 The comparative effect of tirofiban and abciximab on clinical outcomes in 4,000 patients undergoing PCIs is currently being evaluated in the TARGET Trial.

As a class of agents, the GPIIb/IIIa inhibitors (ie, abciximab, eptifibatide, and tirofiban) have demonstrated benefit in improving clinical outcomes within the first 30 days after coronary angioplasty. The primary effect of these agents has been on the reduction of ischemic complications, including non-Q-wave myocardial infarction and recurrent ischemia. There is no consistent evidence that the GPIIb/IIIa inhibitors reduce the frequency of late restenosis in nondiabetic patients, although abciximab may be beneficial in preventing recurrence in diabetic patients undergoing stent implantation. Comparative studies are needed to assess the relative efficacy of these agents.

ANTITHROMBIN THERAPY

Heparin

Since the advent of coronary angioplasty, IV heparin has been used to prevent arterial thrombus formation at the site of arterial injury73 and to reduce the thrombogenicity of coronary guidewires and other catheter equipment used for coronary dilatation.74 Although the degree of heparin anticoagulation after angioplasty has traditionally been evaluated using APTTs and, to a lesser extent, heparin levels, these methods have been less useful for monitoring anticoagulation during coronary angioplasty, because on-site results are needed and because large amounts of heparin are required to prevent thrombus formation during intracoronary instrumentation. In this setting, ACT monitoring has been more useful. The relationship between the ACT and APTT was evaluated in a series of 175 patients undergoing coronary angioplasty.75 The correlation between paired ACT (HemoTec, Inc; Englewood, CO) and APTT (MLA 1000; Medical Laboratory Automation, Inc; Pleasantville, NY) measurements was acceptable at low levels of heparin anticoagulation; there also was a good correlation between the ACT and APTT when extreme (ie, < 22 s or > 150 s) APTT values were eliminated (r = 0.92, p < 0.001).75 However, the APTT was less reliable when higher doses of heparin were given because these high doses produce an APTT beyond the measurable range (ie, > 150 s).75

Two devices are commonly used to measure ACT values in the interventional cardiovascular laboratory, the Hemochrom and HemoTec devices.76 Although comparative measures between the two devices produce a rough linear correlation (r = 0.86),76 the Hemochrom device tends to yield higher values (30 to 50 s) for any given level of systemic anticoagulation than the HemoTec device.75,77 When fixed heparin doses of 10,000 U are administered to patients undergoing coronary angioplasty, 89% will achieve an ACT of > 300 s measured with the Hemochron device, but only 14% of patients will achieve this value with the HemoTec device.77 Guidelines for procedural heparin use should be tailored to the monitoring device used within the catheterization laboratory.

Two studies evaluated the safety of angioplasty performed early after symptom onset in patients with unstable angina and thrombus-containing lesions.78,79 In one of these, patients treated with heparin for > 24 h had higher procedural success rates than those treated with heparin for < 24 h (91% vs 81%, respectively; p = 0.02). The abrupt closure rate also was lower in patients treated with heparin for > 24 h than in those treated for < 24 h (2% vs 8%, respectively; p < 0.01).78,79 In another study of 53 patients with unstable angina undergoing coronary angioplasty for thrombus-containing lesions,78,79 the clinical and angiographic outcomes in 35 patients pretreated with heparin were compared with those of 18 patients who did not receive heparin before the procedure. Patients who were not pretreated with heparin had lower angiographic success rates than those who were (61% vs 94%, respectively; p < 0.05) and an increase in postprocedural thrombotic arterial occlusion (33% vs 6%, respectively; p < 0.05). These results suggest that patients with refractory unstable angina due to thrombus-containing lesions may benefit from heparin pretreatment, although additional prospective studies are needed.

While ACT measurements are commonly made during coronary angioplasty to guide heparin dosing, the ideal target ACT for coronary angioplasty remains uncertain. Empiric recommendations regarding heparin monitoring for coronary angioplasty have come from studies demonstrating that an ACT of > 300 to 400 s is required to prevent fibrin deposition within the extracorporeal circuit in patients undergoing cardiopulmonary bypass.80,81 It has been shown that ACT levels may vary substantially after administration of fixed-dose heparin, due, in part, to differences in body size,73,82 concomitant use of IV nitroglycerin,83 and coexisting conditions that predispose the patient to heparin resistance (eg, heparin antibodies, oral contraceptive use, disseminated intravascular coagulation, and use of intra-aortic balloon pumping).84 Patients with complex coronary lesions (ie, those with irregular borders, overhanging edges, or filling defects)85 and unstable angina82 also have higher heparin dosing requirements, which are attributable to increased clot-bound thrombin generation in these high-risk subgroups. Although patients pretreated with heparin for > 12 h before coronary angioplasty had higher baseline ACT (Hemochron) values than those not receiving heparin pretreatment (163 ± 32 s vs 126 ± 13 s, respectively; p < 0.001), the total dose of heparin required to maintain a perioperative ACT of > 300 s was similar in both patient groups (11,551 ± 3,181 IU and 12,136 ± 2,575 IU, respectively; comparison not significant [NS]).86

Because most analyses of heparin dosing and outcomes during coronary angioplasty have been retrospective and...
nonrandomized, the predictive value of the ACT on the occurrence of ischemic complications during coronary angioplasty has been controversial. Some retrospective studies5,8 have identified an inverse relationship between the probability of ischemic events and the initial ACT measurement on heparin, whereas other studies87 have found no relationship between level of anticoagulation and ischemic complications. One study95 reported a direct correlation between the risk of major ischemic complications and ACT measurements with heparin therapy. In a study of 503 patients undergoing coronary angioplasty, complications occurred in all patients with a final ACT value of < 250 s (HemoTec), but complications occurred in 0.3% of patients with a final ACT of > 300 s. Another study of 1,290 patients showed that patients with abrupt vessel closure had lower ACT values than those without abrupt closure (352 ± 68 s vs 388 ± 81 s; p < 0.002). While higher ACT levels may reduce the frequency of ischemic complications, higher levels of periprocedural anticoagulation have been shown to result in an increased risk for bleeding complications.89,90

More recent studies also have evaluated the safety of lower-dose heparin therapy during PCI. Low-dose bolus heparin therapy (5,000 IU) followed by early (ie, < 12 h) postprocedural sheath removal in 1,375 consecutive patients was associated with infrequent fatal complications (0.3%), emergency CABG (1.7%), myocardial infarction (3.3%), or repeat angioplasty within 48 h (0.7%). Similar results were found in another study using very-low-dose (2,500 IU) bolus heparin.92 Further randomized studies need to compare the clinical outcomes of low-dose and conventional-dose heparin therapy in patients undergoing coronary intervention.

Although weight-adjusted heparin dosing has been empirically recommended smaller comparative studies have not shown a difference in procedural outcome between weight-adjusted and bolus heparin therapy. In a randomized study of 400 patients assigned to treatment with fixed-dose heparin (15,000 IU) or weight-adjusted heparin (100 IU/kg), clinical outcomes were similar in the two groups, including angioplasty success rates (95%), occurrence of the primary end point of freedom from death, myocardial infarction, unplanned revascularization (fixed-dose heparin-treated patients, 91%; weight-adjusted heparin-treated patients, 95%; p = 0.12), and hemoglobin loss (fixed-dose heparin-treated patients, 0.3 ± 0.9 mg/dL; weight-adjusted heparin-treated patients, 0.4 ± 1.0; p = 0.37). However, use of the weight-adjusted heparin did result in earlier sheath removal and more rapid transfer to a stepdown unit.93

Two studies evaluated the usefulness of prolonged infusions of heparin after uncomplicated coronary angioplasty. In one study, prolonged heparin therapy was compared with abbreviated heparin therapy. There was a striking increase in serious bleeding complications with prolonged heparin therapy compared to abbreviated heparin therapy (7% vs 0%, respectively; p < 0.001), but there were no significant differences in the rate of ischemic complications between the two groups. In the other study, prolonged heparin infusion was associated with a trend toward an increase in major bleeding, as defined by a fall in hemoglobin level of > 3 g/dL or by the need for transfusion, compared to that in patients not receiving heparin therapy (8.2% vs 3.8%, respectively; p = 0.09).

The effect of subcutaneous heparin therapy on the reduction in bleeding complications was evaluated in a study in which the outcomes in 77 patients treated with IV heparin infusions (1,000 U/h for 12 to 18 h after angioplasty) were compared to those occurring in 74 patients treated with subcutaneous heparin (12,500 U every 12 h for three doses) who were undergoing early sheath removal.96 The rate of ischemic complications was similar in both groups, but the risk of bleeding was significantly lower in the group managed with early sheath removal and treated with subcutaneous heparin.96

In patients who do not receive GPIIb/IIIa inhibitors, sufficient heparin should be given to achieve an ACT of 250 to 300 s with the HemoTec device and 300 to 350 s with the Hemochron device. The committee recognizes that many clinicians empirically use lower ACT target levels in the event that GPIIb/IIIa inhibitors may be required and additional analyses from prior randomized trials that will lend insight into the optimal heparin dosing regimens are forthcoming. Pending these data, weight-adjusted (60 to 100 IU/kg) bolus unfractionated heparin should be given. If the target ACT values are not achieved after administration of a bolus of heparin, additional heparin boluses (2,000 to 5,000 IU) can be administered. Routine postprocedural infusions of heparin are not recommended after uncomplicated coronary angioplasty. Early sheath removal is strongly encouraged when the ACT falls to < 150 to 180 s.

When GPIIb/IIIa inhibitors are used, the bolus heparin (50–70 IU/kg) can be reduced to achieve a target ACT of 200 s with either the HemoTec or Hemochron device. Postprocedural infusions are not recommended during GPIIb/IIIa therapy. Femoral sheaths should be removed after the procedure when the ACT falls to < 150 to 180 s.

Low-Molecular-Weight Heparin: An increasing number of patients with unstable angina are treated with low-molecular-weight heparin (LMWH) prior to coronary angioplasty.97 Because of the difficulty monitoring anticoagulation levels using LMWH during coronary angioplasty, conventional dosages of unfractionated heparin also are recommended. In this setting, conventional monitoring methods, such as the ACT, may underestimate the true degree of periprocedural anticoagulation. A pilot randomized trial of 60 patients under PCI treated with unfractionated heparin or enoxaparin (1 mg/kg IV) showed no difference in safety between the two anticoagulants.98 Routine substitution of LMWH for unfractionated heparin cannot be recommended at this time.

Direct Thrombin Inhibitors

The development of direct thrombin inhibitors has been based on the characterization of hirudin, a 65-amino acid polypeptide isolated from the salivary gland of the
medicinal leech that is a potent irreversible inhibitor of thrombin.99 Bivalirudin (Angiomax, The Medicines Company; Cambridge, MA) is a 20-amino acid peptide modeled after native hirudin that also irreversibly inhibits the activity of thrombin (see page 95 for the article on new thrombin inhibitors in this supplement).

**Hirudin:** In the Hirudin in a European Trial Versus Heparin in the Prevention of Restenosis after PTCA study,100 1,141 patients with unstable angina scheduled for coronary angioplasty were treated with aspirin and were randomized to one of three anticoagulation regimens. Patients were randomized to treatment with bolus heparin (10,000 U) plus infusion heparin (15 U/kg/h for 24 h), hirudin bolus (40 mg) plus IV infusion hirudin (0.2 mg/kg/h for 24 h), or hirudin bolus (40 mg) plus IV infusion hirudin (0.2 mg/kg/h for 24 h) plus subcutaneous injection hirudin (40 mg twice daily for an additional 3 days). The administration of hirudin was associated with a significant reduction in early cardiac events, which occurred in 11.0%, 7.9%, and 5.6% of patients, respectively.

In the Hirudin in a European Trial Versus Heparin: 101 The administration of hirudin was associated with a significant reduction in early cardiac events, which occurred in 11.0%, 7.9%, and 5.6% of patients, respectively.

**Bivalirudin:** Topol and colleagues23 evaluated the safety and efficacy of bivalirudin as a substitute for heparin in an open-label, dose escalation study involving 258 patients undergoing elective angioplasty. Five successive bolus doses (0.15, 0.25, 0.35, 0.45, and 0.55 mg/kg body weight) matched with five successive infusion doses (0.6, 1.0, 1.4, 1.8, and 2.2 mg/kg/h) were evaluated in five groups of approximately 50 patients each. Bivalirudin produced a dose-dependent anticoagulant effect without an increase in bleeding complications. The incidence of major and minor angioplasty complications, including abrupt vessel closure, myocardial infarction, or the need for emergency bypass surgery, was reduced in patients treated with the highest two doses compared with the lower doses. This study72 suggested that a dose-response curve for bivalirudin exists at the lower end of the dosing range, demonstrated for the first time that coronary angioplasty could be performed with a direct thrombin inhibitor in place of heparin, and provided the basis for a controlled comparison of bivalirudin with heparin in patients undergoing coronary angioplasty. Bivalirudin was compared with unfractionated heparin in the Bivalirudin Angioplasty Study,101 a randomized trial of 4,098 patients with postinfarction or unstable angina undergoing coronary angioplasty then assigned to treatment with heparin bolus (175 U/kg) and infusion (15 U/kg/h) for 18 to 24 h, or bivalirudin bolus (1.0 mg/kg) and infusion (2.5 mg/kg/h) for 4 h followed by infusion (0.2 mg/kg/h) for 14 to 20 h. Compared with unfractionated heparin, bivalirudin had a similar likelihood of in-hospital death, Q-wave or non-Q-wave myocardial infarction, or emergency CABG, but bivalirudin therapy significantly reduced the likelihood of bleeding complications (odds ratio, 0.4; p < 0.001).103 These effects were particularly evident in those patients with unstable angina, who also showed a reduction in clinical events associated with bivalirudin therapy. These data suggest that bivalirudin is at least as effective as heparin with an improved safety profile.104 Bivalirudin recently has been approved in the United States for clinical use during PCI.

**Antithrombotic Agents To Prevent Restenosis After Coronary Angioplasty**

By incorporating platelets, by providing a chemostatic stimulus for leukocytes and macrophages, and by triggering smooth muscle cell migration and proliferation, arterial thrombi may contribute to restenosis that occurs after coronary angioplasty.105 The adhesion of platelets and leukocytes to damaged endothelium or to the extracellular matrix forms a scaffold for subsequent smooth muscle cell migration, proliferation, and arterial remodeling.106 Conventional antithrombotic strategies have not consistently reduced the frequency of angiographic or clinical restenosis after coronary angioplasty, although a large number of agents have been tried.105–107

Randomized studies evaluating the effect of aspirin on restenosis have produced conflicting results6,108–112 (Table 4), attributable, at least in part, to the following: varied dosage, timing, and duration of aspirin therapy; limited sample sizes; and incomplete angiographic follow-up. A study of 376 patients randomly assigned to treatment with the combination of aspirin (900 mg daily) plus dipyridamole (75 mg daily) or placebo for 6 months after coronary angioplasty demonstrated no differences in binary restenosis in the two groups (a ≥ 50% follow-up stenosis: aspirin plus dipyridamole-treated patients, 37.7%; placebo-treated patients, 38.6%).6 Although the late coronary diameters were larger in aspirin plus dipyridamole-treated segments (mean minimal lumen diameter: aspirin plus dipyridamole-treated segments, 1.03 ± 0.45 mm; placebo-treated segments, 0.76 ± 0.52 mm; p = 0.01),110 In a study of 248 patients randomly assigned to treatment with aspirin (325 mg daily) or oral warfarin, there was no significant difference in the angiographic restenosis rates (27% and 36%, respectively).109 Two other reports have suggested that aspirin use may modestly reduce restenosis after coronary angioplasty. In a study of 212 patients, random assignment to continued aspirin therapy (100 mg daily) or placebo was made 2 weeks after successful angioplasty; therapy then was continued for 6 months.109 Angiographic restenosis occurred in 25% of aspirin-treated patients and in 38% of those given placebo (p < 0.025), although there were no significant differences in clinical outcomes (angiographic restenosis or bypass surgery, 35% and 43%, respectively) between the two groups.110 A study112 reported that intermediate-dose aspirin (500 mg daily) was more effective than lower doses of aspirin therapy (40 mg or 100 mg daily) in preventing restenosis (≥ 50% follow-up diameter stenosis) after coronary angioplasty (29%, 43% and 53%, respectively; p < 0.05). In contrast, another study113 of 495 patients that...
assigned aspirin at a dose of either 80 mg or 1,500 mg daily after coronary angioplasty showed no significant difference in the angiographic restenosis rate between low-dose aspirin and high-dose aspirin groups (> 50% follow-up diameter stenosis, 47% and 51%, respectively). Given the failure of aspirin to consistently produce a major reduction in angiographic or clinical restenosis, continued aspirin therapy (160 to 325 mg daily) after coronary angioplasty should be recommended for the secondary prevention of subsequent cardiovascular events (ie, death, myocardial infarction, or stroke) rather than for the prevention of late restenosis.

Platelet thromboxane A<sub>2</sub> and serotonin receptor antagonists also have failed to reduce the frequency of restenosis after coronary angioplasty. The effect of GR32191, a specific thromboxane A<sub>2</sub> receptor inhibitor, was evaluated in the Coronary Artery Restenosis Prevention On Repeated Thromboxane Antagonism trial. A randomized trial of 522 patients randomly assigned to treatment with periprocedural aspirin (250 mg IV) or to oral GR32191B (80 mg orally followed by 40 mg twice daily for 6 months). There was no difference in the rate of angiographic restenosis between the two treatment regimens; the mean loss in minimal lumen diameter was 0.31 ± 0.55 mm in GR32191B-treated patients and 0.31 ± 0.54 mm in patients given aspirin. The effect of sulotroban, another thromboxane A<sub>2</sub> receptor antagonist, was evaluated in a study of 755 patients randomized to treatment with placebo, aspirin (325 mg daily), or sulotroban (3,200 mg daily) after coronary angioplasty. No differences in late lumen diameters were found in the three groups. Similar results were reported in a smaller study of 57 patients treated with either placebo or sulotroban (3,200 mg daily) after coronary angioplasty. Ketanserin, a serotonin S<sub>2</sub>-receptor antagonist, was tested in a study of 658 patients randomly assigned to treatment with ketanserin (40 mg IV loading dose then 40 mg bid × 6 mo) or placebo. The frequency of angiographic restenosis was 32% in both groups, and the rate of clinical restenosis also was not significantly different in the two groups (placebo-treated patients, 32%; ketanserin-treated patients, 28%).

Short-term (48 h) infusion of prostacyclin, a potent platelet inhibitor, failed to prevent angiographic restenosis in a clinical study that included 270 patients undergoing coronary angioplasty (≥ 50% loss of initial gain: prostacyclin, 31.2% versus placebo, 37.9%; p < 0.05).

### Table 4—Effect of Antiplatelet Agents on Restenosis After Coronary Angioplasty

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Clinical Status</th>
<th>Patients, No.</th>
<th>Type of Study</th>
<th>Treatment</th>
<th>Late Outcome, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al 1988</td>
<td>Elective</td>
<td>187 RCT</td>
<td>Aspirin, 330 mg tid</td>
<td>37.7</td>
<td>NR</td>
</tr>
<tr>
<td></td>
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<td>DP, 75 mg tid</td>
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<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>38.6</td>
<td>NR</td>
</tr>
<tr>
<td>Thornton et al 1984</td>
<td>Elective</td>
<td>122 RCT</td>
<td>Aspirin, 325 mg/d</td>
<td>27</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warfarin</td>
<td>36</td>
<td>NR</td>
</tr>
<tr>
<td>Taylor et al 1991</td>
<td>Elective</td>
<td>108 RCT</td>
<td>Aspirin, 100 mg/d</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>Darius et al 1994</td>
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<td>Aspirin, 500 mg/d</td>
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<td></td>
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<td>Aspirin, 40 mg/d</td>
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<td>Aspirin, 80 mg/d</td>
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<td>Aspirin, 1,500 mg/d</td>
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<td>Aspirin, 1,500 mg/d</td>
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<td>38</td>
<td>NR</td>
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<tr>
<td>Serruys et al 1991</td>
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<td>261 RCT</td>
<td>Aspirin, 250 mg IV</td>
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<td>GR32191B, 80 mg orally then 40 mg bid</td>
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<td>Pepine et al 1992</td>
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<td>Aspirin 325 mg/d</td>
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<td>Sulotroban, 3,200 mg/d</td>
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<td>Prostacyclin IV × 48 h</td>
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<td>Raizner et al 1988</td>
<td>Elective</td>
<td>154 RCT</td>
<td>Placebo</td>
<td>53</td>
<td>37</td>
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*p = patients. See Table 1 for abbreviations not used in text.

†p < 0.05.

‡p < 0.10.

§p = 0.001.
Clin-treated patients, 27%; placebo-treated patients, 32%; p = NS.\textsuperscript{118} Periprocedural administration of ciprostene, a stable prostacyclin analog, was evaluated in study of 311 patients undergoing coronary angioplasty.\textsuperscript{119,120} Late (6 months) clinical events (eg, death, myocardial infarction, or repeat revascularization) occurred less often in ciprostene-treated patients than in placebo-treated patients (20% vs 37%, respectively; p = 0.001), and there was a trend toward a decrease in visually determined angiographic restenosis rates (≥ 50% follow-up diameter stenosis: ciprostene-treated patients, 41%; placebo-treated patients, 53%; p = 0.058). On subsequent quantitative angiographic analysis, the magnitude of late lumen loss was also less in ciprostene-treated patients (loss in lumen diameter during follow-up: ciprostene-treated patients, 0.32 ± 0.07 mm; placebo-treated patients, 0.57 ± 0.08 mm; p = 0.025).\textsuperscript{119,120}

The effect of periprocedural administration of a potent GPIIb/IIIa receptor antagonist on late clinical restenosis (ie, freedom from death, nonfatal myocardial infarction, or repeat revascularization) also was evaluated in the EPIC study.\textsuperscript{121} Compared to placebo, patients treated with bolus plus infusion abciximab had a 23% reduction in cumulative 6-month clinical events (35% and 27%, respectively; p = 0.001),\textsuperscript{121} which was attributable to a 26% reduction in target vessel revascularization (22.3% vs 16.5%, respectively; p = 0.007). Subsequent studies have failed, however, to show a reduction in clinical or angiographic restenosis after abciximab.\textsuperscript{121} In a randomized trial of patients undergoing stent implantation, neither a 12-h nor 24-h infusion of abciximab was effective in reducing the magnitude of intimal hyperplasia within the stent.\textsuperscript{122}

There was a significant (p < 0.02) reduction in restenosis after abciximab. In a randomized trial of patients undergoing stent implantation, neither a 12-h nor 24-h infusion of abciximab was effective in reducing the magnitude of intimal hyperplasia within the stent.\textsuperscript{122}

There was a significant (p = 0.02) reduction in restenosis after abciximab. In a randomized trial of patients undergoing stent implantation, neither a 12-h nor 24-h infusion of abciximab was effective in reducing the magnitude of intimal hyperplasia within the stent.\textsuperscript{122}

### Table 5—Effect of Antithrombotic Agents on Restenosis After Coronary Angioplasty\textsuperscript{*}

<table>
<thead>
<tr>
<th>Study/Yr</th>
<th>Clinical Status</th>
<th>Patient No.</th>
<th>Type of Study</th>
<th>Treatment</th>
<th>Late Outcome, %</th>
<th>Overall Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish oils</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dehmer et al 123/1988</td>
<td>Elective</td>
<td>39</td>
<td>RCT</td>
<td>None</td>
<td>36</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>43</td>
<td></td>
<td>Eicosapentaeonic acid, 3.2 g/d</td>
<td>16†</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Docosalhexaenoic acid, 2.2 g/d</td>
<td>26</td>
<td>Negative</td>
</tr>
<tr>
<td>Reis et al 127/1989</td>
<td>Elective</td>
<td>62</td>
<td>RCT</td>
<td>Olive oil</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>124</td>
<td></td>
<td>Omega-3 fatty acid, 6 g/d</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Grigg et al 129/1989</td>
<td>Elective</td>
<td>47</td>
<td>RCT</td>
<td>50% olive oil; 50% corn oil</td>
<td>33</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54</td>
<td></td>
<td>Eicosapentaeonic acid, 1.8 g/d</td>
<td>34</td>
<td>NR</td>
</tr>
<tr>
<td>Milner et al 125/1989</td>
<td>Elective</td>
<td>99</td>
<td>RCT</td>
<td>None</td>
<td>NR</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95</td>
<td></td>
<td>Eicosapentaeonic acid, 3.15 g/d</td>
<td>NR</td>
<td>19†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Docosalhexaenoic acid, 1.35 g/d</td>
<td>48</td>
<td>64</td>
</tr>
<tr>
<td>Bairati et al 124/1992</td>
<td>Elective</td>
<td>60</td>
<td>RCT</td>
<td>Olive oil</td>
<td>31†</td>
<td>41†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59</td>
<td></td>
<td>Eicosapentaeonic acid, 2.7 g/d</td>
<td>48</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Docosalhexaenoic acid, 1.8 g/d</td>
<td>31†</td>
<td>41†</td>
</tr>
<tr>
<td>Kaul et al 129/1992</td>
<td>Elective</td>
<td>49</td>
<td>RCT</td>
<td>None</td>
<td>27</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>58</td>
<td></td>
<td>Eicosapentaeonic acid, 1.8 g/d</td>
<td>32</td>
<td>NR</td>
</tr>
<tr>
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<td></td>
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<td>Docosalhexaenoic acid, 1.2 g/d</td>
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<tr>
<td>Franzén et al 129/1993</td>
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<td>RCT</td>
<td>Olive oil</td>
<td>34</td>
<td>NR</td>
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<td>Omega-3 fatty acid, 3.15 g/d</td>
<td>31</td>
<td>NR</td>
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<tr>
<td>Leaf et al 130/1994</td>
<td>Elective</td>
<td>221</td>
<td>RCT</td>
<td>Corn oil</td>
<td>46</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>226</td>
<td></td>
<td>Eicosapentaeonic acid, 4.1 g/d</td>
<td>52</td>
<td>NR</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>Docosalhexaenoic acid, 2.8 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cairns et al 131/1996</td>
<td>Elective</td>
<td>297</td>
<td>RCT</td>
<td>Omega-3, 5.4 g/d</td>
<td>46</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>293</td>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>293</td>
<td></td>
<td>Enoxaparin, 30 mg sq bid</td>
<td>47</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>297</td>
<td></td>
<td>Placebo only</td>
<td>47</td>
<td>NR</td>
</tr>
<tr>
<td>Antithrombins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellis et al 130/1989</td>
<td>Elective</td>
<td>208</td>
<td>RCT</td>
<td>Dextrose × 18–24 h</td>
<td>36.7</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>208</td>
<td></td>
<td>Heparin × 18–24 h</td>
<td>41.2</td>
<td>NR</td>
</tr>
<tr>
<td>Faxon et al 133/1994</td>
<td>Elective</td>
<td>231</td>
<td>RCT</td>
<td>Placebo</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>227</td>
<td></td>
<td>Enoxaparin, 40 mg sq/d × 30 d</td>
<td>52</td>
<td>40</td>
</tr>
<tr>
<td>Urban et al 134/1988</td>
<td>Elective</td>
<td>54</td>
<td>RCT</td>
<td>Placebo</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56</td>
<td></td>
<td>Warfarin</td>
<td>29</td>
<td>43</td>
</tr>
</tbody>
</table>

\*See Tables 1 and 4 for abbreviations not used in text; sq = subcutaneously.

\textsuperscript{†}p < 0.05.
cularization in diabetic patients assigned to treatment with stenting plus abciximab (8.1%) compared with patients receiving stenting plus placebo (16.6%).

Angiographic restenosis was also reduced in diabetic patients treated with stenting and abciximab in this study.

The effects of omega-3 fatty acid supplements on restenosis after coronary angioplasty have been evaluated in several clinical trials (Table 5). Although the results of three series suggested a beneficial effect of omega-3 fatty acid supplementation on angiographic and clinical restenosis, other studies have failed to confirm these findings (Table 5). Two subsequent studies also failed to demonstrate a significant effect of omega-3 fatty acid supplementation on restenosis after coronary angioplasty. In the first of these, 447 patients were randomly assigned to receive omega-3 fatty acid supplements (4.1 g eicosapentaenoic acid and 2.8 g docosahexaenoic acid daily) or an equivalent amount of corn oil ethyl ester for 6 months after successful angioplasty. The rate of angiographic restenosis was similar in both groups (omega-3 fatty acid supplement-treated patients, 52%; corn oil-treated patients, 46%; p = 0.37). In the second study, a 2 x 2 factorial design was used to randomly assign 814 patients to treatment with omega-3 fatty acid supplementation (5.4 g daily), an LMWH (enoxaparin, 30 mg twice daily), both, or neither. No differences in 6-month angiographic minimal lumen diameters were demonstrated among the four treatment groups (Table 5).

In addition to enoxaparin, the effect of other antithrombins on restenosis after coronary angioplasty also has been evaluated. IV heparin administered for 24 h after successful coronary angioplasty failed to reduce angiographic restenosis in a randomized clinical trial (> 50% diameter stenosis: heparin-treated patients, 41.2%; dextrose-treated patients, 36.7%; p = NS). In a randomized clinical trial that included 458 patients randomly assigned to treatment with either enoxaparin (40 mg daily by subcutaneous injection) or placebo for 1 month after angioplasty, there was no difference in angiographic restenosis (> 50% follow-up diameter stenosis: 43% and 45%, respectively) and clinical restenosis (eg, freedom from death, infarction, revascularization, unstable angina, or asymptomatic angiographic renarrowing) occurred in 40% of patients in both groups.

The effect of r-hirudin on restenosis was evaluated in the Hirudin in a European Trial Versus Heparin in the Prevention of Restenosis after PTCA study. Despite a beneficial effect on early (96 h) clinical events in patients treated with r-hirudin, there were no differences in late minimal lumen diameters or 7-month event-free survival in the r-hirudin-treated patients.

Warfarin also has been tested in patients undergoing coronary angioplasty. In one study that randomly assigned 110 patients to treatment with warfarin or placebo after angioplasty, the frequency of angiographic restenosis was 29% in warfarin-treated patients compared to 37% in placebo-treated patients. These differences were not significant.

### Oral Antiplatelet Agents

1. We recommend pretreatment with aspirin to reduce the incidence of early complications after PCI (grade 1A). The recommended dose for aspirin is 80 to 325 mg (grade 2A).

2. We recommend long-term aspirin therapy (80 to 325 mg daily) for secondary prevention of cardiovascular events (grade 1A). There is no convincing evidence that long-term aspirin therapy influences the rate of restenosis after PCI.

3. For patients undergoing balloon angioplasty or atherectomy alone who cannot tolerate aspirin, we recommend pretreatment with clopidogrel, 300 mg oral loading dose and 75 mg daily before the procedure (grade 2A), or ticlopidine, 500 mg loading dose and 250 mg twice daily before the procedure (grade 2A). Ticlopidine has important side effects.

4. We recommend that clinicians not use dipyridamole as an alternative in aspirin-sensitive patients undergoing PCI (grade 2A).

5. As an adjunct to aspirin therapy in patients undergoing stent implantation, we recommend treatment with clopidogrel, 300 mg oral loading dose and 75 mg daily for 14 to 30 days (grade 2A), or ticlopidine, 500 mg loading dose and 250 mg twice daily for at least 10 to 14 days after the procedure (grade 2A). Ticlopidine has important side effects.

### Platelet GPIIb/IIIa Antagonists

1. We recommend that GPIIb/IIIa receptor inhibition using abciximab, eptifibatide, or tirofiban be considered in all patients undergoing PCI, particularly those patients who have refractory unstable angina or other high-risk features (grade 1A).

2. We recommend that abciximab is considered in patients undergoing primary PCI for acute myocardial infarction to reduce ischemic complications (grade 2A).

### Antithrombin Therapy

**Heparin:**

1. We recommend administration of unfractionated heparin to achieve an ACT of 250 to 300 s with the HemoTec device and 300 to 350 s with the Hemochron device. Weight-adjusted heparin boluses (60 to 100 IU/kg) can be used to avoid excessive levels of anticoagulation (all grade 1C).

2. We do not recommend routine postprocedural infusion of heparin in patients with uncomplicated procedures (grade 1C).
3. We recommend early sheath removal when the ACT falls to < 150 to 180 s to reduce the incidence of complications at the access site (grade 1C).

4. When abciximab therapy is used, the heparin bolus should be reduced to 50 to 70 IU/kg to achieve a target ACT of > 200 s with either the HemoTec or HemoChron device. Femoral sheaths should be removed after the procedure as when the ACT falls to < 150 to 180 s (grade 1A).

**Direct Thrombin Inhibitors:**

1. We recommend that bivalirudin may be given as an alternative to heparin in patients undergoing PCIs (grade 2A).

2. We recommend that direct thrombin inhibitors be used as alternative anticoagulants to unfractionated heparin in patients with known or suspected heparin-induced thrombocytopenia (grade 2A).

**Antithrombotic Agents To Prevent Restenosis After Coronary Angioplasty:**

1. We do not recommend the prolonged use of postprocedural low-dose unfractionated heparin (grade 1C) or LMWH in patients undergoing uncomplicated PCIs for the prevention of restenosis (grade 1A).

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