Antithrombotic Therapy During Percutaneous Coronary Intervention

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This chapter about antithrombotic therapy during percutaneous coronary intervention (PCI) is part of the seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading, see Guyatt et al, *CHEST 2004;126:179S–187S*). Among the key recommendations in this chapter are the following: For patients undergoing PCI, we recommend pretreatment with aspirin, 75 to 325 mg (Grade 1A). For long-term treatment after PCI, we recommend aspirin, 75 to 162 mg/d (Grade 1A). For long-term treatment after PCI in patients who receive antithrombotic agents such as clopidogrel or warfarin, we recommend lower-dose aspirin, 75 to 100 mg/d (Grade 1C+). For patients who undergo stent placement, we recommend the combination of aspirin and a thienopyridine derivative (ticlopidine or clopidogrel) over systemic anticoagulation therapy (Grade 1A). We recommend clopidogrel over ticlopidine (Grade 1A). For all patients undergoing PCI, particularly those undergoing primary PCI, or those with refractory unstable angina or other high-risk features, we recommend use of a glycoprotein (GP) IIb-IIIa antagonist (abciximab or eptifibatide) [Grade 1A]. In patients undergoing PCI for ST-segment elevation MI, we recommend abciximab over eptifibatide (Grade 1B). In patients undergoing PCI, we recommend against the use of tirofiban as an alternative to abciximab (Grade 1A). In patients after uncomplicated PCI, we recommend against routine postprocedural infusion of heparin (Grade 1A). For patients undergoing PCI who are not treated with a GP IIb-IIIa antagonist, we recommend bivalirudin over heparin during PCI (Grade 1A). In PCI patients who are at low risk for complications, we recommend bivalirudin as an alternative to heparin as an adjunct to GP IIb-IIIa antagonists (Grade 1B). In PCI patients who are at high risk for bleeding, we recommend that bivalirudin over heparin as an adjunct to GP IIb-IIIa antagonists (Grade 1B). In patients who undergo PCI with no other indication for systemic anticoagulation therapy, we recommend against routine use of vitamin K antagonists after PCI (Grade 1A).

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Key words: anticoagulation; percutaneous coronary intervention; prophylaxis; stent; unstable angina

Abbreviations: ACT = activated clotting time; CABG = coronary artery bypass graft surgery; CI = confidence interval; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; EPILOG = Evaluation of PTCA to Improve Long-Term Outcome by Abciximab GP IIb-IIIa Blockade; EPISTENT = Evaluation of Platelet IIb-IIIa Inhibitor for Stenting; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy; GP = glycoprotein; IMPACT = Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis; LMWH = low molecular weight heparin; MI = myocardial infarction; NS = not significant; NSTEMI = non–ST-segment elevation MI; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized clinical trial; REPLACE = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; SC = subcutaneous; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; STEMI = ST-segment elevation MI; TIMI = Thrombolysis in Myocardial Infarction; TVR = target vessel revascularization; UA = unstable angina; UFH = unfractionated heparin

The use of percutaneous coronary intervention (PCI) as an alternative to coronary artery bypass graft surgery (CABG) in patients with ischemic heart disease has expanded dramatically over the past 2 decades. In the United States, it is estimated that PCI was performed in $>$ 900,000 patients in 2003, exceeding the number of patients undergoing CABG. The procedural success, safety, and durability of PCI have improved dramatically since its introduction, reflecting continual technological improvements (*eg*, drug-eluting stents, distal protection devices), refinements in periprocedural adjunctive pharmacology (*eg*, glycoprotein [GP] IIb-IIIa inhibitors, alternative thrombin inhibitors), and a better understanding of patient and lesion selection criteria and their relationship to early and late clinical outcomes.

Initially, antithrombotic agents were evaluated based on their capacity to reduce the major ischemic complications associated with balloon angioplasty, including periprocedural death (0 to 1.7%), myocardial infarction (MI) [1.3 to 8.6%], vessel occlusion (immediate or delayed) [6.8 to 8.3%], and the need for early ($<$ 30 days) emergent CABG surgery (1.3 to 3.6%) or repeat PCI (4.5%).[1–5] These complications were caused by arterial thrombus formation at the site of vessel injury, a complication that occurred alone or in association with coronary artery dissection. The introduction of coronary stents reduced the risk of acute complications, thereby lowering the need for emergency CABG surgery to $<$ 1%,[6,7]

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and reducing the rate of recurrent symptoms due to restenosis. With the availability of new drug-eluting stents, late recurrence rates of $< 4\%$ have been reported.[8] Because of these results, coronary stents are now used in $> 90\%$ of patients undergoing PCI.

Appropriate use of antiplatelet agents (*eg*, aspirin, clopidogrel, and GP IIb-IIIa inhibitors) and anticoagulants (*eg*, IV heparin, low molecular weight heparin [LMWH], or bivalirudin) during PCI is aimed at improving early (30-day) clinical outcome, and focuses on preventing complications at the site of intervention. In contrast, extended therapy with antiplatelet drugs may reduce the frequency of thrombotic complications at remote sites. None of the antithrombotic regimens tested to date have had a significant effect on restenosis. In this chapter, the evidence supporting the use of antithrombotic agents in the PCI setting is reviewed and recommendations are provided. Table 1 lists the question definition and eligibility criteria for the studies considered in this review.

1.0 Patients Undergoing PCI: Oral Antiplatelet Therapy

1.1 Aspirin

Aspirin irreversibly inhibits cyclooxygenase, thereby blocking platelet synthesis of thromboxane A_2, a humeral mediator that promotes platelet aggregation. Initial studies evaluating aspirin in the PCI setting were designed to determine whether aspirin prevented restenosis. Although aspirin had no impact on this end point, these studies also provided information on the effect of aspirin on short-term ischemic complications.[9,10] Many of these early studies used aspirin in conjunction with other antiplatelet drugs, such as dipyridamole or ticlopidine.[10,11] Nonetheless, these early trials set the stage for aspirin as part of the foundation of antiplatelet drugs used in PCI. Furthermore, because aspirin reduces

Table 1—*Level of Evidence for Antithrombotic Therapy Trials After PCI*

Recommendation	Inclusion Criteria	Intervention	Outcomes	Methodology
1.1	All PCI patients	Aspirin vs placebo	In-hospital MI and thrombus	RCT, registries
1.1.1	All PCI patients	Low-dose vs high-dose aspirin	In-hospital complications	RCT*
1.1.2	All PCI patients	Short- vs long-term aspirin therapy	Late (9–12 mo) death, MI; Restenosis	RCT
1.1.3	All PCI patients	Aspirin dose plus clopidogrel	Late (12 mo) death, MI, stroke	Subgroup analysis
1.2	All PCI patients	Addition of thienopyridine derivative	30-d ischemic events	RCT
1.2.1	Stented patients	Clopidogrel vs ticlopidine	30-d ischemic events	RCT
1.2.2	All PCI patients	Clopidogrel pretreatment vs none	30-d ischemic events	RCT subgroup analysis
1.2.3	Aspirin-sensitive patients	Alternative antiplatelet agents	30-d ischemic events	RCT*, registries
1.2.4.1	All PCI patients	One month vs 9–12 mo clopidogrel	9–12 mo events	RCT
1.2.4.2	Drug-eluting stent patients	Prolonged therapy with clopidogrel	9–12 mo events	Registry
1.3	All PCI patients	Other antiplatelet agents	30-d and 6-mo events	RCT
2.1	All PCI patients	GP IIb-IIIa inhibitors versus placebo	30-d ischemic events	RCT
2.2	All PCI patients	Abciximab vs eptifibatide	30-d ischemic events	RCT
2.3	All PCI patients	Abciximab or eptifibatide bolus vs placebo	30-d ischemic events	RCT
2.4	All PCI patients	Abciximab or eptifibatide vs tirofiban	30-d ischemic events	RCT
2.5–2.6	NSTEMI-UA patients	Upstream GP IIb–IIIa antagonist vs placebo	30-d ischemic events	RCT
2.7	NSTEMI patients	Early abxicimab vs placebo	30-d ischemic events	RCT
3.1	All PCI patients	Heparin dosing	30-d ischemic events, including bleeding	Registries
3.2	GP IIb–IIIa treated patients	Heparin dosing	30-d ischemic events, including bleeding	RCT
3.3	All PCI patients	Prolonged heparin vs none	30-d ischemic events, including bleeding	RCT
4.1	All PCI patients	UFH after LMWH administration	30-d ischemic events, including bleeding	Registries
5.2.1	All PCI patients	Bivalirudin vs UFH	30-d ischemic events, including bleeding	RCT
5.2.2	PCI patients (low risk)	Bivalirudin vs UFH plus GP IIb–IIIa inhibitor	30-d ischemic events, including bleeding	RCT
5.2.3	PCI patients (high risk)	Bivalirudin vs UFH plus GP IIb–IIIa inhibitor	30-d ischemic events, including bleeding	RCT
6.0	All PCI patients	Warfarin vs placebo or aspirin alone	30-d and 6-mo ischemic events	RCT

*Unpublished abstracts.

cardiovascular death, MI, and stroke in patients with coronary artery disease, most patients are administered this medication.

The studies supporting the use of aspirin in PCI are reviewed in Table 2. In a study of 376 patients randomly assigned to receive aspirin (990 mg/d) plus dipyridamole (225 mg/d) or placebo starting 24 h before angioplasty and continued for 4 to 7 months after the procedure, the frequency of periprocedural MI was significantly lower with combined antiplatelet therapy than with placebo (1.6% and 6.9%, respectively; $p = 0.011$).[9] A second study that has not been published randomized 333 patients undergoing balloon angioplasty to one of three treatment arms; the combination of aspirin (650 mg/d) plus dipyridamole (225 mg/d), to ticlopidine (750 mg/d) or to placebo before the procedure. Immediate procedural complications, such as abrupt occlusion, thrombosis, or major dissection, occurred in 7% of the patients; complications were less frequent in patients treated with aspirin plus dipyridamole or ticlopidine (5% and 2%, respectively) than in those receiving placebo (14%; $p < 0.005$).[9] The beneficial effect of aspirin plus dipyridamole in reducing ischemic complications was also documented in a retrospective study[10] that included 300 patients undergoing 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 thrombosis.[10]

Aspirin alone has been compared with aspirin plus dipyridamole in patients undergoing elective balloon angioplasty. Lembo and colleagues[11] randomized 232 patients to either aspirin (325 mg/d) or the same dose of aspirin plus dipyridamole (225 mg/d). Rates of periprocedural MI were 1.7% and 4.3%, respectively, in the two treatment groups (p = not significant [NS]). Thus, this study failed to demonstrate a benefit of dipyridamole addition to aspirin.

1.1.1 Aspirin dose

Aspirin exerts its inhibitory effect within 60 min of oral administration, and its effect on platelet inhibition lasts for up to 7 days after the last dose of aspirin.[12] The minimum effective aspirin dosage in the setting of PCI has not been established. In an unpublished randomized trial,[13] 495 patients were randomly assigned to low-dose (80 mg/d) or high-dose (1,500 mg/d) aspirin starting 24 h before balloon angioplasty. There were no differences between the two groups with respect to the occurrence of MI (3.6% vs 3.9%, respectively) or need for CABG surgery (3.6% vs 3.7%, respectively) [Table 2]. Because the GI side effects of aspirin are dose related, an empiric dose of aspirin of 75 to 325 mg is administered at least 2 h prior to the procedure. A longer pretreatment period (up to 24 h) should be considered if a lower dose of aspirin (75 to 100 mg) is used because of the potential delay in bioavailability and attainment of a platelet inhibitory effect.

Table 2—*Effect of Antiplatelet Agents on Procedural Outcome After PCI

Source	Year	Clinical Status	Patients, No.	Type of Study	Treatment	Procedural Outcome, %			
						Death	MI	CABG or PTCA	Thrombus or Complications
Schwartz et al[9]	1988	Elective	187	RCT	Aspirin, 330 mg tid and dipyridamole, 75 mg tid	NR	1.6†	2.1	
			189		Placebo	NR	6.9	2.1	
White et al[46]	1987	Elective	111	RCT	Aspirin, 325 mg bid and dipyridamole, 75 mg tid				5‡
			112		Ticlopidine, 250 mg tid				2‡
			110		Placebo				14
Barnathan et al[10]	1987	All patients	32	Observational study	Aspirin and dipyridamole				0†
			110		Aspirin alone				1.8‡
			121		No aspirin				10.7
Mufson et al[13]	1988	Elective	253	RCT	Aspirin, 80 mg/d	0	3.6	3.6	
			242		Aspirin, 1,500 mg/d	0	3.9	3.7	
Lembo et al[11]	1990	Elective	117	RCT	Aspirin, 325 mg tid and dipyridamole, 75 mg tid	0.9	4.3	6.1	
			115		Aspirin, 325 mg tid	0	1.7	2.6	
Knudtson et al[58]	1990	Elective	134	RCT	Prostacyclin for 48 h	0	0.8	1.4	3.0‡
			136		Placebo	0.7	2.0	0.7	10.3

*NR = not reported.
†$p < 0.05$ compared with placebo.
‡$p < 0.01$ compared with placebo.

1.1.2 Effect of aspirin on restenosis

Studies[9,14–16] evaluating the effect of aspirin on the prevention of restenosis after balloon angioplasty have provided conflicting results, likely attributable to the varied dosage, timing, and duration of aspirin therapy, small sample sizes, and incomplete angiographic follow-up (Table 3). Overall, however, there is no evidence that aspirin influences the rate of restenosis. For example, in one trial,[9] 376 patients were randomized to treatment with the combination of aspirin (990 mg/d) and dipyridamole (75 mg/d) or with placebo for 6 months after balloon angioplasty. There was no difference in the rate of binary restenosis in the two treatment groups (37.7% and 38.6%, respectively).[9] A smaller randomized study[16] assigned 212 patients to 6 months of treatment with aspirin (100 mg/d) or placebo within 2 weeks of successful angioplasty. Angiographic restenosis occurred in 25% of aspirin-treated patients and in 38% of those receiving placebo ($p < 0.025$). However, there were no significant differences in clinical outcomes between the two groups. Although these trials suggest that aspirin has little or no effect on angiographic or clinical restenosis, long-term aspirin therapy is useful for secondary prevention of cardiovascular events (*ie*, death, MI, or stroke).[17]

1.1.3 Dose of aspirin when administered in combination with other antithrombotic drugs

When aspirin is administered in combination with other antiplatelet agents or with anticoagulants, it is reasonable to use a daily dose of 75 to 162 mg, rather than 325 mg, to minimize bleeding complications. Although there are no randomized trials comparing 75 to 162 mg with 325 mg of aspirin, the concept is supported by a post hoc analysis of data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study.[18] For this analysis, patients were classified into three aspirin dose groups: < 100 mg, 101 to 199 mg, and ≥ 200 mg.[18] The combined incidence of cardiovascular death, MI, or stroke was reduced by clopidogrel regardless of aspirin dose, but the incidence of major bleeding increased as a function of the aspirin dose, both in patients receiving aspirin plus placebo (1.9%, 2.8%, and 3.7%, respectively; $p = 0.0001$) and in

Table 3—*Effect of Antiplatelet Agents on Restenosis After PCI

Source	Year	Study Design	Total Patients, No.	Angiographic Follow-up	Stent Use	Treatment	Pretreatment Duration	Duration Therapy	Restenosis Rates, %
Schwartz et al[9]	1988	RCT	376	249	No	Aspirin, 330 mg tid; dipyridamole, 75 mg tid	24 h	4–7 mo	37.7
						Placebo			38.6
Taylor et al[16]	1991	RCT	216	212	No	Aspirin, 100 mg qd	NR	6 mo	25†
						Placebo			38
Bussman et al[15]	1987	Registry	356	333	No	Aspirin, 1500 mg qd	NR	6 mo	17‡
						Aspirin, < 1500 mg qd			32
						Aspirin, reduced or discontinued			38
Serruys et al[59]	1991	RCT	697	522	No	GR32191B, 80 mg then 40 mg bid	> 1 h	6 mo	21§
						Placebo			19
Finci et al[60]	1989	RCT	107	57	No	Sulotroban, 3,200 mg qd	24 h	6 mo	66‡
						Placebo			61
Savage et al[61]	1995	RCT	752	503	No	Sulotroban, 800 mg qd	> 1 h	6 mo	53
						Aspirin, 325 mg qd			39
						Placebo			43
Serruys et al[62]	1993	RCT	658	592	No	Ketanserin, 40 mg bid	> 1 h	6 mo	32
						Placebo			32
Fujita et al[63]	2003	RCT	79	NR	Yes	Sarpogrelate	NR	6 mo	4.3†
						Placebo			28.6
Knudtson et al[58]	1990	RCT	270	250	No	Prostacyclin, IV for 48 h	< 1 h	48 h	27‡
						Placebo			32
Gershlick et al[64]	1994	RCT	135	125	No	Prostaglandin I_2, 4 ng/kg/min	NR	36 h	29.2‡
						Placebo			38.3
Darius et al[65]	1992	RCT	32	24	No	Ciprostene, 120 ng/kg/min	None	48 h	63†§
						Placebo			55

*See Table 2 for expansion of abbreviation.
†$p < 0.05$; restenosis defined as > 50% follow-up diameter stenosis unless indicated otherwise.
‡Restenosis defined a loss of 50% of initial gain.
§Mean follow-up percentage stenosis.

those receiving aspirin plus clopidogrel (3.0%, 3.4%, and 4.9%, respectively; p = 0.0009).[18]

Recommendations

1.1.1. For patients undergoing PCI, we recommend pretreatment with aspirin, 75 to 325 mg (Grade 1A).

1.1.2. For long-term treatment after PCI, we recommend aspirin, 75 to 162 mg/d (Grade 1A).

1.1.3. For long-term treatment after PCI in patients who receive antithrombotic agents such as clopidogrel or warfarin, we recommend lower-dose aspirin, 75 to 100 mg/d (Grade 1C+).

1.2 Thienopyridine derivatives

Thienopyridine derivatives produce irreversible inhibition of the platelet adenosine diphosphate receptor, thereby attenuating platelet aggregation in response to adenosine diphosphate released from activated platelets.[19,20] Aspirin and thienopyridines derivatives have complementary mechanisms of action, and the combination of these agents inhibits platelet aggregation to a greater extent than either agent alone.[21] Combined antiplatelet therapy with aspirin and a thienopyridine is superior to systemic anticoagulation therapy for prevention of complications after coronary stent insertion. Thus, subacute vessel closure, which occurred 2 to 14 days after stent placement, was reported in 3 to 5% of cases in the initial series, despite the use of an aggressive antithrombotic regimen that included aspirin, dipyridamole, dextran, and IV heparin overlapping with a vitamin K antagonist. The risk of acute complications is reduced with aspirin plus a thienopyridine.[22,23] Thus, in a randomized trial[24] that included 517 high-risk patients treated with Palmaz-Schatz stents (Cordis Corporation, Warren, NJ) for acute MI, suboptimal angioplasty, or other "high-risk" clinical and anatomic features, patients were assigned to antiplatelet therapy (aspirin plus ticlopidine) or anticoagulant therapy (aspirin, heparin, and a vitamin K antagonist) after successful stent placement. The primary end point, a composite of cardiovascular death, MI, CABG surgery, or repeat angioplasty, occurred in 1.5% of patients receiving antiplatelet therapy and 6.2% of those randomized to anticoagulant treatment (p = 0.01).[24] Subacute stent thrombosis occurred in 0.8% of patients in the antiplatelet therapy group and in 5.4% of those receiving anticoagulants. The Stent Anti-thrombotic Regimen Study[25] randomized 1,653 lower-risk patients to aspirin alone (325 mg/d), the combination of aspirin (325 mg/d) plus ticlopidine (500 mg/d) for 1 month, or to aspirin (325 mg/d) plus warfarin after successful placement of a Palmaz-Schatz stent.[25] The composite of death, target lesion revascularization, angiographic thrombosis, or MI at 30 days was reduced from 3.6% in patients assigned to aspirin alone and 2.7% in those assigned to aspirin plus warfarin to 0.5% in those receiving the combination of aspirin and ticlopidine (p < 0.001).[25] Thus, based on these studies, the combination of aspirin plus a thienopyridine has become the standard of care.

Patients with a compelling need for coronary stenting who have contraindications to thienopyridine derivatives or who require a truncated course of thienopyridine therapy may benefit from heparin-, phosphorylcholine-, or carbon-coated stents because thrombosis rates appear to be low with these types of stents, even if patients are treated only with aspirin.[26,27] Thus, in a multicenter, prospective, nonrandomized, pilot study,[26] 200 patients were treated with aspirin alone after insertion of a heparin-coated stent.[26] The primary end point, stent thrombosis at 30 days, occurred in only 2 of 200 patients (1%).

1.2.1 Ticlopidine vs clopidogrel

Side effects are common with ticlopidine, and the drug can cause neutropenia and thrombocytopenia. Clopidogrel is safer than ticlopidine and easier to administer. Thus, clopidogrel does not cause neutropenia, thereby obviating the need for blood count monitoring (Table 4). Furthermore, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura are rare complications of clopidogrel.[28,29] Finally, unlike ticlopidine, which requires twice-daily administration, clopidogrel can be administered once daily.[30–32]

In two randomized trials,[33,34] clopidogrel and ticlopidine had similar efficacy, but clopidogrel produced fewer side effects. The Clopidogrel Aspirin Stent International Cooperative Study[53] randomized 1,020 patients to clopidogrel (300-mg loading dose followed by 75 mg/d) plus aspirin (325 mg/d) or clopidogrel (75 mg/d without a loading dose) and aspirin, or to ticlopidine (500 mg/d) and aspirin. The primary end point, a composite of major bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug, occurred in 9.1% of patients in the ticlopidine group and 4.6% of patients in the combined clopidogrel groups (relative risk, 0.50; p = 0.005).[33] Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (0.9% with ticlopidine, and 1.5% and 1.2% with clopidogrel, without or with a loading dose; p = NS for all comparisons).[33] In another study,[34] 700 patients were randomly assigned to receive a 4-week course of either ticlopidine (500 mg/d) or clopidogrel (75 mg/d) in addition to aspirin (100 mg/d). The prespecified primary cardiac end point, a composite of cardiac death, urgent target vessel revascularization (TVR), angiographically documented occlusion, or nonfatal MI within 30 days, occurred in 3.1% of patients assigned to clopidogrel and in 1.7% of those receiving ticlopidine (p = 0.24). Side effects were significantly less frequent in patients receiving clopidogrel than in those assigned to ticlopidine (4.5% and 9.6%, respectively; p = 0.01). A meta-analysis[35] of these trials showed that compared with ticlopidine, clopidogrel was associated with a significant reduction in the incidence of major adverse cardiac events (odds ratio [OR], 0.50; p = 0.001) and mortality (OR, 0.43; p = 0.001). If ticlopidine is administered after stent placement, it is reasonable to restrict its use to 14 days so as to minimize

Table 4—*Comparison of Ticlopidine and Clopidogrel After Coronary Stent Placement

Source	Year	Type of Study	Patients, No.	Treatment	Stent Thrombosis, %	Side Effects, %	30-d Outcomes, %			
							Any Event	Death	MI	CABG
Moussa et al[31]	1999	Observational registry	1,406	Aspirin, 325 mg qd Ticlopidine, 250 mg bid	1.5	10.6	3.1	0.9	1.8	0.4
			283	Aspirin, 325 mg qd Clopidogrel 75 mg qd	1.4	5.3‡	2.4	1.0	0.7	0.7
Berger[135]	1999	Observational registry	827	Aspirin, 325 mg qd Ticlopidine, 250 mg bid	0.7	NR	1.6	1.1	0.5	0.5§
			500	Aspirin, 325 mg qd Clopidogrel 75 mg qd	0.2	NR	0.8	0.4	0	0.4
Mishkel et al[32]	1999	Observational registry	361	Aspirin, 325 mg qd Ticlopidine, 250 mg bid	0.3	NR	1.4	0.6	0	0.3
			514	Aspirin, 325 mg qd Clopidogrel 75 mg qd	0.2	NR	2.1	0.9	1.0	0.4
Muller et al[34]	2000	RCT	345	Aspirin, 325 mg qd Ticlopidine, 250 mg bid	0.6	9.6	1.7	0.3	1.2	NR
			355	Aspirin, 325 mg qd Clopidogrel 75 mg qd	2	4.5†	3.1	0.3	2	NR
Bertrand et al[33]	2000	RCT	340	Aspirin, 325 mg qd Ticlopidine, 250 mg bid		9.1	0.9			
			335	Aspirin, 325 mg qd Clopidogrel, 75 mg qd		6.3	1.5			
			345	Aspirin, 325 mg qd Clopidogrel, 300/75 mg qd		2.9	1.2			

*See Table 2 for expansion of abbreviation.
†p = 0.01 compared with ticlopidine.
‡p = 0.006 compared with ticlopidine.
§PTCA or CABG surgery.

the risk of hematologic toxicity. In one large study[36] that evaluated a 14-day course of ticlopidine, the frequency of ischemic events was 0.73%; only 0.27% of patients had possible stent thrombosis between day 15 and day 30 (95% confidence interval [CI], 0.06 to 0.77).

Although the majority of subacute thrombotic events occur within the first 24 h after stent placement in patients treated with aspirin and a thienopyridine derivative,[37] it is reasonable to delay nonemergent, noncardiac surgery for 6 weeks after stent placement.[38] Thus, in a series[38] of 207 patients who underwent surgery shortly after successful coronary stent placement, 4.0% died, suffered an MI, or acquired stent thrombosis. All patients with complications underwent surgery within 6 weeks after stent placement. No events occurred in the remaining patients who underwent surgery between 7 weeks and 9 weeks after stent placement.[38] There are no studies evaluating morbidity and mortality associated with noncardiac surgery after placement of drug-eluting stents.

1.2.2 Pretreatment with thienopyridines prior to PCI

Most randomized trials demonstrating the benefit of ticlopidine or clopidogrel started the drug immediately after PCI was completed. In PCI-CURE,[39] pretreatment with clopidogrel for up to 10 days prior to PCI in patients with acute coronary syndromes resulted in improved 30-day outcomes compared with no clopidogrel pretreatment. An overall beneficial effect of pretreatment with clopidogrel could not be demonstrated in patients undergoing elective stent placement. In a subset analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial[40] (described below), however, patients pretreated with clopidogrel at least 6 h prior to PCI experienced a 38.6% relative reduction in the combined end point of death, MI, or TVR compared with those who did not receive clopidogrel pretreatment (p = 0.01). Additional analysis of the CREDO trial has suggested that the benefit of pretreatment may be limited to those patients who received pretreatment > 15 h prior to PCI.[41]

The platelet inhibitory effects of thienopyridines are delayed after drug administration, but can be achieved more rapidly by giving a loading dose. Thus, higher doses of clopidogrel (450 to 600 mg) prior to PCI may provide additional benefit compared with the conventional 300-mg loading dose.[42] A recent randomized trial[43] demonstrated that after a 600-mg loading dose of clopidogrel administered > 2 h prior to PCI, patients treated with high-dose heparin (140 IU/kg) had outcomes similar to those in patients treated with abciximab and lower-dose heparin (70 IU/kg). However, more information is needed before a high-dose clopidogrel loading regimen can be recommended on a

routine basis. Furthermore, the potential beneficial effect of pretreatment must be balanced against the increased risk of bleeding with clopidogrel should emergency CABG surgery be needed because of unfavorable anatomy or a PCI-induced complication.

1.2.3 Aspirin-intolerant patients

Hypersensitivity to aspirin can be manifested as acute asthma, urticaria, angioedema or, less commonly, as a systemic anaphylactoid reaction.[44] Although rapid oral challenge-desensitization to aspirin can be safely performed after PCI,[44,45] aspirin desensitization provides little protection for the reduction of events during PCI. In aspirin-intolerant patients, thienopyridine derivatives or GP IIb-IIIa inhibitors can be substituted for aspirin prior to PCI. An unpublished, randomized trial assigned 333 patients to treatment with either placebo, a combination of aspirin (650 mg/d) plus dipyridamole (225 mg/d), or ticlopidine (750 mg/d) before balloon angioplasty.[46] Immediate procedure-related complications (abrupt occlusion, thrombosis, or major dissection) occurred in 23 of the 333 patients (7%); complications were less frequent with aspirin plus dipyridamole and ticlopidine than they were with placebo (5%, 2%, and 14%, respectively; $p < 0.005$).[46]

1.2.4 Duration of thienopyridine therapy after stent placement

Extended treatment with the combination of aspirin and clopidogrel after PCI for an acute coronary syndrome[39] or after elective angioplasty[40] appears to reduce the rate of ischemic events (Table 5). The CREDO trial[39] was a randomized, blinded, placebo-controlled trial conducted in 2,116 patients undergoing elective PCI. Patients were randomly assigned to receive a 300-mg clopidogrel loading dose or placebo 3 to 24 h before PCI. Thereafter, all patients received clopidogrel (75 mg/d) until day 28.[39]

Table 5—*Benefits of Combined Use of Aspirin and Clopidogrel After PCI*

	CURE*			PCI-CURE†			CREDO‡		
Variables	Aspirin Alone, %	Aspirin Plus Clopidogrel, %	Relative Risk	Aspirin Alone, %	Aspirin Plus Clopidogrel, %	Relative Risk	Aspirin Alone, %	Aspirin Plus Clopidogrel, %	Relative Risk Reduction, %
Patients, No.	6,303	6,259		1,345	1,313		1,063	1,053	
Events before PCI									
MI or refractory ischemia				15.3	12.1	0.76¶			
MI				5.1	3.6	0.68‖			
Events to 30 d§									
Cardiovascular death, MI, urgent TVR				6.4	4.5	0.70‖	8.3	6.8	0.82
Cardiovascular death, MI				4.4	2.9	0.66‖			
Cardiovascular death				1.0	1.1	1.10	0.4	0	
MI				3.8	2.1	0.56	6.6	5.8	
Q-wave MI				2.4	0.8	0.35			
Urgent TVR				2.8	1.9	0.67	1.3	1.0	
9–12 mo outcomes	Cumulative			From PCI to 9 mo			Cumulative		
Cardiovascular death, MI, stroke	11.4	9.3	0.80#				11.5	8.5‖	26.9‖
Cardiovascular death, MI				8.0	6.0	0.75‖	10.4	7.9	24.0
Cardiovascular death	5.5	5.1	0.93	2.3	2.4	1.07	2.3	1.7	24.6
MI	6.7	5.2	0.77	6.4	4.5	0.71	8.4	6.7	20.8
Q-wave MI	3.1	1.9	0.60‖	3.5	1.5	0.43			
Non-Q-wave MI	3.8	3.5	0.89						
Stroke	1.4	1.2	0.86				0.9	0.9	10.0
Refractory ischemia	9.3	8.7	0.93						
Any revascularization				17.1	14.2	0.82‖	21.0	21.3	− 1.1
Any TVR							13.6	13.1	4.0
Urgent TVR							2.2	2.0	8.1

*From Yusuf et al.[47]
†From Mehta et al.[39]
‡From Steinhubl et al.[40]
§Patients undergoing stent placement received open-label thienopyridines for 28 days after PCI. Strategies assessed pretreatment with clopidogrel.
‖$p < 0.05$.
¶$p < 0.01$.
#$p < 0.001$.

From day 29 through 12 months, patients in the loading-dose group received clopidogrel (75 mg/d), while those in the control group received placebo. Both groups received aspirin throughout the study. The 12-month incidence of the composite of death, MI, or stroke in the intent-to-treat population was reduced by 26.9% in patients treated with long-term clopidogrel ($p = 0.02$).[40] A limitation of this study is that patients assigned to no pretreatment were not administered a loading dose of clopidogrel after the procedure.

Compared with aspirin alone, there was an excess of minor and major bleeding with the combination of aspirin and clopidogrel in patients with non–ST-segment elevation MI (NSTEMI) in the CURE trial (Table 6), although the incidence of life-threatening bleeding was not different between the two groups.[47] Using the Thrombolysis in Myocardial Infarction (TIMI) criteria for major bleeding, the rate of major bleeding with the combination of aspirin plus clopidogrel were similar to that with aspirin alone (1.1% and 1.2%, respectively; $p = 0.70$).[47] Major or life-threatening bleeding in the PCI-CURE study[39] was similar in the two groups, even in patients who received a GP IIb-IIIa inhibitor. In the CREDO trial,[40] major bleeding as defined by the TIMI criteria tended to be higher in the clopidogrel group than in those receiving placebo (8.8 and 6.7%, respectively; $p = 0.07$), although most of the major bleeding episodes were related to invasive procedure, such as CABG. Minor bleeding episodes were significantly more common with combination antiplatelet therapy in both the CURE and PCI-CURE studies. The CREDO trial[40] did not find differences in minor bleeding between the two groups. It is possible that the incidence of bleeding complications can be reduced if lower doses of aspirin are used in combination with clopidogrel.[40]

Three randomized trials[8,48,49] have shown a marked (70 to 80%) reduction in clinical events with the use of sirolimus-eluting stents. Because of the potential for delayed endothelialization of these devices, the combination of aspirin and a thienopyridine derivative, most often clopidogrel, was administered for 2 months[8] or 3 months[49] after the procedure. Subacute stent thrombosis was an uncommon event (< 1%) in these studies. Likewise, with the combination of aspirin plus a thienopyridine for 6 months, clinical events after stenting were reduced by 70% with paclitaxel-eluting stents. Rates of subacute stent thrombosis were similar with drug-eluting and bare metal stents with 6 months of dual antiplatelet therapy with aspirin and clopidogrel.[50,51] Because of cost and risk of potential bleeding complications, some clinicians prefer a shorter course of treatment with clopidogrel after PCI, particularly in patients with an isolated coronary artery lesion or with a low atherosclerotic risk.

Recommendations

1.2.1. Ticlopidine versus clopidogrel after stent placement

1.2.1.1. For patients who undergo stent placement, we recommend the combination of aspirin and a thienopyri-

Table 6—*Bleeding Event Rates Associated with Long-term Clopidogrel Use

	CURE†			PCI-CURE‡			CREDO§		
Variables	Aspirin Alone, %	Aspirin Plus Clopidogrel, %	Relative Risk	Aspirin Alone, %	Aspirin Plus Clopidogrel, %	Relative Risk	Aspirin Alone, %	Aspirin Plus Clopidogrel, %	Relative Risk
Up to 30 d									
Major				1.4	1.6	1.13	3.8	4.8	1.26
Life threatening				0.7	0.7	0.92			
Not life threatening				0.7	0.9	1.37			
Minor				0.7	1.0	1.33	2.2	3.0	1.36
Blood transfusion > 2 U				1.1	1.1	0.96			
Up to 9–12 mo				From PCI to Follow-Up					
Major	2.7	3.7	1.38¶	2.5	2.7	1.12	6.7	8.8	1.31
Life threatening	1.8	2.2	1.21	1.3	1.2	0.91			
Not life threatening	0.9	1.5	1.70¶	1.1	1.5	1.37			
Minor	2.4	5.1	2.12#	2.1	3.5	1.68#	5.6	5.3	0.95
Blood transfusion > 2 U	2.2	2.8	1.30‖	2.0	2.1	1.06			

*Major bleeding was defined as intracranial bleeding or bleeding associated with a decrease in hemoglobin of > 5 g/dL or hematocrit decrease of at least 15%. Life-threatening bleeding included bleeding events that were fatal or led to a reduction in the Hg level of at least 5 g/dL drop or to substantial hypotension requiring the use of intravenous inotropic agents, if it necessitated a surgical intervention, if it was symptomatic intracranial hemorrhage, or if it necessitated the transfusion of ≥ 4 U of blood. TIMI bleeding was defined as disabling bleeding, intraocular bleeding leading to loss of vision, or bleeding necessitating the transfusion of at least 2 U of blood. Minor bleeding included other bleeding that required the discontinuance of study medication.

†From Yusuf et al.[136]

‡From Mehta et al.[39]

§From Steinhubl et al.[40]

‖$p < 0.05$.

¶$p < 0.005$.

#$p < 0.001$.

dine derivative (ticlopidine or clopidogrel) over systemic anticoagulation therapy (**Grade 1A**).

1.2.1.2. We recommend clopidogrel over ticlopidine (**Grade 1A**).

1.2.2.1. We recommend a loading dose of 300 mg of clopidogrel at least 6 h prior to planned PCI (**Grade 1B**). If clopidogrel is started < 6 h prior to planned PCI, we suggest a 600-mg loading dose of clopidogrel (**Grade 2C**).

1.2.2.2. If ticlopidine is administered, we recommend that a loading dose of 500 mg at least 6 h before planned PCI (**Grade 2C**).

1.2.3 Aspirin intolerant patients

1.2.3.1. For PCI patients who cannot tolerate aspirin, we recommend that the loading dose of clopidogrel (300 mg) or ticlopidine (500 mg) be administered at least 24 h prior to planned PCI (**Grade 2C**).

1.2.4 Duration of thienopyridine therapy after stent placement

1.2.4.1. After PCI, we recommend, in addition to aspirin, clopidogrel (75 mg/d) for at least 9 to 12 months (**Grade 1A**).

1.2.4.2. If ticlopidine is used in place of clopidogrel after PCI, we recommend ticlopidine for 2 weeks after placement of a bare metal stent in addition to aspirin (**Grade 1B**).

1.2.4.3. In patients with low atherosclerotic risk such as those with isolated coronary lesions, we recommend clopidogrel for at least 2 weeks after placement of a bare metal stent (**Grade 1A**), for 2 to 3 months after placement of a sirolimus-eluting stent (**Grade 1C+**), and 6 months after placement of a paclitaxel-eluting stent (**Grade 1C**).

1.3 Other oral antiplatelet agents

Cilostazol, which selectively inhibits 3′5′-cyclic nucleotide phosphodiesterase III, has antiplatelet and vasodilating effects. In addition, this agent also inhibits vascular smooth-muscle cell proliferation *in vitro*.[52] Early studies with cilostazol suggested that this agent could be used as an alternative to ticlopidine in patients undergoing stent implantation,[53] but the capacity of cilostazol to prevent subacute thrombosis in patients with drug-eluting stents has been questioned.[54]

Five studies[52,55–57] have evaluated cilostazol for prevention of restenosis after coronary stenting (Table 7), and have yielded conflicting results. Although initial small studies suggested that cilostazol reduces restenosis,[52,55–57] the largest study[53] failed to demonstrate a benefit of cilostazol. This study[53] randomized 409 patients undergoing elective stent placement to receive aspirin plus ticlopidine or aspirin plus cilostazol starting 2 days before stenting. The angiographic restenosis rate was 27% in patients treated with aspirin and ticlopidine, and 22.9% in those receiving aspirin and cilostazol (p = NS).[53] The Cilostazol for Restenosis Trial (CREST) is an ongoing evaluation of 705 patients undergoing elective treatment with stent implantation. Patients are randomized to either aspirin and clopidogrel or to aspirin, clopidogrel, and cilostazol 100 mg twice daily for 6 mo. Preliminary results from this larger study found an approximately 30% reduction in angiographic restenosis associated with the long-term use of cilostazol (William Weintraub, MD; Emory University, Atlanta, GA; personal communication, November 2003).

The addition of dipyridamole to aspirin provides little incremental benefit over aspirin alone for the prevention of early complications after coronary angioplasty. In a study[11] of 232 patients randomly assigned to aspirin alone (975 mg/d) or 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 MI (1.7% vs 4.3%, respectively) or in the need for emergency CABG surgery (2.6% vs 6.1%, respectively). Other antiplatelet agents, such as prostacyclin, ketanserin, sarpogrelate, and sulotroban, have had little or no effect on the prevention of acute complications[58] or restenosis[59–65] after PCI.

Recommendations

1.3.1. For patients after stent placement, we suggest ticlopidine (**Grade 1B**) or clopidogrel (**Grade 1C**) over cilostazol.

Table 7—*Effect of Cilostazol on Restenosis After PCI

Source	Year	Study Design	Total Patients, No.	Angiographic Follow-up, No.	Stent Use	Treatment	Pretreatment Duration	Duration Therapy	Restenosis Rates, %
Kunishima et al[52]	1997	RCT	70	64	Yes	Cilostazol, 200 mg qd	3 d	NR	8.6†
						Aspirin, 250 mg qd			26.8
Tsuchikane et al[57]	1999	RCT	211	193	No	Cilostazol, 200 mg qd	None	3 mo	18
						Aspirin, 250 mg qd			40
Park et al[53]	2000	RCT	409	380	Yes	Cilostazol, 100 mg bid	48 h	6 mo	23
						Ticlopidine	48 h	1 mo	27
Tanabe et al[56]	2001	Registry	109	NR	No	Cilostazol, 200 mg qd	> 48 h	4 mo	12.5†
						Aspirin, 81 mg qd	> 48 h		43.8
Kamishirado et al[55]	2002	RCT	130	111	Yes	Cilostazol, 200 mg qd	48 h	6 mo	13†
						Ticlopidine			31

*See Table 2 for expansion of abbreviation. Restenosis defined as > 50% follow-up diameter stenosis.
†p < 0.05.

1.3.2. In aspirin-intolerant patients undergoing PCI, we suggest clinicians do **not** use dipyridamole as an alternative to a thienopyridine derivative (**Grade 2C**).

2.0 Patients Undergoing PCI: GP IIb-IIIa Inhibitors

Ligation of fibrinogen by platelet GP IIb-IIIa receptors and, under high shear conditions, von Willebrand factor, serves as the "final common pathway" of platelet aggregation by bridging adjacent platelets together. Three IV inhibitors of the GP IIb-IIIa receptor are licensed in North America, and these agents produce a 35 to 50% reduction in clinical events in patients with acute coronary syndromes (Table 8). These agents include abciximab, eptifibatide and tirofiban.

Abciximab

Abciximab was first studied in the Evaluation of 7E3 for the Prevention of Ischemic Complications Trial,[2] which included 2,099 high-risk patients undergoing PCI. All patients received aspirin (325 mg) and a nonweight-adjusted heparin bolus (10,000 to 12,000 IU) prior to PCI. Patients were then randomly assigned to treatment with placebo, a bolus of abciximab (0.25 mg/kg), or the same bolus dose of abciximab followed by a 12-h abciximab infusion (10 μg/min). Compared with placebo, bolus plus infusion abciximab was associated with a 35% reduction in frequency of the end point, a composite of death, nonfatal MI, need for repeat revascularization, or procedural failure (12.8% and 8.3%, respectively; $p = 0.008$).[2] However, major bleeding complications were twice as frequent in patients receiving abciximab, reflecting the high-dose of heparin that was administered in this study.

The Evaluation of PTCA to Improve Long-Term Outcome by Abciximab GP IIb-IIIa Blockade (EPILOG) trial[66] included 2,792 low-risk patients undergoing PCI. All patients in the EPILOG trail received aspirin and were then randomized to weight-adjusted heparin (100 IU/kg with target activated clotting time [ACT] of 300 s) plus placebo; the same heparin dose plus abciximab; or lower-dose heparin (70 IU/kg with minimum ACT target of 200 s) plus abciximab. Compared with placebo, the 30-day end point, a composite of death, MI, or urgent revascularization, was significantly lower in patients treated with abciximab plus lower-dose or usual-dose heparin (11.7%, 5.2%, and 5.4%, respectively; $p < 0.001$).[66] The need for transfusion was 3.9% in patients receiving the usual heparin dose plus placebo, whereas it was 3.3% and 1.9% in the abciximab-treated patients receiving usual-dose or low-dose heparin, respectively. Based on these results, the use of a lower-dose heparin regimen became the standard of care.

The Evaluation of Platelet IIb-IIIa Inhibitor for Stenting (EPISTENT) trial[67] randomly assigned 2,399 patients with ischemic coronary artery disease to stenting plus placebo, stenting plus abciximab, or balloon angioplasty plus abciximab. The primary 30-day end point, a combination of death, MI, or need for urgent revascularization, occurred in 10.8% of patients in the stent plus placebo group, 5.3% of those in the stent-plus-abciximab group (hazard ratio, 0.48; $p < 0.001$), and 6.9% in the group undergoing balloon PTCA and receiving abciximab (hazard ratio, 0.63; $p = 0.007$). No significant differences in bleeding complications were noted among the various treatment groups.

The effect of periprocedural abciximab on the prevention of late restenosis has been controversial. Although the Evaluation of 7E3 for the Prevention of Ischemic Complications study[68] showed a 23% reduction in cumulative 6-month clinical events ($p = 0.001$), these events were primarily related to the prevention of early (< 30-day) periprocedural events. A subgroup of diabetic patients undergoing stent implantation in EPISTENT trial[69] showed a reduction in 6-month TVR, from 16.6% in those receiving placebo to 8.1% in those receiving abciximab; but a larger study[70] of 1,117 diabetics undergoing stent placement and treatment with either tirofiban or abciximab failed to confirm a beneficial effect of GP IIb-IIIa inhibitors on the incidence of late restenosis. In this trial,[70] TVR occurred in 9.5% of patients treated with tirofiban and 11.1% of patients treated with abciximab ($p = 0.366$). Thus, the major benefit of GP IIb-IIIa inhibitors appears to be a reduction of acute ischemic events associated with PCI; these agents do not appear to influence vascular remodeling or restenosis.

Abciximab does not reduce complication rates associated with saphenous venous graft interventions.[71] Although "bailout" abciximab is often administered during or just after PCI if there is residual dissection, thrombus, or suboptimal results,[72] this approach has not been evaluated in prospective studies.

Late mortality benefits have been reported after use of abciximab.[73] In a meta-analysis[73] of 12 trials that enrolled 20,186 patients, 30-day mortality was significantly reduced with GP IIb-IIIa inhibition (OR, 0.73; 95% CI, 0.55 to 0.96; $p = 0.024$). Although 10 of the 12 trials showed a beneficial effect of GP IIb-IIIa inhibitor treatment on mortality, no individual trial detected a statistically significant mortality benefit.[73] At 6 months, the OR was 0.84 (95% CI, 0.69 to 1.03; $p = 0.087$).[73] This survival benefit amounts to a saving of 3.2 lives after 6 months per 1,000 patients treated (number needed to treat, 313).[73]

Eptifbatide

The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT)-II trial[74] enrolled 4010 patients undergoing PCI. Patients were randomized to treatment with placebo, a low-dose bolus of eptifibatide (135 μg/kg) followed by a low-dose infusion (0.5 μg/kg/min for 20 to 24 h), or the same eptifibatide bolus and a slightly higher-dose infusion (0.75 μg/kg/min for 20 to 24 h). In IMPACT-II,[74] the primary end point, a 30-day composite of death, MI, unplanned CABG surgery or repeat PCI, or coronary stenting for abrupt closure, occurred in 11.4% of patients in the

Table 8—*Early and Late Outcome In Randomized Trials of GP IIb–IIIa Inhibitors**

Variables	EPIC†			EPILOG‡			EPISTENT§			ESPRIT‖		RESTORE¶	
		Abciximab			Abciximab			Abciximab					
	Placebo	Bolus	Bolus + Inf	Placebo Plus Same-Dose Heparin	Plus Same-Dose Heparin	Plus Lower-Dose Heparin	Placebo Plus Stent	Plus Stent	Plus PTCA	Placebo	Integrilin	Placebo	Tirofiban
Lesion type	High risk				Low risk			Low risk			Low risk		High risk
Years of entry	November 1991 to November 1992				February 1995 to December 1995			July 1996 to September 1997			June 1999 to February 2000		January 1995 to December 1995
Patients, No.	697	695	708	939	918	935	809	794	796	1,024	1,040	1,070	1,071
Baseline factors													
Mean age, yr	61	60	62	60	60	60	59	59	60	62	62	59	59
Female gender %	27	28	29	28	27	29	25.5	25	25	28	27	28	28
Diabetes mellitus, %	26	23	23	24	22	23	21.4	20.4	19.6	21	20	20	20
UA, %	NA	NA	NA	50	46	46	60.4	56.4	54.8	14	13	68	67
Stent Use, %	0.6	1.7	0.6				96.0	97.3	19.3	97	95	NA	NA
Composite 1° end point	12.8	11.4	8.3	11.7	5.4	5.2	10.8	5.3	6.9	10.5	6.6††	12.2	10.3
Early complications, %													
Death	1.7	1.3	1.7	0.8	0.4	0.3	0.6	0.3	0.8	0.2	0.1	0.7	0.8
Q-wave infarction	2.3	1.0	3.0	0.8	0.5	0.4	1.4	0.9	1.5	4.9	3.3	5.7	4.2
Emergency CABG	3.6	2.3	2.4	1.7	0.9	0.4	1.1	0.8	0.6	NR	NR	2.2	1.9
Emergency PTCA	4.5	3.6	0.8	3.8	1.5	1.2	1.2	0.6	1.3	NR	NR	5.4	4.2
Major bleeding	7	11	14	3.1	3.5	2.0	2.2	1.5	1.4	0.5	0.7	3.7	5.3
Follow-up time		3 yr			6 mo			6 mo			6 mo#		6 mo
Late clinical outcome, %	47.2	47.4	41.1	25.8	22.3	22.8	18.3	13.0	15.5	11.5	7.5††	27.1	24.1
Death	8.6	8.1	6.8	1.7	1.4	1.1	1.2	0.5	1.8	1.4	0.8	1.4	1.8
Q-wave MI	13.6	12.2	10.7	1.6	1.4	1.3	1.5	1.3	2.1			7.6	6.3
Revascularization	40.1	38.6	34.8	19.4	18.4	19.0	10.6	8.7	15.4	9.4	8.6		

*NA = not available.
†From EPIC Investigators.[2]
‡From EPILOG Investigators.[66]
§From EPISTENT Investigators.[67]
‖From ESPRIT Investigators.[75]
¶From RESTORE Investigators.[78]
#From O'Shea et al.[76]

placebo group compared with 9.2% in the 135/0.5 eptifibatide group ($p = 0.063$) and 9.9% in the eptifibatide 135/0.75 group ($p = 0.22$).[74] Eptifibatide treatment did not increase rates of major bleeding or transfusion.

It is now recognized that the eptifibatide dose used in the IMPACT-II trial was insufficient to provide adequate platelet GP IIb-IIIa inhibition during PCI. The Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) trial[75] evaluated a higher-dose, double-bolus, eptifibatide regimen (two 180 μg/kg boluses administered 10 min apart, followed by an infusion of 2.0 μg/kg/min for 18 to 24 h) vs placebo in a randomized study of 2,064 patients undergoing stent implantation in a native coronary artery. The primary end point, a composite of death, MI, urgent TVR, or bailout GP IIb/IIIa inhibitor therapy within 48 h of randomization, occurred in 10.5% of 1,024 patients receiving placebo and in 6.6% of those treated with eptifibatide ($p = 0.0015$). The key 30-day secondary end point was also reduced, from 10.5% to 6.8% ($p = 0.0034$). These effects were sustained 1 year after the procedure, and eptifibatide also was effective in the subgroup of high-risk diabetic patients.[63] Major bleeding was infrequent, but occurred more frequently with eptifibatide than with placebo (1.3% and 0.4%, respectively; $p = 0.027$).[75,76] Based on the results of this trial, the eptifibatide regimen used in the ESPRIT trial has become the standard of care with this agent.

Tirofiban

A nonpeptidyl tyrosine derivative, tirofiban is approved for treatment of patients with acute coronary syndromes.[77] Like the other GP IIb-IIIa inhibitors, tirofiban also has been evaluated in patients undergoing PCI. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial[78] enrolled 2,139 patients undergoing PCI within 72 h of an acute coronary syndrome. After pretreatment with aspirin and heparin, patients were randomized to receive tirofiban (bolus of 10 μg/kg followed by an infusion of 0.15 μg/kg/min over 36 h) or placebo. In the RESTORE trial,[78] the primary 30-day end point, a composite of death, MI, CABG surgery, or repeat angioplasty for recurrent ischemia, or stent insertion for abrupt closure, was 16% lower with tirofiban treatment than with placebo ($p = 0.161$). However, the risk reduction decreased from 38% at 48 h ($p = 0.005$) to 27% at 7 days ($p = 0.022$).[78] Major bleeding occurred in 5.8% of those receiving tirofiban and in 3.7% of those randomized to placebo ($p = 0.096$).

In a larger study,[79] 4,809 patients destined for coronary stent placement were randomly assigned to receive either the same dose of tirofiban used in the RESTORE trial or abciximab prior to the procedure. The primary end point, a composite of death, nonfatal MI, or urgent TVR at 30 days, occurred more frequently in the tirofiban group than in the abciximab group (7.6% and 6.0%, respectively; $p = 0.038$). The relative benefit of abciximab was consistent regardless of age, sex, the presence or absence of diabetes, or the presence or absence of pretreatment with clopidogrel.[79] Subsequent studies[80–83] have suggested that the bolus dose of tirofiban administered in this study may have been suboptimal. Supporting this concept, larger tirofiban bolus doses have been shown to produce more inhibition of platelet aggregation than lower doses.[84] However, a higher-dose tirofiban regimen has yet to be evaluated in a large-scale clinical trial. Based on the results of the studies done with tirofiban to date, this agent is not recommended in the PCI setting.

Upstream use of GP IIb-IIIa inhibitors prior to PCI

Treatment with GP IIb/IIIa inhibitors reduces recurrent ischemia in patients with NSTEMI and unstable angina (UA), at least in part because these patients often undergo PCI.[77,85,86] The TIMI risk score has been used to identify NSTEMI/UA patients at moderate-to-high risk for recurrent ischemic events. These patients benefit from early administration of GP IIb-IIIa inhibitors and routine PCI.[87–89] An elevated troponin level also may help to identify high-risk patients. In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina trial,[85] 275 patients (30.9%) were identified as high risk for recurrent events based on an elevated level of troponin T at presentation.[85] Compared with placebo, the relative risk of death or nonfatal MI with abciximab was 0.32 ($p = 0.002$), attributable to a reduction in the rate of MI (OR, 0.23; $p < 0.001$).[85]

Although tirofiban was inferior to abciximab for the prevention of 30-day events in patients undergoing PCI,[79] favorable clinical outcomes after extended upstream use of tirofiban for NSTEMI/UA have been documented in two studies.[90,91] In the Treat Angina with Aggrestat and determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS) TIMI 18 trial, 2,220 patients with NSTEMI/UA were treated with aspirin, heparin, and tirofiban. Patients were then randomly assigned to an early invasive strategy (cardiac catheterization and revascularization within 4 to 48 h) or to a more conservative (selectively invasive) strategy. With tirofiban pretreatment and frequent use of coronary stents, the 6-month primary end point, a composite of death, nonfatal MI, and rehospitalization, was 15.9% with the early invasive strategy and 19.4% with the conservative strategy ($p = 0.025$). In another study,[90] 410 patients with NSTEMI/UA were assigned to early (< 6 h) PCI after pretreatment with high-dose clopidogrel and tirofiban or delayed (3 to 5 days) PCI after prolonged antithrombotic therapy. The primary end point was reached in 11.6% of the group receiving prolonged antithrombotic pretreatment and in 5.9% of the group receiving early intervention ($p = 0.04$).[90] Based on these trials, eptifibatide or tirofiban is recommended in moderate-to-high-risk patients with NSTEMI/UA. Abciximab is not recommended in this setting unless the coronary anatomy is known and PCI is planned within 24 h.

Use of GP IIb-IIIa inhibitors in ST-segment elevation MI

The use of GP IIb-IIIa inhibitors in patients with ST-segment elevation MI (STEMI) has been controversial. Using a two-by-two factorial design, the Controlled Abcixamab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial[92] assigned 2,082 patients with STEMI to treatment with balloon angioplasty alone, balloon angioplasty plus abciximab therapy, Multilink (Guidant; Santa Clara, CA) stenting alone, or Multilink stenting plus abciximab therapy. There was little incremental benefit with the use of abciximab on the 6-month primary end point, a composite of death, MI, disabling stroke, and ischemia-driven revascularization of the target vessel. Thus, the primary end point occurred in 20.0% of patients after balloon angioplasty, 16.5% after balloon angioplasty plus abciximab, 11.5% after stenting, and 10.2% after stenting plus abciximab ($p < 0.001$). In contrast, a smaller study[93] randomly assigned 300 patients with STEMI to abciximab plus stenting or placebo plus stenting before they underwent coronary angiography. At 30 days, the primary end point, a composite of death, MI, or urgent TVR, occurred in 6.0% of the patients in the abciximab group compared with 14.6% of those in the placebo group ($p = 0.01$).[93] By 6 months, the corresponding figures were 7.4% and 15.9%, respectively ($p = 0.02$).[93] Patients in the abciximab group had a greater frequency of grade 3 TIMI flow than those in the placebo group before the procedure (16.8% and 5.4%, respectively; $p = 0.01$). Immediately after stenting, grade 3 TIMI flow was found in 95.5% and 86.7% of those randomized to abciximab or placebo, respectively ($p = 0.04$); whereas at 6 months, grade 3 TIMI flow was found in 94.3% and 82.8% in the abciximab and placebo group, respectively ($p = 0.04$). Although small series[94] have documented favorable outcomes in STEMI patients treated with eptifibatide prior to PCI, large randomized trials have yet to be performed.

Recommendations

2.1. For all patients undergoing PCI, particularly those undergoing primary PCI, or those with refractory UA or other high-risk features, we recommend use of a GP IIb-IIIa antagonist (abciximab or eptifibatide) [**Grade 1A**].

2.2. In patients undergoing PCI for STEMI, we recommend abciximab over eptifibatide (**Grade 1B**).

Remark: Whenever possible, abciximab should be started prior to balloon inflation.

2.3. We recommend administration of abciximab as a 0.25 mg/kg bolus followed by a 12 h infusion at a rate of 10 μg/min (**Grade 1A**) and eptifibatide as a double bolus (each of 180 μg/kg administered 10 min apart) followed by an 18-h infusion of 2.0 μg/kg/min (**Grade 1A**).

2.4. In patients undergoing PCI, we recommend **against** the use of tirofiban as an alternative to abciximab (**Grade 1A**).

2.5. For patients with NSTEMI/UA who are designated as moderate-to-high risk based on TIMI score, we recommend that upstream use of a GP IIb-IIIa antagonist (either eptifibatide or tirofiban) be started as soon as possible prior to PCI (**Grade 1A**).

2.6. In NSTEMI/UA patients who receive upstream treatment with tirofiban, we recommend that PCI be deferred for at least 4 h after initiating the tirofiban infusion (**Grade 2C**).

2.7. With planned PCI in NSTEMI/UA patients with an elevated troponin level, we recommend that abciximab be started within 24 h prior to the intervention (**Grade 1A**).

Underlying values and preferences: these recommendations for the use of GP IIb-IIIa inhibitors place a relatively high value on preventing cardiovascular events and a relatively low value on cost and bleeding complications.

3.0 Patients Undergoing PCI: Unfractionated Heparin

Unfractionated heparin (UFH) is the most commonly used anticoagulant during PCI. ACT monitoring in the cardiac catheterization laboratory facilitates heparin dose titration during PCI[95] because the required level of anticoagulation is beyond the range that can be measured using the activated partial thromboplastin time.[96] At least two studies[97,98] have retrospectively related ACT values to clinical outcomes after PCI. A third retrospective analysis[99] of data from 5,216 patients receiving heparin during PCI suggested that ischemic complications at 7 days were 34% lower with an ACT in the range of 350 to 375 s than they were with an ACT between 171 s and 295 s ($p = 0.001$). In all of these studies, heparin was administered without adjunctive GP IIb-IIIa inhibitors. In the same setting, two small randomized trials[100,101] have evaluated empiric and weight-adjusted heparin dosing regimens, and have shown comparable results with both approaches. Based on these data, heparin administered in doses of 60–100 IU/kg and a target ACT between 250 s and 350 s are advocated in the absence of adjunctive GP IIb-IIIa inhibition. In contrast, a target ACT of 200 s is advocated when heparin is administered in conjunction with a GP IIb-IIIa inhibitor. Removal of the femoral sheath should be delayed until the ACT is between 150 s and 180 s.

Routine use of IV heparin after PCI is no longer used because several randomized studies[102,103] have shown that prolonged heparin infusions do not reduce ischemic complications, and are associated with a higher rate of bleeding at the catheter insertion site. Like the results with other antithrombotic agents, heparin does not reduce the risk of restenosis after balloon angioplasty (Table 9). Thus, IV heparin administered for 24 h after successful coronary angioplasty failed to reduce

Table 9—*Effect of Thrombin Inhibitors on Restenosis After PCI

Source	Year	Study Design	Total Patients, No.	Angiographic Follow-up, No.	Stent Use	Treatment	Pretreatment Duration	Duration Therapy	Restenosis Rates, %
UFH									
Ellis et al[102]	1989	RCT	416	255	No	UFH, 800–1,200 U/h	None	18–24 h	41
						Placebo			37
Brack et al[104]	1995	RCT	339	299	No	UFH, 12,500 U bid	None	4 mo	41†
						Placebo			51
LMWH									
Faxon et al[117]	1994	RCT	458	357	No	Enoxaparin, 40 mg SQ qd	None	1 mo	43
						Placebo			45
Cairns et al[137]	1996	RCT	653	625	No	Enoxaparin, 30 mg bid	None	6 wk	38
						Placebo			40.4
Karsch et al[138]	1996	RCT	625	514	No	Reviparin, 3,500 U bid	None	28 d	0.25‡
						Placebo			0.29
Schmid et al[139]	1993	RCT	41	37	No	Reviparin, 2,500 U bolus plus 5,000 U SC qd	None	21 d	18
						Reviparin, 5,000 U bolus plus 5,000 U SC qd	None	21 d	20
						Reviparin, 10,000 U bolus plus 10,000 U SC qd	None	21 d	9
						UFH, 10,000 U bolus plus 2,500 U SC qd	None	21 d	25
Lablanche et al[118]	1997	RCT	354	269	No	Nadroparin, 6,150 U SQ qd	72 h	3 mo	51.9
						Placebo			48.8
Amann et al[119]	1993	Registry	20	20	No	Fraxiparin, 0.6 mL SQ qd	24 h	4 wk	30
Grassman et al[140]	2001	RCT	118	102	No	Certoparin, 80 mg SQ bid	NR	3 mo	31
						Placebo	NR	3 mo	49
Direct thrombin inhibitors									
Burchenal et al[128]	1998	RCT	87	87	No	Bivalirudin bolus and infusion	None	36 h	62.2
						Heparin, 175 U/kg bolus			58
Serruys et al[124]	1995	RCT	1,141	986	No	Hirudin, 40 mg bolus plus IV	None	24 h	0.32‡
						Hirudin, 40 mg bolus plus IV plus SQ	None	72 h	0.26
						Heparin, 10,000 U bolus and infusion	None	24 h	0.26

*Restenosis defined as > 50% follow-up diameter stenosis unless indicated otherwise. See Table 2 for expansion of abbreviation.
†Restenosis defined a loss of 50% of initial gain.
‡Restenosis defined as late lumen loss.

angiographic restenosis in a randomized clinical trial (RCT) comparing heparin with dextrose (41.2% and 36.7%, respectively; p = NS).[102] In another study,[104] 339 patients were randomized to no heparin or to twice-daily subcutaneous (SC) heparin (12,500 IU) for 4 months after successful angioplasty.[104] No differences in angiographic or clinical indexes of restenosis were identified between the two groups.

Recommendations

3.1. In patients receiving a GP IIb-IIIa inhibitor, we recommend a heparin bolus of 50 to 70 IU/kg to achieve a target ACT > 200 s (**Grade 1C**).

3.2. In patients not receiving a GP IIb-IIIa inhibitor, we recommend that heparin be administered in doses sufficient to produce an ACT of 250 to 350 s (**Grade 1C+**). We suggest a weight-adjusted heparin bolus of 60 to 100 IU/kg (**Grade 2C**).

3.3. In patients after uncomplicated PCI, we recommend **against** routine postprocedural infusion of heparin (**Grade 1A**).

4.0 Patients Undergoing PCI: LMWH

Increasingly, LMWH is replacing heparin for treatment of patients with NSTEMI/UA, many of whom undergo PCI (Table 10).[105–111] Because of difficulties monitoring levels of anticoagulation with LMWH during PCI, empiric dosing algorithms have been developed.[112] Enoxaparin is the most commonly used LMWH used in this setting. Thus, if the last dose of

Table 10—*LMWHs During PCI

Source	Patients, No.	Indication	Agent	Dose	Route	GP IIb–IIIa Use	Plavix Clopidogrel Pretreatment	30-d Ischemic Events	Major Bleeding	Minor Bleeding
Rabah et al[106]	30	Elective	Enoxaparin	1.0 mg/kg	IV	No	No			
	30		UFH	10,000 U						
Miller et al[112]	198	ACS	Enoxaparin	0.5 mg/kg	IV	Double-bolus eptifibatide	300 mg	0.5	0.5	0
Kereiakes et al[141]	828	Elective or urgent	Enoxaparin	1.0 mg/kg	IV	No	No	7.7	1.1	6.2
Ferguson et al[110]	671	ACS	Enoxaparin	1.0 mg/kg†	SQ	Abciximab, eptifibatide, or tirofiban	No	7.4%	1.4	3.2
Kereiakes et al[141]	818	Elective	Enoxaparin	0.75 mg/kg	IV	Abciximab	No	0.2	0.4	7
Bhatt et al[115]	129	Elective or urgent	Enoxaparin	0.75 mg/kg	IV	Double-bolus eptifibatide	Variable	10	2.5	1.6
	132		UFH	60 U/kg	IV	Double-bolus eptifibatide		7.6	1.6	8.9
Collet et al[142]	132	ACS	Enoxaparin	1.0 mg/kg	SQ	None	None	3.0	0.8	2.4
Choussat et al[143]	242	Elective or ACS	Enoxaparin	0.5 mg/kg	IV	No	No	2.5	0.4	1.2
Kereiakes et al[116]	103	Elective or ACS	Dalteparin	40–60 IU/kg	IV	Abciximab	NR	15.5	2.8	10.3
Preisack et al[111]	306	Elective or ACS	Reviparin	10,500	IV	No	No	3.9‡	2.3	NR
	306		UFH	24,000	IV	No	No	8.2	2.6	NR

*ACS = acute coronary syndrome. See Table 2 for expansion of abbreviation.
†Enoxaparin, 0.1 mg/kg SQ initiated on admission. No further enoxaparin was given if PCI was performed within 8 h of last SQ injection. If PCI was performed between 8–12 h after PCI, an additional 0.3 mg/kg IV was given.
‡$p < 0.05$. Restenosis defined as > 50% follow-up diameter stenosis unless indicated otherwise.

enoxaparin is administered < 8 h before PCI, no additional enoxaparin is used. When the last dose of enoxaparin is administered between 8 h and 12 h before PCI, a 0.3 mg/kg bolus of IV enoxaparin is advocated at the time of PCI; whereas if the last enoxaparin dose is administered > 12 h before PCI, conventional anticoagulation therapy is advocated during PCI.

IV enoxaparin has been evaluated as the primary anticoagulant during PCI, administered in doses of 0.5 to 1.0 mg/kg.[113] This regimen has yet to be compared with heparin. A point-of-care assay for measuring the anti-factor Xa activity of enoxaparin has been developed. Enoxaparin appears to be safe when used in combination with tirofiban[114] or eptifibatide[115] during PCI. A favorable outcome has been reported with the combination of dalteparin and abciximab in patients undergoing PCI.[116]

Short-term administration of LMWH after PCI does not significantly reduce the occurrence of early ischemic events. In the Antiplatelet Therapy alone vs. Lovenox plus Antiplatelet therapy in patients at increased risk of Stent Thrombosis trial,[36] 1,102 patients at increased risk of stent thrombosis (STEMI within 48 h, diffuse distal disease, large thrombus volume, acute closure, or residual dissection) were randomly assigned to receive either enoxaparin (40 mg or 60 mg SC q12h for 14 days based on patient weight < 60 kg or > 60 kg) or placebo; all patients received aspirin (325 mg/d) and ticlopidine (250 mg bid) for 14 days. The primary end point, a 30-day composite of death, nonfatal MI, and urgent revascularization, occurred in 1.8% of patients receiving enoxaparin and in 2.7% of those receiving placebo ($p = 0.295$).[36] LMWH treatment has no effect on restenosis (Table 9).[117–119]

Recommendation

4.1. In patients who have received LMWH prior to PCI, we recommend that administration of additional anticoagulant therapy is dependent on the timing of the last dose of LMWH (**Grade 1C**). If the last dose of enoxaparin is administered ≤ 8 h prior to PCI, we suggest no additional anticoagulant therapy (**Grade 2C**). If the last dose of enoxaparin is administered between 8 h and 12 h before PCI, we suggest a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI (**Grade 2C**). If the last enoxaparin dose is administered > 12 h before PCI, we suggest conventional anticoagulation therapy during PCI (**Grade 2C**).

5.0 Patients Undergoing PCI: Direct Thrombin Inhibitors

Three direct thrombin inhibitors, hirudin, bivalirudin, and argatroban, have been evaluated as alternatives to heparin during PCI.[120–124]

5.1 Hirudin

In the Hirudin in a European Trial vs Heparin in the Prevention of Restenosis After PTCA Study,[124] 1,141 patients with UA undergoing PCI were treated with aspirin and randomly assigned to receive a heparin bolus of 10,000 IU plus infusion of 15 IU/kg/h for 24 h; a hirudin bolus of 40 mg plus IV infusion of 0.2 mg/kg/h for 24 h; or a hirudin bolus of 40 mg followed by an IV infusion of 0.2 mg/kg/h for 24 h, followed by SC hirudin injections of 40 mg bid for an additional 3 days. Hirudin use was associated with a 39% reduction in early (96-h) ischemic events ($p = 0.023$), but the primary outcome, the angiographically detected rate of restenosis at 7 months, was similar in all three treatment groups.

5.2 Bivalirudin

A synthetic 20 amino acid analog of hirudin, bivalirudin has been extensively evaluated as an alternative to heparin in patients undergoing PCI (Table 11).[120–122,125–129] The Bivalirudin Angioplasty Trial[126] compared bivalirudin with UFH in 4,098 patients with postinfarction angina or UA undergoing PCI. Patients were randomized to treatment with a high-dose heparin bolus (175 IU/kg bolus followed by a 15 IU/kg/h infusion for 18 to 24 h) or to bivalirudin (1.0 mg/kg bolus followed by an infusion of 2.5 mg/kg/h infusion for 4 h, which was then reduced to 0.2 mg/kg/h for the subsequent 14 to 20 h). Bivalirudin did not reduce the risk of in-hospital death, Q-wave, or non–Q-wave MI, or emergency CABG surgery, but did reduce the risk of bleeding complications (OR, 0.4; $p < 0.001$).[126] In patients with post-MI angina, a prespecified high-risk group, the rate of major ischemic complications was lower with bivalirudin than with heparin (9.1% and 14.2%, respectively; $p = 0.04$), as was the rate of major bleeding (3.0% and 11.1%, respectively; $p < 0.001$).[126] An intention-to-treat reanalysis of the data from this study using a contemporary composite end point of death, MI, or repeat revascularization[127] demonstrated event rates of 6.2% in the bivalirudin group and 7.9% in the heparin group at

Table 11—*Bivalirudin Use in PCI Trials*

	Bittl*			REPLACE-2†		
Variables	High-Dose, Heparin	Bivalirudin	p Value	Heparin plus GP IIb–IIIa	Bivalirudin	p Value
Patients, No.	2039	2059		3008	2994	
Age	54.70	54.70		62.6	62.6	
Female gender, No.	32	33		25.9	25.3	
Prior MI				36.7	37.4	
UA < 48 h	31	30		14.7	14.3	
MI < 7 d				8.4	8.4	
Stent Use				85.7	85.1	
Multivessel PCI				15	17.2	
Thienopyridine pretreatment				85.4	86.7	
Planned GP IIb–IIIa				96.5		
Abciximab				42.9		
Eptifibatide				53.4		
30-d events						
Death, MI, TVR, bleeding	12.2	11.4		10.0	9.2	0.32
Death, MI, TVR	5.1	4.6	0.42	7.1	7.6	0.40
Death	0.2	0.4	0.27	0.4	0.2	0.26
MI	3.9	3.2	0.20	6.2	7.0	0.23
Q-wave MI				0.4	0.4	0.43
Non-Q-wave MI				5.8	6.6	0.43
Creatine kinase-MB < 3 × control				0.1	0.1	0.41
Creatine kinase-MB 3–5 × control				2.5	2.4	0.41
Creatine kinase-MB 5–10 × control				1.7	2.4	0.41
Creatine kinase-MB > 10 × control				1.3	1.4	0.41
Urgent revascularization	1.7	1.7	1.00	1.4	1.2	0.44
Bleeding events						
Major bleeding	9.8	3.8	0.001	4.1	2.4	< 0.001
Minor bleeding				25.7	13.4	< 0.001
Intracranial	0.09	0.05	0.62	0.1	0	> 0.99
TIMI criteria (major)				0.9	0.6	0.30
Any transfusion				2.5	1.7	0.02
Thrombocytopenia				1.7	0.7	< 0.001

*From Bittl et al.[126,127] Bittl et al[126] is primary publication.
†From Lincoff et al.[121]

7 days (p = 0.039). These differences persisted at 90 days (p = 0.012) and 180 days (p = 0.153).

The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial[121] randomly assigned 6,010 patients undergoing PCI to receive IV bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/h for the duration of PCI) with provisional GP IIb/IIIa inhibition, or heparin (65 IU/kg bolus) plus a GP IIb/IIIa inhibitor (either abciximab or eptifibatide). In REPLACE-2,[121] the primary end point, a composite of death, MI, urgent repeat revascularization, or in-hospital major bleeding at 30 days, occurred in 9.2% of patients in the bivalirudin group and in 10.0% of those receiving heparin plus a GP IIb-IIIa antagonist (p = 0.32). Bivalirudin with provisional GP IIb-IIIa blockade was statistically not inferior to heparin plus planned GP IIb-IIIa blockade in terms of suppression of acute ischemic end points and bivalirudin was associated with less bleeding. It is possible, however, that the higher dose of UFH (65 IU/kg) may have contributed to the increase in bleeding complications that occurred in patients assigned to treatment with UFH plus a GP IIb-IIIa inhibitor.

Bivalirudin may be particularly useful for patients at high risk for bleeding, such as the elderly or those with renal insufficiency. It also may be better than heparin for patients who do not get adjunctive treatment with a GP IIb-IIIa inhibitor.

5.3 Argatroban

A small molecule derivative of arginine, argatroban targets the active site of thrombosis. This agent has been compared with heparin in patients with acute coronary syndromes, but has not been rigorously evaluated as an alternative to heparin in the PCI setting. However, argatroban has been used successfully in PCI in patients with heparin-induced thrombocytopenia.[123]

Recommendations

5.2.1. For patients undergoing PCI who are not treated with a GP IIb-IIIa antagonist or heparin, we recommend bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/h for the duration of PCI) during PCI (**Grade 1A**).

5.2.2. In PCI patients who are at low risk for complications, we recommend bivalirudin as an alternative to heparin as an adjunct to GP IIb-IIIa antagonists (**Grade 1B**).

5.2.3. In PCI patients who are at high risk for bleeding, we recommend bivalirudin over heparin as an adjunct to GP IIb-IIIa antagonists (**Grade 1B**).

6.0 Patients Undergoing PCI: Vitamin K Antagonists

Initially, antithrombotic regimens after stent placement included aspirin, dipyridamole, dextran, IV heparin, and warfarin for 30 days. These aggressive antithrombotic regimens were used in an attempt to prevent subacute stent thrombosis.[22,23] Randomized trials have since shown that warfarin provides little incremental benefit over aspirin alone on early outcomes in patients undergoing stent implantation. In the Stent Anti-thrombotic Regimen Study[25] the primary end point, a composite of death, revascularization of the target lesion, angiographically evident thrombosis, or MI within 30 days, occurred in 3.6% of patients assigned to receive aspirin alone, 2.7% of patients assigned to receive aspirin plus warfarin, and in only 0.5% assigned to receive aspirin plus ticlopidine (p = 0.001 for the comparison of all three groups). In a smaller series of 164 patients who were randomly assigned to aspirin (100 mg/d) or to aspirin plus warfarin after provisional coronary stenting, subacute closure occurred in 10.1% of those receiving aspirin alone and in 3.5% of those receiving aspirin plus warfarin (p = 0.09).[130]

The effect of long-term warfarin on the prevention of restenosis after PCI has been evaluated in five trials (Table 12).[14,131–134] Random assignment to warfarin or placebo was performed in 110 patients after angioplasty.[131] The frequency of angiographic restenosis was not different in the warfarin and placebo groups (29% and 37%, respec-

Table 12—*Effect of Warfarin on Restenosis After PCI**

Source	Year	Study Design	Total Patients, No.	Angiographic Follow-up, No.	Stent Use, %	Treatment	Pretreatment Duration	Duration Therapy	Restenosis Rates, %
Urban et al[131]	1988	RCT	110	85	No	Warfarin (PT > 2.5 × normal)	None	5 mo	29
						Placebo			37
Kastrati et al[134]	1997	RCT	496	432	Yes	Warfarin (INR 3.5–4.5)	None	4 wk	28.9
						Ticlopidine, 250 mg bid			26.8
Garachemani et al[132]	2002	RCT	191	176	36	Warfarin (INR 2.5–4.0)	None	6 mo	33
						Aspirin plus warfarin			30
Thornton et al[14]	1984	RCT	248	178	No	Aspirin, 325 mg qd	24 h	6 mo	27†
						Warfarin (to PT 2.5 × normal)			36
ten Berg et al[133]	2003	RCT	531	480	34	Coumarin (INR 2.1–4.8)	7 d	6 mo	38.9‡
						Placebo			39.1

*INR = international normalized ratio; PT = prothrombin time. Restenosis defined as > 50% follow-up diameter stenosis unless indicated otherwise.

†Restenosis defined a loss of 50% of initial gain.

‡Mean percentage stenosis at follow-up.

tively).[131] A second study of 248 patients randomly assigned to aspirin (325 mg/d) or warfarin also failed to identify an incremental benefit of warfarin over aspirin for the prevention of restenosis.[14] Another study[132] randomized 191 patients undergoing uncomplicated PTCA to aspirin (100 mg/d) or to aspirin plus warfarin for 6 months. Stents were implanted in 33% and 36% of patients in the two respective treatment groups. Restenosis at 6 months occurred in 30% of patients assigned to aspirin and in 33% of those receiving aspirin plus warfarin.[132] The Balloon Angioplasty and Anticoagulation Study[133] studied the effect of pretreatment with coumarins on 6-month angiographic outcomes in 531 patients. Subjects were randomized to aspirin alone or to aspirin plus a coumarin derivative started 1 week before the procedure. Mean luminal diameter at 6 months was similar in both groups.[133]

Recommendation

6.0. In patients who undergo PCI with no other indication for systemic anticoagulation therapy, we recommend **against** routine use of warfarin (or other vitamin K antagonists) after PCI (**Grade 1A**).

Summary of Recommendations

1.0 Patients Undergoing PCI: Oral Antiplatelet Therapy

1.1 Aspirin

1.1.1. For patients undergoing PCI, we recommend pretreatment with aspirin, 75 to 325 mg (**Grade 1A**).

1.1.2. For long-term treatment after PCI, we recommend aspirin, 75 to 162 mg/d (**Grade 1A**).

1.1.3. For long-term treatment after PCI in patients who receive antithrombotic agents such as clopidogrel or warfarin, we recommend lower-dose aspirin, 75 to 100 mg/d (**Grade 1C+**).

1.2.1 Ticlopidine versus clopidogrel after stent placement

1.2.1.1. For patients who underwent stent placement, we recommend the combination of aspirin and a thienopyridine derivative (ticlopidine or clopidogrel) over systemic anticoagulation therapy (**Grade 1A**).

1.2.1.2. We recommend clopidogrel over ticlopidine (**Grade 1A**).

1.2.2.1. We recommend a loading dose of 300 mg of clopidogrel at least 6 h prior to planned PCI (**Grade 1B**). If clopidogrel is started < 6 h prior to PCI, we suggest a 600-mg loading dose of clopidogrel (**Grade 2C**).

1.2.2.2. If ticlopidine is administered, we recommend that a loading dose of 500 mg at least 6 h before planned PCI (**Grade 2C**).

1.2.3 Aspirin intolerant patients

1.2.3.1. For PCI patients who cannot tolerate aspirin, we recommend that the loading dose of clopidogrel (300 mg) or ticlopidine (500 mg) be administered at least 24 h prior to planned PCI (**Grade 2C**).

1.2.4 Duration of thienopyridine therapy after stent placement

1.2.4.1. After PCI, we recommend, in addition to aspirin, clopidogrel (75 mg/d) for at least 9 to 12 months (**Grade 1A**).

1.2.4.2. If ticlopidine is used in place of clopidogrel after PCI, we recommend ticlopidine for 2 weeks after placement of a bare metal stent in addition to aspirin (**Grade 1B**).

1.2.4.3. In patients with low atherosclerotic risk, such as those with isolated coronary lesions, we recommend clopidogrel for at least 2 weeks after placement of a bare metal stent (**Grade 1A**), for 2 to 3 months after placement of a sirolimus-eluting stent (**Grade 1C+**), and 6 months after placement of a paclitaxel-eluting stent (**Grade 1C**).

1.3 Other oral antiplatelet agents

1.3.1. For patients after stent placement, we suggest ticlopidine (**Grade 1B**) or clopidogrel (**Grade 1C**) over cilostazol.

1.3.2. In aspirin-intolerant patients undergoing PCI, we suggest clinicians **not** use dipyridamole as an alternative to a thienopyridine derivative (**Grade 2C**).

2.0 Patients Undergoing PCI: GP IIb-IIIa Inhibitors

2.1. For all patients undergoing PCI, particularly those undergoing primary PCI, or those with refractory UA or other high-risk features, we recommend use of a GP IIb-IIIa antagonist (abciximab or eptifibatide) [**Grade 1A**].

2.2. In patients undergoing PCI for STEMI, we recommend abciximab over eptifibatide (**Grade 1B**).

Remark: Whenever possible, abciximab should be started prior to balloon inflation.

2.3. We recommend administration of abciximab as a 0.25 mg/kg bolus followed by a 12-h infusion at a rate of 10 μg/min (**Grade 1A**) and eptifibatide as a double bolus (each of 180 μg/kg administered 10 min apart), followed by an 18-h infusion of 2.0 μg/kg/min (**Grade 1A**).

2.4. In patients undergoing PCI, we recommend **against** the use of tirofiban as an alternative to abciximab (**Grade 1A**).

2.5. For patients with NSTEMI/UA who are designated as moderate-to-high risk based on TIMI score, we recommend that upstream use of a GP IIb-IIIa antagonist (either eptifibatide or tirofiban) be started as soon as possible prior to PCI (**Grade 1A**).

2.6. In NSTEMI/UA patients who receive upstream treatment with tirofiban, we recommend that PCI be deferred for at least 4 h after initiating the tirofiban infusion (**Grade 2C**).

2.7. With planned PCI in NSTEMI/UA patients with an elevated troponin level, we recommend that abciximab be started within 24 h prior to the intervention (**Grade 1A**).

Underlying values and preferences: These recommendations for the use of GP IIb-IIIa inhibitors place a relatively high value on preventing cardiovascular events and a relatively low value on cost and bleeding complications.

3.0 Patients Undergoing PCI: Unfractionated Heparin

3.1. In patients receiving a GP IIb-IIIa inhibitor, we recommend a heparin bolus of 50 to 70 IU/kg to achieve a target ACT $>$ 200 s (**Grade 1C**).

3.2. In patients not receiving a GP IIb-IIIa inhibitor, we recommend that heparin be administered in doses sufficient to produce an ACT of 250 to 350 s (**Grade 1C+**). We suggest a weight-adjusted heparin bolus of 60 to 100 IU/kg (**Grade 2C**).

3.3. In patients after uncomplicated PCI, we recommend **against** routine postprocedural infusion of heparin (**Grade 1A**).

4.0 Patients Undergoing PCI: Low Molecular Weight Heparin

4.1. In patients who have received LMWH prior to PCI, we recommend that administration of additional anticoagulant therapy is dependent on the timing of the last dose of LMWH (**Grade 1C**). If the last dose of enoxaparin was administered $\leq$ 8 h prior to PCI, we suggest no additional anticoagulant therapy (**Grade 2C**). If the last dose of enoxaparin was administered between 8 h and 12 h before PCI, we suggest a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI (**Grade 2C**). If the last enoxaparin dose was administered $>$ 12 h before PCI, we suggest conventional anticoagulation therapy during PCI (**Grade 2C**).

5.0 Patients Undergoing PCI: Direct Thrombin Inhibitors

5.2.1. For patients undergoing PCI who are not treated with a GP IIb-IIIa antagonist, we recommend bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/h for the duration of PCI) over heparin during PCI (**Grade 1A**).

5.2.2. In PCI patients who are at low risk for complications, we recommend bivalirudin as an alternative to heparin as an adjunct to GP IIb-IIIa antagonists (**Grade 1B**).

5.2.3. In PCI patients who are at high risk for bleeding, we recommend bivalirudin over heparin as an adjunct to GP IIb-IIIa antagonists (**Grade 1B**).

6.0 Patients Undergoing PCI: Vitamin K Antagonists

6.0. In patients who undergo PCI with no other indication for systemic anticoagulation therapy, we recommend **against** routine use of warfarin (or other vitamin K antagonists) after PCI (**Grade 1A**).

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