Review

Antiplatelet and anticoagulant therapy in elective percutaneous coronary intervention

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Abstract

Thrombosis plays a major role in acute vessel closure both after coronary balloon angioplasty and after stenting. This review will address the role of antiplatelet and anticoagulant therapy in preventing early thrombotic complications after percutaneous coronary intervention. The focus will be on agents that are routinely available and commonly used.

Keywords anticoagulant therapy, antiplatelet therapy, coronary thrombosis, percutaneous coronary intervention

The acute success rate of percutaneous coronary intervention (PCI) has increased ever since its introduction, despite a widening scope of indications [1–3]. Nevertheless, abrupt vessel closure during or shortly after balloon angioplasty still occurs in 2–5% of the patients [4–8]. Abrupt closure may result in myocardial infarction (10–35%) and death (2–5%) despite urgent reintervention [4–8]. Stents are nowadays placed in more than 50% of elective interventions, partly because they are very effective in avoiding vessel closure [7,9]. Stenting, however, is associated with a unique and devastating complication, namely (sub)acute thrombosis, which occurs in 1–4% of the procedures [10,11]. Unfortunately, the majority of patients who experience this complication suffer from myocardial infarction and/or die [10,11]. Thrombosis plays a major role in acute vessel closure both after balloon angioplasty and after stenting. This review will address the value of antiplatelet and anticoagulant therapy to prevent thrombotic complications after PCI. We will focus on agents that are routinely available and commonly used. As the role of thrombosis differs for stented and non-stented lesions, the therapeutic options during and after balloon angioplasty and stenting are discussed separately. In addition, the unique pathophysiology of late thrombotic closure after intracoronary brachytherapy and the extended need for antithrombotic therapy will be discussed.

ACT = activated clotting time; ADP = adenosine diphosphate; AMI = acute myocardial infarction; BAAS = Balloon Angioplasty and Anticoagulation Study; CAPTURE = c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina; CI = confidence interval; CLASSICS = Clopidogrel/Aspirin Stent International Cooperative Study; EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications; EPILOG = Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT = Evaluation of Platelet IIb/IIIa Inhibition in Stenting; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; ESSENCE = Enoxaparin versus Heparin in Unstable Angina and Non Q Wave Myocardial Infarction; FANTASTIC = Full Anticoagulation Versus Aspirin and Ticlopidine After Stent Implantation; GP = glycoprotein; HELVETICA = Hirudin in a European Trial versus Heparin in the Prevention of Restenosis after PTCA; IMPACT = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II; ISAR = Intracoronary Stenting and Antithrombotic Regimen; LMWH = low molecular weight heparin; MATTIS = Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting; NICE = National Investigators Collaborating on Enoxaparin; PCI = percutaneous coronary intervention; REDUCE = Reduction of Restenosis after PTCA, Early Administration of Reviparin in a Double-Blind, Unfractionated Heparin and Placebo-Controlled Evaluation; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; STARS = Stent Anticoagulation Restenosis Study; TOPPS = Ticlopidine or Plavix Post-Stent; TVR = target vessel reintervention.

Table 1

The effect of aspirin on acute complications after balloon angioplasty

Reference	Drug (mg/day)	End points	Complications (%)
White *et al* [32] ($n = 333$)	650 mg ASA and 225 mg dipyridamole, or 750 mg ticlopidine, or placebo	AMI and/or CABG	5* versus 2* versus 14
Schwartz *et al* [33] ($n = 376$)	330 mg ASA and 225 mg dipyridamole, or placebo	Q-wave AMI	1.6* versus 6.9
Chesebro *et al* [34] ($n = 207$)	975 mg ASA and 225 mg dipyridamole, or placebo	Occlusion, AMI, urgent reintervention	11 versus 20

AMI, acute myocardial infarction; CABG, coronary artery bypass surgery. *$P < 0.05$ versus placebo.

Balloon angioplasty

Mechanisms of abrupt vessel closure after balloon angioplasty

Studies using angioscopy [12–14] and post-mortem observations [15–17] suggest that balloon angioplasty very often leads to rupture of the obstructing plaque and to dissection of the vessel wall followed by mural thrombus formation. The etiology of abrupt vessel closure is multifactorial: dissection leading to an occlusive 'flap', spasm, elastic recoil and intramural hematoma may all play a role. Mural thrombosis is considered an important associated cause in this process [6,18,19], particularly when the target lesion has a large lipid core [20] and when mural thrombosis is already present before intervention [21–24].

Antiplatelet and anticoagulant therapy to prevent abrupt vessel closure in balloon angioplasty

Aspirin (acetylsalicylic acid)

Aspirin is a dose-dependent inhibitor of platelet cyclooxygenase activity, resulting in a partial inhibition of platelet activation. A dose of 100 mg aspirin almost completely suppresses thromboxane A_2 synthesis in normal subjects and in atherosclerotic patients [25]. The onset of action of aspirin is rapid, showing antiplatelet effects as soon as 1 hour after oral administration [25]. However, the appropriate dosing of aspirin is less clear for several reasons. First of all, the dosage required to inhibit platelet aggregation varies for each subject [26]. Furthermore, the effect of aspirin treatment seems to attenuate over time [27]. This may be overcome by giving a loading dose of at least 500 mg shortly before angioplasty to all patients, including those on daily aspirin, to obtain immediate platelet inhibition [28]. Additional reasons to administer a loading dose are that doses lower than 2 mg/kg body weight per day may take several days to exert maximal effect, and that larger doses (>300 mg) reduce thrombin formation [25,29]. This effect on thrombin formation may be particularly important during PCI, as ruptured lesions and damaged vessel walls activate platelets directly through thrombin. This activation pathway is not blocked by aspirin [30]. Thrombin plays a pivotal role in thrombus formation as it converts fibrinogen to fibrin, and it amplifies its own generation by activating platelets and the blood coagulation factors V, VIII, and XIII, which then stabilizes the fibrin clot [31].

The clinical effects of aspirin during balloon angioplasty have not been studied extensively. Only three randomized placebo-controlled trials have been conducted [32–34]. Limited numbers of patients were included, and two of these studies were primarily designed as angiographic restenosis trials [34,35]. Aspirin nevertheless reduced the acute complication rate in all three trials (Table 1). In addition, Mufson *et al* randomized 495 patients to 80 mg/day aspirin versus 1500 mg/day aspirin and found no significant difference in the acute complication rate after balloon angioplasty [35]. In conclusion, aspirin reduces thrombotic complications during balloon angioplasty. However, aspirin is unable to prevent thrombotic complications completely, even in combination with heparin. In particular, if the intervention damages the deeper layers of the vessel wall, the combination of aspirin and heparin is insufficient [36,37]. Using angioscopy, thrombosis is detected in more than 50% of the dilated vessels despite this combined therapy [14,37,38]. There are at least four reasons why mural thrombi are resistant to the aspirin–heparin combination. First, as already described, thrombin is a potent cyclooxygenase independent platelet agonist. The thrombin receptor on the platelet is not blocked by aspirin [30]. Second, activated platelets bind prothrombin and thrombin, shielding them from inactivation by heparin [39,40]. Bound prothrombin generates thrombin about 10^5 times more efficiently than the unbound form [31]. Third, thrombin also binds to fibrin and to the subendothelial matrix, where it is shielded from the heparin–antithrombin-III complex [41–43]. Finally, heparin is antagonized by platelet factor 4, which is released during aggregation, and by fibrin II monomers, which are a split product from fibrin formed to stabilize the thrombus [44,45].

In summary, aspirin pretreatment is essential for patients undergoing balloon angioplasty. The optimal dosing, however, is still largely unknown. A high-dose bolus of aspirin (500 mg) before intervention in addition to a daily low dose (100 mg/day) seems to be the most efficacious regimen to reduce platelet activation. Nevertheless, aspirin is unable to abolish platelet activation totally, suggesting that additional antithrombotics are necessary during balloon angioplasty.

Unfractionated heparin

Heparin is a glycosaminoglycan, composed of a heterogeneous mixture of molecules of different weights. The anticoagulant action of heparin is due to the binding of one-third of these molecules to antithrombin-III, leading to a conformational change that markedly increases the ability to inactivate thrombin [46]. The anticoagulant response to heparin varies greatly among patients. This may be due to different concentrations of heparin-binding proteins, and receptors on endothelial cells, which have to be saturated before therapeutic plasma levels can be achieved [46]. Natural inhibitors of heparin may, in addition, be released from the thrombus and are more likely to play a role when large amounts of thrombus are present [46].

Anticoagulation during PCI is almost universally accomplished with unfractionated heparin. A bolus injection of 5000–10,000 IU is commonly used at the start of the PCI, and a varying amount is added during the procedure. Few controlled studies have, however, addressed the issue of optimal dosing or duration of heparin therapy. Several observational studies [6,47–49], but not all [50], have associated a low activated clotting time (ACT) with a higher rate of abrupt vessel closure. Moreover, a retrospective analysis suggested a temporal association between discontinuation of heparin and the occurrence of abrupt vessel closure [51]. Monitoring of optimal heparinization and an ACT >300 s therefore seem advisable [47]. In contrast, two prospective non-randomized studies using a single low dose of 2500–5000 IU heparin [52,53] and two small, randomized trials comparing low-dose versus high-dose heparin [54,55] suggested that low-dose heparin is as safe and effective as high-dose heparin in elective PCI. Without defining an optimal dose, these studies have introduced a trend towards the use of lower heparin doses. Recently, however, an analysis combining data from six randomized controlled trials was performed to determine the optimal range of ACT [56]. This analysis included 6146 patients from studies of novel adjunctive antithrombotic regimens in which unfractionated heparin constituted the control arm. An ACT of 350–375 s provided the lowest composite event rate at 7 days follow-up. The lowest level of bleeding was observed in the range of 325–350 s, and it progressively increased at 350–375 s. An ACT of 350 s therefore seems to be optimal to prevent ischemic events during PCI while not increasing bleeding complications [56]. Although heparin is essential during PCI, it should not be continued after successful coronary intervention. Prolonged heparinization does not reduce ischemic complications, but leads to more bleeding complications, longer hospital stay and increased costs [57,58]. Small retrospective data, on the contrary, suggest that pretreatment with heparin reduces the risk of complications during PCI for patients at high risk of coronary thrombus [59–61]. For these high-risk patients, however, the platelet glycoprotein (GP) IIb/IIIa receptor blockers have been shown to be more efficacious (see section 'Platelet GP IIb/IIIa receptor blockers') [62,63].

In summary, unfractionated heparin is effective during elective PCI, and an ACT of 350 s seems to be optimal to prevent ischemic events during PCI while not increasing bleeding complications. Prolonged heparinization after elective PCI does not reduce complications.

Low molecular weight heparin

Low molecular weight heparins (LMWHs) have a number of advantages over unfractionated heparin therapy. LMWHs are fragments of standard heparin molecules with a more predictable anticoagulant effect requiring less stringent monitoring of anticoagulation. They have a higher ratio of antifactor Xa:antifactor IIa, they induce thrombocytopenia less often, and they are resistant to inactivation by activated platelets [64]. However, experience with LMWHs in the setting of coronary intervention is limited. The available data nevertheless suggest that LMWHs are safe and effective during PCI. First, the administration of a single intravenous bolus of enoxaparin was tested in the open-label National Investigators Collaborating on Enoxaparin (NICE)-1 and NICE-4 trials [65]. In NICE-1, 810 patients (up to 85% of who received a stent) were treated with 1 mg/kg intravenously. In NICE-4, 817 patients (again most of them stented) received a lower dose of enoxaparin (0.75 mg/kg intravenously) in combination with abciximab. Preliminary results showed a low clinical event rate and low bleeding rate, which suggests that enoxaparin is effective during PCI without coagulation monitoring [65]. In addition, analysis of sub-groups from the Enoxaparin versus Heparin in Unstable Angina and Non Q Wave Myocardial Infarction (ESSENCE) trial also suggested that enoxaparin is safe during PCI [66]. Second, the LMWH reviparin was tested in the Reduction of Restenosis after PTCA, Early Administration of Reviparin in a Double-Blind, Unfractionated Heparin and Placebo-Controlled Evaluation (REDUCE) trial [67]. A total of 625 patients were randomized to reviparin initiated as a bolus immediately before PCI and continued for 24 hours intravenously plus 28 days subcutaneously, or to unfractionated heparin for 24 hours intravenously. At 30 weeks, the adverse event rate was similar in the two groups. However, less early complications, primarily the need for bailout stenting, occurred in the reviparin group

(3.9% versus 8.2% in the unfractionated heparin group; $P = 0.03$) [67]. Third, Collet *et al* tested a strategy of subcutaneous 1 mg/kg enoxaparin given twice a day for 48 hours followed by angiography and PCI at the treating physician's discretion. A total of 451 consecutive patients with unstable angina or non-Q-wave infarction were included, of whom 65% underwent angiography and 28% underwent PCI. Patients were scheduled for catheterization within 8 hours of an enoxaparin injection and sheaths were pulled ≥10 hours after enoxaparin injection. Results showed no increase in major bleeding rate of PCI patients compared with patients not undergoing catheterization. In addition, enoxaparin was effective as no abrupt closure or urgent revascularization occurred after PCI [68].

In summary, LMWHs seem to be safe during PCI, although the superiority of LMWHs over unfractionated heparin during PCI remains to be proven.

Direct thrombin inhibitors

The most potent direct antithrombin is hirudin, which (unlike heparin) forms a 1:1 complex directly with thrombin. It is able to inactivate both free thrombin and thrombin bound to fibrin. In addition, also unlike heparin, there are no circulating inhibitors of hirudin and it does not bind to endothelial cells or plasma proteins. The result is that hirudin achieves a more specific and consistent state of anticoagulation [69].

In the Hirudin in a European Trial versus Heparin in the Prevention of Restenosis after PTCA (HELVETICA) trial, 1141 unstable patients undergoing angioplasty were randomly assigned to two regimens of hirudin or to unfractionated heparin for the duration of 4 days. Although the primary end point of event-free survival at 7 months was similar in the three groups, the administration of hirudin was associated with a significant reduction of early cardiac events (combined relative risk with hirudin, 0.61; 95% confidence interval [CI], 0.41–0.90), while the incidence of bleeding complications was not increased [70]. In the Hirulog Angioplasty Study, 4098 patients undergoing angioplasty for unstable or post-infarction angina were randomized to either bivalirudin (Hirulog) or unfractionated heparin for the duration of 1 day. Bivalirudin did not reduce the primary end point consisting of any acute complication during hospitalization (11.4% versus 12.2% for heparin, P = not significant), but it did result in a lower incidence of bleeding (3.8% versus 9.8%, $P < 0.001$). Bivalirudin significantly reduced the primary endpoint in the high-risk subgroup of post-infarction angina (9.1% versus 14.2%, $P = 0.04$), again with a lower incidence of bleeding (3.0% versus 11.1%, $P < 0.001$) [71]. A limitation to the use of the direct thrombin inhibitors is that they are more expensive than heparin.

In summary, the direct thrombin inhibitors are promising for the prevention of acute complications during PCI.

Platelet GP IIb/IIIa receptor blockers

Because of the relatively weak antiplatelet effects of aspirin, agonists such as thrombin, collagen, and serotonin can induce the functional expression of the platelet GP IIb/IIIa receptor. This receptor cross-links adjacent platelets by binding fibrinogen and von Willebrand factor. This process takes place regardless of which metabolic pathway initiated platelet activation, and the GP IIb/IIIa receptor is therefore the final common pathway for platelet aggregation. The best-studied parenteral agents that block the GP IIb/IIIa receptor include the chimeric c7E3 monoclonal antibody fragment abciximab, the peptide inhibitor eptifibatide and the non-peptide mimetic tirofiban. In patients undergoing balloon angioplasty, most placebo-controlled studies were performed with the use of abciximab. These studies evaluated the effect on the composite 30-day end point of death, acute myocardial infarction (AMI) or target vessel reintervention (TVR) (Table 2). Patients in these studies were additionally treated with aspirin, but variable dosages of unfractionated heparin and stents were used only for bailout situations (12% of the patients).

Abciximab: In the Evaluation of c7E3 (abciximab) for the Prevention of Ischemic Complications (EPIC) study, 2099 high-risk patients (unstable angina, AMI or adverse angiographic characteristics) undergoing balloon angioplasty or atherectomy were randomly assigned to one of three groups. These received either placebo bolus plus 12 hours abciximab infusion, abciximab bolus plus 12 hours placebo infusion, or abciximab bolus plus 12 hours abciximab infusion. Patients were given full heparin doses (ACT, 300–325 s). There was a significant 4.5% absolute reduction of the composite 30-day end point in the group on abciximab bolus plus infusion. In comparison, the abciximab bolus alone was not effective. The advantages of abciximab were partly nullified by a doubling of the number of bleeding complications [72,73]. In the Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) study, the benefits of abciximab were shown to extend to patients with low risk. The patients with unstable angina and electrocardiogram changes or AMI within the previous 24 hours were excluded. This study was terminated prematurely for efficacy reasons because, after inclusion of 2792 patients, a significant 6.5% absolute reduction of the 30-day composite end point was noted in the abciximab group. Furthermore, the use of weight-adjusted low-dose heparin accounted for a lower risk of major bleeding [74]. The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study evaluated the effect of pretreatment with abciximab in patients with refractory unstable angina who were planned to undergo PCI within 24 hours. Abciximab was started 18–24 hours before PCI and continued for 1 hour after the procedure. This study was also discontinued prematurely ($n = 1266$) with a significant 4.5% absolute reduction of the 30-day composite end point in the abciximab group.

Table 2

Intravenous glycoprotein IIb/IIIa receptor blockers for patients undergoing percutaneous coronary intervention

			Primary end point		
Trial	Patient category	*n*	IIb/IIIa	Placebo	*P* value
EPIC [72]	AMI, UA or high-risk lesion	2099	8.3	12.8	0.008
EPILOG [74]	SA	2792	5.2	11.7	< 0.001
CAPTURE [62]	Refractory UA	1265	11.3	15.9	0.01
IMPACT-II [77]	AMI, SA,UA	4010	9.2	11.4	0.06
RESTORE [78]	UA	2139	10.3	12.2	0.16
EPISTENT [103]	AMI, UA, SA and stent eligible	2399	5.3	10.8	< 0.001

See text for details of patient selection, primary end points, and outcome. In the EPIC, EPILOG, CAPTURE and EPISTENT trials, the primary end point consisted of death, acute myocardial infarction (AMI) or target vessel revascularization (TVR) at 30 days. In the IMPACT-II trial, the need for a bailout stent also included a primary end point. In the RESTORE trial, not only TVR was included, but any revascularizations. UA, Unstable angina; SA, stable angina.

In the CAPTURE study, unfractionated heparin was not dosed according to body weight and, again, the number of bleeding complications doubled [62]. GP IIb/IIIa receptor blockers are therefore best combined with a weight-adjusted dose of unfractionated heparin, with an initial bolus of 70 U/kg and an ACT of approximately 250 s [74,75]. As already discussed, LMWHs may be superior to unfractionated heparin, also when combined with GP IIb/IIIa receptor blockers. There is, as yet, little data on the safety and efficacy of combining LMWHs with GP IIb/IIIa receptor blockers during PCI. Preliminary observational data such as from NICE-4, however, suggest that this combined antithrombotic regime is promising [65]. With respect to the duration of abciximab infusion, the lower relative risk reduction in the CAPTURE study (23%) as compared with that in the EPI trials (35 and 56%) is consistent with the evidence of subtherapeutic platelet inhibition in a subgroup of patients 8–12 hours after abciximab infusion [76]. It therefore seems optimal to continue abciximab infusion for 12 hours after the intervention.

Integrilin and tirofiban: The small molecules integrilin and tirofiban were also shown to reduce the risk of PCI, although less impressively (Table 2). In the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) study, 4010 patients undergoing elective or urgent interventions were randomly assigned to two different doses of integrilin infusion for 20–24 hours, or to placebo. There was a non-significant 2.2% absolute reduction of the 30-day composite primary end point in the best integrilin group, while bleedings were not increased [77]. In the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) study, 2139 patients undergoing PCI within 72 hours after an acute coronary syndrome were randomly assigned to tirofiban bolus plus 36 hours infusion or to placebo. A significant improvement in the tirofiban group was noted after 2 days, although after 30 days more than half of this improvement was lost and finally resulted in a non-significant 1.9% absolute decrease of the composite end point. Also, tirofiban did not increase major bleeding [78] (Table 2).

In summary, platelet GP IIb/IIIa receptor blockers improve the 30-day outcome in almost all subgroups of patients undergoing PCI. For patients undergoing balloon angioplasty with provisional stenting, the efficacy of abciximab is based on the firmest clinical evidence. With respect to unfractionated heparin, GP IIb/IIIa receptor blockers are best combined with a weight-adjusted dose with an initial bolus of 70 U/kg and an ACT of approximately 250 s. Abciximab should be continued for 12 hours after intervention.

Oral anticoagulants

Oral anticoagulants inhibit thrombin generation in both the intrinsic and extrinsic pathways of coagulation. They interfere with the cyclic conversion of vitamin K, which is an essential cofactor in the carboxylation of blood coagulation factors II, VII, IX and X, and proteins C and S. It takes several days to obtain a stable level of anticoagulation with oral anticoagulants.

The effect of oral anticoagulant therapy on acute complications after PCI had, until recently, not been studied. The Balloon Angioplasty and Anticoagulation Study (BAAS) randomized 1058 patients undergoing elective angioplasty for stable or unstable angina to aspirin only or to aspirin plus oral anticoagulants. Oral anticoagulants were started 1 week prior to the procedure and continued for 6 months. The target prothrombin time was 2.1–4.8 International Normalized Ratio (INR) during and after the procedure. Oral anticoagulants significantly improved the 30-day composite primary end point consisting of death, AMI, TVR and stroke (3.4% versus 6.4%; relative risk, 0.53; 95% CI, 0.30–0.92).

Table 3

Aspirin plus ticlopidine versus aspirin plus oral anticoagulants after stenting

Study	Number of patients studied	Number of patients treated	Primary end point (%)			*P* value
			ASA ticlopidine	ASA coumadin	ASA alone	
ISAR [84]	517	626	1.6	6.2	–	0.01
FANTASTIC [85]	473	485	5.7	8.6	–	0.37
STARS [86]	1653	1965	0.5	2.7	3.6	0.001
MATTIS [87]	350	350	5.6	11.0	–	0.07
Hall *et al* [88]	226	358	0.8	–	3.9	0.1

In the ISAR, STARS, MATTIS and Hall *et al* studies, the primary end point comprised cardiac death, acute myocardial infarction or repeat target vessel revascularization at 30 days. In the FANTASTIC study, the composite of death, acute myocardial infarction or stent occlusion at 6 weeks was the secondary end point and did not include repeat target revascularization.

This positive effect was seen only in those patients in whom oral anticoagulants were started at least 3 days before the procedure. Part of this positive effect was offset, however, by more bleedings in the patients treated with oral anticoagulants. The incidence of major bleedings including false aneurysms was 3.2% in the oral anticoagulant group versus 1.0% in the patients treated with aspirin alone (relative risk, 3.39; 95% CI, 1.26–9.11) [79].

In summary, oral anticoagulants started before PCI with an adequate level of anticoagulation during the procedure are effective in reducing the incidence of acute complications.

Stenting

Mechanism of stent thrombosis

The pathophysiology of stent thrombosis is not fully understood. Stent thrombosis seems to be primarily due to platelet activation with exposure of the GP IIb/IIIa receptor for fibrinogen cross-linking and platelet aggregation [80–82]. However, stent thrombosis is not only a platelet-dependent process. Vascular wall damage due to stenting also exposes tissue factor, which subsequently leads to activation of the extrinsic coagulation cascade with the generation of thrombin [81].

Antiplatelet and anticoagulant therapy to prevent early thrombotic complications after stenting

Ticlopidine

Aspirin and ticlopidine interfere with different but complementary pathways of platelet activation. Ticlopidine selectively inhibits adenosine diphosphate (ADP)-induced platelet aggregation and ADP-mediated amplification of other agonists, thereby inhibiting the binding of fibrinogen to the GP IIb/IIIa receptor. Ticlopidine has a delayed onset of action with maximal antithrombotic effect after at least 3 days [83].

Four randomized trials (Intracoronary Stenting and Antithrombotic Regimen [ISAR], Full Anticoagulation Versus Aspirin and Ticlopidine After Stent Implantation [FANTASTIC], Stent Anticoagulation Restenosis Study [STARS], and Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting [MATTIS]) have studied the combination of aspirin plus 4 weeks of ticlopidine (250 mg twice daily) versus aspirin plus oral anticoagulants with overlapping unfractionated heparin treatment in preventing events after stenting [84–87]. All risk categories were included in these studies. The ISAR study population consisted of low-risk as well as high-risk patients, and 24% had an AMI. Randomization took place once the stent was optimally placed [84]. In the FANTASTIC trial, randomization was performed before elective or unplanned stenting. Patients with an AMI were excluded in this study [85]. In the STARS trial, a selected group of patients with successful elective stenting for a lesion in a 3–4 mm native coronary artery was included. Patients in this trial were also assigned to aspirin alone, which was less effective than the other two drug regimens [86]. In an earlier randomized trial, aspirin alone was less effective than aspirin plus ticlopidine for patients with successful intravascular ultrasound-guided stent implantation [88]. In the MATTIS trial, randomization was performed after bailout stenting or if the result of stenting was suboptimal [87]. Overall, these studies show that the combination of aspirin and ticlopidine was more effective than aspirin plus oral anticoagulants or aspirin alone (Table 3). However, oral anticoagulants were started following stent implantation and concomitant unfractionated heparin was used until adequate levels of anticoagulation were obtained. In this setting, coumarins might even lead to a transient hypercoagulable state due to rapid suppression of the anticoagulant activity of protein C relative to the decrease in the level of factor VII as well as other vitamin K-dependent factors [89]. Furthermore, unfractionated heparin might not be effective because it binds to the complex of thrombin and fibrin, thereby shielding it from inactivation by the heparin–antithrombin complex [90]. Unfractionated

heparin also binds variably to plasma proteins, leading to unstable levels of anticoagulation, and it has been shown to activate platelets [90–92]. In contrast, oral anticoagulants in the BAAS were started 1 week before angioplasty. In the 35% of the BAAS patients who received a stent, oral anticoagulants reduced the need for acute reinterventions and the occurrence of procedure-related AMI by almost 50% [79]. Stable anticoagulation with oral anticoagulants might consequently be more effective than intravenous unfractionated heparin.

Despite its potential advantages, the widespread use of ticlopidine has been limited by its significant side effect profile, including diarrhea, nausea, and vomiting, as well as skin rash. Ticlopidine can also induce neutropenia, bone marrow aplasia and thrombotic thrombocytopenic purpura, which may be fatal in some cases [93].

In summary, the combination of aspirin plus ticlopidine is very effective in preventing thrombotic complications after stenting. Due to the delayed onset of action and especially due to its side effect profile, however, ticlopidine has been replaced by clopidogrel in most centers.

Clopidogrel

Clopidogrel is a new thienopyridine derivative chemically similar to ticlopidine. Clopidogrel is many times more potent than ticlopidine and has a more favorable side effect profile [93,94]. In addition, the onset of action is more rapid than that of ticlopidine. In one study, significant inhibition of platelet aggregation appeared 2 hours after the administration of 400 mg in healthy volunteers and atherosclerotic patients [95].

Several observational studies have recently suggested that the combination of aspirin plus clopidogrel is as effective as aspirin plus ticlopidine in preventing stent occlusion [96–99]. The recently reported Clopidogrel/Aspirin Stent International Cooperative Study (CLASSICS) trial randomized a selected group of 1020 patients with successful stent placement to aspirin plus two dosages of clopidogrel (75 mg/day orally with or without a 300 mg loading dose) or to aspirin plus ticlopidine (250 mg twice daily without a loading dose) for 4 weeks. Clopidogrel and ticlopidine were first administered within 6 hours after stent placement. The primary end point consisted of major peripheral or bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of the study drug due to non-cardiac causes. This primary end point was reached less often with the use of clopidogrel than with ticlopidine (9.1% versus 4.6%, $P = 0.005$). Moreover, the loading dose of clopidogrel did not lead to more side effects. The secondary end point, which was cardiac death, AMI or TVR within 30 days, occurred infrequently and was comparable between treatment groups (0.9% with ticlopidine, 1.5 with 75 mg/day clopidogrel only, and 1.2% with clopidogrel 75 mg/day plus a loading dose; P = not significant for all comparisons) [100].

The second randomized comparison of aspirin plus clopidogrel versus aspirin plus ticlopidine after stenting by Müller *et al* was also designed to study the safety of clopidogrel [101]. Among 793 consecutive patients undergoing an elective or urgent procedure, 700 patients were randomized after successful stent placement to a 4-week course of either ticlopidine (500 mg loading dose, then 250 mg/2dd) or clopidogrel (75 mg/day without a loading dose), in addition to 100 mg aspirin. The 30-day primary end point, consisting of non-cardiac death, stroke, severe peripheral vascular or hemorrhagic events, or any adverse event resulting in discontinuation of study medication, occurred in 4.5% of the patients in the clopidogrel group and in 9.6% of the patients in the ticlopidine groups ($P = 0.01$). As in CLASSICS, this difference was mainly due to intolerance to ticlopidine. Cardiac events reflecting stent thrombosis occurred in 3.1% of the patients treated with clopidogrel versus 1.7% of the ticlopidine patients (P = not significant) [101]. Finally, the preliminary data from the randomized Ticlopidine or Plavix Post-Stent (TOPPS) trial also showed clopidogrel (loading dose of 300 mg, then 75 mg/day) to be as effective as ticlopidine (loading dose of 500 mg, then 250 mg twice daily) in a 2-week regimen after successful stenting in 1016 patients [102]. In conclusion, clopidogrel seems to be as effective as ticlopidine and has fewer side effects. One has to bear in mind, however, that so far the combination of aspirin and clopidogrel (without a GP IIb/IIIa blocker) has only been tested in low-risk patients. Whether pretreatment with thienopyridines is more effective than when it is started after stenting, is discussed in the section 'The vulnerable period after stenting'.

In summary, clopidogrel is as effective as ticlopidine and has fewer side effects. A loading dose is essential. Although the most appropriate duration of clopidogrel therapy is unknown, at least 2 weeks should be prescribed.

Platelet GP IIb/IIIa receptor blockers

In the Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT) trial, the complementary effects of stenting and abciximab were studied [103]. A total of 2399 patients scheduled to undergo elective or urgent PCI were randomly assigned to stent plus placebo, stent plus abciximab, or balloon angioplasty plus abciximab. The primary end point consisted of death, AMI, or TVR in the first 30 days. The primary outcome occurred in 10.8% of the cases in the stent plus placebo group, in 5.3% in the stent plus abciximab group (hazard ratio, 0.48; 95% CI, 0.33–0.69) and in 6.9% in the balloon plus abciximab group (hazard ratio, 0.63; 95% CI, 0.45–0.88). Major bleeding complications did not increase with the use of abciximab [103]. Stenting plus abciximab showed superi-

ority at 6-month and 1-year follow-up. Moreover, abciximab induced a modest, but significant, reduction of 1-year mortality as compared with placebo (1.0% versus 2.4%; $P = 0.037$). This reduction was primarily due to the lower death rate in patients with diabetes [104].

The second placebo-controlled randomized trial was the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, in which an almost four times higher dose of eptifibatide than in the IMPACT-II trial was evaluated. A total of 2064 patients were included, who were undergoing planned, elective stenting of native coronaries were included and pretreated with aspirin and clopidogrel. Eptifibatide was administered for 18–24 hours. The primary end point consisted of death, AMI, TVR or bailout GP IIb/IIIa treatment at 48 hours. The trial was terminated early for reason of superior efficacy. The results showed a 37% reduction of the primary end point from 10.5% in the placebo group to 6.6% in the treatment group ($P = 0.0015$). Major bleeding was infrequent but higher with eptifibatide (1.3% versus 0.4%, $P = 0.027$) [105]. In the first direct comparison, the effect of abciximab was compared with tirofiban in the Do Tirofiban and Reopro Give Similar Efficacy Trial (TARGET). This multicenter trial enrolled 4812 patients who were undergoing stenting. Tirofiban was given at the dose previously tested in the RESTORE trial and abciximab was given at the dose used in the EPIC trial. At 30 days, the primary composite end point of death, AMI and urgent TVR occurred in 7.55% of the tirofiban patients and in 6.01% of the abciximab patients ($P = 0.037$). Interestingly, in a subgroup analysis, abciximab showed even more benefit over tirofiban in patients with acute coronary syndromes, whereas tirofiban showed a trend towards a better outcome in patients without acute coronary syndromes [106]. In conclusion, GP IIb/IIIa receptor blockers are very effective in combination with stenting. Abciximab is more effective than tirofiban but may not be affordable to all patients. A direct comparison between the less expensive eptifibatide and abciximab has not been made. Cost aspects may play a role in decision-making when a choice between the various GP IIb/IIIA receptor blockers has to be made.

In summary, platelet GP IIb/IIIa receptor blockers are very effective in combination with stenting. One has to realize, however, that this combined treatment is expensive and may not be affordable to many patients. Nevertheless, GP IIb/IIIa receptor blockers should be used, at least for high-risk patients.

The vulnerable period after stenting

Importantly, there appears to be a vulnerable period in the first days after stenting, which is not fully covered with the currently used antiplatelet regime [11]. In the FANTASTIC trial, the acute occlusion rate during the first day after stenting was higher in the antiplatelet group than in the anticoagulant group (2.4% versus 0.4%, $P = 0.06$) [85]. Also, in the ISAR trial, the antiplatelet regimen became superior only after 3 days of treatment [84]. Furthermore, in the randomized comparison between aspirin plus clopidogrel versus aspirin plus ticlopidine by Müller *et al*, six of the nine cases of stent thrombosis in both treatment groups occurred before day 2 [101]. These studies consequently indicate that thienopyridines should be started several days before intervention. This thesis was also suggested by nonrandomized data [107,108]. In the EPISTENT trial, ticlopidine was started before stenting in 58% of the patients. Among patients randomized to placebo, the incidence of the combined end point of death, AMI or urgent revascularization at 30 days was significantly lower for patients who had received ticlopidine before the procedure, as compared with those who had not (8.9% versus 13.4%, $P = 0.03$). Pretreatment with ticlopidine, however, had no influence on the combined end point at 30 days among patients randomized to abciximab. Ticlopidine pretreatment, irrespective of the treatment group, was not associated with an increase in bleeding complications [107]. Additional data suggested that ticlopidine should be started at least 3 days before stenting to prevent complications [108]. Also for clopidogrel pretreatment seems to be effective. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, more than 12,000 patients presenting with symptoms suggestive of an acute coronary syndrome were randomized to clopidogrel or placebo. This trial showed a 20% relative reduction in the composite end point of death, AMI or stroke after 12 months [109]. Subgroup analysis showed that there was a consistent benefit of clopidogrel across all groups, including the group of patients who had to undergo PCI during follow-up.

In summary, thienopyridines should be started before stenting. Although the optimal duration of pretreatment is unknown, starting 2 days before the procedure with a loading of 300 mg followed by 75 mg/day seems sufficient considering the rapid onset of action of clopidogrel.

Bleeding complications after stenting

In the ISAR, FANTASTIC, MATTIS and STARS studies, bleeding and groin complications occurred less often in the patients treated with antiplatelet therapy than in the patients treated with oral anticoagulation and heparin. Depending on the definitions used, the incidence of bleedings ranged from 1.2% in ISAR to 13.5% in FANTASTIC for patients treated with antiplatelet therapy and from 6.2% in STARS to 21% in FANTASTIC in the anticoagulant groups [84–87]. The higher complication rate in the oral anticoagulant groups may be partly due to the continuation of unfractionated heparin for several days following stenting while awaiting a stable level of anticoagulation with oral anticoagulants. In the BAAS, oral anticoagulant pretreatment obviated the need for post-PCI heparin. The

complication rate in this study, including false aneurysms, was again higher in the anticoagulation group (3.2% versus 1.0%, $P = 0.02$) but far lower than in the previous trials [79,84–87].

In the EPISTENT trial, abciximab did not increase the rate of major bleeding but minor bleedings were increased (2.9% versus 1.7%) [103]. Data from the ESPRIT trial show that eptifibatide increases the risk of major and minor bleedings, but the incidence remains low (major bleeding, 1.3%) [105].

Patient selection in stent trials

We should realize that most of the aforementioned trials do not describe the real world, as these studies only included patients with a successful stent placement, thus excluding patients in whom a stent could not be placed or where suboptimal results were obtained. Furthermore, differences exist in the definition of the end points that were used in these trials. For example, both shortcomings occurred in the STARS trial [86], in which 312 (15.9%) of the 1965 enrolled patients did not meet the angiographic criteria for 'optimal stenting' and were subsequently analyzed in the STARS Suboptimal Stent Registry [110]. The combined 30-day end point comprised death or Q-wave infarction and occurred in 3% of the registry patients compared with 2.2% of the randomized patients (P = not significant). The primary end point did not include non-Q-wave infarction, which was far more frequent in the registry patients (8.7% versus 4.2%, $P = 0.003$). In addition, the mortality rate was significantly higher in the registry part of the study (1.1% versus 0.06%, $P < 0.009$). Eleven patients in the same group were referred directly from the cardiac catheterization laboratory for emergency bypass surgery, and one patient died during stenting. These 12 patients were excluded from analysis. If these 12 patients had been included, the 30-day event rate in the registry would have increased to more than 7% [110].

Intracoronary brachytherapy

Restenosis is the main limiting factor of the late success of balloon angioplasty. Restenosis is due to intimal proliferation and, in particular, due to recoil and remodeling [111,112]. Stents have reduced the restenosis rate by eliminating recoil and remodeling [2]. However, stents enhance intimal proliferation, leading to in-stent restenosis in about one-fifth of the patients [2]. In-stent restenosis is very therapy resistant [113]. Intracoronary brachytherapy, both beta- and gamma-radiation, has recently been proven to be more effective than balloon angioplasty alone in treating in-stent restenosis [114–116]. With respect to thrombotic complications, however, an alarming higher incidence of late myocardial infarctions was noted after brachytherapy [114–116]. It is speculated that this higher late thrombosis rate is due to a delayed re-endothelialization after radiation. A recent review of randomized and non-randomized studies reported a late thrombosis rate after brachytherapy of 9.1%, as compared with 1.2% after conventional treatment [117]. Further analysis showed that the combination of brachytherapy and a new stent is especially prone to late thrombosis [118]. In these initial trials, the combination of aspirin plus a thienopyridine was given for 2–8 weeks [114–116]. Data from two registries (Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting [SCRIPPS]-III and Washington Radiation for In-stent restenosis Trial [WRIST]-Plus) as well as preliminary data from the large randomized BETA-CATH System trial, however, show low late thrombosis rates when the use of antiplatelet therapy was extended to 6–12 months [119–121]. The combined use of aspirin and clopidogrel should therefore be continued for a minimum of 6 months after brachytherapy, and for 12 months if a new stent is implanted [118].

Conclusions

All patients undergoing PCI should be pretreated with aspirin. A high-dose bolus aspirin several hours before the procedure in combination with low-dose daily aspirin seems to be optimal. During PCI, unfractionated heparin dosed to an ACT of 350 s is advised. LMWHs have shown promising results, but we have to wait for randomized trials before replacing unfractionated heparin during PCI. The combination of aspirin and heparin is often insufficient, especially for patients at high risk for ischemic events. For these patients, additional GP IIb/IIIa receptor blockers are useful. Oral anticoagulant pretreatment may be an inexpensive alternative to the GP IIb/IIIa receptor blockers. The placement of a stent should always be anticipated. Patients should therefore be pretreated with clopidogrel in addition to aspirin. For patients at high risk for thrombotic complications after stenting, additional GP IIb/IIIa receptor blockers should be administered.

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