I

PART I

Elective PCI anticoagulation therapy/thrombin inhibitors

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Optimal antithrombotic therapy

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Over the last 25 years, percutaneous coronary intervention (PCI) has been shown to be a very effective method of myocardial revascularization in humans. Improvements in the design of the equipment and increased investigator experience have resulted in a high level of primary procedural success (~99%). However, PCI is inherently thrombogenic, and an optimal antithrombotic treatment is mandatory before, during, and after elective PCI.

Rationale for an optimal antithrombotic therapy

The primary mechanism of PCIs is related to endothelial denudation and extensive disruption of the media, leading to dissection and flaps. Subendothelial components (e.g., collagen, fibronectin, and von Willebrandt factor) are recognized by platelet surface receptors (e.g., GP Ib), and platelet adhesion occurs. This adhesion to the vessel wall activates the platelets, which are able to release from their alpha granules a number of substances, leading to vasoconstriction, chemotaxis, mitogenesis, and platelet aggregation. Aggregated platelets accelerate the production of thrombin by offering the surface for binding cofactors required for the conversion of prothrombin to thrombin, which ultimately catalyzes the conversion of fibrinogen to

fibrin. There is also an immediate release of tissue factor (extrinsic pathway) that is able to induce thrombin formation. Reciprocally, thrombin formation is also an important stimulus for platelet aggregation. The final consequence is a red-stabilized thrombus that is able to create an abrupt acute occlusion of the dilated vessel.

In the early stages of PCI, abrupt closure was not uncommon and occurred in 3.9–8.3% of the cases (1–3). Later, stent implantation resolved this shortcoming of PCI and the number of emergency bypass operations was markedly reduced to around 0.3%. Nevertheless, the metallic prosthesis is highly thrombogenic with a risk of acute and subacute stent thrombosis. Thus, it is mandatory to prescribe an optimal antithrombotic treatment that is based on antithrombinic and antiplatelet drugs.

Antithrombinic drugs

The group of antithrombinic drugs includes indirect antithrombins (unfractionated or low-molecular-weight heparin [LMWH]) and direct antithrombins (bivalirudin or pentasaccharide).

Unfractionated heparin (UHF)

Unfractionated heparin (UHF) needs an antithrombin III cofactor, may not inhibit clot-bound thrombin, and has an unpredictable antithrombin effect with nonlinear kinetics. In addition, UHF activates the platelet and is able to create heparin-induced thrombocytopenia (HIT). At the beginning

of angioplasty, the use of UHF was empirical with a systematic injection of a standard dose (10,000 IU) at the beginning of the procedure. An additional dose of 5,000 IU was injected after each additional hour. Later, it was shown that 10–20% of patients were not adequately anticoagulated and that it was necessary to monitor the activated clotting time (ACT). The pooled data of six randomized, controlled trials (2), in which UHF was the control arm, showed that in 5,216 patients an ACT in the range of 350–375 s provided the lowest ischemic event rate. With an ACT ranging from 350 to 375 s, there was a 34% relative risk reduction in 7-day ischemic event when compared to ACT values of 171–295 s.

Low-molecular-weight heparin

Among numerous LMWH compounds, enoxaparin was the most often used compound in the catheterization laboratory. LMWH compounds have a selective anti-Xa activity and a predictable antithrombin effect with fixed dose–weight adjustment. In addition, monitoring is not necessary. Many small nonrandomized studies or registries have described the effects of decreasing doses (from 1 to 0.5 mg/kg) of IV enoxaparin during PCI. In addition, a meta-analysis (3) of randomized clinical trials including 2,005 patients have shown a similar efficacy of UFH and IV enoxaparin. The SYNERGY (4) trial compared enoxaparin to UFH in 10,027 high-risk patients with acute coronary syndromes (92% underwent catheterization and 46% were treated with PCIs). The results showed that enoxaparin was not superior but was at least as effective as UHF, but with the additional risk of significantly more bleedings. The results were distorted as a number of patients were admitted with a prior antithrombinic treatment and a meta-analysis (5) performed from several trials without prior. Antithrombotic treatment showed a small but significant benefit and that enoxaparin was as safe as UHF, at least on the basis of blood transfusion. The most important trial in the field of PCI is the STEEPLE trial (6). This is a randomized trial of 3,258 patients comparing three antithrombotic regimens during elective PCI performed via a femoral approach. The enoxaparin group included patients receiving 0.75 mg/kg IV and a second group receiving 0.5 mg/kg IV. They

were compared to a group of patients receiving 70–100 IU/kg of UFH if no GP IIb/IIIa was administered. On the contrary, the dose was reduced to 50–70 mg/kg when GP IIb/IIIa was given. The patients receiving UFH were monitored with a targeted ACT of 300–350 s in the first group and 200–300 s. In the case of GP IIb/IIIa administration. STEEPLE (6) was a safety trial and showed that 0.5 mg/kg of enoxaparin was safer than UFH with a significant 57% relative risk reduction of major bleedings from 2.8% to 1.2% ($p = 0.005$) (Figure 1.1). There was no significant difference in terms of ischemic complications but the trial did not address this issue. In addition, less than 20% of the patients receiving UFH reached the targeted ACT while 80% of the patients receiving enoxaparin reached the targeted anti-Xa activity.

Intravenous enoxaparin (0.5 mg/kg) is safer than UFH, is simpler to administer, does not require monitoring, and the same dose might be given when GP IIb/IIIa is also administered. The sheath can be removed at the end of the procedure. Radial approach combined with enoxaparin leads to very low level of major bleedings (0.8%).

Direct antithrombin inhibitors

Direct antithrombin inhibitors do not require a cofactor and are not inhibited by PF-4 or antiheparin proteins. They are effective against clot-bound thrombin without stimulation of platelet aggregation. Finally, they induce predictable anticoagulation without risk of thrombocytopenia. Among the different compounds (hirudin, desirudin, lepirudin, argatroban), bivalirudin was extensively studied in PCI and acute coronary syndromes. Bivalirudin is a polypeptide of 20 amino acids, inducing a reversible direct antithrombin effect, with a half-life of 25 min. The first trials (BAT (7), CACHET (8), REPLACE-1 (9)) suggested the interest of this drug during PCI and this was clearly established by the REPLACE-2 trial. This trial enrolled 6,000 patients undergoing urgent or elective PCI who were randomized in two groups: Bivalirudin (0.75 mg/kg bolus + 1.75 mg/kg/h of procedure) + provisional GP IIb/IIIa inhibitors (abciximab or eptifibatide). The second arm of the study included patients treated by UFH (65 IU/kg) plus GP IIb/IIIa receptor inhibitors (abciximab or eptifibatide). Both groups received aspirin + clopidogrel. Stent

Figure 1.1 Results of the STEEPLE trial: non CABG related bleedings.

Figure 1.2 Results of the REPLACE-2 trial: net clinical outcome and bleedings.

implantation was performed in 85% of the study population. At 30 days, there were no significant differences between heparin + GPI and bivalirudin for a quadruple endpoint (including major ischemic complications [death, MI, urgent revascularization] and major bleeding). But there was a significant reduction in the rate of major bleeding (from 4.1% to 2.4%, $p < 0.001$) (Figure 1.2). All

hemorrhagic endpoints (access site, major organ, and need for transfusion) were significantly reduced ($p < 0.001$). At 1 year of follow-up, the reduction in major bleedings has an impact on the net clinical outcome and particularly on the total mortality of high-risk (unstable angina and diabetics) or elderly patients. Thus this trial has validated bivalirudin as an alternative anticoagulant in PCI.

Fondaparinux

Fondaparinux is a synthetic selective inhibitor of factor Xa. It has been evaluated in two recent trials in patients presenting with acute coronary syndromes. It has never been studied in patients undergoing elective PCI and will be described in Chapter 4.

Antiplatelet drugs

These drugs include aspirin, thienopyridines, and GP IIb/IIIa receptor blockers.

Aspirin

Aspirin irreversibly blocks the cyclooxygenase activity. Since the early beginning of angioplasty, aspirin is advocated to be administered before the procedure, and Gruentzig recommended giving 160–325 mg p.o., at least 1–2 days prior to elective percutaneous transluminal coronary angioplasty (PTCA). Sometimes, interventional cardiologists use an IV injection of 300 mg immediately at the onset of the procedure.

ADP receptor antagonists

ADP receptor antagonists include ticlopidine and clopidogrel. Ticlopidine was shown to be superior to placebo in elective PCI (10,11) with a significant lower rate of acute complications after balloon angioplasty. Later, the combination of aspirin and ticlopidine was consistently superior to full anticoagulation with vitamin K antagonists or aspirin alone (12–15). Thus ticlopidine associated with aspirin became the standard of care in stented patients. However, ticlopidine induced a number of side effects with GI and skin problems and also severe leucopenia. Owing to a faster onset of action and a better safety demonstrated in the CLASSICS trial (16), clopidogrel has replaced ticlopidine and soon became the most frequently used thienopyridine. Initially, a loading dose of 300 mg was given at the moment of stent implantation followed by 75 mg/day during 1 month.

Later, the strategy for clopidogrel was implemented with the results of the CREDO (17) trial. This study of 2,116 patients (stable angina 44% of patients) compared aspirin 325 mg vs clopidogrel 300 mg LD/75 mg/day plus aspirin. The drugs were given 3–24 h before the elective procedure and

pursued for 1 year. CREDO (17) was able to demonstrate two important points:

a The combination of aspirin and clopidogrel given for 1 year significantly decreases the rate of major complications (death, MI, and stroke) from 11.5% to 8.5% or a relative risk reduction of 22% ($p = 0.02$).

b In addition, CREDO (17) was able to arrive at the precise duration of the pre-PCI treatment: initially it was shown that patients receiving the dual antiplatelet treatment for more than 6 h before the procedure had a strong benefit with a 38.2% of relative reduction of MACE at 30 days (5.8% instead of 9.4%) ($p = 0.05$). Later it was shown that the cut-off was around 15 h.

Other trials conducted in nonelective procedures and in patients with acute coronary syndromes (ST or non-ST segment elevation ACS) have confirmed the importance of the dual antiplatelet treatment. Some trials conducted in high-risk patients have suggested a higher loading dose of 600 mg owing to a faster action and a higher level of platelet inhibition.

Glycoprotein IIb/IIIa receptor antagonists

Glycoprotein IIb/IIIa receptor is the most abundant integrin on the platelet surface. Platelet adhesion and aggregation determine conformational changes of these receptors, allowing ligand binding (fibrinogen, fibronectin, and von Willebrandt factor). Fibrinogen is the most potent ligand forming bridges between the platelets, leading to aggregation.

GPI can be divided into two main groups: (1) Small molecules (eptifibatide and tirofiban) with a low molecular weight (ranging from 500 to 800). They have a half-life of 2–2.5 h and the reversibility of the platelet inhibition is obtained 6–7 h after drug discontinuation. (2) Abciximab is a monoclonal antibody with a half-life of 10–15 min but the reversibility of platelet inhibition is achieved after 36 h.

Seven trials have been conducted with GP IIb/IIIa receptor inhibitors and the pooled data show a significant reduction of death or MI from 8.8% to 5.6% ($p < 0.000000001$). The TARGET (18) trial has compared, in patients undergoing elective stenting, a small molecule, namely tirofiban, to abciximab. This trial of 4,300 patients showed the superiority of abciximab over tirofiban at

30 days with a significant reduction of the primary endpoint (death, MI, and urgent target vessel revascularization [TVR]) but with similar results at 6 months (19). The rate of major bleeding was similar between the two groups although minor bleeding and thrombocytopenia occurred less frequently among tirofiban-treated patients.

Finally, a number of trials have demonstrated the benefits of GP IIb/IIIa receptor inhibitors in high-risk patients with acute coronary syndromes (non-ST-ACS). These data will be extensively described in the following chapters. Interestingly, a meta-analysis by Roffi (20) showed a great benefit even in terms of mortality rate reduction in diabetic patients. However, more recent, contemporary trials challenge this somewhat particular finding. A pooled analysis of GP IIb/IIIa and all PCI trials (17,793 patients) by Chew and Moliterno (21) demonstrated a 34% reduction of death and MI (from 8.5% to 5.6%).

Optimal antithrombotic strategy in elective PCI

This strategy has been defined in the ACC/AHA (22) and European Society of Cardiology guidelines (23). Table 1.1 summarizes the main points.

However, special cases should be mentioned, particularly those of patients admitted with prior antithrombotic treatment (UFH, LMWH). In general, switching from one antithrombotic treatment to another is not recommended. Association of UFH and LMWH is not strongly recommended (higher risk of bleeding). However, a post hoc analysis of the ACUTY trial showed that switching from any heparin (either enoxaparin or UFH) to bivalirudin monotherapy was not associated with an increased risk for ischemic events. Furthermore, switch to bivalirudin provided to the patients the 50% bleeding advantage of bivalirudin when compared with consistent therapy on UFH or enoxaparin.

Table 1.1 Optimal antithrombotic–elective PCI.

ESC Guidelines		ACC/AHA Guidelines	
Before an elective PCI procedure in CAD stable patients			
Aspirin			
Patients not chronically pretreated	500 mg before or 300 mg IV beginning	IB 300–325 mg	IA
Patients chronically pretreated		75–325 mg	IA
Clopidogrel	300 mg day before if not 600 mg, 2 h before	300 mg at least 6 h before	IA
		IC	
During the procedure			
Unfractionated heparin			IC
No injection of GP IIb/IIIa	100 IU/kg (ACT 250–300 s)		
If injection de GP IIb/IIIa	50–60 IU/kg (ACT 200–250 s)		
Enoxaparin	0.5 mg/kg	?	?
Bivalirudin: as an alternative to UFH			IB
Bivalirudin to treat HIT		IC	IB
GP IIb/IIIa			
Complex lesions, threatening/actual closure, no or slow reflow		IIaC	
Patients undergoing stent placement			IB
After the procedure			
Aspirin	for life (100 mg)	IB	for life
Clopidogel 75 mg			
Bare metallic stent	1 month	IA	1 month
Drug-eluting stents	6–12 months	IC	3 months (SES) 6 months (PES)
Vascular brachytherapy	12 months	IC	12 months
			IB

Conclusions

Optimal antithrombotic management in elective PCI has markedly changed over time. Since the empirical administration of a systematic standard dose of UFH as given at the beginning of angioplasty, the strategy has been considerably improved. This improvement is the result of trials demonstrating the benefit at the price of lower risk of bleeding. This is also based on a better assessment of bleeding risk following the identification of the predictive factors of this important complication. Nevertheless, this domain is rapidly evolving and changes might again occur in the near future.

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