Novel insights in reperfusion therapy and stent thrombosis in the drug eluting stent era

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Chapter 1

General introduction and outline of the thesis

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INTRODUCTION

Rupture of an atherosclerotic plaque in one of the epicardial coronary arteries is the usual initiating event in an acute coronary syndrome (ACS), leading to subsequent thrombus formation. Persistent thrombotic occlusion results in acute myocardial infarction (MI).

Platelets, in addition to the components of the clotting cascade, play an important role in this process. Aggregating platelets form the core of the growing thrombotic mass, with upstream and/or downstream propagation of fibrin and red blood cell-rich clot.[1]

Platelet-rich thrombi are more resistant to clot lysis than red blood cell-rich thrombi and, if lysis occurs, platelet-rich thrombi promote the development of reocclusion.[2]

The resistance of platelet-rich thrombi to clot lysis is particularly important in patients with an ST elevation MI (STEMI) who are treated with fibrinolytic therapy. Platelets are activated early in the course of fibrinolytic therapy.[3, 4] Although they exert both profibrinolytic and antifibrinolytic effects in vitro, the antifibrinolytic activity appears to dominate in vivo.[5] This effect probably accounts for at least a proportion of infarct-related vessels that fail to reperfuse or that recanalize with a considerable delay during fibrinolytic therapy. Even after successful reperfusion, the ruptured plaque remains supportive of additional platelet activation and aggregation, predisposing to cyclical coronary flow or frank thrombotic reocclusion.[6]

Changes in platelet function have also been observed after primary percutaneous coronary intervention (PPCI) in patients with an acute STEMI.[7] There is a transient reduction in platelet activity eight hours after angioplasty associated with a fall in the platelet count that is probably caused by sequestration of hyperactive platelets. However, 24 to 48 hours after angioplasty, there is an increase in platelet activation with in vitro evidence of hyperaggregability and enhanced adherence to endothelial cells. It is possible that these changes increase the risk of thrombotic reocclusion of the recanalized infarct-related artery. They also constitute part of the rationale for aggressive antiplatelet therapy in such patients.

Platelets and ST-elevation myocardial infarction

Platelet adhesion, activation, and aggregation are stimulated during an ACS (figure 1). Intimal injury due to plaque rupture exposes collagen and von Willebrand factor, to which circulating platelets adhere. Following adhesion, multiple metabolic pathways are stimulated within the platelet, resulting in the production and release of thromboxane A2 (TXA2), ADP, and other substances from platelet granules. These platelet products stimulate further platelet recruitment, activation, and vasoconstriction; they also lead to platelet aggregation by activating the glycoprotein IIb/IIIa (GP IIb/IIIa) complex, which binds platelets to one another through linkage with fibrinogen molecules.

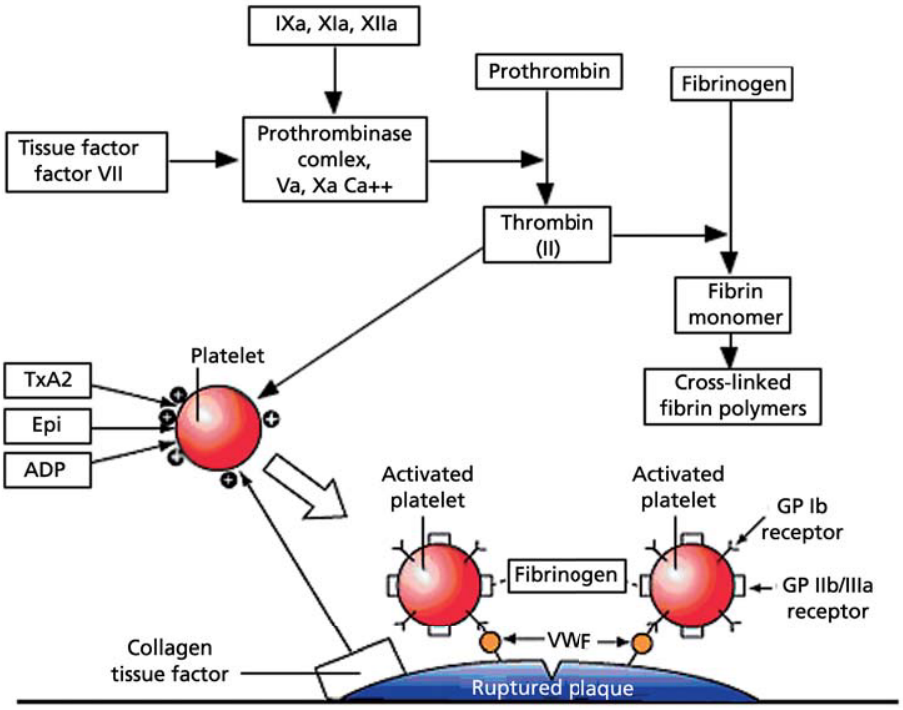
Primary percutaneous coronary interventions versus fibrinolytic therapy

Recent studies have shown that fibrinolytic treatment is not capable of restoring coronary arterial patency in 20-45% of cases, depending on the fibrinolytic agent used.[8] In addition, 5-10% of patients experience an early reocclusion, whereas a late occlusion occurs in 30% of patients.[9,10] Mechanical reperfusion therapy by means of coronary angioplasty is associated with a significantly higher success rate than fibrinolytic therapy.[11] Furthermore, mechanical reperfusion is not associated with an increased risk of life-threatening intracranial bleeding

complications. However, the major challenge of this approach is the treatment delay involved in mobilizing the interventional team and preparing the interventional facility. Under optimal circumstances, this will lead to a 30-minute treatment delay compared with in-hospital initiation of fibrinolytic therapy.[12] When compared with pre-hospital treatment, this delay may range from 60 to 90 minutes.

Figure 1 Role of platelets in thrombosis

A schemea of platelet activation, the adherence of platelets to a ruptured plaque, and the interaction with the coagulation cascade. Platelet activation may be stimulated by thromboxane A2 (TxA2), epinephrine (Epi), adenosine diphosphate (ADP), thrombin, or tissue factor. Activated platelets adhere to the site of plaque rupture primarily by the binding of the platelet surface glycoprotein Ib (GP Ib) receptor to von Willebrand factor (VWF) in the subendothelial matrix. Following platelet activation, the glyocoprotein IIb/IIIa receptor (GP IIb/IIIa receptor) is converted from a low affinity to a high affinity fibrinogen receptor, thus bridging and linking the activated platelets. Thrombin converts fibrinogen to fibrin; factor XIII mediates fibrin cross-linking. Adapted from Alexander et al.[75]



In light of these factors, the comparative effectiveness of 'primary' PCI (angioplasty without prior or concomitant fibrinolytic therapy) and fibrinolysis has been debated over the last decade. Twenty-two randomized trials (7437 patients), which were conducted between 1990 and 2003, addressed this issue. In these trials, primary PCI was associated with a significant

30% reduction in 30-day mortality compared with fibrinolysis (5.3% vs. 7.4% events; odds ratio 0.70 and 95% CI 0.58-0.84).[11] When compared with front-loaded alteplase, primary PCI was associated with a 19% mortality reduction (5.5% vs. 6.8% events; odds ratio 0.81 and 95% CI 0.64-1.0). Primary PCI was also associated with a significantly lower incidence of myocardial reinfarction, stroke and intracranial haemorrhage.

The best results of primary angioplasty were predominantly achieved by experienced operators (> 75 cases per year), in high volume centers (> 200 cases per year) with door-to-balloon times of less than 90 minutes.[13] Additionally, three studies (2622 patients; published between 2000 and 2003) have confirmed the benefit of a transfer for primary PCI strategy over fibrinolytic therapy in acute myocardial infarction.[12,14,5] It remains unclear whether these excellent results could be applied and translated into daily practice. Still, guidelines consider primary PCI as the preferred therapeutic option when it can be initiated within 90 minutes of the first medical contact.

Antiplatelet therapy in percutaneous coronary intervention for ST-elevation myocardial infarction

Primary PCI usually with stenting has become the standard treatment for STEMI. During this procedure, trauma commonly occurs to the arterial endothelium that, among other effects, causes the activation and aggregation of platelets (figure 1). Because platelet aggregation may lead to coronary thrombosis in a patient already vulnerable to it, antiplatelet agents are essential adjunctive therapies in patients with STEMI undergoing primary PCI. The goal of antiplatelet therapy is to provide maximal protection against thrombosis without increasing the risk of bleeding.[16] Aspirin, thienopyridines, and glycoprotein (GP) IIb/IIIa inhibitors are the mainstays of antiplatelet therapy in patients undergoing PCI.

Classification of antiplatelet agents

Antiplatelet agents can interfere with a number of platelet functions, including aggregation, release of granule contents, and platelet-mediated vascular constriction. They can be classified according to their mechanism of action (figure 2):

Aspirin and related compounds (nonsteroidal antiinflammatory drugs and sulfinpyrazone) act by blocking the enzyme cyclooxygenase -1 (COX-1) that mediates the first step in the biosynthesis of prostaglandins and thromboxane A2 (TXA2) from arachidonic acid.

The thienopyridines clopidogrel, ticlopidine and prasugrel achieve their antiplatelet effect by blocking the binding of ADP to a specific platelet receptor, thereby inhibiting the activation of the GP IIb/IIIa complex and platelet aggregation.

Glycoprotein IIb/IIIa (GP IIb/IIIa) antibodies and receptor antagonists inhibit the final common pathway of platelet aggregation (the crossbridging of platelets by fibrinogen binding to the GP IIb/IIIa receptor). They may also prevent initial adhesion to the vessel wall.

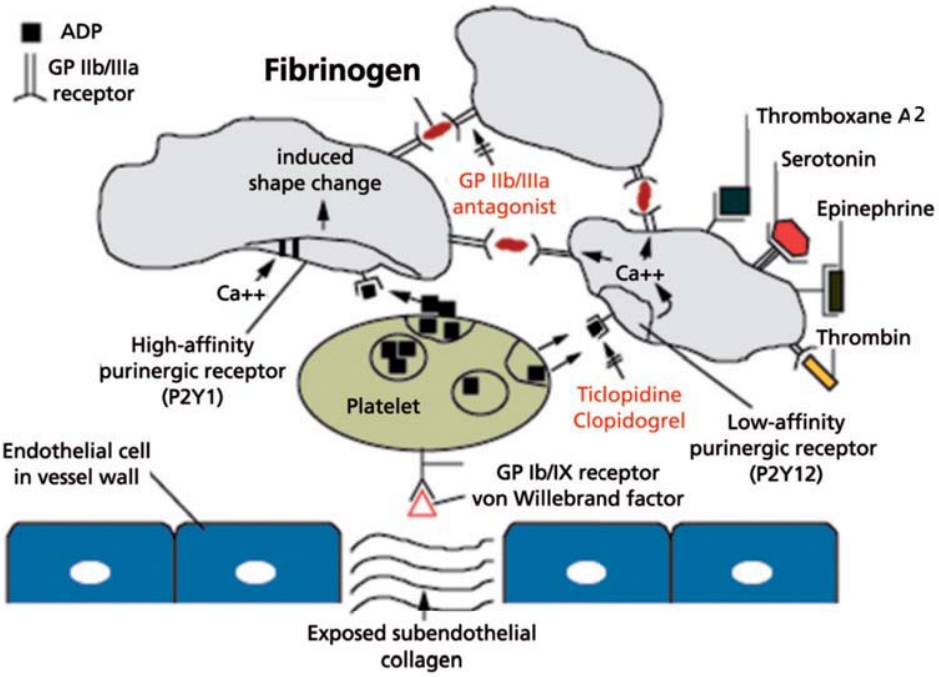
Aspirin

Aspirin has been used in a variety of cardiovascular disorders including primary and secondary prevention of coronary heart disease, transient ischemic attack, and stroke, and in the acute therapy of patients with an ACS. Aspirin therapy is also associated with long-term benefit in patients with an acute MI.

The antiplatelet activity of aspirin appears to be mediated principally through inhibition of the synthesis of thromboxane A2 (TxA2) via irreversible acetylation and inactivation of COX-1 enzyme, which catalyzes the first step of the conversion of arachidonic acid to thromboxane A2.[17] TxA2 is released by platelets in response to a number of agonists, amplifying the platelet response that leads to aggregation. Platelets do not synthesize new cyclooxygenase. As a result, the functional defect induced by aspirin persists for the life of the platelet.

Figure 2 Mechanism of action of antiplatelet agents

Schematic representation of the mechanism of action of antiplatelet agents. When vascular cells are damaged, platelets bind to exposed collagen via glycoprotein (GP) Ib/IX receptors complexed to von Willebrand factor. These bound platelets undergo degranulation, releasing adenosine diphosphate (ADP) and numerous other substances, including thromboxane A2, serotonin, and epinephrine, that play a role in the recruitment and aggregation process. The released ADP binds to two types of receptors, a low-affinity type 2 purinergic receptor (P2Y12) and a high-affinity purinergic receptor (P2Y1). Ticlopidine and clopidogrel block the binding of ADP to the type 2 purinergic receptor and prevent activation of the GP IIb/IIIa receptor complex and the subsequent aggregation of platelets. The GP IIb/IIIa receptor antagonists prevent platelet aggregation by blocking the binding of the GP IIb/IIIa receptor to fibrinogen, thereby inhibiting fibrinogen-platelet bridging. Adapted from Shairs et al.[76]



The Antithrombotic Trialists' Collaboration meta-analysis of 287 studies of antiplatelet therapy in high-risk patients with vascular disease established that antiplatelet therapy, primarily with aspirin, reduces the incidence of death, myocardial infarction (MI), or stroke

by 25%.[18] Therefore, aspirin is given routinely to all patients with ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI), and unstable angina (UA), and is assumed to benefit equally those undergoing and those not undergoing PCI.

Thienopyridines

Irreversibly block the adenosine diphosphate (ADP) receptor P2Y12 on the platelet cell surface, inhibiting the ADP coagulation pathway.[17] Clopidogrel and ticlopidine are prodrugs, requiring metabolism in the liver by the cytochrome P450, as a pathway to active metabolites.[19] With its equivalent efficacy, faster onset of action, and better safety profile, clopidogrel has largely replaced ticlopidine in clinical practice.[19] Clopidogrel has been shown to be as effective as aspirin in the prevention of ischaemic events in patients at risk.[20] Because clopidogrel and aspirin affect distinct pathways in the coagulation cascade, they are most often used in combination, which has been shown to decrease the incidence of ischaemic events by 20% in patients with NSTEMI or UA compared with aspirin alone.[21]

Randomized, controlled trials of clopidogrel vs. placebo in primary PCI for patients with STEMI have not been conducted, and its efficacy in that setting has been assumed based on the results of studies of patients with ACS undergoing elective PCI and patients with STEMI treated with fibrinolysis before PCI.[22] Recently, a trial has been initiated that will randomize patients with STEMI to one of the two groups: the first will receive 600 mg of clopidogrel in the ambulance and the second will not receive clopidogrel before intervention.[23]

The CLARITY study included 1863 patients with STEMI who underwent PCI after fibrinolysis comparing 300mg loading dose of clopidogrel to placebo given upon presentation.[24]. In the clopidogrel group, there was a 46% reduction in the 30-day rate of cardiovascular death, recurrent MI, or stroke compared with the placebo group ($p = 0.008$). Clopidogrel treatment improved outcomes consistently whether PCI was performed on an urgent or elective basis and regardless of the time from drug initiation until the procedure. Since most patients received open-label clopidogrel after the procedure, the observed benefit can be attributed to pre-treatment with clopidogrel. Because platelet aggregation is inhibited ~2 h after a 600 mg loading dose of clopidogrel, PCI started before that time is performed without the benefit of full platelet inhibition.[25] Prasugrel, a new thienopyridine, has a faster onset of action and may provide better protection when PCI is performed urgently.[26]

The TRITON-TIMI 38 trial compared prasugrel and clopidogrel in 13 608 moderate to high-risk patients with ACS scheduled to undergo PCI.[27] Among the 3534 patients with STEMI, the composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was significantly lower in the prasugrel treated patients compared to clopidogrel-treated patients. However, these benefits come at a price of higher rate of major bleeding. The ideal duration of clopidogrel treatment after PCI for STEMI is unknown, but is influenced by the type of stent placed and the patient's risk for bleeding.[28]

Glycoprotein IIb/IIIa inhibitors

The final common pathway of the various mechanisms of platelet aggregation is the binding of fibrinogen to adjacent platelets by means of GP IIb/IIIa integrin on the platelet surface.[21] Abciximab, tirofiban, and eptifibatide are potent GP IIb/IIIa inhibitors for intravenous administration that reduce the incidence of death and recurrent MI in high-risk patients undergoing PCI.[29-32] Of the three available GP IIb/IIIa inhibitors, only abciximab has been extensively studied in patients with STEMI undergoing primary PCI.

– **GP IIb/IIIa versus placebo**

Adjunctive abciximab during primary PCI for STEMI patients, all of whom received intravenous heparin, was evaluated after balloon angioplasty alone in RAPPORT[33] and CADILLAC[34] (by far the largest trial) and with stenting in ISAR-2[35], ADMIRAL[36], CADILLAC[34], and ACE[37]. In RAPPORT, ISAR-2, ADMIRAL, and ACE there was a 50 to 55 percent relative risk reduction with abciximab in 30-day acute ischemic end points (death, reinfarction, or urgent repeat revascularization), similar to that observed in PCI trials of more elective procedures. In contrast, abciximab did not significantly improve 30-day complication rates in CADILLAC in patients undergoing stenting, although a benefit was noted after angioplasty alone.[34] In a meta-analysis that included all five trials, abciximab therapy was associated with significant reductions in mortality at 30 days (2.4% vs. 3.4% with placebo, p = 0.047) and six to twelve months (4.4% vs. 6.2%, p = 0.01) and in reinfarction at 30 days (1.0% vs. 1.9%, p = 0.03). Abciximab did not increase the risk of major bleeding.[38] This analysis provides support for the concept that abciximab is beneficial in reducing acute ischemic events during primary PCI with stenting.

– **GP IIb/IIIa and heparin versus provisional GP IIb/IIIa and bivalirudin**

The relative efficacy and safety of the routine use of GP IIb/IIIa inhibitors in combination with unfractionated heparin (UFH) compared to bivalirudin in patients with STEMI undergoing PPCI was addressed in the HORIZONS AMI trial. In this study, approximately 3600 patients were randomly assigned either to bivalirudin with provisional use (allowed during PCI) of a GP IIb/IIIa inhibitor, or to UFH plus a GP IIb/IIIa inhibitor prior to primary PCI.[39] At 30 days, there was a significant 24% reduction in the primary end point of net adverse clinical events in the group receiving bivalirudin (9.2% vs. 12.3 %, p = 0.005), all of which was attributable to a reduction in major bleeding. Similar findings with bivalirudin alone were noted in the ACUITY trial[40] of patients with non-ST elevation acute coronary syndrome undergoing PCI.

– **Selection of agent**

In the setting of primary PCI, abciximab is the best studied GP IIb/IIIa inhibitor. A meta-analysis examined six trials including 3755 patients who were randomized to abciximab or placebo and followed for 6 months (five trials) or 1 month (one trial).[41] Overall, the treatment with abciximab reduced the rates of death (3.4 vs. 4.9%, p = 0.03), target-vessel revascularization (11.8 vs. 14.4%, p = 0.02), and major adverse cardiac events (MACEs) (17.0 vs. 21.1%, p = 0.001). Reinfarction rates were unaffected by abciximab treatment. The beneficial effects of abciximab were confined to patients who received stents, and did not appear in those treated with balloon angioplasty. Major bleeding occurred more often in abciximab-treated patients, but the difference was significant only in patients who received a heparin dose of 100 U/kg, not in those who received a dose of 70 U/kg. A more recent meta-analysis of three trials of abciximab in patients with STEMI undergoing PCI found that, over 3 years of follow-up, abciximab reduced the rate of death or reinfarction to 12.9 vs. 19.0% with placebo (relative risk [RR], 0.633; 95% confidence interval [CI], 0.452-0.887; p = 0.008).[42] In the RAPPORT trial[33] haemorrhagic complications were significantly increased in patients receiving abciximab, probably as a result of relatively high heparin doses. Therefore, guidelines recommend the use of

abciximab in primary angioplasty only in combination with low-dose heparin. In a study of 4010 patients with ACS undergoing revascularization, eptifibatide treatment failed to demonstrate a significant improvement over placebo in the composite endpoint of death, MI, or urgent revascularization at 30 days.[43] In a similar trial, a higher dose of eptifibatide resulted in a significant reduction in the 30-day occurrence of the composite of death or MI (14.2 vs. 15.7%, p = 0.04), a benefit that was observed 96 h after randomization and maintained throughout the trial.[44]

Facilitated percutaneous coronary interventions

The rationale for facilitated PCI is based on the hypothesis that combining early pharmacologically mediated reperfusion with subsequent and immediate mechanical stabilization of the ruptured plaque will overcome delays to transfer the patient to a second facility.[45] PCI performed as a matter of policy immediately after fibrinolytic therapy, to enhance reperfusion or reduce the risk of reocclusion, showed disappointing results in a number of earlier trials all showing a tendency to an increased risk of complications and death.

– **Facilitated PCI with a combination of fibrinolysis and GP IIb/IIIa inhibitor**
  Combination therapy using a half-dose of a fibrinolytic agent with a GP IIb/IIIa inhibitor may be more likely to restore coronary perfusion, promote ST segment resolution at 90 minutes, and reduce the incidence of recurrent ischemia, nonfatal reinfarction, and rescue PCI. Despite these benefits, two large trials, GUSTO V[46] and ASSENT-3[47] found no improvement in survival compared to conventional fibrinolytic therapy, and bleeding was increased, particularly in patients older than 75y. Facilitated PCI with full or reduced dose of thrombolytic drugs showed disappointing results in several major trials including ASSENT 4, FINESS and meta-analysis.[48-51] with combination therapy, not only an increased risk of major bleeding was noted, but also an increased incidence of major adverse cardiac events.

– **Facilitated PCI with GP IIb/IIIa inhibitors**
  A meta-analysis of nine trials concluded that facilitated PCI using GP IIb/IIIa inhibitor (ie, administration in ambulance or emergency department rather than in the catheterization laboratory) was associated with a significant increase in initial TIMI 3 (normal) flow (37% vs. 15%, p = 0.0001), but no difference in either final TIMI 3 flow after PCI nor in major clinical outcomes.[50] Similar early improvements in angiographic parameters of perfusion and a significant improvement in left ventricular function recovery at one month were noted in the RELAx-AMI trial published after the meta-analysis.[52] Major guidelines published in 2004 and 2005 by national cardiology societies before the meta-analysis, reached differing conclusions. The ACC/AHA STEMI guidelines recommended the administration of a GP IIb/IIIa inhibitor "as early as possible" before primary PCI (with or without stenting) in patients with an STEMI,[53] while the ACC/AHA/SCAI guideline concluded that the weight of evidence was less well established even in the higher risk subset noted in the preceding paragraph.[54] The ESC concluded that there was no evidence to support facilitated PCI.[28] The ACC/AHA and ACC/AHA/SCAI guideline recommendations were not changed in focused updates released in 2007.[55]

Recommendations for antiplatelet therapy in ST-elevation myocardial infarction

A) Early therapy:

For all patients with STEMI, current clinical guidelines recommend initiation of dual antiplatelet therapy with aspirin and clopidogrel as soon as possible after presentation.

- The first aspirin tablet should contain 162 to 325 mg and should be chewed.
- For patients receiving no reperfusion therapy or those less than 75 years of age treated with fibrinolytic therapy a loading dose of clopidogrel 300 mg should be administered. For patients older than 75 years of age who are not at high risk of bleeding who are treated with fibrinolytic therapy, a loading dose of clopidogrel 75 mg is recommended.
- For patients undergoing PPCI, a loading dose of clopidogrel 600 mg should be administered.

For patients in whom PPCI is planned, it is recommended to add a GP IIb/IIIa inhibitor at the time of PCI to heparin. Administration of abciximab before the diagnostic angiogram ('upstream') or just before PCI is acceptable. Eptifibatide and tirofiban are not as well studied in STEMI, but may be considered for use in that setting. [22,54]

B) Long-term therapy:

Indefinite aspirin for all patients with STEMI is recommended. The suggested dose is 75 to 162 mg/day.

- A higher dose of aspirin (162 to 325 mg daily) for one month in patients with a bare metal stent, for three months for those who received a sirolimus-eluting stent, and for six months for those who received a paclitaxel-eluting stent is suggested .

Clopidogrel (75 mg/day) is recommended for at least one year in all patients with STEMI.

- After implantation of a bare-metal stent (BMS), clopidogrel should be continued at 75 mg/day for 4-6 weeks, and after implantation of a drug-eluting stent (DES), for 12 months.
- Continuing clopidogrel indefinitely after DES is suggested in some patients, particularly when the antithrombotic benefit appears to exceed the risk for bleeding, until data are available defining the optimal duration of clopidogrel therapy in this setting.[22]

Stent thrombosis and late stent malapposition

Stent thrombosis is a rare but life-threatening complication and results in death in up to 45% of the cases.[56,57] Acute and subacute stent thromboses have existed since the first stent implantation procedures. Initially recognized as a complication of brachytherapy[58], late stent thrombosis has become a public health issue only during the current era of drug-eluting stent (DES) implantation.[59] Moreover, histopathological animal and human studies demonstrated delayed re-endothelilization and healing of the vessel wall after DES implantation.[60] After bare metal stent (BMS) implantation, stent thrombosis occurred almost exclusively within 30 days and is mainly related to procedure-related variables, such as untreated dissections and stent underdeployment.[61] After BMS implantation late stent thrombosis is incidentally reported.[62] It is assumed that the prevalence of late stent thrombosis after BMS is very rare, although the exact numbers are lacking. In contrast, after DES implantation stent thrombosis beyond 1 year after implantation has been reported frequently. Risk factors associated with late stent thrombosis are premature discontinuation

of dual antiplatelet therapy, diabetes mellitus, renal failure, bifurcation stenting or stent implantation during acute STEMI. Moreover, late stent thrombosis has been associated with late stent malapposition as assessed by IVUS imaging.[62, 63] Discussion about the risk of late stent thrombosis is complicated by use of different definitions of stent thrombosis. Recently, a new definition has been developed (table 1).[64]

In this definition stent thrombosis is categorized as definite, probable or possible, dependent on angiographic and clinical parameters. Moreover, stent thrombosis has been categorized as[64] acute stent thrombosis (0 to 24 hours after stent implantation), subacute stent thrombosis (>24 hours to 30 days after stent implantation), late stent thrombosis (> 30 days to 1 year after stent implantation) and, very late stent thrombosis (> 1 year after stent implantation). Acute or subacute can also be replaced by the term early stent thrombosis (0 to 30 days). (Very) late stent thrombosis includes primary as well as secondary late stent thrombosis (ie, after a target lesion revascularization).

Table 1 Academic Research Consortium criteria for stent thrombosis [64]

Definite stent thrombosis

- Angiographic confirmation of stent thrombosis:

  The presence of an *occlusive or †non-occlusive thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

  - Acute onset of ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical rise and fall in cardiac biomarkers
  - Pathological confirmation of stent thrombosis (Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy).

Probable stent thrombosis

- Any unexplained death within the first 30 days after stent implantation
- Any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis

- Any unexplained death from 30 days after stent implantation

**Occlusive thrombus (TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch); †Nonocclusive thrombus (Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream).*

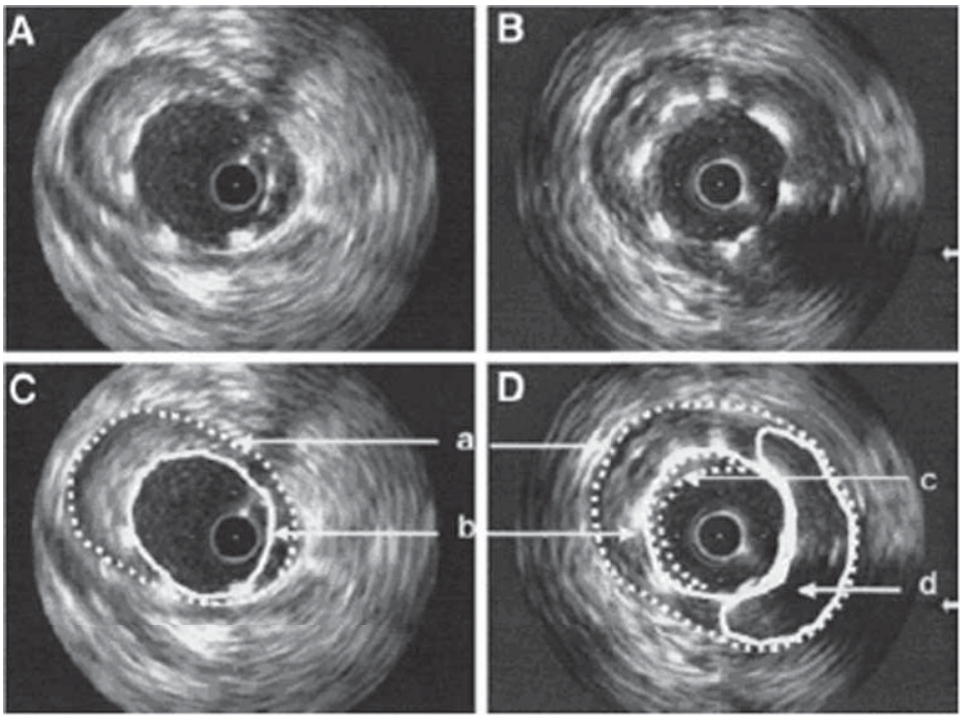
Stent malapposition

Stent malapposition (SM) is defined as a lack of contact between stent struts and the underlying vessel wall not overlying a side branch. SM can be quantified by measuring the number of malapposed struts; the arc subtended by the malapposed struts; the distance between the malapposed struts and the vessel wall; and the area, length, and volume of the gap between the stent and vessel wall.[59]

SM must be differentiated from and not confused with stent underexpansion. Stent expansion is the minimum stent area by itself or compared with a predefined reference.[59]

Figure 3 Intravascular ultrasound assessment of late stent malapposition

Post-stenting (A, C) and follow-up (B, D) intravascular ultrasound (IVUS) studies are shown in one patient with late stent malapposition (LSM). A is identical to C; B is identical to D. Arrow a indicates external elastic membrane (EEM) area; arrow b, stent area; arrow c, intrastent intimal hyperplasia area; and arrow d, LSM area. Plaque and media (P&M) area was calculated as (EEM minus stent) at stent implantation and (EEM minus stent minus LSM) at follow-up. Lumen area was calculated as stent minus intimal hyperplasia at follow-up. Adopted form Hong et al.[67]



Categorization of stent malapposition

SM can be acute, occurring at the time of stent implantation, or late, detected at follow-up. Differentiating among the various types and presentations of SM, specifically identifying the late and acquired variety, requires intravascular imaging (most commonly IVUS) both after stent implantation and at follow-up (figure 3).

Acute SM is mostly technique dependent and can occur after implantation of any type of stent. Acute SM can resolve or persist; acute and persistent SM can increase, remain stable, or decrease in size. It is not clear why some SM resolves and some persists. However, acute and persistent SM after DES implantation is associated with less neointimal hyperplasia compared with acute SM that resolves spontaneously.[65,66] Although reendothelialization is below the resolution of IVUS, it is interesting to speculate that acute and persistent SM also may be associated with reduced reendothelialization compared with acute and resolved SM.

Late SM, detected at follow-up, can be late and acquired (occurring between implantation and follow-up) or acute and persistent as noted above.[65,67-71]

Mechanism of late stent malapposition

Although late and acquired SM can occur after BMS implantation, brachytherapy treatment of BMS restenosis, radioactive stent implantation, and DES implantation, the exact underlying pathological mechanism responsible for positive remodeling remains unknown. Late and acquired SM is a continuum from one malapposed stent strut to aneurysm formation.[59]

Several mechanisms have been proposed :

1. positive arterial remodeling with an increase of external elastic membrane (EEM) out of proportion to the increase in persistent plaque and media;
2. a decrease in plaque and media due to dissolution of jailed thrombus or plaque debris, ie, patients undergoing stent implantation during acute MI;
3. SM not recognized at implantation and detected at follow-up (persistent SM); this may be mediated in part by severely calcified lesions not allowing for homogeneous stent expansion and resulting in stent underexpansion (lever principle); and
4. chronic stent recoil without any change in arterial dimensions.[63]

Relation between stent thrombosis and malapposition

Cook et al[63] reported the IVUS findings in 13 patients who developed stent thrombosis >1 year after DES implantation and concluded that "stent malappostion is highly prevalent in patients with very late stent thrombosis after DES implantation, suggesting a role in the pathogenesis of this adverse event." Previous IVUS studies with BMS[67] and DES[65,70,72] failed to identify late SM as a predictor of clinical adverse events. However, the predictive accuracy of these studies may have been limited by the small number of patients with late SM (13 to 90 patients), the limited follow-up period of only one year after DES implantation, and the infrequent occurrence of very late in-stent thrombosis.[63]

The mechanism by which (late) SM may contribute to stent thrombosis remains unclear. It has been stated that SM may serve as a local nidus for thrombus formation by allowing fibrin and platelet deposition.[73] Thus, SM may be the consequence of chronic inflammation and delayed healing, resulting in tissue necrosis and erosion around the stent.[74] In addition, the positive remodeling of the arterial wall may reduce the blood flow between the aneurysmatic wall and the stent struts. Delayed re-endothelialization, impaired vasomotion, and chronic inflammation may be also regarded as primary stent thrombosis mechanisms (SM being just a marker) by allowing platelet adhesion, initiation of the coagulation cascade, and subsequent thrombotic stent occlusion.[63]

OBJECTIVE AND OUTLINE OF THIS THESIS

The aim of this thesis was: 1) to evaluate the immediate, short and long term outcomes of early abciximab administration prior to primary percutaneous coronary intervention (PPCI) in ST-segment elevation myocardial infarction (STEMI) patients, 2) to study the incidence of aborted infarction in the current PPCI era and its prognostic value, 3) to evaluate the prognostic importance of the early peak of cardiac troponin T in patients with first acute

myocardial infarction treated with PPCI, 4a) to review the prevalence of late acquired stent malapposition in drug eluting stents compared with bare metal stents implantation and, (4b) to investigate its possible association with (very) late stent thrombosis.

Chapter 2 represent the main part of this thesis, where we present a prospective interventional study comparing in-ambulance administration of abciximab (early group) with in-hospital administration prior to primary PCI administration (late group) in patients with STEMI. We illustrate the primary angiographic end point of the study (the presence of early reperfusion, defined as TIMI 2 or 3 flow in the infarction related artery before angioplasty). Secondary end points are post-procedural ST-segment resolution, enzymatic infarct size (measured by cumulative creatine kinase release), left ventricular function at 90 days (evaluated by myocardial scintigraphy) and incidence of major adverse cardiac events (death, recurrent myocardial infarction, revascularization, heart failure or major bleeding) during 7 months clinical follow up were also demonstrated.

In chapter 3 a sub-study of the former is presented. We use a clear, novel definition of aborted myocardial infarction including clinical, electrocardiographic, laboratory and angiographic parameters. The incidence, patient characteristics and predictors of aborted infarction in the primary PCI era are presented. In **chapter 4** we describe the prognostic value of aborted infarction on left ventricular function at 90 days and incidence of major adverse cardiac events (death, recurrent myocardial infarction, revascularization, heart failure) during 12 months clinical follow up. **Chapter 5** includes the prognostic importance of early peak cardiac troponin T in acute first myocardial infarction after primary PCI. We present its significance in predicting impaired left ventricular function and incidence of heart failure through 1 year clinical follow-up. In **chapter 6** we present a meta-analysis and systematic review comparing the risk of late acquired stent malapposition in bare metal stents with drug-eluting stents and investigate the possible association of late stent malapposition with late and very late stent thrombosis. Finally, a general summary, conclusions and future perspectives are described in English and Dutch respectively. (**Chapter 7**)

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