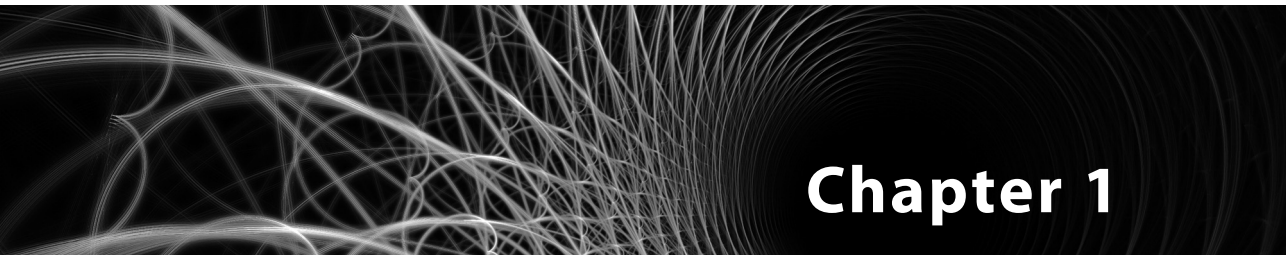
Innovative therapies for optimizing outcomes of coronary artery disease

Ahmed, T.A.H.N.



Chapter 1

General introduction and outline of the thesis

INTRODUCTION

1. Aspiration thrombectomy with primary PCI for STEMI

Primary percutaneous coronary intervention (PCI) has greatly improved outcomes in patients with ST-elevation myocardial infarction (STEMI) and has become the preferred reperfusion strategy in patients with STEMI.

The presence of detectable coronary thrombus at the time of primary PCI creates special challenges for the interventional cardiologist. Large thrombus burden is associated with an increased incidence of distal embolization and no-reflow, and may limit reperfusion at the microvascular level as measured by myocardial blush and ST-segment resolution (STR). Large thrombus burden is associated with a greater frequency of major adverse cardiac events (MACE) and is a strong independent predictor of late mortality[1].

There are many ways to deal with coronary thrombus at the time of primary PCI: pharmacologic strategies (typically glycoprotein IIb/IIIa platelet inhibitors), embolic protection devices (filters and distal balloon occlusion with aspiration), mechanical thrombectomy (AngioJet, Medrad Interventional/Possis, Minneapolis, Minnesota, and X-sizer, EV3, Plymouth, Minnesota), and manual or aspiration thrombectomy devices.

1.1. Major randomized trials

The TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction) Trial was a landmark study that brought manual thrombectomy into the mainstream as adjuctive therapy with primary PCI for STEMI[2]. This trial randomized 1,071 patients with STEMI of less than 12 hours duration to primary PCI with manual thrombectomy with the Export catheter versus primary PCI alone. Aspiration was able to be performed in 90% of patients and retrieved visible thrombus or atheromatous material in 72% of patients. Aspiration resulted in significant improvement in the primary endpoint of frequency of myocardial blush grade 3 (MBG 3) (46% versus 32%, $p<0.001$) and significant improvement in the secondary endpoint of frequency of complete ST-segment resolution within 90 minutes(STR>70%) (57% versus 44%, $p<0.001$). More importantly, this trial showed a significant mortality reduction with aspiration thrombectomy at one year[3]. These results were impressive but not conclusive, since (a) this was a single center study,(b) the study was not powered to detect differences in clinical endpoints, and (c) mortality was not a prespecified endpoint.

The EXPIRA (Thrombectomy with EXPort catheter in Infarct-Related Artery during primary percutaneous coronary intervention) Trial randomized 175 patients with STEMI to primary PCI alone versus primary PCI with manual thrombectomy and showed a significant improvement in the primary endpoints of myocardial blush grade 3 and complete ST-resolution[4]. This study was unique in that it evaluated infarct size by MRI and found that the extent of microvascular obstruction was less in the acute phase with aspiration (31.5% versus 72.9%,

p= 0.0005; 1.7 g versus 3.7 g, p = 0.0003) and improvement in infarct size at 3 months was observed with aspiration but not in the control group.

1.2. Meta-analyses

In addition to the two trials described above, there have been numerous small randomized trials evaluating manual thrombectomy, mechanical thrombectomy, and distal protection devices in patients undergoing primary PCI for STEMI. None of these trials has been adequately powered to evaluate clinical events. For this reason, several meta-analyses have been performed to help evaluate the role of manual thrombectomy (and other devices) as adjunctive therapy with primary PCI for STEMI.

Bavry and Bhatt analyzed 13 trials with manual thrombectomy, 5 trials with mechanical thrombectomy (AngioJet, Medrad Interventional/Possis, Minneapolis, Minnesota, and X-sizer, EV3, Plymouth, Minnesota), and 12 trials with distal protection devices (Percusurge-GuardWire, Medtronic; FilterWire, Boston Scientific, SpideRx, ev3; Angioguard, Cordis)[5]. This meta-analysis showed that manual thrombectomy resulted in better myocardial blush scores and better STR; distal protection resulted in better myocardial blush but no improvement in ST-resolution; and mechanical thrombectomy resulted in no improvement in either myocardial blush or STR. Mortality was improved with aspiration, was neutral with distal protection, and was worse with mechanical thrombectomy. The results of mechanical thrombectomy were driven primarily by the results of the AiMI (AngioJet in Myocardial Infarction) Trial[6]. New data from the JetSTENT Trial suggest better myocardial reperfusion (better ST-segment resolution) and lower MACE at 6 months and 1 year with rotational thrombectomy in patients with moderate and large thrombus burden (grades 3–5)[7] .

De Luca and colleagues analyzed nine randomized trials with 2,417 patients and compared PCI using manual thrombectomy with PCI alone[8]. This meta-analysis found that manual thrombectomy was associated with more frequent TIMI 3 flow post-PCI (87% versus 81%, p<0.0001), more frequent grade 3 myocardial blush (MBG 3) (52% versus 32%, p<0.0001), less distal emboli (7.9% versus 19.5%, p<0.0001) and lower 30-day mortality (1.7% versus 3.1%, p=0.04) compared to PCI alone.

Burzotta and colleagues performed a meta-analysis of 11 randomized trials with mechanical or manual thrombectomy upon primary PCI using a patient level analysis which allowed evaluation of outcomes in subgroups[9]. Overall mortality and MACE were reduced with thrombectomy, but subgroup analyses found that these benefits were observed only in patients treated with manual thrombectomy and only in patients treated with glycoprotein IIb/IIIa inhibitors. Time to reperfusion, infarct-related artery, and initial TIMI flow did not have any significant impact on the benefit of thrombectomy.

Mongeon and colleagues performed a Bayesian meta-analysis of 21 randomized trials, 16 trials evaluating aspiration thrombectomy and 5 trials evaluating mechanical thrombectomy[10]. The authors presented the results of all 21 trials combined and also presented the results of

the 16 trials with aspiration, and the results were similar. In patients treated with aspiration, there were fewer distal emboli, less no-reflow, more frequent TIMI 3 flow post-PCI, more ST resolution >50%, and more MBG3 compared to no aspiration. There were no significant differences in 30-day mortality between both groups of patients.

1.3. Limitations of current evidence

The evidence supporting the benefit of aspiration thrombectomy on surrogate outcomes (TIMI flow, myocardial blush grade, and ST-resolution) and angiographic outcomes (distal emboli and no-reflow) is strong and convincing. However,the evidence supporting the benefit in mortality reduction is less strong and has limitations.

The TAPAS Trial, which showed a significant mortality reduction at 1 year with aspiration thrombectomy, was a single center study and was not powered to evaluate mortality[2]. The 46% reduction in mortality was certainly not expected and may have occurred by chance[3]. Some of the benefit of aspiration may be from direct stenting, which was performed in 59% of patients who underwent thrombus aspiration, although direct stenting would not diminish the benefit of thrombus aspiration.

1.4. Current guidelines

Based on the TAPAS Trial and the meta-analyses mentioned above, the ACC/AHA Guidelines have given aspiration thrombectomy a Class IIa (Level of Evidence B) indication with primary PCI for STEMI, and the ESC Guidelines recently upgraded aspiration thrombectomy to Level of Evidence A[11, 12]. This opinion states that "aspiration thrombectomy is reasonable for patients with STEMI undergoing primary PCI." The committee did not feel that the evidence for benefit on clinical outcomes was strong enough to warrant a Class I indication.

1.5. Selective strategy of thrombus aspiration

All randomized trials with aspiration thrombectomy have been performed in "all comers" with STEMI, and it is not clear which subgroups may benefit most and which subgroups may not benefit at all. There are little data to help answering this question.

Sianos and colleagues have shown that both angiographic outcomes and clinical outcomes are worse in STEMI patients with large thrombus burden[1]. Napodano and colleagues found that patients with RCA infarcts, long lesions and high thrombus score had the highest frequency of distal embolization[13]. We might expect these subgroups to benefit most from thrombectomy, but data from the TAPAS trial do not support this[2]. Improvement in myocardial blush grade with aspiration was no better in patients with RCA infarcts versus non-RCA infarcts, and was no better in patients with visible thrombus compared with patients without visible thrombus[2]. There was a trend for more benefit in patients with reperfusion time of less than 3 hours, but there were no differential benefits in patients stratified by pre-PCI TIMI

flow[2]. Overall, there is scarce data to support selective use of aspiration thrombectomy in any subgroup of STEMI patients treated with primary PCI.

Aspiration thrombectomy has limited ability to remove large thrombi and is occasionally associated with incomplete thrombus removal, no-reflow, and/or distal emboli. There is recent evidence that mechanical thrombectomy may effectively improve outcome in patients with large thrombus burden[7]. Whether mechanical thrombectomy is preferable to aspiration thrombectomy in patients with large thrombus burden or in patients presenting late with organized thrombus remains an unanswered question.

2. Angiographic thrombus burden classification in patients with STEMI treated with primary PCI

Thrombus formation is a sensitive, dynamic process which demands accurate classification and compulsive management. Optimal angiographic visualization of thrombus is the first step**.** Thrombus is assessed according to the criteria summarized by Mabin et al[14]. These criteria include; (i) the presence of an intraluminal central filling defect or lucency surrounded by contrast material that is seen in multiple projections, and (ii) persistence of contrast material within the lumen. Intracoronary thrombus was angiographically identified and scored in five grades as previously described by the TIMI study group[15]. According to this classification, in thrombus Grade 0 (G0), no cineangiographic characteristics of thrombus are present. In thrombus Grade 1 (G1) thrombus may be present, with angiographic characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus. In thrombus Grade 2 (G2), there is definite thrombus, with greatest dimensions ≤ 1/2 the vessel diameter. In thrombus Grade 3 (G3), there is definite thrombus, but with greatest linear dimension > 1/2 but < 2 vessel diameters. In thrombus Grade 4 (G4), there is definite thrombus, with the largest dimension ≥ 2 vessel diameters, and in thrombus Grade 5 (G5), there is total occlusion.

3. Adjunctive abciximab in STEMI

GpIIb-IIIa inhibitors are the most powerful class of antiplatelet therapies, and their adjunctive beneficial effects to improve perfusion and mortality in STEMI patients have been shown in several randomized trials[16-18]. A previous meta-analysis of randomized trials has shown significant benefits of GpIIb-IIIa inhibitors in mortality and re-infarction of STEMI patients[19]. However, these benefits have disappeared in recent large randomized trials (BRAVE-3 and HORIZONS trials)[20, 21] conducted with abciximab on top of clopidogrel administration. In the BRAVE-3 trial[20], 800 patients were randomized to abciximab or placebo before angioplasty, on top of 600 mg clopidogrel loading dose. This study did not show benefits of abciximab either in the primary endpoint (infarct size as estimated by scintigraphic techniques) or mortality (2.5 vs. 3.2%). It should be emphasized that even though the aim of the study was to evaluate the impact of abciximab on infarct size, the median ischemic time was 4.5 h. It may be

arguable whether any adjunctive therapy in the late phase of 'golden hours' would provide adjunctive benefits in terms of infarct size[22]. Furthermore, the risk profile was relatively low to evaluate the benefits in terms of clinical outcome. A relatively low-risk population has been enrolled in BRAVE-3 trial[20] that rather suffer from bleeding complications than from thrombotic complications. In the large HORIZONS trial[21] 3602 STEMI patients were randomized to heparin + GpIIb-IIIa inhibitors, or tobivalirudin. Patients received 300 or 600 mg clopidogrel loading dose (the decision was left to the physician's discretion). Surprisingly, bivalirudin was associated with a mortality reduction, despite the significantly higher rate of acute in-stent thrombosis. The relatively low mortality may have hampered the conclusion of these recent trials. Recently, a meta-regression analysis of randomized trials has also emphasized a mortality benefit of abciximab administration especially in patients with a higher risk profile[23].

3.1. Early abciximab administration

Despite the negative results of the FINESSE trial[24], early administration of abciximab may certainly be encouraged due to the benefits with early administration observed in the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial[17], and in several recent reports[25-28].

Since high-dose clopidogrel administration takes 3–4 h to reach the top of inhibition of platelet aggregation[29], GpIIb-IIIa inhibitors are considered to rapidly inhibit platelet aggregation, with subsequent benefits in mortality according to the risk profile. The use of risk scores, such as the TIMI Risk Score[30], should be strongly encouraged to identify a high risk population with thrombotic complications that largely outweigh the risk of bleeding complications. Those patients may subsequently benefit in terms of mortality from aggressive antithrombotic therapy. It was also concluded in our study (Chapter 3) that absence of pre-infarction angina (PIA) could predict higher thrombus burden compared to patients with PIA and should be taken in consideration, among other risk scores, if a selective strategy of pre-hospital abciximab administration is to be adopted.

4. Drug eluting stents, future perspectives

Drug eluting stents (DES) have changed the landscape of interventional cardiology with their high efficacy in preventing restenosis. Several DES are available for clinical use with different drugs, polymers and platforms. Despite all the benefits of DES, concerns have been raised with regard to their long-term safety, with particular reference to stent thrombosis. Especially the permanent polymers, that carry the drug to be eluted, are inflicted in this regard. In an effort to address these concerns, newer stents have been developed including; DES with biodegradable polymers, DES that are polymer free, stents with novel coatings, and completely biodegradable stents. Many of these stents are currently undergoing pre-clinical and clinical trials; however, early results seem promising[31].

4.1. Biolimus A9

Biolimus A9 is a highly lipophilic sirolimus analogue that has been combined with an abluminal poly-lactic acid (PLA) biodegradable polymer on a number of different stent platforms. The polymer biodegrades within 6 to 9 months, and its abluminal location ensures more targeted tissue release and reduced systemic exposure (Figure 1). Biomatrix® and Nobori® stents are the two main biolimus A9-eluting stents.

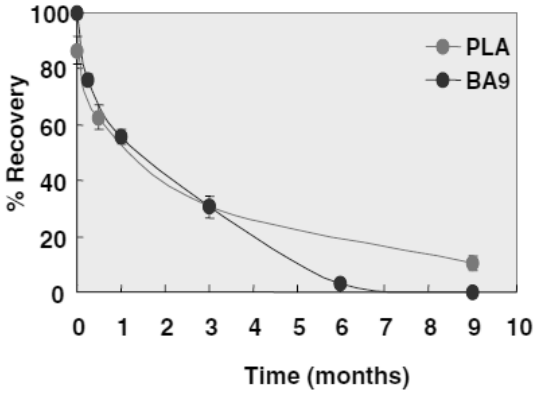


Figure 1: The elution pattern of Biolimus A9 (BA9) and the corresponding biodegradation pattern of the poly-lactic acid (PLA) polymer. Adapted from Garg and Serruys et al[31]

4.1.1. BIOMATRIX STENT®

The Biomatrix stent (Biosensors, Morges, Switzerland), carrying a biodegradable PLA polymer, was shown to be noninferior for MACE, a composite of cardiac death, MI, and ischemia-driven target vessel revascularization (TVR) at 12-month follow-up when compared with the Cypher sirolimus eluting stent (SES) among the 1,707 patients enrolled in the randomized, all-comers LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial (Biomatrix 10.6% vs. Cypher 12.0%, p = 0.37)[32]. More recently, the preservation of this noninferiority has been confirmed at 2-year follow-up[33]. Further promising data in support of a biodegradable polymer were obtained in an optical coherence tomography (OCT) substudy, that demonstrated a higher rate of near complete (>95%) strut coverage with the Biomatrix stent when compared with the Cypher SES at 9-monthsfollow-up (89.3% vs. 63.3%, p = 0.03)[34].

4.1.2. NOBORI STENT®

The Nobori stent (Terumo, Leuven, Belgium) utilizes the same PLA polymer and the same antiproliferative agent as the aforementioned BioMatrix stent. Physically, both stent platforms are identical, the only differences being the delivery system, delivery balloon, and the stent coating process. The BioMatrix stent is coated by an automated autopipette proprietary technology, whereas the Nobori stent is not coated using an automated process. The Nobori

stent has so far been compared with the Cypher SES and TAXUS paclitaxel eluting stent (PES) with promising results[35-37]. In the NOBORI CORE study, the reported late loss at 9-month follow-up between the 99 patients randomized to treatment with either the Nobori stent or the Cypher SES was 0.10 mm, and 0.12 mm, respectively (p =0.66)[37]. Moreover, treatment with the Nobori stent also appeared to result in a significantly better recovery of endothelial function compared to Cypher SES[38]. This finding has subsequently been reconfirmed by Hamilos et al[39] who demonstrated normal vasodilation after implantation of the Nobori stent, in line with other second generation DES and BMS, compared with the paradoxical vasoconstriction observed following implantation of first generation DES. Following on from this, the Nobori I study randomized 243 patients to treatment with either the Nobori stent (n =153) or the TAXUS PES stent (n = 90). Results at 9 months among the 86% of patients returning for follow-up demonstrated non-inferiority, and subsequent superiority, of the Nobori stent with respect to late loss when compared with the TAXUS PES stent (0.11 mm vs. 0.32 mm, p non-inferiority =0.001, p-superiority = 0.001). Similarly, the rate of Academic Research Consortium (ARC)-defined stent thrombosis at 9-month follow-up was also lower with the Nobori stent (0.0% vs. 2.2%)[36]. Overall, the evaluation of the Nobori stent has so far been performed in over 3,000 patients, and encouragingly, no episodes of very late in-stent thrombosis have been reported. Further assessment of the stent is underway, including randomized comparisons in "real-life" populations with the Xience V EES in the COMPARE 2 (n=2,700) and BASKET PROVE 2 (n = 2,400) studies and with the Cypher Select SES in SORT-OUT IV study (n=2,400)[40].

5. In-stent restenosis and thrombosis. Definitions and classifications

Restenosis, or reduction in lumen diameter after PCI, is the result of arterial damage with subsequent neointimal tissue proliferation. Binary angiographic restenosis is defined as ≥ 50% luminal narrowing at follow-up angiography. Mehran and colleagues proposed an angiographic classification of restenosis[41] (Figure 2). The most widely accepted definition of clinical restenosis, assessed as a requirement for ischemia-driven repeat revascularization, was proposed by the Academic Research Consortium[42]. This definition requires both an assessment of luminal narrowing and the patient's clinical context (Table 1). Stent thrombosis frequently presents as myocardial infarction (MI), whereas in-stent restenosis presents as MI in a small minority of cases[43]. The Academic Research Consortium proposed a definition of stent thrombosis that found general acceptance (Table 1). In addition to the level of certainty, stent thrombosis is stratified relative to the timing of the event as: acute stent thrombosis (0-24 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 subacutestent thrombosis can also be replaced by the term early stent thrombosis (0-30 days).

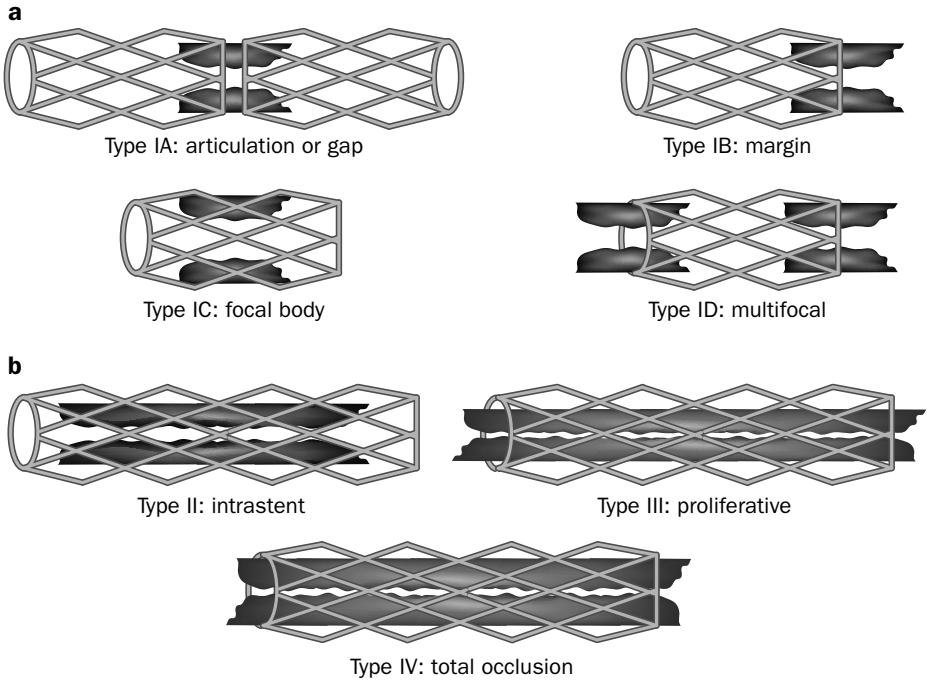


Figure 2: Schematic representation of 4 patterns of in-stent restenosis (ISR). Pattern I contains 4 types (A-D). Patterns II through IV are defined according to geographic position of ISR in relation to previously implanted stent. Adapted from Mehran et al[40]

6. 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
- the area, the length and the volume of the gap between the stent and the vessel wall.[47]

SM can be acute, occurring at the time of stent implantation, or late, detected at follow-up. Focusing on late stent malapposition, several mechanisms have been proposed:

- positive arterial remodeling with an increase of external elastic membrane (EEM) out of proportion to the increase in persistent plaque and media
- a decrease in plaque and media due to dissolution of jailed thrombus or plaque debris, i.e. patients undergoing stent implantation during STEMI

- 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 homogenous stent expansion and resulting in stent under-expansion
- chronic stent recoil without any change in arterial dimensions.[48]

Table 1: Definition and Classification of restenosis and thrombosis according to ARC[41]

Angiographic restenosis and classification (Figure 2)
Diameter stenosis ≥ 50% Type 1 focal: ≤ 10 mm in length IA articulation or Gap IB margin IC focal body ID multifocal Typ2 diffuse: >10 mm intrastent Type 3 proliferative: >10mm extending beyond the stent margin Type 4 total occlusion: restenotic lesion with TIMI flow grade of 0
Clinical Restenosis: Assessed Objectively as Requirement for Ischemia-Driven Repeat Revascularization
Diameter stenosis ≥ 50% *and* one of the following: Positive history of recurrent angina pectoris, presumably related to target vessel Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to target vessel Abnormal results of any invasive functional diagnostic test (e.g., coronary flow velocity reserve, FFR <0.80); IVUS minimum cross-sectional area <4 mm2 (and <6.0 mm2 for left main stem) has been found to correlate with abnormal FFR and need for subsequent TLR[44-46]. TLR with diameter stenosis ≥ 70% even in absence of the above ischemic signs or symptoms
Stent Thrombosis
Definite stent thrombosis • Angiographic confirmation of stent thrombosis Presence of thrombus that originates in stent or in the segment 5 mm proximal or distal to stent *and* at least 1 of the following within a 48-h time window: Acute onset of ischemic symptoms at rest New ischemic ECG changes that suggest acute ischemia Typical rise and fall in cardiac biomarkers • Pathologic confirmation of stent thrombosis Evidence of recent thrombus within stent determined at autopsy or via examination of tissue retrieved following thrombectomy Probable stent thrombosis • Any unexplained death within first 30 days after stent implantation • Irrespective of time after the index procedure, 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 intracoronary stenting

ARC, academic research consortium; ECG, electrocardiography; FFR,fractional flow reserve; IVUS, intravascular ultrasound; MI, myocardial infarction; TIMI,Thrombolysis In Myocardial Infarction; TLR,target lesion revascularization.

6.1. Innovative therapies to handle stent malapposition

Self-expandable stents were the first stents to be implanted in coronary arteries[49], being quickly followed by balloon-expandable stents, such that both technologies were used with-similar frequency in the early days of coronary stenting. Self-expandable stents are made from nitinol, an alloy of nickel and titanium that allow it to withstand large amounts of recoverable strain. In addition to comparable outcomes, self-expandable stents offer distinct advantages over balloon-expandable stents, such as a lower incidence of edge dissections[50, 51], reduced rates of side-branch occlusion and no-reflow[51], and positive remodeling[51]. Unfortunately, the introduction of DES led to a loss of interest among stent companies in pursuing the development of self-expandable stents, and they were largely abandoned for coronary use. However, there is renewed interest in this technology for niche coronary settings following new stent designs that have incorporated thinner struts, a drug coating, and improved delivery systems. In addition to its initial promising results in treatment of bifurcation lesions[52], recent results from the completed APPOSITION II trial (Randomized Comparison Between the STENTYS Self-expanding Coronary Stent and a Balloon-expandable Stent in Acute Myocardial Infarction) (NCT01008085) using the STENTYS™ (STENTYS, Princeton, New Jersey and Paris) self-expanding stent in treatment of patients with acute myocardial infarction, showed that, on optical coherence tomography, 0.51% of the struts were malapposed in the STENTYS group versus 5.33% in the balloon expandable stents at 3 days representing a 10-fold reduction. Taking >5% malapposed struts as a definition of malapposed stent, no STENTYS stents were malapposed compared to 28% of the balloon expandable stents ($p<0.001$). No events of stent thrombosis were recorded in both arms at 30 days follow-up[53].

Another option is the fully biodegradable stent, which offer several potential advantages over conventional bare or drug-coated metallic stents. Since drug elution and vessel scaffolding are only provided by the biodegradable stent until the vessel has healed, no malapposed stent struts are present at long term[54].

7. Objective and outline of this thesis

In light of the issues described in this introduction chapter, the aim of this thesis was: 1) to evaluate the adjunctive role of aspiration thrombectomy among ST-segment elevation myocardial infarction (STEMI) patients receiving early (in-ambulance) abciximab prior to primary percutaneous coronary intervention (PPCI), 2) to assess the predictors of thrombus burden in STEMI patients undergoing PPCI and whether there is a difference in infarct size among patients with high and low thrombus grades, 3a) to evaluate and review the clinical performance of various biodegradable-polymer drug eluting stents (DES) , comparing the incidence of definite stent thrombosis and target lesion revascularization between biodegradable-polymer biolimus-, sirolimus- and paclitaxel-eluting stents, 3b) to compare the incidence of definite stent thrombosis and target lesion revascularization between biodegradable-polymer DES and permanent-polymer DES, 4) to review the recently emerg-

ing drugs for coronary artery disease with special emphasis on antiplatelets, antithrombotics and antidyslipidemics, 5) to provide an overview of the recent innovations for optimizing the outcomes of coronary stenting, as well as up-to-date information about prevention and treatment of in-stent restenosis, and 6) to present a review of late stent malapposition in the bare metal stent (BMS) and DES era.

In **Chapter 2** we present a retrospective analysis in the MISSION! prospective interventional study, comparing PPCI with thrombus aspiration (thrombectomy-facilitated PCI) to PPCI without thrombus aspiration (conventional PCI) in patients with STEMI receiving early (in-ambulance) abciximab. We illustrate the primary end-point of the study (complete ST segment resolution at 90 min. post-PCI), as well as secondary end-points represented by enzymatic infarct size (measured by peak levels of creatine kinase and troponin-T), and left ventricular ejection fraction (LVEF) at 3 months (evaluated by myocardial scintigraphy). Finally we describe the incidence of major adverse cardiac events (all-cause death, cardiac death, recurrent myocardial infarction and revascularization) at 1 year follow-up.

Chapter 3 is a sub-study of the former. We tried to assess the predictors of thrombus grade among different clinical, angiographic and laboratory data. We categorized patients according to baseline TIMI thrombus grade into those with high thrombus grade (HTG) and low thrombus grade (LTG). We also assessed infarct size and scintigraphic LVEF at 3 months in both patient groups.

In **Chapter 4** we present a meta-analysis and systematic review comparing the risk of definite stent thrombosis (DST) and target lesion revascularization (TLR) among biodegradable-polymer biolimus, sirolimus and paclitaxel DES. We also compare the risk of DST and TLR between biodegradable-polymer DES and permanent-polymer DES.

Chapter 5 is a review article in which we provide an almost complete overview of the recent and emerging drug therapies of CAD. This includes drugs for the treatment of atherogenic dyslipidemia, drugs that stabilize atherosclerotic plaques and halt their progression guided by novel anti-inflammatory concepts in atherosclerosis treatment, anti-anginal treatments, renin-angiotensin-aldosterone system inhibitors, antiplatelet drugs and anticoagulant drugs.

In **Chapter 6** we provide an overview of in-stent restenosis as one of the challenges that we encounter in interventional cardiology. We discuss the up-to-date developments in prevention and treatment of in-stent restenosis and optimization of the outcomes of PCI.

Chapter 7 presents a review on late stent malapposition. We discuss its much debated role in stent thrombosis and future perspectives in handling it.

Finally, **in Chapters 8 and 9** a general summary, conclusion and future perspectives are described in English and Dutch respectively.

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