Innovative therapies for optimizing outcomes of coronary artery disease

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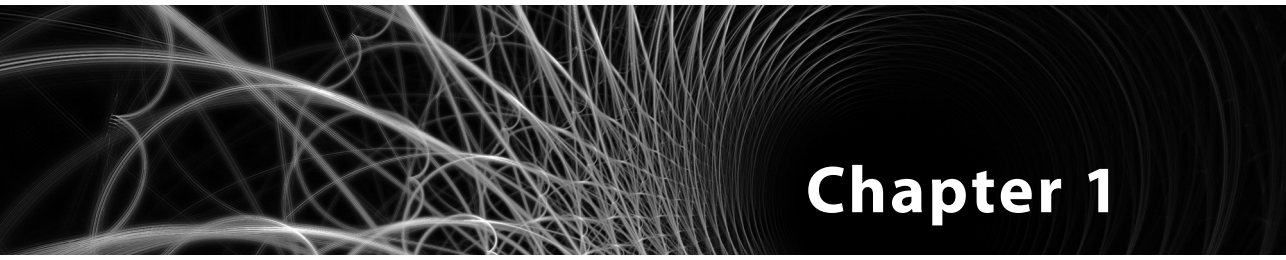

Chapter 1

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.

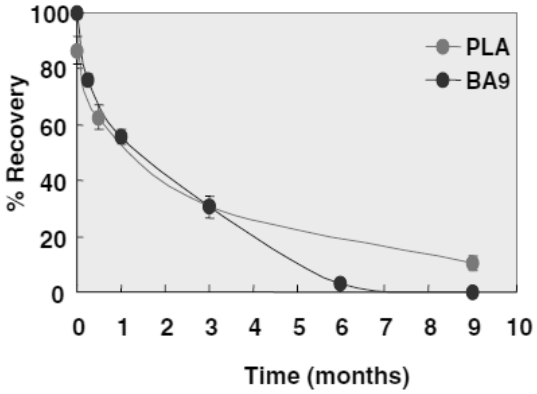

Figure 1: The elution pattern of Biolimus A9 (BA9) and the corresponding biodegradation pattern of the poly-lactic acid (PLA) polymer. Adapted from Garg and Serruys et al[31]

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).

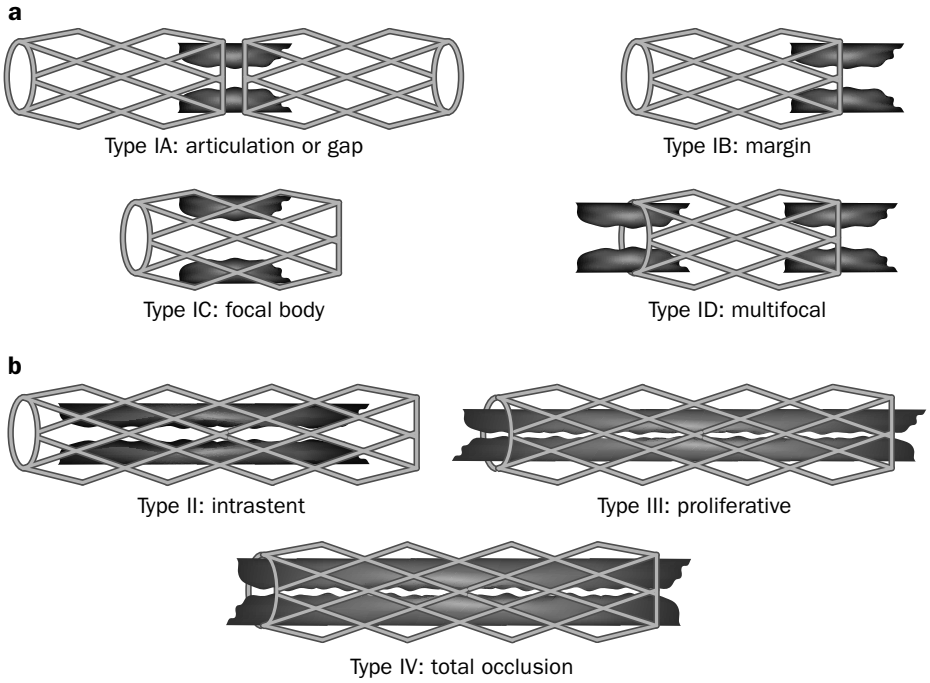

Figure 2: Schematic representation of 4 patterns of in-stent restenosis (ISR). Pattern I contains 4 types (A-D). Patterns II through IV are defined according to geographic position of ISR in relation to previously implanted stent. Adapted from Mehran et al[40]

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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Chapter 2

Aspiration thrombectomy during primary percutaneous coronary intervention as adjunctive therapy to early (in-ambulance) abciximab administration in patients with acute ST elevation myocardial infarction: An analysis from Leiden MISSION! Acute Myocardial Infarction Treatment Optimization Program

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ABSTRACT

Background The benefits of early abciximab administration and thrombus aspiration in ST elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PPCI) have been previously elaborated. However, whether there is adjunctive effect of thrombus aspiration among STEMI patients, with angiographic evidence of thrombus, receiving early pre-hospital abciximab remains unclear.

Methods In the context of a fixed protocol for PPCI, 158 consecutive patients with STEMI were enrolled, in whom abciximab was started early before hospital arrival (in-ambulance); 79 patients who had PPCI with thrombus aspiration (thrombectomy-facilitated PCI group), were compared to 79 who had PPCI without thrombus aspiration (conventional PCI group) in a prospective non-randomized study. The primary end-point was complete ST-segment resolution within 90 min. Secondary end-points included distal embolization, enzymatic infarct size as well as left ventricular ejection fraction (LVEF) assessed by Gated-Single Photon Emission Computed Tomography (SPECT). Major adverse cardiac events (MACE) were evaluated up to 12 months.

Results Both groups were comparable for baseline characteristics. ST-segment resolution was significantly higher in the thrombectomy-facilitated group (p=0.002), and multivariate analysis identified thrombectomy as an independent predictor of ST-segment resolution (OR= 9.4, 95% CI = 2.6-33.5, p=0.001). Distal embolization was higher in the conventional PCI group among patients with higher thrombus grades. No difference was observed between both groups in infarct size assessed by peak CK (p=0.689), and peak Tn-T levels (p=0.435). Also the LVEF at 3-months was similar (p=0.957). At 12 month clinical follow-up, thrombus aspiration was however associated with reduced all-cause mortality (log-rank p= 0.032).

Conclusion Among STEMI patients treated with PPCI and in-ambulance abciximab, it appears that a selective strategy of thrombus aspiration still has additive benefit.

Key words ST segment elevation myocardial infarction, primary percutaneous coronary intervention, abciximab, thrombus aspiration.

INTRODUCTION

It has been widely observed that primary percutaneous coronary intervention (PPCI) offers greater reperfusion benefits in the setting of acute myocardial infarction (MI) compared to intravenous thrombolytic therapy[1]. However, despite a good epicardial flow after PPCI, a considerable percentage of patients have impaired myocardial perfusion mainly due to embolization of the microcirculation[2]. Poor myocardial reperfusion is associated with adverse outcome including reduced left ventricular function and mortality[3-5]

Recent studies demonstrated that Glycoprotein (GP) IIb,IIIa platelet receptor antagonists have positive effects on reperfusion in the setting of primary percutaneous coronary interventions, with improved clinical outcome[6]. Many studies showed that these benefits are more apparent when GP IIb,IIIa platelet receptor antagonists are introduced as early as achievable in the setting of acute myocardial infarction[7-12].

Additionally, numerous adjunctive coronary devices have been developed in an attempt to decrease or prevent distal embolization during revascularization and thereby trying to improve clinical outcome as well.

Recent randomized trials demonstrated that patients treated with a thrombectomy catheter showed better angiographic and electrocardiographic signs of myocardial reperfusion, as well as improved 1 year clinical outcome[13-16]. These data have been confirmed by recent meta-analyses demonstrating that adjunctive manual thrombectomy in the setting of primary PCI is associated with improved epicardial and myocardial perfusion, less distal embolization[17], as well as improved clinical outcome[18]

However, it is still unknown whether there is a possible benefit of using thrombus aspiration devices in the setting of PPCI among STEMI patients receiving early GP IIb,IIIa platelet receptor antagonists. Therefore, in this study the results of adjunctive manual thrombus aspiration using aspiration thrombectomy catheter were compared to no thrombus aspiration in a consecutive group of STEMI patients treated with PPCI and early "in-ambulance" abciximab administration.

METHODS

Study design

This is a single center non-randomized prospective study. All patients were treated according to the institutional STEMI protocol (MISSION!) implemented at Leiden University Medical Centre (LUMC) since February 2004, which includes a standardized prehospital, in-hospital and outpatient clinical framework for decision making and treatment[19, 20]. The tertiary center provides a round-the-clock service of PPCI with highly experienced PCI physicians and dedicated nurses.

Study population

Inclusion and exclusion criteria

The inclusion criterion was a diagnosis of acute MI defined by chest pain suggestive of myocardial ischemia for at least 30 minutes, with a time from onset of symptoms of <9 hours before hospital admission, and an electrocardiogram (ECG) with ST-segment elevation of >0.1 mV in ≥2 leads. Exclusion criteria were recent surgery, recent stroke, hemorrhagic diatheses, and known contraindications for therapy with abciximab, aspirin, clopidogrel or heparin.

Study groups

A total of 158 consecutive patients; who fulfilled the inclusion and exclusion criteria for this study, and who received early in-ambulance abciximab, were enrolled: 79 consecutive patients, in whom a thrombectomy catheter was used at the start of the procedure (the thrombectomy-facilitated PCI group); were compared to 79 consecutive patients within the same period, in whom thrombectomy catheter was not used (the conventional PCI group). The study complies with the Declaration of Helsinki. The MISSION! protocol has been approved by the local ethics committee.

Medication

All patients received abciximab (Centocor B.V., Leiden, The Netherlands) as a bolus injection of 0.25 mg/ kg body weight, followed by 0.125 mcg/kg/min with a maximum of 10 mcg/ min as a continuous infusion for 12 hr. Abciximab administration started early in the ambulance according to the adapted MISSION! protocol[19, 20]. Furthermore all patients received an equivalent of 300 mg of acetylsalicylic acid, 600 mg clopidogrel as a loading dose in the ambulance and heparin given as a bolus of 5000 IU at the start of the PCI procedure. After the procedure, all patients received aspirin (75 mg/day) indefinitely and clopidogrel (75 mg/day) for one year. Other medications, including b-blockers, ACE-inhibitors, nitrates, and statins, were prescribed according to MISSION! protocol.

Invasive Procedure and Angiographic Evaluation

All PPCI was performed through a 6F femoral sheath. Patients underwent PPCI and stenting of the infarct-related artery (IRA) according to standard techniques. The choice of stent (bare-metal stent or drug-eluting stent) was left to the operator's discretion. Direct stenting, which is stent placement without balloon pre-dilatation, was performed only in cases presenting clear views of the arterial lesion with adequate flow. We also considered stent placement which was only preceded by thrombectomy as direct stenting. Otherwise, the patient was subjected to balloon angioplasty and stenting was done subsequently. The choice of the balloon size was left to the operator's decision. Stent implantation was successfully completed in all patients, apart from only one patient in the thrombectomy-facilitated PCI group where

the procedure was complicated by a spiral dissection occurring after thrombectomy and had to undergo emergency coronary artery bypass graft (CABG), and this patient survived and completed the follow-up period. The choice of performing thrombectomy was left to the operator's discretion. Thrombectomy was often, but not exclusively, performed when high thrombus burden was observed at the initial angiographic image of the target vessel. There was no change in the frequency of use of thrombectomy over the time period of the study. Thrombus was assessed according to the criteria summarized by Mabin et al.[21]. These criteria include the presence of an intraluminal central filling defect or lucency surrounded by contrast material that is seen in multiple projections; the absence of calcium within the defect; and persistence of contrast material within the lumen. Thrombus score was graded as previously described by the thrombolysis in myocardial infarction (TIMI) Study Group[22, 23]. We further categorized the thrombus score into 2 overall grades; a high thrombus grade (grades 4 and 5), and a low thrombus grade (grades 1-3). We decided to use this cut-off value in line with 2 recent studies[24, 25] suggesting prognostic implications of this cut-off. Coronary flow was graded according to TIMI criteria[26]. TIMI flow grade was evaluated at baseline and after the PCI procedure. Distal embolization after PCI was defined as a filling defect with abrupt cutoff in the vessel located distally of the culprit lesion. Procedural success was defined as residual stenosis <20% and TIMI flow grade 3. The coronary angiograms were reviewed off-line by two independent interventional cardiologists who were blinded to the clinical data.

Thrombectomy catheter

The Export Aspiration Catheter (Medtronic Corporation, Minneapolis, Minnesota (MN), USA) is a 6F thrombus aspiration catheter[13]. Thrombosuction was started proximal to the occluded site, gently pushing the catheter through the occlusion and then pulling it in a proximal direction, keeping negative pressure once the occlusion was crossed or if there was no longer backflow in the syringe. This could be repeated several times. Withdrawal of the catheter from the artery and from the guiding catheter was performed with permanent negative pressure. After each pass the catheter was flushed and the syringe emptied over a filter, to show the retrieved debris.

End-points and clinical follow-up

According to the MISSION! Protocol all patients were seen at the dedicated out-patient clinic after 1, 3, 6, and 12 months. The primary endpoint was ST-segment resolution within 90 min. after PPCI; secondary endpoints were distal embolization, enzymatic infarct size and LVEF as assessed by Gated-SPECT. Also major adverse cardiac events (MACE) occurring within one year of follow-up were recorded. These include all-cause death, cardiac death, reinfarction, target vessel and target lesion revascularization; death was regarded as cardiac unless an unequivocal non-cardiac cause of death was established. Reinfarction was defined as recurrent symptoms with new ST-segment elevation and elevation of cardiac markers to at least twice the upper

limit of normal. Target vessel (TVR) and target lesion (TLR) revascularization were defined as any revascularization procedure of the target vessel or target lesion (from 5 mm distally to the stent up to 5 mm proximally to the stent), respectively. All major adverse cardiac events were assessed and classified by an interventional cardiologist unaware of the treatment allocation.

Electrocardiographic data

The 12-lead ECG was recorded at presentation and within 90 min after PPCI. The magnitude of ST-segment elevation is measured 60 milliseconds from J point. ST-segment score is calculated as the sum of ST-segment elevation > 0.1 mV for leads V1 through V6 and I, II, and aVL in anterior infarction and I, II, aVF, V5, and V6 in non-anterior infarction[27]. All ECGs were collected and analyzed by an investigator blinded to the assigned treatment. Total ST-segment elevation at inclusion was compared with that taken within 90 min after PPCI. A complete ST-segment resolution was calculated, defined as resolution of the initial ST-segment elevation of ≥70%[28].

Enzymatic Infarct Size

Creatine kinase (CK) activity and cardiac troponin-T (Tn-T) concentration in plasma were determined at admission and every 6 hr in the first 48 hr after PPCI. Subsequently these levels were determined every day up to discharge, unless clinical events suggested repeat measurements. Peak levels of CK and Tn-T in plasma were calculated as a measure of infarct size in each patient by an investigator blinded to the assigned treatment.

Myocardial Perfusion Imaging

According to the MISSION! Protocol all included patients were enrolled for a myocardial perfusion study at 90 days post-PPCI. An ECG-gated single photon emission computed tomography (SPECT) acquisition at rest using intravenous Technetium 99 m Tetrofosmin (MYOVIEW, Amersham, Buckinghamshire, UK) was used to measure the left ventricular ejection fraction (LVEF) 90 days after PPCI. LVEF was calculated using an automated and validated method (QGS software, version 2.0; Cedars-Sinai Medical Center, Los Angeles, CA, USA). Detailed methods are described elsewhere[29]. Patients in whom the gated SPECT could not be performed due to technical difficulties, LVEF estimated by echocardiographic biplane method was used instead. LVEF assessment was done by an investigator blinded to the assigned treatment.

Statistical analysis

Categorical variables were compared using the X^2 test or Fisher's exact test. Continuous normally distributed data were tested by student t-test or in the case of a non-Gaussian distribution by a nonparametric test for independent samples (Mann Whitney *U* test). One year clinical outcomes were analyzed using Kaplan Meier methodology and were compared with log-rank test pooled over strata. Multivariate linear regression and logistic regression

analyses were used to create models for both PCI groups (as the variable of interest) adjusted for all potentially relevant variables including; age, sex, hypertension, smoking, diabetes, dyslipidemia, symptom onset to balloon time, prior medications (aspirin, clopidogrel, statins), as well as angiographic and procedural variables (Infarct related artery, proximal location of the culprit lesion, balloon predilatation and thrombus grade), to identify whether thrombectomy is an independent predictor for the end points of ST-segment resolution, distal embolization, infarct size assessed by cardiac enzymes or LVEF. All tests were two-sided, and a p-value of < 0.05 was considered significant. All analyses were performed with PASW version 17.0 statistical software (SPSS Inc. - An IBM Company, Chicago, IL, USA).

RESULTS

Study population

One-hundred and fifty-eight patients were included in the study according to the eligibility criteria (Figure 1 Flow diagram). The baseline clinical characteristics were comparable between the two groups (Table 1).

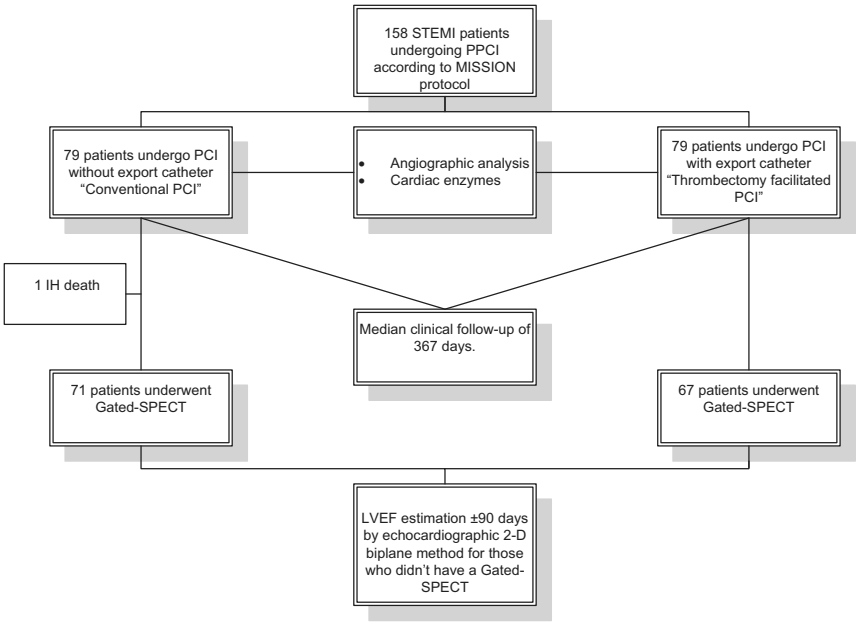

Figure 1: Flow diagram of the study patients. LVEF, left ventricular ejection fraction; PPCI, primary percutaneous coronary intervention; SPECT, single photon emission computed tomography; STEMI, ST elevation myocardial infarction; IH, in hospital.

Table 1: Baseline characteristics.

	Conventional PCI N=79	Thrombus aspiration N=79	*p*
Age in years	59±10	56±12	0.080[a]
Male, n (%)	59(75)	62(78)	0.573[b]
Medical History, n (%)			
Hypertension	28(35)	24(30)	0.498[b]
Hyperlipidemia	17(21)	24(30)	0.204[b]
Smoking	53(67)	49(62)	0.796[b]
Family history	31(39)	36(45)	0.421[b]
Diabetes mellitus	7(9)	6(8)	0.772[b]
Previous MI	8(10)	8(10)	1.0[b]
Previous PCI	5(6)	7(9)	0.548[b]
Previous CABG	1(1)	4(5)	0.173[b]
Killip Class. , n (%)			0.943[b]
Class II	5(6)	5(6)	
Class III/IV	5(6)	4(5)	
Heart rate (beats/min.)	73±16	73±17	0.924[a]
Systolic BP(mmHg)	133±26	127±22	0.145[a]
Symptoms to balloon (min)	135(90-195)	140(93-225)	0.707[c]
Start of abciximab to balloon (min)	40 (25-52)	35 (27-47)	0.554[c]
Previous aspirin	16(20)	10(13)	0.198[b]
Previous clopidogrel	0(0)	1(1)	1.0[b]
Previous statins	12(15)	13(16)	0.827[b]

Data are presented as mean ± standard deviation, number (%) of patients or median (Interquartile range). MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BP, blood pressure.

[a] Compared using unpaired t test.

[b] Compared using Chi-square or Fisher exact test.

[c] Compared using Mann-Whitney U test.

Angiographic and peri-procedural findings

Angiographic and procedural data are summarized in Table 2. There was a significantly higher rate of high grade thrombus in the thrombectomy-facilitated group (p<0.001), also there was a significantly higher rate of balloon predilatation in the conventional PCI group (p= 0.002). The rate of distal embolization was higher in the conventional PCI group, though not significant (p=0.516). However, when the analysis was restricted only to patients with high thrombus grade (grades 4 and 5), the rate of distal embolization turned out to be significantly higher in the conventional PCI group (p=0.012). Multivariate regression analysis including all potentially relevant clinical, angiographic and procedural risk factors, identified only high thrombus grade as an independent predictor for distal embolization (odds ratio= 11.2, 95% CI= 1.6-76.6, p=0.013).

Table 2: Angiographic and procedural results.

	Conventional PCI N=79	Thrombus aspiration N=79	*p*
Infarct related artery, n (%)			0.191[b]
Left main artery	1(1)	2(2)	
Left anterior descending artery	31(39)	28(35)	
Circumflex artery	15(19)	7(9)	
Right coronary artery	32(40)	42(53)	
Diseased vessels, n (%)			0.211[b]
1-vessel	44(56)	48(61)	
2-vessel	26(33)	28(35)	
3-vessel	9(11)	3(4)	
Proximal culprit lesion, n (%)	35(44)	40(50)	0.426[b]
Abciximab	78(98.7)	79(100)	0.924[b]
Initial TIMI flow grade, n (%)			0.779[b]
0	41(52)	39(49)	
1	14(18)	15(19)	
2	13(16)	17(21)	
3	11(14)	8(10)	
Final TIMI flow grade, n (%)			0.319[b]
1	0(0)	2(2)	
2	11(14)	13(16)	
3	68(86)	64(81)	
Drug eluting stents, n (%)	45(57)	52(70)	0.096[b]
Stent number	1.5±0.7	1.5±1.0	0.789[a]
Multiple stents, n (%)	31(39)	24(32)	0.402[b]
Predilatation, n (%)	66(83)	49(62)	0.002[b]
Thrombus detected, n (%)	75(95)	78(99)	0.367[b]
Thrombus grade, n (%)			<0.001[b]
High thrombus grade (Grades 4, 5)	29(39)	65(83)	
Low thrombus grade (Grades 1, 2, 3)	46(61)	13(17)	
Distal embolization	10(13)	8(10)	0.516[b]
Distal embolization in high thrombus grade	9 (32%)	7(11%)	0.012[b]

Data are presented as mean ± standard deviation, number (%) of patients.
TIMI, Thrombolysis In Myocardial Infarction.
[a] Compared using unpaired t test.
[b] Compared using Chi-square or Fisher exact test.

Electrocardiographic evaluation

The rate of post-PCI complete ST-segment resolution of ≥ 70% was observed more frequently in the thrombectomy-facilitated PCI group (87% vs. 65%, p=0.002) (Table 3).

Multivariate logistic regression analysis for ST-segment resolution among both PCI groups adjusted for all relevant clinical, angiographic and procedural variables identified aspiration thrombectomy (odds ratio= 9.4, 95% CI = 2.6-33.5, p=0.001), shorter symptom to balloon time and absence of balloon predilatation as independent predictors of complete ST-segment resolution within 90 min. Post-PPCI.

Table 3: Postprocedural electrocardiographic and laboratory results.

	Conventional PCI N=79	Thrombus aspiration N=79	*p*
Complete ST-segment resolution within 90 min. (%)	45/69(65)	66/76(87)	0.002[b]
Peak CK (U/l)	2117±1927	2286±2168	0.689[a]
Time to peak CK (hours)	13(9-18)	14(10-17)	0.687[a]
Peak Tn-T(μg/l)	6.2±8.5	5.8±6.1	0.435[a]
Time to peak Tn-T (hours)	13(10-19)	14(11-17)	0.535[a]

Data are presented as mean ± standard deviation, number (%) of patients
CK, creatine kinase; Tn-T, Troponin T.
[a] Compared using Mann-Whitney U test.
[b] Compared using Chi-square or Fisher exact test.

Enzymatic infarct size assessment

Peak levels of CK and Troponin-T were comparable in both PCI groups (p = 0.689 and p=0.435, respectively), and so were the time to peak levels of CK and Troponin-T (p=0.687 and p=0.535, respectively) (Table 3.). Multivariate linear regression analysis for Peak levels of CK and Tn-T including the aforementioned factors did not identify PCI groups as an independent predictor of higher peak CK (*B* = 171.6, 95% CI= -620.4 – 963.6, p=0.669) and Troponin T (*B* = 0.77, 95% CI= -2.19 – 3.73, p=0.610).

Three-month LV function evaluation

One-hundred and thirty-eight patients underwent LV function assessment by myocardial perfusion scintigraphy (MYOVIEW) (Figure 1). Patients who did not undergo scintigraphy had their LV function assessed using biplane 2-D echocardiographic evaluation at 3 months, and one patient had unavailable data regarding the LV function assessment post-PCI due to in-hospital death. LVEF was not significantly different between both groups (p=0.957) (Table 4). Multivariate linear regression analysis adjusted for all potentially relevant covariates did not identify aspiration thrombectomy as an independent predictor of improved LVEF (*B* = -1.0, 95% CI= -5.96 – 3.95, p=0.689).

Table 4: Three months scintigraphic and 1-year clinical outcomes.

	Conventional PCI N=79	Thrombus aspiration N=79	*p*
LVEF by Gated-SPECT	53.35±13.8	53.46±11.8	0.957[a]
Clinical follow up period	368(362-397)	367(188-391)	0.138[c]
Clinical end-points, n (%):			
Cardiac death	3(4)	0(0)	0.080[b]
All-cause death	5(6)	0(0)	0.023[b]
Re-infarction	2(3)	0(0)	0.155[b]
Cardiac death/re-infarction	4(5)	0(0)	0.043[b]
TVR	3(4)	5(6)	0.719[b]
TLR	4(5)	2(2)	0.405[b]
MACE	10(13)	7(9)	0.441[b]

Data are presented as mean ± standard deviation, number (%) of patients or median (Interquartile range).
LVEF, left ventricular ejection fraction; SPECT, Single Photon Emission Computed Tomography;
TVR, target vessel revascularization; TLR, target lesion revascularization; MACE, major adverse cardiac events.

[a] Compared using unpaired t test.

[b] Compared using Chi-square or Fisher exact test.

[c] Compared using Mann-Whitney U test.

Clinical outcomes

All patients were followed for a median of 367 days , 5 patients died in the conventional PCI group (including one in-hospital death) vs. 0 patients in the thrombectomy-facilitated PCI group (p= 0.023), three (4%) of those deaths were cardiac (p=0.080). The 2 non-cardiac deaths were due to hepatic failure and terminal renal failure. Three (4%) patients underwent a target vessel revascularization in the conventional PCI group vs. 5(6%) patients in the thrombectomy-facilitated group (p= 0.719). Target lesion revascularization occurred in 4(5%) patients in the conventional PCI group vs. 2(2%) patients in the thrombectomy-facilitated group (p= 0.405). Recurrent myocardial infarction occurred in 2 patients in the conventional PCI group vs. 0 patients in the thrombectomy-facilitated group (p= 0.155). Overall MACE occurred in 10(13%) patients in the conventional PCI group vs. 7(9%) in the thrombectomy-facilitated group (p= 0.441) (Table 4).The Kaplan-Meier curves showed that allocation to thrombectomy was associated with a significant reduction in 1-year all-cause mortality (log-rank p= 0.032) ;(Figure 2), and a trend towards a reduction of the combined endpoint of cardiac death or reinfarction (log-rank p= 0.056); (Figure 3).

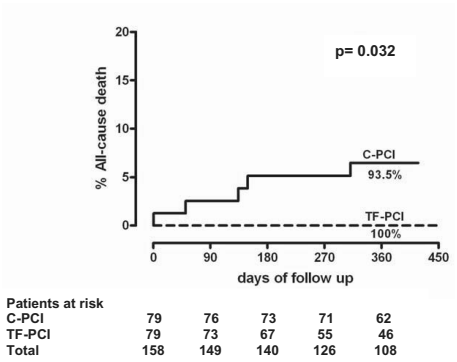

Figure 2: Kaplan-Meier 12 month cumulative event free survival from the endpoint of all-cause death; TF-PCI: Thrombectomy-facilitated PCI group, C-PCI: conventional PCI group.

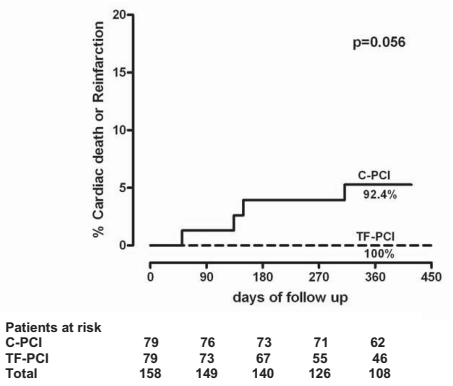

Figure 3: Kaplan-Meier 12 month cumulative event free survival from the combined endpoint of cardiac death or reinfarction. TF-PCI: Thrombectomy-facilitated PCI group, C-PCI: conventional PCI group.

DISCUSSION

The main findings of this study are: 1) A strategy of thrombus aspiration before stenting during primary PCI among patients treated with early abciximab was associated with a higher rate of complete ST-segment resolution (≥ 70%) within 90 min post-PCI, 2) Among patients with high thrombus grades, thrombus aspiration was associated with less distal embolization, 3) Thrombus aspiration was associated with a lower incidence of all-cause mortality, and a trend towards a lower incidence of combined end-point of cardiac death or reinfarction through a 1-year median clinical follow up. TVR, TLR and overall MACE were similar in both groups.

Unlike the TAPAS trial[16], where abciximab was administered during the procedure of PPCI, our study provides a unique experience of the adjunctive influence of thrombus aspiration to early abciximab administration before PPCI. In the ATTEMPT study[18], Burzotta and colleagues have interestingly shown that the benefit of thrombectomy was more evident in patients who received GPIIb,IIIa-inhibitors thus suggesting a possible additive benefit of thrombectomy in patients treated with GPIIb,IIIa-inhibitors. It might be speculated that pharmacological and mechanical thrombus remodeling are synergic to obtain the best myocardial reperfusion and, consequently, the best clinical outcome. Indeed, in the ATTEMPT study, patients treated by both thrombectomy and GPIIb,IIIa-inhibitors had the lowest mortality rate, those who had none of these treatments had the highest mortality rate, while patients receiving only one of these therapies exhibiting intermediate outcome. On the other hand, in the VAMPIRE trial[30], where GP IIb,IIIa receptor antagonists were not used at all, patients presenting late after STEMI (>6 hours after symptoms) appeared to benefit the most from thrombectomy,

suggesting that the use of GP IIb,IIIa receptor antagonists would have influenced the results. In our study, patients received abciximab prior to PCI, where abciximab was started before the arrival to the hospital. The benefits of this has been investigated in previous randomized clinical trials (RCTs)[7, 8, 10-12], and in the study conducted by Hassan et al[9] in the context of the MISSION! protocol, where it has been found that very early administration of abciximab (in-ambulance) significantly improves early reperfusion in STEMI patients treated with PPCI, this was also reflected clinically with smaller infarct size, improved LV function and a lower risk of heart failure on follow up. This may explain why some of our study outcomes including enzymatic infarct size, LVEF, and some of the clinical end-points did not differ between the 2 groups, as it is likely that the early abciximab administration supersedes the influence of thrombectomy catheter.

Procedural and angiographic characteristics

In the current study there was a significantly higher rate of direct stenting among the thrombectomy-facilitated group, a finding which is consistent with other randomized controlled trials[13, 14, 16, 31-35].This can be explained by the fact that thrombus aspiration establishes a better antegrade coronary flow which allows selection and placement of a stent of appropriate length and diameter without the need for further balloon predilatation. The overall rate of distal embolization was not significantly different between both groups. However, limiting the analysis to patients with high thrombus grade (grades 4 and 5), showed a significantly higher rate of distal embolization in the conventional PCI group. This was comparable to the results of the REMEDIA trial, where the overall distal embolization was not significantly different between the studied groups. However, a subgroup analysis showed greater angiographic and electrocardiographic reperfusion benefit with thrombus aspiration among patients with higher thrombus scores[36]. Different studies showed variable results regarding post-PCI distal embolization. Despite its favorable procedural and clinical outcomes, the TAPAS trial showed no difference in the rates of distal embolization between conventional PCI and thrombus aspiration groups[16]. On the other hand, two large meta-analyses showed lower rates of distal embolization in the thrombus aspiration group[37, 38].

ST-segment resolution

The effect of manual thrombus aspiration on the surrogate markers of myocardial reperfusion has been widely discussed in many studies. ST-segment resolution post-PCI is one of the most widely used and assessed markers. In our study there was a significantly higher rate of complete ST-segment resolution within 90 min in the thrombectomy-facilitated PCI group. This outcome is in accordance with some previous randomized controlled trials (RCTs)[14, 16, 32, 35, 36, 39, 40], and two recent large meta-analyses[38, 41]. On the other hand, some other RCTs revealed no significant difference in the rate of ST-segment resolution among both randomized groups[13, 30, 31, 34, 42].

Enzymatic infarct size

In our study there was no significant difference between both study groups regarding the enzymatic infarct size as estimated by peak levels of CK and Tn-T. Several trials assessing thrombus aspiration devices measured infarct size using biochemical markers with variable results. The largest study published to date, using the Export catheter system, the TAPAS trial, also showed no difference in peak CK and CKMB levels between groups with and without thrombus aspiration[16]. The same was also noted in the EXPIRIA trial[14]. On the contrary, it has been noted by Kaltoft and colleagues in their randomized trial that peak Tn-T was significantly higher in the thrombus aspiration group[42], a result that has also been reported in the randomized trial by Anderson and colleagues[43].

Left ventricular ejection fraction (LVEF)

There is a variety of conflicting data about the effect of thrombus aspiration on the infarct size which is the best surrogate end point for the assessment of new therapeutic tools in the setting of acute myocardial infarction[44, 45], and which is reflected by improved LV systolic function. In our study there was no benefit in terms of LVEF after thrombus aspiration, which is consistent with some previous trials[14, 30-32, 34, 42, 43, 46]. Other trials showed different results from our study[39, 47].

Clinical follow-up

In our study clinical data of the patients were available for a relatively long follow-up period (around 1 year), revealing that allocation to export aspiration thrombectomy was associated with lower incidence of all-cause mortality, in accordance with the findings of the 2 large RCTs using the export catheter; TAPAS[16] and EXPIRIA[14], the meta-analysis conducted by Bavry and colleagues[41], and the large patient-data pooled analysis ;ATTEMPT study[18]. In our study also there was a trend towards lower incidence of the combined end-points of cardiac death or re-infarction, in agreement with TAPAS trial[16] and ATTEMPT study[18]. On the other hand, the incidence of cardiac death in our study was not different between both groups, unlike the findings in the TAPAS[16] and EXPIRIA[14] trials; however the large meta-analysis presented by Bavry et al[41], as well as the ATTEMPT study[18] only showed benefits in terms of all-cause mortality and not in cardiac mortality, moreover in the TAPAS trial[16] analysis of cardiac death after 30 days showed no significant difference between export aspiration group and conventional PCI group. Our study, in consistence with the TAPAS trial[16], showed no difference between both groups regarding TVR/TLR, suggesting that thrombus aspiration has no influence on neointima hyperplasia.

LIMITATIONS

Our study is a single-center, non-randomized, prospective study. However, we tried to overcome this limitation by taking two groups of consecutive patients within the same time period, who were comparable regarding the baseline clinical and procedural characteristics. All patients were submitted to the fixed MISSION! protocol throughout the study period. This is a rigorously standardized protocol concerning pre-, peri-, and post-PPCI treatment up to 1 year[19, 20], so it is unlikely that procedural changes over time would have influenced the outcome.

In our study, there was a higher tendency to use the thrombus aspiration catheter in patients with higher thrombus grades, which represents a drawback due to the bias introduced. However, adjusting for thrombus grade among other covariates/confounders during the analysis of ST-segment resolution, cardiac enzymes and LVEF through multivariate regression models showed no significant change in these outcomes among the study groups. Moreover, in our study there was comparable baseline TIMI flow rate between both groups (TIMI flow 0-1 was 70% in the conventional PCI group vs. 68% in the thrombectomy- facilitated PCI group).

Better techniques are required to analyze the thrombus burden, especially with the fact that most of the patients are presented with totally occluded infarct-related artery on the initial angiography which limits the analysis of the thrombus burden; most of those patients subtend large thrombus burden but still some do not.

CONCLUSION

Among STEMI patients treated with PPCI and receiving early (in-ambulance) abciximab, it appears that the adjunctive use of manual thrombectomy significantly improves post-procedural ST-segment resolution, decreases distal embolization and may be associated with a lower clinical event rate. Therefore, although no benefit was observed regarding the enzymatic infarct size or LV function as assessed by Gated-SPECT, it appears that a selective strategy of thrombus aspiration still has an additive benefit, even with early abciximab administration. This needs further confirmation in appropriately powered randomized trials.

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Chapter 3

Pre-infarction angina predicts thrombus burden in patients admitted for ST-segment elevation myocardial infarction

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ABSTRACT

Background High thrombotic burden, subsequent distal embolization and myocardial no-reflow remain a big obstacle which may negate the benefits of urgent coronary revascularization in patients with ST-elevation myocardial infarction (STEMI). We aimed at assessing the predictors of (1) thrombus grade in patients undergoing primary percutaneous coronary intervention (PPCI), and (2) infarct size, in order to optimize therapy to reduce thrombus burden.

Methods One-hundred and fifty-three consecutive patients presenting with STEMI and undergoing PPCI were included. Thrombus was evaluated on angiography and scored according to the TIMI study group score. Next, patients were categorized into two groups having either high thrombus grade (HTG; score 4-5) or low thrombus grade (LTG; score 1-3). We evaluated predictors of angiographic thrombus grade among a number of clinical, angiographic and laboratory data. We also assessed infarct size and scintigraphic left ventricular ejection fraction (LVEF) at 3 months in both patient groups.

Results Ninety-four patients (58±11 y, 75% males) presented with HTG, whereas 59 patients (58±12 y, 78% males) presented with LTG. Pre-infarction angina (PIA) was more frequently encountered in the LTG group than in the HTG group (25% vs. 10%, p=0.009). Pre-procedural TIMI flow was significantly lower in the HTG group (p<0.001), and thrombosuction was more frequently applied in the HTG group (p<0.001). Absence of PIA (OR=0.29, 95% CI=0.11-0.75, p=0.01) and proximal culprit lesion (OR=2.10, 95% CI=1.02-4.36, p=0.04) were the only independent predictors of HTG. HTG proved an independent predictor of higher peak levels of CK (p<0.001) and troponin-T (p<0.001), as well as lower LVEF (p=0.05) along with male gender and absence of prior statin therapy.

Conclusion Absence of PIA and proximal culprit lesions are associated with higher thrombus grade. Higher thrombus grade is associated with larger infarct size and slightly worse LV function. This may have clinical implications in planning strategies, particularly regarding pharmacotherapy, that aim to decrease thrombus burden prior to stent implantation.

Keywords: ST-elevation myocardial infarction, Primary percutaneous coronary intervention, Pre-infarction angina, Thrombus grade, TIMI flow, Infarct size

INTRODUCTION

Primary percutaneous coronary intervention (PPCI) for patients with ST-segment elevation myocardial infarction (STEMI) aims at early restoration of patency and adequate blood flow both in the epicardial and in the microvascular coronary circulation. However, despite adequate epicardial patency many patients fail to recover sustained myocardial perfusion due to microvascular obstruction[1, 2], which carries a prognostic indication of a poor outcome[3, 4].

A high thrombotic grade has been shown to predict distal embolization, and subsequent microvascular obstruction, thus prompting the development of strategies aimed at decreasing thrombus grade before stent deployment such as thrombus aspiration[5] and use of glycoprotein (GP) IIb/IIIa receptor antagonists[6, 7].

Pre-infarction angina (PIA) occurring shortly before the onset of acute myocardial infarction (AMI) has a cardioprotective effect by the mechanism of ischemic preconditioning[8-10], i.e. the phenomenon by which brief episodes of ischemia increase the tolerance of the heart to a subsequent major ischemic insult. Moreover, PIA has been shown to preserve microvascular function after reperfusion[11].

It has been shown that patients with AMI who have intermittent infarct-related pain or unstable angina in the seven days preceding the infarction have faster coronary artery reperfusion and smaller infarcts after thrombolytic therapy than patients without pre-infarction angina, suggesting two different types of thrombus growth and thus different responses to thrombolytic therapy[12]. During PPCI variable grades of thrombus formation are observed that can only be detected on the initial angiography. Ideally it will be possible to predict the thrombus grade clinically or through rapid laboratory investigations prior to PCI procedure. This may help to plan for an earlier and enhanced pre-hospital management using adjunctive pharmacotherapy, particularly with the newly emerging rapid-acting reversible antiplatelet agents which are currently under intense research and are expected to have higher efficacy and safety profiles than the existing treatments.

In this study we aimed at assessing factors predicting angiographic thrombotic grade in a consecutive series of patients presenting with STEMI treated by PPCI. In addition, the subsequent infarct size and left ventricular function were assessed among patients with different thrombus grades.

METHODS

Study population

We studied 158 consecutive patients with a diagnosis of STEMI, having clear evidence of thrombus on the initial angiography who underwent PPCI and received abciximab prior to PPCI. Patients were selected from an ongoing registry (operational since 2004) in Leiden

University Medical Center, which evaluates the effects of an all-phase integrated AMI care program (MISSION!) on short- and long-term outcomes[13,14]. Diagnosis of STEMI was made on the basis of typical electrocardiographic changes with clinical symptoms associated with elevation of cardiac biomarkers. All patients were treated according to the institutional AMI protocol (MISSION!). The MISSION! Protocol is a rather stringent, rigorously standardized protocol. It comprises a well-organized pre-hospital, in-hospital and outpatient clinical framework for decision making and treatment, so it is unlikely that procedural changes over time would have influenced the outcomes. Clinical data were prospectively entered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center) and retrospectively analyzed[13]. The tertiary center provides a round-the-clock service of PPCI with highly experienced PCI physicians and dedicated nurses.

Medication

All patients received abciximab (Centocor B.V., Leiden, The Netherlands) as a bolus injection of 0.25 mg/ kg body weight, followed by 0.125 mcg/kg/min with a maximum of 10 mcg/min as a continuous infusion for 12 hr. Abciximab administration started before PCI according to MISSION! Protocol[13]. Furthermore all patients received an equivalent of 300 mg of acetylsalicylic acid, 600 mg clopidogrel as a loading dose before PCI and heparin given as a bolus of 5000 IU at the start of the PCI procedure. After the procedure, all patients received aspirin (75 mg/ day) indefinitely and clopidogrel (75 mg/day) for one year. Other medications, including b-blockers, ACE-inhibitors, nitrates, and statins, were prescribed according to MISSION! protocol.

Invasive procedure and angiographic evaluation

All PPCI were performed through a 6F femoral sheath. Patients underwent PPCI and stenting of the infarct-related artery according to standard techniques.

The choice of stent (bare-metal stent or drug-eluting stent) was left to the operator's discretion. Direct stenting was performed only in cases presenting clear views of the arterial lesion with adequate flow. Otherwise, the patient was subjected to balloon angioplasty and stenting was done subsequently. Thrombectomy was frequently, but not exclusively, performed when high thrombus burden was observed at the initial angiographic image of the target vessel. Thrombus score was graded as previously described by the TIMI Study Group[6, 15]. Briefly, in TIMI thrombus grade 0, no cineangiographic characteristics of thrombus are present; in TIMI thrombus grade 1, possible thrombus is present with such 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 TIMI thrombus grade 2, there is definite thrombus, with the greatest dimensions ≤ ½ the vessel diameter; in TIMI thrombus grade 3, there is definite thrombus but with greatest linear dimension > ½ but < 2 vessel diameter; in TIMI thrombus grade 4, there is definite thrombus, with the largest dimension ≥ 2 vessel diameters; and in TIMI thrombus grade 5, there is total occlusion.

We further categorized the thrombus score into two overall grades: a high thrombus grade (grades 4 and 5), and a low thrombus grade (grades 1-3) (Figure 1). We decided to use this cut-off value in line with previous studies[16-18] that showed prognostic value of this cut off. The inter-observer agreement was calculated with weighted Kappa statistics and showed good agreement (κ= 0.92, p<0.001). Coronary flow was graded according to Thrombolysis In Myocardial Infarction (TIMI) criteria[19]. TIMI flow grade was evaluated at baseline and after the PCI procedure. Procedural success was defined as residual stenosis <20% and TIMI flow grade 3. The coronary angiograms were reviewed off-line by two independent interventional cardiologists who were blinded to the clinical data.

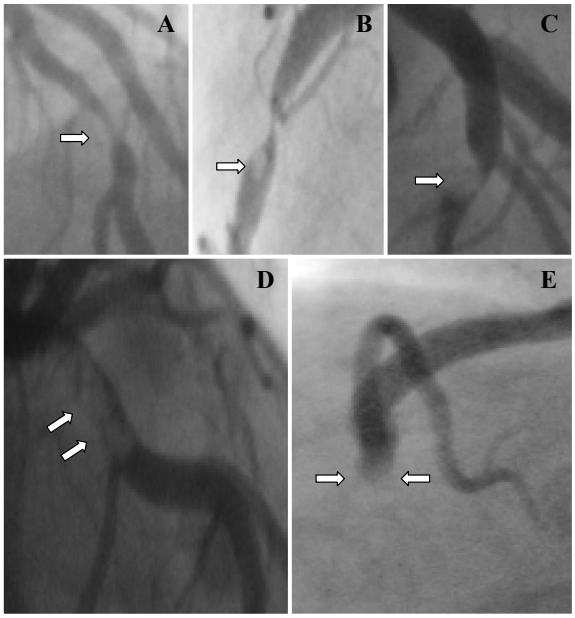

Figure 1: Thrombus (white arrows) graded according to TIMI working group classification: A: Thrombus grade 1; B: Thrombus grade 2; C: Thrombus grade 3; D: Thrombus grade 4; and E: Thrombus grade 5. We further scored the thrombus into two overall grades: a high thrombus grade (grades 4 and 5), and a low thrombus grade (grades 1-3).

Laboratory investigations

Cardiac troponin-T concentration in plasma was measured on a third generation Elecsys 2010 analyzer (Roche Diagnostics, Almere, the Netherlands). Creatine kinase (CK) activity in plasma was measured on a Roche Hitachi Modular P800 analyzer (Roche Diagnostics). According to MISSION! Protocol[13] blood samples were collected at admission and every 6 h in the first 48 h after PPCI. Subsequently these levels were determined every day up to discharge, unless clinical events prompted repeat measurements. Peak levels of CK and troponin-T in plasma were calculated as a measure of infarct size in each patient by an investigator blinded to the assigned treatment.

LVEF assessment by gated-SPECT

According to the MISSION! Protocol[13] all included patients were enrolled for a myocardial perfusion study at 90 days post-PPCI. An ECG gated-single photon emission computed tomography (SPECT) acquisition at rest using intravenous ^{99m}Technetium-Tetrofosmin (MYOVIEW, Amersham, Buckinghamshire, UK) was used to measure the left ventricular ejection fraction (LVEF) 90 days after PPCI. LVEF was calculated using an automated and validated method (QGS software, version 2.0; Cedars-Sinai Medical Center, Los Angeles, CA, USA). Detailed methods are described elsewhere[20]. In patients in whom gated-SPECT could not be performed due to technical difficulties, LVEF was estimated by echocardiographic biplane method. LVEF assessment was done by an investigator blinded to the assigned treatment.

Definition of pre-infarction angina

Pre-infarction angina (PIA) was defined as at least one episode of typical chest or left arm or jaw pain, either at rest or during exercise, less than 7 days before STEMI. The presence of PIA was diagnosed by a physician, blinded to the results of the PCI, from detailed clinical history taken before PCI.

Tested variables

We evaluated predictors of thrombus grade among different clinical, angiographic and laboratory data. Clinical data included age, gender, traditional risk factors, PIA, and symptom to balloon time. Prior pharmacotherapy at admission was also recorded including aspirin, clopidogrel, statins, β-blockers (BB), angiotensin converting enzymes inhibitors or angiotensin receptor blockers (ACEI/ARBs). Among laboratory data plasma troponin-T levels at admission were recorded. Angiographic data included the culprit artery, location of culprit lesion, and number of diseased vessels.

Statistical analysis

Categorical variables were compared using the X^2 test or Fisher's exact test. Continuous normally distributed data were tested by Student's t-test or in the case of a non-Gaussian distribution by a nonparametric test for independent samples (Mann Whitney *U*-test).The inter-observer agreements were calculated using weighted Kappa statistics. Variables that at univariate analysis had a p value ≤ 0.15 were included in a multiple logistic regression model with the 2-categories thrombus grade as the outcome. Infarct size as assessed by peak CK and peak troponin-T (after logarithmic transformation), as well as 3-months LVEF were analyzed in a multivariate linear regression model among different potentially relevant variables. Correlation between the outcomes was tested using Spearman's correlation. Data were expressed as mean ± SD or as median + inter-quartile range for continuous variables according to the data distribution; categorical variables were expressed as percentages. All analyses were performed using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Hundred and fifty-eight consecutive patients were selected for this evaluation. From this group, 5 patients were excluded due to incomplete data sets, the study population thus comprised 153 patients; 94 had high thrombus grade (HTG), and 59 had low thrombus grade (LTG). Baseline clinical and angiographic characteristics of the studied population are presented in Tables 1 and 2, respectively. The rate of PIA was significantly higher in the LTG group (25% vs. 10%, p=0.009) than in the HTG group (Figure 2). Among the angiographic characteristics, there was less initial TIMI flow grade in the HTG group (p<0.001), and higher rate of using a thrombectomy catheter in the HTG group (p<0.001) than in the LTG group. HTG tended to be more frequently encountered in proximal culprit lesions (54% vs. 39%, p=0.06).

Table 1. Baseline clinical characteristics of the study groups

	HTG N=94	LTG N=59	*p*
Age in years	58.4±11.5	57.6±12.0	0.68[a]
Male, n (%)	70(74.5)	46(78)	0.62[b]
Medical History, n (%)			
Hypertension	28(29.8)	23(39)	0.24[b]
Hyperlipidemia	21(22.3)	19(32.2)	0.17[b]
Smoking	55(58.5)	28(47.5)	0.18[b]
Family history	43(45.7)	24(40.7)	0.53[b]
Diabetes mellitus	6(6.4)	8(13.6)	0.16[b]
Previous MI	10(10.6)	5(8.5)	0.66[b]
Previous PCI	6(6.4)	5(8.5)	0.62[b]
Previous CABG	4(4.3)	1(1.7)	0.38[b]
Symptoms to balloon (min)	143(95-226)	135(88-225)	0.47[c]
Abciximab to ballon (min)	37(29-48)	36(24-60)	0.95[c]
Pre-infarction angina	9(9.6)	15(25.4)	0.009[b]
Previous aspirin	16(17)	9(15.3)	0.77[b]
Previous clopidogrel	1(1.1)	0(0)	0.42[b]
Previous statins	15(16)	9(15.3)	0.91[b]

Data are presented as mean ± standard deviation, number (%) of patients or median (Interquartile range). MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

[a] Compared using unpaired t test.

[b] Compared using Chi-square or Fisher exact test.

[c] Compared using Mann-Whitney U test.

Table 2. Angiographic and peri-procedural characteristics of the study groups

	HTG N=94	LTG N=59	*p*
Infarct related artery, n (%)			0.1[b]
Left main artery	3(3.2)	0(0)	
Left anterior descending artery	33(35.1)	24(40.7)	
Circumflex artery	9(9.6)	12(20.3)	
Right coronary artery	49(52.1)	23(39)	
Diseased vessels, n (%)			0.18[b]
1-vessel	57(60.6)	31(52.5)	
2-vessel	33(35.1)	21(35.6)	
3-vessel	4(4.3)	7(11.9)	
Proximal culprit lesion, n (%)	51(54.3)	23(39)	0.06[b]
Abciximab	94(100)	58(98.3)	0.9[b]
Initial TIMI flow grade, n (%)			<0.001[b]
0	61(64.9)	16(27.1)	
1	16(17)	12(20.3)	
2	14(14.9)	16(27.1)	
3	3(3.2)	15(25.4)	
Final TIMI flow grade, n (%)			0.16[b]
1	2(2.1)	0(0)	
2	18(19.1)	6(10.2)	
3	74(78.7)	53(89.8)	
Aspiration thrombectomy	65(69.1)	13(22)	<0.001[b]
Drug eluting stents, n (%)	45(57)	52(70)	0.1[b]
Stent number, n (%)			0.25[b]
0	4(4.2)	0(0)	
1	59(62.8)	37(62.7)	
>1	31(33)	22(37.3)	
Predilatation, n (%)	66(70.2)	46(78)	0.29[b]

Data are presented as mean ± standard deviation, number (%) of patients.
TIMI, Thrombolysis In Myocardial Infarction.
[a] Compared using unpaired t test.
[b] Compared using Chi-square or Fisher exact test.

Predictors of high thrombus grade (HTG)

Univariate and multivariate logistic regression analyses with thrombus grade as outcome revealed that only absence of PIA (OR=0.29, 95% CI=0.11-0.75, p=0.01) and presence of a proximal culprit lesion (OR=2.10, 95% CI=1.02-4.36, p=0.04) were independent predictors of HTG (Table 3).

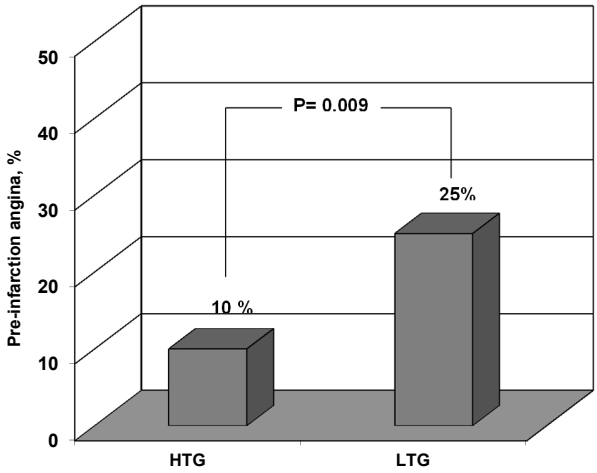

Figure 2: Rate of pre-infarction angina among the two categories of thrombus grade. HTG, high thrombus grade; LTG, low thrombus grade.

Infarct size

Peak levels of CK and troponin-T in plasma were significantly higher in the HTG group than in the LTG group (p<0.001 for both) (Table 4). Among the potentially relevant variables including age, sex, symptom to balloon time, hypertension, current smoking, hypercholesterolemia, diabetes mellitus, PIA, prior drug therapy, number of vessels diseased, culprit artery, proximal culprit lesion, thrombus grade and use of thrombosuction, HTG predicted high peak levels of CK (*B*= -1.0, 95% CI= -1.4 – -0.6, p<0.001) and troponin-T (*B*= -1.1, 95% CI= -1.6 – -0.6, p<0.001).

Scintigraphic LVEF at 3 months

LVEF was not significantly different between both groups of thrombus grade (Table 4). However, when corrected for the aforementioned factors in a multivariate linear regression model, it was found that HTG predicted a slightly worse LVEF (*B*=4.9, 95% CI= -0.06 – 10, p=0.05), along with male gender and absence of prior statin therapy. The outcomes were moderately correlated (r= -0.45, p<0.0001 for LVEF and peak CK, and r= -0.5, p<0.0001 for LVEF and peak TnT)

DISCUSSION

Key findings of the present study were: 1) the absence of PIA and a proximal location of the culprit lesion independently predicted higher angiographic thrombus grade, 2) Higher thrombus grade was associated with significantly higher infarct size as assessed by peak CK

Table 3. Univariate and multivariate logistic regression analyses with thrombus grade as end-point

Predictors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Male gender	0.82	0.38- 1.78	0.62			
Age	1.01	0.97-1.03	0.68			
Symptom to balloon time	1.00	0.99- 1.00	0.72			
Hypertension	1.51	0.76- 2.99	0.24			
Hypercholesterolemia	1.65	0.79- 3.43	0.17			
Current smoking	0.64	0.33- 1.23	0.18			
Family history	0.81	0.42- 1.57	0.54			
Diabetes Mellitus	2.30	0.76- 7.00	0.14	2.61	0.81-8.39	0.11
Pre-infarction angina	0.31	0.13- 0.77	0.01	0.29	0.11-0.75	0.01
Prior aspirin therapy	0.87	0.36- 2.14	0.77			
Prior statin therapy	0.95	0.39- 2.33	0.91			
Prior β-blocker therapy	1.29	0.33- 5.02	0.71			
Prior ACEI/ARB therapy	1.54	0.70- 3.39	0.28			
Infarct related artery † :			0.12			0.17
LAD (including LM)	0.70	0.34-1.44	0.34	0.62	0.29-1.34	0.22
CX	0.35	0.13-0.95	0.04	0.39	0.14-1.11	0.08
Number of diseased vessels *:			0.21			
2-vessel disease	0.85	0.42-1.72	0.66			
3-vessel disease	0.31	0.08-1.14	0.08			
Proximal culprit lesion	1.86	0.96- 3.60	0.06	2.10	1.02- 4.36	0.04
Admission troponin-T	1.15	0.59- 2.24	0.67			

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; LAD, left anterior descending; CX, circumflex.
† Right coronary artery (RCA) as reference.
* 1-vessel disease as reference

Table 4. Peak CK and troponin-T levels and 3-months LVEF in the study groups.

	HTG N=94	LTG N=59	*p*
Peak CK (U/L)	2435±218	1527±234	<0.001[a]
Peak troponin-T (μg/L)	6.5±0.7	3.8±0.7	<0.001[a]
LVEF at 3 months*	52±13	54±12	P=0.4[b]

Data are presented as mean ± standard deviation.
CK, creatine kinase; LVEF, left ventricular ejection fraction;
HTG, high thrombus grade; LTG, low thrombus grade.
[a] Compared using Mann-Whitney *U* test.
[b] Compared using unpaired *t*-test.
* Computed By Myoview, except in 11% of the patients,where 2-D echocardiographic biplane method was utilized.

and troponin-T levels in plasma, as well as lower LVEF at 3 months along with male gender and absence of prior statin therapy.

The issue of identifying predictors of thrombus grade has gained wide interest from the time PPCI was established as the gold standard reperfusion strategy for STEMI. The presence of large thrombus burden has been found to be an independent predictor of major adverse cardiac events (MACE) and infarct-related artery stent thrombosis in patients treated with drug-eluting stents for STEMI[21, 22].

Cardioprotective effect of PIA

PIA is associated with improved prognosis after AMI[9, 12, 23, 24]. Several mechanisms may explain this protective effect of PIA on myocardial reperfusion, such as myocardial ischemic preconditioning[9, 24, 25], enhanced collateral circulation towards the ischemic myocardium[26], and increased sensitivity to thrombolysis[12].

Recently, a new cardioprotective mechanism of PIA was proposed, which is the inhibition of microvascular obstruction phenomenon[27-29]. This was supported by a study conducted by Jesel *et al.*[30], who showed that absence of PIA was the only independent predictor of MRI-detected microvascular obstruction. This provides a new hypothetical mechanism for the clinical benefit of PIA, suggesting that PIA attenuates the development of the no-reflow phenomenon, not only through microvascular ischemic preconditioning[31], but also through limiting the extent of microvascular obstruction induced by distal embolization from large thrombus burden. This has to be further elucidated in larger studies reinforced by IVUS or OCT on one hand, and MRI or myocardial contrast echocardiography on the other for relating the culprit plaque morphology and microvascular obstruction extent respectively with PIA.

Angiographic thrombus burden

In 2010, Sianos et al[18] published a score for stratifying thrombus burden in STEMI patients. It was actually a modification from the established TIMI study group score[6], where they reclassified patients with Thrombus grade 5 into the other categories. They did that either after crossing with a wire or predilating with a balloon. In our study we adopted the original TIMI classification based on the fact that wire crossing and balloon inflation may alter thrombus grade, by inducing distal embolization. TIMI study group was precise in defining thrombus grade 5 not only on basis of total occlusion, but also based on the shape of this total occlusion, which ended abruptly, with a squared-off or an upstream convex termination, creating a stump or arterial cul-de-sac from which dye washout was delayed.

PIA and thrombus burden

Our study is the first to address the relation between PIA and thrombus grade in patients with STEMI. Previous studies have shown the benefits of PIA on surrogate markers of reperfusion[29], as well as on clinical outcomes[32].

Using IVUS, Higashikuni *et al.*[33] found that the culprit plaques of patients without PIA contained larger amount of necrotic core component than patients with PIA, whereas the plaques of patients with PIA consisted of larger amounts of the fibrofatty component than the plaques of patients without PIA. Moreover, they found more plaque rupture among patients without PIA than in those with PIA. This difference may explain the difference in thrombus burden and consequently the difference in clinical outcomes between both groups of patients. The necrotic core component was shown to be the most thrombogenic component in human atherosclerotic plaques[34, 35]. Exposure of the necrotic core component (plaque rupture) leads to exposure of Tissue Factor, thereby increasing thrombogenicity and abrupt thrombus formation. Thus, necrotic core-rich plaques may produce large thrombus burden, which may often result in sudden onset of AMI without PIA. Previously, Kojima *et al.*[36] demonstrated that patients with PIA were more likely to have plaque erosion as a substrate rather than plaque rupture, with subsequent exposure of the proteoglycan-rich matrix without a large lipid core; this has less potent thrombogenicity than plaques with lipid-rich core and consequently leads to less thrombus burden. In a study by Capone *et al.*[37], the incidence of thrombus by angiographic analysis was higher in patients with recent onset of rest angina than in those with slowly progressive PIA.

Proximal location of culprit lesion and thrombus burden

The present study revealed proximal location of the culprit artery as an independent predictor of HTG. To our knowledge, there was one previous study which has addressed this issue[16], revealing no predictive role for the location of the culprit lesion on the thrombus grade. However, in their study they analyzed the thrombus in the majority of the cases after the insertion of a 6F perfusion catheter, in contrast to our study in which the thrombus was analyzed and graded on the initial angiogram.

The PAMI study[38] showed that patients with proximal culprits had worse angiographic features with higher rates of initial TIMI 0-1 flow, and consequently worse in-hospital clinical outcomes despite rapid and successful reperfusion in the vast majority, thus arguing for the inclusion of proximal culprit lesion in the angiographic prognostication of AMI patients.

Coronary thromboses leading to AMI are distributed in a nonuniform manner. They tend to cluster within the proximal one-third of the coronary arteries and the likelihood of clinically significant plaque rupture decreases by 13–30% for each 10 mm distally from the coronary artery ostia[39, 40].

Thrombus burden and infarct size

Our study showed that HTG was a predictor of larger infarct size and when corrected for other relevant risk factors, HTG was associated with a lower LVEF.

Although no previous study has related thrombus grade to infarct size or LVEF, previous studies have shown that distal embolization and the subsequent no-reflow, which is partly

related to higher thrombus burden, were associated with larger infarct size, LV remodeling, and depressed LV function[41, 42].

PIA: a predictor of infarct size?

Although the myocardial protective benefits of PIA have been established in previous studies[10, 11, 43], we could not reproduce this finding. A possible explanation is that a study with a relatively small sample size (only 24 patients had PIA) lacks statistical power. In a previous study[44], it has been concluded that the protective effect of PIA in AMI is overwhelmed by the protective effects of complete revascularization provided by PPCI.

Future clinical implications

The present study argues for the consideration of PIA as a clinical predictor of thrombus burden in STEMI patients, thus setting the basis for implementing strategies aiming to decrease thrombus grade before stent implantation such as thrombus aspiration and the use of platelet glycoprotein IIb/IIIa antagonists in selected patients. Earlier administration of Gp IIb/IIIa antagonists results in higher pre-interventional TIMI flow with subsequently improved perfusion post-PCI[45-47], which in turn reflects less thrombus burden. Earlier Gp IIb/IIIa antagonists administration requires treatment in the pre-hospital setting, which for many dedicated primary PCI centers may pose substantial logistical obstacles. Therefore, the early administration of Gp IIb/IIIa antagonists could be limited to patients in whom high thrombus burden is predicted.

This may set a strategy for pre-hospital triage of STEMI patients receiving early pre-hospital antithrombotic treatment. Since high-dose clopidogrel administration takes 3–4 h to reach the top of inhibition of platelet aggregation[48], Gp IIb-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[49], should be strongly encouraged to identify a high risk population with thrombotic complications that largely outweigh the risk of bleeding complications, and in whom a selective strategy of pre-hospital/pre-PCI aggressive anti-thrombotic therapy is to be adopted.

Recently, a great deal of research has focused on development of new antiplatelet agents that could be administered orally or intravenously and, unlike the currently applied thienopyridines, could provide direct-acting reversible inhibition of the platelet P2Y12 receptor. New agents as "Cangrelor"[50-53] and "Elinogrel"[54, 55] are characterized by a rapid onset of action, more effective platelet inhibition, and favorable safety profile with rapid reversal of its antiplatelet effect post-infusion, thus allowing for surgery without a significant delay. Furthermore, "Vorapaxar" (SCH 530348)[56, 57] and "Atopaxar" (E5555)[58, 59] are orally administered agents that reversibly inhibit platelet protease activated receptor (PAR)-1, through which thrombin induces its effect on platelet aggregation, and thus, thrombus formation. This concept of rapidly acting and rapid reversibility of platelet inhibition could fuel further research about

the triage of pre-hospital treatment among STEMI patients with suspected high thrombotic burden.
We believe that the next step towards further optimization of care among STEMI patients is to improve pre-hospital triage, not only by diagnosing STEMI patients in the ambulance, but also starting early pre-hospital pharmacotherapy which necessitates the implementation of a risk/benefit scoring system. This scoring system should take in consideration clinical (as PIA) as well as rapid bed-side laboratory data (cardiac biomarkers), among others, to identify patients who would benefit most from early pre-hospital treatment.

LIMITATIONS

The study may have been limited by its observational design, and the relatively small sample size which may hinder the prognostic power. However, implementation of a stringent protocol for the study population (MISSION! protocol)[13] reinforces our results. No long-term clinical follow-up was performed. Therefore, a correlation between thrombus burden and clinical outcomes is lacking.
Owing to the small number of included population, and the retrospective nature of the study, we could not perform reliable testing of each single thrombus subgroup. However, Sianos et al[18] validated this categorization in a large cohort of 900 STEMI patients, and found that large thrombus (≥ twice the vessel diameter) independently predicted mortality and MACE.
Many factors can influence the angiographic assessment of thrombus burden (such as the TIMI flow, vessel size, culprit complex lesions with ulcers or intra-plaque dissections) that can confuse the analyst. More reliable methods to assess thrombus burden should be considered such as; the amount of aspirated thrombus, or thrombus assessed by optical coherence tomography.

CONCLUSION

PIA is associated with a decreased angiographic thrombus grade, whereas proximal culprit lesions are associated with higher thrombus grade. Higher thrombus grade was in turn associated with larger infarct size as well as slightly worse LV function. This may have clinical implications in planning strategies, particularly regarding pharmacotherapy, that aim to decrease thrombus burden prior to stent implantation, particularly in high risk patients without PIA.

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Chapter 4

Clinical performance of drug eluting stents with Biodegradable polymeric coating, a meta-analysis and systematic review

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ABSTRACT

Aim Different biodegradable-polymer drug eluting stents have not yet been systematically analysed. We sought to; 1) evaluate the risk of target lesion revascularisation (TLR) and definite stent thrombosis (DST) among different groups of biodegradable-polymer (BioPol) DES, and 2) to compare them with permanent polymer (PermPol) DES.

Methods and results We searched PubMed and relevant sources from January 2005 until October 2010. Inclusion criteria were (a) Implantation of a drug eluting stent with biodegradable polymer; (b) available follow-up data for at least one of the clinical endpoints (TLR/DST) at short term (30 days) and/or mid-term (one year). A total of 22 studies, including randomised and observational studies, with 8264 patients met the selection criteria; 9 studies (2042 patients) in whom biodegradable-polymer sirolimus eluting stents (BioPol-SES) were implanted, 8 studies (1731 patients) in whom biodegradable-polymer paclitaxel eluting stents (BioPol-PES) were implanted, and 7 studies (4491 patients) in whom biodegradable-polymer biolimus-A9 eluting stents (BioPol-BES) were implanted. At 30 days, there was a higher risk of DST (p=0.04) and subsequently TLR (p=0.006) in the BioPol-BES compared to BioPol-SES, with no significant difference in the other stent comparisons. At 1 year, there was higher risk of TLR in the BioPol-PES (p= 0.01), and the BioPol-SES (p=0.04) compared to BioPol-BES. One-year stent thrombosis was not statistically different between the studied groups (overall p= 0.2). In another analysis comprising 7 randomised trials comparing BioPol-DES (3778 patients) and PermPol-DES (3291 patients), the risks of TLR and stent thrombosis at 1 year were not significantly different (p= 0.5 for both).

Conclusion Performance of different BioPol-DES seems to vary from each other. The short and mid-term success rates may not be superimposable. Furthermore, they may not be necessarily better than PermPol-DES.

Keywords Meta-analysis, biodegradable-polymer drug eluting stents, permanent-polymer drug eluting stents, target lesion revascularization, definite stent thrombosis.

INTRODUCTION

Drug eluting stents (DES) represent a major breakthrough in the field of percutaneous coronary interventions (PCI), since they have dramatically reduced the need for repeated revascularization procedures[1, 2].

Along with the increasing number of patients receiving DES and the availability of long-term follow-up data, concern has arisen regarding the safety of these devices with the potential for increased inflammatory response and stent thrombosis which could have life-threatening consequences[3-5].

Polymers used for the delivery of antirestenotic agents have been accused for the development of late stent thrombosis. This is thought to be secondary to polymer-induced inflammatory reaction, with delayed healing and re-endothelialization of the DES[6]. Given these issues more focus has been placed upon developing bio-degradable polymers, which degrade over time, and therefore possibly eliminate the problems of polymer-induced inflammation.

In some cases, findings from pre-clinical studies can be misinterpreted, especially in cases where the drug may be toxic. The polymer may be blamed for the inflammation or excessive fibrin deposition and lack of endothelialization. Yet the difference in pharmacokinetics and anti-restenotic efficacy of the different drugs could also be held responsible for variation in clinical outcomes. Thus, a "polymer only" control is essential in distinguishing the culpability between polymer versus drug[7]. However, this is a control difficult to implement in clinical studies.

Various studies were conducted to test the clinical performance of a variety of biodegradable polymer-based stents eluting sirolimus (BioPol-SES), biolimus A9 (BioPol-BES) or paclitaxel (BioPol-PES).

The aims of the present meta-analysis were: 1) to compare the short term (1 month) and mid-term (1 year) performance of sirolimus, biolimus A9 and paclitaxel biodegradable-polymer DES and 2) to compare, where information was available, the 1-year performance of biodegradable-polymer DES (BioPol-DES) with permanent-polymer DES (PermPol-DES).

METHODS

Eligibility and search strategies

To be included in this meta-analysis, studies had to meet the following criteria: (a) Implantation of a drug eluting stent with biodegradable polymer; (b) available follow-up data for at least one of the clinical end-points at short term (30 days) and/or mid-term (up to one year). Studies dedicated to specific lesion subsets including; left main stenting, bifurcation lesions, chronic total occlusions, long lesions, in-stent restenosis and venous grafts were excluded.

We searched PubMed, Web of Science, and Embase (OVID) from January 2005 and onwards for studies on biodegradable DES. The PubMed search strategy was formulated as the AND-combination of 1) DES terms and 2) terms denoting biodegradable or permanent polymer as follows: 1) "Drug-Eluting Stents"[Mesh] OR DES[tiab] OR "drug eluting stent"[tiab] OR "drug eluting stents"[tiab] OR "drug eluted stent"[tiab] OR "drug eluted stents"[tiab] OR "drug coated stent"[tiab] OR "drug coated stents"[tiab]; 2) "biodegradable polymer"[tiab] OR "permanent polymer"[tiab] OR "nonbiodegradable polymer"[tiab] OR biodegradable[tiab] OR bioabsorbable[tiab] OR "durable polymer" OR ("Polymers"[Mesh] AND (biodegradable[tiab] OR bioabsorbable[tiab] OR permanent[tiab] OR nonbiodegradable[tiab])). This search strategy was translated to the corresponding vocabulary of Embase and Web of Science. Relevant websites (http://www.tctmd.com, www.europcr.com) were searched for pertinent abstracts and expert slide presentations. The search was kept updated until October 2010. No language restriction was applied.

Data abstraction

Two investigators (T.A.N.A. and S.C.B.) independently extracted all data, and disagreements were solved in consultation with a third investigator (J.W.M.P.). A number of 144 papers were identified from PubMed, 52 papers from Web of Science and 125 papers from EMBASE, and 4 additional clinical trials from relevant websites (total of 325 citations) (Figure 1). After reading the titles and abstracts, a total of 25 potentially relevant studies were initially identified from which 22 were eligible for inclusion.

Definitions and end-points

The clinical end-points of the study were the rates of target lesion revascularization (TLR) and definite stent thrombosis (DST) at 30 days and one year follow-up. Even in the few studies with follow-up more than one year only the data at one year were used.

TLR was defined as percutaneous or surgical revascularization of the target lesion. Definite stent thrombosis was defined, whenever available, according to the definition of the Academic Research Consortium[8].

Statistical analysis

For the comparison of the 3 biodegradable-polymer stent types (BioPol-SES, BioPol-PES and BioPol-BES), 20 studies provided one patient series and 2 studies provided two patient series. Since there were only two studies with two series, we analyzed the 24 patient series as independent studies. For each patient series we extracted from the publications the number of events (TLR or DST within 30 days or one year) and the corresponding number of patients. For each stent type, type of event and follow-up period the exact 95% confidence interval for a binomial proportion was calculated and depicted in a forest plot. If the observed proportion was zero, the one-sided 97.5% confidence interval was given. To compare

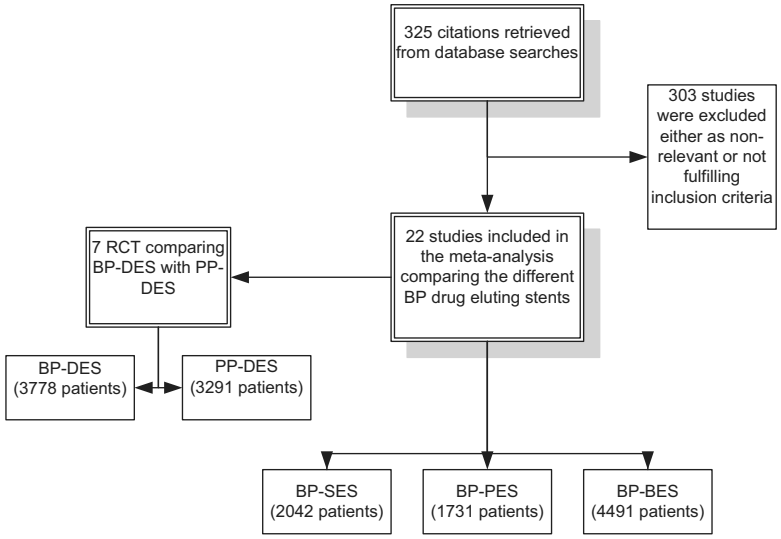

Figure 1: Flow diagram of the review process: Process of identification and selection of the studies for inclusion in the meta-analysis. BP; biodegradable polymer, PP; permanent polymer, SES; sirolimus eluting stents, PES; paclitaxel eluting stents; BES; biolimus eluting stents, DES; drug eluting stents.

the incidences of the different types of events between the different stent types, we used random effects meta-analysis. More specifically, we used random intercept logistic regression with two dummy variables representing the three stent types, as described in Stijnen et al[9]. This analysis assumes that the between studies variance was equal for the different stent types. In the analysis, the random effects take into account the possibility that there may be many differences between the patient populations of the different studies, influencing the risks of the considered endpoints. To adjust for multiple comparisons, we first tested at $\alpha=0.05$ the overall null hypothesis that all three stent types had equal incidence. If this test was significant, the three pair-wise tests were done at $\alpha=0.05$. For the incidence of TLR within 30 days, the estimate of the between studies variance was zero. In that case the analysis reduces to ordinary logistic regression and we used exact tests and confidence intervals for the odds ratios.

Seven studies comprised trials comparing BioPol-DES with PermPol-DES. To make forest plots, we calculated exact 95% confidence intervals for the odds ratio except for studies in which less than 2 events in total were observed. We used random effects meta-analysis to estimate and test the overall odds ratio across studies. Due to the scarcity of data at 30 days among the included studies, we decided to assess the events at 1 year only. Because of the small numbers of events in some of the studies, the hypergeometric-normal model as described in Stijnen et al was used[9].

All statistical analyses were performed using SAS statistical package version 9.1.3. The procedure NLMIXED was used for the random-effect meta-analysis.

Study Quality assessment

This meta-analysis was especially designed to extract data from various types of available studies: observational studies presenting data about BioPol-DES; randomized clinical trials (RCTs) in which different BioPol-DES are compared among each other, and RCTs in which BioPol-DES is compared with PermPol-DES. Only for the latter category, it was of interest to perform an RCT study quality assessment. We have used the *Delphi list* for the quality assessment of RCTs as described by Verhagen et al[10]. In short, the Delphi list allocates 'yes', 'no', or 'do not know' to a total number of nine questions. Quality of RCTs is defined as the likelihood of the trial design to generate unbiased results. When five or more questions are answered 'yes', the RCT is considered to have a low risk of bias. In a respective manner, RCTs may have unclear or high risk to cause bias.

RESULTS

Trials and study characteristics

A total of 22 studies[11-33] with a total of 8264 patients were included in this meta-analysis (table 1); 9 trials[11, 13, 14, 17, 21, 23-25, 30, 32] (2042 patients) with biodegradable polymer sirolimus eluting stents (BioPol-SES), 8 trials[12, 20, 22, 23, 27, 28, 31, 32] (1731 patients) with biodegradable polymer paclitaxel eluting stents (BioPol-PES) of which two were randomized trials against BioPol-SES[23, 32]; and 7 trials[15, 16, 18, 19, 26, 29, 33] (4491 patients) with biodegradable polymer biolimus A9 eluting stents (BioPol-BES). Many of the retrieved trials were observational non-randomized trials. The mean age of the participants in individual trials ranged from 53 to 67 years, with males representing the majority. The percentage of diabetics was 28% among the BioPol-SES, 26% among the BioPol-PES and 28% among the BioPol-BES. The recommended duration of thienopyridine therapy after stent implantation was variable between the studies; 3 months in 2 studies[19, 30], 6 months in 12 studies[12-16, 21, 22, 25-28, 31, 32], 12 months in 5 studies[11, 20, 23, 24, 33], indefinitely in one study[17] and unidentified in 2 studies[18, 29]. The follow–up (FU) duration ranged from 6 months to 30 months, with only two studies with FU of 6 months[11, 24].

Among the included studies there were 10 randomized clinical trials (RCT)[13-16, 19, 22, 23, 25, 29, 32, 33], two studies were randomizing BioPol-SES versus BioPol-PES[23, 32], two studies; one randomizing BioPol-SES versus permanent polymer sirolimus eluting stent (PermPol-SES)[13, 25], and another randomizing BP-SES versus permanent polymer sirolimus (PermPol-SES) plus everolimus eluting stents (PermPol-EES)[14], one study randomizing BioPol-PES versus permanent polymer paclitaxel eluting stent (PermPol-PES)[22], two studies randomizing BioPol-BES versus PermPol-SES[29, 33], two studies randomizing BioPol-BES versus PermPol-PES[15, 16], and finally one study randomizing BioPol-BES versus bare metal stent[19].

Table 1: Characteristics of the source studies

References	Trial Acronym	Year	Stent type	Study design	Number of patients	Inclusion criteria	D.M. (N)	Male (%)	Mean age	Duration of Thienopyridines (months)	Maximum follow-up period (months)
Tin Hay et al [30]	CURAMI	2007	SES	OS	49	AMI	15	86	55	3	24
Liu et al [24]		2007	SES	OS	97	SA+UA	23	70	58	12	6
Han et al [21]		2008	SES	OS	100	SA+UA	18	79	59	6	24
Dani et al [17]	SERIES I	2008	SES	OS	100	SA+UA	29	NA	NA	Indefinite	30
Bhargava et al [11]	BIORAPID	2008	SES	OS	43	SA+ACS	6	79	53	12	6
Lemos et al [23]	PAINT	2009	SES	RCT	106	SA+UA	37	67	60	12	12
Wessely et al [32]		2007	SES	RCT	46	SA+UA	16	85	67	6	9
Mehilli et al [25] Byrne et al [13]	ISAR TEST III	2008,2009	SES	RCT	202	SA+UA	58	78	66	6	24
Byrne et al [14]	ISAR TEST IV	2009	SES	RCT	1299	SA+ACS	376	75	67	6	12
Wessely et al [32]		2007	PES	RCT	45	SA+UA	12	89	67	6	9
Lemos et al [23]	PAINT	2009	PES	RCT	111	SA+UA	32	61	60	12	12
Buszman et al [12]		2008	PES	OS	116	SA+ACS	25	74	54	6	12
Vranckx et al [31]	SIMPLE II	2006	PES	OS	103	SA+UA	29	71	58	6	9
Serruys et al [28]	PISCES‡	2005	PES	OS	68	SA+UA	13	76	57	6	12
Krucoff et al [22]	COSTAR II	2008	PES	RCT	989	SA+UA	271	73	64	6	9
Ostovan et al [27]		2008	PES	OS	196	SA+UA	40	67	55	6	12
Grube et al [20]	JACTAX	2008	PES	OS	103	SA+UA	22	81	66	12	9
Windecker et al [33]	LEADERS	2008	BES	RCT	857	SA+ACS	223	75	65	12	12
Grube et al [19]	STEALTH I	2005	BES	RCT	80	SA+UA	21	60	62	3	24
Chevalier et al [15]	NOBORI I	2007	BES	RCT	85	SA+UA	18	69	65	6	9
Chevalier et al [16]	NOBORI I- 2nd phase	2009	BES	RCT	153	SA+UA	25	74	63	6	10
Danzi et al [18]	NOBORI II	2010	BES	OS	3068	SA+ACS	887	78	64	NA	12
Ostojic et al [26]	NOBORI-CORE	2008	BES	OS	54	SA+UA	10	68	57	6	12
Takeshita et al [29]	NOBORI-JAPAN	2010	BES	RCT	194	SA+UA	75	72	67	NA	12

‡ In this study the slow release arm only of the BP-PES were included to match the other studies; SES: sirolimus eluting stent; PES: paclitaxel eluting stent; BES: biolimus eluting stent; OS: observational study; RCT: randomized clinical trial; SA: stable angina; UA: unstable angina; AMI: acute myocardial infarction; ACS: acute coronary syndrome; NA: not available.

Clinical end-points at 30 days follow-up (Table 2)

TLR

Among the studied population the incidence of TLR at 30 days was 0.4% in the BioPol-SES, 0.7% in the BioPol-PES and 1.4% in the BioPol-BES. These incidences were statistically significantly different (overall p-value=0.01); the three pair-wise comparisons were; OR= 3.4, 95%CI= 1.3-9.6, p=0.006 for BioPol-BES vs. BioPol-SES, OR= 1.7, 95%CI= 0.6-5.1, p= 0.3 for BioPol-PES vs. BioPol-SES and OR= 2.0, 95%CI= 0.9-4.7, p= 0.08 for BioPol-BES vs. BioPol-PES.

DST

The incidence of DST at 30 days was 0.2% in the BioPol-SES, 0.3% in the BioPol-PES and 0.9 % in the BioPol-BES. The overall test on equality of these incidences showed a trend towards statistical significance (p-value=0.06); the three pair-wise comparisons were; OR= 3.9, 95%CI= 1.1-14.0, p=0.04 for BioPol-SES and BioPol-BES, OR=1.4, 95%CI= 0.3-6,0, p= 0.6 for BioPol-SES vs. BioPol-PES and OR= 0.4, 95%CI= 0.1-1.2, p= 0.09 for BioPol-BES vs. BioPol-PES.

Clinical end-points at one year follow-up (Table 2)

TLR

Over a follow-up period up to 12 months, the incidence of TLR among the studied population was 4.9% in the BioPol-SES, 6.1% in the BioPol-PES and 2.3% in the BioPol-BES. These incidences varied significantly among the different stents (overall p-value=0.03). There was almost 3 times higher risk of TLR in the BioPol-PES compared to the BioPol-BES (OR=2.8, 95%CI= 1.3-6.0, p= 0.01), and twice higher risk of TLR in the BioPol-SES compared to BioPol-BES (OR=2.2, 95%CI= 0.2-1.0, p=0.04), and no significant difference in the risk ratio of BioPol-SES vs. BioPol-PES (OR= 1.3, 95%CI= 0.6-2.6, p= 0.5).

DST

The incidence of DST at one year follow-up was 0.3% in BioPol-SES, 1% in the BioPol-PES and 0.8% in the BioPol-BES. The pooled odds-ratio was not significant among the different stent comparisons (overall p-value=0.2).

Clinical end-points at one year in randomized clinical trials of BioPol-DES vs. PermPol-DES (Table 3)

In another analysis, in which clinical end-points were assessed in studies comparing BioPol-DES with PermPol-DES in a randomized manner (seven randomized controlled studies)[13-16, 22, 25, 29, 33], it was observed that risk of developing TLR at 1 year follow-up was not significantly different in PermPol-DES compared to BioPol-DES (OR=0.8, 95% CI=0.5-1.4, p= 0.5) (figure 2).

Table 2: Clinical events at 30 days and within 12 months among biodegradable-polymer DES:

References	Trial Acronym	Number of patients at 30 days	TLR (N) at 30 days	DST (N) at 30 days	Number of patients at 1 year follow-up	TLR (N) at 1 year	DST (N) at 1 year
Tin Hay et al [30]	CURAMI	49	0	0	49	4	0
Liu et al [24]		97	0	0*	97	0	0*
Han et al [21]		100	0	0*	100	4	0*
Dani et al [17]	SERIES I	100	0	0*	100	4	0*
Bhargava et al [11]	BIORAPID	43	0	0	43	2	0
Lemos et al [23]	PAINT	106	NA	0*	106	5	1*
Wessely et al [32]		46	NA	0	46	4	0
Mehilli et al [25] Byrne et al [13]	ISAR TEST III	202	NA	NA	202	12	0*
Byrne et al [14]	ISAR TEST IV	1299	7	5*	1299	109	8*
Wessely et al [32]		45	NA	0	45	12	0
Lemos et al [23]	PAINT	111	NA	0*	111	6	2*
Buszman et al [12]		116	1	1	116	8	1
Vranckx et al [31]	SIMPLE II	103	0	0	103	5	1
Serruys et al [28]	PISCES	68	1	0	68	2	0
Krucoff et al [22]	COSTAR II	989	9	5*	989	80	6*
Ostovan et al [27]		196	0	0	196	6	6
Grube et al [19]	JACTAX	103	0	NA	73	2	NA
Windecker et al [33]	LEADERS	857	15	14*	857	46	16*
Grube et al [19]	STEALTH I	80	1	1	80	1	1
Chevalier et al [15]	NOBORI I	85	0	0*	85	4	0*
Chevalier et al [16]	NOBORI I- 2nd phase	153	0	0*	152	2	0*
Danzi et al [18]	NOBORI II †	3068	NA	3 †	2976	65	18 †
Ostojic et al [26]	NOBORI-CORE	54	1	1*	54	1	1*
Takeshita et al [29]	NOBORI-JAPAN	194	NA	0*	194	1	0*

* Stent thrombosis as defined by the Academic research consortium (ARC); TLR: target lesion revascularization; DST: definite stent thrombosis; NA: not available

† The stent thrombosis (ST) recorded in NOBORI II trial included definite + probable, so we didn't include it in the analysis which was confined to definite ST. However we thought to include it in the table for comparative purposes (see later table 4)

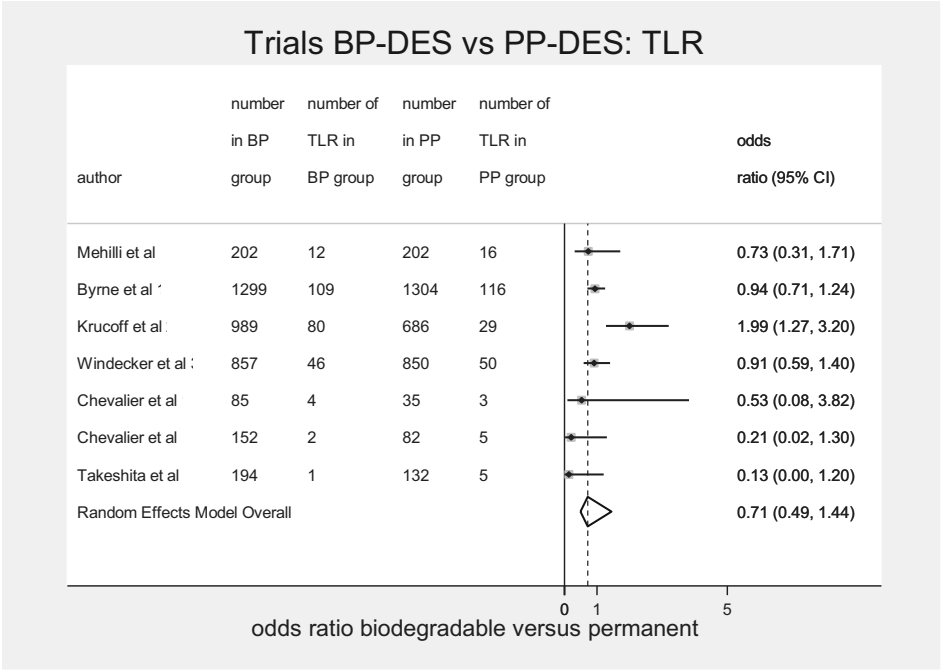

Figure 2: One year TLR in BP-DES vs. PP-DES. TLR; target lesion revascularization, BP; biodegradable polymer, PP; permanent polymer, DES; drug eluting stents.

Similarly, the one year risk of DST was not significantly different in PermPol-DES compared to BioPol-DES (OR=0.7, 95% CI= -0.2-2.4, p=0.5) (figure 3).

Randomized clinical trials quality assessment

Each of the RCTs comparing BioPol-DES with PermPol-DES had five or more questions answered with 'yes' when assessed with the Delphi list. Therefore, all seven RCTs were considered to have a low risk of introducing bias in the assessment of TLR or DST in BioPol-DES vs. PermPol-DES.

DISCUSSION

Three types of biodegradable polymer based DES were analyzed in our study; sirolimus, paclitaxel and biolimus A9.

Rapamycin (sirolimus), is a macrolide with cytostatic properties that blocks progression from G1 to S in the cell cycle and inhibits thus the vascular smooth muscle cell migration and proliferation[34].

Biolimus A9 is an analogue of rapamycin that binds to FK binding protein 12 and subsequently to the mammalian target of rapamycin. The formed complex inhibits smooth muscle cells

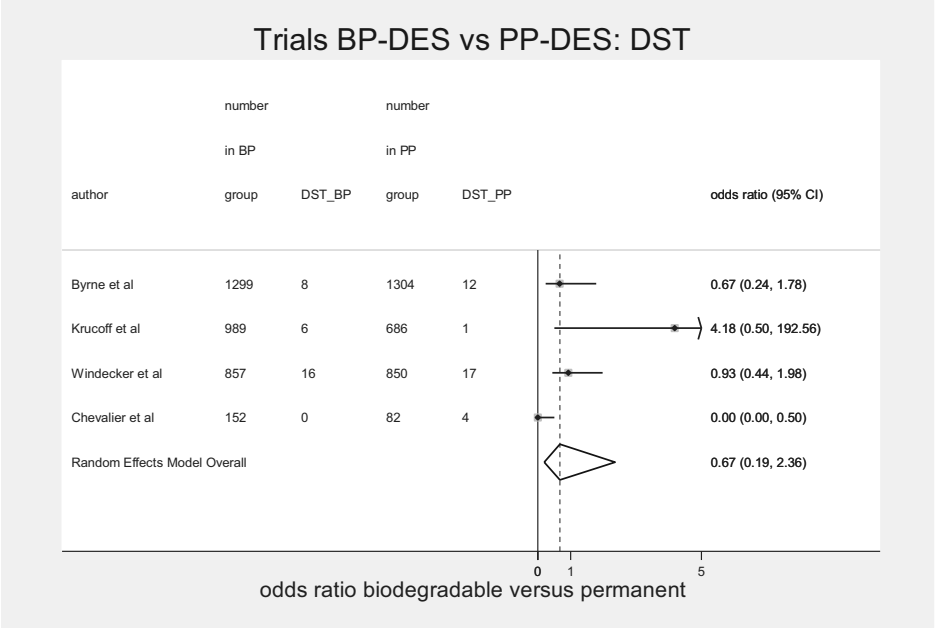

Figure 3: One year DST in BP-DES vs. PP-DES. DST; definite stent thrombosis, BP; biodegradable polymer, PP; permanent polymer, DES; drug eluting stents.

Table 3: Clinical events at 1 year in RCTs of BioPol-DES vs. PermPol-DES:

References	Trial Acronym	Stent	Number of patients	TLR (N)	DST (N)
Mehilli et al [25]	ISAR TEST III	BP-SES	202	12	0*
Byrne et al [13]		PP-SES	202	16	1*
Byrne et al [14]	ISAR TEST IV	BP-SES	1299	109	8*
		PP-SES&PP-EES	1304	116	12*
Krucoff et al [22]	COSTAR II	BP-PES	989	80	6*
		PP-PES	686	29	1*
Windecker et al [32]	LEADERS	BP-BES	857	46	16*
		PP-SES	850	50	17*
Chevalier et al [15]	NOBORI I	BP-BES	85	4	0*
		PP-PES	35	3	0*
Chevalier et al [16]	NOBORI I- 2nd phase	BP-BES	152	2	0*
		PP-PES	82	5	4*
Takeshita et al [29]	NOBORI-JAPAN	BP-BES	194	1	0*
		BP-SES	132	5	0*

BioPol: biodegradable polymer; PermPol: permanent polymer; SES: sirolimus eluting stent; PES: paclitaxel eluting stent; BES: biolimus eluting stent; EES: everolimus eluting stent; TLR: target lesion revascularization; DST: definite stent thrombosis; NA: not available.
* Stent thrombosis as defined by ARC

proliferation by blocking the cell cycle progression between the G1 and S phase. The main difference between biolimus A9 and rapamycin is replacement of hydrogen by alkoxy-alkyl group at 40-O position, increasing its lipophilicity which is expected to optimize the drug distribution[16]. Two similar types of biolimus A9 eluting stents were tested in previous studies, The BioMatrix® (Biosensors International- Singapore) and The NOBORI® (TERUMO Europe NV, Leuven, Belgium).

Paclitaxel inhibits vascular smooth muscle cell migration and proliferation mainly as a result of binding to and stabilizing cellular microtubules[34, 35].

All stents are coated with a biodegradable poly-lactic acid (PLA) or poly–lactic-co-glycolic acid (PLGA) polymer[7]. In principle, after drug delivery and subsequent complete polymer degradation, only the biologically inert bare-metal platform remains.

To our knowledge this is the first meta-analysis that compares the performance of different DES with biodegradable polymers in a large cohort of patients with similar inclusion criteria, aiming to judge the individual drug performance without the influence of permanent polymer. The key findings were that: a) the risk of TLR and DST were highest in the BioPol-BES group within short term follow-up (30 days); b) The risk of TLR at one year follow-up was three times higher in the BioPol-PES and twice higher in the BioPol-SES when compared to the BioPol-BES; c) There was no significant difference in the one year risk of DST between the studied groups, however we could still observe a higher incidence of stent thrombosis in BioPol-PES compared to BioPol-SES (1% vs. 0.3%).

This meta-analysis is based on comparisons between studies. A consequence is that the results are more amenable to risk of bias than most meta-analyses, which are based on comparisons of meta-analyzed data randomized within studies. Thus our analysis yields valid results only under the assumption that, on the average, throughout these different studies the patient populations are not systematically different, though they are treated with different types of biodegradable-polymer DES. In our view this assumption is likely to be fulfilled since the inclusion and exclusion criteria were very comparable and were not different between the groups of studies with different types of stent.

In an additional analysis performed in randomized trials only, we found that the 1-year risks of TLR and DST were not significantly different between BioPol-DES and PermPol-DES.

Long term follow up results (> 2years) are not yet fully available for the majority of biodegradable polymer DES and therefore we did not perform a long-term analysis.

Early stent thrombosis and target lesion revascularization (TLR)

One of the interesting findings in this study was the significantly higher incidence of early stent thrombosis (EST), within 30 days, in the BioPol-BES group, and the subsequent higher incidence of 30 days-TLR compared to BioPol-SES and BioPol-PES.

These results should be interpreted cautiously, especially in the considerations that polymer- or drug-related stent thrombosis tends to present more likely as a mid- or late-term event,

and that most of the early thrombotic events which have occurred in the BioPol-BES group were encountered in the LEADERS trial[33], which involved a diversity of complex lesions. However, although ISAR TEST-IV trial[14] which tested BioPol-SES, had similar inclusion criteria and diverse complex lesions, yet resulted in less early thrombotic events. Moreover, when comparing the LEADERS[33] and NOBORI-2[18] clinical trials, the 2 leading "all comers" biolimus A9 trials, we could observe that the incidence of EST was obviously different between both trials (1.6% vs. 0.1% respectively, Table 2).

It is still too early to adopt the hypothesis that a more intense antiplatelet regimen should be adopted in patients receiving BioPol-BES. Probably a more dedicated pharmacokinetic study, that addresses the issue of biolimus A9 tissue distribution and polymer degradation rates in different settings as acute coronary syndromes and complex coronary lesions, would shed further light on this issue.

Target lesion revascularization (TLR) at mid-term follow-up (1 year)

From this study it was concluded that the incidence of TLR was significantly lower in the BioPol-BES compared to both BioPol-SES and BioPol-PES. This goes along with the results of the NOBORI series of clinical trials[15, 16, 26, 29]. A sub-analysis of the LEADERS trial compared outcomes at 1 and 2 years[36] in BioPol-BES vs. PermPol-SES patients, stratified according to Syntax score[37] tertiles. Authors showed that BES offered significant clinical benefit over SES among patients with high Syntax scores, among which was significantly less TLR at 1 year, with a strong trend at 2 years follow-up. Recently, the 3 years follow-up of the LEADERS trial has been announced, showing the sustained benefit of BES over SES in patients with high Syntax score and among patients with STEMI[38]. In view of these long-term results, it would be advisable to use BioPol-BES among patients with high-risk lesions.

Biolimus A9 possesses enhanced anti-inflammatory and antiproliferative activity with an improved pharmacokinetic profile. Unlike currently approved drug eluting stents utilizing drugs originally developed for other indications, biolimus A9 has specifically been developed for local delivery to coronary arteries[39]. Biolimus A9 is a novel rapamycin derivative that, like sirolimus, inhibits smooth muscle cell proliferation via binding to the FK-binding protein and subsequent inhibition of the mammalian target of rapamycin (mTOR)[40-42].

The newly developed biolimus A9 eluting stents; Nobori® and BioMatrix® share several unique features. The most important are biodegradable polymer carrier (poly lactic acid), and coating only on the abluminal stent surface. The later feature allows direct release of biolimus A9 into the vessel wall and, enhanced by its high lipophilicity (~10-fold higher than sirolimus), fast uptake by the surrounding tissue[15, 16, 33, 43].

It has been previously reported that sirolimus and paclitaxel drug eluting stents were associated with paradoxical coronary vasoconstriction up to 12 months after implantation[44-47]. This observation may be attributable to delayed endothelialization caused by the drug and/or endothelial dysfunction caused by polymer-induced inflammation or hypersensitivity reac-

tion. On the contrary, in a recent study, it has been shown that biolimus A9 eluting stents are associated with better preserved endothelial function in coronary arteries compared to the first generation DES, which could be partly explained by the better drug release kinetics[48].
Animal studies showed that after BES implantation, the tissue concentration of the drug in segments 5 mm proximal and distal to the stent edges is almost non-measurable[43] . In addition, SES and BES have different drug release kinetics: total drug content is released from the SES within 60 days with more than 60% released shortly after stent implantation[49], versus a small initial burst and sustained simultaneous drug release and polymer degradation taking place over 6-9 months in the BES[43], exposing the surrounding tissue at any given time to a lower amount of drug.

Definite stent thrombosis (DST) at mid-term follow-up (1 year)

Because durable polymers have been held responsible for some of the thrombotic events that are assumed to occur as a result of polymer-mediated inflammatory reaction and delayed endothelialization, it was expected that degradation of the polymer will improve arterial healing and thus negate this adverse outcome. This leaves us with the assumption that a higher incidence of thrombotic events, if any, would be a "drug only" effect.
In this meta-analysis, the risk of DST was not significantly different between the different BioPol-DES at one year follow-up; however we could still observe that the incidence of stent thrombosis was numerically 3 times lower in SES vs. PES (0.3% vs.1% respectively). Previous data, comparing first generation DES, have shown that there is higher risk of ST in PES compared to SES[3, 50, 51].

Biodegradable-polymer Biolimus A9 stents (BioMatrix® vs. NOBORI®)

Despite using the same biodegradable polymer (poly-lactic acid) coated on the abluminal stent surface, recent pharmacokinetic studies of the two main biolimus A9 stents; Biomatrix®[52] and NOBORI®[43], have shown that there is an obvious difference between the pharmacokinetics of the the two main biolimus A9 stents, which may be an explanation for the more favourable clinical outcomes encountered with the latter (Table 4).
The NOBORI® stent design and coating process differ from that of the BioMatrix® stent. The maximum Biolimus A9 concentrations in blood with a median of 18 pg/mL (range<LLOQ to 32 pg/mL) and the $AUC_{0-\tau}$ (median 2.9 ng/mL·h, range <LLOQ to 33.1 ng/mL·h) were lower than those after BioMatrix® implantation, suggesting that stent design and coating process have an impact on Biolimus A9 release kinetics.
In addition to drug distribution and elimination, biolimus A9 pharmacokinetics are significantly affected by the polymer degradation rate which in turn is influenced by the state of the vessel. In a vessel with inflammation, the pH is expected to be low which will accelerate the degradation of the polymer material and the subsequent drug release into the vessel wall[7]

Table 4: Comparison of pharmacokinetics and clinical end-points of the two main Biolimus A9 DES:

		BioMatrix II	NOBORI
Design & Pharmacokinetics:			
Stent platform and Primer coating		316L Stainless Steel-Parylene C	316L Stainless Steel-Parylene C
Drug-Polymer coating		Abluminal *	Abluminal
Total length (mm)		25.5±10.3	21.4±7.2
Drug concentration(μg/mm)		14.2-17.5	15.6
Total Biolimus A9 dose (μg)		381.7±155.8	336.55±112.99
t_{max} (h)	Mean ± SD Median (min.-max.)	67.2±179.9 1.0 (0.08-672)	178.4±554.3 2.0 (0.05-2160)
t_{last} (h)	Mean ± SD Median (min.-max.)	434.7±294.4 672 (2-672)	984.4±1246.1 420 (3-4320)
% of patients having measurable concentration of Biolimus A9(>LLOQ) at 28 days		48%	30%
C_{max} (pg/ml)	Mean ± SD Median (min.-max.)	131.5±108.3 121 (19-394)	17.4±10.2 17.7 (<LLOQ-32.2)
C_{last} (pg/ml)	Mean ± SD Median (min.-max.)	47.5±34.3 45 (10-121)	11.7±7.0 11.4 (<LLOQ-30.3)
$AUC_{0-\tau}$ (ng/ml·h)	Mean ± SD Median (min.-max.)	16.4±15.6 13 (0.3-48.7)	7.0±10.2 2.9 (<LLOQ-33.1)
Clinical end-points:			
TLR 30 days		1.7%	0.3%
TLR 1 year		5.0%	2.1%
DST 30 days		1.6%	0.2% (0.1%) †
DST 1 year		1.8%	0.2% (0.5%) †

t_{max}, time to maximum concentration; t_{last}, time to last quantifiable biolimus A9 concentration (<10 pg/ml); LLOQ, lower limit of quantitation (<10 pg/ml); C_{max}, maximum concentration; C_{last}, last quantifiable concentration; $AUC_{0-\tau}$, area-under-the-time-concentration curve over the observation period; TLR, target lesion revascularization; DST, definite stent thrombosis. Values are expressed as mean ± SD and median (minimum -maximum) or as percentages (%).

* Using automatic micropipette coating (AMPC) process.

† Percentages between parentheses show the incidence of DST after including NOBORI-2 results; taking in consideration that they include definite & probable stent thrombosis.

Clinical outcomes in randomized clinical trials of BioPol-DES vs. PermPol-DES

In the sub-analysis confined to randomised clinical trials comparing BioPol-DES and PermPol-DES, it was found that the risks of TLR or late DST at 1 year were not significantly different between both groups.

Unexpectedly, it was found that the presence of biodegradable polymeric coating did not influence the risk of stent thrombosis in DES at 1 year follow-up. A lot of awareness has been raised lately about the biocompatibility of permanent polymer implants and their potential role in contributing to stent thrombosis. Many animal studies have shown that a hypersensi-

tivity reaction may occur as a result of polymer induced inflammation[7, 53]. Given these issues more focus has been placed upon developing biodegradable polymers which degrade over time.

In a previous study, van der Giessen et al has demonstrated that biodegradable polymers may induce marked inflammatory reactions in the porcine coronary arteries, and that this may be attributable to the combination of the parent polymer compound, and biodegradation products[54]. Moreover, there are several factors which influence the velocity of degradation, either by accelerating or slowing it. Accordingly, It is has be stated that a balance between drug release kinetics, the rate of degradation of the polymer and the degradation products are essential for the success of bio-erodible stent systems in coronary vasculature[7]. New families of biodegradable polymers have been tested recently in animal studies implemented by Lockwood and colleagues[55] which yield fewer acidic by-products than standard biodegradable polymers (PLGA, PLA) used in the currently available BioPol-DES, thus making it well-tolerated *in vivo* by providing a better degradation rate and biocompatibility profile.

In an attempt to overcome the problems encountered with polymers or their degradation products, "polymer-free" drug eluting stents have evolved and have been proven to be safe in some clinical studies[13, 56], and they were even associated with less late lumen loss compared to biodegradable-polymer and permanent-polymer stents in one study[13]. In a recent animal study, polymer-free biolimus A9 coated stents demonstrated more sustained intimal inhibition, improved healing and reduced inflammation compared with the polymer coated sirolimus eluting Cypher® stent[57]. One would expect that a DES without polymer will release the drug in a relatively short amount of time, resulting in relatively high systemic and tissue peak concentrations, however the superior pharmacokinetics and long half life of Biolimus A9 in the target tissues (Biolimus A9 was present in the coronary tissue until 180 days after stent implantation), made it a suitable drug for coating on non-polymer stents.

LIMITATIONS

To maximize the utilization of all available data, we included abstract presentations that have not been subjected to as much peer review and scrutiny as with full papers, and may not be as of high quality; however, we felt that this was necessary for two reasons. Including abstracts served as an additional tool to avoid any potential publication bias. The second reason is that the magnitude of treatment effect can be overestimated by analyzing only the published data[58].

In our study only DST was used in the analysis, which may underestimate the true incidence of stent thrombosis among the studied stents. We preferred to use this end-point rather than overall stent thrombosis since not all the included studies reported stent thrombosis as definite, probable or possible according to the ARC definition[8]. In studies not using ARC

definition, they stated in their definition of stent thrombosis that it was angiographically documented which matches definite stent thrombosis as defined by the ARC.

CONCLUSIONS

This meta-analysis, comparing different biodegradable-polymer DES, showed that the risk of early DST and subsequently TLR were highest in the BioPol-BES at 30 days follow-up, whereas at 1 year there was significantly less TLR in the BioPol-BES. We could observe a three times higher incidence of ST in BioPol-PES compared to BioPol-SES at 1 year. On comparing BioPol-DES and PermPol-DES in randomized clinical trials, there was no significant difference in the risk of either TLR or stent thrombosis at 1 year.

These results point to the fact that BioPol-DES do not necessarily perform better than PermPol-DES and that short-mid and long term results are to be carefully judged separately for newly emerging BioPol-DES before they can become a new standard.

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Chapter 5

Emerging drugs for coronary artery disease. From past achievements and current needs to clinical promises

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ABSTRACT

Introduction Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide, exerting a huge economic burden. Although drug treatment in the past decades has made large advances, significant residual risk remains. However, in the coming years there is still a lot ahead with great advances and major breakthroughs expected.

Areas covered New treatments are expected to provide higher efficacy, with favorable safety profile. In this review article we are providing an almost full coverage of the recent and emerging drug therapies of CAD. This includes: drugs for treatment of atherogenic dyslipidemia, drugs that stabilizes atherosclerotic plaque and halts its progression guided by novel anti-inflammatory concepts in atherosclerosis treatment, anti-anginal treatments, renin-angiotensin-aldosterone system (RAAS) inhibitors, antiplatelet and anticoagulant drugs.

Expert opinion Efforts have been made to improve the clinical effectiveness and safety of established treatment strategies, or to target new frontiers through developing novel treatment strategies that tackle different mechanisms of action. Better understanding of the different molecular and cellular mechanisms underlying CAD resulted in more innovations and achievements in CAD drug therapy, and still a lot is anticipated in the forecoming years.

Keywords CAD, emerging drugs, lipid.

1. BACKGROUND

Coronary artery disease (CAD) is one of the most important causes of morbidity and mortality world-wide, and it is estimated that mortality from cardiovascular diseases will have increased worldwide by 90% by the year 2020 when compared with the situation in 1990[1]. Over the past decade drug development in the field of primary and secondary prevention of CAD has shown broad advances, particularly after getting to know more about the molecular and cellular biology of atherosclerosis, thrombosis and lipid disorders which are the main entities contributing to the occurrence of CAD.

Results from 2 large randomized trials for the management of coronary artery disease; COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)[2] and BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes)[3] have drawn much attention towards optimizing drug therapy of coronary artery disease before invasive/operative vascular procedures. There are two main treatment goals in patients with coronary artery disease: relief of symptoms and ischemia; and prevention of progression of coronary artery disease leading to myocardial infarction, left ventricular dysfunction, congestive heart failure, and premature cardiovascular death. Currently, coronary artery disease cannot be fully eradicated but with the newly emerging drug treatments and other risk factor modifications, the natural history of the disease can be significantly altered in the right direction.

2. MEDICAL NEED

2.1 Lipid therapy

Elevated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) are among the major risk factors for the development of cardiovascular disease (CVD). Despite the widespread use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) therapy, the incidence of cardiovascular morbidity and mortality remains elevated in many patients with dyslipidaemia, and particularly in those exhibiting metabolic disease and insulin resistance[4]. In large landmark trials, reduction in low-density lipoprotein cholesterol (LDL-C) levels with statins has been shown to decrease the incidence of major cardiovascular events by 25–45%[5-7]. Nonetheless, considerable residual cardiovascular risk, which includes a high frequency of recurrent events, remains even with an aggressive statin treatment regimen[8-12]. New therapeutic options, targeting additional lipid risk factors, are clearly needed to further improve the treatment of atherogenic dyslipidaemia by reducing residual cardiovascular risk.

The Framingham Heart Study in the 1980s demonstrated that the risk of coronary heart disease (CHD) was significantly lower among persons with higher levels of high-density lipoprotein cholesterol (HDL-C) (normal range 40 to 60 mg/dl)[13]. Significantly, a recent post

hoc analysis of the 'Treating to New Targets' trial demonstrated that low HDL-C is predictive of major cardiovascular events in patients receiving aggressive statin therapy[14].
Clinical studies have shown that therapeutic raising of HDL-C levels was associated with attenuated progression of intima-media thickening in the carotid artery, slowed progression of coronary artery atherosclerosis, and reduced cardiovascular risk[6, 15-18]. The clinical benefits of raising low HDL-C levels observed in lipid intervention trials and the limitations of available therapies have stimulated the search to identify new, more efficacious HDL-raising agents.

2.2 Atherosclerosis anti-Inflammatory therapy

For a long time atherosclerosis was considered as a lipid-driven disease, but now it is evident that it also involves the simultaneous and combined effect of inflammation and immunological pathways[19-21]. The development of new treatments specifically targeted against inflammatory mediators can be seen as a new phase in cardiovascular drug development.

2.3 Anti-anginal medications

2.3.1 Heart rate reduction

In patients with coronary artery disease, epidemiological studies have demonstrated that a low resting heart rate is associated with low total mortality and low cardiovascular mortality[22-25]. A recent study confirmed the impact of resting heart rate on cardiovascular events in a prospective setting[26]. Not all patients could tolerate the classical treatments to achieve HR reduction (B-Blockers and non-dihydropyridine Ca antagonists); which although effective, could present negative effects on regional myocardial blood flow and negative inotropic effects.

2.3.2 Coronary vasodilators

Nitrates are known to be effective coronary vasodilators, although their effect is limited by the side effects of nitrate-induced flushing, hypotension and syncope, as well as the reported nitrate tolerance. Moreover, intact epicardial coronary arteries dilate promptly after the administration of nitrates or other kinds of vasodilators[27], while in contrast, it remains controversial[28-30]as to whether the coronary atherosclerotic site responds to vasodilator agents; this continues to be an important topic in terms of the treatment of stable angina pectoris. Therefore, other vasodilators than nitrates should be used to more accurately assess the vasodilator potential at atherosclerotic lesions.

2.4 RAS Inhibition

Epidemiologic and experimental data suggest that activation of renin-angiotensin system (RAS) has an important role in pathogenesis of atherosclerosis. Although angiotensin converting enzyme (ACE) inhibitors and angiotensin-2 (AT2) receptor blockers have been used for more than a decade, their benefit in terms of absolute risk reduction is modest. Many

patients with established atherosclerosis continue to suffer from recurrent events related to ongoing disease. There is direct experimental animal evidence to support direct renin inhibitor therapy as means to reduce atherosclerotic plaque progression in thoracic aorta[31].

2.5 Antiplatelet therapy

The use of antiplatelet agents, both oral and parenteral, in the treatment of CHD was introduced based on the solid evidence for the major role of platelets both in the early stages of atherosclerosis as well as in thrombus formation during rupture of the vulnerable plaque.
Despite the progress achieved, it is generally accepted that our strategies are far from being considered optimal. The need for new oral antiplatelet agents is mainly driven by two reasons: the increased bleeding risk, particularly in those patients in need for double or triple antiplatelet therapy, and the variable response or "resistance" of patients to treatment clinically expressed as thrombotic complications or "treatment failure". The increased bleeding risk is strongly associated with the irreversible nature of current agents' platelet inhibition and represents a major issue in the setting of urgent cardiac or non-cardiac surgery. This has led to a lot of discussion regarding the appropriate selection of cases suitable for glycoprotein (GP) IIb/IIIa inhibitors administration, timing of their administration (in respect to patients' catheterization) and duration of treatment. On the other hand, "resistance" to antiplatelet treatment is both difficult to be assessed and multi-factorial in its nature involving (commonly neglected) parameters such as poor compliance and inadequate absorption but also drug interactions and pharmacogenetic factors. Moreover, it has been shown that lower response to aspirin and clopidogrel is frequent among acute coronary syndrome (ACS) patients as well as in those with hypertension, diabetes type 2, smoking, obesity (particularly in females), heart failure and hypercholesterolemia with the involved pathophysiological mechanisms to a significant extent unclear[32].

2.2 Antithrombotic therapy

Given the central role of thrombosis in the pathophysiology of ST elevation myocardial infarction and ACS, heparin and other antithrombotic agents have always been considered fundamental elements of our treatment strategies. Despite the availability of wide range of parenteral and oral anticoagulants with different mechanisms of action, yet it still remains with many limitations regarding increased bleeding risk, dosing regimens, therapeutic response, and thrombocytopenia[33]. All this have urged the development of newer classes that are supposed to have better safety and tolerability profiles, especially among oral anticoagulants, with the increasing need of triple antithrombotic therapy (dual antiplatelet plus oral anticoagulant therapy) in treating co-morbidities directly or indirectly related to CAD e.g. vein thromboembolism, prosthetic valves, atrial fibrillation, severe left ventricular (LV) dysfunction, LV aneurysms and thrombi.

3. EXISTING TREATMENT

Given the fact that atherosclerosis is a multifactorial disease, current medical treatment of CHD is diverse and includes a broad spectrum of agents with a variety of pharmacological and physiological effects. To date the conventional drug treatment for coronary artery disease has been:

Nitrates: Mainly relieve symptoms by increasing myocardial oxygen supply (coronary artery vasodilatation and redistribution of blood flow to ischemic areas) and decreasing myocardial oxygen demand (decreased preload and afterload)[34].

ß-Blockers: Reduce death and nonfatal MI in patients who have had a previous MI[35, 36]. Symptomatic improvement of angina[37]by decreasing myocardial oxygen demand (decreased inotropy, chronotropy, and hypertension) and increasing myocardial oxygen supply (increased duration of diastole).

Ca antagonists: Not only relieve symptoms but diminish clinical events as well[38]. It exerts its anti-ischemic effect by reducing myocardial oxygen demand (decreased afterload ± decreased inotropy and chronotropy) and increasing myocardial oxygen supply (coronary artery vasodilatation ± increased duration of diastole). It is the drug of choice for coronary vasospasm[39].

Renin-angiotensin-aldosterone system (RAAS) blockers: ACE inhibitors decrease cardiovascular death, all-cause death, nonfatal MI, stroke, revascularization procedures, and chronic heart failure (CHF)[40, 41]. The effects of ACE inhibitors extend beyond blood pressure reduction to endothelial protective effect and possibly directly influencing the atherosclerosis process[42]. A recent meta-analysis of 3 large clinical trials left no doubt that CAD patient should receive ACE inhibitors unless contraindicated[43]. However, the same cannot be said of ARBs, The major ARB trials in high risk patients demonstrated almost complete lack of reduction in MI and mortality despite significant reduction in blood pressure. In fact, the rates of MI in some trials have actually increased with ARBs[44, 45], raising the issue of "ARB-MI paradox"[46]which has triggered a lot of discussion and debate. So far, there is no consensus on whether ARBs have a tendency to increase MI, but there is also no substantive evidence to indicate that ARBs are able to reduce MI.

A recent meta-analysis has raised further debate suggesting that ARBs, particularly Tilmesartan, may be associated with a modestly increased risk of new cancer diagnosis[47]. This has been refuted by a later meta-analysis and trial sequential analysis of 324,168 participants from randomized trials, nevertheless showing that an increased risk of cancer with the combination of ACE inhibitors and ARBs couldn't be ruled out[48].

Lipid therapy

The reduction of LDL-C with **statins** has a strong positive effect on the occurrence of cardiovascular events[49]. A decrease in LDL-C levels from statin therapy is associated with a decrease

in the progression of atherosclerosis[50]. Increases in HDL-C between 5% and 15% have been reported with statin-mediated therapy, with an average increase of ~ 9%[16].

Fibrates are peroxisome proliferator-activated receptor (PPAR) - α agonists that lower LDL-C by 10% to 20%, lower triglycerides by 25% to 45%, and increase HDL-C modestly by 10% to 15%, and have shown, at least in subgroups, to reduce cardiovascular events[51].

Ezetimibe selectively blocks absorption of dietary and biliary cholesterol from the gut by blocking uptake of cholesterol into jejunal enterocytes[52]. Ezetimibe has an additional LDL cholesterol-lowering effect of around 15–20%, either alone or in the presence of a statin[53]. In a recent meta-analysis of randomized trials, ezetimibe monotherapy was found to induce significant potentially favorable changes in lipid and lipoprotein levels relative to baseline[54]. Nevertheless, ezetimibe monotherapy has never been shown to reduce event rates in a mortality-morbidity trial. In the recently published ARBITER 6-HALTS trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis)[55], comparing the effect of ezetimibe versus extended-release niacin (ER niacin) on atherosclerosis, showed that the regression of carotid intima-media thickness (CIMT) induced by ER niacin is superior to ezetimibe in patients taking statins. This trial was terminated early on the basis of the pre-specified interim analysis showing superiority of niacin over ezetimibe on change in CIMT.

Bile-acid sequestrating agents or resins that are currently available are colestyramine, colestipol and colesevelam. Their mode of action is usually considered to be similar. They are anion exchange resins which bind bile acids in the intestinal lumen. Therapy with bile-acid sequestrants has been shown to lower circulating LDL cholesterol by increasing hepatic catabolism via the LDL receptor-mediated pathway[56]. Colesevelam is a newer bile-acid sequestrant which causes fewer side-effects and, in combination with a statin, has been shown to decrease C-reactive protein levels more markedly than with statin alone[57], which might confer greater protection against CHD.

Antiplatelet therapy

The Antithrombotic trialists' meta-analysis published in 2002 can be considered as the cornerstone for the implementation of guidelines of current oral antiplatelet therapy[58]. Overall, antiplatelet therapy reduces the combined outcome of any serious vascular event by 25%, non-fatal myocardial infarction by 30%, non-fatal stroke by 25% and vascular mortality by 16% with no apparent adverse effect on other cause mortality. Furthermore, for this group of patients studied, clopidogrel and its analogue ticlopidine further reduced serious vascular events by 10% when compared with aspirin.

Aspirin has always been considered the "reference" to which any other compound is compared. It irreversibly inhibits platelet cyclo-oxygenase-1 (COX-1), therefore impairing activated platelets' ability to produce endoperoxides PGG2 and PGH2 and eventually thromboxane A2 (TXA2). TXA2 is a potent prothrombotic agent that stimulates platelet activation

and increases their aggregation by mediating the expression of the glycoprotein complex GPIIb/IIIa in the cell membrane of platelets. An intrinsic limitation of aspirin, bound to its mechanism of action, is that it invariably inhibits endoperoxide PGH2 synthesis in endothelial cells as well, therefore preventing the production of prostacyclin (PGI2) in the endothelium, a potent anti-aggregating and vasodilator agent. Its value in primary prevention has been questioned in recent meta-analysis, considering the increase of major bleeding events[59], while there have been concerns regarding its effectiveness in women[60].

Thienopyridines / P2Y12 antagonists: Ticlopidine was the first agent of a new class of antiplatelet drugs, the thienopyridines, that exert their action through inhibition of adenosine diphosphate (ADP) binding to P2Y12 receptors on the platelet surface. Despite its proven efficacy, particularly in ACS patients undergoing percutaneous coronary intervention (PCI) with stent implantation[61, 62], ticlopidine was also characterized by significant side effects the most common being gastrointestinal (diarrhea 12.4%) and the most severe hematological toxicity (neutropenia 2.4%, rare cases of aplastic anemia and thrombotic thrombocytopenic purpura). Therefore it was replaced in clinical practice by clopidogrel, a thienopyridine with less toxicity but mostly the same pharmacodynamic properties[63-65]. Clopidogrel's main disadvantage is that it's actually a pro-drug that undergoes a two-step metabolism to an active compound by cytochrome (CYP) P450 isoenzymes in the liver, making its bio-availability more sensitive to other drugs' co-administration.

Platelet Glycoprotien (GP) IIb/IIIa receptor anatgonists: Abciximab, eptifibatide and tirofiban are potent parenteral antiplatelet agents, exhibiting their action through inhibition of platelet surface membrane glycoprotein (GP) IIb/IIIa receptors. Following platelet activation, the GP IIb/IIIa receptor undergoes a conformational change rendering it competent to bind protein ligands including fibrinogen, fibronectin, von Willenbrand factor and vitronectin thereby facilitating and stabilizing platelet adhesion and thrombus formation. Abciximab is a Fab fragment of a chimeric human-murine monoclonal antibody irreversibly inhibiting GP IIb/IIIa receptor, while tirofiban and eptifibatide are high affinity non-antibody receptor inhibitors demonstrating a reversible mode of action with platelet activity restored within 4 to 5 hours following discontinuation of intravenous infusion. GP IIb/IIIa receptor antagonists have all proved particularly beneficial in reducing major cardiovascular peri-procedural events for both elective and urgent PCIs[66-69]. The benefit seems to be higher for diabetics and high risk patients[70], while for tirofiban and eptifibatide there is evidence for a possible beneficial effect in ACS patients even if a PCI is not scheduled[68, 71]. The major drawback of GPIIb/IIIa inhibitors has to do with the observed increased risk of bleeding, due mainly to their potent platelet anti-aggregatory properties although a small risk of thrombocytopenia has also been reported (1.5 to 2.8%). The potent inhibition of platelet aggregation represents a significant problem in cases where an urgent coronary artery bypass graft (CABG) operation is warranted or major hemorrhagic complications from the puncture site are observed. This has led to a lot of discussion regarding the appropriate selection of cases suitable for GPIIb/

IIIa inhibitors administration, timing of their administration (in respect to patients' catheterization) and duration of treatment.

Anticoagulant therapy

Unfractionated heparin (UFH) exerts its action by forming a complex with antithrombin (AT, formerly known as ATIII) therefore becoming a potent inhibitor of thrombin, factor Xa and to a lesser extent factors XIIa, XIa, and IXa. Despite its extensive use, heparin's limitations are well recognized. A major limitation, deriving from its mechanism of action, has to do with its dependency on antithrombin to exert its function and its inability to inhibit clot-bound thrombin. Moreover, it is characterized by a marked interpatient variability in its therapeutic response and the need for frequent partial thromboplastin time (PTT) monitoring. Therapeutic window is relatively small and the risk of bleeding increases substantially in patients with low body weight, female gender and advanced age. Moreover, heparin induced thrombocytopenia (HIT) is a well-recognized and potentially fatal complication of UFH therapy, occurring to 2.6% of patients exposed to heparin for more than 4 days while there have been concerns for reactivation of ischemia in ACS patients treated conservatively following heparin discontinuation, most likely due to a rebound thrombin generation[72].

Many of these issues have been addressed with the use of **low molecular weight heparins (LMWH)** the main representatives being enoxaparin, nadroparin, dalteparin and tinzaparin. Compared to UFH they have a better bioavailability when given by subcutaneous injection and a longer duration of anticoagulant effect permitting administration once or twice daily. Despite their potent Xa inactivation, they have a smaller effect on thrombin and they do not prolong PTT. This characteristic, along with their weight-adjusted dosing scheme, makes regular monitoring unnecessary (for non-pregnant patients) and they have proven safe for administration even in the outpatient setting[73]. Finally, they are much less likely to induce HIT compared to UFH[74]. Main limitations of LMWH have to do with the increased bleeding risk, particularly in patients above the age of 75, cumbersome dose calculation in patients with renal insufficiency and lack of an efficient antidote to reverse its action in case of emergency.

Fondaparinux is a synthetic pentasaccharide closely related but not belonging to the class of LMWH. It binds to AT with a higher affinity compared to UFH or LMWH, therefore effectively inhibiting Xa, it lacks however any kind of action against thrombin. The use of fondaparinux as an antithrombotic agent in the setting of unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) and ST elevation myocardial infarction (STEMI) was tested in the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-5 and 6) trials where it proved as least as effective to enoxaparin and UFH respectively in terms of primary end point reduction, while significantly reducing bleeding rates[75, 76].

Vitamin K antagonists are not any more routinely prescribed for secondary prevention of STEMI/NSTEMI survivor patients, since dual antiplatelet therapy proved more convenient, safer and at least as efficacious[77, 78]. The narrow therapeutic window, the increased bleeding

risk, the need for frequent international normalized ratio (INR) control, the potential teratogenic effects when prescribed during pregnancy, set significant limitations in vitamin K antagonists' use.

4. CURRENT RESEARCH GOALS

Based on a better understanding of the molecular and cellular mechanisms underlying atherosclerosis, thrombosis and lipid disorders, and given the shortcomings and restrictions of the current therapy, the current research goals and new drug developments in CAD are focused on: 1) Lipid therapy; including HDL-raising medications, and novel treatments of dyslipidemia among diabetics, 2) Anti-inflammatory treatment of atherosclerosis and vulnerable plaque stabilization, 3) New anti-anginal medications; including novel heart rate-reducing and vasodilating agents, and 4) New antiplatelet and anticoagulant treatment.
Medical research is simultaneously pointing into two directions, namely evolution of current therapeutic strategies by developing newer agents that will prove either more effective or with less side-effects and research for novel therapeutic targets that have not been explored yet.

5. SCIENTIFIC RATIONALE

5. 1 Novel HDL-C raising therapies

There are different proposed mechanisms for the HDL-C protective role; reverse cholesterol transport, the process of transporting excess cholesterol from the arterial wall's foam macrophages to the liver, bile, and feces is one of HDL's anti-atherogenic properties[79, 80]. Furthermore, HDL's anti-oxidative activity further protects against atherosclerosis[81, 82]. In the endothelium, nitric oxide protects against inflammation, HDL promotes vasoprotection by enhancing nitric oxide synthase and thereby increasing the production of nitric oxide[83, 84]. In addition to protection against platelet activation through endothelial protection, HDL inhibits the coagulation cascade through serine protease protein C, which inactivates factors Va and VIIa[83].
Circulating HDL particles are very heterogeneous with a very complex metabolic profile. There are three subclasses of HDL which vary in quantitative and qualitative content of lipids; discoid HDL particles (lipid-free HDL or apolipoprotein A-1) which mediates reverse cholesterol transport; further esterification of these HDL particles generates the other two subclasses; HDL2 and HDL3 which are spherical HDL particles. These mature HDL particles may induce further cholesterol efflux. Smaller HDL3 particles may more efficiently promote cholesterol efflux[79, 85]. Thus it appears that the subtype of HDL seems to matter. The next few years should provide answers to whether we should target raising specific HDL subclasses rather than HDL-C itself.

Structural and functional changes accompany HDL in the setting of acute or chronic inflammation, CHD or type 2 diabetes mellitus. These changes are induced by leukocyte myeloperoxidase which may alter the function of the normally atheroprotective anti-inflammatory HDL molecules into the so-called dysfunctional HDL with pro-inflammatory properties. This results in reduced efficacy of reverse cholesterol transport, and the ability of HDL to counteract the inhibitory effect of oxidized LDL on vascular relaxation[86, 87].

5.1.1 CETP inhibitors

Cholesteryl ester transfer protein (CETP) is a plasma protein that catalyzes the exchange of cholesteryl esters and triglycerides (TG) between the atheroprotective HDL and the atherogenic apolipoprotein (apo) B– containing lipoproteins, especially very low density lipoprotein (VLDL)[88]. Reduction in CETP activity resulting from genetic mutations or pharmacologic inhibition has been associated with reductions in cholesterol within the apo B-containing particles and cholesterol enrichment of HDL[89, 90].

5.1.2 Extended-release (ER) Niacin and ER Niacin/Laropiprant combination

Niacin was the first lipid-lowering drug developed[91]. Despite clear lipid-lowering effects and some proof of clinical benefit in early prevention studies[92, 93], niacin is not used very often in clinical practice. There are multiple reasons, the most important being the high rate of side effects and the stronger LDL-C reduction and the better documented effects of statins[94, 95]. Currently, with the rising interest in HDL-raising therapies, niacin has been under intense re-evaluation.

The main side effect of niacin is flushing, which is a result of cutaneous vasodilatation mediated via prostaglandin D2 (PGD2)[96], although the rate of flushing was decreased by using the extended-release formulations, it still represents a hurdle for its clinical use. Since the flush induced by niacin is primarily mediated through the interaction of prostaglandin D2 with a specific receptor (prostaglandin-D2-receptor-1) a selective antagonist of this receptor was developed (MK-0524, laropiprant)[97, 98], thus it seems rational to combine ER niacin with laropiprant especially that the addition of laropiprant doesn't change the effect of niacin on lipoproteins[99].

5.1.3 Dual Peroxisome proliferator-activated receptor (PPAR)-α/γ agonists

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors that control gene expression. Dual PPARα/γ agonists have the potential to combine the beneficial PPARα agonist properties of fibrates (decreasing plasma levels of triglycerides and very low-density lipoprotein particles and increasing levels of high-density lipoprotein cholesterol) with the beneficial PPARγ agonist effects of thiazolidinediones (reduction of free fatty acid flux, insulin resistance, and blood glucose levels)[100].

5.1.4 Reconstituted HDL infusion

Short-term infusions of reconstituted HDL have been a target of reverse cholesterol transport therapy. CSL-111 is reconstituted HDL consisting of apolipoprotein A-1 from human plasma combined with soyabean phosphatidylcholine and chemically and biologically resembles native HDL[101].

5.1.5 Apolipoprotien A-1(Apo A-1) Milano infusion

ApoA-I Milano is a variant of apolipoprotein A-I identified in individuals in rural Italy who exhibit very low levels of HDL (10-30 mg/dl), yet despite of that had a reduced atherosclerotic disease burden and longer lives[102, 103]. Infusion of recombinant Apo A-I Milano–phospholipid complexes (ETC-216) produces rapid regression of atherosclerosis in animal models, which can occur in as little as 48 hs[104, 105]. Moreover, it was recently found in animal studies that ApoA-1 Milano administration not only induced plaque size regression but was also associated with a significant reduction in markers of plaque vulnerability, suggesting further plaque stabilization[106].

5.2 Atherosclerosis anti-inflammatory and antioxidant therapy

5.2.1 Selective phospholipase A2 inhibitors

There are two groups of phospholipase A2; secretory phospholipase A2 (sPLA2), and lipoprotein-associated phospholipase A2 (Lp-PLA2). The sPLA2 represent a family of enzymes that hydrolyze fatty acids, in a calcium-dependent process, producing lipoprotein particles that are proatherogenic[107]. Lp-PLA2 represents a calcium-independent phospholipase that is predominantly synthesized by macrophages[108, 109]. Lp-PLA2-modified and sPLA2-modified lipoproteins and the resulting oxidized bioactive by-products activate redox-sensitive inflammatory pathways[110], impair endothelial-dependent vasorelaxation[111] and serve as chemo-attractants for monocytes[110, 112]. The products of Lp-PLA2 activity have been identified in human atherosclerotic vessel wall[113]. Lp-PLA2 and sPLA2 have gained more interest as emerging biomarkers of CV risk that are pharmacologically modifiable.

5.2.2 Heme oxygenase-1 inhibitors (Probucol analogues)

Probucol is a lipid-lowering prototype agent which exhibits vascular protective effect through anti-inflammatory and antioxidant activities. Probucol has demonstrable anti-inflammatory actions in animal models of atherosclerosis[114]. It reduces adhesion of mononuclear cell to the endothelium in vivo[115] and inhibits the expression of vascular cell adhesion molecule-1[116]. This result in reduced macrophage infiltration, associated with a decrease in matrix metalloproteinases and other enzymes that may participate in plaque rupture and proatherogenic activities which likely translates into improved plaque stability[116].

However, Probucol is no longer available in many countries due to concerns of efficacy[117] and safety[118, 119]. In search of other compounds with similar anti-inflammatory and antioxidant properties but without the potentially deleterious effect of probucol, succinobucol, previously known as AGI-1067, was developed[120].

5.3 New Anti-anginal treatments

5.3.1 Ivabradine

Ivabradine (IVA) is a novel, specific, heart rate (HR)-lowering agent that acts in sinoatrial node (SAN) cells by selectively inhibiting the pacemaker I*f* current in a dose-dependent manner by slowing the diastolic depolarization slope of SAN cells, and reducing HR at rest and during exercise with minimal effect on myocardial contractility, blood pressure, and intracardiac conduction[121]. It has been shown to be non-inferior to B-Blockers[122] or calcium antagonists[123] in HR reduction. Whether Ivabradine has a role beyond mere heart rate reduction is still a matter of focused scientific research.

5.3.2 Rho-Kinase (ROCK) Inhibitors

Rho-kinase (ROCK) inhibits myosin phosphatase activity by phosphorylating the myosin-binding subunit of the enzyme, promoting actin-myosin-mediated contractile force generation, thus resulting in the augmented vascular smooth muscle contraction in a calcium-independent manner[124, 125].

The activation of ROCK is involved in the regulation of vascular tone, endothelial dysfunction, inflammation and remodeling .The inhibition of ROCK has a beneficial effect in a variety of cardiovascular disorders. Evidence from animal models and from clinical use of ROCK inhibitors, such asY-27632, fasudil supports the hypothesis that ROCK is a potential therapeutic target[126].

5.3.3 Ranolazine

Ranolazine, a piperazine derivative, acts through the inhibition of the late sodium current (I_{Na} current) in cardiac myocytes. During myocardial ischemia, there is a build-up of intracellular sodium, which leads to an increase in intracellular calcium via the sodium-calcium exchanger[127]. By regulating this imbalance in ion shifts, ranolazine may improve myocardial relaxation and reduce left ventricular diastolic stiffness, which in turn can enhance myocardial contractility and perfusion. Ranolazine has minimal effects on the resting and exercise heart rate and blood pressure in patients with angina, and has shown antiarrythmic activity in experimental models[128].

5.4 RAS inhibition- Direct renin inhibitors

Renin catalyzes the rate-limiting step in RAS activation, i.e. the formation of angiotensin I from angiotensinogen and shows remarkable substrate specificity for angiotensinogen. These characteristics make it an attractive target for a therapeutic RAS blockade. Renin inhibition differs mechanistically from the established strategies of RAS blockade with angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). The increase of plasma rennin concentration caused by renin inhibition is much more pronounced compared to ACE inhibitors and ARBs[129]. This may be of clinical relevance because recent evidence suggests that renin, besides its enzymatic function, might exert direct, angiotensin II-independent, cellular effects via the (pro)renin receptor (PRR). Stimulation of this receptor may increase profibrotic pathways and activate gene programs implicated in vascular end organ damage and atherogenesis[130, 131].

5.5 Novel antiplatelet agents

1.5.1 Cox-1 Inhibitors

As mentioned before, a major limitation of aspirin is that irreversibly inhibits COX-1 of both platelets and endothelium therefore reducing the production of beneficial prostacyclin as well. Aiming the same pathophysiological mechanism, i.e. inhibition of TXA2 pathway, three different alternatives would seem feasible: selective inhibition of platelet only COX-1, thromboxane-synthase direct inhibition (therefore reducing the end-product) and thromboxane-receptors blockade since it has been shown that accumulating peroxides can per se activate them, the same way as TXA2[132].

5.5.2 Novel ADP/P2Y12 receptor anatgonists

Introduction of platelet ADP receptor inhibitors represented a breakthrough in the modern treatment of ACS, especially in the field of interventional cardiology. Newer agents resolving the bioavailability issues of clopidogrel are expected to minimize treatment failures and improve outcomes whereas it seems reasonable that agents with reversible inhibition of the ADP receptor will result in less bleeding complications.

5.5.3 Protease Activator Receptor 1 (PAR-1) inhibitors

Thrombin is arguably the most potent activator of platelets, exerting its action through the protease activator receptor 1 (PAR-1). *In vitro* studies suggest that minimal concentrations of thrombin are sufficient to activate this platelet receptor leading to platelet shape modification and aggregation, making development of PAR-1 inhibitors a challenging therapeutic option.

5.5.4 Selective 5-Hydroxytryptamine,5-HT2A receptor antagonists

Serotonin (5-Hydroxytryptamine, 5-HT) is known to participate in the regulation of cardiovascular system and is therefore linked to cardiovascular events. Serotonin release following a vascular injury induces platelet aggregation, vasoconstriction, increase of vascular permeability and cell proliferation following a vascular injury. These functions are mediated by the $5\text{-}HT_{2A}$ receptor and development of selective inhibitors could be used for the effective treatment of ischemic heart disease.

5.6 Novel antithrombotics

The previously mentioned limitations of current antithrombotic agents have led medical research to the development of new compounds. The major classes of these newer anticoagulants are the factor Xa inhibitors and the direct thrombin inhibitors with some of these agents being orally administered.

5.6.1 Direct thrombin inhibitors

Thrombin is the final enzyme in the clotting cascade, representing a reasonable target of most of the current clinical anticoagulants. The rationale for the clinical use of direct thrombin inhibitors is their ability to inactivate fibrin-bound thrombin, in contrast to both UFH and LMWH – AT complexes. They are also unaffected from other limitations of current therapeutic strategies like acquired or inherited AT deficiency, they demonstrate a better bioavailability profile, and avoid the problem of HIT.

5.6.2 Factor Xa inhibitors

Factor Xa inhibitors demonstrate a high affinity to Xa, without the need of AT, achieving effective inhibition of the thrombotic cascade. As in the case of thrombin inhibitors, these agents seem to have a rapid onset and offset of action making the concomitant use of UFH/LMWH obsolete while at the same time being safer in terms of bleeding complications. They are designed to have a relatively stable pharmacodynamics profile, without need for routine monitoring, making them theoretically superior to vitamin K antagonists for long-term use.

5.6.3 Other agents

Other agents have also been tested, taking advantage of our extensive knowledge regarding the clotting cascade. Factors V, VII, VIII, IX, and XII have all been considered as potential targets of treatment, therefore interfering in the different steps of the cascade. Thrombin is unique among the serine proteases of this cascade that possesses both pro-coagulant and anti-coagulant properties. It induces coagulation by activating platelets through their PAR-1 receptors, activating factors V, VIII, XI and XIII and inhibiting fibrinolysis through the thrombin-activated fibrinolysis inhibitor; on the other hand, when bound to thrombomodulin on the vascular endothelial cell surface it becomes an anticoagulant enzyme by activating

protein C. Since currently developed thrombin inhibitors interfere with both types of thrombin activity, engineering an inhibitor that would selectively inhibit thrombin's pro-coagulant properties, leaving its anti-coagulant functions intact would seem reasonable. In the same context, administration of recombinant activated protein C, therefore promoting natural anti-coagulation mechanisms, could be expected to produce favorable results.

6. COMPETITIVE ENVIRONMENT (TABLE)

6.1 Novel HDL-C raising therapies

6.1.1 CETP inhibitors

Several efficacious CETP inhibitors have been identified; these include torcetrapib (Pfizer, New York, NY, USA), dalcetrapib (previously referred to as RO4607381/JTT-705, Roche/Japan Tobacco, Basel, Switzerland), and anacetrapib (MK-0859, Merck & Co., Whitehouse Station, NJ, USA).

Torcetrapib, a CETP inhibitor, has been shown to produce substantial increases in HDL-C and modest reductions in LDL-C[133-138]. However, in a study conducted on hyperlipidemic mice, it was found that torcetrapib did not reduce atherosclerosis beyond atorvastatin and induced more proinflammatory lesions than atorvastatin[139]. Moreover, treatment with torcetrapib was associated with an increase in blood pressure, an effect that has not been reported with other CETP inhibitors in development[140, 141]. This blood-raising effect of torcetrapib may be merely compound-specific and unrelated to the mechanism of CETP inhibition, and is thought to be related to an increase in plasma aldosterone and corticosterone levels[142]. A clinical outcomes study of torcetrapib in high-risk patients, ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events), was stopped early owing to an excess in cardiovascular events and death in patients treated with the combination of torcetrapib and atorvastatin versus atorvastatin alone[133]. Subsequently, 3 studies have reported that torcetrapib did not reduce the atherosclerotic burden assessed in the coronary arteries (by intravascular ultrasonography) and in the carotid arteries (by ultrasonography of intima-media thickness)[134, 136, 138].

Dalcetrapib has demonstrated a favorable safety profile in a phase II study, and no changes in vital signs including blood pressure have been observed[143-145]. Several phase III clinical trials are ongoing with the objective of evaluating the clinical efficacy and safety of dalcetrapib. One of these, dal- VESSEL, is focused on modulation of vascular function by CETP inhibition and will shed further light on the mechanisms implicated in the improved endothelial function which was recently observed in hypercholesterolaemic subjects with low baseline HDL-C subsequent to dalcetrapib treatment[146]. Another trial, the impact of dalcetrapib on atherosclerotic plaque development (dal-PLAQUE), has been initiated in some 100 patients with CHD

using positron emission tomography/computerized tomography and magnetic resonance imaging[147]. Finally, in order to evaluate the effects of dalcetrapib on mortality and morbidity, >15 600 high-risk CHD patients considered to have stable disease after a recent acute coronary syndrome event have been recruited into the ongoing dal-OUTCOMES trial[148, 149].

Anacetrapib is currently the most potent CETP inhibitor under evaluation, with associated increases in HDL-C levels up to 129% and decreases in LDL-C levels of up to 38%[141]. Two phase I RCTs for anacetrapib have demonstrated the efficacy and safety of the new drug without blood pressure effects or serious side effects[141], and a phase III RCT recruiting a total of 1623 patients with CAD or CAD equivalents is still ongoing in order to obtain sufficient safety and efficacy data[150, 151].

Table: Newly developing drugs in CAD treatment:

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Torcetrapib	Pfizer	CETP inhibitor	CAD	Phase III-terminated	HDL-raising therapy
Dalcetrapib	Hoffmann-La Roche	CETP inhibitor	CAD	Phase II/III- expected results in 2011-2013	HDL-raising therapy
Anacetrapib	Merck	CETP inhibitor	CAD	Phase III-expected results by end of 2012	HDL-raising therapy
ER Niacin	Abbott	Water-soluble vitamin-B complex	CAD	Phase III-expected results in 2012	HDL-raising therapy
ER Niacin/ Laropiprant	Merck	Niacin/selective prostaglandin-D receptor antagonist	CAD	Phase III-expected results by beginning 0f 2013	HDL-raising therapy
Ragaglitazar	Novo-Nordisk	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase II-completed	HDL-raising therapy
Tesaglitazar	AstraZeneca	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase II-completed	HDL-raising therapy
Muraglitazar	Bristol-Myers Squibb/Merck	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase III-completed	HDL-raising therapy
Aleglitazar	Hoffmann-La Roche	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase III-expected results by mid-2014	HDL-raising therapy

Table: Continued

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
CSL 111	CSL limited	Reconstituted HDL	CAD	Phase II-completed	HDL-raising therapy
CSL 112	CSL limited	Reconstituted HDL	CAD	Phase I-expected results by 2011	HDL-raising therapy
APL 180	Novartis	Reconstituted HDL	CAD	Phase I/II-completed but no results yet	HDL-raising therapy
CER-001	Cerenis Therapeutics,SA	Apo-A1 based HDL mimetic	CAD	Phase II-expected results by end of 2012	HDL-raising therapy
Varespladib	Anthera	sPLA2 inhibitor	CAD	Phase II/III- expected results 2009/2010-2012	Atherosclerosis anti-inflammatory treatment
Darapladib	GlaxoSmithKline	Lp-PLA2 inhibitor	CAD	Phase III-expected results 2012-2014	Atherosclerosis anti-inflammatory treatment
Succinobucol	AtheroGenics	Heme oxygenase-1 inhibitor	CAD	Phase III-completed	Atherosclerosis anti-inflammatory treatment
Ivabradine	Servier	I_f current blocker	CAD	Phase IV-expected results in 2012	Anti-anginal treatment
Fasudil	Schering AG	Rho-Kinase inhibitor	CAD	Phase II-completed but no results yet	Anti-anginal treatment
Ranolazine	A. Menarini Pharma/ Gilead Sciences	Late sodium current (I_{Na}) blocker	CAD	Phase III completed/ Phase IV-expected results in 2011	Anti-anginal treatment
Aliskiren	Novartis	Direct rennin inhibitor	Hypertension/ CAD	Phase II/III-completed/ expected results	Anti-hypertensive and plaque stabilization
Triflusal	Uriach Laboratories	COX-1 inhibitor	CAD, CVD	Phase IV	Antiplatelet agent
Prasugrel	Eli Lilly / Daiichi Sankyo	P2Y12 receptor inhibitor	CAD, PCI	Phase III and IV	Antiplatelet agent
Ticagrelor	Astra Zeneca	P2Y12 receptor inhibitor	CAD, PCI	Phase III	Antiplatelet agent

Table: Continued

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Cangrelor	Medicines Company	P2Y12 receptor inhibitor	CAD, PCI Bridge to CABG	Phase III	Antiplatelet agent
Elinogrel	Portola Pharmaceuticals / Novartis	P2Y12 receptor inhibitor	CAD, PCI	Phase II	Antiplatelet agent
Vorapaxar	Merck	PAR-1 receptor inhibitor	CAD, PCI, CVD	Phase II and III	Antiplatelet agent
Atopaxar	Eisai Inc.	PAR-1 receptor inhibitor	CAD	Phase II	Antiplatelet agent
Terutroban	Servier	TXA2 receptor inhibitor	CAD, CVD	Phase III	Antiplatelet agent
Picotamide	LGM Pharma	TXA2 receptor and TXA2 synthase inhibitor	PAD	Phase III	Antiplatelet agent
Cilostazol	Otsuka Pharmaceutical	Phosphodiesterase inhibitor	CAD, PAD, CVD, PCI	Phase III and IV	Antiplatelet agent
DZ-697b	Daiichi Sankyo	Ristocetin-mediated platelet activation inhibitor	CAD, CVD	Phase I	Antiplatelet agent
Hirudin	Speedel Pharma Ltd.	Direct thrombin inhibitor	HIT	Established therapy	Anticoagulant
Lepirudin	Schering AG / Pharmion GmbH	Direct thrombin inhibitor	HIT	Established therapy	Anticoagulant
Argatroban	GlaxoSmithKline	Direct thrombin inhibitor	HIT, CVD	Phase IV	Anticoagulant
Bivalirudin	The Medicines Company	Direct thrombin inhibitor	HIT, CAD, PCI	Phase IV	Anticoagulant
Ximelagatran	AstraZeneca	Direct thrombin inhibitor	AF	Phase III, withdrawn due to hepatotoxicity	Anticoagulant
Dabigatran	Boehringer Ingelheim	Direct thrombin inhibitor	VTE, AF	Phase III and IV	Anticoagulant
Idraparinux	Sanofi-Aventis	Factor Xa inhibitor	VTE, PE, AF	Phase III, withdrawn due to bleeding complications	Anticoagulant
Idrabiotaparinux	Sanofi-Aventis	Factor Xa inhibitor	VTE, AF	Phase III	Anticoagulant
Otamixaban	Sanofi-Aventis	Factor Xa inhibitor	CAD, PCI	Phase II and III	Anticoagulant
Ultra low molecular weight heparin	Sanofi-Aventis	Factor Xa inhibitor	VTE	Phase III	Anticoagulant
Rivaroxaban	Johnson & Johnson / Bayer	Factor Xa inhibitor	VTE, PE, AF, CAD	Phase II and III	Anticoagulant

Table: Continued

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Apixaban	Bristol-Myers Squibb / Pfizer	Factor Xa inhibitor	VTE, PE, AF, CAD	Phase III	Anticoagulant
Edoxaban	Daiichi Sankyo	Factor Xa inhibitor	VTE, PE, AF	Phase III	Anticoagulant
SR123781A	Sanofi-Aventis	Factor Xa inhibitor, thrombin inhibitor	VTE, CAD	Phase II and III	Anticoagulant
LY517717	Eli Lilly	Factor Xa inhibitor	VTE	Phase II	Anticoagulant
Betrixaban	Portola Pharmaceuticals	Factor Xa inhibitor	VTE, AF	Phase II	Anticoagulant
YM150	Astellas Pharma	Factor Xa inhibitor	VTE, AF, CAD	Phase II and III	Anticoagulant

PCI: percutaneous coronary intervention, CAD: coronary artery disease, CVD: cerebrovascular disease, PAD: peripheral artery disease, HIT: heparin induced thrombocytopenia, VTE: venous thromboembolism, AF: atrial fibrillation, PE: Pulmonary embolism.

6.1.2 Extended-release (ER) Niacin and ER Niacin/Laropiprant combination

Two recently published Phase III RCT[93, 152], have shown the efficacy of ER Niacin as regards to lipid lowering and retarding atherosclerosis progression. It has been recently documented that endothelial-vasoprotective effects of HDL-C are impaired in patients with type 2 diabetes mellitus compared to healthy subjects, and that ER Niacin not only increases HDL-C plasma levels but markedly improves endothelial-protective functions, which is potentially more important[153].

In studies evaluating the combination of niacin with laropiprant on flushing it was shown that the rate of flushing was significantly decreased compared to patients on niacin without laropiprant[99, 154, 155]. Currently, the AIM-HIGH study (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) is an ongoing RCT which randomly allocates patients (45 years and older) with vascular disease and atherogenic dyslipidemia to therapy with simvastatin alone or simvastatin and ER niacin, and are being evaluated over a 5-year period to better define the additive effect of HDL-raising therapies[156]. Another trial, the HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events)[157], is recruiting 25,000 patients with a history of CHD, stroke, or peripheral arterial disease and randomizing them to placebo or the new ER niacin/laropiprant combination.

6.1.3 Dual Peroxisome proliferator-activated receptor (PPAR)-α/γ agonists

Ragaglitazar increased HDL-C by 31%, decreased triglycerides by 62%, and decreased hemoglobin A1c by 1.3%, but the adverse events of edema, anemia, and leukopenia have drawn concern[158, 159]. *Muraglitazar* increased HDL-C by as much as 16% in type 2 diabetic patients, but, as with ragaglitazar, weight gain and edema were more common with muraglitazar therapy[160, 161]. An analysis of muraglitazar's phase 2 and 3 data revealed an increase in risk of

death, cardiovascular events, and congestive heart failure associated with muraglitazar[162]. *Tesaglitazar*, a third agent in this drug class, can increase HDL-C by 13%[163-165]. Because of the observed side-effects, all these aforementioned compounds were stopped. Recently, a phase 2 trial of *aleglitazar* was shown to increase HDL-C by 20% and also decrease hemoglobin A1c in a dose-dependent manner, with a small increase in edema but not congestive heart failure or myocardial infarction[166]. As a result, a phase 3 study (Alecardio study) of aleglitazar in type 2 diabetic patients with a recent acute coronary syndrome is now ongoing[167].

6.1.4 Reconstituted HDL(rHDL) infusion

In a small study of healthy subjects, these intravenous infusions promoted reverse cholesterol transport[168]. Based on that a randomized placebo-controlled trial was conducted, ERASE[101], which showed that short-term infusions of reconstituted HDL (CSL 111) in patients with recent onset acute coronary syndromes showed no significant reduction in coronary atheroma volume, nonetheless, it induced a possibly favorable change in the quality of coronary atheroma. There was a high incidence of liver function test abnormalities with the high doses of HDL infusions, these were however self-limiting without any clinical consequence or intervention. Recently published results from a first-in-man randomized controlled study evaluating the safety and feasibility of autologous delipidated HDL plasma infusions (Plasma selective delipidation converts αHDL to preβ-like HDL, the most effective form of HDL for lipid removal from arterial plaques) in patients with ACS showed promising results regarding regression in the atheroma volume. Two ongoing phase I/II trials are testing the safety and efficacy of single intravenous infusions of rHDL in healthy volunteers[169, 170].

6.1.5 Apolipoprotien A-1(Apo A-1) Milano infusion

This therapy was piloted in humans when ETC-216, recombinant apolipoprotein A-I Milano complexed with phospholipid, was randomly infused in 57 patients within 2 weeks of an acute coronary syndrome (ACS) over 5 weekly treatments[171]. There was significant reduction in intravascular ultrasound (IVUS)-measured coronary atheroma burden with ETC-216, with 1 patient reported to have a significant rise in transaminases[171]. In a trial of 47 patients after an acute coronary syndrome, recombinant apolipoprotein A-I Milano infusion was associated with reverse coronary remodeling and reduced atheroma burden[172]. A future study will assess the effects of CER-001, an ApoA-I-based HDL mimetic, on indices of atherosclerotic plaque progression and regression as assessed by IVUS measurements in patients with ACS[173].

6.2 Atherosclerosis anti-inflammatory and antioxidant therapy

6.2.1 Selective phospholipase A2 (PLA2) inhibitors

6.2.1.1 Selective secretory phospholipase A2 (sPLA2) inhibitors

Varespladib sodium (A-001; Anthera Pharmaceuticals, San Mateo,CA or previously Eli-Lilly LY 315920), and varespladib methyl (A-002; Anthera Pharmaceuticals, San Mateo,CA or previously Eli-Lilly LY 333013) are both selective sPLA2 inhibitors. Varespladib sodium is intravenous formulation and varespladib methyl is the oral formulation of the selective sPLA2 inhibitors.

A phase II, randomised, double-blind, placebo-controlled, dose-response study (Phospholipase Levels and Serological Markers of Atherosclerosis [PLASMA])[174] conducted in 393 CAD patients showed that varespladib methyl reduced the enzymatic activity of sPLA2, LDL-C and oxidized LDL levels in a dose-dependent manner, and had anti-inflammatory effects as evidenced by a reduction in inflammatory markers, which suggest that A-002 might be an effective anti-atherosclerotic agent. In the 500 mg A-002 treatment group, there was one serious adverse event (exacerbation of underlying chronic obstructive pulmonary disease), but the proportion of patients reporting treatment-emergent adverse events did not differ from placebo. The main side-effects of the drug included headache, nausea, and diarrhea. PLASMA II is an ongoing RCT that examines the effects of once daily dosing of varespladib methyl (250mg, 500mg) on sPLA2 mass, lipids and lipoproteins in 135 patients with stable CAD[174, 175]. Other ongoing studies, FRANCIS-ACS and VISTA-16 trials, will assess the safety and efficacy of A 002 in subjects with ACS[176, 177]. Furthermore, The sPLA 2 Inhibition to Decrease Enzyme Release after PCI (SPIDER-PCI) trial will investigate the effects of treatment with varespladib methyl on peri-percutaneous coronary intervention (PCI) myocardial infarction incidence in patients undergoing elective PCI[178].

6.2.1.2 Selective lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitors

Several selective and highly potent azetidinone inhibitors have been developed as pharmacological tools. Darapladib (SB 480848, GlaxoSmithKline, Philadelphia, PA) represents the azetidinone selected for human clinical trials.

In a phase II multicenter, randomized, double-blind, parallel-groups study involving 959 stable CAD or CAD equivalent patients receiving atorvastatin, it was found that darapladib produced sustained inhibition of plasma Lp-PLA2 activity, and reduction of cardiovascular inflammatory biomarkers with no serious adverse events, only malodor of urine and faeces was reported in the darapladib treated group[179]. In another study, Integrated Biomarker and Imaging Study-2 (IBIS-2)[180], Lp-PLA2 inhibition with darapladib prevented necrotic core expansion, a key determinant of plaque vulnerability. Further ongoing phase III trials are addressing the potential role of darapladib in atherosclerotic plaque stabilization[181, 182]

and improved endothelial function[183]. These findings suggest that Lp-PLA2 inhibition may represent a novel therapeutic approach, whether this was associated with favorable effects on CV events needs to be further emphasized in future studies.

6.2.2 Heme oxygenase-1 inhibitors (Probucol analogues)

Succinobucol (AGI-1067, AtheroGenics Inc., Alpharetta, GA, USA) is a metabolically stable, orally available derivative of probucol. It has greater intracellular antioxidant efficacy in vitro than probucol without its QT prolonging effect[184]. Succinobucol has anti-inflammatory properties[185, 186], and has been found to reduce some circulating biomarkers of inflammation namely myeloperoxidase, but not C-reactive protein (CRP)[187]. Both succinobucol and probucol lower the risk of restenosis after percutaneous coronary intervention[184]. Additionally, succinobucol seemed to reduce progression of atherosclerosis in non-treated coronary reference segments[184], although this was not confirmed in a recently published study[187].

In a phase III, randomized, double-blind, placebo-controlled study among 6144 patients with recent acute coronary syndromes, the Aggressive Reduction of Inflammation Stops Events (ARISE) trial[188], succinobucol had no effect on the composite primary endpoint (of time to first occurrence of cardiovascular death, resuscitated cardiac arrest, MI, stroke, unstable angina, or coronary revascularization), however, the composite secondary endpoint of cardiovascular death, cardiac arrest, MI or stroke occurred in fewer patients in the succinobucol group, and there was 63% relative reduction in the tertiary endpoint of the occurrence of new-onset diabetes. These results were seen despite the unfavorable changes in lipids (increasing LDL-C and decreasing HDL-C), blood pressure, and CRP, suggesting that the antioxidant and anti-inflammatory effects of succinobucol might have favorably affected the clinical outcomes. These hypothesis-generating observations should draw further attention to future trials with succinobucol targeting high risk CAD patients.

In the ARISE trial, it is worth mentioning that there were more cases of hepatic derangement in the succinobucol arm, and one patient had liver failure which resolved after discontinuation of the drug. There was an increase in the occurrence of new onset atrial fibrillation in the succinobucol arm. Whether this observation is related to the small increase in blood pressure noted with succinobucol needs further studies.

6.3 New Anti-anginal treatments

6.3.1 Ivabradine

Ivabradine (Procoralan, Les Laboratories Servier, France; also available under the following names: Coralan, Corlentor, and Coraxan) has been established as an effective treatment to prevent myocardial ischemia in patients with chronic stable angina[122, 189, 190], and recent subgroup analysis raised the hypothesis that ivabradine may be helpful to reduce major cardiovascular events[26, 191]. This constituted the rationale for an ongoing study, Study assess-

InG the morbidity–mortality beNefits of the I_f inhibitor ivabradine in patients with coronarY artery disease (SIGNI_fY), which will assess the effects of ivabradine in terms of CV morbidity and mortality[192]. It has been found as well, that ivabradine therapy on top of commonly used dosage of B-Blocker therapy had an additional efficacy with no untoward effect on safety or tolerability[193].

In the recently published results of the SHIFT randomized placebo-controlled study (Ivabradine and outcomes in chronic heart failure)[194], it was found that in patients allocated to ivabradine , the relative risk of the primary end-point (cardiovascular death or hospital admission for worsening heart failure) dropped by 18% compared to placebo, supporting the importance of heart rate reduction with ivabradine for improvement of clinical outcomes in heart failure patients.

Pre-clinical animal studies have shown that ivabradine effect might extend beyond heart rate reduction. It was associated with decreased vascular oxidative stress, improved endothelial fuction and reduced atherosclerotic plaque formation[195]. This has stimulated further research with a planned phase IV RCT, to assess the effect of ivabradine therapy on reducing inflammatory markers in patients with acute coronary syndromes[195, 196].

6.3.2 Rho-Kinase (ROCK) Inhibitors

Recently, it was shown that inhibition of ROCK's activity by fasudil (Schering AG, Berlin, Germany) exerts anti-ischemic benefits. Fasudil inhibits coronary vasospasm in patients with unstable angina pectoris[197], and significantly increases the ischemic threshold of angina patients during exercise with a trend toward increased exercise duration[198]. The vasodilatory effect of fasudil is more potent than that of nitroglycerin[199] and has been shown to further dilate segments of vasospastic coronary artery that have already been pre-treated with nitroglycerin[200]. These findings support the potential of fasudil as a novel therapeutic agent for coronary vasospasm and ischemia.

Furthermore, Fasudil has been found to improve endothelial function in patients with CAD, through restoration of NO bioavailability in humans with atherosclerosis.[201]. This has fueled further research to determine whether fasudil would be useful in treating atherosclerosis and hypercholesterolemia[202]

6.3.3 Ranolazine

Ranolazine (Ranexa, A. Menarini Pharma UK, High Wycombe, UK) has been shown in several large trials to be an efficacious adjunctive agent in reducing symptoms of CAD[203-206]. It has been shown to increase exercise duration, reduce frequency of angina and reduce need for increased antianginal therapy. Ranolazine was generally well tolerated with the most commonly occurring side effects being dizziness, nausea, asthenia, and constipation[207], and its safety has been emphasized on long term follow-up[208]. Interestingly, the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN)-

TIMI 36 trial has indicated potential antiarrhythmic effects of ranolazine in a large population of NSTEMI-ACS patients, through reducing the percentage of clinically significant ventricular arrhytmias[205]. Currently, a phase IV RCT is ongoing to evaluate the effect of ranolazine 1000 mg administered twice daily compared to placebo on exercise-induced reversible myocardial perfusion defect size (PDS), assessed by gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in subjects with documented exercise induced myocardial ischemia at baseline[209].

6.4 RAS inhibition-Direct rennin inhibitors

Aliskiren is a direct renin inhibitor, with potent antihypertensive effects. Recently, a group of phase 2 and 3 clinical trials have been launched to assess the influence of aliskiren on plaque progression in established atherosclerosis using high resolution 3-D MRI[210] or using intravascular ultrasound[211], and to examine the influence of aliskiren in improving ventricular hemodynamics in subjects stabilized after ACS[212]. Also another study is planned; hypothesizing that long-term Aliskiren treatment will improve endothelial function and the production and function of endothelial progenitor cells (EPCs) in patients with early atherosclerosis[213]. We are still awaiting the results of the ASPIRE trial evaluating the efficacy and safety of aliskiren on the prevention of left ventricular remodeling in high risk post-acute myocardial infarction patients when added to optimized standard therapy[214].

6.5 New Antiplatelet agents

6.5.1 COX-1 inhibitors

Triflusal is an antiplatelet agent structurally related to aspirin, although it does not belong to salicylates. Its mechanism of action involves inhibition of TXA2 production through selective COX-1 inhibition, while at the same time preserving vascular prostacyclin synthesis. Moreover, triflusal is also a phosphodiesterase inhibitor resulting in cyclic AMP increase and therefore leading to reversible inhibition of platelet aggregation, vasodilation, and inhibition of vascular smooth muscle cell proliferation. Evidence from small clinical studies suggest that it is as effective as aspirin in prevention of vascular events (myocardial infarctions and strokes) while associated with lower risk of bleeding complications[215].

6.5.2 Novel ADP/P2Y12 receptor anatgonists

6.5.2.1 Prasugrel

Prasugrel (CS-747, LY640315) is an orally administered thienopyridine prodrug that, as in the case of clopidogrel, is activated in the liver through CYP. The active metabolite irreversibly binds platelet ADP receptor, to a similar extent as the active metabolite of clopidogrel. However, in the case of plasugrel, in vivo availability of the active metabolite is significantly higher

compared to clopidogrel. As a result, the recommended loading dose of 60 mg followed by a 10 mg daily maintenance regimen induces a more rapid, potent and consistent inhibition of platelet function compared to the currently used doses of clopidogrel (300 to 600 mg loading, followed by 75 mg daily for maintenance)[216]. Prasugrel has already been established as a valuable therapeutic option in clinical practice following the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), a phase III 13608-patient randomized trial, including moderate to high risk ACS patients undergoing PCI. In this study where prasugrel (60 mg loading and 10 mg maintenance) in addition to aspirin was immediately compared to clopidogrel (300 mg loading and 75 mg maintentance) plus aspirin, prasugrel was associated with a significant reduction of the primary end point (cardiovascular death, nonfatal MI, or nonfatal stroke) over a 15-month follow up period, in the expense of an increase in major bleeding (including fatal bleeding)[217]. The beneficial results of prasugrel were associated with a significant reduction of definite or probable stent thrombosis (1.1 vs 2.4%) while as predicting determinants of major bleeding were identified the history of stroke or transient ischemic attack, age of more than 75 years and body weight of less than 60 kg. In a pre-specified TRITON-TIMI 38 study of 3524 STEMI patients undergoing primary PCI, prasugrel also proved more effective than clopidogrel in preventing ischemic events, without a significant excess of bleeding complications[218]. Largely based on the TRITON-TIMI 38 trial, prasugrel has now been approved both in Europe and by FDA for the prevention of ischemic events in ACS patients undergoing PCI.

6.5.2.2 Ticagrelor

Ticagrelor (AZD6140) belongs to a new class of antiplatelet agents, the cyclopentyltriazolopyrimidines. Although its mechanism of action is also exerted through P2Y12 platelet receptor inhibition, in contrast to clopidogrel and prasugrel, this inhibition is reversible. It's an active metabolite (no metabolism of a pro-drug is required) with a rapid onset of action and greater degree of platelet inhibition compared to clopidogrel. The efficacy and safety of ticagrelor were evaluated in the Platelet Inhibition and Patient Outcomes (PLATO) trial where 18624 ACS patients (38% of them with STEMI) were randomly assigned to either ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300 to 600 mg loading dose followed by 75 mg daily) for one year. All patients were also receiving aspirin. At the end of the follow up period, patients on ticagrelor presented significantly lower rates of the composite primary end point (cardiovascular death, myocardial infarction or stroke) compared to clopidogrel (9.8 vs 11.7%) without any significant difference in the rates of major bleeding among the two groups[219]. Despite the encouraging results, ticagrelor is not clinically available yet, while some have serious concerns regarding the effects of a possible poor compliance to medication; given the reversible nature and the not yet fully explained side-effect of dyspnea. Pending in official registration, ticagrelor is already, like prasugrel,

announced in the new ESC guidelines for myocardial revascularization as class I indication for the treatment of NSTE-ACS and STEMI[220].

6.5.2.3 Cangrelor

Cangrelor is a direct acting reversible platelet P2Y12 inhibitor. Unlike the previously described agents, cangrelor is administered intravenously with its effect rapidly reversed following end of the infusion. Similar to prasugrel and ticagrelor, cangrelor is characterized by a rapid onset of action and more effective platelet inhibition compared to clopidogrel, with a favorable safety profile concluded from the initial phase II trials. Cangrelor underwent two phase III clinical trials, the "Clinical Trial to Demonstrate the Efficacy of Cangrelor (PCI)"[221, 222] and the "Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (Platform)"[223] that were discontinued due to insufficient evidence of cangrelor's clinical effectiveness. Cangrelor is still being studied as a bridge for patients on clopidogrel who are planned for CABG operation (BRIDGE: Maintenance of Platelet inihiBition With cangRelor After dIscontinuation of ThienopyriDines in Patients Undergoing surgery)[224].

6.5.2.4 Elinogrel

Elinogrel (PRT060128) is a novel, direct-acting, reversible P2Y12 antagonist that can be administered both orally and intravenously resulting in a simplified and effective treatment regimen and covering the full spectrum of care from acute onset to chronic care. A recent pilot trial (Early Rapid ReversAl of Platelet ThromboSis with Intravenous Elinogrel before PCI to Optimize REperfusion in Acute Myocardial Infarction, ERASE-MI) provided preliminary data about the feasibility and tolerability of escalating doses of intravenous elinogrel as an adjunctive therapy for primary PCI for STEMI[225]. Another double blind, randomized, phase II trial completed earlier this year (a Novel Antiplatelet Therapy in Patients Undergoing Non-urgent Percutaneous Coronary Interventions, INNOVATE-PCI), evaluated the safety, tolerability and efficacy of elinogrel in patients undergoing non-urgent PCI[226].

6.5.3 PAR-1 receptor inhibitors

Vorapaxar (SCH 530348) is an orally administered agent that reversibly inhibits platelet protease activated receptor-1, through which thrombin induces its effect on platelet aggregation, and thus, thrombus formation. A number of phase II clinical trials have provided promising results and two phase III clinical trials are ongoing; Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome (TRA•CER)[227] and Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P - TIMI 50)[228]) examining the safety and efficacy of vorapaxar in preventing the composite end-point of cardiovascular death, MI, stroke or urgent coronary revascularization in patients with an ACS (UA/NSTEMI) or atherosclerosis. Results of these studies are still pending.

Another agent of this class, Atopaxar (E5555) with potential antithrombotic and anti-inflammatory properties has recently completed two phase II trials (Japanese - Lesson from Antagonizing the Cellular Effect of Thrombin or J-LANCELOT, and Lesson from Antagonizing the Cellular Effect of Thrombin in Acute Coronary Syndromes or LANCELOT ACS)[229, 230] in a Japanese population with either ACS or high risk CAD. Results from these studies have been announced in the ESC 2010 and TCT 2010 congresses with atopaxar demonstrating a satisfactory safety profile in terms of bleeding complications and a potential to reduce major adverse cardiovascular events. There were some concerns regarding the liver function and prolongation of the QTc interval which may be due to the increased atopaxar doses used[231]. Further studies with phase III clinical trials and reduced dosing schemes are expected.

6.5.4 Thromboxane synthase and thromboxane receptor inhibitors

Terutroban (S 18886) is a selective antagonist of thromboxane receptor, inhibiting thromboxane induced platelet aggregation and vasoconstriction. Preliminary studies in humans have shown that terutroban induced regression and stabilization of atherothrombotic plaques in magnetic resonance studies[232] and that it successfully inhibited platelet aggregation in peripheral artery disease patients (an effect comparable to aspirin). A phase III clinical study (Prevention of cerebrovascular and cardiovascular events of ischemic origin with terutroban in patients with a history of ischemic stroke or transient ischemic attack, PERFORM) has recently been completed and the results are expected[233]. Recruiting 18000 patients, this study investigated the efficacy of terutroban in secondary prevention of further cerebrovascular and cardiovascular events following a stroke or a TIA, compared to aspirin.

Picotamide acts as an equally effective TXA2 synthase and TXA2 receptor inhibitor. It inhibits aggregation of human platelets while it also preserves prostacyclin production by re-orienting endoperoxides' metabolism, accumulated as a result of the TXA2 synthase blockade[234]. Picotamide inhibits TXA2 formation both intra and extra-vascular while, apart from platelets, it has an effect on other cells (monocytes etc) and seems to interact *in vivo* with the vascular endothelium[235]. The effects of picotamide in clinical practice have been tested in the double blind, randomized ADEP (Atherosclerotic Disease Evolution by Picotamide) and DAVID (Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics) trials that both involved patients with peripheral artery disease (PAD)[236, 237]. In the DAVID study, 1200 patients with PAD and diabetes were randomized to receive either picotamide (600 mg twice daily) or aspirin (320 mg once daily), with all-cause mortality as a primary end point. Patients on picotamide did significantly better with a total mortality of 3% vs 5.5% for the aspirin group[237]. Moreover this didn't come on the expense of more bleedings, with the agent being well tolerated. The DAVID study was a landmark study, demonstrating the increased efficacy of an agent (compared to aspirin) in the highly problematic group of diabetic patients. However its potential role in the treatment of patients with CAD needs further investigation.

6.5.5 Other agents

We previously discussed the potential role of triflusal in the treatment of CAD. The role of other phosphodiesterase inhibitors is also under investigation; cilostazol has been approved for the treatment of intermittent claudication. It has also been found to reduce smooth muscle proliferation and intimal hyperplasia after endothelial injury, properties that led to trials evaluating its efficacy for the prevention of restenosis after PCI[238, 239]. In the largest of these trials, cilostazol on top of regular aspirin and clopidogrel treatment significantly reduced angiographic in-stent restenosis, although this did not reflect to a difference in the rate of target vessel revascularization[238]. Moreover, these studies were performed before the era of drug eluting stents that largely resolved the issue of in-stent restenosis. Further studies are needed to determine a possible role of cilostazol (or other phosphodiesterase inhibitors) in current treatment strategies.

Better understanding of platelet biology and function has indicated other potential treatment targets; DZ-697b is a new orally active antiplatelet agent that inhibits collagen and ristocetin-mediated platelet activation. It does not require metabolisation to generate its active compound and has a safer profile than clopidogrel in pre-clinical studies. In a recently published study, oral DZ-697b showed potent, dose-dependent, antithrombotic effects comparable to clopidogrel, without prolonging bleeding times[240]. Its clinical efficacy remains yet to be studied.

6.5.6 Reduced dose of GP IIb/IIIa receptor antagonists

Although GPIIb/IIIa inhibitors are routinely used in clinical practice, increased concern of bleeding complications and their potential effect on outcomes, has led to re-evaluation of our strategies and set the pace for studies investigating the safety and efficacy of bolus-only GPIIb/IIIa receptor antagonists schemes[241]. In a study reporting single-center experience with 1001 patients, bolus-only dosing schemes of abciximab, tirofiban and eptifibatide resulted in low rates of in-hospital death (0.1%), myocardial infarction (4.3%), and repeat revascularization (0%) that are comparable to the outcomes observed when mainstream dosing schemes are followed, while achieving lower rates of major or minor bleeding (2.3%)[242]. However, since this was an observational and not a randomized trial, the results must be cautiously evaluated.

6.6 New Antithrombotic agents

6.6.1 Direct thrombin inhibitors

6.6.1.1 Parenteral direct thrombin inhibitors

Hirudin, lepirudin (a recombinant hirudin), argatroban and bivalirudin are all parenterally administered direct thrombin inhibitors. The rationale for their clinical use as well as their benefits over UFH and LMWH has been analyzed before.

Hirudin and (its recombinant analogue) lepirudin are mainly used for the treatment of HIT. Lepirudin has also been evaluated for the treatment of acute coronary syndromes (both unstable angina and non-ST elevation myocardial infarction) but results were disappointing; a benefit was indeed observed in terms of death, re-infarction and revascularization reduction, but this was on the expense of increased moderate or major bleeding, attributed to its narrow therapeutic window[243, 244]. Similarly, in the case of STEMI patients, randomized trials failed to support a substantial benefit from the use of either hirudin or lepirudin, although in this case an increased risk of bleeding was not observed[243, 245].

Argatroban has also been FDA approved for the treatment of HIT. It has a short in vivo half-life and dose adjustments are not required in the presence of renal failure. As in the case of hirudin/lepirudin, a randomized trial failed to prove a benefit from using it in the setting of acute myocardial infarction patients[246].

Bivalirudin has also a short plasma half-life (of about 25 minutes) and undergoes predominantly non-organ elimination (proteolysis), inclining for a rather safe profile in terms of bleeding complications. It is the first agent of this class that has been approved as an effective anticoagulant in the setting of interventional cardiology. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) study (involving 14000 patients with moderate or high risk ACS undergoing PCI) bivalirudin (as the only anticoagulant) proved as effective as the combination of UFH or enoxaparin with GPIIb/IIIa in terms of ischemic complications at 30 days, while significantly reducing the bleeding complications, with the greater benefit observed in those aged more than 75 years[247]. The efficacy of bivalirudin in the setting of STEMI was further studied in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial, where bivalirudin plus provisional use of GPIIb/IIIa was tested against standard therapy, in a series of 3600 patients. Both at the 30-day and 12-month time points, bivalirudin proved safer in terms of the combined end point of major bleeding or major cardiovascular event[248]; however a slightly higher risk of acute stent thrombosis (i.e within the first 24 hours) was observed in the bivalirudin group, underlying the need for early P2Y12 inhibitors initiation and possibly for a prolonged bivalirudin infusion, in selected patients[249]. Based on the results of HORIZONS AMI and ACUITY, bivalirudin has been included in the guidelines of treatment of ACS patients. Bivalirudin (with provisional use of GPIIb/IIIa inhibitors) can also be used as a substitute of UFH-GPIIb/IIIa

combination for stable angina and low risk ACS patients, as demonstrated in the Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events (REPLACE-2) study[250].

6.6.1.2 Oral direct thrombin inhibitors

Ximelagatran was the first oral direct thrombin inhibitor to get into phase III clinical trials. However, despite the promising results of the Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trials in terms of thromboembolism prevention, it was withdrawn due to the observed incidence of hepatotoxicity[251, 252].

Dabigatran etexilate is a prodrug of the active compound dabigatran that has been tested for the prevention and treatment of both venous and arterial thromboembolic disease[253, 254]. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial published recently, 18113 patients with atrial fibrillation and at least one risk factor for stroke (mean CHADS2 score 2.1) were randomly assigned to receive either dabigatran (two dosing schemes were tested, 110 or 150 mg twice daily) or warfarin (target INR 2.0-3.0). Dabigatran in the lower dosing scheme proved as effective as dose adjusted warfarin (in terms of ischemic stroke and systemic embolism prevention) while safer in terms of hemorrhagic stroke and major bleeding incidence. On the other hand, the higher dosing scheme of dabigatran proved more effective in terms of thromboembolic events' prevention, being at the same time as safe as warfarin in major bleeding incidence[253]. Dabigatran represents an attractive alternative to contemporary warfarin treatment, since (in addition to the advantages of both dosing schemes mentioned) it does not require monitoring of the INR, it's less susceptible to dietary and drug interactions and it's not limited by warfarin's narrow therapeutic window. On the other hand, besides the increased cost of therapy, adoption of the new agent cannot yet be recommended due to the lack of long term safety data. Other issues that can be mentioned are the inconvenient dosing scheme (twice daily), the lack of data for patients with renal insufficiency and the lack of an effective antidote.

6.6.2 Factor Xa inhibitors

In addition to the thrombin inhibitors previously mentioned, a new class of direct factor Xa inhibitors is under clinical development. This new class of agents (xabans) that has both oral and parenteral representatives is generally characterized by a rapid onset of action and a rather stable pharmacodynamics profile without a need for routine monitoring, making them an attractive option as a substitute of traditional anti-coagulants.

6.6.2.1 Parentral factor Xa inhbitors

Idraparinux sodium (SR34006) is a synthetic pentasaccharide administered subcutaneously with a similar chemical structure and same method of action as fondaparinux but with a much longer elimination half-life, making feasible a once-a-week dosing scheme. The drug

never reached the market due to concerns of excessive bleeding following the use of this agent, documented in the AMADEUS trial which tested its efficacy in preventing thromboembolic events, against adjusted dose vitamin K antagonists, in patients with atrial fibrillation[255]. Instead Idrabiotaparinux (SSR126517), a biotinylated version of idraparinux, was developed. Despite the similar mode and duration of action, Idrabiotaparinux can be safely inactivated, if this becomes necessary, by i.v. infusion of avidin that neutralizes its anti-Xa activity[256]. Results from phase III trials, assessing idrabiotaparinux's efficacy in preventing thromboembolism in the setting of deep vein thrombosis and atrial fibrillation, are expected[257, 258].

Otamixaban (XRP0673) is a short-acting, intravenously administered, selective inhibitor of factor Xa. It has already been tested in two phase II trials in the setting of routine PCI interventions and NSTEMI ACS ((Prevention of Ischemia with Anti-Xa inhibition in acute coronary syndromes 1 - Thrombolysis in Myocardial Infarction 42, SEPIA-ACS1 TIMI 42 and Otamixaban in Comparison to Heparin in Subjects Undergoing Non-Urgent Percutaneous Coronary Intervention, SEPIA-PCI) with promising results[259, 260]. A Phase III trial, comparing it to standard therapy in high risk ACS patients undergoing early invasive strategy, is currently recruiting patients[261].

Ultra low molecular weight heparin (AVE5026) is a hemi-synthetic molecule with an average molecular weight of 2000 to 3000 Da (almost half compared to other LMWH). It has nearly pure anti-Xa activity and is currently being assessed in phase III trials as an alternative to standard therapy for prevention of DVT thromboembolism[262-264].

6.6.2.2 Oral factor Xa inhibitors

Rivaroxaban (BAY 59-7939) is an orally administered direct factor Xa inhibitor with a bioavailability of 80 percent and peak plasma concentrations occurring 2.5 to 4 hours following administration. As in the case of previous agents mentioned in this category, it does not require routine monitoring. It has proved favorable to enoxaparin in the prevention of venous thromboembolism in patients undergoing orthopedic surgery, without increasing the bleeding complications[265]. A phase II clinical trial in ACS patients demonstrated a beneficial effect in terms of ischemic events reduction along with a dose-dependent increased bleeding risk[266]. Phase III clinical trials are currently testing its efficacy in the setting of ACS[267], recurrent thromboembolism prevention[268] and prevention of stroke in the setting of non-valvular atrial fibrillation[269].

Apixaban (BMS-562247-01) has also been tested for the prevention of thromboembolism, mainly in the setting of orthopedic surgery. In a recently published study, apixaban did not meet the pre-specified non-inferiority criteria compared to enoxaparin but its use was associated with lower rates of clinically relevant bleeding[270]. However, in another phase III clinical trial also involving knee-replacement surgery patients, apixaban proved more effective than enoxaparin without increasing bleeding risk[271]. Further studies, assessing its efficacy in the setting of atrial fibrillation[272] and ACS patients[273] are on their way.

Edoxaban (DU-176b) has completed a number of phase II clinical trials testing its efficacy in non-valvular atrial fibrillation[274] and phase II and III trials in thromboembolism prevention following orthopedic surgery[275, 276]. A large phase III trial (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48, Engage AF-TIMI 48) comparing edoxaban to warfarin in terms of stroke prevention in patients with non-valvular atrial fibrillation is currently recruiting patients[277], with results expected in 2012.

SR123781A is a synthetic hexadecasaccharide with a mixed profile of AT-dependent anti-Xa and anti-thrombin activities. In a dose-ranging study for the prevention of thromboembolism following orthopedic surgery (NCT00338897), it demonstrated a reasonable risk to benefit ratio compared to enoxaparin[278].

LY517717 and Betrixaban (PRT-054021) are two more agents of this category that have been tested in phase II trials against enoxaparin in orthopedic patients[279, 280]. Both were well tolerated and gave promising results, with further phase III trials expected in the near future.

YM150 is another direct factor Xa inhibitor that is currently being tested in a phase II study in subjects with acute coronary syndromes[281] after proving safe and effective for prevention of venous thromboembolism after hip replacement.

7. POTENTIAL DEVELOPMENT ISSUES

7.1 Cell-based therapy

Cell-based revascularization strategies have the potential to become a major therapeutic advance for severe CAD. Intra-myocardial bone marrow stem cell injection is currently being investigated as a new therapeutic option for patients with chronic ischemia who are ineligible for revascularization. Bone marrow mononuclear CD34+ stem cells, harvested from the iliac crest or by leukapheresis after granulocyte colony–stimulating factor, are injected into the ischemic myocardium. In small randomized placebo- controlled studies[282, 283], myocardial injection was found to be safe and to be associated with a modest but statistically significant improvement in myocardial perfusion, left ventricular ejection fraction (LVEF), exercise capacity, and Canadian cardiology society (CCS) class. This technique is still in the experimental stages, and further studies are required to assess long-term results and efficacy for reducing mortality and morbidity.

7.2 New therapeutic targets of cholesterol metabolism

With the increasing burden of CAD, there will be a continuing demand for on-going research into cholesterol metabolism and the development of drugs to modify it favorably:

7.2.1 Squalene Synthase inhibitors

Squalene synthase inhibitors decrease circulating LDL cholesterol by the induction of hepatic LDL receptors in a similar manner to statins without the risk of myotoxicity[284]. Two new potent squalene synthase inhibitors (EP2306 and EP2302) have been described *in vitro*[285], the squalene synthase inhibitor EP2302 inhibited cholesterol synthesis in a dose-dependent manner with a similar potency to that of simvastatin. Further *in vivo* studies are required for further evaluation.

7.2.2 Microsomal triglyceride transfer protein (MTP) inhibitors and Apo-B mRNA antisense oligonucleotides

An alternative approach to lowering LDL-C is to limit hepatic assembly of very low density lipoprotein (VLDL), the precursor of LDL. One strategy is to develop inhibitors of MTP (which is essential for the assembly of VLDL). Whilst this may effectively lower LDL cholesterol, it also causes hepatic triglyceride accumulation[286]. Another approach is to use Apo B mRNA antisense oligonucelotides (Apo B is the principal protein of VLDL and LDL)[287]. These hold the promise of preventing VLDL formation without causing hepatic steatosis[288], and might hold promise for treatment of patients not reaching target LDL cholesterol levels on stable statin therapy[289]

7.3 Anticoagulants in development

Apart from improving the pharmacodynamics and pharmacokinetics of currently available agents, new anticoagulants aiming other factors of the coagulation cascade are also developed and tested. In a relatively recent study, recombinant nematode anticoagulant protein c2 (rNAPc2), a potent inhibitor of the tissue factor/factor VIIa complex, gave promising results without increasing major or minor bleeding[290]. In the same perspective, selective inhibitors of factors IXa and XIIa have also been considered as potential therapeutic agents[291, 292].

An alternative method seems to be manipulating the clotting cascade pathway by either interfering with key-cofactors (like factors Va and VIIIa) or modulating the pro-coagulant/anticoagulant balance of thrombin activities. In this context recombinant activated protein C, that inactivates factors Va and VIIIa, has been shown to ameliorate the coagulopathy associated with severe sepsis and reduce mortality[293]. Whether this agent would prove effective as an anticoagulant in the treatment of CAD is not yet known. Furthermore, recombinant soluble thrombomodulin (ART-123), an agent that binds thrombin and inactivates its procoagulant effects while leaving its anti-coagulant properties intact, has been tested in septic patients with disseminated intravascular coagulation[294] while another phase II trial suggests it's efficacious for venous thromboembolism prophylaxis following total hip replacement surgery[295].

8. EXPERT OPINION

- There is established evidence that high levels of HDL-C in nature are associated with a lower risk of CAD. Unlike LDL-C, the mechanisms controlling HDL-C are more complex. Lifestyle interventions are safe but only modestly increase HDL-C. The best treatments available currently seem the niacin derivatives, although the newer CETP inhibitors, reconstituted HDL infusion and apolipoprotein A-1 Milano infusion hold much promise. The next 5 years should provide information on whether improving vascular protective function of HDL is more important than HDL-C levels and also whether we should target raising specific HDL subclasses rather than HDL-C itself.
- Treatment of dyslipidemia in diabetic patients remains a very challenging issue in CAD prevention, there is an increased interest in treatments that has a dual favorable effect on both glycemic control and lipid control, most important in this issue is the up-growing role of glitazars, especially aleglitazar, which is foreseen to be the upcoming treatment for lipid regulation in diabetic patients.
- Nowadays, with a better understanding of the immunological and inflammatory mechanisms underlying atherosclerosis, treatments that stabilize vulnerable plaques and halts atherosclerosis progression are gaining wide interest and will show promising results within the next few years. Lp-PLA2 is an emerging biomarker of CV risk that is pharmacologically modifiable through specific Lp-PLA2 inhibitors, as darapladib. Moreover, Aliskiren, a direct renin inhibitor is gaining wide interest in terms of plaque stabilization and regression in established atherosclerosis.
- Combination therapy can provide marked lipoprotein changes in patients at risk for atherosclerotic events. Three large clinical trials, involving more than 45,000 patients in aggregate, are currently testing the effect on major clinical endpoints of adding niacin or ezetimibe to statin treatment in patients at high risk[156, 157, 296]. Results of these trials are expected in 2012–2013. Nevertheless, a recent systematic review of 102 studies found no benefit of combination therapy over high-dose statin monotherapy in terms of mortality, MI, stroke, and revascularization procedures in patients requiring intensive lipid-lowering therapy[297]. An effective strategy in patients requiring intensive lipid-lowering therapy is critically needed and still controversial, and is a field for further research.
- Novel anti-anginal treatments, as ivabradine, fasudil and ranolazine have gained wide interest because of the absence of effect on blood pressure, regional myocardial blood flow or myocardial contractility, a benefit that they have over conventional anti-anginal therapies. They have proved to have an additive benefit in terms of anginal pain relief and exercise tolerance. Whether these treatments have a further role beyond anti-anginal effect, as vasoprotective and endothelial function influence, is still a field of intensive research and the ongoing studies will answer this question.

- Antiplatelet agents and anti-thrombotics represent a major advancement in the current treatment of ACS and CAD. Despite the progress achieved, the fraction of non-responders among the population treated, the narrow therapeutic window of many of the agents used and the increased bleeding complications often observed limit their usefulness and sets the pace for the research and introduction of novel therapeutic options.

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Chapter 6

Restenosis after PCI. Part 2: prevention and therapy

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ABSTRACT

The techniques and materials used during percutaneous coronary intervention have advanced considerably over the past 3 decades, yet restenosis remains one of the major drawbacks of this procedure. Many innovative technologies, including drug-eluting stents, with or without specific polymers, and fully biodegradable stents have been and continue to be developed in the search for a safe and effective antirestenosis therapy. Remarkable advances in stent design and nanoparticle delivery systems ('nanovehicles') have already fueled revolutionary changes in the prevention and treatment of in-stent restenosis. In this Review we provide an overview of the latest innovations for optimizing outcomes of coronary stenting, and up-to-date information about prevention and treatment of in-stent restenosis.

KEY POINTS

- Although drug-eluting stents decrease the incidence of restenosis, they do not yet fully prevent this problem; furthermore, long-term safety issues indicate that new technologies are still warranted
- New-generation polymer coatings, including biocompatible permanent polymers and biodegradable polymers, and stents without a polymer, represent innovative technologies that aim to preserve vascular biology in the long-term
- Biodegradable stents prevent the long-term problems associated with foreign material in the coronary arteries; the first human studies employing these stents show promising results
- Nanoparticle-mediated drug delivery systems are expected to revolutionize the development of innovative therapeutic devices, allowing local or targeted delivery of the drug with an excellent biocompatibility profile
- Drug-eluting balloons provide homogenous drug distribution in the vascular wall and represent a favorable option for the treatment of restenosis
- Gene-eluting stents are expected to play an important role in the prevention of in-stent restenosis, particularly in patients with a high genetic-risk profile

INTRODUCTION

Since its introduction in the late 1970s,[1] percutaneous coronary intervention (PCI) has become the most important and widely used treatment for patients with obstructive coronary disease. Although the technique and the materials used during the procedure have advanced tremendously, restenosis—the renarrowing of the treated obstruction—remains one of the major complications of PCI.[2] Intravascular stents were developed as an adjunct to primary angioplasty for the management of early complications, including arterial dissection, and for the treatment for early elastic recoil. Despite the beneficial effects of stenting, however, rates of restenosis remained persistently high, giving rise to a new problem—in-stent restenosis (ISR). The introduction of drug-eluting stents (DESs) was seen as a solution to this problem and, initially, DESs reduced the incidence of ISR considerably.[3] However, these promising results led to increased use of DESs in a diverse range of complex coronary lesions, and for off-label indications, leading to a resurge in the rates of ISR.[4,5]

In light of the increasing number of PCI procedures being performed, the difficulty of treating ISR, and the increasing cost of adjuvant medication and devices, defining subsets of patients at increased risk for restenosis would be useful. These patients could benefit from additional treatment modalities. Until now, identification of subgroups has been only partially successful, as was discussed in detail in Part 1 of this Review.[6] The ongoing efforts to better understand the underlying pathophysiological mechanisms of restenosis and vascular biology continuously fuel research on the prevention and treatment of ISR. Here, in Part 2 of the Review, we will assess the most important innovations for optimizing the outcomes of coronary stenting, and data on the prevention and treatment of restenosis in general, and ISR in particular, published in the 5-year period up to August 2011.

PREVENTION OF RESTENOSIS

In general, PCI with DESs is currently the best approach for the prevention of restenosis.[7] However, safety concerns about stent malapposition, late stent thrombosis, and delayed restenosis have arisen.[8,9] The main cause of these problems has, in addition to patient-related and lesion-related factors, been attributed to the stent polymer.[10] Additionally, the eluted antiproliferative agent and the stent platform (metal alloys and strut thickness) have been implicated in ISR. These concerns have fueled research in stent development, utilizing new antiproliferative agents, polymer technology, and metal stent platforms (Table 1).

Antiproliferative agents

Sirolimus (rapamycin)-eluting stents (SESs; Cypher®, Cordis Corporation, Bridgewater, NJ, USA) and paclitaxel-eluting stents (PESs; Taxus®, Boston Scientific, Maple Grove, MN, USA),

Table 1: Developments in preventive measures for restenosis

Target	Development	Status
Antiproliferative drug	Sirolimus derivatives (biolimus A9[18,19,22] and novolimus[23])	Clinical*
Polymer	Biolinx® (Medtronic Vascular, Inc., Santa Rosa, CA, USA)[25,26]	Clinical*; preliminary‡
Polymer	PolyzeneF[27–29]	Clinical*; preliminary‡
Polymer	Biodegradable (polylactic acid, polylactic-co-glycolic acid,[30–32] SynBiosys® [InnoCore Technologies, Groningen, the Netherlands], Eureka® SOLO [Surmodics, Inc., Eden Prairie, MN, USA])[37]	Clinical*
Stent design	Polymer-free stent (Biofreedom®, Biosensors International Group, Hamilton, Bermuda)[41,42]	Clinical*; preliminary‡
Coating	Endothelial progenitor cell capturing stent (Genous®,[48–50,56] Combo Stent®[38,53] [OrbusNeich Medical, Inc., Fort Lauderdale, FL, USA])	Clinical*
Coating	Titanium-nitride-oxide-coated stents (Titan2™ stent [Hexacath, Rueil-Malmaison, France])[55–61]	Clinical*
Stent platform	Bioabsorbable stent (magnesium stent [Biotronik, Berlin, Germany])[71–76]	Clinical*
Drug delivery	Nanomedicine[79,80]	Preclinical§
Stent platform/ metal alloys	Platinum–chromium alloy stents (Promus Element® and Taxus Element® (Boston Scientific, Maple Grove, MN, USA)[66–69]	Clinical*
Drug delivery	Magnetic targeting stents[81]	Preclinical§
Miscellaneous	Gene-based therapy[82–90]	Preclinical§
Miscellaneous	Systemic treatment[91,93,95–97,99–101,104,105]	Clinical*

*Clinical: development is currently being tested in a clinical setting. ‡Preliminary: first clinical results in small studies await replication in larger trials. §Preclinical: development is currently being tested in animal models

which were approved by the FDA in 2003 and 2004, respectively, were the first two DESs that were approved for use in humans. Although they both effectively reduce rates of restenosis compared with bare-metal stents (BMSs), their local adverse effects on the vasculature are fairly divergent. High concentrations of locally released paclitaxel have been shown to have detrimental effects on the vascular wall in a mouse model,[11] suggesting a narrower therapeutic range of this potent drug. On the other hand, sirolimus has a less-harmful effect than paclitaxel on the vascular wall.[11] Data from comparisons of first-generation DESs show that PESs are associated with a higher risk of ISR and stent thrombosis than SESs.[7,12] Two stents eluting sirolimus analogs—everolimus (Xience V®, Abbott Cardiovascular Systems, Inc., Santa Clara, CA, USA) and zotarolimus (Endeavor®, Medtronic Vascular, Inc., Santa Rosa, CA, USA)—have also been approved by the FDA.

Many studies have been dedicated to comparing the various available DESs. In 2011, the 2year follow-up results of two large-scale, randomized, controlled trials showed a sustained

benefit of everolimus-eluting stents (EESs) over PESs in terms of safety and efficacy.[13,14] On the other hand, zotarolimus-eluting stents (ZESs) were found to have a higher angiographic restenosis rate compared with PESs, although clinically driven repeat revascularization rates were similar for both stent types.[15] In patients receiving routine clinical care, SESs have proven to be superior to ZESs.[16] The 2year outcomes of the RESOLUTE All Comers trial[17] showed sustained similar safety and efficacy between ZESs and EESs. Unfortunately, few data are available on the direct EES versus SES comparison. Therefore, sirolimus and its analogs seem to be marginally superior to paclitaxel, whereas differences between the various limus-eluting stents remain to be elucidated.

In search for greater antirestenotic efficacy and improved long-term safety, new compounds specifically designed for use with DESs are being developed and studied. Biolimus A9 is a novel rapamycin derivative that, like sirolimus, inhibits smooth muscle cell proliferation via binding to the FK506-binding protein 1A and subsequent inhibition of the mammalian target of rapamycin (mTOR) and is specifically developed for local delivery to coronary arteries (Figure 1).[18] Besides its anti-inflammatory and antiproliferative potential and improved pharmacokinetic profile, the increased lipophilicity of biolimus A9 improves uptake by the coronary vessel wall, resulting in a more localized effect and lower systemic drug exposure[19] than sirolimus eluted from the Cypher® stent.[20,21] Compared with first-generation DESs, biolimus A9-eluting stents (BESs) have been shown to be associated with better recovery of endothelial function in coronary arteries, which could be partly explained by the better drug release kinetics.[22]

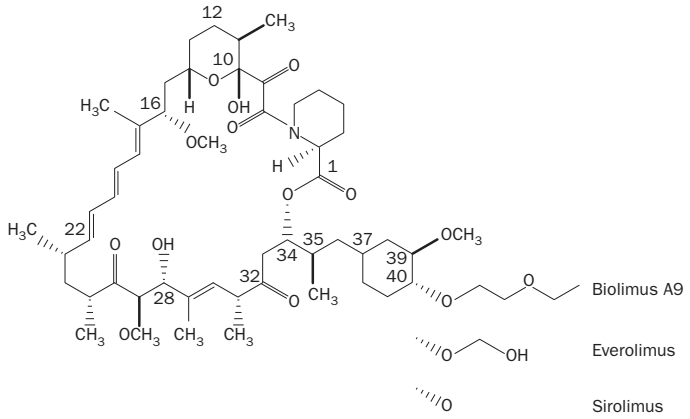

Figure 1: Chemical structure of biolimus A9. This compound consists of a 31-membered triene macrolide lactone that preserves the core sirolimus ring structure with a 2ethoxyethyl group addition to the hydroxyl group at position C (40) of the sirolimus molecule. One rationale for the inclusion of the ethoxyethyl group was to increase lipophilicity and, thus, to improve uptake by the coronary vessel wall. Permission obtained from John Wiley and Sons © Ostojic, M. *et al. Catheter. Cardiovasc. Interv.* **72**, 901–908 (2008).

Novolimus is a metabolite of sirolimus and represents another new antiproliferative mTOR inhibitor specifically developed for the stent. The newly developed DESyne® (Elixir Medical, Sunnyvale, CA, USA) novolimus-eluting stent has been tested in a clinical study, showing superiority over ZESs regarding angiographic in-stent late loss.[23]

Polymer technology

New-generation polymer coatings have been produced with the specific aim of mimicking the endothelial lining in order to prevent late thrombotic complications. Basic research has shown that some polymeric materials could potentially upregulate genes related to inflammation, proliferation, thrombosis, and vasoconstriction[24]—processes that are considered to be pivotal in the development of restenosis.[6]

One example of current progress is the Biolinx® (Medtronic Vascular, Inc.) polymer, currently used in the Endeavor Resolute® ZES. This blend of three different polymers—the hydrophobic C10 polymer to control drug release, the biocompatible and hydrophilic C19 polymer, and polyvinyl pyrrolidone—allows an early burst followed by controlled drug release[25] so that at least 85% of the zotarolimus is released within 60 days and the remainder within 180 days, avoiding long-term release of the drug. Such release patterns are designed to match the delayed healing times seen in complex lesions. The Resolute® ZES was shown to significantly lower target lesion revascularization (TLR) compared with an earlier Endeavor® ZES, which utilized a phosphorylcholine coating.[26]

Another polymer, polyzeneF is highly biocompatible and has anti-inflammatory, bacteria-resistant, and prohealing qualities. The coating ensures that the stent has a very low surface thrombogenicity, potentially reducing the risk of stent thrombosis. Evaluation of cobalt chromium stents nanocoated with polyzeneF in an animal model yielded favorable results.[27] Preliminary studies evaluating the Catania™ (CeloNova Biosciences, Newnan, GA, USA) stent in humans demonstrated a good safety profile and high-level efficacy.[28,29] Efforts to improve polymer stent coatings are ongoing.

Biodegradable polymers

Given the issues of polymer-induced inflammation, thrombosis, and restenosis, the development of biodegradable polymers has become a focus for research. The most-studied biodegradable polymers are polylactic acid and polylactic-co-glycolic acid, which degrade over time and could, therefore, eliminate the problems associated with lack of polymer biocompatibility and polymer-induced inflammation. To date, several biodegradable polymer stents eluting biolimus A9, sirolimus, or paclitaxel have been clinically evaluated, which have so far proven to be effective and safe in the short term (≤30 days) and midterm (≤1 year).[30–32] In 2010, the 3year follow-up data from the LEADERS trial[33] was presented, showing the sustained benefit of BESs with a biodegradable polymer over SESs with a durable polymer. Great expectations exist within the cardiology community that biodegradable-polymer DESs

could become the stents of choice in years to come; the results of the ongoing ISAR-TEST6 trial,[34] testing the safety and efficacy of the Nobori® (Terumo Corporation, Tokyo, Japan) biodegradable polymer BES and the Xience V® permanent polymer ZES will, therefore, be eagerly awaited.

New polymer technology presents some challenges, such as establishing the optimal degradation time, biocompatibility, composition, and formulation of the polymer. Several factors influence the velocity of degradation; therefore, the balance between drug-release kinetics and the rate of polymer degradation, as well as the effects of the degradation products all affect the efficacy of biodegradable polymer stent systems in the coronary vasculature.[35] Furthermore, studies in porcine coronary arteries have shown that even biodegradable polymers can cause inflammatory reactions, which could be attributable to the combination of the parent polymer compound and the biodegradation products.[36] Two new biodegradable polymers (SynBiosys® [InnoCore Technologies, Groningen, the Netherlands] and Eureka® SOLO [SurModics, Inc., Eden Prairie, MN, USA) have been tested in animal studies and yielded fewer acidic byproducts, and had a better degradation rate and biocompatibility profile than polylactic acid and polylactic-co-glycolic acid making them well-tolerated *in vivo*.[37] In a pig model, stainless-steel R Stents® (OrbusNeich Medical, Inc., Fort Lauderdale, FL, USA) with SynBiosys® coating and high-dose sirolimus (5 µg/mm) was associated with the lowest amount of neointima thickness after 28 days when compared with Xience V® and Cypher® stents.[38]

Polymer-free stents

In an attempt to overcome the problems encountered with polymers or their degradation products, 'polymer-free' DESs have been developed and have proven to be safe in clinical studies.[39,40] In an animal study, polymer-free biolimus A9 coated stents (Biofreedom®, Biosensors International Group, Hamilton, Bermuda) demonstrated more sustained intima inhibition, improved healing, and reduced inflammation compared with the polymer-coated sirolimus eluting Cypher® stent at 180-day follow-up.[41] The ongoing first-in-man study of the Biofreedom® stent showed promising results compared with the Taxus® PES.[42]

Polymer-free, dual DESs have been tested over the past few years. No apparent benefit was observed by adding estradiol to a polymer-free SES in the ISAR-PEACE trial.[43] However, results from the ISAR-TEST2 study[44] revealed that a novel, polymer-free sirolimus-eluting and probucol-eluting dual DES was noninferior to the Cypher® SES and the Endeavor® ZES. The antirestenotic efficacy of both the dual DES and the ZES remained durable during the 2year follow-up period.[44] The larger ISAR-TEST5 study,[45] which was powered for clinical events, showed similarly durable results for the dual DES.

Novel prohealing stent coatings

Endothelial progenitor cell-capturing stent

An increased rate of endothelialization is thought to lead to reductions in restenosis and stent thrombosis.[46] This hypothesis underlies the development of the endothelial progenitor cell (EPC)-capturing stent. The bioengineered Genous® (OrbusNeich Medical, Inc.) EPC-capturing stent has a stainless-steel platform that is coated with an abluminal polysaccharide matrix and covalently coupled monoclonal murine antihuman CD34 antibodies. These antibodies bind bone-marrow-derived EPCs from the peripheral blood. These EPCs are hypothesized to differentiate into a functional endothelial layer after immobilization and populate the surface of the stent.[47] The safety and efficacy of the Genous® stent have been shown in preliminary human studies,[48,49] and further evaluation and comparison with other stents is currently ongoing.[50]

Despite its benefit in enhancing re-endothelialization, and thereby possibly preventing stent thrombosis, EPC capturing is not expected to potently inhibit neointimal proliferation. On the contrary, CD34 antibodies have even been shown to capture other progenitor cells, for example, smooth muscle cell progenitor cells, which could exaggerate restenosis.[51] Therefore, a major challenge in the development of an EPC-capturing DES is to maintain sustained inhibition of smooth muscle cell proliferation while promoting formation of a functional endothelial layer. This concept was tested in an animal study showing that immobilization of anti-CD34 antibody on SESs enhances endothelialization.[52] The REMEDEE study[38,53] investigators are currently testing the Combo Stent® (OrbusNeich Medical, Inc.), which incorporates low-dose abluminal sirolimus together with EPC-capturing technology and a biodegradable polymer. The combination of an EPC-capturing stent with a drug-eluting balloon is also an attractive alternative, as has been shown by the results of the PERFECT STENT study.[54]

Titanium-nitride-oxide-coated stent

The Titan2™ stent (Hexacath, Rueil-Malmaison, France) is a stainless-steel stent coated in titanium-nitride oxide that has been shown to inhibit platelet aggregation, minimize fibrin deposition, reduce inflammation, and promote healing.[55] This stent significantly reduced late lumen loss and TLR compared with a BMS at 6months follow-up,[56] with preserved benefits up to 5years.[57] Additionally, the Titan2™ stent demonstrated favorable results compared with the Taxus® PES in a randomized controlled trial of 425 patients with STsegment elevation myocardial infarction,[58] as well as in routine clinical practice.[59] Despite the absence of an antiproliferative drug, use of the Titan2™ stent resulted in less TLR than the Taxus® stent, although this reduction was not statistically significant.[58] The Titan2™ stent was noninferior to the Xience V® EES in the primary results of the large randomized controlled BASE-ACS trial[60] conducted in patients with acute coronary syndrome. However, the Titan2™ stent failed to prove noninferiority to the Endeavor® ZES in terms of angiographic in-stent late lumen

loss at 6 months in the TIDE study,[61] although clinical outcomes at 1 year were comparable for both stent types.

Future prohealing stent designs

A step further to optimize the prohealing stent design is to create a bioactive stent that also elutes a drug (a bioeluting stent). Animal studies of a newly designed titanium-nitride-oxide stent eluting L-arginine, a precursor of nitric oxide with positive effects on endothelium function,[62] or a sulfated polysaccharide extracted from seaweed have shown up to 50% reduction in late lumen loss compared with the standard titanium-nitride-oxide stent.[63] A future clinical trial (the VINCI first-in-man study) is planned to test the efficacy and safety of this new generation of stents.[63]

Another approach to creating a prohealing stent would be to reduce the binding of platelets to an implanted stent, thereby reducing the inflammatory response and allowing surrounding endothelial cells to properly re-endothelialize the stent.[64] A stent created from a bioactive ligand, such as an integrin-binding motif, has been successfully used in noncardiac applications *in vivo* to promote device integration.[65] The ideal ligand should only interact with integrins uniquely present on endothelial cells and not on platelets, inflammatory cells, or smooth muscle cells.[64] Continued *in vitro* and *in vivo* studies with such biomaterials could lead to the creation of next-generation prohealing stent surfaces that promote the endothelialization of the stent while simultaneously inhibiting the adhesion and thrombus formation, and not stimulating smooth muscle cell proliferation.

Stent platforms

Metal alloys

A platinum–chromium alloy developed in the early 2000s has been combined with everolimus on the Promus Element® (Boston Scientific) and with paclitaxel on the Taxus Element® (Boston Scientific) stents, which were granted 'CE' European safety marks in November 2009 and May 2010, respectively. Unlike stainless steel and cobalt–chromium alloys, platinum–chromium has the advantage of increased radial strength enabling the stent to have thinner struts, which have been proven to reduce clinical and angiographic restenosis.[66,67] In PLATINUM,[68] the Promus Element® stent was shown to have comparative efficacy and safety when compared with Xience V®. Similarly, the efficacy and safety of the Taxus Element® stent is comparable with that of the Taxus Express2® (Boston Scientific) stent.[69] In a first-in-man study published in 2010, the Taxus® Petal™ (Boston Scientific) platinum–chromium bifurcation stent was successfully implanted in 25 of 28 patients (89.3%), with satisfactory clinical and angiographic outcomes at 1 year.[70]

Bioabsorbable platforms

The problems encountered with DES have encouraged research into innovative, temporary vascular scaffolds or bioabsorbable stent platforms, which gradually degrade until healing and re-endothelialization have occurred. Eventually, no foreign material is left exposed to the blood, thus mitigating the problem of late stent malapposition and stent thrombosis. These stents have the potential to preserve endothelial function, reactive vasomotion of the artery, and permit late lumen enlargement (expansive remodeling).[71] Initially, a high restenosis rate of 45% was observed in the PROGRESS-AMS trial[72] in which a non-drug-eluting bioabsorbable magnesium stent (Biotronik, Berlin, Germany) was evaluated. Yet more favorable results with stents with a poly-L-lactic acid backbone eluting everolimus (Abbott Vascular, Santa Clara, CA, USA) were reported in the ABSORB trial[71,73] with sustained clinical benefit at 3years follow-up. The first generation (revision 1.0) of bioabsorbable vascular scaffolds showed slight signs of shrinkage at 6 months contributing to late luminal loss.[74] However, the second generation (revision 1.1) showed substantial improvements with efficacy comparable to that of current DESs, and enhanced conformability to the angulations and curvatures of the vessel (Figure 2).[75,76]

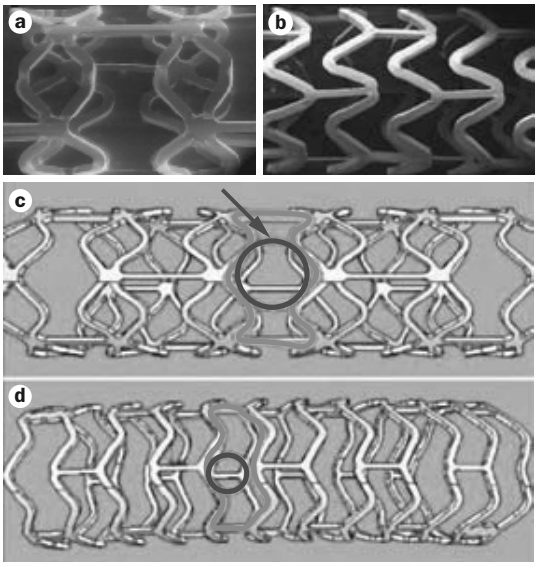

Figure 2: The bioabsorbable stent. a | The first-generation (revision 1.0) and b | the second-generation (revision 1.1) of a bioabsorbable, everolimus-eluting stent. A clear change in the device design between the two generations is evident, with the out-of-phase zigzag pattern connected directly or by straight bridges in revision 1.0 being replaced by the in-phase hoops linked by straight bridges in revision 1.1. c | In addition, the maximum circular (red circles) unsupported cross-sectional areas (green contours) are larger in revision 1.0 than in d | revision 1.1. Parts a | and b | reprinted from *Journal of the American College of Cardiology*, **56** (Suppl. 10), Garg, S. & Serruys, P. W., Coronary stents: looking forward. S43–S78, © 2010, with permission from Elsevier. For parts c | and d |, permission obtained from Wolters Kluwer Health © Serruys, P. W. *et al. Circulation* **122**, 2301–2312 (2010).

Nanomedicine

In addition to its promising application in cancer chemotherapy, great interest has been generated in the application of nanotechnology in optimization of local drug delivery. Nanoparticles are liposomes consisting of lipids and polymers that can be loaded with a drug and used to nanotexture stents, in molding processes to make stents, and for drug delivery from stents.[77] Nanoparticle-mediated drug delivery systems are expected to revolutionize the development of innovative therapeutic devices, allowing local or targeted delivery of the drug with an excellent biocompatibility profile. This strategy controls the concentration and duration of drug release, thereby potentially reducing systemic toxicity.[78] Of the drugs investigated for restenosis prevention and treatment, only paclitaxel and sirolimus have been successfully administered through nanoparticle-based delivery systems and only in preclinical studies.[79,80] Paclitaxel eluted from a cobalt–chromium stent coated with porous carbon–carbon nanoparticles showed promising results with respect to endothelialization and neointimal hyperplasia.[79] Sirolimus incorporated into nanoparticle delivery systems (poly-D,L-lactide) showed improved release kinetics.[80] Furthermore, these sirolimus-loaded nanovehicles selectively inhibited cell viability and proliferation of cultured human coronary artery smooth muscle cells, while human coronary artery endothelial cells were inhibited to a less extent, thus leaving endothelial cells viable to an extent that allows re-endothelialization of a stented vessel and still prevents smooth muscle cell proliferation.[80]

In another approach, Chorny *et al.* have investigated the novel concept of 'magnetic targeting stents' by combining uniform field-induced magnetization and a biocompatible magnetic nanoparticle formulation in a rat model of carotid stenting.[81] Magnetic targeting allows a drug to be delivered on demand to an *in vivo* site with various dosing regimens. These investigators demonstrated that the magnetic nanoparticles loaded with paclitaxel adequately inhibited neointima formation after uniform-field-controlled targeting when compared with nonmagnetically-treated animals.[81] Nanomedicine is, therefore, an innovative and promising perspective in stent design, but has yet to be demonstrated as safe and effective in clinical practice.

Gene-based therapy

Gene-based therapy has emerged over the past few years as a promising tool for the prevention of ISR. Numerous transgenes have shown to be effective in reducing ISR in animal models (Table 2) and various modes of local gene delivery have been developed. An effective method of gene delivery is by means of 'gene-eluting stents', which elute plasmid DNA or adenoviral vectors.[82,83] Pyrrole–imidazole polyamide is a powerful gene-regulating compound ('gene silencer') that inhibits the interaction between proteins, such as transcription factors, and DNA.[84] An *in vivo* animal study conducted by Yao *et al.* showed that synthetic pyrrole–imidazole polyamide can suppress neointimal hyperplasia by downregulation of transforming growth factor β1 and connective tissue growth factor,[85] as well as monocyte chemotactic

Table 2: Preclinical studies of gene therapy for restenosis

Study	Transgene (approved gene name)	Mode of delivery	Findings
Brito *et al.*[82]	eNOS (*NOS3*)	Plasmid-mediated gene delivery from lipopolyplex-embedded stents	Accelerated RE and reduced ISR
Takemoto *et al.*[83]	pE-NTPdase (*ENTPD*)	Plasmid-mediated gene transfer via cationic gelatin-coated stents	Accelerated RE, reduced ISR, and inhibition of subacute IST
Fishbein *et al.*[136]	iNOS (*NOS2*)	Adenoviral-mediated gene delivery from stents	Reduced ISR
Sharifi *et al.*[137]	eNOS (*NOS3*)	Adenoviral-mediated gene delivery from stents	Accelerated RE and inhibition of ISR
Johnson *et al.*[138]	TIMP3	Adenoviral-mediated gene delivery from stents	Reduced ISR
Egashira *et al.*[139]	Anti-MCP1 (anti-*CCL2*)	Plasmid-mediated gene delivery from stents	Reduced ISR
Walter *et al.*[140]	VEGF2 (*VEGFC*)	Gene-eluting stent of naked plasmid DNA	Increased RE and reduced ISR
Brasen *et al.*[141]	EC-SOD (*SOD3*)	Catheter-mediated intramural delivery of adenovirus	Accelerated RE and reduced ISR

Abbreviations: Anti-MCP 1, antimonocyte chemoattractant protein 1; CCL2, chemokine (CC motif) ligand 2; ENTPD, ectonucleoside triphosphate diphosphohydrolase; ECSOD, extracellular superoxide dismutase; eNOS: endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; ISR, in-stent restenosis; IST, in-stent thrombosis; NOS2, nitric oxide synthase 2, inducible; NOS3, nitric oxide synthase 3 (endothelial cell); pE-NTPdase, placental ectonucleoside triphosphate diphosphohydrolase; RE, re-endothelialization; SOD3, superoxide dismutase 3, extracellular; TIMP3, tissue inhibitor of matrix metalloproteinase 3; VEGF2, vascular endothelial growth factor 2; VEGFC, vascular endothelial growth factor C.

protein 1, matrix metalloproteinase 9, and intercellular adhesion molecule 1,[86] making it a promising next-generation agent.

Nuclear 'orphan' receptors comprise a group of ligand-activated receptors for which specific ligands have not yet been identified, but which are known to directly bind and interact with the promoter of target genes.[87] Nuclear receptor related proteins 1 and 77 have been identified as having a role in ISR development; overexpression of these proteins inhibits intimal proliferation and ISR in animal models.[88,89] A small-molecule drug that enhances the activity of these receptors, namely 6mercaptopurine, represents an attractive novel target for local intervention in restenosis.[89]

Finally, reducing the proliferative capacity of vascular smooth muscle cells could be of benefit in reducing neointimal hyperplasia following PCI. The biology of microRNAs and their ability to modify smooth muscle biology has been reviewed by O'Sullivan and colleagues.[90] Two microRNAs, mir143 and mir145, were shown to have a key role in the regulation of vascular smooth muscle cells *in vivo* and might, therefore, have therapeutic potential.

Systemic treatment

Since local drug delivery does not eradicate ISR completely, systemic treatment has also been explored, despite the obvious risk of adverse effects. We will briefly discuss the evidence for the antirestenotic effects of several antiproliferative and anti-inflammatory drugs.

The major role of the inflammatory system in restenosis formed the rationale for using prednisone for the prevention of this condition. The IMPRESS trial[91] showed favorable results with oral prednisone in patients undergoing coronary BMS implantation both in angiographic and clinical outcomes. In addition, a subanalysis from the ongoing CEREA-DES trial,[92] reported by Pesarini *et al.* in 2010,[93] showed that high doses of oral prednisone reduced late lumen loss, probably via a reduction in the release of tumor necrosis factor.

Preclinical studies have demonstrated that systemically administered sirolimus (rapamycin) reduces neointimal proliferation after vascular injury.[94] Several clinical trials confirmed the benefit of oral sirolimus in reducing ISR after BMS implantation,[95,96] making it a possible effective and cost-saving alternative to DES implantation. However, the long-term results of the OSIRIS trial,[97] reported by Kufner and co-workers in 2009, showed an attenuated benefit of oral sirolimus after 4 years and, moreover, raised concerns regarding a related increase in newly diagnosed malignancies.

Cilostazol, a phosphodiesterase III inhibitor, has antiproliferative effects[98] and has been shown to reduce intimal hyperplasia and restenosis after both BMS and DES implantation.[99,100] In a meta-analysis published in 2011, Kamal *et al.* concluded that addition of cilostazol to standard dual antiplatelet therapy reduces angiographic restenosis without significantly affecting rates of major adverse cardiac events or bleeding.[101] However, cilostazol was associated with an increase in the incidence of minor adverse effects, such as headaches, gastrointestinal complaints, and palpitations.[102]

Pioglitazone, a thiazolidinedione peroxisome proliferator-activated receptor gamma agonist, is used for the treatment of diabetes. An additional antiatherogenic effect of the drug in vascular cells limiting lesion development in animal models of atherosclerosis has been described.[103] Several clinical studies have demonstrated a reduced incidence of ISR after stent deployment with thiazolidinedione (pioglitazone or rosiglitazone) administration.[104,105]

Although rates of ISR have been shown to be reduced with the systemic use of various drugs, the concentration of drug accumulated at the site of interest is limited by toxicity. Systemic treatment will, therefore, probably never be superior to local drug delivery with DESs. This strategy could, however, be useful as an adjunct to BMS implantation.

RESTENOSIS: PRESENTATION AND OUTCOMES

If measures to prevent the development of restenosis fail, the clinical presentation of this condition is not always benign and can have a spectrum of acuity.[106] Multiple mechanisms

underlie myocardial infarction associated with ISR. An occlusive restenosis can be difficult to differentiate from a thrombotic event and a highly stenotic ISR lesion can promote local non-occlusive thrombosis and lead to a clinical presentation of non-ST-segment elevation myocardial infarction or troponin-positive unstable coronary syndrome.[107] Whether a difference exists between the use of DESs and BMSs in this entity of 'thrombosis on top of restenosis' remains to be elucidated. A pathology study by Nakazawa *et al.* confirmed the occurrence of neoatherosclerosis in the neointimal growth after implantation of both BMSs and DESs, but unstable features of neoatherosclerosis were encountered more frequently and earlier with DESs.[108] Whether this finding translates into a difference in outcomes between stent types is still questionable.[109]

One factor that does influence outcomes associated with ISR is the angiographic pattern of restenosis (Figure 3), which can be broadly classified into focal (<10 mm) and nonfocal (>10 mm) lesions. Mehran *et al.* showed that the pattern of ISR independently predicts the long-term need for revascularization, with an increase in the rate of TLR with increasing ISR class.[110]

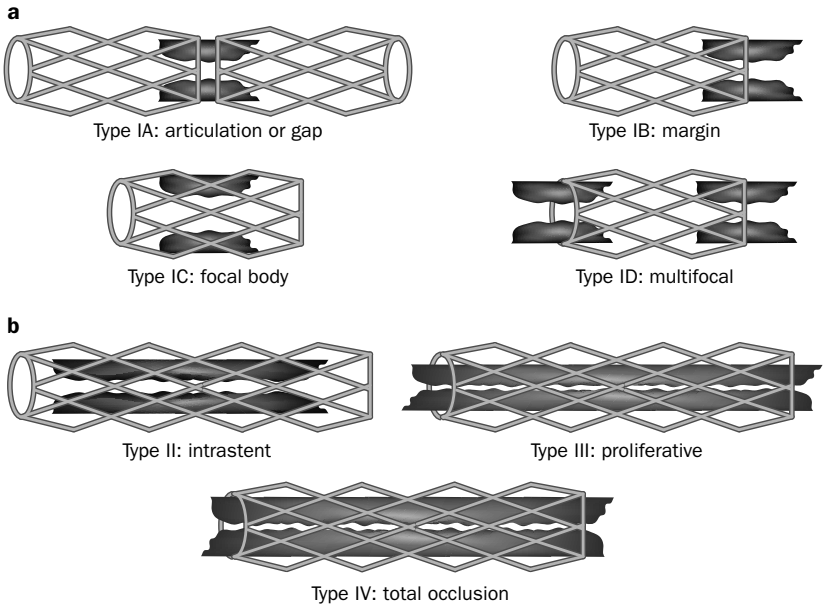

Figure 3: Patterns of in-stent restenosis. Schematic image of four patterns of in-stent restenosis (ISR). a | Pattern I (focal ISR) contains four types (A–D). Restenotic lesions are ≤10 mm and are located at the articulation or gap between stents (Type IA), at either the distal or proximal margin of the stent (Type IB), within the body of a stent (Type IC), or a combination of these distributions (Type ID). b | Patterns II–IV (diffuse ISR) are defined according to the anatomical position of ISR in relation to the previously implanted stent. Type II lesions are >10 mm and do not extend beyond the margins of the stent; Type III lesions are >10 mm and extend beyond the stent margins; Type IV lesions represent total occlusion and have a Thrombolysis in Myocardial Infarction flow grade of 0. Permission obtained from Wolters Kluwer Health © Mehran, R. *et al. Circulation* **100**, 1872–1878 (1999).

The morphologic patterns of DES restenosis are different from those of BMS, favoring a more focal and easily treated pattern with expected improved clinical outcomes.[111] In DES-treated patients, the rates of TLR were significantly higher in diffuse ISR compared with focal ISR.[112]

TREATMENT OF RESTENOSIS

The optimal treatment for ISR remains debatable. The options include vascular brachytherapy; conventional balloon, cutting balloon, or drug-eluting balloon angioplasty; BMS or DES implantation; and CABG surgery. This diversity of available treatments and the variability in the underlying etiology of restenosis make selection of the most appropriate modality difficult. In other words, the treatment of ISR should be tailored and individualized according to the clinical situation and in view of the underlying etiological factors. Several of the treatment options for restenosis are discussed in detail below.

Vascular brachytherapy

Intracoronary brachytherapy was once recommended as an effective treatment for ISR on the basis of data from several randomized, controlled trials published in the early 2000s.[113,114] Antiproliferative δ (iridium192) or β (phosphorus32) irradiation is delivered locally to the target lesions via dedicated catheters. Currently, however, brachytherapy with either β or δ radiation is of very limited use. The difficulty in performing this procedure, particularly handling the radioactive substances, and the increasingly widespread use of DESs has gradually displaced brachytherapy from the armamentarium of the interventionist. Nevertheless, the 5year follow-up data from the SISR study, presented at the 2011 ACC i2 summit, suggest that brachytherapy could be an equivalent treatment option to SES implantation for the treatment of ISR.[115]

Cutting-balloon angioplasty

The cutting balloon consists of a balloon catheter with three to four blades or 'atherotomes' designed to create discrete longitudinal incisions in the atherosclerotic lesion during balloon inflation. Such controlled dilatation theoretically reduces the force needed to dilate an obstructive lesion compared with standard balloon angioplasty and avoid slipping-induced vessel trauma during PCI, potentially decreasing the risk of ISR development.[116] Although this expected benefit was not demonstrated when the device first came into use in the early 1990s,[117] the later REDUCE III study did show that an IVUS-guided cutting balloon procedure followed by BMS implantation yielded restenosis rates similar to those achieved with DESs, thereby, providing an effective alternative.[118] However, use of the cutting balloon remains uncommon for the treatment of ISR, especially when used without stent placement. In 2010, Park *et al.* raised concerns that cutting-balloon angioplasty might be associated with a higher

risk of myocardial infarction than conventional balloon angioplasty;[119] this technique is, therefore, unlikely to become an important ISR treatment modality.

Drug-eluting balloon angioplasty

Non-stent-based local delivery of an antiproliferative drug, particularly using drug-eluting balloons, theoretically represents a very attractive treatment for ISR that avoids the limitations associated with DES platforms. Drug-eluting balloons improve drug delivery by allowing homogenous drug transfer to the entire vessel wall rather than only to the areas covered by stent struts, as with DESs. All currently available drug-eluting balloons use paclitaxel in various coating formulations with a typical dose of 3 μg/mm^2 of balloon surface. Drug-eluting balloon angioplasty has been shown to be more effective than conventional balloon angioplasty,[120] and as effective as PES implantation[121] for the treatment of ISR. However, drug-eluting balloons of course cannot prevent the almost immediate elastic recoil phenomenon. Currently, research in this area is focused on comparisons of the various available drug-eluting balloons. For example, in a preclinical study in an advanced porcine model of coronary restenosis, Joner *et al.* found that the Pantera® Lux (Biotronik, Berlin, Germany; 3.0 μg/mm^2 paclitaxel), the SeQuent® Please (B. Braun Melsungen AG, Berlin, Germany; 3.0 μg/mm^2 paclitaxel), and the Elutax™ (drug-eluting balloons (Aachen Resonance, Aachen, Germany; 2.0 μg/mm^2 paclitaxel) all resulted in delayed healing when compared with conventional balloon angioplasty.[122] However, the investigators also demonstrated significant heterogeneity in neointimal suppression between the balloons, with superiority of Pantera® Lux.[115] This difference was attributed to the 'excipient' used as an effective carrier for paclitaxel in the Pantera® Lux and SeQuent® Please balloons. The 6month results of the PEPPER trial,[123] which were presented at the ACC i2 summit in April 2011, showed excellent results for the Pantera® Lux balloon for the treatment of ISR both in BMSs and DESs. The detailed subgroup analysis, and 12-month follow-up data, are expected to be announced in late 2011.

In the 2010 guidelines for myocardial revascularization published by the European Society of Cardiology, drug-eluting balloons were considered a class IIa indication for the treatment of ISR.[124] Nevertheless, further large studies need to be implemented before these devices can be fully integrated into clinical practice. Patients are currently be recruited for an ongoing trial[125] to investigate the efficacy of a drug-eluting balloons for the treatment of ISR in patients with DESs.

Drug-eluting stents

DESs are known to have fairly low rates of ISR.[4,5] The proportion of restenotic lesions treated with DES in the studies providing this data is, however, low. Since restenotic lesions have a tendency towards recurrent restenosis, as discussed in Part 1 of this Review,[6] the outcomes associated with stent (DES) implantation in these lesions is likely to be different to those for DES placement in *de novo* lesions. In addition, ISR after BMS implantation differs from ISR

associated with DES use and, therefore, a distinction between these two types of restenosis should also be made in terms of treatment.

Favorable outcomes of DES treatment for BMS-related ISR have been reported in several studies, even after long-term follow up.[118–121] Treatment with DES placement was found to be more effective and safer than conventional balloon angioplasty,[126] vascular brachytherapy,[127,128] or BMS implantation within the original stent.[129] DESs should, therefore, be the treatment of choice for the treatment of BMS-related ISR. By contrast, the same cannot be said for DES-related ISR, which continues to be a therapeutic challenge. To date, the treatment of this condition has been investigated in only one randomized controlled trial, which showed comparable efficacy for SES reimplantation or a switch to PES implantation in patients with SES-related ISR.[130] Other small nonrandomized trials have produced inconsistent results, limiting the possibility of drawing any definitive conclusions about the optimal treatment of DES-related ISR.[107]

An individual's resistance to a particular eluted drug can be a factor in restenosis development.[131,132] This hypothesis provides the rationale for switching to a different DES for the treatment of DES-related ISR. However, to date, no clinical study has demonstrated clear clinical benefit of implanting an alternative different DES.[130,133] Whether resistance to sirolimus also implies resistance to other limus derivatives remains questionable, as no reports have been published on the use of zotarolimus, everolimus, or biolimus A9-eluting stents for the treatment of SES-related ISR. Another uncertainty is whether the angiographic pattern of DES-related ISR provides a clue to the involvement of drug resistance. Drug resistance is expected to cause a diffuse pattern of ISR, so perhaps a future study focused on patients with diffuse patterns of ISR would clarify the potential benefits of changing the agent eluted by the stent. In the ongoing prospective, randomized Italian GISE-CROSS trial,[134] treatment with a stent that elutes the same drug as the original restenosed stent (no CROSS group) is being compared with a crossover to an alternative DES in patients with ISR after either PES or SES implantation. The results of this study are eagerly awaited. Patients treated with DES for ISR are at high risk for recurrent ischemic events and should be maintained on dual antiplatelet therapy unless a complication emerges.[107] Therefore, individuals who have a contraindication for, or show noncompliance with, dual antiplatelet therapy should be considered for CABG surgery.

CABG surgery

CABG surgery is usually considered as the 'last resort' treatment for ISR in the clinic. However, this strategy is an appropriate first-line therapy for certain complex cases, such as multivessel ISR, diffuse ISR, multiple subsequent DES restenosis treated by repeat DES implantation, a strong genetic predisposition to ISR that precludes further interventional options, or in cases where dual antiplatelet therapy is not appropriate, as discussed above. To our knowledge, no studies of CABG surgery for the treatment of in-stent restenosis have been conducted.

CONCLUSIONS

Restenosis is a complex disease with a diversity of underlying mechanisms that are still not fully understood. Many innovative technologies, including DESs (with or without specific polymers) and fully biodegradable stents, have been and continue to be developed in the diligent search for an ideal antirestenosis therapy that is both effective and safe in the long term. Developments in the field of gene therapy might also impact future restenosis therapies. Advances in stent design and nanoparticle delivery systems ('nanovehicles') in the past 5 years have already fueled revolutionary changes in the concept of ISR prevention and treatment. In addition, several clinical algorithms for ISR treatment have been proposed on the basis of angiographic pattern of restenosis.[107,134,135] Treatment of ISR should be tailored to the individual, taking into consideration the available evidence and the best strategy for the patient, as well as the best method of treating the lesion. We believe that investing in the prevention of ISR is worth much more than investing in its treatment.

REVIEW CRITERIA

The articles on which this Review is based were identified by searching MEDLINE using the following keywords and Medical Subject Headings (MeSH) terms: "coronary restenosis", "drug-eluting stent", "biodegradable stent", "gene therapy of restenosis", and "nanomedicine". We checked for papers published up to August 2011. Only papers in the English language were included. Although we realize that not all available evidence could be incorporated, the most relevant and influential articles were selected for inclusion in this Review.

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J. W. Jukema, T. A. N. Ahmed and J. J. W. Verschuren researched data for and wrote the article. All authors contributed to the discussion of content. J. W. Jukema, J. J. W. Verschuren and P. H. A. Quax reviewed/edited the article before submission. J. W. Jukema and T. A. N. Ahmed contributed equally to this paper.

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Chapter 7

(Late) Stent Malapposition in the BMS and DES Era

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INTRODUCTION

Since the introduction of drug eluting stents (DES), the incidence of coronary stent restenosis has been significantly reduced. However, the safety of DES became a major issue after several studies associated DES with an increased risk of the rare but often devastating development of late and very late stent thrombosis [1-3]. Several risk factors have emerged as being important in the development of stent thrombosis, including stent malapposition. Although it is still under debate what the exact role of stent malapposition in this respect is, it appears undeniable that stent malapposition is involved in the development of this severe complication after stent implantation in at least a part of the cases [4-10].
In this chapter several aspects of stent malapposition will be discussed.

DEFINITION AND CLASSIFICATION

Stent malapposition (SM), also known as incomplete stent apposition, is defined by a separation of at least one stent strut from the intimal surface of the arterial wall with evidence of blood behind the strut, without involvement of side branches [11]. Stent malapposition may increase the thrombotic risk due to the presence of intraluminal stent struts [12]. Although appropriate apposition of the stent to the vessel wall is an important aspect for all stents, it seems to be critical in the case of DESs to ensure antiproliferative drug delivery as well as circumferential vascular support.
Depending on the time point of detection, the following classification can be made; acute if present immediately after the index procedure and late if detected at follow-up.
Furthermore, resolved if present after stent implantation but not at follow up, persistent if present both directly after stent implantation and at follow up and as acquired when the stent is well apposed after the index procedure but SM is detected at follow up. Differentiating between the different forms of SM therefore requires intravascular imaging both at stent implantation and at follow up. Schematically this is shown below as depicted by Hur et al., Cardiovasc Revasc Med 2009 [13].(Figure 1)
It is important to realize that the distinction between acute and late SM also implies different pathogenetic mechanisms for these two entities. Furthermore, each form will require a different therapeutic approach, which will be addressed later in the chapter.

PATHOPHYSIOLOGY

The current thought is that acute SM is mostly technique dependent and may result from inadequately sized stent selection or inadequate stent expansion, whereas late acquired SM

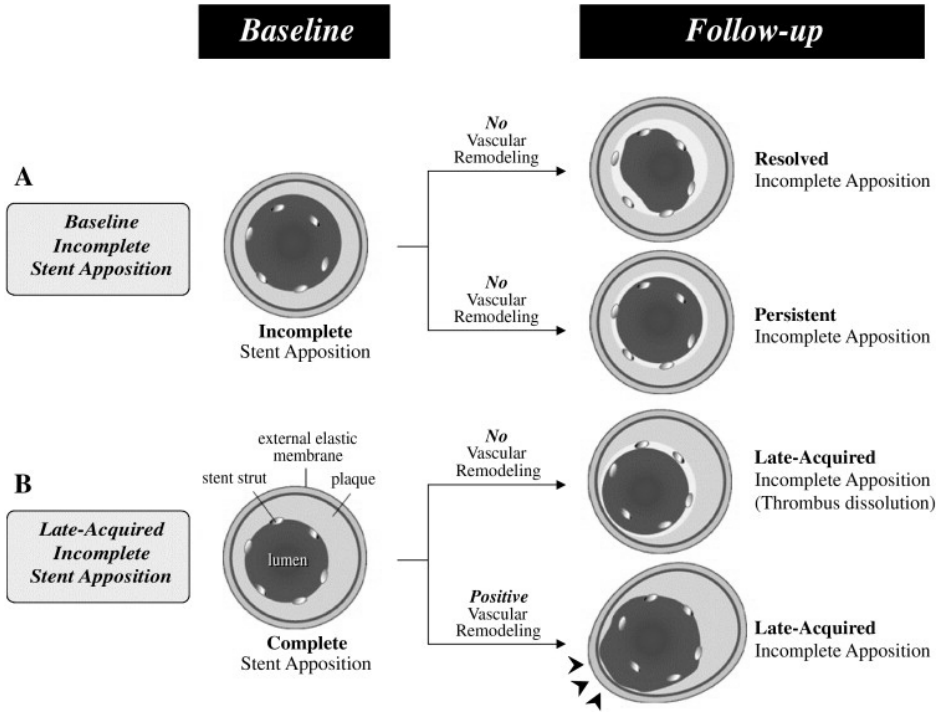

Figure 1. Various types of stent malapposition by Hur et al., Cardiovasc Revasc Med 2009. [13]

may result from vessel wall changes in the stented segments that occur during the follow-up period.

Focusing on late SM, several mechanisms have been postulated;[1] positive vascular remodeling of the vessel wall;[2] decrease in plaque volume;[3] chronic stent recoil and[4] a hypersensitivity reaction to one of the stent constituents.

Positive remodeling is the increase in vascular dimension measured by intravascular imaging using intravascular ultrasound (IVUS) or optical coherence tomography (OCT) by analyzing the change in cross sectional area of the external elastic membrane (EEM) in comparison with the change in plaque volume over time. Several studies reported a greater increase of the EEM compared to the change in plaque volume. Since the size of the stent cannot increase over time, except for the now rarely used self expanding stents, this process will eventually lead to stent malapposition [13-19]. A recent study of Kang et al. used IVUS immediately after intervention and at the 6-month and 2-year of follow-up to evaluate serial vascular changes after DES implantation [19]. Their main conclusion was that the development of malapposition was not limited to the first 6 months after implantation as a result of ongoing vascular remodeling even after this period. Therefore, the reported incidence of acquired late SM in previous studies (between 0% and 25% [20]) maybe underestimated due to relative short-term follow-up periods [19].

Besides an increase of the vascular dimensions, another possible mechanism to stent malapposition is a decrease of the plaque volume. This can be caused by dissolution of a thrombus, present at the stent implantation, mainly seen in patients with acute myocardial infarction [4, 13, 14, 21, 22]. Furthermore, regression of the plaque under stringent statin treatment can result in creating space between the stent and the vessel wall; however this seems to be only the case in a minority of lesions [12, 21, 23].

The pattern of late acquired SM is usually focal and is more often found at the borders of the stents (up to 90%, as reported by Mintz et al.)[17]. Additionally, acquired SM is more likely to occur in the relatively disease-free side of the vessel wall, probably because the normal vessel gets more injured during DES implantation and the delayed healing due to the drugs loaded on these stents [13, 24] . It is therefore more likely that positive remodeling is the most important mechanism for the development of late SM and that the contribution of plaque change is more limited [13]. Although chronic stent recoil could theoretically be one of the causes of SM, it has not been detected using IVUS in patients with SM, making it therefore unlikely to be a factor in the development of SM [17, 25].

Another factor of possible influence is the inflammatory response to these stents. In contrast to bare-metal stents (BMS), DES provokes inflammatory responses in animal models, either by a local hypersensitivity reaction to the non-biodegradable polymers of the stent or to the drug released by the stent. Since in a pig model the hypersensitivity reaction only peaks after complete release of the drug, it appears more likely that the polymer is the cause [22]. Also in human thrombectomy specimens, histopathological signs of inflammation were found, thus supporting the theory that a hypersensitivity reaction underlies the development of SM and stent thrombosis [5]. Furthermore, a growing number of reports documented the formation of coronary artery aneurysm (CAA) after DES implantation. Although the exact mechanism is still unknown, the available evidence suggest that it may be a hypersensitivity-mediated reaction to the delivery polymer [26]. Studies of related polymers have demonstrated local and systemic hypersensitivity reactions to intravascular polymers [5, 27-29]. Also, animal studies of DES show that 25% of pigs receiving DES develop eosinophilic infiltrates [29]. Bare-metal stents have not been demonstrated to elicit such hypersensitivity reactions in human autopsy series of over 400 stents [29].

RISK FACTORS

Predictors of acute SM include aneurysmal appearance of the target lesion, larger vessels, lesion calcification, higher patient age, longer lesions and lower balloon pressure [21, 30]. This is in line with the above statement that acute SM is most likely technique dependent, since these predictors are contributing to the complexity of the target lesion or to the technique itself.

Also for late SM, several factors related to the different proposed mechanisms of SM have been shown to be independent predictors.

The highest incidence of 25% of late SM in DES stented patients has been reported in the MISSION! Intervention study, including patients with acute myocardial infarction [21]. Several studies have shown AMI as an independent predictor of SM [14, 16]. The explanation for this can be found in the second proposed mechanism of SM, since the presence of a thrombus, particularly large thrombus load, which is frequently encountered in AMI may predispose to the occurrence of SM later after the dissolution of the thrombus at the site of stent implantation.

Diabetes mellitus has been associated with a lower rate of stent malapposition. The diabetic subpopulation is known to have an increased neointimal growth leading to more restenosis in BMS. Poor glycemic control has been associated with diminished efficacy of sirolimus on smooth muscle cell proliferation, which may explain the lower rate of late SM in these patients [21, 30-32]. Opposing these reports however, another study found a significant greater proportion of diabetic patients in DES cohort with late SM compared to the BMS cohort [14]. They reasoned that the proinflammatory role of diabetes may be responsible for a local enhanced inflammatory reaction after DES implantation eventually increasing the risk of late SM.

Another predictor of SM is directional coronary atherectomy (DCA) before stenting. The higher incidence of late SM in DCA before stenting might be explained by the fact that aggressive debulking with DCA is associated with deep vessel injury and promotes more positive remodeling [15].

Despite angiographic optimization with high pressures and adequately sized balloons, malapposed stent struts are frequently found in complex coronary lesions and more often following the implantation of Cypher Select stents which have a thicker stent strut and closed cell design [33]. Other factors associated with the lesion complexity, such as longer stent length, C-type lesions and overlapping stents, larger vessel reference diameter, have also been associated with an increased risk of SM [14, 16, 21]. Also, chronic total occlusion (CTO), defined by the absence of antegrade flow or only minimal flow of contrast distal to the occlusion during coronary angiography before stent implantation, has been reported as an independent predictor of late SM after DES implantation [16].

Patient age has been associated with the risk of SM, although not consistently. In a recent report of Steinberg et al., subjects with acute SM are older than those without acute SM, whereas (younger) age was the only independent predictor of late acquired SM. Their explanation for this last finding is that most of the other reported risk factors for SM were excluded from their study [30].

As will be discussed in the next section, also the stent type is associated with the risk of late stent malapposition. All risk factors are summarized in Table 1.

Table 1. Risk factors for stent malapposition

Clinical factors	Procedure related factors
Acute myocardial infarction (L)	Drug eluting stent (L)
Absence of diabetes mellitus (L)	Lower maximum balloon pressure (A, L)
Chronic total occlusion (L)	Larger vessel reference diameter (A, L)
Patient age (A,L)	Longer stent length (A, L)
	Overlapping stents (A, L)
	C-type lesion (A,L)
	Directional coronary artherectomy (L)

(A) Risk factor for acute stent malapposition, (L) Risk factor for late stent malapposition

BMS VERSUS DES

Acute SM is frequently observed both after DES and BMS implantation [21, 30]. Considering the mechanism of acute SM, a similar incidence in both DES and BMS is in the line of expectation. Late SM is rare after BMS and seems to be related to stent under-expansion in most patients [21]. Although not all, several studies have reported that late SM is much more common after DES implantation [6, 14, 21, 24, 30, 34]. A recent meta-analysis of Hassan et al, aimed on clarifying this, included 2453 patient after BMS implantation and 2195 patients receiving DES from a total of 17 studies [20]. The incidence of late acquired SM after DES varied between 0% and 25%, whereas after BMS implantation the highest reported incidence of SM was 6% at 6 months. They concluded that the risk of late acquired SM was 4.4-fold higher in patients after DES implantation compared to those with BMS. A comparison of paclitaxel- with –limus-eluting stents did not yield significant findings. The higher risk of SM after DES is likely due to the effects of the drugs on the vessel wall, resulting in positive remodeling [20, 21] In BMS the lumen changes at the site of SM are more related to plaque burden [21].

Furthermore, Hassan et al. also conducted a meta-analysis on the risk of (very) late stent thrombosis in patients with late SM. They concluded that the risk of stent thrombosis is 6.5 times higher (95% confidence interval 1.34-34.91) in patients with late SM compared with those without late SM [20].

So late SM appears to be more frequent after DES implantation and is associated with an increased risk of late stent thrombosis. After adequately lowering the incidence of restenosis, the primary complication of balloon dilatation and BMS implantation, we may have created a potentially more devastating obstacle with late SM and subsequent stent thrombosis in DES.

DIAGNOSTICS

Although intravascular ultrasound (IVUS) has been usually regarded as the gold standard for in vivo assessment of stent strut apposition to the vessel wall, more accurate evaluation of stent strut apposition cannot be successfully performed in some lesions with minimal stent malapposition due to the limited resolution capacity in IVUS (100-150um) [35]. Furthermore, this limited axial resolution of IVUS makes it virtually impossible to discriminate between atherosclerotic plaque and thrombus [21]. It also has problems with stent-related artifacts [12], possibly resulting in underestimation of the evaluation of re-endothelialization. SM is associated with a decreased re-endothelialization after DES implantation [22], which is in turn associated with an increased risk of stent thrombosis [7].

Optical coherence tomography (OCT) is a relatively new imaging modality. In contrast with IVUS, OCT visualizes intra-coronary features using near-infrared light instead of ultrasound, leading to a far better axial resolution, able to resolve detail up to 10 μm [12]. Multiple studies investigating stent malapposition using OCT and comparing it with IVUS findings have already been published. There is evidence that minimal stent malapposition which is not detectable by IVUS may disappear or decrease in follow-up OCT evaluation [35] and SM without complete re-endothelialization is associated with presence of OCT-detected thrombus [12]. More detailed information provided by OCT imaging also led to the conclusion that rate of stent strut coverage and malapposition were significantly different among different DES types and among the type of clinical presentation. More SM was found in sirolimus-eluting stents and paclitaxel-eluting stents compared to zotarolimus-eluting stents and the rate of SM was higher in patients presenting with acute coronary syndrome compared to those with stable angina pectoris [36, 37]. Despite the clear advantages of OCT over IVUS, some disadvantages should also be mentioned. The cost of the device is higher than that of IVUS and the device is not available in every center. A major limitation of OCT is the requirement of a blood-free imaging field because red blood cells scatter light. This can be achieved with a continuous saline flush administration or with a temporary balloon occlusion catheter, leading to transient ischaemia which is not desirable and or tolerated in all cases. Another disadvantage of OCT is poor penetration into non-transparent tissues thus allowing evaluation of only superficial structures including coronary plaques with thin-caps [38].

TREATMENT

The most important and potential devastating complication of SM is stent thrombosis. The mechanism by which SM may contribute to stent thrombosis remains unclear. SM may serve as a local nidus for thrombus formation, allowing fibrin and platelet deposition. Delayed re-endothelialization, impaired vasomotion and also involvement of chronic inflammation

and delayed healing, leading to tissue necrosis around the stent, all contribute to creating a thrombogenic environment [20, 23].
When performing intravascular imaging directly post stent implantation, immediate action can be taken after diagnosing acute stent malapposition by re-dilatation of the target lesion, further expanding the stent. Considering dissolution of a jailed thrombus as a possible mechanism of SM, it may be important to effectively remove thrombotic material prior to stent implantation. Unfortunately, it has been shown that immediate post-intervention IVUS showing no malapposition does not guarantee an uneventful course after DES implantation [8].
After diagnosing stent malapposition during follow-up, defining a proper treatment strategy is difficult, especially when the patient is asymptomatic. The main goal should be off course to prevent stent thrombosis. One option could be pharmacological with long-term double anti-thrombotic treatment [11]. However, this will also lead to a continuous increased bleeding risk and it is evident that SM may also persist for years without leading to complications, creating a risk of exposing patients to unnecessary side effects of the treatment without having the benefit of it. Another option could be dilatation and implantation of a second, larger, stent [39].

FUTURE PERSPECTIVES

It goes without saying that all the, until now, unanswered questions about the mechanism of stent malapposition, its association with stent thrombosis and the best treatment of SM are to be clarified in future larger studies.

One of the current developments in this field is the development of a bioabsorbable stent. The theoretical advantages of such a stent is that it might have less potential for late stent thrombosis because there will eventually be no foreign material exposed to the bloodstream.
Also problems with later surgical revascularization, eliminating vasomotor reactions and interference with imaging techniques could be prevented [40]. However, this remains to be proven and also partial/unequal stent dissolution may perhaps cause problems.

Lately, there have been some ongoing clinical trials addressing the use of self-expandable nitinol stents in the treatment of AMI patients with long-term follow-up IVUS and OCT [41-43]. The hypothesis generated in these trials was that the self-expandable stents would better accommodate to early changes in the vessel wall (thrombus dissolution and vasodilatation) with better apposition due to its self-expandable properties. Initial results have shown that these stents provided 20% increase in lumen area with perfect apposition on 3 days follow up OCT. However, long-term (safety) results are still lacking.

CONCLUSION

Stent malapposition appears to be a relative common finding after stent implantation, especially diagnosed using OCT which has a superior resolution compared to IVUS. The incidence of late SM is higher after DES implantation, mainly caused by positive vascular remodeling. Although SM is associated with stent thrombosis, this is a relatively rare complication. Since the incidence of SM is vastly greater than that of stent thrombosis, SM is not necessarily sine qua non, but more likely only one factor in a complex system. Nevertheless, stent thrombosis is a devastating complication and must be prevented where possible. Therefore, further research unraveling the exact mechanisms of stent malapposition and stent thrombosis and possible treatments will continue in future clinical trials.

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Chapter 8

Summary, conclusions and future perspectives

SUMMARY AND CLOSING REMARKS

This thesis aimed to evaluate the importance of combined pharmacological and mechanical adjunctive therapies for optimization of outcomes of primary percutaneous coronary intervention (PPCI) in the setting of ST-elevation myocardial infarction (STEMI), and to assess the predictors of large thrombus burden among STEMI patients and to what extent that would influence the outcomes and the pre-hospital triage of these patients. Furthermore, a special focus was granted on the clinical performance of biodegradable-polymer drug eluting stents (DES) comparing the incidence of definite stent thrombosis (DST) and target lesion revascularization (TLR); a) between biodegradable-polymer biolimus, sirolimus and paclitaxel DES, and b) between biodegradable-polymer DES and permanent polymer DES. We also discussed the recently emerging drugs for coronary artery disease, with special focus on antiplatelets, antithrombotics and antidyslipidemics. Finally, we provided an overview of post-stenting problems of in-stent restenosis and late stent malapposition.

SUMMARY

The introduction and outline of this thesis **(chapter 1)** begin with a description of current insights in aspiration thrombectomy and abciximab as adjunctive therapies in PPCI to decrease thrombus burden. We then tackle the subject of biodegradable-polymer DES as a new generation of stents. Finally, we provide a brief overview of in-stent restenosis and thrombosis definitions and classification, as well as stent malapposition and the recent innovations that may prevent its occurrence.

In **Chapter 2**, we evaluate the adjunctive role of aspiration thrombectomy in PPCI for STEMI patients receiving early, in-ambulance, abciximab within a fixed protocol (Leiden MISSION! Project). 158 patients with STEMI were enrolled, in whom abciximab was started early before arrival at the hospital (in-ambulance); 79 patients had PPCI without thrombus aspiration (Conventional PCI group), and 79 had PPCI with thrombus aspiration (thrombectomy-facilitated PCI group). The 2 groups were comparable for baseline clinical and angiographic characteristics. The rate of complete ST-segment resolution at 90 minutes was significantly higher in the thrombectomy-facilitated group (p=0.002), and multivariable logistic regression analysis identified only thrombectomy as an independent predictor of ST-segment resolution (odds ratio= 9.4, 95% CI = 2.6-33.5, p=0.001). Among patients with higher thrombus grades, distal embolization was higher in the conventional PCI group. No difference was observed between both groups in enzymatic infarct size assessed by peak CK (p=0.7), and peak Tn-T levels (p=0.4). Also the LVEF at 3-months was similar (p=0.9). At 12 month clinical follow-up, thrombus aspiration was however associated with reduced all-cause mortality (log-rank p=

0.03). Thus it appears that a selective strategy of thrombus aspiration still may have an additive benefit, even with early abciximab administration.

The hypothesis of the study presented in **Chapter 3** was that early prediction of thrombus grade is possible which may influence the pre-hospital triage of STEMI patients. One-hundred and fifty-three consecutive patients presenting with STEMI and undergoing PPCI were included. Thrombus was evaluated on angiography and scored according to the TIMI study group score. Next, patients were categorized into two groups having either high thrombus grade (HTG; score 4-5) or low thrombus grade (LTG; score 1-3). We evaluated predictors of angiographic thrombus grade among a number of clinical, angiographic and laboratory data. We also assessed infarct size and scintigraphic left ventricular ejection fraction (LVEF) at 3 months in both patient groups. Ninety-four patients (58±11 y, 75% males) presented with HTG, whereas 59 patients (58±12 y, 78% males) presented with LTG. Pre-infarction angina was more frequently encountered in the LTG group than in the HTG group (25% vs. 10%, p=0.009). Pre-procedural TIMI flow was significantly lower in the HTG group (p<0.001), and thrombosuction was more frequently applied in the HTG group (p<0.001). Absence of pre-infarction angina (OR=0.29, 95% CI=0.11-0.75, p=0.01) and proximal culprit lesion (OR=2.10, 95% CI=1.02-4.36, p=0.04) were the only independent predictors of HTG. HTG proved an independent predictor of higher peak levels of CK (p<0.001) and troponin-T (p<0.001), as well as lower LVEF (p=0.05) along with male gender and absence of prior statin therapy. Thus, pre-infarction angina is associated with lower thrombus grade, whereas proximal culprit lesions are associated with higher thrombus grade. Higher thrombus grade is associated with larger infarct size and slightly worse LV function. This may have clinical implications in planning strategies, particularly regarding pharmacotherapy, that aim to decrease thrombus burden prior to stent implantation.

In **Chapter 4** we present a meta-analysis and systematic review on biodegradable-polymer DES. We sought to; 1) evaluate the risk of target lesion revascularization (TLR) and definite stent thrombosis (DST) among different groups of second generation biodegradable-polymer (BioPol) DES, and 2) to compare them with permanent polymer (PermPol) DES. We searched PubMed and relevant sources from January 2005 until October 2010. Inclusion criteria were (a) Implantation of a drug eluting stent with biodegradable polymer; (b) available follow-up data for at least one of the clinical end-points (TLR/DST) at short term (30 days) and/or mid-term (up to one year). A total of 22 studies, including randomized and observational studies, with 8264 patients met the selection criteria; 9 studies with 2042 patients in whom biodegradable-polymer sirolimus eluting stents (BioPol-SES) were implanted, 8 studies with 1731 patients in whom biodegradable-polymer paclitaxel eluting stents (BioPol-PES) were implanted, and 7 studies with 4491 patients in whom biodegradable-polymer biolimus A9 eluting stents were implanted (BioPol-BES). At 30 days, there was a higher risk of TLR in the BioPol-BES compared to BioPol-SES (OR= 3.4, 95% CI= 1.3-9.6, p= 0.006), which was obviously attributed to a higher risk of DST in the former (OR= 3.9, 95% CI= 1.1-14.0, p=0.04). There

was no significant difference in the other stent comparisons at short term. At 1 year there was an almost 3 times higher risk of TLR in the BioPol-PES (OR=2.8, 95%CI= 1.3-6.0, p= 0.01), and a more than twice higher risk of TLR in the BioPol-SES (OR=2.2, 95%CI= 0.2-1.0, p=0.04) compared to BioPol-BES, with no significant difference between BioPol-SES and BioPol-PES. The risk of 1-year stent thrombosis was not statistically different between the studied groups (overall p= 0.2), although numerically there was a 3 times higher incidence of ST in BioPol-PES compared to BioPol-SES (1% vs. 0.3%). In another analysis comprising randomized clinical trials (7 trials) comparing BioPol-DES (3778 patients) and PermPol-DES (3291 patients), the risks of TLR and stent thrombosis at 1 year were not significantly different between both groups, (OR=0.8, 95% CI=0.5-1.4, p= 0.5) and (OR=0.7, 95% CI= -0.2-2.4, p=0.5) respectively. Accordingly, performance of different BioPol-DES seems to vary from each other. The short and mid-term success rates may not be superimposable. Furthermore, BioPol-DES may be not necessarily better than PermPol-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 and anticoagulant drugs.

Chapter 6 is a review article about in-stent restenosis (ISR). Here we provide 1) an overview of the recent innovations for optimizing the outcomes of coronary stenting, and 2) up-to-date information with regard to prevention of ISR. This includes improving stent design, novel stent coatings, nanoparticle-based drug delivery as well as gene therapy. We also highlight the current treatment options for ISR.

In **Chapter 7** we presented an overview of late stent malapposition (LSM) in bare metal stent (BMS) and DES era. In this chapter several aspects of stent malapposition are discussed including; definition and classification, pathophysiology, risk factors, incidence in BMS vs. DES, new diagnostic tools, and finally current treatment options and future perspectives.

MAIN CONCLUSIONS

- Among STEMI patients treated with PPCI and receiving early (in-ambulance) abciximab, it appears that the adjunctive use of manual thrombectomy significantly improves post-procedural ST-segment resolution, reduces distal embolization, and may be associated with a lower clinical event rate. Therefore, although no benefit was observed regarding the enzymatic infarct size or LV function as assessed by Gated-SPECT, it appears that a selective strategy of thrombus aspiration still may have an additive benefit, even with early abciximab administration.

- Pre-infarction angina is associated with a decreased angiographic thrombus grade, whereas proximal culprit lesions are associated with higher thrombus grade. Higher thrombus grade was in turn associated with larger infarct size as well as slightly worse LV function. This may have clinical implications in planning strategies, particularly regarding pharmacotherapy, that aim to decrease thrombus burden prior to stent implantation, particularly in high risk patients without pre-infarction angina.
- Performance of different BioPol-DES seems to vary from each other. The short and mid-term success rates may not be superimposable and are to be carefully judged separately for newly emerging BioPol-DES before they can become a new standard. BioPol-DES do not necessarily perform better than PermPol-DES.
- Efforts have been made to improve the clinical effectiveness and safety of established treatment strategies for CAD and target new frontiers through developing novel treatment strategies that tackle different mechanisms of action. Better understanding of the different molecular and cellular mechanisms underlying CAD has resulted in more innovations and achievements in CAD drug therapy, and still a lot more is anticipated in the coming years.
- Over the years many predictive factors of in-stent restenosis have been identified. These factors not only are very useful in stratification of the patients at risk for restenosis, they all contribute to our understanding of this complex disease. Many innovative technologies have been generated in the context of the diligent search for an ideal anti-restenosis therapy.
- Stent malapposition appears to be a relative common finding after stent implantation. Although SM is associated with stent thrombosis, this is a relatively rare complication. Since the incidence of SM is vastly greater than that of stent thrombosis, SM is not necessarily sine qua non, but more likely only one (important) factor in a complex system.

FUTURE PERSPECTIVES

1. Primary percutaneous coronary intervention

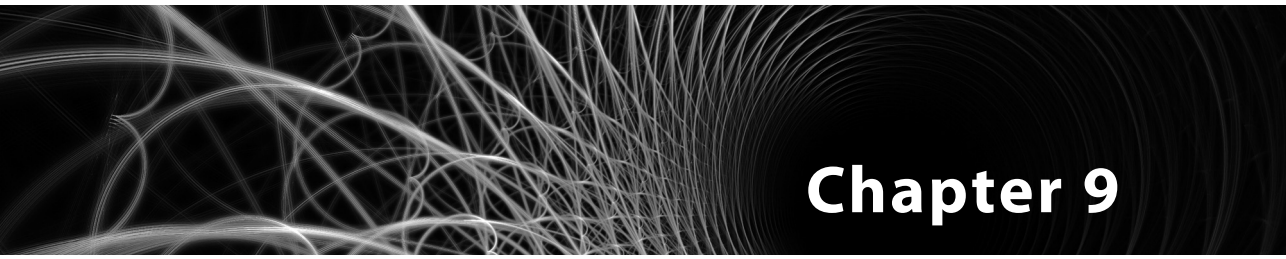
- Primary angioplasty is the established treatment for recanalization of coronary arteries during acute myocardial infarction (AMI). In addition to the pharmacological approaches, aspiration thrombectomy devices have been investigated to reduce the risk of embolization. So far, it is still unknown which group of patients would benefit most from thrombus aspiration, and whether a selective strategy for thrombectomy would be the best option based on a pre-specified risk score that takes in consideration the thrombus grade, time to treatment among other relevant factors. Large scale multi-center randomized clinical trials powered for clinical end-points are still required to answer many questions regarding aspiration thrombectomy and to provide evidence-based data to be upgraded from

the current class IIa indication (i.e. reasonable to perform the procedure) to class I indication (i.e. procedure should be performed).

- Pre-hospital triage of STEMI patients is gaining wide interest, however it subtends substantial logistical obstacles for many dedicated PPCI centers. In our study we present the experience of Leiden University Medical Center (LUMC), which implements a rigorously standardized protocol for management of patients with AMI (MISSION! Protocol). This protocol supports an integrated approach of early pharmacotherapy and mechanical reperfusion to attain the optimal results in patients with AMI.
- Recently, a great deal of research has focused on development of new antiplatelet agents that could be administered orally or intravenously and, unlike the currently applied thienopyridines, could provide direct-acting reversible inhibition of the platelet P2Y12 receptor. This concept of rapidly acting and rapid reversibility of platelet inhibition could fuel further research regarding the pre-hospital triage of STEMI patients with suspected high thrombotic burden.
- In our thesis we concluded that absence of pre-infarction angina predicts high thrombus burden. It might be of interest to develop a scoring system that utilizes clinical (like PIA), and rapid laboratory data (cardiac biomarkers) and integrates this with other established scoring systems, e.g. TIMI risk score, to identify which group of patients will benefit most from early pre-hospital treatment.

2. In-stent restenosis

- Restenosis is a complex disease and all the mechanisms causing restenosis to develop have not been identified yet. Especially genetic markers help us in unraveling the mechanisms underlying the process of restenosis. They furthermore could provide evidence for more tailored treatment and subsequently aid in the development of novel treatment modalities.
- Current developments in the field of gene therapy might belong to future possibilities. The recent discoveries and advances in stent design and nanoparticle delivery systems "nano-vehicles" have already fueled revolutionary changes in the concept of (in-stent) restenosis prevention and treatment.
- The new biodegradable-polymer DESs may represent a step ahead on the road to reach an ideal stent. According to our meta-analysis, they were not clearly better than permanent-polymer DESs. However, Biolimus biodegradable-polymer stents provided very promising results, especially at long-term follow-up. Integration of improvements in; the anti-proliferative drug and its pharmacokinetics (biolimus/novolimus), the polymer (biodegradable-polymer/polymer-free), and the stent platform (biodegradable stents), are expected to provide a solution for the problem of in-stent thrombosis and restenosis.



Chapter 9

Samenvatting, conclusies en toekomstperspectief

SAMENVATTING, CONCLUSIES EN TOEKOMSTPERSPECTIEF

Het doel van dit proefschrift is om te evalueren wat de relevantie is van gecombineerde farmacologische en aanvullende mechanische therapieën ter verbetering van de uitkomst van primaire percutane interventies (PPCI) voor de behandeling van het ST-segment elevatie myocardinfarct (STEMI). Ook worden de voorspellende factoren van de hoeveelheid stolsel (thrombus graad) bij STEMI patiënten in kaart gebracht en is beschreven hoe de relatie is met de uitkomst en het effect op de pre-hospitale behandeling van deze patiënten. Daarnaast wordt speciale aandacht geschonken aan de klinische resultaten van biodegradable-polymer drug-eluting stents (DES = medicijnafgevende stents) met betrekking tot het risico op stent thrombose en hernieuwde revascularisatie procedures van het behandelde vaatsegment. Daarbij wordt er een vergelijking gemaakt tussen a) biodegradable-polymer biolimus-, sirolimus- en paclitaxel-eluting stents en tussen b) biodegradable-polymer eluting en permanente polymer eluting stents. Vervolgens worden enkele nieuw verschenen geneesmiddelen voor de behandeling van coronairlijden besproken, met speciale aandacht voor middelen die de bloedplaatjes remmen, antistollingsmiddelen en middelen voor de behandeling van dyslipidemieën. Tenslotte geven we een overzicht van problemen die na het plaatsen van een stent kunnen optreden, in het bijzonder in-stent restenose en stent malappositie.

SAMENVATTING

De introductie van dit proefschrift **(Hoofstuk 1)** begint met een beschrijving van de huidige inzichten in de toepassing van stolselverwijdering door middel van aspiratie en abciximab als aanvullende behandelingen rondom de PPCI om de hoeveelheid stolsel te verminderen. Daarna worden de nieuwe biodegradable-polymer DES beschreven. Tenslotte wordt er een overzicht gegeven van in-stent restenose en thrombose definities en classificaties, en van stent malappositie en de recente innovaties die het optreden hiervan kunnen voorkomen.

In **Hoofdstuk 2** wordt de aanvullende rol van mechanische thrombus verwijdering door middel van aspiratie gedurende de PPCI voor STEMI patiënten onderzocht die in de ambulance abciximab hebben gekregen volgens het Leidse MISSION! protocol. Daarbij werden 158 patiënten onderzocht die voor aankomst in het ziekenhuis al abcixmab hadden gekregen: 79 patiënten ondergingen PPCI met thrombusaspiratie en 79 zonder thrombusaspiratie. De groepen waren vergelijkbaar qua pre-procedurele klinische en angiografische karakteristieken. Het voorkomen van compleet ST-segment herstel na 90 minuten was hoger in de groep behandeld met thrombusaspiratie (p=0.002), en multivariate logistische regressieanalyse identificeerde alleen thrombusaspiratie als een onafhankelijke voorspeller van ST-segment herstel (odds ratio= 9.4, 95% CI = 2.6-33.5, p=0.001). Er werd geen verschil gezien tussen

de groepen in enzymatische infarctgrootte zoals bepaald met de piek-CK (p=0.7) en piek troponine-T (p=0.4) waarden. Ook de LV ejectiefractie na 3 maanden was vergelijkbaar tussen de groepen (p=0.9). Na 12 maanden klinische follow-up, liet de thrombusaspiratie groep een lagere sterfte zien (log-rank p=0.03). Op basis van deze studie lijkt een selectieve benadering van thrombusaspiratie een aanvullende waarde te hebben, ook wanneer abciximab is toegediend.

De hypothese van de studie zoals beschreven in **Hoofdstuk 3** was dat vroege voorspelling van de hoeveelheid stolsel mogelijk is, en dat dit effect zou kunnen hebben op de prehospitale triage van STEMI patiënten. 153 opeenvolgende patiënten die zich presenteerden met een STEMI werden geïncludeerd. De aanwezigheid van thrombus werd vastgesteld door middel van angiografie en gecategoriseerd volgens de TIMI Study Group score. Vervolgens werden patiënten ingedeeld in twee groepen: hoge thrombus graad (HTG: score 4-5) of lage thrombus graad (LTG: score 1-3). Naar voorspellers voor angiografische thrombus graad werd gezocht onder klinische, angiografische en laboratorium parameters. De infarctgrootte en scintigrafische LV ejectiefractie na 3 maanden werd in beide groepen bepaald. 94 patiënten (58±11 jaar, 75% man) presenteerden zich met HTG en 59 patiënten (58±12 jaar, 79% man) met LTG. Pre-infarct angina pectoris werd vaker gezien in de LTG groep (25% vs. 10%, p=0.009). De pre-procedurele TIMI flow was lager in de HTG groep (p<0.001). Thrombusaspiratie werd vaker verricht in de HTG groep (p<0.001). De afwezigheid van pre-infarct angina pectoris (OR=0.29, 95% CI=0.11-0.75, p=0.01) en proximale lokalisatie van de culprit laesie (OR=2.10, 95% CI=1.02-4.36, p=0.04) waren de enige onafhankelijke voorspellers van HTG. HTG was een onafhankelijke voorspeller van hogere piek-CK (p<0.001) en -troponine-T (p<0.001) waarden en een lagere LV ejectiefractie (p=0.05), naast mannelijk geslacht en het niet gebruiken van een statine. Geconcludeerd werd dat pre-infarct angina pectoris is geassocieerd met minder thrombus en proximale lokalisatie van de culprit laesie geassocieerd is met meer thrombus. Meer thrombus is geassocieerd met grotere infarctgrootte en iets lagere LV ejectiefractie. Deze studie kan klinische implicaties hebben voor de behandelstrategie, vooral in de toepassing van farmacotherapie met als doel de hoeveelheid thrombus te verminderen voorafgaand aan stent implantatie.

In **Hoofdstuk 4** wordt een meta-analyse en systematisch overzicht beschreven van biodegradable-polymer (BioPol) DES om 1) het risico van hernieuwde revascularisatie van het behandelde vaatsegment en het risico op stent thrombose onder verschillende groepen BioPol DES vast te stellen, en 2) dit te vergelijking met permanente polymer sirolimus-eluting stents. Op PubMed werden alle relevante artikelen tussen januari 2005 en oktober 2010 opgezocht. Inclusiecriteria waren (a) implantatie van een DES met biodegradable polymer, (b) beschikbare follow-up data van klinische eindpunten van minimaal 30 dagen en/of middellange follow-up (tot 1 jaar). In totaal werden 22 gerandomiseerde en observationele studies

gevonden met daarin 8264 patiënten, die voldeden aan de selectiecriteria: 9 studies met 2042 patiënten waarin biodegradable polymer sirolimus-eluting stents (BioPol-SES) werden geïmplanteerd; 8 studies met 1731 patiënten waarin biodegradable-polymer paclitaxel-eluting stents (BioPol-PES) werden gebruikt; en 7 studies met 4491 patiënten waarin biodegradable-polymer biolimus A9-eluting stents (BioPol-BES) werden geïmplanteerd. Na 30 dagen was er een hoger risico op revascularisatie van het behandelde vaatsegment in de BioPol-BES groep vergeleken met de BioPol-SES groep (OR = 3.4, 95% CI = 1.3-9.6, p=0.006), dat vooral veroorzaakt werd door het hogere risico op stent thrombose in de BioPol-BES groep (OR = 3.9, 95% CI = 1.1-14.0, p=0.04). Er waren geen significante verschillen tussen de andere stents op de korte termijn. Na een jaar was er een bijna 3x zo hoger risico op revascularisatie van het behandelde vaatsegment in de BioPol-PES (OR = 2.8, 95% CI = 1.3-6.0, p=0.01), en een meer dan 2x zo hoog risico in de BioPol-SES groep (OR = 2.2, 95% CI = 0.2-10, p=0.04), vergeleken met de BioPol-BES. Er was geen significant verschil tussen de BioPol-SES en BioPol-PES. Het risico op stent thrombose na 1 jaar was niet significant verschillend tussen de verschillende studiegroepen (p=0.2), hoewel er numeriek 3x zo vaak stent thrombose in de BioPol-PES groep optrad in vergelijking met de BioPol-SES groep (1% vs. 0.3%). In een andere analyse waarin alle gerandomiseerde studies (7 studies) met BioPol-DES (3778 patiënten) en PermPol-DES (3291 patiënten) werden opgenomen was het risico op hernieuwde revascularisatie van het behandelde vaatsegment en het risico op stent thrombose niet significant verschillend tussen de groepen (OR = 0.8, 95% CI = 0.5-1.4, p=0.5 en OR = 0.7, 95% CI -0.2-2.4, p=0.5, respectievelijk). De conclusie was dat de verschillende BioPol-DES van elkaar verschillen. De korte en middellange succespercentages zijn niet vergelijkbaar. Ook bleken BioPol-DES niet noodzakelijk beter dan PermPol-DES).

Hoofdstuk 5 bevat een review artikel waarin een vrijwel volledig overzicht wordt gegeven van recent verschenen nieuwe geneesmiddelen ter behandeling van coronairlijden. De besproken geneesmiddelen zijn: geneesmiddelen ter behandeling van dyslipidemie, geneesmiddelen die de atherosclerotische plaque stabiliseren en hun progressie stoppen, anti-angineuze middelen, renine-angiotensine-aldosteron-systeem remmers, anti-bloedplaatjes middelen en anticoagulantia.

Hoofdstuk 6 is een review artikel met betrekking tot in-stent restenose (ISR). Hierin geven we 1) een overzicht van recente innovaties voor het optimaliseren van de uitkomsten van coronaire stenting procedures, en 2) up-to-date informatie over preventie van ISR. Dit omvat het verbeteren van stent ontwerpen, nieuwe stent coatings, nanodeeltjes op basis van drug delivery en gentherapie. We belichten ook de huidige behandel opties voor de ISR.

In Hoofdstuk 7 presenteren we een overzicht over late stent malappositie (LSM) in het bare-metal stent (BMS) en het DES tijdperk. In dit hoofdstuk worden verschillende aspecten van

stent malappositie besproken: de definitie en classificatie, de pathofysiologie, de risicofactoren, de incidentie in BMS en DES, de nieuwe diagnostische middelen om het vast te stellen en tenslotte de huidige mogelijkheden voor de behandeling ervan en een toekomstperspectief.

CONCLUSIES

- In STEMI patiënten die behandeld worden met PPCI en vroeg (in de ambulance) abciximab toegediend krijgen, lijkt manuele thrombusaspiratie de post-procedurele ST-segment resolutie te verbeteren en te leiden tot een betere klinische uitkomst. Daarom lijkt een selectieve strategie van thrombusaspiratie, ook na toediening van abciximab, waarde te hebben, ondanks het feit dat er enzymatisch geen verschillen waren in infarctgrootte en er geen verschillen in LV functie waren bij Gated-SPECT.
- Pre-infarct angina pectoris is geassocieerd met een lagere angiografische thrombus graad, in tegenstelling tot proximale locatie van de culprit lesie. Hogere thrombus graad is geassocieerd met grotere infarctgrootte en slechtere LV functie. Dit kan klinische implicaties hebben bij de keuze van de behandelstrategie, vooral de farmacotherapie met als doel de thrombus graad te doen afnemen voor stent implantatie. Dit geldt vooral bij patiënten zonder pre-infarct angina pectoris.
- De uitkomst van de diverse BioPol-DES is verschillend. Het korte- en middellange termijn succes is niet uitwisselbaar en vragen om een zorgvuldige beoordeling van nieuwe BioPol-DES die verschijnen voordat ze een nieuwe standaard van zorg kunnen worden. De uitkomst van BioPol-DES is niet noodzakelijk beter dan de uikomst van PermPol-DES.
- Er is veel geïnvesteerd om tot een betere klinische effectiviteit en veiligheid te komen van nieuwe geneesmiddelen ten opzichte van de reguliere behandeling van coronairlijden. Een beter begrip van de verschillende moleculaire en cellulaire mechanismen die aan coronairlijden ten grondslag liggen, hebben geleid tot innovaties en nieuwe geneesmiddelen voor de behandeling ervan. De komende jaren kunnen meer geneesmiddelen worden verwacht.
- Gedurende de laatste jaren zijn veel voorspellende factoren voor in-stent restenose geïdentificeerd. Deze factoren zijn niet alleen zinvol voor de risicostratificatie van patiënten, maar hebben ook geleid tot een beter begrip van de oorzaak van deze complexe aandoening. Vele innovatieve therapieën zijn ontwikkeld om tot een optimale anti-restenose therapie te komen.
- Stent malappositie is een relatief veelvoorkomende bevinding na stent implantatie. Hoewel stent malappositie is geassocieerd met stent thrombose, blijft het laatste een zeldzame complicatie. Omdat de incidentie van stent malappositie veel groter is dan die van stent thrombose, is stent malappositie waarschijnlijk een van de vele factoren die het risico op stent thrombose verhogen.

TOEKOMSTPERSPECTIEF

1. Primaire percutane coronaire interventie

- Primaire PCI is de gevestigde behandeling om reperfusie van de coronairen te verkrijgen tijdens de behandeling van het acute myocardinfarct (AMI). In aanvulling op farmacologische behandelingen, zijn verschillende thrombusaspiratie methoden onderzocht om het risico van embolisatie te verminderen. Tot dusver is het niet bekend welke groep patiënten de meeste baat heeft bij thrombusaspiratie en of een selectieve strategie voor thrombusaspiratie op basis van thrombusgraad, tijd tot behandeling of andere factoren, niet beter is. Gerandomiseerde studies die voldoende 'gepowered' zijn op klinische uitkomsten zijn nodig om de vele vragen over de effectiviteit van thrombusaspiratie te beantwoorden en om de huidige klasse 2 indicatie (redelijk om de procedure uit te voeren) te verhogen naar klasse 1 (procedure dient te worden uitgevoerd).
- Pre-hopsitale triage van STEMI patiënten wordt steeds breder toegepast. Echter, voor PPCI centra is dit niet mogelijk zonder belangrijke logistieke obstakels te overwinnen. In deze studie worden de ervaringen van het Leidse Universitair Medisch Centrum (LUMC) beschreven waarbij een sterk gestandaardiseerd protocol wordt gehanteerd voor de behandeling van STEMI patiënten (MISSION! protocol). Dit protocol omvat een geïntegreerde benadering van vroege farmacotherapie en mechanische reperfusie om een optimale uitkomst te bereiken.
- Er is veel geïnvesteerd in de ontwikkeling van nieuwe antithrombotische medicatie die oraal of intraveneus kan worden toegediend en, in tegenstelling tot de huidige thiënopyridines, resulteren in een directe werking en een reversibel effect hebben op de remming van de thrombocyt P2YP12 receptor. Het concept van snelwerkende en reversibele thrombocyten remming zal leiden tot verder onderzoek om de pre-hospitale farmacotherapeutische behandeling te optimaliseren bij patiënten met een hoge thrombus graad.
- In dit proefschrift concluderen we dat de afwezigheid van pre-infarct angina pectoris geassocieerd is met een hoge thrombus graad. Het kan nuttig zijn om een score te ontwikkelen waarin diverse klinische en snel beschikbare laboratoriumwaarden, eventueel in combinatie met andere scores (bijvoorbeeld TIMI risk score) kunnen worden geïntegreerd om te voorspellen welke patiënten de meeste baat hebben bij vroege prehospitale behandeling.

2. In-stent restenose

- Restenose is een complexe aandoening waarvan nog niet alle pathofysiologische mechanismen die eraan ten grondslag liggen, worden begrepen. Vooral genetische markers helpen ons bij het ontrafelen van het proces van restenose. Hierdoor kunnen meer gerichte behandelingen worden ontwikkeld en toegepast.

- De huidige ontwikkelingen in het veld van gen-therapie behoren wellicht tot de toekomstige behandelopties van restenose. Ontwikkelingen op het gebied van stent design en nanodeeltjes-gebaseerde toedieningsmethoden (nano-vehicles) hebben inmiddels geleid tot conceptuele veranderingen in de preventie en behandeling van restenose.
- De nieuwe biodegradable polymer DES zouden weleens een belangrijke stap voorwaarts kunnen zijn op weg naar de ideale stent. Zoals de meta-analyse laat zien zijn ze niet duidelijk beter dan de permanente polymer DES. Echter, met de biolimus-biodegradable stents zijn veelbelovende resultaten geboekt, vooral bij de lange-termijn follow-up. De integratie van nieuwe inzichten in de anti-proliferatieve drugs en de farmacokinetica ervan (biolimus/novolimus), de polymer (biodegradale-polymer/polymer-free) en het stent platform (biodegradable stents), zal naar verwachting leiden tot een oplossing van het probleem van in-stent thrombose en restenose.

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Curriculum Vitae

CURRICULUM VITAE

Tarek Abdel-Hameed Nagib Ahmed, MD, MSc

T. A. N. Ahmed was born on August 29, 1976 in Asyut, Egypt. After having been awarded his high school diploma by Al-Salam Language School, he started studying medicine at Asyut University-Asyut-Egypt from which he graduated, cum laude, in 2000, and was awarded the prize for the best undergraduate achievement in internal medicine. He received his cardiology training in the same University and completed it in 2005; he had his master degree in Cardiology in the same year including a master thesis entitled "Added value of tissue Doppler imaging during low dose dobutamine echocardiography in the assessment of myocardial viability". Since then he has been working as an assistant lecturer of Cardiology at Asyut University Hospital, where he was fully involved in the clinical duties of the department with its various units, as well as teaching medical students of the Faculty of medicine- Asyut University. In 2009 he was granted a scholarship for Ph.D. studies from the Egyptian Ministry of Higher Education. Since July 2009 and still, he joined Leiden University Medical Center (LUMC) in the Netherlands for clinical and research training in interventional cardiology under the supervision of Professors J. Wouter Jukema and M.J. Schalij. During his fellowship he was fully involved in the interventional procedures held out in the catheterization laboratories of LUMC, as an assistant and then as a primary operator building up a growing experience in interventional cardiology. He also received training courses in the fields of percutaneous valvular interventions including, percutaneous aortic valve implantations (TAVI), and percutaneous mitral valve interventions and he is currently participating in these procedures at the LUMC.

Interventional experience

- Diagnostic coronary angiograms: over 1200 cases (first operator).
- Right heart catheterizations: over 50 cases (first operator).
- Percutaneous coronary interventions: over 900 cases (first operator).
- Primary percutaneous coronary interventions: over 170 cases (first operator).
- Radial percutaneous coronary procedures: over 30 cases (first operator)
- Rotablation, intra-aortic balloon pump insertion, aortic valve dilatation, ASD/PFO closure, septal ablation for HOCM, pericardial puncture, heart biopsies: about 80 cases (first and second operator).
- Intra-myocardial stem cell injection and ventricular mapping: over 40 cases (second operator).
- Transcatheter aortic valve implantation; transfemoral and transapical: about 15 cases (second operator).

Scientific attendances and contributions

- Poster presentation at the American College of Cardiology conference, April, 2011- New Orleans- Louisiana.
- Two oral presentations at the Euro-PCR conference, May, 2011- Paris.
- Poster presentation at the European society of Cardiology conference, August, 2011- Paris.
- Leiden Cardiology Course 2010, 2011.
- Course on "Basic methods and reasoning in biostatistics", LUMC- December 14-18, 2009
- Advanced course in biostatistics "Regression analysis: statistical model building", LUMC- May 17-21, 2010.
- "Percutaneous transcatheter aortic valve implantation" training program on June 15-16, 2011.
- "Percutaneous Mitral Valve Repair: Multidisciplinary Team Training", on June 9-10, 2011.

List of Publications

LIST OF PUBLICATIONS

- ***Tarek A.N. Ahmed, MD***; Amro A. Yousef, MD, PhD; Hossam I. Kandil, MD, PhD; Samir S. Abdel-Kader, MD, PhD. Added value of tissue Doppler imaging during low dose dobutamine echocardiography in the assessment of myocardial viability. Thesis for partial fulfillment of the Master degree in Cardiology in 2005
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- ***Tarek A. N. Ahmed, MD***; Joannis Karalis, MD; J. Wouter Jukema, MD, PhD. Late acquired stent malapposition: why, when and how to handle? *Heart (In press)*
- Jeffrey J. W. Verschuren, MD; ***Tarek A. N. Ahmed, MD***; Joannis Karalis, MD; Paul H. A. Quax, MD; PHD; and J. Wouter Jukema; MD, PHD. Late stent malapposition in the bare metal stent and drug eluting stent era. *Book Chapter In: Coronary Stent Restenosis (eds. Tintoiu IC, Popma JJ, Bae J-H, Rivard A, Galassi AR, Gabrie C. – Bucharest: The Publishing House of the Romanian Academy, 2011, ISBN 978-973-27-2034-9. Chapter 16)*