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# Innovative therapies for optimizing outcomes of coronary artery disease

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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.