The merit of radial access, thrombus aspiration, and drug-eluting stents in primary PCI: controversies in the treatment of acute myocardial infarction
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Summary, conclusions, and future directions
For patients presenting with acute ST-segment elevation myocardial infarction (STEMI), the treatment of choice to re-establish coronary flow is prompt mechanical reperfusion by primary percutaneous coronary intervention (PCI). The goal of this thesis was to evaluate and critically assess the merit of the following contentious treatment strategies in primary PCI.

PART I TRANSRADIAL ACCESS IN PRIMARY PCI

Although the transradial approach (TRA) for coronary diagnostics or intervention has been recognized to be a valuable alternative to the transfemoral approach, it is not widely adopted yet. Predominantly in primary PCI many interventional cardiologists withhold from the TRA due to the fear of technical difficulties that may delay adequate reperfusion of the infarct-related coronary artery. In our institution, the TRA is the preferred approach also in primary PCI since more than a decade ago. In chapter 2 procedural aspects of transradial primary PCI are discussed. We retrospectively analyzed all procedures performed for STEMI (excluding patients in cardiogenic shock) at the Onze Lieve Vrouwe Gasthuis in Amsterdam during the years 2001 to 2008. We evaluated the effect of obtaining a routine TRA in primary PCI on success rates of arterial access as well as procedural parameters including success of PCI. Procedural success was defined as TIMI flow grade 3 or an improvement of TIMI flow of 2 grades and ≤30% stenosis in the culprit lesion at the end of the procedure. We found that successful transradial access could be acquired in the vast majority of patients (2125 of 2209 procedures, 96.2%). Moreover, in 2007 and 2008 the need for arterial access-site crossover decreased to only 1.5% of all procedures performed. From 2001 to 2008, the procedural success rate maintained stable at an average of 94.1%, which is suitable considering the constant progress in procedural complexity over the years (e.g. the increased use of thrombus aspiration and multivessel PCI).
Chapter 9

Conclusions and future directions

Part I of this thesis shows that the implementation of TRA as standard approach results in successful arterial access and acute procedural success in the vast majority of patients. Given its proven benefits in preventing vascular complications, as opposed to the femoral approach, TRA should be considered the preferred approach in STEMI. Furthermore, since the TRA is rapidly growing worldwide, more data come available revealing further advantages of TRA over the femoral approach. In the recently published Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL) trial, a subanalysis of TRA in STEMI even showed a significant mortality benefit, when performed by experienced operators. Within a few years TRA-primary PCI will possibly be standard of care worldwide, thereby reducing the risk of vascular complications to further improve patient prognosis.

PART II THROMBUS ASPIRATION IN PRIMARY PCI

STEMI is typically caused by intracoronary thrombotic occlusion following disruption of an atherosclerotic plaque. The removal of thrombus from the culprit coronary artery may limit distal embolization of atherothrombotic material and thus reduce microvascular dysfunction. Several studies have indeed found a positive effect of thrombus aspiration (TA) on parameters of myocardial reperfusion. Nevertheless, it has been difficult to demonstrate a distinct clinical benefit of TA in adjunct to primary PCI.

Chapter 3 describes the results of a prospective, randomized trial in which thrombus removal was performed by either manual TA using the Export aspiration catheter, or by mechanical thrombectomy using the X-sizer system. In the Onze Lieve Vrouwe Gasthuis in Amsterdam, a total of 201 patients were randomly assigned to receive manual or mechanical removal of intracoronary thrombus prior to PCI. The primary end point was the occurrence of cardiac death, recurrent myocardial infarction, or target lesion revascularization at 3-year follow-up. In addition, we evaluated technical success of TA including ST-segment resolution as a marker of microvascular function.
We found that the manual aspiration catheter was safer, quicker and could more easily cross the infarct-related lesion, as compared with the X-sizer system. Furthermore, there was a minor although statistically non-significant difference regarding ST-segment resolution in favor of manual TA. However, no difference in the occurrence of major adverse cardiac events at 3 years was observed. In chapter 4 the results of a post-hoc analysis of the Paclitaxel-eluting versus Conventional Stent in Myocardial Infarction with ST-segment Elevation (PASSION) trial are described. The PASSION trial was conducted in 2 centers in The Netherlands, the Onze Lieve Vrouwe Gasthuis in Amsterdam and St. Antonius Hospital in Nieuwegein. A total of 619 patients presenting with STEMI were allocated to either a paclitaxel-eluting stent (PES) or a conventional bare-metal stent (BMS) in primary PCI. The use of thrombus aspiration was at the discretion of the operator and was performed in 311 patients (50.2%), whereas 308 patients (49.8%) underwent conventional primary PCI. We investigated if TA affected clinical outcome. The primary outcome of interest was the occurrence of cardiac death, recurrent myocardial infarction, or target lesion revascularization at 2 years. With the use of a propensity score we accounted for baseline clinical, angiographic, and procedural differences that might have affected the probability of TA. At 2-year clinical follow-up we found no difference in the occurrence of major adverse cardiac events in patients who received TA, as compared with patients who underwent conventional treatment.

Once an interventional cardiologist decides to proceed with thrombus aspiration, it has been shown that the aspiration catheter fails to cross the infarct-related lesion in a considerable proportion of patients. In chapter 5 we analyzed demographic, angiographic, and procedural data of all patients who underwent TA in the Academic Medical Center in Amsterdam from August 2001 to October 2007. We examined which factors may predict for failure of TA or failure to aspirate when the lesion could be crossed. In addition, we investigated whether unsuccessful TA affected 1-year mortality. TA was attempted in a total of 1,399 patients. In 144 patients (10.3%) the aspiration catheter could not cross the lesion. Even after successful crossing of the infarct-related lesion, no thrombotic material could be retrieved in 283 patients (27.3%). The presence of marked proximal turtuosity, a calcified lesion, or a bifurcation lesion were independent predictors of the failure of TA. Neither unsuccessful passage
of the catheter nor the absence of aspirate affected the incidence of all-cause death at 1 year.

Conclusions and future perspectives
In part II of this thesis we investigated the value of the removal of intracoronary thrombus in adjunct to primary PCI. The routine use of manual TA during primary PCI is recommended in current clinical practice guidelines. Yet, in our prospective comparison of manual versus mechanical thrombus removal we found no difference in the occurrence of major adverse cardiac events at long-term follow-up. Furthermore, in our post-hoc analysis of the PASSION trial TA did not affect 2-year clinical outcome, as compared with conventional PCI. Finally, we demonstrated that in a real-world setting TA cannot be accomplished in a substantial amount of attempts. We observed that 1-year mortality was not influenced by failure of TA or the absence of aspirate. Hence, our findings question an overt clinical value of TA during primary PCI. Since our studies were either performed with a limited number of patients, or had a retrospective design, the results should be interpreted with caution. In view of earlier contradictive results, however, it may perhaps be reasonable to apply a more selective approach of thrombus removal (i.e. in the presence of large thrombus). Currently, two large randomized controlled trials comparing TA with conventional treatment are recruiting STEMI patients. The results of these studies will provide an ultimate answer to whether TA should be performed in every patient presenting with STEMI.

PART III DRUG-ELUTING STENTS IN PRIMARY PCI

Early this century, various randomized studies demonstrated that additional stenting in primary PCI reduces the incidence of restenosis, as compared with balloon angioplasty alone. The event of in-stent restenosis, though, remained a challenging dilemma occurring in a considerable proportion of patients. Subsequently, the development of drug-eluting stents (DES) significantly reduced the risk of in-stent restenosis when implanted in elective PCI for stable coronary artery disease.
Observational studies revealed a possible drawback, though, due to an increased and enduring risk of stent thrombosis that was assumed to exist after the implantation of a first generation DES. Therefore, long term follow-up of studies examining DES was warranted. The use of DES in the setting of STEMI was not investigated until a few years ago. The PASSION trial was one of the first randomized trials to compare DES with BMS in patients undergoing primary PCI for STEMI, of which the short-term clinical results were previously published. In chapter 6 the 2-year clinical results of the PASSION trial are described. At 2 years no statistically significant difference was found in the occurrence of the primary end point cardiac death, recurrent myocardial infarction, or target lesion revascularization. Likewise, no difference in the incidence of stent thrombosis was observed between both stent groups. Chapter 7 is the final report of the PASSION trial. Our aim was not only to address the possible long-term benefit of PES, but also to clarify a potential continuing risk of stent thrombosis. At 5 years, the occurrence of the primary end point did not significantly differ between both stent groups. In addition, stent thrombosis continued to be a rare event up to 5 years, although beyond 1 year it was almost exclusively confined to the PES group. Bearing in mind the low number of events, however, this observation could have been by chance. Finally, in chapter 8 the results of an angiographic follow-up study are discussed. Patients originally included in the PASSION trial, who were free from target lesion related adverse cardiac events, were asked to undergo repeat angiography 4 years after stent implantation. Very late luminal loss was assessed by quantitative coronary angiography. We included a total of 116 patients, of which 61 had received a PES, and 55 had been treated with a BMS. We found that even 4 years after implantation stent patency was secured in the majority of patients in both stent groups, whereas very late luminal loss was less pronounced in the PES group.

Conclusions and future directions
Drug-eluting stents have unequivocally proved to be superior in preventing in-stent restenosis, when compared with BMS. In STEMI, though, the benefit of DES (particularly first-generation DES) has been of a lesser magnitude, especially in view of a possible higher risk of stent thrombosis. Part III of this thesis addressed the long-term outcome of DES in STEMI. The reports of 2-year and 5-year clinical follow-
up of the PASSION trial demonstrated no significant difference in the occurrence of major adverse cardiac events after implantation of a PES or a BMS. Even though late stent thrombosis was found primarily in PES, no final judgment could be made as the PASSION trial was not powered to detect a difference in the occurrence of this endpoint. In conclusion, in the absence of a clear reduction of adverse cardiac events and consistent with a possible higher risk of stent thrombosis, the results of the PASSION trial justify the use of BMS in primary PCI, as opposed to first-generation PES. Meanwhile, newer generation DES have been developed with improved stent design, thinner polymers and alternative antiproliferative drugs. They have shown to further reduce the need for target lesion revascularization in various indications including STEMI. Additionally, the use of these newer generation stents has extensively diminished the risk of stent thrombosis. The recently developed bioabsorbable vascular scaffolds or drug-eluting balloons may serve as the ultimate method to reduce restenosis and at the same time virtually eliminate the risk of (stent) thrombosis. At this moment, the implementation of these devices in primary PCI remains to be investigated in randomized controlled trials.