PCI of complex coronary lesions, new stent technologies, and clinical outcomes

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Summary and conclusions
Summary

This thesis focuses on different aspects of percutaneous coronary interventions. The first part (Chapters 2 and 3) focuses on the percutaneous treatment of complex coronary lesions. The second part (Chapters 4 and 5) describes angiographic and clinical outcomes of two new stent technologies, the Genous™ endothelial progenitor cell (EPC) capturing stents and the XIENCE V™ everolimus-eluting stent (EES). The third part (Chapter 6) evaluates the several biomarkers as predictors for clinical and angiographic outcomes after stenting.

Part I: Treatment of complex coronary lesions

In Chapter 2.1, we performed a retrospective analysis of 3883 consecutive patients undergoing nonurgent percutaneous coronary intervention (PCI) comparing bare metal stent (BMS) (n=2050) with drug-eluting stent (DES) (n=1833) using the National Institute for Clinical Excellence (NICE) guidelines. In these guidelines, lesions with a reference vessel diameter of less than 3.0mm or lesions with a length of greater than 15mm are considered carrying a high risk of restenosis and should preferably be treated with a DES. In contrast, lesions with a reference vessel diameter of at least 3.0mm or a lesion length of 15mm or less are considered at low risk of restenosis and could be treated be a BMS. The results of this study show that in patients with lesions carrying a low risk of restenosis, no differences were observed between BMS and DES in composite end points, target lesion revascularization (TLR), or stent thrombosis (ST) at 1-year follow-up. In patients with lesions carrying a high risk of restenosis, patients treated with BMS had a significantly higher rate of TLR by PCI, but a significantly lower rate of TLR by coronary artery bypass grafting (CABG) compared with patients treated with DES. Furthermore, a nonsignificant lower rate of definite ST was observed in the BMS group compared with the DES group.

Chapter 2.2 evaluate the long-term outcomes of the selected patients by the local Heart Team to undergo PCI of unprotected left main coronary artery (ULMCA) stenosis and to compare patients considered at low surgical risk versus at high surgical risk for CABG. A total of 227 patients were included and long-term follow-up was up to 8 years with a mean of 3.9±2.6 years. Overall, the Kaplan–Meier estimate of the composite of cardiac death, myocardial infarction (MI), or TLR was 14.8% at 1 year, 18.3% at 3 years, and 20.9% at 5 years with no events occurring thereafter. Patients considered at low surgical risk for CABG had a significantly lower incidence of cardiac death or MI compared to patients considered at high surgical risk at 8 years; however, no significant difference was observed for cardiac death, MI, or TLR.

Chapter 2.3 describes the 1-year clinical outcome after treatment of bare-metal stent in-stent restenosis (ISR) with the Taxus paclitaxel-eluting stent (PES) in an unselected cohort of 214 patients. The majority of BMS ISR treated lesions had a diffuse pattern of ISR. The results showed that treatment of BMS ISR with PES in an unselected cohort of consecutive
Chapter 3 studies and discusses the percutaneous treatment of bifurcation lesions. In Chapter 3.1 we studied the 1-year clinical outcomes after percutaneous treatment of bifurcation lesions using a simple technique with a single bare metal R stent in 465 patients. A total of, 105 patients were treated for a true bifurcated lesion (TBL) and 360 patients were treated for a lesion with involvement of a significant side branch (ISB). During follow-up, 8.6% treated for TBL had a clinically driven TLR. In patients treated for ISB, 13% had a clinically driven TLR. Cardiac death occurred in 1.9% and 2.5% respectively.

Chapter 3.2, we evaluate the 1-year clinical outcome in 178 patients treated with the Genous™ endothelial progenitor cell (EPC) capturing stent for a bifurcation lesion using a provisional T-stenting technique and compared these to a historical control group (n=465) treated with an identical BMS. We performed a multivariate and propensity-score analyses to adjust for differences in clinical and angiographic characteristics between the Genous™ EPC capturing stent group and the BMS group. At 1-year follow-up, we observed that treatment of bifurcation lesions with the Genous™ EPC capturing stent (relative to BMS treatment) was associated with a numerical reduction (statistically non-significant) in the rate of cardiac death, MI, or TLR. Moreover, the rate of definite ST in the Genous™ EPC capturing stent group as well as the control group was low.

Chapter 3.3 describes the 12-month clinical outcomes after coronary stenting with the Genous™ bio-engineered R stent™ in patients with a bifurcation lesion from the worldwide, prospective, non-randomized e-HEALING registry. We show that at 12-month follow-up, coronary bifurcation stenting with the Genous™ EPC capturing stent results in favourable clinical outcomes and low incidences of repeat revascularization and stent thrombosis. Moreover, ≥1 stents per lesion, pre-dilatation performed, and lesions located in the RCA were independent predictors of the primary end point target vessel failure.

Interpretations and conclusions of part I

From Chapter 2.1, we conclude that in patients with lesions carrying a low risk of restenosis, the use of BMS is safe and does not increase the risk of cardiac events compared to DES. In patients with lesions carrying a high risk of restenosis, the use of DES is favored with respect to the need for repeat intervention, however, BMS showed a nonsignificant lower rate of stent thrombosis. These findings are in line with the current the European Society of Cardiology guidelines for PCI that refer to the National Institute for Clinical Excellence Institute guidance that indicates DES is recommended for patients with symptomatic coronary artery disease, in whom the target coronary artery is less than 3mm in diameter or the lesion length is greater than 15 mm. The results of Chapter 2.2 indicates that in patients with unprotected left main coronary artery stenosis selected by the local Heart Team to undergo PCI, stenting is safe and effective in the very long-term. Furthermore, our results suggest patients considered
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at high surgical risk for CABG have worse outcomes than patients considered at low surgical risk for CABG. Although, our study extends the results of previous studies evaluating the long-term follow-up after unprotected left main coronary artery stenting, more data is needed investigating the very long-term follow-up for DES. Chapter 2.3 confirms the safety and efficacy of treatment of bare-metal ISR with the PES in unselected patients. These data is in accordance with a growing number of studies indicating that DES is the preferred treatment. The role of drug-eluting balloons for treatment of bare-metal ISR is to be investigated, however, promising results have been reported.

As shown in Chapter 3.1, our stepwise approach with BMS placement in the main branch and balloon angioplasty in the side branch of bifurcation lesions showed acceptable long-term results, indicating that in these lesions side branch stenting can be avoided. Moreover, in Chapter 3.2 the outcomes after treatment of bifurcation lesions with the Genous™ EPC capturing stent were improved compared with the BMS. The results of the Genous™ EPC capturing stent are comparable to the outcomes reported from studies evaluating DES. Finally, Chapter 3.3 suggests that in an unselected patient population treatment of bifurcation lesions with the Genous™ EPC capturing stent is safe and effective. Therefore, a randomized study comparing the Genous™ EPC capturing stent versus the DES may be performed.

Part II: New stent technologies

Chapter 4 represents the outcomes after stenting with the Genous™ EPC capturing stent.

In Chapter 4.1 the available data on the Genous™ EPC capturing stent system is reviewed.

As described in Chapter 4.2, we randomized 193 patients with de novo coronary lesions with a high-risk of coronary restenosis to the Genous™ EPC capturing stent versus the Taxus Liberté PES. Lesions were considered high-risk of restenosis if one of the following applied: chronic total occlusion, lesion length >23 mm, vessel diameter <2.8 mm, or any lesion in a diabetic patient. The primary end point in this randomized, single-centre, pilot study was target vessel failure (TVF) at 1-year follow-up. TVF was 17.3% in the Genous stent group as compared with 10.5% in the Taxus stent group (risk difference 6.8%, 95%CI -3.1% - 16.7%), a difference predominantly due to a higher incidence of repeat revascularization in patients treated with the Genous stent. In contrast, no stent thrombosis was observed in the Genous stent group as compared with 10.5% in the Taxus stent group (risk difference -4.2%; 95%CI -10.3%-0.3%). Repeat angiography between 6 and 12 months in a subgroup of patients showed a significantly higher late loss in the Genous stent compared to the Taxus stent (1.14±0.64 mm and 0.55±0.61mm).

In addition, Chapter 4.3 reports the 2-year follow-up of the Genous™ EPC capturing stent versus the Taxus Liberté PES in patients with de novo coronary lesions with a high-risk of coronary restenosis. Between 1 and 2 years, patients treated with the Genous stent compared with the Taxus stent tended to have fewer episodes of TLR. As a result,
the non-significant difference in target vessel revascularization (TVR) was maintained at 2-year follow-up in the TRIAS pilot study, with convergence of the Kaplan-Meier curves between 1 and 2 years. Very late stent thrombosis was observed with the Taxus stent but no stent thrombosis was observed with the Genous stent in the follow-up period of 2 years.

**Chapter 4.4** describes the design and rationale of the multicenter, randomized, controlled, 2-armed TRI-stent adjudication study (TRIAS) program. This study program aims to include a total of 2560 patients. In the TRIAS Low Risk trial, a total of 1300 patients with lesions carrying a low risk of restenosis are randomized between the EPC capturing stent and a BMS, assuming superiority in the incidence of target lesion failure (TLF) at 1 year. In the TRIAS High Risk trial, 1260 patients with lesions carrying a high risk of restenosis are randomized, assuming the non-inferiority in TLF at 1 year of the EPC capturing stent as compared to DES.

In **Chapter 4.5** the results of the TRIAS High Risk study are demonstrated. Early cessation of the trial was recommended by the data and safety monitoring board after an interim analysis with 50% of the patients enrolled because TLF in the EPC capturing stent population was substantially higher and treatment of new patients with an EPC capturing stent would be unreasonable. The trial was terminated for safety reasons. At one year, TLF occurred in 17.4% of the EPC capturing stent-treated patients and in 7.0% of the DES-treated patients (p=0.98 for non-inferiority). Our results suggest that within one year, inhibition of intimal hyperplasia by the EPC capturing stent is not sufficiently strong to compete with DES in terms of restenosis prevention in patients/lesions with a high risk of restenosis.

In **Chapter 4.6** the clinical outcomes after PCI with the Genous™ EPC capturing stent was evaluated an unselected patient population. A total of 405 unselected patients were included and the primary end point was defined as the composite of cardiac death, MI, and TLR. At 1-year follow-up the Genous™ EPC capturing stent showed good results with a low occurrence of definite and probable ST. Moreover, based on the risk of restenosis, in patients with lesions with an estimated high risk of restenosis, the composite primary endpoint was significantly higher compared with patients with lesions with an estimated low risk. Furthermore, the one year clinical outcomes in diabetic patient compared well with the non-diabetic patients. Finally, a matched-pair analysis was performed in which all Genous-treated patients were matched in a 1:1 ratio with BMS-treated patients. No statistically significant differences were found between both stent groups.

Finally, in **Chapter 4.7**, we investigated late luminal loss after Genous™ EPC capturing stenting measured by quantitative coronary analysis. This study illustrates a significant intimal hyperplasia regression between 6 and 18 months.

**Chapter 5** reports on the outcomes of the XIENCE V™ EES. In **Chapter 5.1** the available data on the XIENCE V™ EES system, a second-generation DES, is reviewed.

In **Chapter 5.2**, we studied 2-year results of the prospective, single-blinded, randomised, multi-center study evaluating the safety and efficacy of the XIENCE V™ EES versus an identical BMS in the treatment of patients with a single de novo coronary artery stenosis of ≥50% and <100% and a vessel diameter of 3.0 mm that could be covered by a single 18 mm stent. Sixty patients were randomised. The 2-year hierarchical major adverse cardiac events
(MACE) rate comprised of cardiac death, Q-wave or non-Q-wave MI, or clinically-driven surgical or percutaneous TLR, was 15.4% for the EES group versus 25.0% for the control group. No stent thrombosis was observed in the EES group or in the control group.

In Chapter 5.3, the 2-year clinical outcomes of the XIENCE V™ EES are compared with the PES in the treatment of patients with de novo coronary artery lesions. In this prospective, single-blind clinical trial a total of 300 patients were randomized to either EES or PES in a 3:1 fashion and a subset of 152 patients underwent serial angiographic and intravascular ultrasound analyses at 6 months and 2 years. At 2 years, no significant difference was observed between both stents in the primary end point TLF defined as the composite of cardiac death, MI, and ischemia-driven TLR, nor in the individual components. The incidence of ST was low and comparable in both groups. At 6 months, a significant reduction in angiographic in-stent late luminal loss and percentage volume obstruction measured by intravascular ultrasound was observed in the EES group. However, at 2-year follow-up, a late increased intimal hyperplasia growth after implantation of an EES was observed. Although, our results showed that the angiographic and clinical superiority of the EES at 1-year follow-up has diminished over time, this report confirms and extends the previously demonstrated non-inferiority in terms of in-stent late loss of the EES when compared with the PES up to 2-year follow-up.

Interpretations and conclusions of part II

Although, the HEALING FIM and HEALING II studies showed promising results after percutaneous treatment with the Genous™ EPC capturing stent in non complex de novo coronary lesions, our results suggest that, in lesions considered high-risk of restenosis, the Genous™ EPC capturing stent was less effective in preventing restenosis compared to DES. However, the Genous™ EPC capturing stent showed a higher safety profile without the need for long-term dual antiplatelet therapy. Moreover, late catch-up phenomenon as seen DES was not observed after Genous™ EPC capturing stenting. In fact, we have illustrated a significant intimal hyperplasia regression between 6 and 18 months in the Genous™ EPC capturing stent. Currently, the Genous™ EPC capturing stent may be an attractive alternative to DES or BMS in patients with an increased risk of ST, with a contra indication for dual antiplatelet therapy, with a (recent) history of bleeding or for patients that are scheduled for surgery. Further investigation is needed to observe the balance between the occurrence of clinical restenosis versus the risk of late and very late ST and the impact on short and long term patient outcomes. Importantly, based on the results of the current analyses and the potentially ongoing intimal hyperplasia observed in DES, we suggest that, in order to fairly compare late loss numbers of the Genous™ EPC capturing stent to DES, study-related angiographic follow-up should be performed after 18 months or later. Moreover, clinical outcome comparison between ECS and DES requires perhaps an even longer follow-up. Furthermore, considering the outcomes of these studies, repeat revascularization of angiographically moderate restenosis may best be avoided in patients
without anginal complaints or ECG changes in the first year after Genous™ EPC capturing stent implantation.

As part of the SPIRIT program, our results suggest that the XIENCE V™ EES, a second-generation DES, is effective and safe and the clinical and angiographic outcomes are comparable with PES in the long-term. These data are in accordance with the SPIRIT III trial, having a similar design as the SPIRIT II study and including over a 1000 patients. At 2 years of follow-up, treatment with the EES compared with the PES resulted in a 32% reduction (10.7% versus 15.4%; P=0.04) in TVF (the composite of cardiac death, MI, or TVR). This favourable balance of safety and efficacy with the EES was driven by fewer episodes of early and late MI and fewer TLR procedures required between 6 and 12 months. Between 1 and 2 years, there tended to be fewer ST with the EES compared with the PES, especially in patients who had discontinued clopidogrel after 6 months, which in part contributed to the improved outcomes. In addition, the clinical outcomes at 2 years of the large-scale, prospective, multicenter, randomized SPIRIT IV trial and the ‘all-comers,’ randomized, open label COMPARE trial also demonstrated substantial clinical benefit of the EES over the PES with regard to both safety and efficacy. Whether the XIENCE V™ EES will be superior to newer stents with different stent platforms such as titanium-nitride-oxide coated stents or bioabsorbable stents needs to be established in the future.

Part III: Predictors of clinical outcomes

In Chapter 6.1, we investigated whether multiple biomarkers improve prognostication in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary PCI. In this retrospective analyses we used data from 1034 STEMI patients and investigated whether combining N-terminal pro-brain natriuretic peptide (NTproBNP), glucose, C-reactive protein, estimated glomerular filtration rate (GFR), and cardiac troponin T improved the prediction of mortality. We developed a risk score based on the strongest predicting biomarkers in multivariate Cox regression. The additional prognostic value of the strongest predicting biomarkers to the established prognostic factors (age, body weight, diabetes, hypertension, systolic blood pressure, heart rate, anterior myocardial infarction, and time to treatment) was assessed in multivariable Cox regression. In the Cox regression, glucose, estimated GFR, and NTproBNP were the strongest predictors for mortality. A risk score incorporating these biomarkers identified a high-risk STEMI subgroup with a significantly higher mortality when compared with an intermediate- or low-risk subgroup. Addition of the 3 biomarkers to established prognostic factors significantly improved prediction for mortality, as shown by the net reclassification improvement and integrated discrimination improvement.

Cystatin C has been proposed as a more sensitive marker of renal function than serum creatinine or creatinine-based estimating equations, in particular for detection mild to moderate decrements in the GFR. In Chapter 6.2, we determined whether plasma concentration of cystatin C in patients undergoing non-urgent PCI has prognostic value. In a
total of 1293 patients included in the prospective, multicenter GENetic Determinants of Restenosis (GENDER) study, cystatin C was available. Patients were stratified according to tertiles of the cystatin C concentration at baseline and the primary end point was TVR within 1 year. Regarding the primary end point, patients in the lowest teritile of cystatin C had significantly higher rate of TVR at 1-year follow-up; in contrast, patients in the highest teritile of cystatin C had a significant higher rate of cardiac death. After adjustment for baseline characteristics (including estimated GFR), cystatin C was found to be independently associated with TVR at 1-year follow-up. The results of this study suggest that in patients undergoing non-urgent PCI, cystatin C may act as a potential marker for enhancement of risk stratification to identify patients with a higher risk of TVR and mortality.

Chapter 6.3 examined whether polymorphisms at the toll-like receptor 4 (TLR4) locus, that are associated with impaired innate immune system and with an increased risk of cardiovascular events, were associated with clinical and/or angiographic restenosis after PCI. In total of 2682 patients included in the GENDER study, the frequencies of the TLR4 896A/G (Asp299Gly) and 1196C/T (Thr399Ile) polymorphisms and haplotypes were assessed. No association was observed between genotypes and the risk of late luminal loss at 6-months angiographic follow-up or TVR at 1 year. Absence of association between genotypes with TVR or late luminal loss was replicated in the GEnetic risk factors for In-Stent Hyperplasia study Amsterdam (GEISHA) cohort study of 674 patients and in a subgroup of 550 patients with angiographic follow-up available. Moreover, in both the studies, no significant differences between haplotypes A/C and G/T were observed for TVR at late luminal loss. In contrast to animal data, our clinical results showed that these polymorphisms are not useful for pre-PCI identification of patients at risk for restenosis.

As the cyclin-dependent kinase inhibitor p27kip1 is a key regulator of smooth muscle cell and leukocyte proliferation in vascular disease, including ISR. Chapter 6.4 sought to find out whether common genetic variations or single nucleotide polymorphisms (SNP) in p27kip1 may serve as a useful tool in risk stratification for ISR. Three SNP's concerning the p27kip1 gene (─838C>A, ─79C>T, +326G>T) were determined in a cohort of 715 patients undergoing coronary angioplasty and stent placement. The results of our study showed that the p27kip1─838C>A SNP is associated with clinical ISR; the ─838AA genotype decreases the risk of TVR. This finding was replicated in the GENDER cohort study in 2309 patients. In both cohorts, no association was found between TVR and the p27kip1─79C>T and +326G>T SNPs. We subsequently studied the functional importance of the ─838C>A SNP and detected a 20-fold increased basal p27kip1 transcriptional activity of the ─838A allele containing promoter. Our results suggest that patients with the p27kip1─838AA genotype have a decreased risk of ISR corresponding with enhanced promoter activity of the ─838A allele of this cell-cycle inhibitor, which may explain decreased smooth muscle cell proliferation.
Interpretations and conclusions of part III

Restenosis remains the main drawback of PCI. Biomarkers and genetic variances pose an opportunity to enhance stratification of individuals who will be prone to develop restenosis. Furthermore, it can contribute to optimalization of medical therapy and proper assignment of revascularization strategy. From Chapter 6.1, we conclude that addition of a multiple biomarkers to a model including established risk factors improves the prediction of mortality in STEMI patients undergoing primary PCI. Furthermore, the use of a simple risk score based on these biomarkers identifies a high-risk subgroup. The results of our single center will have to be confirmed in a larger multicenter study. In the GENDER study, we demonstrate that cystatin C may act as a potential marker for enhancement of risk stratification to identify patients with a higher risk of TVR and mortality in patients undergoing elective PCI. Whether these results can be applied to patients treated with DES needs to be established. In contrast, in the GENDER study, absence of association between TLR4 polymorphism and clinical or/and angiographic restenosis was observed. Therefore, TLR4 polymorphism can not be used in the individual for risk stratification of restenosis. Finally, we show that the p27\(^{kip1}\)\(-838AA\) genotype was associated with a decreased risk of ISR corresponding with enhanced promoter activity of the\(-838A\) allele of this cell-cycle inhibitor that might explain the decreased smooth muscle cell proliferation observed. As this is the first study to clearly show a decreased risk of ISR, further research is needed. At this moment it is unclear whether the p27\(^{kip1}\)\(-838AA\) genotype can act as a therapeutic target. The clinical and practical introduction of gene polymorphisms as novel risk factors in the near future will depend on the availability of rapid and affordable genotyping techniques. Since restenosis is a multifactorial disease it can be expected that more candidate genes will be discovered.

Future considerations

The number of PCIs is expected to increase in the near future as a result of application of PCI in STEMI, acute coronary syndromes and the shift of surgical treatment, i.e. CABG, to percutaneous treatment for patients with coronary artery disease. In-stent restenosis may therefore be translated in an economic burden. Development of new stent technologies, adjunctive therapies and improved risk stratification is needed to improve outcomes after PCI especially in high-risk patients. Our results on restenosis after percutaneous treatment of complex coronary lesions, on angiographic and clinical outcomes of two new stent technologies, and on several biomarkers as predictors for outcome may encourage further research in the field of PCI.