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

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CHAPTER 1

General introduction and outline of the thesis

General introduction

Percutaneous coronary intervention (PCI) has become common practice in the treatment of coronary artery disease (CAD). Technical advances in equipment, stents, mechanical assist devices, and developments in adjunctive pharmacotherapy have improved the outcomes in patients. In addition, a greater understanding of the underlying pathophysiology, the identification and appropriate management of risk factors have extended the indications for PCI to patients and lesions with varying degrees of complexity. Although the introduction of drug-eluting stents (DES) has improved clinical and angiographic outcomes compared to bare-metal stents (BMS), the major drawback remains in-stent restenosis (ISR) and acute stent thrombosis. On a daily basis, the interventional cardiologist is confronted with clinical decision-making on which patient/lesion to select to treat with DES or BMS taking into account the long-term efficacy and safety. Moreover, the need for repeat revascularization is illustrative for the clinical efficacy of the initial treatment, whereas, repeat PCI in lesions other than the index lesion in the target vessel may provide information about progression of the underlying atherosclerotic disease in general.

Stenting of coronary artery lesions prevents the occurrence of recoil and negative remodelling. ISR is mainly the result of vascular smooth muscle cell migration and proliferation (neo-intima formation).[1,2] ISR may cause recurrence of anginal symptoms or cardiac events and remains an important clinical problem. The pathophysiology of coronary ISR is multifactorial and has not been fully elucidated. The cascade of events is induced by balloon inflation with vascular injury of the endothelial layer and medial dissection (barotrauma outside stented segment). The injured vessel wall is exposed to platelets, inflammatory cells, smooth muscle cells, and endothelial cells which release a number of cytokines that are able to induce neo-intimal formation.[3]

Stent configuration has an important influence on ISR. The bare metal Palmaz-Schatz stent had a rigid slotted tube design, providing a high radial strength – an important component of its high antirestenotic efficacy – though resulted in a limited flexibility and reduced deliverability. Wire coil stents had a more flexible design but limited radial strength causing higher degrees of stent recoil, plaque prolapse and restenosis and, subsequently, fell out of use.[4] Currently, modular stent designs combine multiple short repeating modules which result in significantly improved flexibility without comprising radial strength or restenosis rates. Stent strut thickness also has a significant influence on ISR. Thinner stent struts reduce arterial injury during stent placement which translates into lower rates of restenosis at follow-up.[5-7] Stent composition also plays an important role in the development of ISR. The most commonly used stent material is 316L stainless steel due to its high radial strength and biological inertness. Other materials were evaluated such as gold-plating stents, providing high biocompatibility, increased radiopacity and reduced platelet activation but significantly increased restenosis rates.[8,9] More recently, cobalt-chromium platforms utilises superior mechanical properties compared with 316L stainless steel, including greater strength and increased density. This allows thinner stent struts offering increased flexibility and deliverability without comprising radial strength or radiopacity.[10]

Finally, titanium-nitride-oxide coated stents demonstrated high biocompatibility, reduced platelet adhesion and decreased fibrinogen binding in comparison with uncoated stents. Preliminary data shows promising results.[11,12]

Besides the stent platform, the performance of DES is also related to the carrier polymer (to control the drug release kinetics) and the active drug. The next generation (or 'second generation') of DES have incorporated modification in stent design aiming to attenuate the problem of delayed vascular healing after DES implantation. Such improvements have involved a switch away from durable coatings for drug loading and release, as well as the incorporation of reduced drug dosages and self-degrading backbones. A significant body of evidence implicates that polymer coating as a cause of persistent vessel wall inflammation, which continues to delay healing and drive neointimal formation late after DES implantation.[13] Therefore, a major improvement was the utilization of self-degrading biopolymer (which degrades over 3-9 months) instead of a permanent polymer. The novel biodegradable polymer biolimus-eluting stent has demonstrated non-inferiority in comparison with the sirolimus-eluting stent (SES).[14] In addition to a biodegradable coating, a biodegradable stent backbone was developed. Although, inferior radial strength compared to metal alloy stents has limited this technology, the ABSORB trial compared an everolimus eluting DES with a biodegradable polylactic acid stent backbone and reported satisfactory anti-restenotic efficacy.[15] To date, two different classes of drugs have been successfully employed on DES platforms in order to inhibit smooth muscle cell proliferation: a). "limus" family immunosuppressive drugs (i.e. sirolimus, everolimus, zotarolimus, biolimus) which halt the cell cycle progression in G1 phase; and b). paclitaxel, a microtubule stabalizing drug which interrupts mitotic division in late metaphase, resulting in M phase cycle arrest.[16]

Several clinical risk factors like diabetes mellitus, male gender, hypertension and smoking have been associated with the occurrence of ISR, however, the underlying mechanisms are not always completely understood. [17-20] In addition, lesion characteristics such as bifurcation lesions, long and/or calcified lesions, chronic total occlusions, lesions in vessels with a small diameter (≤3.0 mm) are also identified as risk factors for ISR.[21-24] Finally, the use of long stents or multiple stents also increases the risk of ISR.[25] Whether bioabsorbable stents can overcome the problem of in-stent restenosis remains to be investigated.

Stent thrombosis (ST) is a serious clinical event that in approximately 70% of patients leads to MI and short-term mortality has ranged from 15 to 45%.[26,27] Acute ST (within 24 hours after stent placement) and sub acute ST (within 1-30 days) are mostly caused by mechanical issues such as vessel injury of balloon/stent placement, underexpansion of the stent or stent malapposition.[28,29] Minor differences in stent design and manufacturing can impact significantly the immediate and long-term clinical outcomes.[30] Due to improved deployment techniques and the use of more potent dual antiplatelet agents, the occurrence of acute and subacute ST is rare for both DES and BMS, taking place in approximately 0.5% of the patients.[31,32] Late ST (after 30 days) is extremely rare with BMS and its incidence with DES has been reported to be a linear risk of 0.4–0.6% per year up to 4 years, a phenomenon that was not apparent after BMS placement.[33,34] Late ST is related to delayed intimal healing and endothelialisation. The causes of late ST are most likely to be multifactorial,

with delayed healing in combination with other clinical and procedural risk factors playing a role.[31,32] Several lesion characteristics such as long lesions, lesions in small vessels, bifurcation lesions, lesions in diabetic patients are associated with stent thrombosis.[26] Although not fully elucidated, cessation of antiplatelet therapy has also been found to contribute to late ST.[26,29]

Part I: Treatment of complex coronary lesions

PCI in complex lesions remains a challenge for the interventional cardiologist, in particular, unprotected (no prior bypass surgery) left main coronary artery lesions and bifurcation lesions. PCI for unprotected left main coronary artery stenosis has long been the subject of debate because of periprocedural risks and the incidence of restenosis. The left main coronary artery disease supplies >50% of the myocardium and patients with acute closure after stent placement in this part of the coronary tree are at high risk of acute cardiac death. Therefore, coronary artery bypass grafting (CABG) has been the standard treatment for significant unprotected left main coronary artery stenosis and PCI was recommended only as an alternative for stable patients considered not eligible for surgery. However, as a result of improvement of techniques, devices and antiplatelet therapy, the percutaneous treatment of left main stenosis has become of particular interest. Several studies have reported increasingly good a immediate and long-term outcomes after unprotected left main stenting with BMS[35-42] and DES[43-50]. Recently, subgroup analyses from the large, randomized SYNTAX trial showed that patients treated for left main stenosis by PCI or CABG had comparable MACCE rates (13.7% TAXUS vs. 15.8% CABG) at 1-year but repeat revascularization was significantly higher in the PCI group (11.8% TAXUS vs. 6.5% CABG; P=0.02).[51] Importantly, the results of the SYNTAX study are limited to 1-year follow-up and long-term follow-up data are still needed.

In addition to percutaneous treatment of left main stenosis, PCI of bifurcation lesions also remains the subject of debate. Coronary bifurcation lesions occur in approximately 15-20% of all percutaneous interventions and are associated with an increased risk of adverse events and inferior outcomes when compared to non-bifurcation lesions.[21,23,52,53] Many different treatment strategies and techniques have been proposed. Most strategies aim to achieve optimal angiographic procedural success in both branches, often with stent placement in both mian branch and side branches. However, fractional flow reserve (FFR) measurements in the side branch after PCI showed that in up to 70% such branches, angiographic ostial side branch stenosis following main branch stenting (e.g. due to plaque shift) was functionally not significant.[54] Moreover, lesions with <75% side branch stenosis had a FFR of >0.75. In contrast, wide variations were found in side branch lesions with >75% stenosis suggesting that not all angiographically significant side branch stenoses needed to be treated. These findings formed the rationale for a single-center study of PCI of bifurcation lesions using a stepwise approach aiming at an optimal functional result in the side branch. Moreover, the European Bifurcation Club has reached consensus that, with BMS and DES,

a stepwise provisional T-stent strategy is the preferred approach.[55] We have evaluated the novel endothelial progenitor cell capture stent for treatment of bifurcation lesions using the provisional T-stenting technique.

Part II: New stent technologies

Randomized trails have shown a significant reduction in restenosis rates in patients with CAD with DES compared with BMS.[56-60] The cytotoxic or cytostatic drugs eluted from the DES inhibits the vascular smooth muscle cell proliferation and neointimal hyperplasia induced by stent placement. Consequently, the natural healing response is also impeded due to the delayed functional endothelialization of the stent struts, associated with an increased incidence of stent related thrombosis and vasomotor dysfunction.[26,27,61-65] The novel bio-engineered Genous™ endothelial progenitor cell (EPC) capturing stent has a stent technology with a 'pro-healing'approach. The EPC capturing stent is coated with CD 34+ antibodies which are able to bind bone marrow derived circulating EPCs from the peripheral blood. In an animal model, scanning electron microscopic images have demonstrated a complete re-endothelialization of the stent struts and vessel segments within only a few hours following EPC capturing stent placement.[66,67] It is hypothesized that these 'captured' EPCs can rapidly differentiate into a functional endothelial layer on the stent surface. This accelerated re-endothelialization after stent placement may reduce in-stent restenosis by reducing neo-intimal hyperplasia and SMC proliferation and additionally may prevent the occurrence of ST.[68]

The safety and feasibility of the EPC capturing stent was evaluated in the non randomized HEALING FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man)[69] registry and HEALING II study.[68,70] The HEALING FIM was a prospective registry including 16 clinically stable patients with native coronary artery disease eligible for stent placement. At 6-month angiographic follow-up a mean late luminal loss of 0.63±0.52mm and a percent in-stent restenosis of 27%±21% was observed. At 9-month clinical follow-up, the composite of cardiac death, stroke, MI, and target vessel revascularization (TVR) was 6.3% with no cases of ST. The HEALING II registry confirmed and extended the outcomes of the HEALING FIM study. The prospective HEALING II registry included 63 patients with de novo, native coronary artery stenosis. Clinical and angiographic follow-up was obtained at 6 and 18 months with measurements of EPCs at baseline. At 18 month follow-up, the primary end point (composite of cardiac death, MI, and target lesion revascularization (TLR)) was 7.9%, predominantly due to the clinically-driven TLR rate of 6.3%. Again, no acute or sub acute ST was observed during the 18 month follow-up, despite only 1 month of dual anti-platelet therapy. In-stent late loss at 6 months was 0.78±0.39 mm and percent in-stent obstruction was 22.9±13.7%. A remarkably significant late regression of neointimal hyperplasia was observed between 6 and 18 months on quantitative coronary angiography (late loss 0.59±0.31 mm, a reduction of 24.4%) and IVUS (percent in-stent volume obstruction 20.3±14.3%, a reduction of 11.4%). Clearly, there was no evidence for

positive remodeling. This late regression of neointimal hyperplasia has been observed after BMS placement but not after DES. In this thesis, we report the results of the post-marketing, international, multicenter e-HEALING registry including 5,000 patients. Moreover, we report on the first randomized study of the Genous ^{TM} EPC capturing stent compared with DES in the TRIAS pilot study and TRIAS program.

Although randomized trials have shown superiority of first-generation DES over BMS, concerns have risen about the safety of these devices. The profound inhibition of vascular cell proliferation after DES placement may lead to rare but serious complications such as late incomplete stent apposition, aneurysm formation and impaired re-endothelialization causing late or very late ST.[71,72] In unselected patients, the rate of ST was reported to be continuously of 0.4% to 0.6% per year after DES placement up to 4 years, a phenomenon that was not apparent after BMS placement.[33,34] The second-generation DES, the XIENCE V™ everolimus-eluting stent (EES), provides potential improvements over prior generation of DES. The cobalt chromium stent platform may provide enhanced deliverability and radiopacity with thinner stent struts. Due to the chemical structure, everolimus has a less extensive tissue penetration as compared to the parent drug sirolimus[73], which is believed to be desirable in terms of local application of an anti-proliferative agent via a DES system. Moreover, pharmacokinetic studies showed that more than 75% of the total stent drug dose of everolimus is released from the stent during the first 28 days post-stenting, with approximately 25% released during the first 24 hours. Almost 90 % of the drug is released by 60 days and 100% release is completed at 120 days following stent implantation. Finally, in a porcine coronary model, the EES containing almost twice the doses everolimus per cm^2 stent as used in clinical trials, was implanted and compared with a SES and a BMS. At 28 days, the neointimal thickness was significantly lower in the EES and SES groups compared to the BMS. Both the EES and BMS showed 100% endothelialization at 28 days post-implantation, whereas, the SES almost reached a 100%. This show that the low strut profile polymeric EES appears to be a potentially viable clinical alternative to the higher strut profile polymeric SES for the prevention of restenosis.[74] The safety and feasibility of XIENCE V™ EES was evaluated in the SPIRIT program. The outcomes of the randomized SPIRIT I and SPIRIT II studies are reported in this thesis. Recently, the clinical outcomes at 2 years of the large-scale, prospective, multicenter, randomized SPIRIT IV trial[75] demonstrated a significantly lowered stent thrombosis rate after the XIENCE V™ EES compared with the paclitaxel-eluting stent (PES) , 0.4% versus 1.2% respectively (P=0.008). Subsequently, in the 'all-comers', randomized, open label COMPARE trial[76] also showed a lower rate of definite or probable stent thrombosis after the XIENCE V™ EES compared with the TAXUS Liberté PES (0.9% vs. 3.9%; RR: 0.23; 95% CI: 0.11 to 0.49). Abovementioned studies suggest a substantial benefit of the second-generation XIENCE V™ EES. Importantly, dual antiplatelet agents may also contribute to the safety of stents after PCI as shown in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38.[77] This study showed that in patients with acute coronary syndromes prasugrel therapy compared with clopidogrel was associated with significantly reduced rates of ischemic events, including

stent thrombosis (1.1% vs. 2.4%; P<0.001), but with an increased risk of major bleeding (2.4% vs. 1.8%; P = 0.03), including fatal bleeding (0.4% vs. 0.1%; P = 0.002).

Part III: Predictors of clinical outcomes

The use of risk stratification plays a pivotal role in guiding the management of patients treated with PCI. Amongst clinical and angiographic parameters, the use of biomarkers for prediction of clinical events may be of help to identify patients at risk clinical events. The use of biomarkers in such way is based on a supposed pathophysiological relationship between markers and the process of subsequent events.

The rationale for presence of genetic risk factors for restenosis was postulated from studies that showed an interlesion dependence of the risk of restenosis and a bimodal distribution of angiographic measures at angiographic follow-up which provided arguments for the presence of a distinct group of patients with collective characteristics, independent from other factors that influence restenosis.[78,79] Hypothetically, neointimal tissue formation is partly influenced by genes and many efforts were taken to identify single nucleotide gene polymorphisms (SNP) that could be related to angiographic or clinical restenosis. The search to identify of SNPs as a potential risk factor for restenosis is usually based on known or expected functionality (i.e. protein functionality or quantity) in cell proliferation, matrix formation, or inflammation. Cell proliferation regulatory pathways and pro-inflammatory transcription factors, such as nuclear factor kappa B (NFkB), have been associated with the progression of cardiovascular disease and several genes involved in inflammation and cell proliferation appeared to be common denominators of these diseases.[80-83] Genetic associations may not only play an important role in basic insights but may also be useful as future therapeutic targets or tools.

Outline of the thesis

This thesis will first focus on the percutaneous treatment of complex coronary lesions. The treatment of unprotected left main lesions, bifurcation lesions and in-stent restenosis lesions will be addressed. Hereafter this thesis will focus on the use of new stent technologies, in particular the Genous™ EPC capturing stents and the XIENCE V™ EES. Finally, this thesis will focus on predictors of outcome after PCI. The prognostic value of several markers and polymorphisms are evaluated.

Part I (Chapters 2-3)

Part I focuses on the percutaneous treatment of complex coronary lesions. In **Chapter 2.1** we evaluate consecutive patients undergoing nonurgent percutaneous coronary intervention comparing bare metal stents with drug-eluting stents using the National Institute

for Clinical Excellence criteria. **Chapter 2.2** describes the long-term follow-up after non-urgent PCI in unprotected left main coronary arteries. In **Chapter 2.3** we show the one-year clinical outcome after treatment of BMS ISR with the paclitaxel-eluting stent. **Chapter 3.1** studies a simple technique with a single bare metal R stent for percutaneous treatment of bifurcated lesions. In **Chapter 3.2** the provisional T-stenting technique for bifurcation lesions with the endothelial progenitor cell capturing stent is compared with the BMS. In **Chapter 3.3,** a substudy from the e-HEALING registry, we demonstrate the clinical outcomes after coronary stenting with the Genous^{TM} Bio-engineered R stent^{TM} in patients with a bifurcation lesion.

Part II (Chapters 4-5)

Part II comprises studies on two new stent technologies. Data on the Genous^{TM} endothelial progenitor cell-capturing stent system is reviewed in **Chapter 4.1**. In **Chapter 4.2** and **Chapter 4.3**, in the TRIAS pilot study we have evaluated the Genous^{TM} endothelial progenitor cell capturing stent compared with the Taxus Liberte stent in patients with de novo coronary lesions with a high-risk of coronary restenosis. The design and rationale of the TRI-stent adjudication study (TRIAS) program is presented in **Chapter 4.4**. The results of the multicenter TRIAS High Risk study, comparing Genous^{TM} EPC Capturing Stents with Drug-Eluting Stents, are presented in **Chapter 4.5**. In **Chapter 4.6** an unselected patient population treated with the genous™ endothelial progenitor cell capturing stent is studied. In **Chapter 4.7** illustrates significant intimal hyperplasia regression between 6 and 18 months following Genous™ endothelial progenitor cell capturing stent placement.

Data on the XIENCE V everolimus-eluting coronary stent system is reviewed in **Chapter 5.1**. **Chapter 5.2** presents the outcomes of the SPIRIT FIRST Trial, a randomized comparison of the XIENCE V™ EES with the BMS in de novo coronary artery stenosis. **Chapter 5.3** describes the clinical, angiographic, and intravascular ultrasound outcomes of the SPIRIT II trial in which the XIENCE V™ EES is compared with the paclitaxel-eluting stent in the treatment of patients with de novo native coronary artery lesions.

Part III (Chapter 6)

Part III evaluates the prognostic value of several markers and polymorphisms. In **Chapter 6.1** we studied the additional value of multiple biomarkers at admission in the prediction of mortality in patients undergoing primary PCI for STEMI. In **Chapter 6.2** Cystatin C is tested for enhancement of risk stratification in patients undergoing non-urgent PCI. In **Chapter 6.3,** the toll-like receptor 4 gene polymorphism is evaluated as predictor of clinical or angiographic restenosis. Finally, in **Chapter 6.4,** the association with restenosis of $p27^{kip1}$-838C>A single nucleotide polymorphism is evaluated.

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