Prognostic factors in primary and elective percutaneous coronary intervention
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Chapter 27

Summary and Concluding Remarks
Summary of the thesis

Percutaneous coronary intervention (PCI) is performed in over 30,000 patients in the Netherlands annually, and more than one million patients in the United States. In the current era of refinement of devices and techniques used in PCI, great efforts are made to reduce the incidence of procedural complications and to improve the outcome of high-risk patients. The research presented in this thesis addresses prognostic factors in both primary PCI for ST-segment elevation myocardial infarction and elective PCI for stable coronary artery disease. The works in the thesis concern a variety of high-risk patient and lesion subgroups, periprocedural complications, coronary artery stents, and adjunctive devices, reflecting different aspects of PCI. The main findings reported in this thesis are presented thematically below.

Part 1: Prognostic factors after primary PCI

Chronic total occlusions in acute ST-segment elevation myocardial infarction

In chapter 1, we reported that STEMI patients with a chronic total occlusion (CTO) in a non-infarct related artery (IRA) have an increased risk of both early (<30 days) and late (30 days – 5 years) mortality. Multivessel disease (MVD) without a CTO is only an independent predictor of early mortality. Moreover, patients with a CTO in a non-IRA, and not MVD without a CTO was associated with reduced residual left ventricular ejection fraction (LVEF) after the index event and a further decline in LVEF at a mean follow-up of 6 months.

We investigated the prognostic impact of MVD with and without a CTO in a cohort of STEMI patients with cardiogenic shock (CS) in chapter 2. One-year mortality increased with greater complexity of coronary artery disease. After multivariable adjustment, MVD was only a significant predictor of mortality if a CTO was present.

Chapter 3 dealt with the high-risk subgroup of STEMI patients with diabetes mellitus (DM). STEMI patients with DM more often had MVD, both with and without a CTO in a non-IRA, compared with non-diabetic STEMI patients. MVD with a CTO in a non-IRA was an independent predictor of 5-year mortality, whereas MVD without a CTO was not.

Data used in chapters 1-3 were from the institutional database of the Academic Medical Center – University of Amsterdam. In chapter 4, to investigate the impact of MVD with and without a CTO on prognosis after STEMI, we performed an analysis in the large-scale HORIZONS-AMI (Harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. Compared to patients with single vessel disease (SVD) and MVD patients without a CTO, patients with MVD and a non-IRA CTO were significantly less likely to achieve postprocedural TIMI 3 flow, more often had absent myocardial blush, and less frequently achieved complete ST-segment resolution. By multivariable analysis, a MVD with CTO in a non-IRA was an independent predictor of both 0-30 day mortality and 30 day-3 year mortality, while MVD without a CTO was a significant predictor for 0-30 day mortality but not late mortality. The impact of a CTO was especially profound in patients with triple vessel disease.

Chapter 5 detailed the study design of the first randomized clinical trial in the field of CTO PCI powered for clinical endpoints: the EXPLORE (Evaluating Xience V and Left Ventricular Function in PCI on occlusions in STEMI) trial. Observational studies in a number of different datasets from across the globe have shown that STEMI patients with a CTO in a non-IRA have a dire prognosis, even after primary PCI. Therefore, EXPLORE will randomize 300 patients 1:1 to additional PCI of the non-IRA CTO within one week after the index event versus optimal medical management. The primary endpoints are LVEF and left ventricular end diastolic volume measured by cardiac magnetic resonance imaging at 4 month follow-up. Clinical follow-up will continue up to 5 years. EXPLORE is currently enrolling patients and first results are expected to be reported within the next few years.

Biomarkers in primary PCI

Chapters 6-8 described the clinical outcome of patients according to a variety of biomarkers.
In chapter 6, we investigated whether the use of biomarkers might be of utility to identify patients who remain at risk for drug-eluting stent (DES) in-stent restenosis (ISR) after primary PCI. In a formal substudy of the HORIZONS-AMI trial, a total of 26 inflammatory and thrombotic biomarkers were measured at admission and at 30 days and analyzed at a central core laboratory in 501 STEMI patients treated with paclitaxel-eluting stents. Low levels of IL-6 and PLGF at admission were associated with both higher in-stent late loss at 13 months and ischemia-driven target lesion revascularization (TLR) at 3 years. Additionally, low admission levels of CT-1 were associated with higher rates of ischemia-driven TLR. At 30-day follow-up lower values of IL-1ra, MMP9, and MPO, and a decline relative to admission in IL-1ra, MCP-1, and MMP9 were associated with higher in-stent late loss. Low values of IL-6 at 30 days were also associated with ischemia-driven TLR.

We showed in chapter 7 that patients with chronic kidney disease (CKD, defined as creatinine clearance < 60 ml/min) in the HORIZONS-AMI trial have significantly higher rates of death and major bleeding compared to those without CKD at 3 year follow-up. In patients with CKD there appears to be no benefit of bivalirudin compared to heparin + glycoprotein IIb/IIIa inhibitors, or DES versus BMS during primary PCI in improving clinical outcomes.

Chapter 8 showed that raised baseline glucose levels are associated with higher mortality within the first 30 days after primary PCI for STEMI but not with late mortality (30 days - 3 years) in an analysis from the institutional database of the Academic Medical Center – University of Amsterdam.

**Patient groups at high risk for adverse events after primary PCI**

Chapter 9 raised awareness of a rapidly growing high-risk subgroup of STEMI patients; those aged 80 years and older. The proportion of octogenarian STEMI patients undergoing primary PCI at the Academic Medical Center – University of Amsterdam increased significantly from 3.5% in 1997 to 8.9% in 2007. Thirty-day mortality was 21%, and did not improve during the study period. Therefore, further studies into the optimal treatment of STEMI in octogenarians are warranted.

Chapter 10 was a post-hoc analysis in the HORIZONS-AMI trial. Of 3,345 patients undergoing primary PCI, 218 (6.5%) developed in-hospital major bleeding. Patients with in-hospital major bleeding had higher mortality and more major adverse cardiac events at 3-year follow-up compared with patients without in-hospital major bleeding. Importantly, the deleterious effect of major bleeding was observed within 1 month, between 1 month and 1 year, and between 1 and 3 years.

**Adjunctive physiological and intracoronary imaging devices in primary PCI**

In chapter 11, we review the available literature concerning the use of the Doppler flow guidewire in acute myocardial infarction. The Doppler flow guidewire can be used immediately after primary PCI to identify patients with apparently restored epicardial flow but impaired reperfusion at the myocardial microcirculatory and tissue level. Characteristic findings by intracoronary Doppler flow velocity measurements such as a reduced coronary flow velocity reserve, and, in particular, systolic flow velocity reversal and a short diastolic deceleration time are associated with the presence of microvascular obstruction. Further study is warranted to determine whether patients with microvascular obstruction as detected by Doppler flow guidewire may benefit from adjunctive therapy after primary PCI.

We performed a systematic review and meta-analysis to investigate whether plaque characteristics measured by virtual histology intravascular ultrasound (VH-IVUS) are associated with distal embolization after percutaneous coronary intervention (PCI) in chapter 12. Although there was considerable heterogeneity in patient characteristics, outcome definitions, and reporting of VH-IVUS findings, the necrotic core plaque component - either by itself or as a constituent of a VH thin cap fibroatheroma (VH-TCFA) - was associated with distal embolization in the vast majority of published studies. Further studies are currently being conducted investigating whether selective use of embolic protection devices in high-risk lesions reduces the incidence of distal embolization.
**Stent thrombosis after primary PCI**

Ever since the onset of coronary stent implantation, stent thrombosis (ST) has been a major concern. Patients undergoing stent implantation after primary PCI are at an increased risk to develop ST. We showed in chapter 13 that at one year after the ST event, patients with in-hospital compared to out-of-hospital ST had significantly greater mortality in the HORIZONS-AMI trial, despite the proximity to cath labs and coronary care units. Most deaths occurred within one week of the ST event. Moreover, patients with in-hospital ST had higher rates of major bleeding, but a lower rate of myocardial infarction.

In order to personalize risk assessment for ST after PCI for acute coronary syndromes (ACS), we developed and validated a risk score based upon a pooled analysis from the HORIZONS-AMI and ACUITY (Acute catheterization and urgent intervention triage strategy) trials in chapter 14. Cox regression methods were used to identify clinical, angiographic, and procedural characteristics associated with ARC-defined definite/probable ST at one year. Each covariate in the model was assigned an integer score based on the regression coefficients. Variables included in the risk score were: type of ACS (STEMI, NSTE-ACS with ST-segment deviation, or NSTE-ACS without ST-segment changes), current smoking, insulin dependent diabetes mellitus, prior PCI, baseline platelet count, absence of early (pre-PCI) anticoagulant therapy, aneurysmal/ulcerated lesion, baseline TIMI flow grade 0/1, final TIMI flow grade under 3, and number of treated vessels. DES as compared with BMS were not associated with an increased risk for ST. Risk score 1-6 was considered low risk, 7-9 intermediate risk, and 10 or greater high risk for ST. Rates of ST at 1-year in low, intermediate and high risk categories were 1.36%, 3.06%, and 9.18%, respectively in the development cohort (p for trend <0.001), and 1.65%, 2.77%, and 6.45% in the validation cohort (p for trend 0.006). We believe that this simple and practical risk score can be implemented in clinical practice and can guide clinicians in therapeutic decision making.

**Part II: Prognostic factors after elective PCI**

Chapters 15 & 16 act as an introduction to the second part of the thesis, focused on prognostic factors after elective PCI. In these two chapters, currently available preclinical and clinical data regarding a variety of DES are summarized. Furthermore, we reflected on the future of DES, such as fully bioabsorbable scaffolding devices.

**Drug-eluting stents in clinical practice**

Bioabsorbable DES are not expected to be in widespread use anytime soon. Therefore there is a need to investigate and monitor the clinical safety and efficacy of currently available metallic DES. Two-year clinical outcomes of the first commercially available DES, the sirolimus-eluting stent (SES) are presented in chapter 17. The results of the MATRIX (coMprehensive AssesmenT of siRolImus-eluting stents in compleX lesions) registry, showed that the use of SES in unselected patients was associated with a target vessel failure rate of 15.5% at 2 years and a definite/probable stent thrombosis rate of 0.9%. Adherence to dual antiplatelet therapy was carefully collected and no relationship between cessation of dual antiplatelet therapy and stent thrombosis was found.

In chapter 18 we present the results of subanalysis in the MATRIX registry investigating the impact of IVUS-guided SES implantation. In MATRIX, 631 patients (42%) underwent IVUS-guided stenting, and 873 (58%) had only angiographic guidance. A propensity score-matched population was derived for comparisons. In this analysis, IVUS-guided SES implantation seemed to be associated with a reduction in adverse events, in particular myocardial infarction (MI). This reduction in MI was evident early after stent implantation (30 days), possibly reflecting improved technical stent implantation, and remained significant up to 2-year follow-up. These findings may be considered hypothesis-generating and further investigation in an adequately powered randomized controlled
The two-year clinical, angiographic, and IVUS results of the randomized SPIRIT II (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) trial were presented in chapter 19. In SPIRIT II, 300 patients with relatively non-complex coronary artery disease were randomized to treatment with the next generation everolimus-eluting stent (EES) or the first-generation paclitaxel-eluting stent (PES). At two years follow-up, a delayed neointimal hyperplasia was observed in the EES group. Two year mean in-stent late loss was 0.33±0.37mm for the EES group and 0.34±0.34mm for the PES group (p=0.84) against 0.17±0.32 and 0.33±0.32 (p<0.01) at six months. Despite this late catch-up in neointimal hyperplasia, no such trend in the composite clinical endpoint of target lesion failure was observed.

In chapter 20 we performed a meta-analysis of 4 randomized clinical trials, SPIRIT II, III, IV, and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) comparing the EES with the PES. At one year, patients treated with the EES had significantly lower rates of myocardial infarction (Risk ratio [RR] 0.57), target lesion revascularization (RR 0.49), and ARC definite or probable stent thrombosis (RR 0.36). These results could be explained by differences between both DES in the underlying stent platforms, differences in the drug and differences in the polymer eluting the drug.

In chapter 21, we reported the impact of lesion length and reference vessel diameter on clinical outcomes after PCI with EES vs. PES. Using pooled data from 4 with 2-year follow-up from the aforementioned 4 randomized clinical trials comparing EES with PES, we divided the patients into three groups: short lesions in large vessels (group A, n=1297); long lesions or small vessels, but not both (group B, n=2981); and long lesions in small vessels (group C, n=1905). Two-year MACE rates increased with both stents with greater lesion length and smaller reference vessel diameter, although stent thrombosis rates after EES were independent of lesion complexity. In all three groups, MACE rates were lower with EES compared with PES. There was no interaction between stent type and lesion group in terms of 2-year MACE. However, the absolute differences were larger in the more complex groups (B&C) resulting in significantly reduced MACE rates.

In-stent restenosis

Restenosis after angioplasty and stent implantation has been historically considered the most significant problem in coronary interventional treatment. In Chapter 22 we report the one-year clinical outcome of 214 patients with bare-metal stent (BMS) restenosis treated with a PES. Treatment of BMS restenosis with PES was associated with low rates of the combined endpoint of cardiac death, nonfatal MI, and target lesion revascularization (7.5% at one-year follow-up). As data on the use of newer generation DES for the treatment of BMS restenosis are currently scarce, this study supports the use of PES to treat BMS ISR.

DES have dramatically reduced the rates of restenosis and target lesion revascularization compared with BMS. However, a low rate of in-stent restenosis (ISR) after DES still exists, and its prevalence is not negligible because the population treated with DES is large. Although the low frequency of ISR events with DES makes clinical investigation difficult, many studies have addressed the incidence, mechanism, predictors, and optimal treatment of DES restenosis. We provided a comprehensive overview of the pathophysiologic mechanisms, clinical presentation, morphologic patterns, and management options of DES ISR in Chapter 23. Moreover, a practical treatment algorithm for DES ISR was developed.

Selective PCI of chronic total occlusions

Coronary CTOs have been called the “final frontier” in contemporary PCI. These complex lesions require a skilled and experienced operator who is familiar with specialized techniques and devices. As a randomized clinical trial evaluating clinical outcomes after elective PCI of CTOs is still
lacking, the results of the large Multinational CTO Registry, presented in chapters 24-26, provide important information on long-term safety and efficacy of these complex procedures. This 1,791 patient-registry is a combined effort from the San Raffaele Scientific Institute in Milan, Italy, Asan Medical Center in Seoul, South Korea, and Columbia University Medical Center, New York, NY. Patients were included between 1998 and 2007.

Chapter 24 reports the five-year clinical outcome after successful vs. failed PCI of CTOs, and after the use of BMS vs. DES in successful CTO PCI. Procedural success was obtained in 68% of patients. Compared with failed CTO PCI, successful CTO PCI was associated with reduced long-term cardiac mortality and need for coronary artery bypass surgery (CABG). Treatment of CTO with DES rather than BMS is associated with a significant reduction in target vessel revascularization with similar rates of stent thrombosis. PES and SES had similar long-term safety and efficacy outcomes. This study showed that CTO PCI can be performed safely by experienced operators in this selected population. However, a randomized controlled trial is needed to assess the potential benefit of CTO PCI, as the present study is hampered by selection bias.

We investigated five-year clinical outcomes after CTO PCI in the high-risk subgroup of patients with DM in Chapter 25. A total of 395 patients in the multinational CTO registry had DM. Procedural success was similar in patients with vs. without DM (69.6% vs. 67.9%). In patients with DM, successful CTO PCI was associated with reduced long-term mortality (10.4% vs 13.0%, p <0.05) and a reduced need for CABG (2.4% vs 15.7%, p <0.01). The use of DES was associated with a reduction in target vessel revascularization in patients with DM (14.8% vs 54.1%, p <0.01) and in those without DM (17.6% vs 26.5%, p <0.01). Multivariate analysis identified insulin-dependent DM as an independent predictor of mortality in the DM cohort.

We investigated whether there is a differential prognostic effect of successful PCI of CTOs according to the target vessel where the CTO is located in Chapter 26. The need for CABG at 5-year follow-up was lower after successful CTO PCI in all three groups (LAD 4.6% vs. 16.0%, p<0.01; LCX 2.9% vs. 18.2%, p<0.01, RCA 2.3% vs. 8.4%, p<0.01). However, successful CTO PCI was only associated with lower mortality in the LAD (6.7% vs. 11.0%, p=0.03) and LCX groups (5.5% vs. 13.9%, p<0.01), but not in the RCA group (6.6% vs 4.1%, p=0.80). After multivariate analysis, successful CTO PCI remained associated with lower mortality in the LAD (HR 0.41, p=0.02) and LCX groups (HR 0.32, p<0.01). As an adequately powered randomized clinical trial investigating a potential survival benefit of CTO PCI has not yet been performed, the data from the current study may help guide clinical decision-making.

Concluding remarks and future directions

Scientific research for this thesis was performed in the Academic Medical Center of the University of Amsterdam, and at the New York based Cardiovascular Research Foundation, affiliated with Columbia University Medical Center and Mount Sinai Medical Center. The works presented here were mostly created by analyzing large single-center institutional registries and multi-center randomized controlled trials and concern a variety of stable and acute coronary syndromes, high-risk subgroups, biomarkers and interventional devices. The following paragraphs offer a number of take-home messages that could be drawn from this thesis:

**Chronic total occlusions in stable and acute coronary syndromes**

We have shown in this thesis that PCI of CTOs is safe and feasible, offering a potential survival benefit after opening CTO's in the left anterior descending and left circumflex coronary arteries. A major breakthrough in CTO PCI was the introduction of the DES, which dramatically reduced in-stent restenosis compared with BMS. Five-year stent thrombosis rates were similar for both stent types. DES are particularly effective in diabetic patients, where target vessel revascularization rates are similar to patients without diabetes mellitus.

In the setting of acute myocardial infarctions, regardless of diabetic and hemodynamic status, the presence of a CTO in a non-IRA confers a long-term risk of mortality, whereas MVD without
a CTO only has short-term prognostic implications. STEMI patients with a CTO in a non-IRA have suboptimal markers of reperfusion after primary PCI, have a reduced left ventricular ejection fraction shortly after the procedure, and a further deterioration in ejection fraction during one-year follow-up. The ongoing EXPLORE trial will answer the important question whether a CTO in a non-IRA is a target for additional intervention, or merely a marker of high risk for mortality after STEMI. Furthermore, it is important to mention that EXPLORE is the first trial in the field of CTO PCI powered for clinical endpoints.

**Risk stratification after primary PCI**

Primary PCI for STEMI has long been proven to reduce morbidity and mortality compared with fibrinolysis. Nonetheless, several high-risk subgroups still have suboptimal outcomes, even after primary PCI. This thesis has shown that, in addition to the aforementioned patients with a CTO in a non-IRA, those with renal insufficiency, raised glucose levels at hospital admission, those aged 80 years and older, and those who develop in-hospital bleeding complications or in-hospital stent thrombosis require further study. Randomized controlled trials are warranted to determine whether their prognosis can be influenced by medical intervention.

The current thesis has also shown that several inflammatory biomarkers, measured at admission and at 30 days, may be helpful to identify patients at increased risk for restenosis after DES implantation for STEMI. Moreover, a risk score was developed to personalize risk assessment for the feared complication of ST after STEMI. Finally, use of a Doppler guide wire and/or VH-IVUS may be useful to identify patients with apparently restored epicardial flow, but obstructed flow at the myocardial tissue level.

**Drug-eluting stents**

Compared with BMS, DES showed an impressive reduction in the need for repeat intervention. Even in the era of DES, restenosis remains a significant problem and a practical treatment algorithm is presented in this thesis.

On the other hand, concerns have arisen about the long-term safety of first-generation DES, which were shown to have a higher risk of very late stent thrombosis compared with their bare-metal counterparts. The current thesis has shown that rates of repeat intervention, myocardial infarction, and stent thrombosis are lower with the next-generation EES compared with the first generation PES. These results remained robust over time, despite a late catch-up in neointimal hyperplasia, observed at two-year angiographic and IVUS follow-up in the EES.

Future generations of DES will likely be bioabsorbable. These stents could facilitate coronary lumen enlargement, seal dissection planes, and drug delivery to reduce restenosis just like metallic stents, but would dissolve after 1-2 years, after which the susceptible plaque and the restenosis process has stabilized and the need for the metallic stent itself has become redundant. The disappearance of a life long intracoronary foreign object would intuitively result in a disappearance of very late stent thrombosis. In addition it enables the return of normal vasomotion and does not preclude surgical revascularization of the targeted segment of the coronary artery.