Prognostic factors in primary and elective percutaneous coronary intervention
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Introduction and general outline of the thesis
Introduction

Since its introduction in the 1970s, percutaneous coronary intervention (PCI) has emerged as the preferential mode for coronary revascularization. Andreas Gruentzig started a revolution in the world of cardiology in 1976, when he reported experimental results obtained from animal and cadaver studies of treating coronary artery disease by balloon angioplasty. (1, 2) He encountered skepticism and derision, as this practice was thus far confined to the treatment of peripheral arteries. Surely, you would have to be a little weird to want to inflate a balloon in a person's coronary artery......

Nonetheless, on September 16, 1977 a determined Gruentzig first performed coronary balloon angioplasty in a 37-year old insurance salesperson with an isolated left anterior descending coronary artery (LAD) lesion using home-made equipment (Gruentzig famously constructed his balloon catheters in his kitchen).(3) Although 2 of the 3 balloons that were brought to the hospital burst during preparations, the 3rd balloon was successfully delivered to the LAD lesion (without an intracoronary wire) and successfully dilated the lesion with 2 inflations. Angiography revealed a marked reduction of the LAD stenosis and the distal lumen coronary pressure normalized. Twenty-three years after his initial procedure, this patient underwent a follow-up cardiac catheterization revealing no restenosis after balloon angioplasty only!(4) In the decades that were to follow PCI evolved from a treatment for single-vessel coronary artery disease into a real alternative to coronary artery bypass grafting (CABG) for treatment of complex multivessel disease thanks to many improvements to its safety and effectiveness.(5)

Two important complications of balloon angioplasty were restenosis and abrupt vessel closure which was associated with significant morbidity and mortality and the need for emergency coronary artery bypass surgery.(6) The introduction of coronary artery stents which provide a mechanical scaffold to the vessel wall proved an effective means to prevent abrupt vessel closure and significantly reduced the incidence of restenosis.(7, 8) The first commercially available coronary artery stent, the Palmaz-Schatz stent, was approved by the United States Food and Drug Administration (FDA) in 1994. The introduction of drug-eluting stents (DES, FDA approved in 2003) coated with antiproliferative drugs, typically eluted from a polymer attached to the stent surface caused a further reduction in restenosis rates.(9) However, coronary artery stents introduced a new complication which is still very relevant in current clinical practice: stent thrombosis (ST). Whereas in the early BMS era, ST was thought to be a complication occurring almost exclusively within one year after stent implantation, the introduction of DES was accompanied by concerns of late and very late ST.(10, 11) First-generation DES raised concerns about very late stent thrombosis which occurred at an annual rate of approximately 0.6%. This led to the development of thinner polymers with increased biocompatibility, biodegradable polymers, and even bioabsorbable stents. Furthermore, restenosis is still an important clinical phenomenon, even though its occurrence was significantly reduced by DES.(12)

The therapeutic application of PCI did not remain limited to stable coronary artery disease alone but eventually became the preferred treatment for acute myocardial infarction. Mortality from acute myocardial infarction was reduced for the first time after the introduction of coronary care units in the 1960 and the ability to prevent and treat lethal arrhythmias. The important discovery by DeWood et al. in the late 1970s that a thrombotic occlusion of a coronary artery was the pathophysiological mechanism causing myocardial infarction initiated the era of reperfusion therapy. (13) Large-scale trials of thrombolysis undertaken in the 1980s for acute myocardial infarction involving tens of thousands of patients led to the recognition that prompt restoration of coronary blood flow reduces infarct size and reduces mortality.(14, 15) However, coronary reperfusion by thrombolysis has several important disadvantages, such as the occurrence of hemorrhagic strokes, and the fact that reocclusion of the infarct related artery (IRA) occurs in ~30% of patients, leading to a worse long-term clinical prognosis.(16) Therefore, mechanical reperfusion with primary PCI
was investigated as a potential alternative for thrombolysis. A meta-analysis of primary angioplasty versus thrombolytic therapy for acute myocardial infarctions showed significant reductions in mortality (absolute risk reduction [ARR] 2%), non-fatal reinfarction (ARR 4%), and stroke (ARR 1%).(17) As a result, primary PCI is now the preferred reperfusion strategy for patients with acute ST-Elevation Myocardial Infarction (STEMI) in the European Society of Cardiology guidelines and the American College of Cardiology/American Heart Association guidelines.(18, 19)

This thesis aims to provide further insight into prognostic factors after PCI in the current era of further refinement of this treatment modality which is now used on a global scale. Part I of the thesis, comprising chapters 1-14, deals with prognostic factors after primary PCI, and part II reports on prognostic factors after elective PCI.

CTO lesions have been dubbed “the last frontier”. These notoriously complex lesions are challenging to recanalize percutaneously and are associated with a high failure rate and high doses of radiation and contrast agents. Recent advances in the field of medical devices such as microcatheters, specialized CTO guidewires, and imaging techniques, combined with the development of novel PCI techniques such as the retrograde approach have made CTO lesions realistic targets for PCI. Our group was the first to study the prognostic impact of chronically occluded lesions in patients with acute myocardial infarction.

Patients with an acute STEMI stratified as having single-vessel disease (SVD), multivessel disease (MVD) without a chronic total occlusion (CTO), or a CTO in a non-IRA are studied in chapters 1-5. We study the impact of a CTO in a non-IRA on short- (<30 days) and long-term (30 days-5 years) mortality in a large patient cohort from the institutional database of the Academic Medical Center - University of Amsterdam in chapter 1. Furthermore, we investigated the impact of a CTO in a non-IRA on left ventricular ejection fraction within one year after primary PCI. Chapter 2 reports one-year mortality of SVD, MVD without CTO, and CTO patients in a cohort of STEMI patients with cardiogenic shock. The prevalence of a CTO in a non-IRA and its impact on 5-year mortality is reported in chapter 3. In chapter 4 we investigate the prognostic significance of SVD, MVD without a CTO and a CTO in a non-IRA in a different dataset to investigate the results of analyses similar to those performed in the institutional database of the Academic Medical Center. To this end, we used data from the large-scale randomized HORIZONS-AMI (Harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. Chapter 5 presents the trial design of EXPLORE (Evaluating Xience V and Left Ventricular Function in PCI on occlusions in STEMI). This trial will determine whether additional PCI of a CTO within seven days after primary PCI for STEMI results in improved left ventricular dimensions and ejection fraction. Interestingly, EXPLORE is the first randomized clinical trial comparing an invasive with a conservative approach towards the management of CTOs.

Not only angiographic but also several biochemical parameters can be used for risk assessment as is described in chapter 6 showing the clinical utility of 26 inflammmatory and thrombotic biomarkers to predict the occurrence of angiographic and clinical restenosis after primary PCI with paclitaxel-eluting stents in the HORIZONS-AMI trial. Chapter 7 reports the long-term clinical outcome of patients with chronic kidney disease in the HORIZONS-AMI trial. Chapter 8 reports the prognostic impact of admission glucose levels on short- and long-term mortality after primary PCI for STEMI in the institutional database of the Academic Medical Center. In chapter 9, we report trends and outcomes of primary PCI for STEMI in the high-risk but not well-studied subgroup of patients aged 80 years and older in the institutional database of the Academic Medical Center. Chapter 10 investigates the impact of in-hospital major bleeding on late clinical outcomes in the HORIZONS-AMI trial.

Chapters 11 and 12 return to the value of understanding the pathophysiology of ACS and investigate the role of virtual-histology intravascular ultrasound (VH-IVUS) and the Doppler flow wire in optimizing outcomes of PCI. Restoration of epicardial blood flow does not guarantee restoration of flow at the myocardial tissue level. Microvascular obstruction is known to occur
in 15-70% of patients after primary PCI depending on the definition and imaging modality used. (20, 21) Chapter 11 summarizes the literature on the use of the Doppler flow wire to diagnose microvascular obstruction and predict left ventricular function and clinical outcome after primary PCI. Chapter 12 investigates the relationship between atherosclerotic plaque components assessed by VH-IVUS on the occurrence of distal embolization, one of the major mechanisms involved in causing microvascular obstruction. To this end, a systematic review and meta-analysis of relevant literature was performed.

Chapters 13 and 14 deal with the dreaded complication of stent thrombosis (ST) after primary PCI. We report one-year clinical outcomes in patients with in- vs. out-of-hospital ST in the HORIZONS-AMI trial in chapter 13. In chapter 14 we pooled the databases of the HORIZONS-AMI and ACUITY (Acute catheterization and urgent intervention triage strategy) trials to develop and validate a risk score to predict ST in patients with acute coronary syndromes undergoing stent implantation.

In part II of the thesis the focus is shifted to elective PCI. Chapters 15 and 16 introduce the current status of drug-eluting stents. Chapter 15 is focused on drug-eluting stents coated with drugs from the –limus family. Chapter 16 provides a comprehensive review of preclinical and clinical studies with the XIENCEV everolimus-eluting stent (EES, Abbott Vascular, santa clara, CA).

Chapters 17-21 investigate long-term clinical outcome after PCI with DES in randomized clinical trials evaluating the EES and a registry evaluating the Cypher sirolimus-eluting stent (SES, Cordis, Warren, NJ). Chapter 17 reports two-year safety and efficacy outcomes of patients undergoing SES implantation in the MATRIX (Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions) registry. Chapter 18 studies the impact of IVUS-guided SES implantation compared with angiography-only guidance in the MATRIX registry on long-term clinical outcome. Chapter 19 reports two-year clinical, angiographic and IVUS outcomes of the randomized SPIRIT II (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) trial which randomized patients with relatively non-complex coronary artery disease to treatment with EES or a TAXUS paclitaxel-eluting stent (PES, Boston Scientific, Natick, Ma). Chapter 20 details the results of a meta-analysis comparing one-year outcomes in 4 trials of EES vs. PES, SPIRIT II, III, IV and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice). Chapter 21 investigates the impact of lesion length and vessel size on two-year clinical outcome in a patient-pooled analysis of the SPIRIT II, III, IV and COMPARE trials.

Chapters 22 and 23 deal with restenosis. In chapter 22 we report the outcomes after treating restenosis of a BMS with a Taxus PES. Chapter 23 is a comprehensive review of the current state-of-the-art in the field of restenosis after PCI with DES.

In the final section of the thesis, we revisit the field of CTO PCI. In chapters 24-26 we report clinical outcomes after attempted elective PCI of CTOs in the multinational CTO registry, a combined effort of Columbia University Medical Center, New York, NY, San Raffaele Hospital, Milan, Italy, and Asan Medical Center, Seoul, South Korea. Chapter 24 reports 5-year clinical outcome after failed versus successful CTO PCI and the use of BMS as compared with DES. Chapter 25 reports long-term clinical outcome after failed versus successful CTO PCI in patients with and without diabetes mellitus. In Chapter 26 we investigated the impact of target vessel on long-term mortality after PCI of CTOs.

Reference List