Adverse outcomes following percutaneous transcatheter interventions
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Part I

Introduction and outline of the thesis
“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less”

-Marie Curie

During the past decades interventional cardiology has strongly developed. This has resulted in the introduction of new and less invasive treatment options for patients with coronary artery and valve disease, starting from percutaneous transluminal dilatation in 1977 by Andreas Grünzig towards transcatheter aortic valve implantation.

These non-invasive interventions have resulted in a shorter recovery period and improved survival. Moreover, the number of procedures in percutaneous coronary interventions has strongly increased. Aging and the increased life expectancy will further increase the number of patients treated with transcatheter percutaneous interventions. With the advancement of these new techniques it is important to constantly evaluate the benefits and possible adverse outcomes.

This thesis aims to provide a further understanding of adverse outcomes following specific transcatheter percutaneous interventions. First we investigated the thromboembolic and bleeding complications in both percutaneous coronary and aortic valve interventions. Second we focused on the efficacy and safety outcomes of a novel percutaneous coronary stent, the ABSORB bioresorbable vascular scaffold. Finally we investigated adverse remodeling in ST-elevated myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (PPCI).

THROMBO-EMBOLIC AND BLEEDING COMPLICATIONS

The introduction of the first self-expanding bare metal stent in 1986 was successful as it resulted in a decrease of acute recoil and constrictive remodeling observed in patients treated with coronary angioplasty. However, the thrombogenic metallic stents were causing subacute thrombotic occlusions in more than 10 percent of the cases and in-stent neointimal hyperplasia leading to in-stent restenosis. Treatment with anticoagulant regimens resulted in less subacute thrombotic occlusions. In ST-elevation myocardial infarct patients, primary percutaneous coronary intervention (PPCI) in conjunction with potent anti-thrombotic therapy has resulted in significant reductions in recurrent ischemic events and mortality. Unfortunately, anti-thrombotic therapy increases the bleeding risk. In particularly, non-access site bleeding complications have been shown to be associated with a threefold higher risk of cardiac and all-cause mortality within one
year after primary percutaneous coronary interventions.\textsuperscript{11} This illustrates the precarious balance between thrombo-embolic and bleeding complications.

This challenge in anti-thrombotic treatment is also of importance in Transcatheter Aortic Valve Implantation (TAVI). After its introduction in 2002\textsuperscript{12}, TAVI has become the routine treatment for patients with severe aortic valve stenosis considered inoperable or at high-surgical risk.\textsuperscript{12-15} In comparison to other percutaneous interventions, TAVI has a high thrombo-embolic and bleeding risk. The incidence of stroke following TAVI averages about 3% and the incidence of bleeding complications has been reported in up to 40% of patients.\textsuperscript{16}

There should be a careful risk evaluation of the bleeding risk versus thrombo-embolic events. Therefore, it is of clinical importance that the efficacy and safety of antiplatelet therapy in TAVI patients is investigated. In order to answer these questions we need more insight in thrombo-embolic complications of TAVI. Innovation in imaging techniques can aid in the awareness of asymptomatic cerebral infarcts; silent cerebral infarcts.

**BIOABSORBABLE VASCULAR SCAFFOLDS**

After the introduction of the coronary balloon-angioplasty, bare-metal, and drug-eluting stent, the bioresorbable scaffold was hypothesized to be fourth revolution in interventional cardiology.\textsuperscript{17} The concept of bioresorbable vascular scaffold is that it serves as a temporary scaffold by disappearing after complete biodegradation. Several advantages of a bioresorbably scaffold are postulated.\textsuperscript{17} First, it might share the advantages of metallic stents regarding acute gain and prevention of acute vessel occlusion by providing transient scaffolding. Secondly, it can potentially overcome many of the safety concerns of drug eluting stents including late stent thrombosis and may also reduce the need for prolonged dual antiplatelet therapy. Third, the disappearance of a rigid scaffold might facilitate positive vascular remodeling and restore normal vessel wall physiology. The first bioresorbable stent was implanted in the early 1980s.\textsuperscript{18}

The ABSORB bioresorbable vascular scaffold (BVS) was the first bioresorbable scaffold to receive a Conformité Européene mark in 2011. Although favorable results were observed in randomized clinical trials for safety and efficacy\textsuperscript{19-21}, the inclusion criteria in these studies were highly restricted and limited to the treatment of relatively simple coronary artery lesions. While awaiting the results of randomized controlled trials on the safety, efficacy and performance of the ABSORB compared to the drug-eluting stents in more complex coronary lesions, its use has been widely disseminated. Therefore it is of importance to investigate its use and performance in clinical practice.
ADVERSE LEFT VENTRICULAR REMODELING

The introduction of PPCI and improved potent anti-thrombotic therapy has resulted in improved survival.\(^{22}\) However more patients face the deleterious effects of post-infarct heart failure.\(^{23}\) Adverse LV remodeling is defined as alterations in ventricular morphology involving both the infarct and non-infarct zones leading to progressive increase in systolic and diastolic LV volumes.\(^{24}\) Identification of determinants of adverse left ventricular remodeling is important for a better understanding of the underlying pathophysiological mechanisms and could aid in targeting effective therapeutic strategies.

In 30 to 40% of STEMI patients, myocardial tissue perfusion remains compromised despite restoration of epicardial patency resulting in microvascular dysfunction.\(^{25}\) In prior studies this was been proposed as a pathophysiological mechanism in adverse LV remodelling.\(^{26,27}\) Currently it is not fully understood whether microvascular dysfunction is related to long term LV function, nor is it known if improvement in microvascular function is associated with LV function improvement.

Electrocardiogram (ECG) markers can aid in early risk-stratification in order to determine optimal treatment strategies in STEMI patients. After all, the ECG is the first available diagnostic modality in STEMI patients.

Finally, cardiovascular magnetic resonance (CMR) is an important diagnostic modality in identifying patients with adverse LV remodeling and those who have developed subsequent left ventricular thrombus formation (LVT). It is currently considered the gold standard for assessing the functional and morphological changes of the LV.\(^{24}\) Several studies have investigated adverse remodeling within the initial months following STEMI. However, limited data is available on the long term LV remodeling process in STEMI using CMR. Advancements in 4D flow phase contrast CMR with subsequent visualization of three directional components of blood flow velocities allows us to further investigate the role of blood flow and vortices in the process of LV remodeling.\(^{28}\)

OUTLINE OF THE THESIS

Section 1 of this thesis addresses the thrombo-embolic and bleeding complications in several percutaneous transcatheter interventions. Chapter 1 provides an overview of the occurrence of cerebral emboli resulting in subclinical or silent cerebral infarcts and its occurrence in multiple cardiac diseases and procedures. In chapter 2 we investigate the predictors of gastrointestinal bleeding in STEMI and the prognostic consequences. In chapter 3 we assess the efficacy and safety of single versus dual antiplatelet therapy following transcatheter aortic valve implantation, including the thrombo-embolic and bleeding complications.
In section 2 of this thesis we focus on the adverse outcomes following the implantation of the bioresorbable vascular scaffolds. Chapter 4 is a review that introduces the new technique of the bioresorbable vascular scaffold and expands on the rationale and design of the ABSORB bioresorbable vascular scaffold. In chapter 5 we investigate the acute angiographic results and six-month clinical outcomes of the implantation of the ABSORB BVS in a patient registry including both high-risk lesions and patients, reflecting daily clinical practice. In chapter 6, we report the 2-year clinical outcome of the AMC Absorb registry as stratified by the complexity of lesion and patient characteristics.

In the final section (section 3) of this thesis we focus on adverse left ventricular remodeling after ST-segment elevation myocardial infarction. In chapter 7, we investigate the long term functional outcome of STEMI patients as assessed by serial CMR at different time points. In chapter 8, we assess whether the occurrence of microvascular dysfunction following STEMI and its absolute improvement in large and small infarct sizes is associated with long-term left ventricular function. In chapter 9, we investigate whether QRS distortion on the initial ECG, as a marker for the severity of ischemia, can be predictive for infarct size and left ventricular ejection fraction at 4 months in anterior versus inferior infarct locations. In chapter 10, we investigate the vortex flow as assessed by 4D flow Cardiac Magnetic Resonance imaging (CMR) in STEMI patients with and without left ventricular thrombus formation compared to healthy controls.
REFERENCES

Part I


