Reducing the risks of transcatheter aortic valve implantation

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Introduction
Of all heart valve diseases, aortic stenosis (AS) occurs the most in the western population, requiring treatment when becoming severe and symptomatic. At the age of 75 years and older around 12% of the population develops AS which eventually leads to symptoms and subsequently to a significantly reduced quality of life and life expectancy. Transcatheter aortic valve implantation (TAVI) is currently the treatment of choice in these elderly patients with an intermediate or high surgical risk. In the years 2016 to 2020, more than 10,000 TAVI procedures were performed in the Netherlands, and currently over 2,500 TAVI’s are performed annually. Due to advanced aging and an indication shift towards lower risk and younger patients, these TAVI numbers will increase even further. Despite the technical improvement and operator’s experience throughout the years, complications such as bleeding and thromboembolic complications, paravalvular leakage (PAR) and permanent pacemaker implantation still occur often. Therefore, optimization of TAVI is required before implementing this treatment in the low risk population. This thesis describes aims at reducing the risks and improving outcome of TAVI, with special interest for antithrombotic therapy.

In part I, the topic of interest is the antithrombotic therapy in patients undergoing TAVI. All patients undergoing TAVI need antithrombotic therapy to reduce the risk of valve thrombosis and thromboembolism. However, antithrombotic therapy also increases bleeding especially in this old and fragile population. Balancing the antithrombotic therapy will minimize both the bleeding risk and the thromboembolic risk, and subsequently impact quality of life and mortality. However, when starting the POPular TAVI trial, the optimal antithrombotic treatment after TAVI was not completely determined and therefore the leading guidelines were based on expert consensus only.

The rationale for the suggested antithrombotic treatment strategies in the guidelines were actually copied from the patient population undergoing elective percutaneous coronary intervention, consisting of a P2Y12 inhibitor additional to aspirin (in patients without an indication for anticoagulation) or oral anticoagulation (in patients with an indication for oral anticoagulation) plus antiplatelet therapy (clopidogrel or aspirin). However, a TAVI population is quite different from a PCI population, with a more advanced age and numerous comorbidities influencing the balance between thromboembolic and bleeding risks. Therefore, we performed the POPular TAVI trial, where we aimed to reduce the bleeding risk without compromising the thromboembolic risk in TAVI patients by omitting clopidogrel.
In part II, we explore the use of patient specific computer modelling and other new image strategies for TAVI procedures. Standard TAVI workup includes multi-slice computer tomography (MSCT), which is mainly used for assessment of aortic annulus measurements to find the optimal prosthetic valve size. The HEARTguide software developed by FEops (FEops, Ghent, Belgium) enables to create a patient specific computer model of the TAVI procedure, based on the MSCT images. This model can predict the best fitting prosthetic valve size and implantation depth for each patient according to the predicted valve morphology, PAR and pressure on the cardiac conduction system. Especially in patients with a challenging anatomy (i.e. bicuspid aortic valve stenosis or imprecise aortic annulus measurements), it could be of great benefit to know the optimal predicted TAVI procedure.

In part III, we describe several common and uncommon complications of TAVI and hope to stimulate new research on reducing the risks of complications of TAVI.

**Target groups**
The target group of this thesis includes all physicians directly involved in the treatment of patients with severe symptomatic aortic valve stenosis (using TAVI). This includes physicians working in a TAVI treating center but also those in a referring center, but also primary care physicians and other physicians responsible for treatment of possible complications (for example vascular surgeons or neurologists). The results of PART II of this thesis are mainly of interest to physicians who have a role in the TAVI procedure itself. This thesis might also trigger scientists to start new clinical trials in order to further improve the outcome of TAVI.

**Results and impact**
In part I, we describe the results of the POPular TAVI trial. This multicenter randomized clinical trial in Europe compared an aspirin alone strategy with aspirin plus 3 months of clopidogrel in patient without a long-term indication for oral anticoagulation (OAC) (cohort A) and an OAC alone strategy with OAC plus 3 months clopidogrel in patient with a long-term indication for OAC (cohort B). Both cohorts showed beneficial results with less bleeding events and no increase in thromboembolic events in the group without clopidogrel. Additionally, we confirmed the findings of cohort A in a patient-level meta-analyses of all randomized data at that moment.

The results of both cohorts of the POPular TAVI trial were separately presented at the two largest cardiology scientific meetings (cohort A: European Society of Cardiology Congress 2020, cohort B: American College of Cardiology Annual Scientific Session 2020) and simultaneously published in the New England Journal of Medicine, one of the leading medical journals. Multiple news agencies have reported the results to inform their readers. At the moment of writing, both article have been cited over 135 times. Moreover,
the results have been adopted in the latest European Society of Cardiology guideline on the management of valvular heart disease, now recommending routinely an aspirin or OAC alone strategy without clopidogrel. Other international guidelines might follow in the future when they are being updated. Many centers have already modified their clinical practice based on these guidelines and now prescribing aspirin or OAC alone. By reducing the bleeding complications after TAVI, without increasing the thromboembolic complications, we hypothesize a higher quality of life for patients as well as lower healthcare costs. We are currently performing a cost-effectiveness analysis to measure the effects of omitting clopidogrel in quality of life and healthcare costs.

In part II, we display promising results with the use of the HEARTguide computer modeling software in complex patient populations at higher risk for periprocedural complications such as severe PAR. The model was in most cases able to correctly predict the best fitting valve sizing and implantation depth with corresponding results on PAR. This makes the use HEARTguide useful for further optimization of complex TAVI procedures and possibly even in all TAVI procedures. However, before implementation on a larger scale, the model first needs to be tested in randomized clinical trials. Currently, HEARTguide is available for TAVI patients and patients undergoing transcatheter left atrial appendage closure. Multiple trials that further investigate the use of HEARTguide in these patients are ongoing, as well as preliminary trials investigating the use of HEARTguide in patients undergoing other structural heart interventions (such as transcatheter mitral valve replacement).

In part III of the thesis, we describe the outcomes of TAVI in large patient populations. First, we showed that complications such as bleeding and thromboembolic complications are still frequent and most prevalent within the first 30 days after TAVI. Especially the occurrence of stroke within the first 30-day has not decreased over time. As seen in the POPular TAVI trial, the use of clopidogrel did not influence the rates of stroke after TAVI. Other potential strategies for stroke reduction, such as cerebral embolic protection devices, are currently investigated. Second, we searched for tools to predict the outcomes of TAVI. We demonstrated that proteinuria seems to be a good marker for early signs of kidney improvement after TAVI. On the other hand, we observed that the Academic Research Consortium High Bleeding Risk Criteria for predicting bleeding after coronary artery stenting were not able to discriminate the bleeding risk in TAVI patients. Third, we tested a new vascular closure device (MANTA device) for the closure of the access site following a TAVI procedure. In POPular TAVI we showed that most bleeding events are access site related. The MANTA device seems to be a safe alternative for closing the access site after TAVI with less bleeding events in a selected patient population. Last, we described the occurrence of rare complications such as prosthetic valve endocarditis and the need for coronary artery stenting after TAVI. We observed that all patients with prosthetic valve endocarditis were treated conservatively with antibiotics, most likely
due to the high surgical risk for re-intervention. Acute coronary syndrome was the main indication for coronary artery stenting within the first two years after TAVI, while chronic coronary syndrome was more prevalent after two years. Concluding, in this part of the thesis, we describe common and uncommon complications in large TAVI populations, which hopefully will foster new research in order to reduce the risk of TAVI.

All research presented in this thesis is published in peer-reviewed national and international scientific journals. In addition, some studies were presented at international congresses, discussed online and on news media.