Clinical and hemodynamic effects of transcatheater aortic valve implantation
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Summary

Since the introduction of transcatheter aortic valve implantation (TAVI) in the AMC in 2007, there has been a rapid growth in the number of TAVI procedures in our centre. In the last few years, we have gathered more insight into patient screening and selection for TAVI, procedural techniques, the occurrence and prevention of TAVI-related complications and the effect of TAVI on short- and long-term clinical outcome. In this thesis, different aspects are discussed of the transcatheter aortic valve implantations performed in our single-centre experience.

In chapter 2.1 the feasibility, safety and efficacy are described of the first 30 transfemoral TAVI’s with the Medtronic-CoreValve® device performed in the AMC. End points of this study were defined in a carefully designed clinical protocol approved by the Medical Ethics Committee. The study shows that TAVI was successfully performed in our center in high risk patients, with a procedural success of 90%, 30 days major adverse cardiovascular and cerebral events of 23% and mortality of 20%. When successful, TAVI was shown to result in marked hemodynamic improvement and relief of symptoms.

Within a few years after the first transfemoral TAVI was performed in our center, there was a fast growth in number of TAVI procedures. Furthermore, the addition of another prosthesis type (Edwards SAPIEN®) and of other access types (transfemoral, transapical, subclavian and transaortic) were an enrichment for our TAVI program. The outcome results from our single-centre TAVI program using different devices and access routes are described in chapter 2.2. In this study we investigated the incidence and predictors of short- and long-term mortality of 264 patients who had undergone a TAVI by transfemoral route with the Medtronic-CoreValve prosthesis (n=147) or by transapical (n=69) or transfemoral (n=48) route with the Edwards SAPIEN prosthesis. Thirty-day mortality was 11.7% and shown to be predicted by preprocedural hospitalization, left ventricular mass index, logistic EuroSCORE, acute kidney injury (AKI), major vascular access site complication, major stroke and paravalvular aortic regurgitation (PAR) grade ≥2. Cumulative late mortality was 23% (median follow-up duration of 14 months) and predicted by PAR≥2, Society of Thoracic Surgeons (STS) risk score and AKI. This study identified certain preprocedural risk factors of early and late mortality, which could be helpful to contribute to an optimal selection of patients for TAVI.

There are certain complications associated with TAVI, which may or may not have consequences for clinical outcome. Chapter 3 describes the incidence, predictors and clinical impact of some of these complications. In chapter 3.1 cardiac conduction disorders as complication after TAVI are described. We studied the occurrence and predictors of cardiac conduction disturbances in 34 patients who underwent TAVI with the CoreValve bioprosthesis. Following TAVI, 7 patients required
permanent pacemaker implantation (PPI) because of total atrioventricular block that developed periprocedurally or within three days postprocedurally. A smaller left ventricular outflow tract diameter, more left-sided heart axis on the EKG, more mitral annular calcification and a smaller post-implantation effective orifice area were associated with PPI. The incidence of new left bundle branch block (LBBB) was 65% and was associated with a deeper implantation of the prosthesis. Another important complication of TAVI could be myocardial injury, which is known to be common during cardiac surgery and percutaneous coronary intervention and to be associated with postprocedural cardiovascular morbidity and mortality. Chapter 3.2 focuses on the incidence, predictors and prognostic value of myocardial injury during TAVI with the Medtronic-CoreValve bioprosthesis. In the 119 patients we showed that the incidence of myocardial injury (postprocedural increase of CK-MB and/or cTnT level above 5 times the upper reference limit) was 17%. Independent predictors for myocardial injury were procedural duration, absence of preprocedural beta-blocker use, peripheral arterial disease and prosthesis depth. Myocardial injury had a major impact on early outcome, since it was shown to be an independent predictor for 30-day mortality.

Acute kidney injury (defined as a decrease in estimated glomerular filtration rate compared with baseline of ≥25% within 5 days postprocedurally) is an important prognostic factor following cardiac surgery and in chapter 3.3 this complication is described in the setting of TAVI. In this single-center prospective study, 195 patients were included who had undergone a TAVI either through transfemoral approach with the Medtronic-CoreValve bioprosthesis (n=129) or through transapical route with the Edwards SAPIEN bioprosthesis (n=66). Following TAVI the incidence of AKI was 23%, which was independently predicted by loop diuretic use ≥2 units, post-implantation diastolic arterial blood pressure, maximum leukocyte count and chronic obstructive pulmonary disease. Acute kidney injury was found to be a strong independent predictor for both in-hospital mortality, and 1 year cumulative mortality. Based on these results, we suggested that pre- and peri-procedural preventive measures focused on the predictive factors of AKI may have an impact on the occurrence of this complication and subsequently on the outcome after TAVI.

Chapter 3.4 focuses on paravalvular aortic regurgitation, which has a very high incidence following TAVI. In this study the determinants and short- and mid-term clinical consequences of PAR were examined in 140 patients who underwent a TAVI with the Medtronic-CoreValve bioprosthesis. Following TAVI, PAR grade ≥2 occurred in 29% of the patients and a wider sinus of Valsalva was found to be its only independent predictor. All-cause and cardiac mortality at both 30 days and 1 year were significantly higher in patients with PAR grade ≥2 compared with PAR < 2, which demonstrates that significant PAR after TAVI is a clinically relevant
complication.
Direct improvement of valve hemodynamics after TAVI has been shown in our studies with non-invasive measurements. This change in valve hemodynamics after TAVI translates into significant improvement in left ventricular ejection fraction (LVEF) in other studies, especially in patients with low baseline LVEF. Also, LV pressure unloading associated with TAVI is expected to result in regression of left ventricular hypertrophy, which could result in improvement of diastolic LV function. Invasive LV pressure-volume (PV) assessment by means of the conductance catheter is an accurate method to load-independently determine systolic and diastolic LV function. This method could be a useful tool to assess immediate and long term effects of TAVI on LV hemodynamics. In our centre much experience has been acquired with invasive LV PV measurements in patients who underwent percutaneous coronary intervention (PCI). In chapter 4.1 a study is described in which LV hemodynamic changes were examined between three days and 4 months after successful primary PCI in 11 patients with anterior ST elevation myocardial infarction (STEMI) by invasively obtained LV pressure-volume loops. These measurements showed an increase in LV end-diastolic volume after 4 months as a result of LV remodeling after STEMI. This remodeling was accompanied by LV diastolic improvement as demonstrated by a downward shift of the end-diastolic compliance curve and a decrease in end-diastolic elastance. Improvement in systolic LV function was shown by an increase in stroke volume after four months.

Also periprocedural PV-loop measurements were performed in our centre during PCI. In chapter 4.2, periprocedural LV hemodynamics are compared between patients with or without reperfusion induced accelerated idioventricular rhythm (AIVR) during primary PCI for STEMI. The study showed that patients with reperfusion induced AIVR had more pronounced diastolic LV dysfunction before the onset of this arrhythmia as demonstrated by a delayed active relaxation period, a worse compliance curve and a higher end-diastolic stiffness. At the end of the procedure, patients with AIVR showed less improvement in diastolic LV function, indicated by a downward shift of the compliance curve and a decrease in end-diastolic stiffness and pressure. This study suggests that diastolic dysfunction contributes to the occurrence of AIVR and that AIVR could be a sign of diastolic LV dysfunction.

Other transcatheter valve therapies are being performed and studied in our centre, including percutaneous mitral valve repair of moderate to severe mitral valve regurgitation with the MitraClip®. Chapter 4.3 describes a successful clip implantation in a patient with a symptomatic severe mitral regurgitation and comorbidity, which has resulted in a dramatic reduction of his mitral regurgitation from severe to mild.
Concluding remarks

In conclusion, our single-centre experience with transcatheter aortic valve implantation has demonstrated that it is a safe and feasible technique that forms a good alternative treatment option for patients with symptomatic aortic valve stenosis, who are considered inoperable or have a high surgical risk. Thirty day and one-year mortality of our TAVI procedures are low: approximately 11.7% and 23% respectively, which is comparable with mortality rates reported in other single-centre and multicentre studies and registries. Furthermore TAVI is shown to result in short-term hemodynamic and symptomatic improvement in the majority of our patients.

However, TAVI is associated with certain complications, many of which have consequences for clinical outcome. Cardiac conduction disorders, myocardial injury, acute kidney injury, vascular access site complications and significant paravalvular aortic regurgitation are clinically important complications of TAVI, that are described in this thesis. Preventive measures to reduce the incidence of these complications will result in better clinical outcome. In addition, certain preprocedural risk factors for early and late mortality after TAVI have been identified in our studies. Assessment of mortality risk using these factors could be a useful tool to optimize selection of patients for TAVI. Although the majority of the patients considered for TAVI can be treated with a low mortality risk, certain patients can be identified who have an unacceptable high risk for peri- and postprocedural mortality. For these patients conservative treatment should be considered.

Periprocedural and long-term invasive assessment of change in LV hemodynamics is shown to be feasible and safe in the setting of percutaneous coronary intervention. Invasive LV pressure-volume loop measurements during and after TAVI, could give us more insight in the precise short- and long-term hemodynamic effects of TAVI and its relationship with clinical outcome.

Future perspectives

TAVI has been proven to be a breakthrough technique that has revolutionized the treatment of aortic valve stenosis in the last decade. Longer follow-up studies are needed before TAVI can be extended to younger and/or lower-risk groups of patients with aortic valve stenosis. The main unanswered question yet concerns the duration or longevity of the transcatheter valve devices. Ultimately these valves would need to meet or exceed the durability standards (approximately 20 years) of surgical bioprosthetic valves that are currently in use. Preclinical tests suggest that the Edwards SAPIEN and CoreValve anticipated durability should be similar to currently available bioprosthetic valves. So far, there has been no structural deterioration observed on routine follow-up beyond 7 years with the Cribier-Edwards valve and up to 5 years with the CoreValve prosthesis.
Reduction of certain TAVI-related complications is another important step towards treatment of lower risk patients with TAVI. Next-generation Edwards SAPIEN and Medtronic-CoreValve devices may be helpful to reduce the frequency of these procedure-related complications. Smaller diameters of valve profiles will reduce the size of the delivery catheters and sheaths, which will result in a lower frequency of vascular and bleeding complications. Future studies will have to evaluate the usefulness of embolic protection devices in reducing cerebral embolic events during TAVI procedures. Other advancements in the TAVI world are focused on techniques to reduce paravalvular aortic regurgitation, endoluminal resection of diseased aortic valve leaflets to avoid valvuloplasty, and the ability to retrieve and reposition the valve before final deployment. New transcatheter valve devices have been developed, which are striving to achieve some of these capabilities. Four of such new devices, which have entered clinical trials before CE Mark attainment are: The Portico valve (St Jude Medical Inc., St. Paul, Minnesota, USA), The Sadra Lotus Valve System (Sadra Medical Inc., recently acquired by Boston-Scientific Inc., Natick, Massachusetts, USA), The Direct Flow Medical Aortic Valve 18F (Direct Flow Medical Inc., California, USA) and The Jena Valve (Jena Valve, Munich, Germany). There a lot of other products at earlier stages of development. Future studies and developments in the fascinating area of TAVI, will ultimately determine whether this treatment modality will have a position in the standard treatment of aortic valve stenosis.