Clinical and hemodynamic effects of transcatheter aortic valve implantation
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Chapter 1

General introduction and outline of the thesis

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Introduction

Due to a growing elderly population, the number of patients with degenerative calcific aortic valve stenosis (AS) seeking treatment is increasing. After the occurrence of symptoms (angina, syncope, heart failure), severe AS has a high death rate (about 50% in 2 years) when left untreated. Surgical aortic valve replacement (SAVR) is currently the standard treatment of symptomatic aortic valve stenosis, which provides symptomatic relief and long-term survival. Although the overall perioperative mortality of SAVR is low (2.5 to 4.0%), symptomatic AS is most prevalent in elderly patients, who are often frail and do not seldom have other serious comorbidities, which increase the risk of perioperative complications and death. For this reason at least 30% of the patients are not presented or are denied for surgical replacement of the aortic valve, due to advanced age, left ventricular dysfunction, or the presence of multiple coexisting conditions. Consequently, a large part of elderly patients with severe AS are left untreated, despite their poor prognosis without intervention. Therefore, an alternative less invasive valve treatment option for these patients is mandatory. Transcatheter aortic valve implantation (TAVI) is a novel technique in which a bioprosthetic valve is inserted through a catheter and implanted within the diseased native aortic valve. Since the first-in-man procedure in 2002, there has been a rapid growth worldwide in the use of TAVI in the treatment of patients with symptomatic AS who are considered inoperable or have a high surgical risk. Improvements in device technology and procedural management of TAVI in the last decade have lead to incremental success rates.

Transcatheter valve technology and delivery

Presently, two TAVI devices are commercially available (Figure 1): the balloon-expandable Edwards SAPIEN® prosthesis (Edwards Lifesciences, Irvine, CA, USA) and the self-expandable Medtronic-CoreValve® prosthesis (Medtronic Inc, Minneapolis, MN, USA). Both devices are in clinical use as Conformité Européenne (CE)–approved devices. The first two generations of the Edwards valve (Cribier-Edwards and Edwards SAPIEN) comprised three leaflets of bovine pericardium mounted in a stainless steel frame. The valves were implanted using 22 French and 24 French delivery catheters. The Edwards SAPIEN XT is the third generation of the balloon-expandable Edwards valve, which consists of a trileaflet pericardial bovine valve mounted in a cobalt chromium frame, which is available in three sizes (23, 26 and 29 mm). The CoreValve device has three porcine pericardial leaflets within a larger, self expanding nitinol frame and is available in 26, 29 and 31 mm sizes delivered via an 18-F sheath.
Transcatheter aortic valve implantation is performed under general anesthesia or under local anesthesia with or without sedation, in a cardiac catheterization laboratory or in an operating room equipped with fluoroscopy and transesophageal/transsthoracic echocardiography. The TAVI procedures are performed through the transfemoral (retrograde, with CoreValve and Edwards system), the transapical (antegrade, with Edwards system), the subclavian or transaxillary approach (both with CoreValve system), or the recently developed direct aortic approach (with CoreValve and Edwards system). Balloon aortic valvuloplasty under rapid ventricular pacing (160–220 bpm) is systematically performed before valve implantation for both types of prosthetic valves presently used in TAVI. CoreValve positioning is usually performed by fluoroscopy and angiography, and the valve is deployed without rapid pacing, by retracting the outer sheath of the delivery catheter (Figure 2). The Edwards valve is positioned using fluoroscopy, angiography, and sometimes transesophageal echocardiography, and valve expansion is achieved by balloon inflation under rapid pacing to minimize cardiac output and avoid valve embolization during valve implantation (Figure 3). The transfemoral (TF) route (access through the femoral artery) is the first choice of approach in the vast majority of centers performing TAVI procedures. An accurate preprocedural evaluation of the iliofemoral anatomy is of major importance to determine the appropriateness of this approach for each individual patient. Although surgical cut-down was the technique used for the TF approach at the beginning of the TAVI experience, most centers are now using percutaneous closure devices such as Prostar® or Perclose® (both Abbott Vascular Inc, Red City, CA, USA) in TF cases performed with 18 French catheters. This strategy makes it possible to avoid the use of general anesthesia. The transapical (TA) approach (access through the left ventricular
apex) was first reported as an alternative to the transfemoral approach in 2006, for which the Cribier-Edwards valve system was used. Only the Edwards valve and Jena Valve are currently available for use via the TA route. Access to the left ventricular apex is gained through a left anterolateral minithoracotomy, which obviously requires general anesthesia.

![Fluoroscopic images of transfemoral TAVI with the Medtronic-CoreValve® prosthesis in a patient with prior cardiac surgery. A,B. Deployment of the self-expandable prosthesis, achieved by retraction of the outer sheath of the delivery catheter. C. Fully deployed prosthesis in its final position.](image)

**Figure 2:** Fluoroscopic images of transfemoral TAVI with the Medtronic-CoreValve® prosthesis in a patient with prior cardiac surgery. A,B. Deployment of the self-expandable prosthesis, achieved by retraction of the outer sheath of the delivery catheter. C. Fully deployed prosthesis in its final position.

![Fluoroscopic images of transfemoral TAVI with the Edwards SAPIEN® XT prosthesis. A,B. Deployment of the balloon-expandable prosthesis, achieved by inflation of the balloon inside the prosthesis. C. Fully deployed prosthesis in its final position.](image)

**Figure 3:** Fluoroscopic images of transfemoral TAVI with the Edwards SAPIEN® XT prosthesis. A,B. Deployment of the balloon-expandable prosthesis, achieved by inflation of the balloon inside the prosthesis. C. Fully deployed prosthesis in its final position.
Patient screening and selection

Optimal patient selection in a multidisciplinary heart team is critical for accomplishment of a successful TAVI program. The multidisciplinary transcatheter heart valve team should at least consist of interventional cardiologists, cardiac surgeons, imaging cardiologists and cardio-anaesthesiologists. Criteria for the selection of patients for TAVI differ between centers. In general, patients are considered for TAVI if the logistic EuroSCORE exceeds 15%, age exceeds 80 years and/or at least one of the following comorbidities are present: liver cirrhosis, impaired lung capacity or function (forced expiratory volume in 1 second <1 L), previous cardiac surgery, porcelain aorta, history of mediastinal radiotherapy, severe connective tissue disease with contraindication for surgery, or frailty. General exclusion criteria for TAVI are bicuspid or noncalcified aortic valve stenosis, recent acute myocardial infarction, significant coronary artery disease without revascularization options, a diameter of the aortic annulus of less than 18 mm or more than 27 mm, recent stroke and left ventricular thrombus. A left ventricular ejection fraction of less than 20% is a relative contraindication for TAVI. Systematic work-up of patients for TAVI includes laboratory analysis, 12-lead electrocardiography, transthoracic and/or transoesophageal echocardiography, coronary angiography, imaging of the aorta and iliac and femoral arteries by either angiography or computed tomography, pulmonary function assessment and preoperative assessment by the anaesthesiologist. Assessment of the anatomy of the aortic annulus and root can be performed with different imaging modalities, and is an important component of patient selection. The measured annular dimensions determine which prosthesis size (and in some cases prosthesis type) is used for a particular patient, which is important to prevent prosthesis under- or oversizing. Aortic root anatomy is particularly important when implantation of a CoreValve device is considered, since a diameter of < 43 mm and an angle of < 45° of the ascending aorta is required for optimal prosthesis insertion in the native aortic annulus. Furthermore, evaluation of the distance of the coronary origins to the annulus and localization and amount of native valve leaflet calcification is performed, in combination with sinus width assessment, in order to avoid coronary occlusion after TAVI. Evaluation of the size (by CT angiography or iliofemoral angiography), tortuosity, and degree of calcification (assessed by CT) of iliofemoral arteries is mandatory to determine the suitability for the transfemoral approach.

Outcome of TAVI

The evidence base for TAVI has grown steadily in recent years, with results published from multicenter registries and series. Procedural success is defined in most studies as successful placement of the transcatheter valve with the absence of major adverse cardiovascular and cerebral events (MACCEs) during
the first 48 hours after device implantation. Overall, the procedural success rate was >90%, for both transfemoral and transapical implantations. Valve embolization or conversion to open heart surgery occurred in ~1% of the patients (0.3–3.0% for valve embolization; 0.5–2.3% for conversion to open heart surgery). These multicenter registries and series show that currently, mortality is <10% in patients treated using the transfemoral approach and ranges from 11.3% to 16.9% in patients treated using the transapical approach, probably owing to the higher risk profile of the patients treated via the latter route. Recent clinical studies showed that the rate of death from any cause at 1 year among patients treated with TAVI (by any approach) is approximately 25%.\textsuperscript{9,10,12,17} When considering the type of approach, the survival rates were ~80% (75–85%) for the transfemoral approach and ~70% (63–78%) for the transapical approach.\textsuperscript{11,12,14,23-28} Very few data on the long-term results after TAVI procedures exist. A survival rate of 51% at 3 year follow-up has been reported in 88 patients who had undergone TAVI with the balloon-expandable Cribier-Edwards or Edwards SAPIEN valves.\textsuperscript{29} Another study reported a survival rate of 72% at 2 year follow-up after TAVI with the CoreValve system.\textsuperscript{30} However, the patients included in these studies represent the initial TAVI experience and the use of very early versions of the transcatheter valve and delivery catheter systems, which probably had a negative influence on the results. The results of the Placement of AoRTic tranScatheter valves (PARTNER) trial, which is the first randomized, prospective and controlled trial in TAVI, represent a major milestone in the development of aortic valve therapy (Figure 4).\textsuperscript{25,31} The PARTNER cohort B included 358 patients with severe, symptomatic aortic stenosis deemed inoperable for traditional open heart surgery.\textsuperscript{25} Patients were evenly randomized to receive either the Edwards SAPIEN valve or standard therapy. Although the 30-day rates of death (5.0% versus 2.8%; $P = 0.41$), stroke (3.8% versus 2.1%; $P = 0.20$) and vascular complications (11% versus 3.0%; $P < 0.001$) were higher in the TAVI group, survival at 1 year was dramatically higher in patients receiving the valve compared with those who received best medical therapy (69.3% versus 49.3%; $P < 0.001$). Furthermore, patients who received the valve had fewer hospitalizations and better symptom relief than those receiving standard medical care. The Food and Drug Administration (FDA) approved the SAPIEN valve for the US market on the basis of the PARTNER B results. The PARTNER Trial Cohort A was composed of 699 patients with severe, symptomatic aortic stenosis deemed at high risk for traditional open heart surgery.\textsuperscript{31} Patients were evenly randomized to receive either the Edwards SAPIEN valve with transfemoral or transapical delivery or traditional open heart surgery. In this cohort, 30-day mortality was 3.4% in the TAVI group, compared with 6.5% in the SAVR group ($P = 0.07$). Furthermore the study found that TAVI was non-inferior to SAVR for all-cause mortality at 1 year, 24.2% versus 26.8%, respectively.
This study also showed that there were important differences in procedural complications between TAVI and SAVR. The stroke rate and major vascular complications were higher in the TAVI group, while major bleeding was more frequent in the SAVR group.

![Kaplan–Meier curves for all-cause mortality in Placement of AoRTic traNscathetER (PARTNER) valves study. A. Cohort A (transcatheter aortic valve implantation vs. surgical aortic valve replacement. B. Cohort B (transcatheter aortic valve implantation vs. medical therapy).](image)

**Complications of TAVI**

Complications of cardiac surgery and the prognostic consequences of these complications have been extensively reported in the literature. Since TAVI is less invasive than its surgical equivalent, the incidence of certain complications is expected to be less after TAVI. For example the incidence of myocardial injury and bleeding complications are less after TAVI compared with SAVR and other cardiac surgery. Other complications are expected to occur in a higher incidence after TAVI, because of the differences in approach, technique of valve delivery and prosthesis design. Complications of TAVI, whether or not preventable, are important determinants of the procedural outcome and success. In early 2011, the Valve Academic Research Consortium (VARC) proposed standardized consensus definitions for important clinical end points, including major complications after TAVI. The application of these standardized definitions have made comparison of study results of different TAVI centers meaningful and contributes to a more appropriate evaluation of TAVI technology. The most frequent and clinically important complications of TAVI will be discussed below.

Vascular access complications can be significant after TAVI. The PARTNER B and the PARTNER A trials reported a 16% and 17% incidence of major vascular complications respectively versus 3.8% for SAVR. Complications included thoracic aortic dissection, access site or vascular injury requiring at least 3 units of blood, unplanned percutaneous or surgical intervention, irreversible end-organ damage, distal embolization from a vascular source, or left ventricular perforation. Importantly, the occurrence of major vascular complications has been shown to be an independent predictor of 30-day mortality. Access site complications were
previously the most common serious complications of the TAVI procedure, but the incidence has significantly decreased (by up to 2%) since the advent of smaller delivery systems.\textsuperscript{59}

Many of the older, high-risk patients undergoing TAVI have significant atherosclerosis predisposing them to stroke. Stroke incidence within 30 days following TAVI was \(~3.5\%\) (ranging from 1.2\% to 6.7\%) in the multicenter registries and series and the PARTNER trial.\textsuperscript{11,12,14,23-28,31} Embolization of valve particles from the native calcified aortic valve leaflets, especially occurring during balloon valvuloplasty and stent expansion, might be an important mechanism for cerebral emboli associated with TAVI.\textsuperscript{60,61}

More than 50\% of patients undergoing TAVI have coronary artery disease.\textsuperscript{11} Largely dependent on the different definitions used for periprocedural myocardial infarction (MI), the incidence of this complication ranges from 0\% to 10\% of TF implants,\textsuperscript{62-64} and from 0\% to 1\% TA implants.\textsuperscript{62-66} Myocardial infarction can occur during TAVI if the transcatheter stent blocks a coronary ostium or a large, bulky coronary leaflet is displaced against a coronary ostium by the valve stent or frame. Calcium fragments can embolize down a coronary artery during balloon valvuloplasty or during valve placement, and this can also result in MI.

Patients undergoing TAVI are at risk for acute kidney injury (AKI) due to compromised preprocedural cardiac output, chronic diuretic use, age-induced decreased glomerular filtration, contrast use during the procedure, potential atheroembolism (especially with TF procedures), and brief episodes of hypotension during balloon valvuloplasty and valve placement. The incidence of acute kidney injury, and the need for hemodialysis, after TAVI has ranged from 11.7\% to 28\%, and from 1.4\% to 15.7\%, respectively.\textsuperscript{46,67-71} Early and mid-term mortality after TAVI are shown to be strongly associated with AKI.\textsuperscript{46,67-71}

New-onset cardiac conduction disorders following TAVI are frequent after TAVI.\textsuperscript{72-79} Direct injury of the cardiac conduction tissue caused by manipulation of the metal stent of the prosthesis and by balloon valvuloplasty, is a potential mechanism of new onset cardiac conduction disorders after TAVI. The incidence of atrioventricular block requiring pacing and persistent bundle-branch block, respectively, is approximately 4\% and 5\% after valvuloplasty.\textsuperscript{80} The incidence of permanent pacemaker (PPM) implantation after TAVI is 3\% to 7\% for TF Edwards implants,\textsuperscript{10,12,14,24,25,62-64,72,81,82} and 0\% to 10\% for TA Edwards implants.\textsuperscript{10,12,14,24,62-66,72,75,82-85}

For CoreValve, PPM implants are 10\% to 48\% for TF implants,\textsuperscript{54,86-89} which is considerably higher compared with Edwards implants. The incidence of new left bundle branch block (LBBB) is 15\% to 18\% with the Edwards valve\textsuperscript{75,76} and 40\% with the CoreValve,\textsuperscript{73} which is likely related to direct pressure on the left bundle branch. A higher rate of deeper implantation of the CoreValve system (>5 mm from aortic annulus) might partially explain the differences in occurrence of LBBB.
between the two devices. Most TAVI studies note the presence of some degree of paravalvular aortic regurgitation (PAR) that is generally mild and rarely severe. Nevertheless PAR remains a frequent complication, with a reported incidence of 40-77% of mild and 8-34% of at least moderate regurgitation. Paravalvular AR occurs as the transcatheter valves are not sutured to the aortic wall and the aortic annulus is often eccentric, especially when calcified, while the transcatheter valve is concentric. Notably, the presence of moderate or severe residual aortic regurgitation has been identified as an independent predictor of acute and late mortality following TAVI.26,27,90

This thesis

Our transcatheter aortic valve program was started in October 2007, under a predefined Medical Ethical Committee approved protocol. The first TAVI procedures in the AMC were performed by transfemoral route with the self-expandable Medtronic-CoreValve device. In May 2009 the transapical approach of TAVI with the balloon-expandable Edwards SAPIEN prosthesis was introduced in our centre, making it possible to treat patients unsuitable for transfemoral TAVI because of severe peripheral arterial disease. Since November 2010 transfemoral TAVI with the Edwards device was added as treatment modality in our TAVI program. After the successful results of our first TAVI procedures, we soon realized that this was a promising alternative treatment option in our centre for patients with aortic valve stenosis who are deemed inoperable or are at a high surgical risk. As in other single centre early experiences, we were confronted with challenges in our TAVI program, such as patient selection issues, procedural learning curve and the occurrence of periprocedural complications. Optimization of patient screening and selection, improvement of device technology and procedural performance have improved success rates of TAVI procedures at our centre. This development has lead to a growing referral of patients to our hospital for TAVI. From the beginning of our TAVI program, all patients were entered prospectively in a dedicated database. Data were systematically collected from patient screening, periprocedural monitoring and patient follow-up. In the last few years we have learnt a lot about the benefits and possible disadvantages of this novel treatment option, based on these collected data. This thesis forms an extensive description of the different aspects of our single-center experience with TAVI.

Outline of the thesis

Chapter 2.1 describes the safety and feasibility of the first 30 TAVI procedures performed with the Medtronic-CoreValve device in our centre. Safety and feasibility end points of this study were defined in a carefully designed clinical protocol ap-
proved by the Medical Ethics Committee. Chapter 2.2 is an overview of the results of 264 TAVI procedures performed in single-centre heart team based TAVI program with the availability of two different devices and two different access routes. Predictors of short- and midterm outcome of this real-world patient population are also described in this report.

Procedural en device related complications have been extensively described in surgical aortic valve replacement. Similar complications are expected to occur in TAVI, which is the focus of Chapter 3. Incidence and predictors of cardiac conduction disorders associated with prosthesis implantation with the CoreValve device are described in Chapter 3.1. Periprocedural myocardial injury is a common phenomenon during percutaneous coronary intervention and cardiac surgery and has been scarcely described in the setting of TAVI. Chapter 3.2 is the first study to report the incidence, predictors and clinical consequence of myocardial injury during TAVI with the CoreValve device. Chapter 3.3 focuses on the incidence, predictors and prognostic importance of acute kidney injury following TAVI performed with the transapical en transfemoral approach. Because of the incomplete adherence of the TAVI prosthesis against aortic annular wall, partly due to the presence of calcifications of the native aortic valve, significant paraprosthetic regurgitation is not uncommon after TAVI. Predictors, incidence and clinical consequences of paravalvular aortic regurgitation following TAVI with the CoreValve device are described in Chapter 3.4.

TAVI is expected to result in immediate hemodynamic improvement of left ventricular function due to direct afterload reduction and long-term improvement due to reverse remodeling of left ventricular hypertrophy as a result of chronic afterload reduction. Accurate load-independent hemodynamic assessment of left ventricular (LV) function can be performed by means of invasive pressure-volume (PV) measurements with the conductance catheter. Preparing work for PV measurements in the left ventricle before and after TAVI has been done in our centre in patients undergoing percutaneous coronary intervention. In Chapter 4.1 long-term hemodynamic effects are described of primary PCI in acute anterior wall ST elevation myocardial infarction (STEMI). Periprocedural invasive pressure-volume loop measurements were also performed during primary PCI in anterior wall STEMI patients. Chapter 4.2 is a study in which periprocedural LV hemodynamics are compared between patients with or without accelerated idioventricular rhythm after reperfusion by primary PCI.

Other transcatheter valve therapies are being performed in our centre, including percutaneous mitral valve repair of moderate to severe mitral valve regurgitation with the MitraClip. Chapter 4.3 describes a case of a successful and uncomplicated implantation of a MitraClip resulting in immediate reduction of mitral regurgitation in a patient with severe comorbidity.
References


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