Clinical and hemodynamic effects of transcatheter aortic valve implantation
Yong, Z.Y.

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Transcatheter aortic valve implantation (TAVI) is a relatively novel treatment modality to treat patients with symptomatic aortic valve stenosis, who are deemed inoperable or have a high surgical risk. Early studies showed that TAVI is a feasible and safe procedure, with low mortality rates. It also results in short-term hemodynamic and symptomatic improvement in the majority of the patients. More recent studies demonstrated positive results on long-term, also in comparison with conventional open-heart aortic valve replacement. However, TAVI is associated with certain complications, which have impact on clinical outcome. Prevention of these complications by identifying risk factors and the improvement of device technology, may result in better clinical outcome. This will be the next step towards expanding the indication of TAVI to lower risk patients with aortic valve stenosis.
Clinical and hemodynamic effects of transcatheter aortic valve implantation
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ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde commissie,
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Ze Yie Yong

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Faculteit der Geneeskunde
A journey of a thousand miles begins with one step

_Lao Tse (≈600 B.C.)_
## Contents

<table>
<thead>
<tr>
<th>Chapter 1</th>
<th>General introduction and outline of the thesis</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chapter 2</strong></td>
<td><strong>Feasibility and outcome of transcatheter aortic valve implantation</strong></td>
<td></td>
</tr>
<tr>
<td>Chapter 2.1</td>
<td>Percutaneous implantation of the CoreValve aortic valve prosthesis in patients at high risk or rejected for surgical valve replacement: Clinical evaluation and feasibility of the procedure in the first 30 patients in the AMC-UvA <em>Neth Heart J.</em> 2010 Jan;18(1):18-24</td>
<td>29</td>
</tr>
<tr>
<td>Chapter 2.2</td>
<td>Incidence and predictors of mortality and adverse events following transcatheter aortic valve implantation with different devices and access routes <em>Submitted</em></td>
<td>45</td>
</tr>
<tr>
<td><strong>Chapter 3</strong></td>
<td><strong>Complications of transcatheter aortic valve implantation</strong></td>
<td></td>
</tr>
<tr>
<td>Chapter 3.1</td>
<td>Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis <em>Am Heart J.</em> 2010 Mar;159(3):497-503</td>
<td>65</td>
</tr>
<tr>
<td>Chapter 3.2</td>
<td>Predictors and Prognostic Value of Myocardial Injury During Transcatheter Aortic Valve Implantation <em>Circ Cardiovasc Interv.</em> 2012 Jun 1;5(3):415-23</td>
<td>81</td>
</tr>
<tr>
<td>Chapter 3.3</td>
<td>Predictors and clinical relevance of acute kidney injury following transcatheter aortic valve implantation <em>Submitted</em></td>
<td>99</td>
</tr>
<tr>
<td>Chapter 3.4</td>
<td>Predictors and clinical outcome of significant paravalvular aortic regurgitation following transcatheter aortic valve implantation <em>Submitted</em></td>
<td>117</td>
</tr>
</tbody>
</table>
Chapter 4 Pressure-volume measurements in percutaneous coronary intervention & Other transcatheter valve therapies

Chapter 4.1 Improved long-term LV hemodynamics after primary percutaneous coronary intervention for anterior ST elevation myocardial infarction
Submitted

Chapter 4.2 More pronounced diastolic left ventricular dysfunction in patients with accelerated idioventricular rhythm after reperfusion by primary percutaneous coronary intervention

Chapter 4.3 Immediate reduction of mitral regurgitation by percutaneous mitral valve repair with the MitraClip®
Neth Heart J. 2010 Nov;18(12):606

Chapter 5 Summary and conclusions
Samenvatting en conclusies

Chapter 6 Dankwoord
List of publications
Curriculum vitae
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.\(^1\) Surgical aortic valve replacement (SAVR) is currently the standard treatment of symptomatic aortic valve stenosis, which provides symptomatic relief and long-term survival.\(^2\) Although the overall perioperative mortality of SAVR is low (2.5 to 4.0%),\(^3-5\) 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.\(^3\) 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,\(^6\) 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.\(^7-17\) Improvements in device technology and procedural management of TAVI in the last decade have lead to incremental success rates.\(^7,9,11,16-19\)

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.
Figure 1: Transcatheter aortic valves currently in use for TAVI. A. Third generation Medtronic-CoreValve® prosthesis (Medtronic Inc, Minneapolis, MN, USA). B. Edwards SAPIEN® THV prosthesis (Edwards Lifesciences, Irvine, CA, USA). C. Edwards SAPIEN® XT prosthesis (Edwards Lifesciences, Irvine, CA, USA).

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/ transthoracic 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.

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.

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.\textsuperscript{21,22} 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 $<45^\circ$ 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.\textsuperscript{11,12,14,23-28} 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%.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.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.29 Another study reported a survival rate of 72% at 2 year follow-up after TAVI with the CoreValve system.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).25;31 The PARTNER cohort B included 358 patients with severe, symptomatic aortic stenosis deemed inoperable for traditional open heart surgery.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.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.

Complications of TAVI

Complications of cardiac surgery and the prognostic consequences of these complications have been extensively reported in the literature.\cite{32,53} 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.\cite{31,39,44,54-56} 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.\cite{57} 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.\cite{25,53} 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.\cite{27,58} 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 $\sim$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}.\textsuperscript{59} 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{24;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.

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 and 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 and 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.
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Chapter 2
Feasibility and outcome of transcatheter aortic valve implantation
Chapter 2.1

Percutaneous implantation of the CoreValve aortic valve prosthesis in patients at high risk or rejected for surgical valve replacement

Clinical evaluation and feasibility of the procedure in the first 30 patients in the AMC-UvA

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Chapter 2.1

ABSTRACT

Objective To report the feasibility, safety and efficacy of percutaneous aortic valve implantation (PAVI) with the CoreValve self-expanding aortic valve bioprosthesis in elderly patients with aortic valve stenosis who are rejected for surgery or have a high surgical risk.

Methods PAVI using the CoreValve ReValving System was performed under general anesthesia in thirty (surgical) high risk patients with a symptomatic severe aortic valve stenosis.

Results The patients had a mean age of 80.5±7.7 years, a mean aortic valve area of 0.71±0.19 cm², a peak transvalvular aortic gradient of 79±25 mmHg, as measured with echo Doppler, a logistic EuroSCORE of 15±10% and a Society of Thoracic Surgeons (STS) score of 5.2±2.9%. Device success was achieved in all patients and acute procedural success in 27 patients (90%). In the surviving patients there was a reduction of the peak aortic pressure gradient from 76±24 mmHg to 22±7 mmHg (n=24, P<0.00001) 30 days after successful device implantation. At 30 days, major adverse cardiovascular and cerebral events had occurred in seven patients (23%). This included mortality in six patients (20%), of which one death was cardiovascular. The other five non-cardiovascular deaths involved two patients who died of an exacerbation of severe pre-existent pulmonary disease and three of infectious complications.

Conclusions Percutaneous aortic valve implantation was successfully performed in our centre in highrisk patients, with a 30-day mortality of 20%. When successful, marked haemodynamic improvement and relief of symptoms was achieved.
Clinical evaluation and feasibility of transcatheter aortic valve implantation

2.1

Introduction

Currently the standard therapy of symptomatic aortic valve stenosis (AS) is open chest aortic valve replacement. However, since symptomatic AS usually occurs in the elderly, a high prevalence of comorbidities is present in these patients. The common comorbidities in these patients, such as advanced age, previous cardiac surgery, reduced systolic left ventricular function, pulmonary disease and renal insufficiency are known to be associated with a high periprocedural and postprocedural risk of mortality and morbidity. Therefore almost one third of AS patients with these comorbidities are not referred or are rejected for surgery.\(^1\)\(^-\)\(^2\) Furthermore, the long revalidation period after open chest surgery may be a reason for high-risk patients to withhold from surgery.

Therefore, the development of a less invasive, percutaneous approach of aortic valve replacement was required. Currently there are two Crédit Européen (CE) certified aortic bioprostheses available for percutaneous retrograde implantation: the CoreValve and the Cribier Edwards valve.\(^3\)\(^-\)\(^6\) Previous reports have shown that percutaneous retrograde implantation of aortic bioprosthetic valves is feasible but that mortality and morbidity remain high in these patients.

This report is an evaluation of the feasibility, safety and efficacy of percutaneous aortic valve implantation (PAVI) with the CoreValve ReValvingTM System in the first 30 patients in our center.

Patients and methods

From October 2007 to June 2009 percutaneous aortic valve implantation was performed in thirty patients. A carefully designed clinical protocol was approved by the institutional research and ethical committee. This protocol included an independent data safety and monitoring board including an experienced interventional cardiologist.

After evaluation in a team of two interventional cardiologists, a cardiac surgeon, an echocardiographist and a cardioanaesthesiologist, 30 patients with severe symptomatic native aortic valve stenosis and a high surgical risk were selected to undergo PAVI. The patients were all considered poor surgical candidates with a high surgical risk: 21 patients were considered inoperable. All patients gave written informed consent.

Inclusion and exclusion criteria

Patients were considered as candidates for PAVI if the AS was severe i.e. aortic valve area <1 cm\(^2\) and symptomatic, the aortic annulus diameter of 20-27 mm, a sinotubular junction diameter ≤43 mm, and either patient age ≥80 years or logistic
EuroSCORE ≥15% or one or more of the following complicating factors: previous cardiac surgery, right ventricular insufficiency, pulmonary insufficiency, pulmonary hypertension, history of mediastinal radiotherapy, burning thoracic sequelae, severe connective tissue disease, liver cirrhosis, cachexia, morbid overweight, porcelain aorta and patients (n=9) who refused aortic valve surgery.

Patients were considered not suitable for PAVI in case of known hypersensitivity or contraindication for aspirin, heparin, ticlopidine, clopidogrel or Nitinol, refusal of rescue aortic valve surgery by the patient if considered possible by the surgeon, sepsis (including active endocarditis), recent (<30 days) myocardial infarction, ventricular or atrial thrombus, previous surgical aortic valve replacement, evolutive or recent cerebrovascular accident, severe femoral, iliac or aortic stenosis, tortuosity or aneurysm (not applicable for PAVI via subclavian route), uncontrolled bleeding diathesis or coagulopathy, refusal of blood transfusion, and enrollment in another investigational study.

Transcatheter aortic valve procedure

The technique of PAVI with the CoreValve ReValving™ System has been described in previous studies. Procedures were performed in the catheterization laboratory, with the patient under general anesthesia. Vascular access was obtained via the femoral artery (n=29) or left subclavian artery (n=1) and femoral vein. The procedure was initiated with a balloon valvuloplasty under rapid pacing using an Amplatz superstiff guidewire placed in the left ventricle (LV). Next, the CoreValve delivery system was advanced through the femoral artery or the subclavian artery (n=1) to the aortic annulus under fluoroscopic guidance. After reaching a correct
position of the delivery system the aortic valve prosthesis was deployed (figure 1A and B). After complete deployment of the prosthesis, valve position and function were assessed with angiography and transoesophageal echocardiography and if necessary a postdilatation of the valve was performed (n=2).

Follow-up and endpoints
Clinical follow-up, blood analysis and transthoracic echocardiography were obtained before discharge and at 1 month after discharge.
Three feasibility endpoints were defined: (1) device success, (2) acute procedural success and (3) the occurrence of major adverse cardiovascular and cerebral events (MACCEs) within 30 days follow-up. (1) Device success was defined as stable device placement and adequate function as assessed by angiography and echocardiography. (2) Acute procedural success: device success with absence of periprocedural MACCEs in the first 48h after device implantation. The combined endpoint of MACCEs includes death from any cause, myocardial infarction, cardiac tamponade, stroke, urgent or emergent conversion to surgery or balloon valvuloplasty, emergent percutaneous coronary intervention, cardiogenic shock, endocarditis, aortic dissection or major bleeding.
Other clinical endpoints were the presence of symptoms, New York Heart Association (NYHA) class and cardiac function and valve performance measured with echocardiography.

Statistical analysis
Statistical analysis was performed using SPSS 16.0.1. Descriptive summaries of the distributions of continuous baseline variables are presented in terms of frequencies and percentages. Categorical variables are presented as frequencies and compared by a binomial test or a Fisher’s exact probability test. Continuous variables are presented as mean ± standard deviation (SD). A paired Student t test for within group comparison of continuous variables is used. Values of P<0.05 is considered statistically significant.

Results
Patient population
Between October 2007 and April 2009, 30 patients (15 men, 15 women; mean age 80.5 years; range 55 to 89 years) underwent a PAVI. Baseline patient characteristics are shown in table 1.
All patients had a severe symptomatic AS with an echocardiographic peak transvalvular aortic gradient of 79±25 mmHg, a mean gradient of 52±20 mmHg and a mean calculated aortic valve area of 0.71±0.19 cm². Twenty-three patients were in
NYHA functional class of III or IV. The predicted inhospital mortality rates were 15±10% according to the logistic EuroSCORE and 5.2±2.9% according to the Society of Thoracic Surgeons (STS) score in case of cardiac surgery. Table 2 shows the co-morbidity and contraindications for heart surgery of the individual patients.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline patient characteristics (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Chronic renal insufficiency,a n (%)</td>
</tr>
<tr>
<td>Peripheral vascular disease,b n (%)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
</tr>
<tr>
<td>Prior bypass graft surgery, n (%)</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention, n (%)</td>
</tr>
<tr>
<td>Chronic atrial fibrillation, n (%)</td>
</tr>
<tr>
<td>Chronic pulmonary disease,c n (%)</td>
</tr>
<tr>
<td>Pulmonary hypertension,d n (%)</td>
</tr>
<tr>
<td>Permanent pacemaker, n (%)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Left ventricular function, n (%)</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Logistic EuroSCORE, mean ± SD</td>
</tr>
<tr>
<td>STS Risk score, mean ± SD</td>
</tr>
<tr>
<td>Peak pressure gradient, mm Hg, mean ± SD</td>
</tr>
<tr>
<td>Mean pressure gradient, mm Hg, mean ± SD</td>
</tr>
<tr>
<td>Aortic valve area, cm², mean ± SD</td>
</tr>
</tbody>
</table>

a Renal insufficiency = estimated Glomerular filtration rate <60 using the 4-variable modified diet in renal disease (MDRD) equation: eGFR (ml/min/1.73 m²) = 32788 × serum creatinine⁻¹.₁₁₅ × age⁻₀.₂₀₃ × 0.₇₄₂ [if the patient is female] × 1.₂₁₀ [if the patient is black]. Where serum creatinine is in μg/dL, and age is in years.

b Peripheral vascular disease is defined by a history of symptomatic claudication, previous or planned intervention on abdominal aorta or limb arteries and/or evident peripheral arterial disease on angiogram.

c Chronic pulmonary disease = a history of respiratory problems associated with maintenance inhaled bronchodilator therapy.

d Pulmonary hypertension = Pulmonary artery systolic pressure >30 mmHg.
Clinical outcomes

Procedural data (table 3)  
Device success was achieved in all 30 PAVI patients. Acute procedural success rate was 90% (27 patients), due to MACCEs in 3 patients within 48 hours after device implantation (described hereafter).

30 days mortality (table 3)  
At 30 days follow-up, the mortality rate was 20% (6 patients), which included 1 cardiovascular death and 5 non-cardiovascular...
deaths. The cardiovascular death involved a 76-year-old man (patient 4) with a prior CABG, a poor LV function, three vessel coronary artery disease with only one functioning jump-graft, severe peripheral arterial disease and renal insufficiency, who was therefore rejected for surgery. During the procedure the patient developed a retroperitoneal hematoma after injury of the right iliac artery, which was treated with a covered stent and blood transfusion. A few hours after PAVI he died however of hypovolemic and cardiogenic shock on the intensive care unit (ICU). Autopsy showed extensive myocardial fibrosis due to previous performed transmyocardial laser therapy and multiple myocardial infarctions. The cause of death was deemed to acute heart failure due to hypotension caused by bleeding in a patient with a preprocedural poor left ventricular function. The valve position was good with no obstruction of the coronary ostia or venous bypass graft ostium. Of the five non-cardiovascular related deaths, two patients (patients 3 and 9) died of respiratory failure due to an exacerbation of their pre-existent chronic pulmonary disease (severe pulmonary fibrosis and severe COPD, respectively). The other non-cardiovascular deaths involved three patients (no. 16, 21 and 25) who died of infectious complications: 1 patient died one week after PAVI on the ICU as a direct consequence of sepsis, probably caused by an infection of the central venous line or external pacemaker wire. Two patients died eventually of an aspiration pneumonia, one week and three weeks after PAVI, respectively. Both patients were in a poor clinical condition, due to renal failure in one patient and severe left ventricular hypertrophy with obliteration and advanced stage T-cell lymphoma in the other patient. No autopsy was performed in the three patients who died of infectious causes.

Other 30 days MACCE’s (table 3). An 85-year-old lady (patient 2), developed a cardiac tamponade one day after PAVI caused by an incorrect removal of the right ventricular external pacemaker wire. This was initially treated with pericardial drainage but required surgical repair. She recovered uneventfully and resumed her former activities.

Echocardiographic evaluation (table 4). The peak transvalvular aortic pressure from the patients who were alive after 30 days, decreased from 76±24 mmHg preprocedurally to 22±7 mmHg (n=24, P<0.00001) a few days after the procedure (figure 2) and the aortic valve area increased from 0.69±0.18 cm² to 2.0±0.6 cm² (n=24, P<0.00001; figure 3).
### TABLE 3. Procedural data and 30 days MACCEs and outcome (n=30)

<table>
<thead>
<tr>
<th>Device success, n (%)</th>
<th>30 (100.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute procedural success, n (%)</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>Predilatation balloon diameter, mm, mean±SD</td>
<td>22.9±2.4</td>
</tr>
<tr>
<td>Median procedure time, min, mean±SD</td>
<td>90±29</td>
</tr>
<tr>
<td>Postdilatation, n (%)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>MACCEs within 30 days, n (%)</td>
<td></td>
</tr>
</tbody>
</table>
| Death | 6 (20.0)  
| Major arrhythmia | 0 (0.0)  
| Myocardial infarction | 0 (0.0)  
| Cardiac tamponade | 2 (6.7)  
| Cardiogenic shock | 1 (3.3)  
| Respiratory failure | 3 (10.0)  
| Stroke | 0 (0.0)  
| Conversion to surgery | 0 (0.0)  
| Conversion to valvuloplasty | 0 (0.0)  
| Emergent PCI | 0 (0.0)  
| Endocarditis | 0 (0.0)  
| Aortic dissection | 0 (0.0)  
| Major bleeding | 1 (3.3)  
| Other events within 30 days, n (%) |  |
| Bradyarrhythmia | 9 (30.0)  
| New permanent pacemaker | 7 (23.3)  
| New left bundle branch block | 18 (60.0)  
| Median duration of admission, days, mean±SD |  |
| Intensive Care Unit | 2±6  
| Hospital | 10±6  

**MACCEs**, Major adverse cardiovascular and cerebral events; **PCI**, percutaneous coronary intervention.

* Patient no. 3; b Patient no. 4; c Patient no. 9; d Patient no. 16;  
* e Patient no. 21; f Patient no. 25; g Patient no. 2

### TABLE 4. Postprocedure Hemodynamic Valve Performance in Patients With Immediate Procedural Success (see also figures 2 and 3)

<table>
<thead>
<tr>
<th>Before implantation (n=30)</th>
<th>At discharge (n=24)</th>
<th>At 30 day follow-up (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak pressure gradient, mmHg, mean±SD</td>
<td>79±25</td>
<td>22±7</td>
</tr>
<tr>
<td>Mean pressure gradient, mmHg, mean±SD</td>
<td>52±20</td>
<td>13±5</td>
</tr>
<tr>
<td>Aortic valve area, cm², mean±SD</td>
<td>0.71±0.19</td>
<td>2.0±0.6</td>
</tr>
<tr>
<td>Aortic regurgitation (AR)</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 2: Improvements in aortic valve mean pressure before and after PAVI (n=30).

Figure 3: Improvements in aortic valve area before and after PAVI (n=30).
Other clinical outcomes. Of the 24 patients who were alive after 30 days follow-up 23 were clinically improved, as partially expressed by the improvement of NYHA class (figure 4). One patient, who was treated with PAVI via a subclavian access route, did not improve clinically after the procedure, eventhough postprocedural echocardiography showed a good function of the prosthetic valve. None of the surviving 24 patients had any major adverse events within 30-day follow-up after PAVI. Repeat echocardiography 1 month after discharge showed a stable position of the device with sustained performance of the prosthetic valve compared with the immediate postprocedural echo. Figure 5 shows the stable position of the CoreValve prosthesis on a cardiac MRI, performed in one of the patients six months after PAVI.

Postmortem device assessment. Autopsy which was performed in three deceased patients showed good position of the prosthetic valve device and no device-related complication as cause of the deaths (figure 5). All coronary and bypass graft ostia were patent and no structural damages were observed.

Figure 4: Improvements in New York Heart Association functional class before and one month after PAVI (n=24, P=0.002).
Figure 5: Coronal MRI image of the heart with the CoreValve prosthesis in situ, 6 months after implantation (patient no. 7).

Figure 6: Postmortem with a caudal view of the aortic root and the CoreValve prosthesis in situ (patient no. 9).
Discussion

This study shows that percutaneous aortic valve implantation performed in patients with a high-risk for conventional treatment is feasible in our center. Direct device success was achieved in all patients. Proper and fixed device position without obstruction of coronary ostia was reached in all patients directly after implantation, demonstrated by means of angiography. This was confirmed in the post-mortem assessments of three patients. Maintenance of stable device position at 30 days after PAVI was shown in the other 24 patients by means of transthoracic echocardiography. Feasibility of PAVI has also been demonstrated by the instantaneous improvement of aortic valve performance with a marked reduction of the transvalvular pressure gradient, which sustained after 30 days follow-up. Hemodynamic improvement translated in the relief of symptoms after PAVI in at least 18 of the 24 patients at 30 days follow-up.

The postprocedural 30 days mortality rate of 20% (patients) is considerably higher than the predicted mortality rate according to the logistic EuroSCORE. However, there was only one cardiovascular death, which involved an extreme high risk patient (patient 4). The other five deaths, which were not cardiovascular, occurred between one week and one month after the procedure and were caused by an exacerbation of pre-existing pulmonary disease and infectious complications. It is of important notice that all six deceased patients were highly symptomatic, had a poor prognosis and were declined for conventional aortic valve replacement.

Patient characteristics, device success and acute procedural success rates and occurrences of postprocedural MACCEs of our study are comparable with those reported by Grube et al. and Webb et al.\textsuperscript{4,5,7}

An important lesson that can be learned from this study is that the mortality risk of PAVI is substantial in patients with comorbidity who does not tolerate general anaesthesia nor temporary hypotension. A critical patient selection, in which appropriate risk stratification and proper outweighing of the expected benefits against the risks of PAVI are essential, may reduce the mortality rate.

The decision to perform PAVI as a “last resort treatment” on this high risk patient group should only be made after the risks of the procedure have been properly discussed with and accepted by the patient. Performing PAVI in the six patients who deceased in the 30 day follow-up period of this study had been a well-considered choice of both patient and relatives.

Another lesson from this study is that PAVI’s can be performed with good results in patients who are not rejected for surgery and/or have an intermediate risk for surgical treatment. Such an approach would expand the indication to perform PAVI in patients with lower risks for a surgical valve replacement, i.e. patients, specifically at older age who prefer a less invasive treatment.
The costs of these novel treatment techniques are mainly determined by the high cost of the new devices. However, the shorter ICU and hospital stay as well as the shorter rehabilitation may eventually result in a more cost-effective treatment.

Conclusion

We report the successful initiation of our percutaneous aortic valve implantation program. Before initiation we drew up a specific protocol, in which the feasibility and safety parameters were defined. Feasibility and safety of this procedure by means of the CoreValve self-expandable device is shown by the high rates of direct and acute device success and a direct and long-term hemodynamic improvement in the majority of the patients. However, the postprocedural mortality and morbidity rates remain high in patients who have severe comorbidities. When successful, PAVI can reduce symptoms and improve quality of life in patients with severe symptomatic aortic stenosis who are considered at high risk for conventional aortic valve surgery.

Acknowledgments

The authors acknowledge our nursing staff of the cardiac catheterization laboratory for their skilled assistance, especially W.B.J. Zwiers, RN, M.S. Gorlewska, RN, L. Venckus – Venckiene, RN, W.J. Rohling, RN, and S. van Gilst, RN.
References


Chapter 2.2

Incidence and predictors of mortality and adverse events following transcatheter aortic valve implantation with different devices and access routes

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Submitted
ABSTRACT

Background Little has been reported about the outcome results from a single-centre transcatheter aortic valve implantation (TAVI) program using different devices and access routes. Therefore we aimed to evaluate the incidence and predictors of short- and long-term mortality after TAVI with data from our single-centre experience.

Methods Between October 2007 and June 2012, 264 consecutive patients were included, 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.

Results Device success was 96.6% and procedural success 93.2% of the TAVI procedures. Thirty-day mortality was 11.7% and independently predicted by preprocedural hospitalization (odds ratio (OR): 3.08), left ventricular mass index (LVMI) (per 100 g/m^2, OR: 2.92), logistic EuroSCORE (per 10%, OR: 1.35), acute kidney injury (AKI) stage 1 (OR: 5.69), major vascular access site complication (OR: 8.73), major stroke (OR: 12.37), and paravalvular aortic regurgitation (PAR) grade ≥2 (OR: 2.85). The Valve Academic Research Consortium-combined safety end point occurred in 16.7% of the patients, and was determined by PAR≥2 (OR: 2.57) and preprocedural hospitalization (OR: 2.42). Late mortality was predicted by PAR≥2 (hazard ratio (HR): 2.77), STS score (HR: 1.11) and AKI (HR: 2.11).

Conclusions In a single-centre heart team based TAVI program, transfemoral and transapical TAVI were performed with high success rates. Preprocedural hospitalization, left ventricular mass, EuroSCORE, acute kidney injury, access site complications and significant paravalvular aortic regurgitation, are determinants for early mortality. Long-term mortality is associated with significant PAR, STS and AKI.
Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as a good alternative treatment option to surgical aortic valve replacement for patients with symptomatic severe aortic valve stenosis who are otherwise left untreated due to their high surgical risk. Currently, two transcatheter valve devices are in postmarketing surveillance in Europe: the self-expandable Medtronic-CoreValve prosthesis (Medtronic Inc, Minneapolis, MN, USA) and the balloon-expandable Edwards SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA, USA). Recent high patient volume studies have shown positive short-term outcome results of TAVI, with procedural success rates up to 98% and 30-day mortality rates of 5-14%. All-cause mortality within 1 year following TAVI is reported to be around 25%. Many of these reports, that evaluated the short- and long-term clinical outcome after TAVI, focused either only on one type of valve device or on one type of access route. However, the presence of a heart team based TAVI program with the availability of two types of valves and different access routes makes it possible to choose the most suitable transcatheter aortic valve intervention for an individual patient. Furthermore, short-term procedural success is not only determined by mortality but also by other clinical end points, for which recently the Valve Academic Research Consortium (VARC) criteria have been developed. The incidence and predictors of safety end points after TAVI using these VARC criteria have scarcely been described. Also, little has been reported about the incidence and predictors of mid- and long-term mortality after TAVI, with exclusion of 30-day mortality. Therefore the purposes of our study were to evaluate the incidence and predictors of mortality and VARC-combined safety end point at 30 days and of late mortality after TAVI procedures which have been performed within a single-centre heart team based TAVI program with the availability of different devices and access routes.

Methods

Patient population

Between October 2007 and June 2012, 440 patients with severe symptomatic aortic valve stenosis were referred to our centre for transcatheter aortic valve implantation (figure 1). All patients were first discussed in our heart team and a multidisciplinary transcatheter heart valve team consisting of interventional cardiologists, cardiac surgeons, imaging cardiologists and anaesthesiologists. In general, patients were considered for TAVI if the logistic EuroSCORE exceeded 15%, the age exceeded 80 years and/or at least one of the following comorbidities were present: liver cirrhosis, pulmonary insufficiency (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. Exclusion criteria for TAVI were bicuspid or noncalcified aortic valve stenosis, recent acute myocardial infarction, significant coronary artery disease without revascularization options, a left ventricular ejection fraction of less than 20%, a diameter of the aortic annulus of less than 18 mm or more than 27 mm, recent stroke and left ventricular thrombus.

Patients considered unsuitable for surgical AVR and eligible for TAVI, underwent a systematic screening program, which included 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 anesthesiologist. After screening, patients were re-discussed in the multidisciplinary transcatheter heart valve team. The choice of access route (transfemoral versus transapical) was mainly based on the suitability of vascular access through the iliac and femoral arteries. Different factors were of influence for the choice of valve type (CoreValve versus Edwards), including annulus diameter (< 20 mm: Edwards; > 24 mm: CoreValve), diameter and angle of the ascending aorta (> 43 mm or > 45°: Edwards), severe or calcified mitral valve disease (Edwards), transapical access (only Edwards) and early experience (before May 2009: no transapical implantations, before November 2010: no Edwards for transfemoral route). During this whole process 176 patients were eventually not treated with TAVI: 24 expectative, 30 patients treated with surgical AVR, 93 rejected for any type of valve intervention and 29 patients died before treatment allocation. Of the 440 patients referred, 264 were ultimately accepted to undergo TAVI, 195 via transfemoral and 69 through transapical approach.

**Figure 1:** Flow-chart of treatment allocation in our single-centre transcatheter aortic valve implantation program.
Device and procedure description

Design characteristics of the self-expandable Medtronic-CoreValve and balloon-expandable Edwards SAPIEN bioprosthesis as well as the procedural characteristics of transfemoral (TF-AVI) and transapical (TA-AVI) TAVI have been described in detail in previous reports. Briefly, the Edwards SAPIEN valve is a biological heart valve manufactured with bovine pericardial tissue that is mounted into a balloon-expandable stent. The valve is available in 23 and 26 mm for annulus sizes ranging from 18 to 24.5 mm and can be implanted by transfemoral or transapical approach. The CoreValve prosthesis consists of a tri-leaflet bioprosthetic porcine pericardial tissue valve, which is sutured into a self-expanding nitinol frame. We used the third generation 18 French device, for which two different sizes are available accommodating annulus dimensions from 20 to 27 mm. Patients receiving a CoreValve prosthesis were pretreated with aspirin and clopidogrel and after the procedure with life-long aspirin daily and clopidogrel daily for 3 to 6 months. In patients who received an Edwards prosthesis, pretreatment and life-long treatment after TAVI with aspirin were applied. In the early experience (67 patients) TF-AVI was performed under general anesthesia and afterwards only under local anesthesia accompanied by mild sedation if necessary. All TA-AVI procedures were performed under general anesthesia. In all of the TAVI procedures, deployment of the prostheses in the aortic annulus was preceded by pre-dilatation with a balloon of the native aortic valve. Post-dilatation of the prosthesis after deployment was considered, in case of moderate to severe paravalvular regurgitation. Implantation of a second prosthesis was considered in case of a suboptimal position of the first prosthesis with or without moderate to severe paravalvular regurgitation.

Data collection and end point definitions

All data were prospectively collected and entered in a dedicated database, which included baseline clinical, laboratory, echocardiographic, computed tomography, and angiographic data, as well as procedural and clinical follow-up data. Preprocedural hospitalization was defined as at least 1 week hospitalization of the patient directly prior to TAVI due to severe symptomatic disease. Left ventricular mass (LVM) was calculated from end-diastolic left ventricular internal dimension, interventricular septal thickness and posterior LV wall dimension, using the corrected formula from Devereux and colleagues. Grading of (para)valvular aortic regurgitation (PAR) was performed semiquantitatively based on jet width in the left ventricular outflow tract. Clinical follow-up data were obtained from all patients until hospital discharge or in-hospital death, and included procedural and postprocedural major adverse events and laboratory, electrocardiographic and echocardiographic findings.

Follow-up of the patients was documented at a median of 14 months (interquartile
range: 4 to 22 months). Six months follow-up was available in 75% and one year follow-up in 50% of the patients. Death and the cause of death at any time during the follow-up period were recorded.

For the clinical end point definitions, the criteria of the Valve Academic Research Consortium were used. Device success was defined as stable device placement and function as assessed by angiography and echocardiography. Procedural success was defined as device success in the absence of major adverse cardiovascular and cerebral events (MACCEs) during the first 48 hours after device implantation. Cardiovascular mortality was defined as death due to a proximate cardiac cause. Periprocedural myocardial infarction (MI) was defined as ischemic symptoms or signs combined with elevated cardiac biomarkers (peak value > 10 times the upper reference limit or a peak value > 5 times the upper reference limit with new pathologic Q waves in at least 2 contiguous leads) within 72 hours after the index procedure. Stroke was defined as rapid onset of a neurologic deficit of ≥ 24 hours of duration, necessitating therapeutic intervention or documentation of a new intracranial defect using neuroimaging.

Major stroke was defined as cerebrovascular events with a modified Rankin score ≥ 2 and a National Institutes of Health Stroke Scale score ≥ 3. Bleeding events were assessed as life threatening or disabling (1) in case of bleeding into a critical area or organ, (2) bleeding causing hypovolemic shock or requiring vasopressors or surgery, or (3) with an overt source of bleeding with a decrease in hemoglobin level ≥ 5 g/dL or packed red blood cells transfusion ≥ 4 U. Major bleeding was considered in the setting of overt bleeding associated with a decrease in the hemoglobin level of at least 3.0 g/dL. Major vascular access site complications (VASC) included access-related vascular injuries leading to death, need for blood transfusions (≥ 4 U), percutaneous or surgical intervention, or irreversible end-organ damage. Minor vascular complications were recorded in case of failure of percutaneous access site closure resulting in interventional or surgical correction. Acute kidney injury (AKI) was defined according to the modified Risk, Injury, Failure, Loss, End-stage (RIFLE) classification.

Major adverse cardiovascular and cerebral event (MACCE) was defined as the composite of all-cause death, major stroke, and MI. The VARC-combined safety end point refers to the occurrence of either one of the following events up to 30 days postprocedure: all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury stage 3, periprocedural MI, and repeat procedure for valve-related dysfunction (surgical or interventional therapy). Other device related end points were the peri- and postprocedural occurrence of third degree atrioventricular block requiring permanent pacemaker implantation, new left bundle branch block and grade 2 or more (para)valvular aortic regurgitation (PAR≥2).
Statistical methods

Continuous variables are presented as mean and standard deviation (SD) or as median and interquartile range (IQR), where appropriate. Differences of a continuous variable between three treatment groups (Medtronic-CoreValve transfemoral, Edwards SAPIEN transapical and Edwards SAPIEN transfemoral) were analyzed using analysis of variance or Kruskal-Wallis test, where appropriate. Categorical variables are expressed as numbers and percentages and were compared between three independent groups using the $\chi^2$ test. Univariate and multivariate logistic regression analysis were performed to identify independent predictors for 30-day mortality and VARC-combined safety end point, which were expressed as Odds Ratio (OR) and 95% confidence interval (CI). All variables of tables 1, 2 and 3 were included for univariate analysis of predictors for 30-day mortality, except for device success, acute procedure success, all-cause mortality, cardiovascular mortality, MACCE, life threatening bleeding, admission and VARC-combined end point. For analysis of predictors of VARC-combined safety end point all variables from table 1 were included, from table 2 all variables except for device success and acute procedure success and from table 3 only permanent pacemaker implantation, new left bundle branch block (LBBB) and paravalvular aortic regurgitation $\geq$ 2. A Cox multivariate analysis including all variables with $p$ value $< 0.2$ in the Cox univariate analysis was used to determine the predictive factors of cumulative late mortality (occurring from 30 days and on), which were expressed as hazard ratio (HR) and 95% CI. Survival rates up to 30 days and 2 years were presented as Kaplan-Meier curves, and the log-rank test was used for comparison between the patients treated with the transfemoral versus transapical approach. A predictive score for 30-day mortality was developed, which was based on the variables that were identified as independent predictors for 30-day mortality with logistic regression analysis. Receiver-operating characteristic analysis was performed for an exploratory evaluation of the best cut-off point of this score to predict 30-day mortality. Sensitivity and specificity were derived using this cut-off value. Statistical significance was defined as $P<0.05$. Statistical analysis was performed using GraphPadPrism version 5.00 and the statistical software PASW Statistics 18 for Windows (SPSS Inc., Chicago, IL).

Results

Pre- and periprocedural characteristics

A total of 264 patients who underwent TAVI were included in the study, of whom 147 were treated with the Medtronic-CoreValve device (146 transfemoral and 1 transsubclavian) and 69 with a transapical approach and 48 with a transfemoral approach using the Edwards SAPIEN device. Baseline characteristics of the total
Chapter 2.2

patient population and per treatment group are shown in table 1. The Edwards transapical group was younger (p=0.01), had significantly more male patients (p=0.026), more hypercholesterolemia (p=0.022), more prior myocardial infarction (p=0.037) and CABG (p<0.001) and peripheral arterial disease (p<0.001), but less atrial fibrillation (p=0.032) and less preprocedural hospitalization (p=0.03) compared with the other treatment groups. The Edwards transfemoral group had a significantly lower aortic valve annulus diameter compared with the other groups (p=0.002).

<table>
<thead>
<tr>
<th>Table 1: Baseline clinical characteristics (n=264)</th>
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</thead>
<tbody>
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<td>Total (n = 264)</td>
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<td>----------------</td>
</tr>
<tr>
<td><strong>Patient data</strong></td>
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<td>Age, yrs</td>
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<td>Hypertension</td>
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<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
</tr>
<tr>
<td>Prior PCI</td>
</tr>
<tr>
<td>Prior CABG</td>
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<tr>
<td>Prior stroke</td>
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<tr>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
</tr>
<tr>
<td>Prior neoplasia</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Prior pacemaker</td>
</tr>
<tr>
<td>NYHA class ≥ 3</td>
</tr>
<tr>
<td>Preprocedural hospitalization</td>
</tr>
<tr>
<td>Logistic EuroSCORE</td>
</tr>
<tr>
<td>STS score</td>
</tr>
<tr>
<td><strong>Preprocedural variables</strong></td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
</tr>
<tr>
<td>AVA, cm²</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
</tr>
<tr>
<td>Annulus diameter, mm</td>
</tr>
<tr>
<td>AR grade ≥ 2</td>
</tr>
<tr>
<td>MR grade ≥ 3</td>
</tr>
<tr>
<td>TR grade ≥ 2</td>
</tr>
<tr>
<td>PAP, mmHg</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; STS, society of thoracic surgeons; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; EOA, effective orifice area; AVPG, aortic valve pressure gradient; AR, aortic regurgitation; MR, mitral regurgitation; TR, mitral regurgitation; PAP, pulmonary artery pressure.
Procedural characteristics are shown in table 2. In the Medtronic-CoreValve group, 2 patients received a bioprosthesis using a surgical access (one with femoral access and one through subclavian access) and 6 patients received a second bioprosthesis during the index procedure (valve-in-series), with implantation of the second valve inside the first prosthesis in three patients and implantation of a second prosthesis after retrieval of the first prosthesis in the other three patients.

In the transapical Edwards SAPIEN group a prosthesis was implanted in a patient who had a previous surgical aortic valve bioprosthesis (valve-in-valve). Device success was 96.6% and acute procedural success 93.2%, which were not significantly different between the three treatment groups. The contrast use was significantly lower in the transapical group (p<0.001), but procedural duration significantly higher compared with the Medtronic-CoreValve transfemoral treatment group (p<0.001).

Clinical outcome within 30 days after the procedure is shown in table 3. All-cause mortality at 30 days was 11.7% of which 9.1% was cardiovascular, which was caused by low cardiac output (n=10), stroke (n=4), cardiogenic shock (n=3), hemorrhagic shock (n=3), sudden cardiac arrest (n=2), ventricular fibrillation (n=1) and cardiac tamponade (n=1). Non-cardiovascular mortality was the result of aspiration pneumonia (n=3), sepsis (n=3) and exacerbation COPD (n=1). Both 30-day all-cause mortality and cardiovascular mortality were not statistically significantly different between the three treatment groups. Myocardial infarction (p=0.003) and major bleeding (p=0.014) occurred significantly more in the transapical group, while minor vascular access site complications (p=0.049), permanent pacemaker implantation (p=0.012) and new LBBB (p<0.001) occurred more in the Medtronic-CoreValve transfemoral group compared with the other two groups. Cumulative 30-day mortality of all the patients and the transfemoral versus transapical treatment group is shown in figure 2. The incidence of VARC-combined safety end
point was 16.7% in the total patient population, with a significantly lower incidence in the Edwards SAPIEN transfemoral group (p=0.036).

### Table 3: 30 days clinical outcome (n=264)

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 264)</th>
<th>CoreValve transfemoral (n = 147)</th>
<th>Edwards transapical (n = 69)</th>
<th>Edwards transfemoral (n = 48)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>31 (11.7%)</td>
<td>20 (13.6%)</td>
<td>9 (13.0%)</td>
<td>2 (4.2%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>24 (9.1%)</td>
<td>14 (9.5%)</td>
<td>9 (13.0%)</td>
<td>1 (2.1%)</td>
<td>0.12</td>
</tr>
<tr>
<td>MACCE</td>
<td>37 (14.0%)</td>
<td>23 (15.6%)</td>
<td>12 (17.4%)</td>
<td>2 (4.2%)</td>
<td>0.089</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (1.5%)</td>
<td>0 (0.0%)</td>
<td>4 (5.8%)</td>
<td>0 (0.0%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (4.9%)</td>
<td>11 (7.5%)</td>
<td>1 (1.4%)</td>
<td>1 (2.1%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Major stroke</td>
<td>7 (2.7%)</td>
<td>7 (4.8%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.057</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>6 (2.3%)</td>
<td>3 (2.0%)</td>
<td>1 (1.4%)</td>
<td>0 (0.0%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life threatening bleeding</td>
<td>15 (5.7%)</td>
<td>9 (6.1%)</td>
<td>6 (8.7%)</td>
<td>0 (0.0%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>47 (17.8%)</td>
<td>22 (15.0%)</td>
<td>20 (29.0%)</td>
<td>5 (10.4%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Vascular access</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complication</td>
<td>30 (11.4%)</td>
<td>22 (15.0%)</td>
<td>6 (8.7%)</td>
<td>2 (4.2%)</td>
<td>0.088</td>
</tr>
<tr>
<td>Major</td>
<td>13 (4.9%)</td>
<td>8 (5.4%)</td>
<td>4 (5.8%)</td>
<td>1 (2.1%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Minor</td>
<td>18 (6.8%)</td>
<td>15 (10.2%)</td>
<td>2 (2.9%)</td>
<td>1 (2.1%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>49 (18.6%)</td>
<td>28 (19.0%)</td>
<td>16 (23.2%)</td>
<td>5 (10.4%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Stage 2</td>
<td>9 (3.4%)</td>
<td>6 (4.1%)</td>
<td>2 (2.9%)</td>
<td>1 (2.1%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2 (0.8%)</td>
<td>2 (1.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Cardiac conduction disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent PM implantation</td>
<td>28 (10.6%)</td>
<td>23 (15.6%)</td>
<td>3 (4.3%)</td>
<td>2 (4.2%)</td>
<td>0.012</td>
</tr>
<tr>
<td>New LBBB</td>
<td>71 / 204</td>
<td>57 / 109</td>
<td>10 / 55</td>
<td>4 / 40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paravalvular AR ≥ 2</td>
<td>62 (23.5%)</td>
<td>43 (29.3%)</td>
<td>10 (14.5%)</td>
<td>9 (18.8%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Admission, days</td>
<td>12 ± 10</td>
<td>12 ± 8</td>
<td>15 ± 13</td>
<td>10 ± 11</td>
<td>0.016</td>
</tr>
<tr>
<td>VARC-combined end point</td>
<td>44 (16.7%)</td>
<td>28 (19.0%)</td>
<td>14 (20.3%)</td>
<td>2 (4.2%)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. MACCE, major adverse cardiac and cerebral events; PM, pacemaker; LBBB, left bundle branch block; VARC, Valve Academic Research Consortium.

**Figure 2:** Cumulative 30-day mortality of all TAVI patients, and according to the approach of TAVI: transfemoral versus transapical. Log-rank test for comparison between TF and TA: p=0.78.
Predictors of 30-day outcome

Univariate analysis revealed that 30-day mortality was associated with a lower body mass index, male gender, atrial fibrillation, preprocedural hospitalization, a higher logistic EuroSCORE, a higher STS risk score, left ventricular ejection fraction (LVEF) ≤40%, a higher LVMI, a lower mean aortic valve pressure gradient (AVPG) and major stroke, major VASC, AKI stage 1, 2 and 3 and PAR≥2. Multivariate analysis identified preprocedural hospitalization (Odds ratio (OR): 3.08; 95% CI: 1.26-7.54), LVMI (per 100 g/m², OR: 2.92; 95% CI: 1.16-7.38), logistic EuroSCORE (per 10%, OR: 1.35; 95% CI: 1.03-1.80), AKI stage 1 (OR: 5.69; 95% CI: 2.32-13.91), major VASC (OR: 8.73; 95% CI: 2.14-35.61), major stroke (OR: 12.37; 95% CI: 2.03-75.47) and PAR≥2 (OR: 8.73; 95% CI: 2.14-35.61) as independent predictors for 30-day mortality after TAVI. The independent predictors of 30-day mortality divided into preprocedural and postprocedural variables are shown in tables 4A and 4B, respectively.

Table 4A: Multivariate predictor analysis for 30-day mortality: preprocedural variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprocedural hospitalization</td>
<td>3.08</td>
<td>(1.26 - 7.54)</td>
<td>0.013</td>
</tr>
<tr>
<td>LVMI, per 100 g/m²</td>
<td>2.92</td>
<td>(1.16 - 7.38)</td>
<td>0.023</td>
</tr>
<tr>
<td>Logistic EuroSCORE, per 10%</td>
<td>1.35</td>
<td>(1.03 - 1.80)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Table 4B: Multivariate predictor analysis for 30-day mortality: peri- and postprocedural variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury stage 1</td>
<td>5.69</td>
<td>(2.32 - 13.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major VASC</td>
<td>8.73</td>
<td>(2.14 - 35.61)</td>
<td>0.003</td>
</tr>
<tr>
<td>Major stroke</td>
<td>12.37</td>
<td>(2.03 - 75.47)</td>
<td>0.006</td>
</tr>
<tr>
<td>Paravalvular AR≥ 2</td>
<td>2.85</td>
<td>(1.11 - 7.27)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

For VARC-combined safety endpoint, univariate analysis showed an association with a lower body mass index, NYHA class ≥ 3, preprocedural hospitalization, a higher logistic EuroSCORE, a higher STS risk score, LVEF≤40%, a higher LVMI, more MR grade ≥ 3, general anesthesia and PAR≥2. With multivariate analysis PAR≥2 (OR: 2.57; 95% CI: 1.20-5.50) and preprocedural hospitalization OR: 2.42; 95% CI: 1.11-5.26) were identified as the only independent predictor for VARC-combined safety end point (table 5).
Table 5: Multivariate predictor analysis for 30-day VARC-combined safety end point

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paravalvular AR ≥ 2</td>
<td>2.57</td>
<td>(1.20 - 5.50)</td>
<td>0.015</td>
</tr>
<tr>
<td>Preprocedural hospitalization</td>
<td>2.42</td>
<td>(1.11 - 5.26)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Predictors of long-term mortality

Of the 233 patients that were alive after 30 days, 54 died during follow-up (cumulative late mortality: 23%). Cumulative late mortality of all the patients is shown in figure 3. Univariate Cox regression analysis revealed that late mortality was associated with diabetes, prior myocardial infarction, renal insufficiency, atrial fibrillation, NYHA class ≥ 3 at baseline, a higher logistic EuroSCORE and STS risk score, LVEF ≤ 40%, a higher LVMI, a higher AVPG, tricuspid regurgitation grade ≥ 2, AKI stage 1 and paravalvular AR ≥ 2.

Table 6 shows the independent predictors of cumulative late mortality, which are PAR ≥ 2 (Hazard ratio (HR): 2.77; 95% CI: 1.40-5.50), STS score (HR: 1.11; 95% CI: 1.03-1.19) and AKI stage 1 (HR: 2.11; 95% CI: 1.03-4.32).

Table 6: Multivariate Cox regression analysis for late mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paravalvular AR ≥ 2</td>
<td>2.77</td>
<td>(1.40 - 5.50)</td>
<td>0.004</td>
</tr>
<tr>
<td>STS score</td>
<td>1.11</td>
<td>(1.03 - 1.19)</td>
<td>0.009</td>
</tr>
<tr>
<td>Acute kidney injury stage 1</td>
<td>2.11</td>
<td>(1.03 - 4.32)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Predictive score for 30-day mortality

Based on the independent predictors and individual β1 coefficients of these variables found with multivariate logistic regression, a formula was developed to calculate a prognostic score for 30-day mortality. The model was further simplified to a more practical formula:

\[
\text{Risk score} = 2 \times (\text{Major stroke} + \text{Major VASC} + \text{AKI stage 1}) + \text{Preprocedural hospitalization} + \text{PAR} \geq 2 + \frac{\text{EuroSCORE}}{30} + \frac{\text{LVMI}}{100}.
\]

The receiver-operator-curve (figure 4) shows that 4.25 as the optimal cut-off value to predict 30-day mortality with a sensitivity of 70.4% and a specificity of 85.9%.

**Discussion**

This study describes the short- and long-term clinical outcome of transcatheter aortic valve implantations performed as part of a single-centre heart team based TAVI program, with the availability of two different valve types and different access routes. Device and procedural success rates of the TAVI procedures were high. Mortality at 30 days was 11.7% and predicted by preprocedural hospitalization, left ventricular mass index, logistic EuroSCORE, acute kidney injury, major vascular access site complication, major stroke and paravalvular aortic regurgitation grade ≥2. The VARC-combined safety end point occurred in 16.7% of the patients and was independently predicted by paravalvular aortic regurgitation grade ≥2 and preprocedural hospitalization. Cumulative late mortality that occurred from 30 days and on was 23%, which was predicted by PAR≥2, STS score and AKI.
Early outcome compared with previous studies

The 30-day mortality rate of 11.7% is comparable with that reported in previous studies.\textsuperscript{6,9-13} Mortality rates after TAVI vary from centre to centre, which depends on the TAVI experience and patient selection of the individual centre. As is the case in previous studies, our mortality rate is lower than the estimated surgical risk according to the calculated EuroSCORE. In general, EuroSCORE tends to overestimate the mortality risk of surgical aortic valve replacement and to a larger extent that of TAVI. However, we found EuroSCORE to be one of the independent predictors for 30-day mortality, which indicates that there is a correlation between this score and mortality risk after TAVI. We failed to find an independent association between the STS risk score and early mortality after TAVI.

Predictors of early outcome

In our study, early mortality is determined by several baseline patient characteristics and periprocedural complications. Preprocedural hospitalization was found to be a strong independent predictor for both 30-day mortality and VARC-combined end point. Patients who were hospitalized for at least one week directly prior to TAVI were often admitted because of severely symptomatic aortic valve stenosis. These patients were in a much worse clinical condition compared with patients who awaited TAVI at home and were admitted one day before the procedure. Periprocedural problems, especially hemodynamic instability, probably have a higher impact on frail patients compared with physically healthy patients. This has also been demonstrated in a previous study, that showed that a lower preprocedural Karnofsky score was predictive for both mortality and major adverse events following TAVI.\textsuperscript{9}

A higher left ventricular mass index was identified as an important independent predictor for 30-day mortality, which to our knowledge has never been reported in the setting of TAVI. In line with our finding, left ventricular hypertrophy is shown to be associated with postoperative mortality and morbidity after aortic valve surgery for aortic valve stenosis and regurgitation.\textsuperscript{20-23} Potential mechanisms that can explain the increased mortality risk of patients with excessive left ventricular hypertrophy are contractile impairment and diastolic dysfunction of the left ventricle which can result in heart failure and abnormalities in coronary flow reserve.\textsuperscript{24-27} Acute kidney injury is a serious complication after TAVI and shown to be predictive for early mortality.\textsuperscript{29-31} The cardio-renal syndrome which leads to a vicious circle of cardiac and renal failure is the proposed mechanism of the relationship between AKI and mortality.

Significant paravalvular aortic regurgitation has been identified as predictor for in-hospital mortality in an earlier report.\textsuperscript{32} Especially in non-compliant hypertrophic left ventricles, which most of the patients have developed as result of their chronic
Outcome after transcatheter aortic valve implantation

aortic valve stenosis, moderate to severe aortic valve regurgitation can result in a low cardiac output syndrome and eventually death. As expected and in line with previous studies, early mortality after TAVI was also independently predicted by periprocedural complications, such as major vascular access site complication and major stroke, which can result in hemodynamic instability, prolonged procedural duration and hospitalization and risk for infection.

Predictors of late outcome
Late mortality was defined in this study as mortality occurring from 30 days after TAVI and further. Independent predictors for late mortality found in our study were grade 2 or more paravalvular aortic regurgitation, STS score and acute kidney injury. Significant PAR and acute kidney injury were found as determinants of late mortality in previous studies. While not being independently predictive for early mortality and clinical outcome, STS score is shown to be predictive for late mortality after TAVI. The combination of the different preprocedural factors, that is needed to calculate the STS score, is probably an important determinant of late mortality.

Transfemoral versus transapical approach
In our heart team based TAVI program, the majority of our patients were treated transfemorally because in most of the cases this least invasive approach was the first choice and the transapical route the alternative choice in case of severe peripheral arterial disease. Furthermore, the transapical approach was not yet available during our early experience (before May 2009). Our study did not show a significant difference in 30-day mortality, VARC-combined safety end point and in late mortality between patients treated with the TF versus the TA approach. This is consistent with the results reported by a recently published study. Generally, patients who have been treated by TA approach have a higher risk profile compared with TF-AVI patients. Except for a lower age, more prior myocardial infarction, peripheral arterial disease and CABG in our TA-AVI group, no other risk factors were significantly different between both groups, in particular not the EuroSCORE and STS score. Other studies have shown a higher mortality or adverse event rate in patients treated with TA-AVI compared with TF-AVI. Randomized studies in the future are needed to exactly compare the outcome results of TF-AVI versus TA-AVI procedures in two treatment arms that are comparable in patient characteristics and risk factors.

Clinical implications
Several risk factors for early and late mortality have been identified in our study.
reprocedural factors that have been identified as predictors for adverse outcome after TAVI should be taken into account for the risk assessment as part of patient selection for TAVI. For example, patients in our study who were hospitalized prior to TAVI had a 22% risk of 30-day mortality, while the mortality risk was only 9% for patients who were not hospitalized. Some peri-procedural complications increase the risk of early mortality and should be avoided where possible, especially in patients with already an increased risk based on their baseline profile. We developed a formula in which the different independent predictors for 30-day mortality were incorporated to calculate a prognostic score. Patients with a score above the cut-off value of 4.25 (positive test) had a probability of almost 40% to die within 30 days while patients with a negative test had a probability of only 4%. Interestingly, the risk model reveals that the vast majority of the patients (80%) were treated successfully with TAVI at a very low risk for early mortality (4%).

Limitations
An important limitation of this study is that predictor analysis was performed with data obtained from a single centre, including those from both the early and late experience procedures. The outcome results and predictors highly depend on the selection process, the availability of different devices and approaches and the procedural learning curve, which all differ between centres. Therefore, it remains the question whether our results will also be found in other single centre experiences. Larger multi-centre studies are needed to confirm our findings. Another limitation is that the follow-up of our study was still ongoing, with 50% of the patients lacking one year follow-up and relatively little follow-up events, which may have affected the late survival predictor analysis. Finally, preprocedural hospitalization was chosen in our study as the reflection of a poor preprocedural clinical condition of the patient. Application of frailty scores may be a better way to assess the functional status of the patient. However, these scores have not yet been validated in large prospective TAVI studies.

Conclusion
In a single-centre comprehensive transcatheter aortic valve implantation program, using different devices and approaches, TAVI was performed with high success rates. Poor preprocedural status, left ventricular hypertrophy, EuroSCORE, acute kidney injury, major access site complications, stroke and significant paravalvular aortic regurgitation are predictors of adverse early outcome. Late mortality is associated with significant valvular aortic regurgitation, STS score and acute kidney injury. Preprocedural risk factors of early and late mortality should be taken into consideration in the selection process for TAVI.
References


Chapter 3
Complications of transcatheter aortic valve implantation
Chapter 3.1

Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis

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Bas A.J.M. de Mol

* These authors contributed equally

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ABSTRACT

**Background**  Cardiac conduction disorders (CCD) and requirement for permanent pacemaker implantation (PPI) are not uncommon after surgical aortic valve replacement and have important clinical implications. We aimed to investigate the incidence of CCD after percutaneous aortic valve implantation (PAVI) and to identify possible clinical factors associated with their development.

**Methods**  We studied 34 patients (mean age 80±8 years, 18 male) who underwent PAVI with the CoreValve bioprosthesis (CoreValve Inc, Irvine, CA). Electrocardiographical evaluation was performed pre- and postprocedurally, and at 1 week and 1 month follow-up. Other clinical variables were obtained from the medical history, echocardiography and angiography.

**Results**  After PAVI, 7 patients required PPI, all of whom developed total atrioventricular block within three days postprocedurally. A smaller left ventricular outflow tract diameter (20.3±0.5 vs. 21.6±1.8 cm; p=0.01), more left-sided heart axis (-20±29 vs. 19±36°; p=0.02), more mitral annular calcification (10±1 vs. 5±4 mm; p=0.008) and a smaller post-implantation indexed effective orifice area (0.86±0.20 vs. 1.10±0.26 cm²/m²; p=0.04) 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: 10.2±2.3 mm in the new LBBB group versus 7.7±3.1 mm in the non-LBBB group (p=0.02).

**Conclusion**  Percutaneous aortic valve implantation with the CoreValve prosthesis results in a high incidence of total atrioventricular block requiring permanent pacemaker implantation and new onset left bundle branch block. Pre-existing disturbance of cardiac conduction, a narrow left ventricular outflow tract and the severity of mitral annular calcification predict the need for permanent pacing, while the only factor shown to be predictive for new onset LBBB is the depth of prosthesis implantation.
Introduction

Due to the close proximity of the aortic valve to the atrioventricular (AV) node and bundle of His, the development of new cardiac conduction disorders (CCD) following surgical aortic valve replacement (SAVR) is not uncommon. The incidence of cardiac conduction disorders after SAVR requiring a permanent pacemaker implantation (PPI) on short-term ranges from 3 to 6%.\(^1\)\(^-\)\(^3\) New bundle branch block (BBB) after SAVR is even more common and has recently been reported as high as 18%.\(^4\)

Cardiac conduction disorders following SAVR have important clinical implications. Persistent AV block after SAVR requiring PPI increases mechanical ventilation times, intensive care unit stay, and overall hospital stay.\(^5\)\(^-\)\(^7\) Also, development of new BBB after SAVR is associated with higher rates of complete AV block, syncope and sudden cardiac arrest at long-term.\(^4\)

Percutaneous aortic valve implantation (PAVI) is an alternative therapy for patients with aortic valve stenosis who have a high risk for serious complications after SAVR. Many reports have been published about its feasibility and safety.\(^8\)\(^-\)\(^{13}\) However, the occurrence of CCD during or after PAVI has only been reported briefly in some of these studies. The issue of CCD following PAVI and its possible predicting factors have been addressed recently.\(^14\)\(^-\)\(^{16}\) The incidence of PPI after PAVI in these reports ranges from 20 to 33% and that of new LBBB from 40 to 50%.

In this study, we aim to report the incidence and timing of cardiac conduction problems during and after PAVI. Secondly, we aim to identify the possible factors associated with these conduction problems in order to obtain insight into the mechanisms of their development.

Methods

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Patients

We included a total of 34 consecutive patients who underwent a percutaneous aortic valve implantation using the third-generation percutaneous self-expanding CoreValve® prosthesis (CoreValve Inc, Irvine, CA). The indication for PAVI was a severe symptomatic aortic valve stenosis in patients who were rejected or had a high risk for conventional surgical aortic valve replacement. Clinical and anatomical criteria defined by CoreValve were applied for patient selection.\(^11\)\(^,\)\(^14\) The CoreValve prosthesis implantation was performed under general anesthesia, and has
been described in previous studies.\textsuperscript{10, 11}

**Electrocardiographical evaluation**
All patients underwent standard 12-lead resting electrocardiography the day before the procedure, almost every day after PAVI up to discharge from the hospital, and at one month follow-up. Also during PAVI continuous electrocardiographical monitoring was performed. Permanent pacemaker implantation was performed in case of the presence of complete heart block or symptomatic bradycardia, persisting after at least the second postprocedural day. Other cardiac conduction abnormalities, such as left BBB, right BBB and left fascicular hemiblock were diagnosed by a cardiologist according to criteria recommended by the World Health Organization and the International Society and Federation for Cardiology Task Force.\textsuperscript{17} Left axis deviation was defined as a frontal mean QRS angle between -30 and -90 degrees.

**Evaluation of other parameters**
Complete pre- and postprocedural transthoracic echocardiographic examinations were performed in all patients, using the GE Vivid Dimension machine (GE Healthcare, Horten, Norway). Aortic (prosthetic) valve hemodynamics were assessed before and after PAVI and included aortic valve effective orifice area (EOA), peak and mean aortic valve pressure gradient (AVPG), (paravalvular) aortic regurgitation (AR) grade and location of postimplantation paravalvular AR. In the preprocedural echocardiograph left ventricular outflow tract (LVOT) diameter and end-diastolic interventricular septal dimension (IVSd) were assessed in the parasternal long axis view. The severity of mitral annular calcification (MAC) was assessed in the apical four chamber view by measuring the largest diameter of echodense calcium located at the posterior part of the mitral annulus. The prosthesis depth in the LVOT was assessed with direct post-implantation contrast angiography and was defined as the distance between the lower end of the metal frame and the original aortic annulus level. Laboratory analysis included preprocedural NT-proBNP levels and postprocedural CK-MB peak levels.

**Follow-up and study end-points**
Data collection was completed for every patient at one month follow-up or in case of death. End-points for this study were the development of high degree AV block, requiring permanent pacemaker implantation and the development of left bundle branch block. To assess the possible risk factors for developing new LBBB or PPI, pre-, peri-, and postprocedural variables were compared between two groups with or without the specific cardiac conduction disturbance.
Statistical analysis

Statistical analysis was performed using the statistical software SPSS 16.0 for windows (SPSS Inc., Chicago, IL). Data are expressed as mean value ± standard deviation for continuous variables and as numbers with percentage for categorical variables. For comparison of continuous variables between two groups Student’s t-test was used, and for comparison of categorical variables, chi-square test and Fischer’s exact chi-square test were used. For comparison of variables, which were not normally distributed, non-parametric tests were used. P-values <0.05 were considered to be significant.

Results

Baseline clinical characteristics of the 34 patients are shown in Table 1. The mean age was 80±8 years and 18 (53%) patients were male. All patients had a severe symptomatic aortic valve stenosis and were at high risk for surgical AVR; 23 (71%) patients were considered inoperable. Two patients had a DDDR pacemaker implanted within two months before PAVI because of symptomatic bradycardia. Successful aortic valve implantation was achieved in all 34 patients. One patient died a few hours after PAVI and could not be included in the analysis at the median follow-up timepoints of 1 week and 1 month. Another 6 patients died between 1 week and 1 month after PAVI and were excluded for analysis at 1 month follow-up (Figure 1).

Aortic valve hemodynamics improved immediately after PAVI: the indexed EOA increased from 0.39±0.10 cm²/m² at baseline to 1.03±0.25 cm²/m² postprocedurally and the peak AVPG decreased from 79±25 to 22±8 mmHg (both p<0.0001).

Electrocardiographical cardiac conduction parameters

The baseline electrocardiographical cardiac conduction parameters of the 34 patients and the postprocedural changes in cardiac conduction at three different timepoints are shown in Table 2. Preprocedurally, 14 patients were in atrial fibrillation and 12 patients had one or more CCD’s, with left axis deviation being the most frequent conduction problem (7 patients), followed by first degree AV block (5 patients) and right BBB (3 patients) and left BBB (2 patients). The two patients with a previously implanted permanent pacemaker had neither an atrial nor a ventricular paced rhythm at baseline.
### Table 1. Baseline characteristics (n=34)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>80.4 ± 8.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 5.4</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.88 ± 0.22</td>
</tr>
<tr>
<td>Male gender</td>
<td>18 (53)</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7 (21)</td>
</tr>
<tr>
<td>CAD</td>
<td>16 (47)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>9 (27)</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14 (42)</td>
</tr>
<tr>
<td>Permanent PM</td>
<td>2 (6)</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (21)</td>
</tr>
<tr>
<td>NYHA class ≥ 3</td>
<td>24 (74)</td>
</tr>
<tr>
<td>Rejected for surgery</td>
<td>23 (71)</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>14.3 ± 10.1</td>
</tr>
<tr>
<td>STS score</td>
<td>5.0 ± 2.8</td>
</tr>
<tr>
<td><strong>Heart rate limiting medication</strong></td>
<td></td>
</tr>
<tr>
<td>Betablocker</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Nondihydropyridin CCI</td>
<td>5 (15)</td>
</tr>
<tr>
<td><strong>Preoperative variables</strong></td>
<td></td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>0.73 ± 0.20</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>0.39 ± 0.10</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>78 ± 25</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>51 ± 20</td>
</tr>
<tr>
<td>AR grade ≥ 2</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Impaired systolic LVF</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD (range). BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PM, pacemaker; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; STS, society of thoracic surgeons; CCI, calcium channel inhibitor; AVA, aortic valve area; EOA, effective orifice area; AVPG, aortic valve pressure gradient; LVMI, left ventricular mass index; AR, aortic regurgitation; LVF, left ventricular function.
Directly after PAVI, there was a large increase in the prevalence of CCD’s. The prevalence of LBBB increased from 6% at baseline to 71% directly after implantation (p<0.0001). This was also expressed in the increase of QRS duration from 102±25 to 140±26 ms (p<0.0001).

In total, 7 (21%) patients developed high degree AV block after PAVI requiring permanent pacemaker implantation. Clinical and electrophysiological details of these patients are shown in Table 3. Three patients developed persisting high degree AV block direct after balloon valvuloplasty during PAVI, requiring ventricular pacing and eventually permanent pacemaker implantation. In the other four patients high degree AV block developed between one and three days post-PAVI. Thus, the prevalence of persisting high degree AV block requiring permanent ventricular pacing increased from 0% at baseline to 19% at discharge after PAVI (p=0.01; not shown in table). The prevalence of first degree AV block and left axis deviation did not statistically significantly increase after PAVI.

Except from a decrease of the PQ time from 226±68 to 193±36 ms (p=0.02) in 15 patients with sinus rhythm, no significant changes in the prevalence of CCD and electrocardiographical measures for cardiac conduction were observed between 1 week and 1 month post-PAVI.
### Table 2. Changes in electrocardiographical parameters for cardiac conduction after percutaneous aortic valve implantation (n=34)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=34)</th>
<th>Direct post (n=34)</th>
<th>1 week (n=33)</th>
<th>1 month (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value*</td>
<td>P-value*</td>
<td>P-value*</td>
<td>P-value*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14/34 (42)</td>
<td>0.2</td>
<td>12/34 (35)</td>
<td>0.2</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>12/34 (35)</td>
<td>&lt;0.0001</td>
<td>29/34 (85)</td>
<td>0.08</td>
</tr>
<tr>
<td>PM rhythm</td>
<td>0/34 (0)</td>
<td>0.08</td>
<td>5/34 (9)</td>
<td>0.05</td>
</tr>
<tr>
<td>1 AVB</td>
<td>5/20 (25)</td>
<td>0.3</td>
<td>9/22 (41)†</td>
<td>0.7</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>7/34 (21)</td>
<td>0.08</td>
<td>19/31 (62)‡</td>
<td>1</td>
</tr>
<tr>
<td>LBBB</td>
<td>3/34 (9)</td>
<td>0.3</td>
<td>2/31 (6)‡</td>
<td>1</td>
</tr>
<tr>
<td>QRS angle, °</td>
<td>2/34 (6)</td>
<td>&lt;0.0001</td>
<td>22/31 (71)‡</td>
<td>0.2</td>
</tr>
<tr>
<td>PQ interval, ms</td>
<td>178 ± 34</td>
<td>0.07</td>
<td>190 ± 40</td>
<td>0.09</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>102 ± 25</td>
<td>&lt;0.0001</td>
<td>140 ± 26</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD (range). * P values denote significance of Wilcoxon signed rank sum test or paired-samples t test for differences between adjacent time point for each variable. † Two patients converted to sinus rhythm after percutaneous valve implantation. ‡ Three patients had a pacemaker rhythm. § One patient died before 1 week follow-up. ¶ Seven patients had a pacemaker rhythm. \ Seven patients had died at one month follow-up. ** Six patients had a pacemaker rhythm. PM, pacemaker; 1 AVB, 1st degree AV block; RBBB, right bundle branch block; LBBB, left bundle branch block.

### Table 3. Clinical and electrophysiological characteristics of the patients requiring permanent pacemaker implantation following percutaneous aortic valve implantation

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Intrinsic rhythm</th>
<th>Preprocedural CCD</th>
<th>Indication for PPI</th>
<th>Day of PPI</th>
<th>Pacing mode</th>
<th>% VP at 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>81</td>
<td>F</td>
<td>SR</td>
<td>1 AVB, LAD</td>
<td>Total AVB at day 3</td>
<td>9</td>
<td>DDDR</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>M</td>
<td>AF</td>
<td>AIB, LAFB</td>
<td>Total AVB at day 1</td>
<td>17</td>
<td>DDDR</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>74</td>
<td>F</td>
<td>AF</td>
<td>None</td>
<td>Total AVB periprocedural</td>
<td>3</td>
<td>VVIR</td>
<td>92</td>
</tr>
<tr>
<td>15</td>
<td>84</td>
<td>F</td>
<td>AF</td>
<td>None</td>
<td>Total AVB periprocedural</td>
<td>8</td>
<td>VVIR</td>
<td>100</td>
</tr>
<tr>
<td>19</td>
<td>88</td>
<td>M</td>
<td>AF</td>
<td>None</td>
<td>Total AVB at day 3</td>
<td>4</td>
<td>DDDR</td>
<td>95</td>
</tr>
<tr>
<td>26</td>
<td>89</td>
<td>F</td>
<td>SR</td>
<td>AIB</td>
<td>Total AVB at day 2</td>
<td>2</td>
<td>DDDR</td>
<td>90</td>
</tr>
<tr>
<td>27</td>
<td>87</td>
<td>F</td>
<td>SR</td>
<td>1 AVB</td>
<td>Total AVB periprocedural</td>
<td>2</td>
<td>DDDR</td>
<td>100</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD (range). CCD, cardiac conduction disorder; PPI, permanent pacemaker implantation; VP, ventricular pacing; F, female; SR, sinus rhythm; 1 AVB, first degree atrioventricular block; LAD, left axis deviation; M, male; AF, atrial fibrillation; AIB, aspecific interventricular block; LAFB, left anterior fascicular hemiblock.

### Identification of possible predictors for cardiac conduction disorders

Permanent pacemaker implantation was required in 7 patients before discharge and in 19 patients not. Seven patients were excluded for group analysis because of 2 patients with preprocedural PPI and 5 patients who died before the need for PPI could be considered.

Of these excluded patients, one developed in-hospital total AV block, which was
treated with right ventricular pacing by means of a temporary pacemaker wire. This patient remained hospitalized and died eventually on the intensive care unit without PPI. Before discharge after PAVI, 18 patients had developed a new LBBB and 7 patients did not. The remaining eight patients were excluded for group analysis because of the presence of ventricular paced rhythm in 7 patients and pre-existing LBBB in 2 patients.

Table 4. Pre-, peri- and postprocedural data of patients (n=27)

<table>
<thead>
<tr>
<th>No PPI (n=20)</th>
<th>PPI (n=7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>78.3 ± 8.1</td>
<td>83.4 ± 5.3</td>
</tr>
<tr>
<td>Male gender</td>
<td>12 (60)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.8 ± 6.1</td>
<td>30.2 ± 3.9</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.90 ± 0.24</td>
<td>1.92 ± 0.22</td>
</tr>
<tr>
<td>NT-proBNP, μg/L</td>
<td>2940 ± 4016</td>
<td>3782 ± 6682</td>
</tr>
</tbody>
</table>

Preprocedural conditions

- Hypertension: 9 (45) vs. 5 (71), P = 0.4
- Diabetes: 9 (45) vs. 1 (14), P = 0.2
- Coronary artery disease: 9 (45) vs. 2 (29), P = 0.7
- AR grade ≥ 2: 5 (25) vs. 2 (29), P = 1
- Rate limiting medication: 15 (75) vs. 3 (43), P = 0.2

Preprocedural EKG

- Atrial fibrillation: 6 (30) vs. 4 (57), P = 0.4
- PQ duration, ms: 173 ± 29 vs. 210 ± 59, P = 0.1
- QRS angle, °: 19 ± 36 vs. -20 ± 29, P = 0.02
- QRS duration, ms: 101 ± 27 vs. 101 ± 19, P = 1
- Conduction disorder: 8 (40) vs. 3 (43), P = 1
- 1 AVB: 3/14 (21) vs. 2/3 (67), P = 0.2
- LBBB: 2 (10) vs. 0 (0), P = 1
- RBBB: 2 (10) vs. 0 (0), P = 1
- Left axis deviation: 4 (20) vs. 2 (29), P = 0.6

Periprocedural variables

- 29 mm prosthesis: 9 (45) vs. 2 (29), P = 0.7
- Prosthesis depth, mm: 9.5 ± 2.7 vs. 9.2 ± 3.2, P = 0.8
- Balloon diameter, mm: 23 ± 3 vs. 23 ± 2, P = 0.7
- Postdilatation: 3 (15) vs. 0 (0), P = 0.5

Postprocedural variables

- Indexed EOA, cm²/m²: 1.10 ± 0.26 vs. 0.86 ± 0.20, P = 0.04
- Max AVPG, mmHg: 21 ± 9 vs. 24 ± 4, P = 0.2
- AR grade ≥ 2: 8 (40) vs. 4 (57), P = 0.7
- AR located posteriorly: 6 (30) vs. 5 (71), P = 0.08
- CK-MB peak level, μg/L: 18 ± 13 vs. 16 ± 8, P = 0.6

Values are n (%) or mean ± SD (range). PPI, permanent pacemaker implantation; BMI, body mass index; BSA, body surface area; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AR, aortic regurgitation; LVOT, left ventricular outflow tract; EOA, effective orifice area; AVPG, aortic valve pressure gradient; IVSd, interventricular septal dimension; EKG, electrocardiograph; 1 AVB, 1st degree AV block; LBBB, left bundle branch block; RBBB, right bundle branch block.
### Table 5. Pre-, peri- and postprocedural data of the patients (n=25)

<table>
<thead>
<tr>
<th></th>
<th>No LBBB (n=7)</th>
<th>New LBBB (n=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>80.3 ± 8.0</td>
<td>80.0 ± 9.0</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>5 (71)</td>
<td>9 (50)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>24.4 ± 3.4</td>
<td>27.6 ± 6.0</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>BSA, m²</strong></td>
<td>1.86 ± 0.21</td>
<td>1.88 ± 0.23</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>NT-proBNP, μg/L</strong></td>
<td>1912 ± 877</td>
<td>6096 ± 11068</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Associated conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (43)</td>
<td>9 (50)</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (29)</td>
<td>7 (39)</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (43)</td>
<td>11 (61)</td>
<td>0.7</td>
</tr>
<tr>
<td>AR grade ≥ 2</td>
<td>2 (29)</td>
<td>5 (28)</td>
<td>1</td>
</tr>
<tr>
<td>Rate limiting medication</td>
<td>4 (57)</td>
<td>14 (78)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Preprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVOT, mm</td>
<td>21.7 ± 1.8</td>
<td>21.6 ± 1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>0.38 ± 0.05</td>
<td>0.43 ± 0.10</td>
<td>0.2</td>
</tr>
<tr>
<td>Max AVPG, mmHg</td>
<td>80 ± 20</td>
<td>74 ± 29</td>
<td>0.6</td>
</tr>
<tr>
<td>IVSd, cm</td>
<td>1.60 ± 0.13</td>
<td>1.69 ± 0.37</td>
<td>0.4</td>
</tr>
<tr>
<td>Mitral annular calcification, mm</td>
<td>4 ± 2</td>
<td>6 ± 5</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Preprocedural EKG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (29)</td>
<td>7 (39)</td>
<td>0.7</td>
</tr>
<tr>
<td>PQ duration, ms</td>
<td>173 ± 19</td>
<td>178 ± 23</td>
<td>0.7</td>
</tr>
<tr>
<td>QRS angle, °</td>
<td>16 ± 44</td>
<td>23 ± 37</td>
<td>0.7</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>111 ± 34</td>
<td>93 ± 15</td>
<td>0.2</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>2 (29)</td>
<td>5 (28)</td>
<td>1</td>
</tr>
<tr>
<td>1 AVB</td>
<td>1/5 (20</td>
<td>2/11 (18)</td>
<td>1</td>
</tr>
<tr>
<td>RBBB</td>
<td>2 (29)</td>
<td>1 (6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>1 (14)</td>
<td>3 (17)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Periprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 mm prosthesis</td>
<td>3 (43)</td>
<td>8 (44)</td>
<td>1</td>
</tr>
<tr>
<td>Prosthesis depth, mm</td>
<td>7.7 ± 3.1</td>
<td>10.2 ± 2.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Balloon diameter, mm</td>
<td>24 ± 3</td>
<td>23 ± 2</td>
<td>1</td>
</tr>
<tr>
<td>Postdilatation</td>
<td>2 (29)</td>
<td>1 (6)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Postprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>1.19 ± 0.27</td>
<td>1.04 ± 0.25</td>
<td>0.3</td>
</tr>
<tr>
<td>Max AVPG, mmHg</td>
<td>19 ± 10</td>
<td>22 ± 9</td>
<td>0.5</td>
</tr>
<tr>
<td>AR grade ≥ 2</td>
<td>4 (57)</td>
<td>6 (33)</td>
<td>0.4</td>
</tr>
<tr>
<td>AR located posteriorly</td>
<td>4 (57)</td>
<td>3 (17)</td>
<td>0.1</td>
</tr>
<tr>
<td>CK-MB peak level, μg/L</td>
<td>22 ± 19</td>
<td>26 ± 22</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD (range). PPI, permanent pacemaker implantation; BMI, body mass index; BSA, body surface area; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AR, aortic regurgitation; LVOT, left ventricular outflow tract; EOA, effective orifice area; AVPG, aortic valve pressure gradient; IVSd, interventricular septal dimension; EKG, electrocardiograph; 1 AVB, 1st degree AV block; RBBB, right bundle branch block.

The differences in pre-, peri- and postprocedural variables between the groups with and without the specific CCD are shown in Table 4 for PPI and in Table 5 for new LBBB. A smaller LVOT diameter (20.3±0.5 versus 21.6±1.8 mm; p=0.01), a more calcified mitral annulus (10±1 versus 5±4 mm; p=0.008) and a smaller postimplantation indexed EOA (0.86±0.20 versus 1.10±0.26 cm²/m²; p=0.04) were associated with PPI.
From the baseline electrocardiographical parameters for cardiac conduction, only a more left-sided QRS axis was shown to be associated with PPI (-20±29 versus 19±36°; p=0.02).
The only variable which differed significantly between the new LBBB and no LBBB group was prosthesis depth: 10.2±2.3 versus 7.7±3.1 mm (p=0.02).

Discussion

In our study, we found that the incidence of permanent pacemaker implantation due to total atrioventricular block after percutaneous implantation of the CoreValve aortic valve prosthesis, was 21%. In all patients the cardiac conduction disorders requiring PPI occurred within the first 3 days after PAVI. Associated predictors of PPI were a smaller left ventricular outflow tract, more mitral annular calcification, preexisting left heart axis, and a postprocedural smaller effective orifice area. We also found a new left bundle branch block incidence after PAVI of 65%, occurring immediately after valve expansion, which was related to a deeper position of the valve prosthesis in the LVOT.
The high incidence in our study of high degree AV block after PAVI requiring PPI, is comparable with the incidences reported in recent studies.\textsuperscript{14-16} Three of our PPI patients developed total AV block directly after balloon valvuloplasty during PAVI and in the other four patients high degree AV block occurred between 1 and 3 days post-implantation, which means that the indication for PPI is clearly early postprocedurally.
The patients requiring PPI had a significantly smaller preprocedural LVOT diameter compared with those without PPI, while baseline indexed EOA was not significantly different. Since the body mass index and body surface area did not differ significantly between both groups, a smaller LVOT diameter in the group requiring PPI could be the result of more fibrous thickening or calcification of the endocardium in the subaortic valvular region. Similarly, in patients who underwent surgical aortic valve replacement, annular calcification extending to the subaortic level was a strong predictor for PPI, whereas calcification of the aortic valve itself was not.\textsuperscript{1,2} This relationship between excessive calcific depositions near the conduction tissue and the development of AV conduction problems following PAVI is further supported by our finding of significantly more mitral annular calcification in the PPI group versus the non-PPI group (Figure 2). The association between MAC and PPI after surgical AVR has been reported previously and was explained by the close proximity of the atrioventricular node and bundle of His to the cardiac fibrous skeleton.\textsuperscript{18} Degenerative calcification of the aortic and mitral annulus is probably a diffuse process, in which the cardiac conduction system is often involved as well, making it prone to injury when exposed to compressing or stretching forces during
percutaneous or surgical AVR.

Figure 2: Apical four chamber echocardiographical views of a patient with permanent pacemaker implantation (left side) and one without PPI after percutaneous aortic valve implantation (right side). Notice the difference between both patients in severity of mitral annular calcification, here measured as the diameter of echo dense calcium located at the posterior part of the mitral annulus.

In our study, the three cases of early total AV block were the direct cause of balloon valvuloplasty. The cause of the late cases of total AV block, occurring a few days after PAVI, is less clear, and may have been the result of prolonged or further postprocedural expansion of the CoreValve prosthesis. The significantly lower postprocedural effective orifice area in the PPI group compared with the non-PPI group could be a reflection of the smaller and more calcified aortic annulus in these patients, which prohibits full expansion of the valve prosthesis.

In our study, preprocedural CCD was associated with PPI after PAVI, shown by the fact that the PPI group had a significantly more negative (left sided) deviated heart axis compared with the non-PPI group, indicating a conduction disturbance of the left anterior fascicle. Likewise, the association between preprocedural left axis deviation and LBBB and PPI after PAVI was recently described. Also in surgical aortic valve replacement, the presence of preoperative LBBB or RBBB were shown to be strong predictors of postoperative PPI.

The postprocedural incidence of new LBBB in our study was 65%, which is comparable with previous studies which reported a new LBBB incidence of 40-60% after PAVI. All new left bundle branch blocks in our patients developed during the PAVI procedure and almost all after expansion of the CoreValve prosthesis. Interestingly, deeper implantation of the prosthesis was shown to be the only factor associated with a higher chance of new onset LBBB. Thus, new onset LBBB can be attributed directly to the expanding valve prosthesis causing impingement of the left bundle conduction tissue. None of our patients with a new LBBB showed recovery of this conduction disorder at 1 month follow-up.

The clinical significance of new LBBB after surgical aortic valve replacement has
been described previously.\textsuperscript{4, 20, 21} Whether new LBBB development after PAVI is associated with higher risk for complete AV block or sudden cardiac death at long-term remains to be investigated. There have been a few reports on the incidence of cardiac conduction disorders and permanent pacing after transcatheter implantation of the balloon-expandable Edwards SAPIEN prosthesis, reporting an incidence of AV conduction block requiring PPI from 0 to 6\% and new onset LBBB of 3.3\%\textsuperscript{,13, 22, 23} The much shorter Edwards SAPIEN prosthesis extending less into the left ventricular outflow tract can explain the lower incidence of cardiac conduction problems compared with the CoreValve prosthesis.

Limitations

The occurrence of cardiac conduction disorders and requirement of permanent pacemaker implantation after PAVI was observed in a one month period. Whether there will be an improvement or worsening of cardiac conduction disorders on the long-term after PAVI remains to be investigated.

Conclusion

We report the early occurrence and a high incidence of high degree atrioventricular block requiring permanent pacemaker implantation and new onset left bundle branch block following percutaneous aortic valve implantation with the CoreValve prosthesis. The factors associated with permanent pacing are a smaller LVOT diameter, a more calcified mitral annulus, a more negative preprocedural heart axis and a smaller postoperative effective orifice area. The only factor shown to be predictive for new onset LBBB is the depth of the prosthesis implantation.
References


Chapter 3.2

Predictors and Prognostic Value of Myocardial Injury During Transcatheter Aortic Valve Implantations

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Jan Baan, Jr

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ABSTRACT

Background  Myocardial injury is a common complication during cardiac surgery and percutaneous coronary intervention and is associated with postprocedural cardiovascular morbidity and mortality. Limited data have been reported about the occurrence of myocardial damage associated with transcatheter aortic valve implantation (TAVI). Therefore, our purpose was to investigate the incidence, the predictors and prognostic value of myocardial injury during TAVI.

Methods and Results  We studied 119 patients (age 81±8 years, 47 male), who had undergone a TAVI with the Medtronic-CoreValve® bioprosthesis. Serum CK-MB and cTnT levels were measured before and after the procedure. Myocardial injury was defined as a postprocedural increase of CK-MB and/or cTnT level above 5 times the upper reference limit. Following TAVI the incidence of myocardial injury was 17%, which was independently predicted by procedural duration (minutes, OR: 1.04; 95%CI: 1.01-1.06), preprocedural beta-blocker use (OR: 0.12; 95%CI: 0.03-0.45), peripheral arterial disease (OR: 6.36; 95%CI: 1.56-25.87) and prosthesis depth (mm, OR: 1.31; 95%CI: 1.08-1.59). Thirty-day mortality following TAVI was 13%, and independently predicted by myocardial injury (OR: 8.54; 95%CI: 2.17-33.52), preprocedural hospitalization (OR: 9.36; 95%CI: 2.55-34.38) and left ventricular mass index (g/m², OR: 1.02; 95%CI: 1.00-1.03).

Conclusion  Following transcatheater aortic valve implantation, serum levels of both CK-MB and cTnT increase, which reflects the occurrence of periprocedural myocardial injury. A longer procedural duration, the absence of beta-blocker use, peripheral arterial disease and a deeper prosthesis insertion are associated with myocardial injury. Together with preprocedural hospitalization and left ventricular mass, myocardial injury is an independent predictor for 30-day mortality following TAVI.
**Introduction**

Transcatheter aortic valve implantation (TAVI) is a novel technique, which in the last few years has evolved as an effective alternative treatment of severe degenerative aortic valve stenosis in patients rejected for conventional surgical valve replacement or who have a high risk for peri- and postoperative morbidity and mortality.\(^1\)–\(^8\) Perioperative myocardial injury, manifested as myocardial stunning or infarction, is a frequent complication during cardiac surgery and percutaneous coronary intervention (PCI) and is shown to be strongly associated with postprocedural cardiovascular morbidity and mortality.\(^9\)–\(^18\) In the setting of cardiac surgery, myocardial damage is not only caused by direct myocardial trauma, but more importantly, by global myocardial ischemia during aortic cross-clamping and cardiac arrest, and by insufficient myocardial protection.\(^10\)–\(^11\),\(^19\)–\(^23\) In some patients, reperfusion injury may play a role.\(^24\),\(^25\)

Since there is no need for cardioplegia and aortic cross-clamping during TAVI, myocardial injury is expected to be less. However, myocardial damage during TAVI could be caused by periprocedural conditions resulting in myocardial oxygen supply-demand mismatch, such as balloon valvuloplasty, acute aortic regurgitation and temporary hypotension during rapid ventricular pacing and gradual deployment of the bioprosthesis. Furthermore, direct myocardial injury by catheter, wire and prosthesis manipulation may play a role. As in PCI,\(^26\),\(^27\) another potential mechanism for myocardial injury during TAVI is particle embolization into the coronary arteries arising from the mentioned manipulation at the calcified aortic valve leaflets. On the other hand, cardioprotective effects of certain preprocedural medication may protect the myocardium from damage during TAVI. Therefore, the purpose of this study was to investigate the incidence, predictors and prognostic value of myocardial injury during TAVI.

**Methods**

**Patients**

In a prospective single-center observational study, 119 consecutive patients were included, who were planned between October 2007 and June 2011 for a transcatheter aortic valve implantation with the Medtronic-CoreValve® bioprosthesis (Corevalve Inc, Irvine, CA) via the retrograde transfemoral approach. All patients were selected for TAVI based on their symptomatic severe degenerative aortic valve stenosis and because they were rejected or had a high risk for conventional aortic valve surgery due to high age and comorbidity. The clinical and anatomical criteria for selection of patients for TAVI with the third generation 18F Medtronic-CoreValve device are described elsewhere.\(^2\),\(^4\) Patients, who died within 12 hours
after the procedure (n=3), precluding adequate assessment of postprocedural cardiac enzyme serum levels, were excluded, as well as patients in whom cardiac enzymes were not assessed until they reached their peak level (n=3) and patients who underwent concomitant PCI during the TAVI procedure (n=2). All patients underwent coronary angiography as part of the screening for TAVI. In case of significant coronary artery disease, the strategy was to treat all significant coronary artery lesions (≥70% stenosis) by means of percutaneous coronary intervention (PCI), where possible. Percutaneous coronary intervention was performed at least one week prior to TAVI. All patients were pretreated with aspirin and clopidogrel, with a loading dose of 300 mg, where needed. After TAVI, daily aspirin was continued for life-long and daily clopidogrel for at least 3 months after the procedure. Patients who used coumarines (n=42), had to discontinue with it at least three days before TAVI. In case of coumarin use and a CHADS score of ≥ 3, low weight molecular heparin (LWMH) was given in therapeutic dose for at least two days prior to TAVI. All patients received LWMH in prophylactic dose after TAVI, to prevent thromboembolic events. Of the 39 patients with atrial fibrillation prior to TAVI, 32 patients received coumarin treatment. Implantation of the third generation 18F Medtronic-CoreValve aortic valve bioprosthesis was performed in the catheterization laboratory under general anesthesia (n=62) or only sedation (n=57). The procedural technique of TAVI with the Medtronic-CoreValve bioprosthesis has been described previously.\(^1,^4,^28\) Heparin was given during the procedure at a dose of approximately 100 IU/kg aimed at an activated clotting time of 300 seconds. All patients treated in our percutaneous valve program have been entered in a prospectively designed protocol and dedicated database.

**Blood sampling and analysis**

Venous blood samples were drawn one day before TAVI (T0) and at 1 hour (T1), 6 (T6), 12 (T12), 18 (T18), 24 (T24) and 30 (T30) hours after the procedure until serum levels of CK-MB and cTnT reached their peak and started to decrease. Before analysis, the blood samples were centrifuged at 1000g and stored at -20 °C. The serum levels of CK-MB and cTnT were determined by using electrochemiluminescence immunoassay on the Roche Elecsys 2010 immunoassay analyzer (Roche Diagnostics GmbH, Germany). The upper reference limit (URL) (99th percentile) was 5.2 ng/mL for CK-MB and 0.1 ng/mL for cTnT. Myocardial injury was defined as postprocedural elevations of serum CK-MB or cTnT levels greater than 5 times the URL with or without new Q-waves or new wall motion abnormalities. Periprocedural myocardial infarction was defined as postprocedural elevations of serum CK-MB and/or cTnT levels greater than 5 times the URL in combination
with either new-Q waves and/or echocardiographically determined new persistent wall motion abnormalities, as obtained from the Valve Academic Research Consortium consensus definitions of endpoints following TAVI.\textsuperscript{29}

\textbf{Evaluation of other parameters}

A 12-lead electrocardiogram (EKG) was recorded one day before TAVI, direct after TAVI and every day after the procedure until discharge. Transthoracic echocardiography was performed within three months before TAVI and within a week postprocedurally, using the GE Vivid 7 machine (GE Healthcare, Horten, Norway). Aortic (prosthetic) valve hemodynamics were assessed before and after TAVI and included aortic valve effective orifice area (EOA), peak and mean aortic valve pressure gradient (AVPG), and (paravalvular) aortic regurgitation (AR) grade. Other echocardiographical parameters assessed before and after TAVI were: global left ventricular (LV) systolic function, LV internal and wall dimensions, mitral regurgitation grade and pulmonary artery pressure. Left ventricular mass (LVM) was calculated using the corrected formula from Devereux and colleagues.\textsuperscript{30}

Preprocedural hospitalization was defined as hospital admission for at least one week just prior to the TAVI procedure because of severe symptomatic disease, direct or indirectly related to aortic valve stenosis. Significant coronary artery disease was defined as the presence of at least one unvascularized coronary artery stenosis of more than 50% prior to TAVI.

\textbf{Clinical outcomes}

Clinical outcomes included: (1) 30-day all cause mortality, (2) major cardiac events occurring between 1 day and 30 days after TAVI, including low cardiac output (requiring medical or mechanical left ventricular support), peri-operative myocardial infarction (postprocedural elevations of serum CK-MB or cTnT levels greater than 5 times the URL in combination with either new-Q waves and/or echocardiographically determined new persistent wall motion abnormalities, as obtained from the VARC consensus definitions),\textsuperscript{29} and sustained ventricular arrhythmia. The VARC-combined safety endpoint is defined as the occurrence of either one of the following events up to 30 days postprocedure: all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury stage 3, periprocedural MI, and repeat procedure for valve-related dysfunction (surgical or interventional therapy).\textsuperscript{31}

\textbf{Statistical analysis}

Categorical variables are expressed as number and percentages and compared between groups with a Fisher Exact test. Continuous variables are presented as mean
and standard deviation. Differences of a continuous variable between two groups were analyzed with a two-tailed Student’s t-test or Mann-Whitney U test, where appropriate. The Wilcoxon signed rank test was used for within group comparison of biomarker levels between different time points. A stepwise logistic regression analysis including all variables with P-value < 0.1 in the univariable analysis was used to determine the predictive factors of both myocardial injury and 30-day mortality. Cumulative survival plots of patients with and without myocardial injury were estimated using the Kaplan-Meier method. The log-rank test was used to compare the difference in survival between both groups of patients. To identify predictors of death within 1 year after TAVI, a Cox proportional hazard model was applied. Results are reported as adjusted hazard ratio (HR) with 95% confidence interval (CI). P-values <0.05 were considered to be significant. Statistical analysis was performed using the statistical software SPSS 17.0 for windows (SPSS Inc., Chicago, IL).

Results

Pre-, peri and postprocedural characteristics of the 119 patients are summarized in table 1. The mean age was 81±8 years and 47 (39%) patients were male. Two concomitant PCI’s were performed and one valve-in-valve procedure (implantation of a CoreValve in a CoreValve prosthesis, because the first one was inserted in a too high position). The mean duration of the TAVI procedure was 80±23 minutes. The 30-day mortality rate was 15 (13%), which included 9 non-cardiac deaths (due to pulmonary failure, infectious complications or stroke) and 6 cardiac deaths (due to terminal heart failure), all occurring between 1 week and 30 days after the procedure. Cardiac events within 30 days after TAVI occurred in 16 patients, which all involved a low cardiac output syndrome, requiring intravenous therapy with inotropics and/or diuretics. The cumulative one-year mortality rate was 30 (25%), which included 13 non-cardiac deaths and 17 cardiac deaths. Following TAVI, CK-MB and cTnT serum levels increased in all patients compared to baseline and reached values above the URL. The mean CK-MB level increased from 3.8±1.3 ng/mL at baseline to a peak of 15.9±15.8 μg/L (p<0.0001) which occurred 9.5±7.0 hrs after the procedure. The mean serum concentration of cTnT increased from 0.04±0.03 to 0.28±0.30 ng/mL at peak (p<0.0001), which was reached 14.3±11.2 hrs after TAVI. Twenty patients had postprocedural peak values greater than 5 times the URL of one or both serum markers. Seventeen patients had postprocedural CK-MB peak values of greater than 5 times the URL. No periprocedural myocardial infarction had occurred in these patients as defined by the previously stated VARC criteria, since they had no new-Q waves or echocardiographically determined new wall motion abnormalities. Mean concentrations, as multiple of
### Table 1: Pre-, peri- and post-operative parameters of patients (n=119)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 119)</th>
<th>Myocardial injury (n = 20)</th>
<th>No myocardial injury (n = 99)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>80.7 ± 7.8</td>
<td>83.4 ± 5.0</td>
<td>80.2 ± 8.2</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7 ± 5.5</td>
<td>25.2 ± 4.7</td>
<td>28.2 ± 5.5</td>
<td>0.010</td>
</tr>
<tr>
<td>Male gender</td>
<td>47 (39)</td>
<td>10 (50)</td>
<td>37 (37)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (50)</td>
<td>9 (45)</td>
<td>51 (52)</td>
<td>0.63</td>
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<tr>
<td>Diabetes</td>
<td>31 (26)</td>
<td>2 (10)</td>
<td>29 (29)</td>
<td>0.095</td>
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<td>Hypercholesterolemia</td>
<td>17 (14)</td>
<td>2 (10)</td>
<td>15 (15)</td>
<td>0.73</td>
</tr>
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<td>Prior myocardial infarction</td>
<td>22 (18)</td>
<td>2 (10)</td>
<td>20 (20)</td>
<td>0.36</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>35 (29)</td>
<td>6 (30)</td>
<td>29 (29)</td>
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</tr>
<tr>
<td>Prior CABG</td>
<td>15 (13)</td>
<td>2 (10)</td>
<td>13 (13)</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI / CABG</td>
<td>41 (34)</td>
<td>6 (30)</td>
<td>35 (35)</td>
<td>0.80</td>
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<td>Significant CAD</td>
<td>24 (20)</td>
<td>6 (30)</td>
<td>18 (18)</td>
<td>0.23</td>
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<tr>
<td>Periperal arterial disease</td>
<td>31 (26)</td>
<td>2 (10)</td>
<td>29 (29)</td>
<td>0.048</td>
</tr>
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<td>COPD</td>
<td>40 (34)</td>
<td>6 (30)</td>
<td>34 (34)</td>
<td>0.80</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>39 (33)</td>
<td>5 (25)</td>
<td>34 (34)</td>
<td>0.60</td>
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<td><strong>EuroSCORE</strong></td>
<td>18.5 ± 12.7</td>
<td>19.4 ± 9.8</td>
<td>18.3 ± 13.2</td>
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<tr>
<td><strong>Preprocedural hospitalization</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sedative anesthesia</td>
<td>57 (48)</td>
<td>5 (25)</td>
<td>52 (53)</td>
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<tr>
<td>Valve-in-valve procedure</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Large prosthesis size</td>
<td>36 (30)</td>
<td>5 (25)</td>
<td>31 (31)</td>
<td>0.79</td>
</tr>
<tr>
<td>Prosthesis depth, mm</td>
<td>7.0 ± 3.1</td>
<td>8.7 ± 3.2</td>
<td>6.7 ± 3.0</td>
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<tr>
<td>Contrast amount, mL</td>
<td>148 ± 59</td>
<td>158 ± 76</td>
<td>146 ± 55</td>
<td>0.75</td>
</tr>
<tr>
<td>Procedural duration, min</td>
<td>80 ± 23</td>
<td>93 ± 30</td>
<td>77 ± 21</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Postprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB (ng/mL)</td>
<td>3.8 ± 1.3</td>
<td>3.9 ± 1.1</td>
<td>3.8 ± 1.3</td>
<td>0.71</td>
</tr>
<tr>
<td>cTnT (ng/mL)</td>
<td>0.04 ± 0.03</td>
<td>0.03 ± 0.01</td>
<td>0.04 ± 0.03</td>
<td>0.35</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>7.9 ± 1.1</td>
<td>7.6 ± 1.1</td>
<td>7.9 ± 1.1</td>
<td>0.13</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>67.7 ± 24.4</td>
<td>72.0 ± 16.4</td>
<td>68.8 ± 25.7</td>
<td>0.44</td>
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<td>Betablocker use</td>
<td>66 (55)</td>
<td>6 (30)</td>
<td>60 (61)</td>
<td>0.014</td>
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<tr>
<td>Statin use</td>
<td>49 (41)</td>
<td>8 (40)</td>
<td>41 (41)</td>
<td>1</td>
</tr>
<tr>
<td>Coumarin use</td>
<td>42 (35)</td>
<td>5 (25)</td>
<td>37 (37)</td>
<td>0.44</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>151.8 ± 46.0</td>
<td>166.4 ± 51.9</td>
<td>148.8 ± 44.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>0.41 ± 0.11</td>
<td>0.40 ± 0.07</td>
<td>0.41 ± 0.12</td>
<td>0.68</td>
</tr>
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<td>AVPG max, mmHg</td>
<td>76 ± 23</td>
<td>82 ± 25</td>
<td>75 ± 22</td>
<td>0.26</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>49 ± 16</td>
<td>54 ± 21</td>
<td>48 ± 15</td>
<td>0.33</td>
</tr>
<tr>
<td>AR grade ≥ 3</td>
<td>10 (8)</td>
<td>1 (5)</td>
<td>9 (9)</td>
<td>1</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>42 ± 12</td>
<td>40 ± 9</td>
<td>42 ± 13</td>
<td>0.53</td>
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<td><strong>Procedural data</strong></td>
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<td>77 ± 21</td>
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<td><strong>Postprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB (ng/mL)</td>
<td>15.9 ± 15.8</td>
<td>43.6 ± 21.5</td>
<td>10.3 ± 4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cTnT (ng/mL)</td>
<td>0.28 ± 0.30</td>
<td>0.79 ± 0.40</td>
<td>0.18 ± 0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBCT</td>
<td>29 (24)</td>
<td>7 (35)</td>
<td>22 (22)</td>
<td>0.26</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>1.09 ± 0.27</td>
<td>1.05 ± 0.23</td>
<td>1.10 ± 0.28</td>
<td>0.68</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>20 ± 7</td>
<td>20 ± 8</td>
<td>20 ± 7</td>
<td>0.99</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>12 ± 5</td>
<td>12 ± 5</td>
<td>11 ± 5</td>
<td>0.80</td>
</tr>
<tr>
<td>AR grade ≥ 3</td>
<td>7 (6)</td>
<td>3 (15)</td>
<td>4 (4)</td>
<td>0.092</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>45 ± 10</td>
<td>48 ± 16</td>
<td>45 ± 9</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Postprocedural outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New PM</td>
<td>21 / 104</td>
<td>3 / 15</td>
<td>18 / 88</td>
<td>1</td>
</tr>
<tr>
<td>New LBBB</td>
<td>49 / 89</td>
<td>13 / 17</td>
<td>36 / 72</td>
<td>0.060</td>
</tr>
<tr>
<td>VARC-combined endpoint</td>
<td>24 (20)</td>
<td>7 (35)</td>
<td>16 (16)</td>
<td>0.065</td>
</tr>
<tr>
<td>Hospital admission, days</td>
<td>12 ± 8</td>
<td>16 ± 12</td>
<td>11 ± 7</td>
<td>0.047</td>
</tr>
<tr>
<td>30-day cardiac events</td>
<td>16 (13)</td>
<td>8 (40)</td>
<td>8 (8)</td>
<td>0.001</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>15 (13)</td>
<td>7 (35)</td>
<td>8 (8)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; SITS, society of thoracic surgeons; CK-MB, creatin kinase-MB; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; EOA, effective orifice area; AVPG, aortic valve pressure gradient; MR, mitral regurgitation; PAP, pulmonary artery pressure; RBCT, red blood cell transfusion; AR, aortic regurgitation; PM, pacemaker; LBBB, left bundle branch block.
the upper reference limit, of serum CK-MB and cTnT levels before and at different time points after TAVI are shown in figure 1.

Figure 1: Mean and standard error of the mean of changes in serum levels of creatine kinase-MB (CK-MB) and cardiac troponin T (cTnT) at baseline and at different time points following transcatheter aortic valve implantation. Values are represented as multiples of the upper reference limit (URL). The URL (99th percentile) is 5.2 ng/mL for CK-MB and 0.1 ng/mL for cTnT. T0: baseline; T6-T30: 6, 12, 18, 24 and 30 hours after TAVI, respectively.

Predictors for myocardial injury

Periprocedural myocardial injury occurred in 20 (17%) patients (table 1). Compared with the patients without myocardial injury (n=99), the patients with myocardial injury had a lower body mass index (25.2±4.7 vs. 28.2±5.5 kg/m², p=0.010), used less beta-blocker (30% vs. 61%, p=0.014), were treated less with only sedation (25% vs. 53%, p=0.029), had a deeper prosthesis insertion (8.7±3.2 vs. 6.7±3.0 mm, p=0.005) and a longer procedural duration (97±30 vs. 77±21 minutes, p=0.031). The independent predictors for myocardial injury are shown in table 2 and included preprocedural beta-blocker use (OR: 0.12; 95%CI: 0.03-0.45), procedural duration (minutes, OR: 1.04; 95%CI: 1.01-1.06), prosthesis depth (mm, OR: 1.31; 95%CI: 1.08-1.59) and peripheral arterial disease (OR: 6.36; 95%CI: 1.56-25.87).

Univariate predictors for CK-MB peak levels above the 5 times URL are somewhat different (See the Appendix in the online-only Data Supplement).

Figure 2 shows the differences in peak CK-MB and cTnT serum levels between two groups which have been divided based on these four independent predictors.

Table 2: Independent predictors for myocardial injury following TAVI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betablocker use</td>
<td>0.12</td>
<td>0.03 - 0.45</td>
<td>0.002</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>6.36</td>
<td>1.56 - 25.87</td>
<td>0.010</td>
</tr>
<tr>
<td>Prosthesis depth (mm)</td>
<td>1.31</td>
<td>1.08 - 1.59</td>
<td>0.007</td>
</tr>
<tr>
<td>Procedural duration (minutes)</td>
<td>1.04</td>
<td>1.01 - 1.06</td>
<td>0.005</td>
</tr>
</tbody>
</table>
### Table: Pre-, peri- and post-operative parameters of patients (n=119)

<table>
<thead>
<tr>
<th>CK-MB &gt; 5 URL (n = 17)</th>
<th>CK-MB ≤ 5 URL (n = 102)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>83.2 ± 5.2</td>
<td>80.3 ± 8.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.7 ± 4.9</td>
<td>28.1 ± 5.5</td>
</tr>
<tr>
<td>Male gender</td>
<td>9 (53)</td>
<td>38 (37)</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (47)</td>
<td>52 (51)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (12)</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1 (6)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>0 (0)</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>4 (24)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>2 (12)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Prior PCI / CABG</td>
<td>4 (24)</td>
<td>37 (36)</td>
</tr>
<tr>
<td>Significant CAD</td>
<td>6 (35)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>5 (29)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>COPD</td>
<td>5 (29)</td>
<td>35 (34)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (18)</td>
<td>36 (35)</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>18.0 ± 8.5</td>
<td>18.5 ± 13.3</td>
</tr>
<tr>
<td>STS score</td>
<td>5.7 ± 2.8</td>
<td>6.2 ± 4.7</td>
</tr>
<tr>
<td>Preprocedural hospitalization</td>
<td>4 (24)</td>
<td>22 (22)</td>
</tr>
<tr>
<td><strong>Preprocedural variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB (ng/mL)</td>
<td>4.0 ± 1.1</td>
<td>3.8 ± 1.3</td>
</tr>
<tr>
<td>cTnT (ng/mL)</td>
<td>0.03 ± 0.00</td>
<td>0.04 ± 0.03</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>7.6 ± 1.0</td>
<td>7.9 ± 1.1</td>
</tr>
<tr>
<td>cGFR, mL/min/1.73m²</td>
<td>74.2 ± 16.4</td>
<td>66.6 ± 25.3</td>
</tr>
<tr>
<td>Betablocker use</td>
<td>5 (29)</td>
<td>61 (60)</td>
</tr>
<tr>
<td>Statin use</td>
<td>6 (35)</td>
<td>43 (42)</td>
</tr>
<tr>
<td>Coumarin use</td>
<td>4 (24)</td>
<td>38 (37)</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>4 (24)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>167.1 ± 56.2</td>
<td>149.2 ± 43.9</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>0.40 ± 0.07</td>
<td>0.41 ± 0.12</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>88 ± 24</td>
<td>75 ± 22</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>57 ± 22</td>
<td>48 ± 14</td>
</tr>
<tr>
<td>MR grade ≥ 3</td>
<td>1 (6)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>42 ± 12</td>
<td>40 ± 9</td>
</tr>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative anesthesia</td>
<td>5 (29)</td>
<td>52 (51)</td>
</tr>
<tr>
<td>Valve-in-valve procedure</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Large prosthesis size</td>
<td>5 (29)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>Prosthesis depth, mm</td>
<td>8.3 ± 3.0</td>
<td>6.8 ± 3.1</td>
</tr>
<tr>
<td>Contrast amount, mL</td>
<td>151 ± 74</td>
<td>147 ± 56</td>
</tr>
<tr>
<td>Procedural duration, min</td>
<td>91 ± 28</td>
<td>78 ± 22</td>
</tr>
<tr>
<td><strong>Postprocedural variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB (ng/mL)</td>
<td>48.0 ± 20.2</td>
<td>10.6 ± 5.0</td>
</tr>
<tr>
<td>cTnT (ng/mL)</td>
<td>0.82 ± 0.42</td>
<td>0.19 ± 0.14</td>
</tr>
<tr>
<td>RBCT</td>
<td>6 (35)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>1 (6)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>1.04 ± 0.25</td>
<td>1.10 ± 0.28</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>20 ± 8</td>
<td>20 ± 7</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>12 ± 5</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>AR grade ≥ 3</td>
<td>3 (18)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>48 ± 19</td>
<td>45 ± 9</td>
</tr>
<tr>
<td><strong>Postprocedural outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New PM</td>
<td>3 / 13</td>
<td>18 / 91</td>
</tr>
<tr>
<td>New LBBB</td>
<td>10 / 14</td>
<td>39 / 75</td>
</tr>
<tr>
<td>VARC-combined endpoint</td>
<td>7 (41)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Hospital admission, days</td>
<td>17 ± 13</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>30-day cardiac events</td>
<td>7 (41)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>7 (41)</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD.
Predictors for 30-day mortality

The 30-day mortality rate was 15 (13%) and was associated with a higher Society of Thoracic Surgeons (STS) risk score (7.8±3.7 vs. 5.9±4.6, p=0.013), more preprocedural hospitalization (60% vs. 16%, p=0.001), a higher left ventricular mass index (181.5±45.6 vs. 147.5±44.7, p=0.008), and a higher incidence of myocardial injury (47% vs 13%, p=0.004) and postprocedural AR grade ≥3 (20% vs 4%, p=0.042) (table 3). Multivariate analysis revealed myocardial injury (OR: 8.54; 95%CI: 2.17-33.52), preprocedural hospitalization (OR: 9.36; 95%CI: 2.55-34.38), and LVMI (g/m², OR: 1.02; 95%CI: 1.00-1.03) to be independent predictors for 30-day mortality (table 4).

Predictors for 1 year cumulative mortality

The Kaplan-Meier survival analysis shows a significant difference in survival between the patients with myocardial injury and those without myocardial injury (p=0.013 by log-rank test) as shown in figure 3. Multivariable analysis of 1 year cumulative survival after TAVI revealed that myocardial injury was an independent predictor for one-year cumulative mortality (HR: 2.86, 95%CI 1.28-6.39; p=0.011), together with preprocedural hospitalization (HR: 2.76, 95%CI 1.30-5.83; p=0.008), left ventricular mass index (per g/m², HR: 1.01, 95%CI 1.00-1.02; p=0.035) and preprocedural mean AVPG (per mmHg, HR: 0.97, 95%CI 0.94-1.00; p=0.033).

Table 4: Independent predictors for 30-day mortality following TAVI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprocedural hospitalization</td>
<td>9.36</td>
<td>2.55 - 34.38</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial injury</td>
<td>8.54</td>
<td>2.17 - 33.52</td>
<td>0.002</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>1.02</td>
<td>1.00 - 1.03</td>
<td>0.035</td>
</tr>
</tbody>
</table>
### Table 3: Pre-, peri- and post-operative parameters of patients (n=119)

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Deceased (n = 15)</th>
<th>Alive (n = 104)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>83.3 ± 7.0</td>
<td>80.3 ± 7.9</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9 ± 4.9</td>
<td>28.0 ± 5.5</td>
<td>0.083</td>
</tr>
<tr>
<td>Male gender</td>
<td>9 (60)</td>
<td>38 (37)</td>
<td>0.096</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (53)</td>
<td>52 (50)</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (27)</td>
<td>27 (26)</td>
<td>1</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3 (20)</td>
<td>14 (13)</td>
<td>0.45</td>
</tr>
<tr>
<td>Prior myocardial Infarction</td>
<td>4 (27)</td>
<td>18 (17)</td>
<td>0.48</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>5 (33)</td>
<td>30 (29)</td>
<td>0.77</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (7)</td>
<td>14 (13)</td>
<td>0.69</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>3 (20)</td>
<td>18 (17)</td>
<td>0.73</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (40)</td>
<td>34 (33)</td>
<td>0.57</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (47)</td>
<td>32 (31)</td>
<td>0.25</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>21.4 ± 13.1</td>
<td>18.0 ± 12.7</td>
<td>0.14</td>
</tr>
<tr>
<td>STS score</td>
<td>7.8 ± 3.7</td>
<td>5.9 ± 4.6</td>
<td>0.013</td>
</tr>
<tr>
<td>Preprocedural hospitalization</td>
<td>9 (60)</td>
<td>17 (16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preprocedural variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB (ng/mL)</td>
<td>3.5 ± 1.2</td>
<td>3.9 ± 1.3</td>
<td>0.35</td>
</tr>
<tr>
<td>cTnT (ng/mL)</td>
<td>0.05 ± 0.03</td>
<td>0.04 ± 0.03</td>
<td>0.017</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>7.4 ± 0.9</td>
<td>7.9 ± 1.1</td>
<td>0.13</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>64.9 ± 26.0</td>
<td>68.1 ± 24.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Betablocker use</td>
<td>8 (53)</td>
<td>58 (56)</td>
<td>1</td>
</tr>
<tr>
<td>Impaired systolic LVF</td>
<td>6 (40)</td>
<td>22 (21)</td>
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</tr>
<tr>
<td>LVMI, g/m²</td>
<td>181.5 ± 45.6</td>
<td>147.5 ± 44.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>0.42 ± 0.08</td>
<td>0.41 ± 0.12</td>
<td>0.54</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>78 ± 27</td>
<td>76 ± 22</td>
<td>0.73</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>47 ± 18</td>
<td>49 ± 16</td>
<td>0.61</td>
</tr>
<tr>
<td>MR grade ≥ 3</td>
<td>2 (13)</td>
<td>8 (8)</td>
<td>0.61</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>45 ± 9</td>
<td>41 ± 12</td>
<td>0.33</td>
</tr>
<tr>
<td>Procedural data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative anesthesia</td>
<td>7 (47)</td>
<td>50 (48)</td>
<td>1</td>
</tr>
<tr>
<td>Large prosthesis size</td>
<td>3 (20)</td>
<td>33 (32)</td>
<td>0.55</td>
</tr>
<tr>
<td>Prosthesis depth, mm</td>
<td>8.4 ± 3.1</td>
<td>6.8 ± 3.1</td>
<td>0.091</td>
</tr>
<tr>
<td>Contrast amount, mL</td>
<td>167 ± 88</td>
<td>145 ± 53</td>
<td>0.53</td>
</tr>
<tr>
<td>Procedural duration, min</td>
<td>83 ± 32</td>
<td>80 ± 22</td>
<td>0.78</td>
</tr>
<tr>
<td>Postprocedural variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB max (ng/mL)</td>
<td>30.1 ± 27.7</td>
<td>13.9 ± 12.2</td>
<td>0.11</td>
</tr>
<tr>
<td>cTnT max (ng/mL)</td>
<td>0.59 ± 0.44</td>
<td>0.24 ± 0.25</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial injury</td>
<td>7 (47)</td>
<td>13 (13)</td>
<td>0.004</td>
</tr>
<tr>
<td>RBCT</td>
<td>5 (33)</td>
<td>24 (23)</td>
<td>0.52</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>4 (27)</td>
<td>12 (12)</td>
<td>0.12</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>1.07 ± 0.19</td>
<td>1.09 ± 0.28</td>
<td>0.93</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>19 ± 6</td>
<td>20 ± 7</td>
<td>0.51</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>10 ± 4</td>
<td>12 ± 5</td>
<td>0.20</td>
</tr>
<tr>
<td>AR grade ≥ 3</td>
<td>3 (20)</td>
<td>4 (4)</td>
<td>0.042</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>46 ± 10</td>
<td>45 ± 11</td>
<td>0.72</td>
</tr>
<tr>
<td>Postprocedural outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New PM</td>
<td>3 / 8</td>
<td>18 / 96</td>
<td>0.20</td>
</tr>
<tr>
<td>New LBBB</td>
<td>5 / 9</td>
<td>44 / 80</td>
<td>1</td>
</tr>
<tr>
<td>30-day cardiac events</td>
<td>10 (67)</td>
<td>6 (6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD.
Discussion

The present study is the first to describe the clinical value of measuring biochemical markers of myocardial injury after transcatheter aortic valve implantation with the Medtronic-CoreValve device. Serum levels of creatine kinase-MB and cardiac troponin T increase after TAVI, which reflects the procedure-related myocardial injury. Myocardial injury appears to be independently predicted by a longer procedural duration, the absence of beta-blocker use, the presence of peripheral arterial disease and a deeper prosthesis insertion. Periprocedural myocardial injury is revealed as an independent predictor of 30-day mortality after TAVI, together with preprocedural hospitalization and left ventricular mass.

Following TAVI, both CK-MB and cTnT levels increased in all patients, reaching an average peak level of 3 times the upper reference limit. These mean postprocedural cardiac marker levels are comparable with those reported after TAVI (with transfemoral and transapical approach) with the Edwards SAPIEN (Edwards Lifesciences Inc., Irvine, California) device. The values of postprocedural markers are remarkably low compared with those found after surgical valve replacement and CABG, and higher compared with those following PCI. The absence of aortic cross-clamping and cardioplegia in combination with less direct myocardial trauma could explain the relatively lower biomarker levels after TAVI compared with cardiac surgery. Importantly, no periprocedural myocardial infarction occurred, since none of our patients showed new Q-waves or new regional wall motion abnormalities. The higher levels of biomarkers in the TAVI patients compared with PCI could be explained by the presence of more particle embolization into the coronary circulation,
Myocardial injury during transcatheter aortic valve implantation

In order to investigate the etiology of myocardial injury during TAVI, multivariate logistic regression analysis was performed, which showed that a longer procedural duration, the absence of beta-blocker use, the presence of peripheral arterial disease and a deeper prosthesis implantation were independent predictors for myocardial injury. Periprocedural myocardial damage during TAVI is probably for a large part attributed to global myocardial ischemia, as a result of a myocardial oxygen demand-supply mismatch. Especially hypertrophied left ventricles are susceptible for subendocardial myocardial damage, due to the reduced myocardial capillary density and high intracavitary pressures, even in the absence of obstructive coronary artery disease. During TAVI, reduced myocardial oxygen supply may result from temporary aortic valve occlusion during balloon valvuloplasty and from hypotension by rapid ventricular pacing, bradycardia due to cardiac conduction disorders and theoretically distal embolization into the coronary (micro)circulation. Patient coronary arteries were verified with aortic angiography in all patients after prosthesis deployment, which excludes (partial) coronary obstruction as cause of myocardial injury. Increased myocardial oxygen demand during TAVI may result from an acute increase in aortic regurgitation (causing increased wall stress due to increased end-diastolic pressures), exposure to intravenous inotropics, and tachycardia. A longer procedural duration is associated with a longer exposure to the aforementioned factors that result in myocardial oxygen demand-supply mismatch, which explains why procedural duration is a strong predictor for myocardial injury. Alternatively, a longer procedural duration could be a reflection of the complexity and susceptibility of the treated patient.

Reduction of myocardial oxygen consumption may account for less myocardial injury during TAVI in patients pretreated with a beta-blocker, as shown in our study. This is in line with studies which have demonstrated the cardioprotective effect of beta-blockers during PCI. Our finding of a deeper prosthesis implantation as an independent predictor, may be explained by direct injury of the left ventricular outflow tract by the deployed metal frame of the Medtronic-CoreValve device. Accordingly, we previously reported that a deeper insertion of the Medtronic-CoreValve prosthesis was associated with a higher incidence of new left bundle branch block, and injury of the perivalvular myocardium may in part be the cause of the injured conduction system. Furthermore, oversizing of the balloon-expandable Edwards prosthesis with respect to the aortic annulus, was found to be associated with more myocardial injury in a previous study. Myocardial stretching by both a self-expandable or a balloon-expandable valve prosthesis probably results in direct myocardial trauma.

direct myocardial trauma and especially the presence of concentric left ventricular hypertrophy in most of the patients treated with TAVI.

Our study showed that a longer procedural duration, the absence of beta-blocker use, the presence of peripheral arterial disease and a deeper prosthesis implantation were independent predictors for myocardial injury. Periprocedural myocardial damage during TAVI is probably for a large part attributed to global myocardial ischemia, as a result of a myocardial oxygen demand-supply mismatch. Especially hypertrophied left ventricles are susceptible for subendocardial myocardial damage, due to the reduced myocardial capillary density and high intracavitary pressures, even in the absence of obstructive coronary artery disease. During TAVI, reduced myocardial oxygen supply may result from temporary aortic valve occlusion during balloon valvuloplasty and from hypotension by rapid ventricular pacing, bradycardia due to cardiac conduction disorders and theoretically distal embolization into the coronary (micro)circulation. Patient coronary arteries were verified with aortic angiography in all patients after prosthesis deployment, which excludes (partial) coronary obstruction as cause of myocardial injury. Increased myocardial oxygen demand during TAVI may result from an acute increase in aortic regurgitation (causing increased wall stress due to increased end-diastolic pressures), exposure to intravenous inotropics, and tachycardia. A longer procedural duration is associated with a longer exposure to the aforementioned factors that result in myocardial oxygen demand-supply mismatch, which explains why procedural duration is a strong predictor for myocardial injury. Alternatively, a longer procedural duration could be a reflection of the complexity and susceptibility of the treated patient.

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and a rise in cardiac enzyme levels. Finally, peripheral arterial disease was identified as an independent predictor of myocardial injury. Patients with peripheral arterial disease may have a higher susceptibility to incur myocardial injury, since they have a higher extent of coronary artery disease (as expressed in significantly more prior myocardial infarction and coronary revascularization) and since they have a more complex TAVI procedure, leading to a longer procedural duration.

The present study shows that myocardial injury is strongly associated with mortality within 30 days after TAVI. This finding corresponds with many previous reports, showing that peak levels of cardiac troponins and CK-MB are strong predictors for in-hospital mortality and other major adverse events, following percutaneous coronary intervention, coronary bypass and heart valve surgery. Myocardial injury was also found as an independent predictor for one-year cumulative mortality. This is in line with an earlier report, which found that the degree in rise of cTnT was an independent predictor of cardiac mortality after TAVI. However, as can be seen in the Kaplan-Meier survival curves in figure 3, the effect of myocardial injury on one-year cumulative mortality is rather a reflection of its large impact on 30-day mortality. Preprocedural hospitalization was a strong predictor for 30-day mortality and cumulative one-year mortality after TAVI in our study. Most of the patients in our study who were preprocedurally hospitalized for at least one week, were admitted because of decompensated aortic valve stenosis. These patients consequently had a much poorer functional status than patients who were admitted only one day before the procedure. In line with a previous report, we show that TAVI patients with a poorer preprocedural clinical and functional status have an increased risk of post-procedural mortality.

An increased left ventricular mass index was identified in our study as an independent predictor for 30-day mortality and cumulative one-year mortality after TAVI, an expected finding in line with surgical aortic valve replacement. The underlying mechanisms which can explain the relationship between myocardial injury and 30-day mortality after TAVI remain unclear. The extent of myocardial injury during TAVI is relatively small and diffuse and is not shown to impair myocardial function or cause ventricular arrhythmias leading to sudden cardiac death.

It is therefore more likely that the amount of myocardial injury is a reflection of more extensive disease (for example these patients have more peripheral arterial disease) that makes a patient susceptible for postprocedural cardiovascular morbidity and mortality. Specifically in these susceptible patients, optimization of the aforementioned predictive factors may improve their clinical outcome, such as beta-blocker treatment (if tolerated by the patient with severe aortic stenosis), shorten-
ing of procedural duration and prevention of a deep prosthesis insertion. This study is limited by the relatively small number of events, which may have resulted in model overfitting in multivariable analysis. Furthermore the results were obtained from a prospective observational study, such that the effect of other unmeasured or unknown confounding factors on myocardial injury and mortality cannot be ruled out. The amount of myocardial injury was measured with post-procedural cardiac enzyme levels, which did not manifest in new Q-waves or new wall motion abnormalities. Cardiac MRI could be a helpful imaging modality to determine the presence, localization and amount of myocardial injury following TAVI.

**Conclusion**

The present study shows that periprocedural myocardial injury occurs in all patients after transcatheter aortic valve implantation, albeit very limited compared with surgical aortic valve replacement. The occurrence of myocardial injury is associated with a longer procedural duration, the absence of beta-blocker use, peripheral arterial disease and a deeper prosthesis insertion. Together with preprocedural hospitalization and left ventricular mass, myocardial injury is shown to be prognostic for 30-day mortality following TAVI. Certain preventive measures could reduce the amount of myocardial injury and subsequently improve clinical outcome following TAVI.
References


Devereux RB, Alonso DR, Lutas EM, Gottlieb GI, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-458.
Chapter 3.2


Chapter 3.3
Predictors and clinical relevance of acute kidney injury following transcatheter aortic valve implantation

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Esther M.A. Wiegerinck
Kirsten Boerlage-van Dijk
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Submitted
ABSTRACT

Background  During transcatheter aortic valve implantation (TAVI), episodes of hypotension, contrast administration and embolization of debris may result in acute kidney injury (AKI). Following cardiac surgery, AKI is known to be strongly associated with short- and long-term mortality. Therefore, our purpose was to investigate the incidence, predictors and prognostic relevance of AKI in TAVI.

Methods  We studied 195 patients (age 80±8 years, 86 male), 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). Clinical data were collected from the medical history, laboratory analysis and echocardiography. Acute kidney injury was defined as a decrease in estimated glomerular filtration rate compared with baseline of ≥25% within 5 days after TAVI.

Results  Following TAVI the incidence of AKI was 23%, which was independently predicted by loop diuretic use ≥2 units (OR: 3.80; 95% CI: 1.52-9.47), post-implantation diastolic arterial blood pressure (per mmHg, OR: 0.95; 95% CI: 0.91-0.99), maximum leukocyte count (per 10^9/L, OR: 1.12; 95% CI: 1.02-1.23) and chronic obstructive pulmonary disease (OR: 2.37; 95% CI: 1.00-5.65). Acute kidney injury was found to be a strong independent predictor for both in-hospital mortality (incidence: 13%; OR: 9.71; 95% CI: 3.18-29.65), and 1 year cumulative mortality (incidence: 24%; HR: 2.97; 95% CI: 1.45-6.07).

Conclusion  The incidence of acute kidney injury following transcatheter aortic valve implantation is 23%. Cardio-renal syndrome and severe inflammatory response syndrome are potential mechanisms for AKI. In-hospital and mid-term mortality following TAVI is strongly associated with AKI.
Introduction

A substantial number of patients with severe symptomatic aortic valve stenosis is not referred or is rejected for surgical aortic valve replacement (SAVR), due to their high age and other comorbidities, which increase their risk of peri- and postoperative mortality and morbidity. Transcatheter aortic valve implantation (TAVI) has in the last few years emerged as a good alternative treatment of these patients with a high surgical risk. Special care should be given to the prevention of acute kidney failure following this procedure, since renal dysfunction is frequent in this patient population. Acute kidney injury (AKI) and the need for temporary hemodialysis is a frequent complication following cardiac surgery with a reported incidence of 3 to 25% depending on the different definitions used. The incidence of AKI after TAVI is reported to be less compared with that following SAVR. However, irrespective of its occurrence in the setting of SAVR, other cardiac surgery or TAVI, AKI is shown to be associated with a higher incidence of in-hospital and long-term mortality.

Possible mechanisms of AKI during TAVI are exposure to periods of hypotension (rapid ventricular pacing, balloon valvuloplasty and valve deployment), nephrotoxicity of contrast, calcium/cholesterol embolizations due to catheter and wire manipulation in the often calcified aorta, and inflammatory response. Two factors have been reported to be predictors for AKI in TAVI in at least two studies: periprocedural red blood cell transfusions and postprocedural systemic inflammatory response syndrome. However other predictors were found in one study, which other studies failed to identify, such as chronic obstructive pulmonary disease, logistic EuroSCORE, previous myocardial infarction and hypertension. Therefore our aim was to examine the predictors in our single-centre patient population and to compare them with those reported by previous studies. Secondly our purpose was to determine the short- and mid-term prognostic value of AKI following TAVI.

Methods

Patients and transcatheter valve procedure

In a single-centre prospective observational study between October 2007 and June 2012, we included 195 consecutive patients who were treated with either transfemoral (n=129) or transapical (n=66) aortic valve implantation for their severe symptomatic aortic valve stenosis. All patients had a high surgical risk or were rejected for conventional aortic valve replacement, as determined by our heart team, consisting of an interventional cardiologist, a cardio-thoracic surgeon and a cardio-anaesthesiologist. All patients treated in our transcatheter heart valve program...
have been entered in a prospectively designed protocol and dedicated database. Patients with terminal renal failure requiring chronic hemodialysis (n=4) and patients who died within 24 hours following TAVI (n=6) were not included in our study. All patients received N-acetylcysteine before and after TAVI and patients with a preprocedural estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m$^2$ were pre- and post-hydrated with intravenous NaCl 0.9% or bicarbonate, according to our hospital protocol to prevent contrast-induced nephropathy.

The technique of transcatheter aortic valve implantations has been described in detail in previous studies.$^{21,22}$ Access to the aortic valve was obtained either through the transfemoral artery or through the apex of the heart using a mini-thoracotomy. For the transfemoral approach the Medtronic-CoreValve self-expandable valve prosthesis (CoreValve Inc, Irvine, CA, USA) was used and for the transapical approach the balloon-expandable Edwards SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA, USA). All transapical valve implantations were performed under general anesthesia and the transfemoral valve implantations either under general (n=61) or local anesthesia (n=68). The duration of the procedure, the amount of contrast use and the arterial blood pressure were recorded during the procedure.

**Renal function assessment and acute kidney injury**

Serum creatinine levels were measured in all patients the day before TAVI and daily in the first five days after the procedure. The eGFR was calculated using the simplified modification of diet in renal disease (MDRD) formula. Acute kidney injury was defined as a decrease in eGFR of >25% within the 5 postprocedural days, in accord with the RIFLE (risk, injury, failure, loss and end-stage kidney disease) criteria and/or the need of hemodialysis during the index hospitalization.$^{23}$ Data on urinary output were not complete and therefore not included in our definition of AKI.

**Evaluation of other parameters**

General patient data were collected from the medical history. As part of routine patient care, blood samples were collected the day before TAVI and daily up to at least 5 days after the procedure. Laboratory analysis of these blood samples included serum creatinine and whole blood hemoglobin level, platelet and leukocyte count. Transthoracic echocardiography was performed within three months before TAVI and within a week postprocedurally, using the GE Vivid 7 machine (GE Healthcare, Horten, Norway). Aortic (prosthetic) valve hemodynamics were assessed before and after TAVI and included aortic valve effective orifice area (EOA), peak and mean aortic valve pressure gradient (AVPG), and (paravalvular) aortic regurgitation (AR) grade. Other echocardiographical parameters assessed before
and after TAVI were: global left ventricular (LV) systolic function, LV internal and wall dimensions, mitral regurgitation grade and pulmonary artery pressure. Left ventricular mass (LVM) was calculated using the corrected formula from Devereux and colleagues.\textsuperscript{24} Clinical follow-up until hospital discharge was available of every patient. In-hospital mortality was defined as death irrespective of cause during index hospitalization. The VARC-combined safety endpoint is defined as the occurrence of either one of the following events up to 30 days postprocedure: all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury stage 3, periprocedural MI, and repeat procedure for valve-related dysfunction (surgical or interventional therapy).\textsuperscript{25} The date and cause of death occurring within 1 year follow-up after TAVI were established.

**Statistical methods**

Categorical variables are expressed as number and percentages and compared between groups with a Fisher Exact test. Continuous variables are presented as mean and standard deviation. Differences of a continuous variable between two groups were analyzed with a two-tailed Student’s t-test or Mann-Whitney U test, where appropriate. The Wilcoxon signed rank test was used for within group comparison of biomarker levels between different time points. A stepwise logistic regression analysis including all variables with P-value < 0.2 in the univariable analysis was used to determine the predictive factors of both AKI and in-hospital mortality. Cumulative survival plots of patients with and without AKI were estimated using the Kaplan-Meier method. The log-rank test was used to compare the difference in survival between both groups of patients. To identify predictors of death within 1 year after TAVI, a Cox proportional hazard model was applied. Results are reported as adjusted hazard ratio (HR) with 95% confidence interval (CI). P-values <0.05 were considered to be significant. Statistical analysis was performed using GraphPadPrism version 5.00 and the statistical software SPSS 17.0 for windows (SPSS Inc., Chicago, IL).

**Results**

Baseline patient characteristics and procedural and post-procedural data are shown in table 1. The incidence of acute kidney injury following TAVI was 23\% (44 patients). The other changes in eGFR after TAVI are shown in figure 1.
Table 1: Pre-, peri- and post-operative parameters of patients (n=195)

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Total (n = 195)</th>
<th>AKI (n = 44)</th>
<th>No AKI (n = 151)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>80.1 ± 7.6</td>
<td>81.0 ± 7.1</td>
<td>79.9 ± 7.7</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>27.5 ± 5.4</td>
<td>27.8 ± 5.6</td>
<td>27.5 ± 5.3</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>86 (44)</td>
<td>21 (48)</td>
<td>65 (43)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>95 (49)</td>
<td>24 (55)</td>
<td>71 (47)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>52 (27)</td>
<td>12 (27)</td>
<td>40 (26)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>35 (18)</td>
<td>4 (9)</td>
<td>31 (21)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Prior myocardial infarction</strong></td>
<td>47 (24)</td>
<td>10 (23)</td>
<td>37 (25)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Previous PCI</strong></td>
<td>63 (32)</td>
<td>13 (30)</td>
<td>50 (33)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>39 (20)</td>
<td>5 (11)</td>
<td>34 (23)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>65 (33)</td>
<td>20 (45)</td>
<td>45 (30)</td>
<td>0.069</td>
</tr>
<tr>
<td><strong>Peripheral arterial disease</strong></td>
<td>63 (32)</td>
<td>14 (32)</td>
<td>49 (32)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>44 (23)</td>
<td>14 (32)</td>
<td>30 (20)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Logistic EuroSCORE</strong></td>
<td>19.2 ± 12.5</td>
<td>20.2 ± 14.1</td>
<td>18.8 ± 12.0</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>STS score</strong></td>
<td>6 ± 4.2</td>
<td>6.7 ± 4.1</td>
<td>5.8 ± 4.3</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Preprocedural hospitalization</strong></td>
<td>37 (19)</td>
<td>12 (27)</td>
<td>25 (17)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Preprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eGFR, mL/min/1.73m²</strong></td>
<td>70 ± 23.9</td>
<td>66.3 ± 26.9</td>
<td>71.0 ± 23.0</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Hemoglobin, mmol/L</strong></td>
<td>7.9 ± 1</td>
<td>7.7 ± 1.2</td>
<td>7.9 ± 1.0</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Oral antidiabetic use</strong></td>
<td>35 (18)</td>
<td>5 (11)</td>
<td>30 (20)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Loop diuretics ≥ 2 units</strong></td>
<td>38 (19)</td>
<td>16 (36)</td>
<td>22 (15)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>LVEF ≤ 40%</strong></td>
<td>37 (19)</td>
<td>8 (18)</td>
<td>29 (19)</td>
<td>1</td>
</tr>
<tr>
<td><strong>LVMI, g/m²</strong></td>
<td>148.6 ± 42.2</td>
<td>162.6 ± 41.9</td>
<td>144.6 ± 41.6</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Indexed EOA, cm²/m²</strong></td>
<td>0.42 ± 0.11</td>
<td>0.41 ± 0.11</td>
<td>0.42 ± 0.12</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>AVPG max, mmHg</strong></td>
<td>74 ± 22</td>
<td>77 ± 24</td>
<td>72 ± 21</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>AVPG mean, mmHg</strong></td>
<td>47 ± 15</td>
<td>49 ± 17</td>
<td>47 ± 14</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>MR grade ≥ 3</strong></td>
<td>17 (9)</td>
<td>7 (16)</td>
<td>10 (7)</td>
<td>0.069</td>
</tr>
<tr>
<td><strong>PAP, mmHg</strong></td>
<td>41 ± 11</td>
<td>41 ± 10</td>
<td>40 ± 12</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Contrast CT / CAG ≤ 5 days</strong></td>
<td>13 (7)</td>
<td>3 (7)</td>
<td>10 (7)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transapical approach</strong></td>
<td>66 (34)</td>
<td>14 (32)</td>
<td>52 (34)</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Local anesthesia</strong></td>
<td>68 (35)</td>
<td>9 (20)</td>
<td>59 (39)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Contrast amount, mL</strong></td>
<td>139 ± 64</td>
<td>138 ± 70</td>
<td>140 ± 63</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Procedural duration, min</strong></td>
<td>90 ± 31</td>
<td>88 ± 32</td>
<td>90 ± 31</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Post systolic ABP, mmHg</strong></td>
<td>125 ± 27</td>
<td>116 ± 25</td>
<td>128 ± 27</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Post diastolic ABP, mmHg</strong></td>
<td>52 ± 13</td>
<td>47 ± 11</td>
<td>53 ± 13</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Post mean ABP, mmHg</strong></td>
<td>78 ± 18</td>
<td>71 ± 14</td>
<td>80 ± 18</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Postprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Min eGFR, mL/min/1.73m²</strong></td>
<td>67.4 ± 31.8</td>
<td>38.1 ± 18.1</td>
<td>75.9 ± 29.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>RCBT</strong></td>
<td>55 (28)</td>
<td>15 (34)</td>
<td>40 (26)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Max leucocyte count 10³/L</strong></td>
<td>12 ± 4.1</td>
<td>13.5 ± 4.6</td>
<td>11.5 ± 3.9</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Indexed EOA, cm²/m²</strong></td>
<td>1.08 ± 0.27</td>
<td>1.12 ± 0.30</td>
<td>1.07 ± 0.27</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>AVPG max, mmHg</strong></td>
<td>21 ± 8</td>
<td>21 ± 8</td>
<td>21 ± 8</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>AVPG mean, mmHg</strong></td>
<td>12 ± 5</td>
<td>12 ± 4</td>
<td>12 ± 5</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>AR grade ≥ 2</strong></td>
<td>49 (25)</td>
<td>14 (32)</td>
<td>35 (23)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>PAP, mmHg</strong></td>
<td>44 ± 11</td>
<td>48 ± 11</td>
<td>42 ± 11</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>New PM</strong></td>
<td>24 / 179</td>
<td>8 / 38</td>
<td>16 / 141</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>New LBBB</strong></td>
<td>62 / 151</td>
<td>18 / 36</td>
<td>44 / 115</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>In hospital RRT</strong></td>
<td>4 (2)</td>
<td>4 (9)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>30-day mortality</strong></td>
<td>19 (10)</td>
<td>12 (27)</td>
<td>7 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>In hospital mortality</strong></td>
<td>25 (13)</td>
<td>15 (34)</td>
<td>10 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>VARC-combined end point</strong></td>
<td>31 (16)</td>
<td>16 (36)</td>
<td>15 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Admission duration (days)</strong></td>
<td>13 ± 10</td>
<td>19 ± 11</td>
<td>11 ± 10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. AKI, acute kidney injury; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; STS, society of thoracic surgeons; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; EOA, effective orifice area; AVPG, aortic valve pressure gradient; MR, mitral regurgitation; PAP, pulmonary artery pressure; CT, computed tomography; CAG, coronary angiography; ABP, arterial blood pressure; RBC, red blood cell transfusion; AR, aortic regurgitation; PM, pacemaker; LBBB, left bundle branch block; RRT, renal replacement therapy; VARC, valve academic research consortium.
Acute kidney injury following transcatheter aortic valve implantation

The patient cohort was dichotomized according to the presence or absence of AKI. In univariable analysis, AKI was associated with more loop diuretic use, a higher left ventricular mass, less local anesthesia, a lower post-implantation systolic, diastolic and mean arterial blood pressure (ABP), a higher maximum postprocedural leukocyte count and a higher postprocedural pulmonary artery pressure. Independent predictors for AKI (shown in table 2) were identified using multivariable logistic regression analysis and included: loop diuretic use ≥ 2 units (OR: 3.80; 95% CI: 1.52-9.47), post-implantation diastolic ABP (per mmHg, OR: 0.95; 95% CI: 0.91-0.99), maximum leukocyte count (per 10⁹/L, OR: 1.12; 95% CI: 1.02-1.23) and chronic obstructive pulmonary disease (COPD) (OR: 2.37; 95% CI: 1.00-5.65). The individual effects of these factors on change in serum creatinine levels are shown in figure 2.

Table 2: Independent predictors for acute kidney injury following TAVI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics ≥ 2 units</td>
<td>3.80</td>
<td>1.52 - 9.47</td>
<td>0.004</td>
</tr>
<tr>
<td>Post diastolic ABP, per mmHg</td>
<td>0.95</td>
<td>0.91 - 0.99</td>
<td>0.009</td>
</tr>
<tr>
<td>Max leukocyte count, per 10⁹/L</td>
<td>1.12</td>
<td>1.02 - 1.23</td>
<td>0.022</td>
</tr>
<tr>
<td>COPD</td>
<td>2.37</td>
<td>1.00 - 5.65</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Chapter 3.3

In-hospital all-cause mortality in the total group was 13% (n=25), of which 15 patients (34%) were in the AKI group versus 10 (7%) in the non-AKI group (p<0.001). All deaths occurred between 3 days and 44 days after TAVI (median: 20 days), and included death due to low cardiac output (n=10), pneumonia (n=5), sepsis (n=3), ventricular fibrillation (n=2), COPD (n=1), hemorrhagic shock (n=1), cardiac tamponade (n=1), stroke (n=1) and terminal sedation (n=1). Figure 3 shows a comparison in baseline and post-procedural creatinine levels between survivors and non-survivors during index hospitalization after TAVI.

Figure 2: Comparison of the absolute change in serum creatinine levels (mean ± SEM) between two patient groups based on their loop diuretic (LD) use, post-implantation diastolic (diast.) arterial blood pressure (ABP), postprocedural maximum leucocyte count and chronic obstructive pulmonary disease (COPD). * p<0.05.

Figure 3: Comparison of pre- and postprocedural serum creatinine levels (mean ± SEM) between patients who were alive at discharge (survivors, n=170) and who patients who died during index hospitalization (non-survivors, n=25) following TAVI.
In table 3 the patient cohort was dichotomized according to the presence or absence of in-hospital mortality. Compared with patients who were alive after index hospitalization, the patients who died during index admission had a significantly higher age, lower body mass index (BMI), more COPD, a higher logistic EuroSCORE and STS risk score, had a higher frequency of preprocedural hospitalization, a lower left ventricular ejection fraction (LVEF), a higher left ventricular mass index (LVMI), more mitral regurgitation, a lower forced expiratory volume in 1 second and a higher incidence of acute kidney injury.

Table 3: Pre-, peri- and post-operative parameters of patients (n=195)

<table>
<thead>
<tr>
<th></th>
<th>Non-survivors (n = 25)</th>
<th>Survivors (n = 170)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>82.8 ± 6.3</td>
<td>79.7 ± 7.7</td>
<td>0.045</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.0 ± 4.3</td>
<td>27.9 ± 5.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Male gender</td>
<td>13 (52)</td>
<td>73 (43)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (56)</td>
<td>81 (48)</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (28)</td>
<td>45 (26)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4 (16)</td>
<td>31 (18)</td>
<td>1</td>
</tr>
<tr>
<td>Prior myocardinal infarction</td>
<td>8 (32)</td>
<td>39 (23)</td>
<td>0.32</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>11 (44)</td>
<td>52 (31)</td>
<td>0.25</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (16)</td>
<td>35 (21)</td>
<td>0.79</td>
</tr>
<tr>
<td>COPD</td>
<td>13 (52)</td>
<td>52 (31)</td>
<td>0.042</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>9 (36)</td>
<td>54 (32)</td>
<td>0.65</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9 (36)</td>
<td>35 (21)</td>
<td>0.12</td>
</tr>
<tr>
<td>Logistic EuroSCORE</td>
<td>27.2 ± 16.6</td>
<td>18.0 ± 11.4</td>
<td>0.003</td>
</tr>
<tr>
<td>STS score</td>
<td>9.0 ± 6.0</td>
<td>5.5 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preprocedural hospitalization</td>
<td>11 (44)</td>
<td>26 (15)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Preprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>65.7 ± 29.9</td>
<td>70.6 ± 23.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>7.5 ± 1.0</td>
<td>7.9 ± 1.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Oral antidiabetic use</td>
<td>4 (16)</td>
<td>31 (18)</td>
<td>1</td>
</tr>
<tr>
<td>Loop diuretics ≥ 2 units</td>
<td>9 (36)</td>
<td>29 (17)</td>
<td>0.054</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>16 (64)</td>
<td>142 (84)</td>
<td>0.029</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>173.1 ± 36.1</td>
<td>145.3 ± 42.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>0.43 ± 0.10</td>
<td>0.42 ± 0.12</td>
<td>0.51</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>75 ± 28</td>
<td>73 ± 21</td>
<td>0.85</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>46 ± 18</td>
<td>47 ± 14</td>
<td>0.51</td>
</tr>
<tr>
<td>MR grade ≥ 3</td>
<td>6 (24)</td>
<td>11 (6)</td>
<td>0.011</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>40 ± 10</td>
<td>41 ± 12</td>
<td>0.72</td>
</tr>
<tr>
<td>FEV₁, L/min</td>
<td>1.53 ± 0.63</td>
<td>1.77 ± 0.60</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transapical approach</td>
<td>8 (32)</td>
<td>58 (34)</td>
<td>1</td>
</tr>
<tr>
<td>Local anesthesia</td>
<td>7 (28)</td>
<td>61 (36)</td>
<td>0.51</td>
</tr>
<tr>
<td>Contrast amount, mL</td>
<td>158 ± 102</td>
<td>136 ± 56</td>
<td>0.81</td>
</tr>
<tr>
<td>Procedural duration, min</td>
<td>97 ± 39</td>
<td>89 ± 30</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Postprocedural variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>15 (60)</td>
<td>29 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>1.07 ± 0.19</td>
<td>1.09 ± 0.28</td>
<td>0.87</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>21 ± 7</td>
<td>21 ± 8</td>
<td>0.98</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>11 ± 4</td>
<td>12 ± 5</td>
<td>0.38</td>
</tr>
<tr>
<td>AR grade ≥ 3</td>
<td>10 (40)</td>
<td>39 (23)</td>
<td>0.085</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>47 ± 9</td>
<td>43 ± 11</td>
<td>0.23</td>
</tr>
<tr>
<td>New PM</td>
<td>5 / 20</td>
<td>19 / 159</td>
<td>0.15</td>
</tr>
<tr>
<td>New LBBB</td>
<td>9 / 19</td>
<td>53 / 132</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. FEV₁, forced expiratory volume in 1 second.
Independent predictors for in-hospital mortality are shown in Table 4 and included: AKI (OR: 9.71, 95% CI 3.18-29.65), BMI (per kg/m\(^2\), OR: 0.84, 95% CI 0.74-0.95), pre-procedural hospitalization (OR: 3.89, 95% CI 1.17-12.90) and LVMI (per g/m\(^2\), OR: 1.01, 95% CI 1.00-1.03).

### Table 4: Independent predictors for in-hospital mortality after TAVI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>9.71</td>
<td>3.18 - 29.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, per kg/m(^2)</td>
<td>0.84</td>
<td>0.74 - 0.95</td>
<td>0.006</td>
</tr>
<tr>
<td>Preprocedural hospitalization</td>
<td>3.89</td>
<td>1.17 - 12.90</td>
<td>0.026</td>
</tr>
<tr>
<td>LVMI, per g/m(^2)</td>
<td>1.01</td>
<td>1.00 - 1.03</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Follow-up was available of all patients with a median follow-up time (interquartile range) of 17.0 (6.0-25.9) months. The cumulative 1 year mortality after TAVI was 24% (n=46), of which 22 (50%) were in the AKI group and 24 (16%) in the non-AKI group (p<0.001). Causes of death within 1 year were: low cardiac output (n=18), pneumonia (n=6), COPD (n=5), sepsis (n=4), ventricular fibrillation (n=2), hemorrhagic shock (n=2), stroke (n=2), sudden cardiac arrest (n=2), metastatic cancer (n=2), terminal sedation (n=1), cardiac tamponade (n=1), and pulmonary embolism (n=1).

The Kaplan-Meier survival analysis shows a statistically significant difference in survival between the patients with AKI and those without AKI (p<0.0001 by log-rank test) as shown in Figure 4. Multivariable analysis of 1 year cumulative survival after TAVI (Table 5) revealed that AKI was an independent predictor for mid-term mortality (HR: 2.97, 95% CI 1.45-6.07), together with postprocedural aortic regurgitation grade ≥ 2 (HR: 2.41, 95% CI 1.15-5.05) and left ventricular mass index (per g/m\(^2\), HR: 1.01, 95% CI 1.01-1.02).

---

**Figure 4:** One-year survival after TAVI according to the occurrence of postprocedural acute kidney injury.
Table 5: Multivariate Cox regression analysis of association between clinical parameters and 1-year mortality after TAVI

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>2.97 (1.45 - 6.07)</td>
<td>0.003</td>
</tr>
<tr>
<td>Postprocedural AR grade ≥ 2</td>
<td>2.41 (1.15 - 5.05)</td>
<td>0.02</td>
</tr>
<tr>
<td>LVMI, per g/m²</td>
<td>1.01 (1.00 - 1.02)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Discussion

The present single-centre prospective study shows that acute kidney injury occurs in 23% of the patients who had undergone a TAVI. More periprocedural use of loop diuretics, a lower post-implantation mean arterial blood pressure, a higher postprocedural leukocyte count and COPD are identified as independent predictors of AKI after TAVI. Together with a lower body mass index, preprocedural hospitalization and left ventricular mass index, AKI is shown to be an independent predictor for in-hospital mortality. Also for mid-term cumulative mortality, AKI is identified as a strong independent predictor.

The clinical importance of preprocedural renal function disorders and postprocedural acute kidney deterioration in the setting of invasive procedures has been highlighted in many previous studies. The incidence of AKI in our study is comparable with the reported incidences of 12-28% following TAVI. The variability in incidence reported in those studies could be explained by the different criteria used for defining acute kidney injury, and perhaps also by the differences in patient characteristics and in contrast amount used during the procedures. In contrast with other studies, we chose to define AKI as a renal function deterioration within 5 days instead of within 2-3 days. This definition is also used in previous studies of PCI and cardiac surgery patients. Furthermore, the increase in creatinine after contrast exposure is known to reach its peak at 3 to 5 days after the procedure.

Several factors have been identified as independent predictors of AKI in our study. A strong independent predictor for AKI after TAVI found in our study was the periprocedural use of 2 or more units of loop diuretics. Similarly, continuous infusion of furosemide during cardiac surgery has been reported to result in a higher incidence of postoperative acute renal failure compared with infusion of saline or dopamine. A straightforward explanation is that loop diuretics cause hypovolemia and subsequently a decrease in renal perfusion. Alternatively, loop diuretics have been shown to activate the sympathetic and renin-angiotensin systems, which
can result in an increase in left ventricular afterload and a decrease in cardiac output.\textsuperscript{32} Furthermore, when a loop diuretic is administered prior to the procedure, it can exacerbate the nephrotoxic effect of contrast exposure by diverting the medullary blood flow to the cortical circulation.\textsuperscript{33} Our finding that patients treated with more loop diuretics are at a higher risk for postprocedural kidney deterioration, suggests that periprocedural administration of loop diuretics should be avoided, as much and as reasonably possible.

Our study showed that a lower diastolic arterial blood pressure directly after valve implantation was associated with acute kidney injury. The low ABP during TAVI is probably a result of both procedure- and patient-related factors. Temporary periprocedural hypotension during TAVI is created by balloon valvuloplasty, rapid pacing, valve deployment and by vasodilatation due to exposure to certain anesthetics. A low ABP can also be caused by the hemodynamic instability as a result of an impaired cardio-circulatory homeostasis due to an impaired left ventricular function and/or significant aortic regurgitation. When renal parenchyma is exposed to a reduced perfusion and oxygen tension, it results in tubular epithelial and vascular endothelial injury.\textsuperscript{34, 35} Close monitoring of arterial blood pressure during the TAVI procedure and where possible prevention and treatment of sudden drops in blood pressures is of paramount importance to maintain adequate renal perfusion and to prevent AKI.

The maximum leukocyte count measured post-procedurally was related to AKI in our study. This relationship was also found in previous studies, in which an increase in both leukocyte count and C-reactive protein were attributed to a systemic inflammatory response syndrome (SIRS).\textsuperscript{18-20} Comparable with cardiac surgery,\textsuperscript{15} certain pro-inflammatory events during TAVI can cause SIRS, notably direct tissue trauma by manipulation with a wire or valve prosthesis, ischemia-reperfusion (myocardial) injury and contact of blood components with an artificial surface. Inflammation is thought to play an important role in the pathophysiology of ischemic kidney injury, which explains the association between SIRS and AKI.\textsuperscript{34, 35} Patients with chronic obstructive pulmonary disease are shown to have a twofold higher risk to develop AKI after TAVI compared with patients without COPD. Previous studies have reported COPD as independent predictor for AKI in patients undergoing cardiac surgery\textsuperscript{12, 36} or TAVI.\textsuperscript{12} Decreased renal perfusion and periprocedural episodes of severe hypoxemia-hypercapnia are proposed mechanisms of renal function deterioration in patients with COPD undergoing TAVI.\textsuperscript{37, 38}

In correspondence with previous reports, our study did not show a relation between the amount of peri-procedural contrast use during TAVI and the occurrence of AKI following the procedure.\textsuperscript{10, 18, 19} This is explained by the fact that a relatively low amount of contrast was used during our TAVI procedures, especially in patients with pre-existing renal dysfunction. This is supported by the fact that in our
study, patients with an eGFR of ≤60 mL/min/1.73m² received significantly less contrast compared with patients with an eGFR of >60 mL/min/1.73m² (123±63 vs. 148±64 cc, p=0.002).

In contrast with three previous reports, our study did not find any relationship between periprocedural (<24 hours post TAVI) red blood cell transfusion and the occurrence of postprocedural AKI. With a mean of 0.7 units per patient, the amount of periprocedural RBCT in our study is much less compared with that reported in earlier studies. This can explain why RBCT was of little impact on kidney injury in our patient population.

Our in-hospital mortality was 13% and 30-day mortality 10%, which is comparable with those reported in other TAVI studies. The strong relationship we found between AKI and in-hospital mortality can be partly attributed to the comorbidities of the AKI group, such as a higher age, more COPD, a higher STS risk score and a lower baseline eGFR, making these patients more susceptible for poor outcome. However, like in previous studies, we show that AKI predicts in-hospital mortality, independently from these factors, which means that there is a somewhat direct causality between kidney failure and mortality. Since a low post-implantation diastolic arterial blood pressure was found to be predictive for AKI, a poor peri- and postprocedural cardio-circulatory performance probably plays an important role in the development of acute kidney failure. Therefore, a plausible explanation for AKI being predictive for mortality after TAVI may be that it forms a part of the development of a cardio-renal syndrome, in which neurohumoral activation (renin-angiotensin and sympathetic system) leads to a vicious circle of renal and cardiac failure, finally resulting in the death of the patient. Like in two previous studies, AKI was found to be also an independent predictor for cumulative one-year mortality in our study. However, this rather reflects the large impact of AKI on early (in-hospital) mortality than a true mid-term risk of mortality.

In addition to AKI, left ventricular mass index and lower body mass index were identified as important predictive factors for in-hospital mortality and in case of LVMI and significant postprocedural aortic regurgitation, also for one-year mortality after TAVI. Previous studies have shown a similar association between low BMI and adverse outcome after cardiac surgery. Left ventricular hypertrophy is a known predictor of poor short- and long-term outcome in patients who had undergone surgical aortic valve replacement. Significant paravalvular aortic regurgitation has been identified as predictor for in-hospital mortality after TAVI in an earlier report. We demonstrate that it also has an important impact on survival on the longer term.

Like reported previously, we have found that the development of AKI after TAVI is determined by a multiple of factors, which are not all modifiable. However, some preventive measures could decrease the risk of postprocedural AKI,
such as periprocedural intravenous hydration, reduction of the amount of periprocedural contrast exposure and avoidance of diuretic administration. Close monitoring of periprocedural arterial blood pressure and adequate treatment of a sudden decline in blood pressure are clinically relevant. In patients with COPD, careful monitoring and optimization of periprocedural oxygen saturation could be important to reduce renal function deterioration. Prospective or randomized studies in the future are needed to investigate whether certain periprocedural preventive measures will have impact on the occurrence of acute kidney failure, or even more importantly on the occurrence of short- and mid-term mortality following TAVI. This study is limited by the relatively small sample size and small amount of events, which may have resulted in model overfitting in multivariable analysis. Furthermore the results were obtained from a prospective observational study, such that the effect of other unmeasured or unknown confounding factors on AKI and mortality cannot be ruled out.

Conclusion

This single-center prospective observational study identified more loop diuretic use, a low post-implantation arterial blood pressure, a higher postprocedural leucocyte count and COPD to be predictive for acute kidney injury following transcatheter aortic valve implantation. The occurrence of acute kidney injury following TAVI is of great clinical importance since it is an independent predictor for both short- and mid-term mortality. Pre- and periprocedural preventive measures may have an impact on the occurrence of AKI and subsequently on the outcome after TAVI.

Acknowledgments

We would like to thank the nurses of our catheterization laboratory for their skilled assistance during the TAVI procedures and their meticulous registration and collection of the periprocedural data. Also, we would like to thank the nurses and physicians of the cardiology and cardio-thoracic surgery ward and the cardiac and intensive care unit for their important contribution to the data collection.
References


Chapter 3.4

Predictors and clinical outcome of significant paravalvular aortic regurgitation following transcatheter aortic valve implantation

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Submitted
ABSTRACT

Background Although transcatheter aortic valve implantation (TAVI) has emerged as a good alternative treatment option for high surgical risk patients with severe aortic valve stenosis, significant paravalvular aortic regurgitation (PAR) remains a frequent complication. Therefore our aim was to investigate the determinants and short- and mid-term clinical consequences of PAR.

Methods We studied 140 patients (mean age 81±8 years, 54 male) who underwent a TAVI with the Medtronic-CoreValve bioprosthesis. Clinical parameters were obtained from the medical history, laboratory analysis, echocardiography, cardiac computed tomography and angiography. Clinical outcome was assessed up to 12 months after TAVI.

Results Following TAVI, PAR grade ≥2 occurred in 41 patients (29%). Multivariate analysis identified sinus width (per mm, OR: 1.34, 95%CI: 1.13-1.59, p=0.001) as only independent predictor for PAR≥2. Both thirty-day mortality (20% vs. 7%; p<0.039) and 1 year cumulative mortality (Hazard ratio (HR): 2.11, 95%CI: 1.01-4.40) were significantly higher in the PAR≥2 group versus the PAR<2 group. Cardiac mortality at 1 month (15% vs. 0%; p<0.001) and 1 year (HR: 5.25, 95%CI: 1.68-16.39) were significantly higher in the PAR≥2 group versus the PAR<2 group.

Conclusions Significant paravalvular aortic regurgitation occurs in 29% of patients treated with transcatheter aortic valve implantation using the Medtronic-CoreValve device. A wider diameter of the sinus of Valsalva was strongly associated with a higher risk for significant PAR. Significant PAR is associated with all-cause mortality, mainly determined by cardiac death. In comparison with non-significant PAR, significant PAR does not result in a worse functional class at follow-up.
Introduction

In the last few years, transcatheter aortic valve implantation (TAVI) has emerged as a successful alternative treatment option for patients with severe degenerative aortic valve stenosis, who are considered not suitable for conventional aortic valve surgery, due to their high surgical risk.\textsuperscript{1-4} Although the procedural success and marked short- and midterm hemodynamic and clinical improvements have been demonstrated in most of the patients treated with TAVI, paravalvular aortic regurgitation (PAR) remains a frequent complication, with a reported incidence of 40-77\% of mild and 8-34\% of at least moderate regurgitation.\textsuperscript{2-13} Paravalvular aortic regurgitation is caused by incomplete attachment and alignment of the valve prosthesis to the aortic annulus and may result from non-circular stent deployment, a large annulus relative to the prosthesis (undersizing), severe calcifications of the native aortic valve captured between the device and the annular wall, or a combination of these factors.\textsuperscript{7;8;11;14} A recent study reported that the angle and depth of the Medtronic-CoreValve prosthesis implantation determined significant PAR.\textsuperscript{12} Significant PAR after TAVI is thought to be tolerated well by the majority of the patients, and is therefore usually accepted. However, the short- and mid-term clinical consequences of significant PAR following TAVI have been scarcely described.\textsuperscript{5;11} Therefore the purposes of our study were: (1) to investigate the occurrence of significant PAR following TAVI, (2) to identify possible determinants of significant PAR and (3) to evaluate the short- and mid-term clinical effects of PAR.

Methods

Patients and transcatheter valve procedure

In a single-center prospective observational study, 140 consecutive patients were recruited between October 2007 and March 2012, who underwent successful transcatheter aortic valve implantation with the Medtronic-CoreValve\textsuperscript{®} bioprosthesis (Corevalve Inc, Irvine, CA) via the transfemoral approach. Patients who died during (n=1) or within 24 hours after the procedure (n=2) were excluded, since no adequate postprocedural echocardiography could be performed. All patients who were selected for TAVI had symptomatic severe degenerative aortic valve stenosis (aortic valve area < 1.0 cm\textsuperscript{2}), aortic valve annuli of 20-27 mm, a suitable femoral access and were rejected or had a high risk for conventional aortic valve surgery. Patients with annuli of 20-24 mm received a small (26 mm) prosthesis and patients with annuli of 24-27 mm a large (29 mm) prosthesis. Other clinical and anatomical criteria for our selection of patients for TAVI were in accord with the investigational study of the third generation 18F CoreValve device.\textsuperscript{1;15} All patients treated in our transcatheter valve program have been entered in a prospectively designed
protocol and dedicated database. Implantation of the third generation 18 F CoreValve aortic valve bioprosthesis was performed in the catheterization laboratory under general (n=62) or local anesthesia (n=78). The procedural technique of TAVI with the Medtronic-CoreValve bioprosthesis has been described previously. In all patients, the device was implanted via the retrograde transfemoral approach.

Echocardiographic assessments
Preprocedural and postprocedural transthoracic echocardiography was performed in all patients as routine patient care using the GE Vivid 7 machine (GE Healthcare, Horten, Norway) equipped with 2.5-3.5 MHz transducers with M-mode, two-dimensional, pulsed, continuous, and color-flow Doppler capabilities. In the apical-5 chamber view or occasionally the suprasternal notch or right parasternal views, mean and maximal instantaneous aortic pressure gradients were calculated from velocities measured in the left ventricular outflow tract and the aorta using the modified Bernoulli equation. The aortic valve area was calculated by the continuity equation. The diameter of the left ventricular outflow tract was measured from the parasternal long-axis view. Cross-sectional, two-dimensionally guided M-mode recordings were performed to assess left ventricular dimensions in the parasternal long axis view, including LV end-diastolic internal diameter (LVEDd), LV end-diastolic interventricular septal thickness (IVSd) and LV end-diastolic posterior wall thickness (PWd). Left ventricular mass (LVM) was calculated using the corrected formula from Devereux and colleagues. Pre- and postprocedural (paravalvular) aortic regurgitation severity were evaluated semi-quantitatively using an integrative approach of Doppler parameters consisting of jet deceleration rate (i.e. pressure half time), jet width or jet area in the left ventricular outflow tract, diastolic flow reversal in the descending aorta and also where appropriate aortic valve regurgitant volumes and fractions, according to the criteria of the American Society of Echocardiography. Severity of aortic regurgitation was graded as: none (grade 0), trivial or mild (grade 1), moderate (grade 2), moderate-severe (grade 3) and severe (grade 4). Other echocardiographic parameters, included pulmonary artery pressure and mitral valve regurgitation. The presence of postprocedural significant paravalvular aortic regurgitation was defined as at least grade 2 aortic regurgitation of paravalvular origin, as assessed by transthoracic echocardiography 3 to 7 days after TAVI.

Multi-detector row computed tomographic assessment
In 87 patients, a 64 slice multi-detector CT scanner (Brilliance 64, Philips Medical Systems, Netherlands) was used prior to the procedure to obtain cardiac images, as
part of the screening for TAVI suitability. Scanning was performed with a dedicated protocol: 120 kV, average 500 mA, a detector collimation of 0.625 mm and a gantry rotation speed of 420 ms.

Analysis of scans was performed on a dedicated workstation (Philips Extended Brilliance Workspace) by consensus of 2 observers. The double oblique transverse (DOT) cuts through the aortic root and valve were obtained by correct orientation of the reconstructed single oblique sagittal and coronal projections of the aortic valve, as described before. This axial view allows the assessment of aortic valve morphology as well as the extent and location of calcifications. The aortic annulus (base of the native valve leaflets) diameters were measured in the oblique sagittal plane (smallest diameter) and in the oblique coronal plane (largest diameter). The mean annulus diameter was calculated by dividing the sum of the sagittal and coronal diameters by two. The eccentricity index was calculated as 1-(sagittal diameter/coronal diameter). The closer to 0, the more circular the annulus is. An ellipsoid-shaped aortic annulus was considered when the eccentricity index was >0.1. Aortic root dimensions included diameters of the sino-tubular junction (smallest, largest and average diameter) and sinus of Valsalva (sagittal, coronal and mean diameter). The “cover index” represents the degree of congruence between the aortic annulus and the device and is expressed as a ratio of: 100 × ([prosthesis diameter - CT annulus diameter]/prosthesis diameter). Aortic valve calcification was assessed in the transverse views and calculated as the total valvular Agatston score with a detection threshold of 500 Hounsfield units (contrast enhanced images), as described previously.

**Angiographic assessment of aortic root anatomy and device position**

Aortic root angiography in the 50° left anterior oblique (LAO) view and 30° right anterior oblique (RAO) view was performed in all patients within 1 month prior to the TAVI procedure, as part of the routine work-up for TAVI. The angle between the LVOT and ascending aorta axes (\(\angle LVOT-Ao\)) was measured in the RAO 30° view as described previously. At the end of the TAVI procedure, post-deployment device position was assessed with a final aortic root angiography in the RAO projection with the inflow part of the metal frame aligned as much as possible in one plane. Prosthesis depth was defined as the distance between the native aortic valve annulus and the deepest (most proximal) edge of the stent-frame. An optimal prosthesis depth was defined as between 5 and 10 mm below the annular margin, as previously described.

**Clinical follow-up and other parameters**

Follow-up of the patients after TAVI took place as part of the routine patient care. Data were collected at the follow-up time points of 1 month, 6 and 12 months,
and included NYHA class, serum NT-proBNP concentrations and echocardiographic parameters. Cardiac mortality was defined as death as a direct result of a cardiac problem, such as low cardiac output (requiring medical or mechanical left ventricular support), myocardial infarction, sudden cardiac arrest or ventricular fibrillation. The VARC-combined safety endpoint is defined as the occurrence of either one of the following events up to 30 days postprocedure: all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury stage 3, periprocedural MI, and repeat procedure for valve-related dysfunction (surgical or interventional therapy). Mortality within one year following TAVI was recorded, as well as the cause and date of death.

Statistical analysis

Continuous variables are presented as mean and standard deviation or as median and interquartile range (IQR: 25-75%), where appropriate. Differences of a continuous variable between two independent groups were analyzed with a two-tailed Student’s t-test or Mann-Whitney U test, where appropriate. Categorical variables are expressed as number and percentages and were compared between two independent groups using the Fisher exact test. A stepwise logistic regression analysis including all variables with P-value < 0.1 in the univariable analysis was used to determine the predictive factors of grade 2 or more PAR.

To compare the change in aortic regurgitation grade or NYHA class within 1 group between different time points, the Wilcoxon signed rank test was used. The log-rank test was used to assess differences in survival between the group with PAR less than grade 2 and the group with PAR grade 2 or more. Statistical significance was defined as P<0.05. Statistical analysis was performed using GraphPadPrism version 5.00 and the statistical software SPSS 17.0 for windows (SPSS Inc., Chicago, IL).

Results

Patients

Baseline characteristics of the 140 patients who underwent TAVI are shown in table 1. The mean age was 81±8 years and 54 (39%) of the patients were male. All patients had a severe aortic valve stenosis with a mean indexed aortic valve area of 0.41±0.12 cm²/m² and a peak aortic pressure gradient of 75±23 mmHg. All patients were denied conventional open heart surgery by the heart team due to an unacceptable surgical risk: mean logistic EuroSCORE: 18.7±12.6 and mean STS score: 6.0±3.7. Thirty-nine patients (28%) received a 29-mm (large) prosthesis, and 101 patients a 26-mm (small) prosthesis. Four patients needed postdilatation of the valve prosthesis performed during the index procedure, because of significant
paravalvular aortic regurgitation discovered directly after prosthesis implantation by transoesophageal echocardiography. The final aortic regurgitation grades after postdilatation in these patients were 1, 2, 2 and 3, respectively. The 30-day all cause mortality was 15 (11%), with 6 cardiac deaths (low cardiac output) and 9 non-cardiac deaths (stroke and infectious or pulmonary causes).

### Table 1. Pre-, peri- and postprocedural data of patients (n=140)

<table>
<thead>
<tr>
<th>Patient data</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>80.8 ± 7.7</td>
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<tr>
<td>BMI, kg/m²</td>
<td>27.7 ± 5.4</td>
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<tr>
<td>BSA, m²</td>
<td>1.85 ± 0.19</td>
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<td>Male gender</td>
<td>54 (39)</td>
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<table>
<thead>
<tr>
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<th></th>
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</thead>
<tbody>
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<td>71 (51)</td>
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<tr>
<td>Diabetes Mellitus</td>
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</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>30 (21)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>48 (34)</td>
</tr>
<tr>
<td>CABG</td>
<td>17 (12)</td>
</tr>
<tr>
<td>COPD</td>
<td>46 (33)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>42 (30)</td>
</tr>
<tr>
<td>NYHA class ≥ 3</td>
<td>97 (69)</td>
</tr>
<tr>
<td>Logistic EuroSCORE</td>
<td>18.7 ± 12.6</td>
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<tr>
<td>STS score</td>
<td>6.0 ± 3.7</td>
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<td>Indexed EOA, cm²/m²</td>
<td>0.41 ± 0.12</td>
</tr>
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<td>AVPG max, mmHg</td>
<td>75 ± 23</td>
</tr>
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<td>AVPG mean, mmHg</td>
<td>49 ± 16</td>
</tr>
<tr>
<td>LVOT diameter, mm</td>
<td>21 ± 2</td>
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<tr>
<td>Annulus diameter, mm</td>
<td>23.7 ± 2.5</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>33 (24)</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>151.0 ± 44.0</td>
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<tr>
<td>AR grade ≥ 2</td>
<td>27 (19)</td>
</tr>
<tr>
<td>MR grade ≥ 3</td>
<td>12 (9)</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>42 ± 12</td>
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</table>

<table>
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<th>Procedural data</th>
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<tbody>
<tr>
<td>Sedative anesthesia</td>
<td>78 (56)</td>
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<tr>
<td>29 mm prosthesis</td>
<td>39 (28)</td>
</tr>
<tr>
<td>Balloon diameter, mm</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>Postdilatation</td>
<td>4 (3)</td>
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<tr>
<td>Procedural duration, min</td>
<td>85 ± 30</td>
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<table>
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<th>Postprocedural variables</th>
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<tbody>
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<td>Indexed EOA, cm²/m²</td>
<td>1.08 ± 0.27</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>20 ± 8</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>12 ± 5</td>
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<tr>
<td>AR grade ≥ 2</td>
<td>41 (29)</td>
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<tr>
<td>30-day mortality</td>
<td>15 (11)</td>
</tr>
<tr>
<td>VARC combined endpoint</td>
<td>23 (16)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. BMI, body mass index; BSA, body surface area; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; STS, society of thoracic surgeons; EOA, effective orifice area; AVPG, aortic valve pressure gradient; LVOT, left ventricular outflow tract; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; AR, aortic regurgitation; MR, mitral regurgitation; PAP, pulmonary artery pressure; VARC, valve academic research consortium.
Figure 1: Change in aortic regurgitation grade following transcatheter aortic valve implantation up to 1 year follow-up. * P-value for difference in AR grade with previous time point. † P-value < 0.05 for difference in AR grade with baseline.

Predictors for significant postprocedural aortic regurgitation

The patient cohort was divided according to their presence or absence of PAR≥2 as determined by postprocedural echocardiography. Comparison of pre- and periprocedural characteristics of the two PAR groups are shown in table 2. Compared with the PAR<2 group, the PAR≥2 group had a higher percentage of male patients, a higher left ventricular mass index, more preprocedural AR grade ≥2, a larger LVOT-Ao, a larger sino-tubular junction diameter, a wider sinus of Valsalva, a larger annulus diameter, a lower cover index, and a deeper prosthesis insertion. Multivariate analysis was used for the 87 patients from whom CT parameters were available. The only independent predictor identified for PAR≥2 was sinus width (per mm, OR: 1.34, 95% CI: 1.13-1.59, p=0.001).

Short-term clinical follow-up

Clinical outcome at 30 days after TAVI is shown in table 3. The patient group with PAR≥2 had a significantly higher all-cause (20% vs. 7%, p=0.039) and cardiac (15% vs. 0%, p<0.001) mortality rate compared with patients with PAR<2. No statistically significant differences were found between both groups in stroke, acute kidney injury, VARC combined endpoint and new cardiac conduction disturbances within 30 days.
## Table 2: Pre-, peri- and post-operative parameters compared between two groups based on postprocedural AR grade (n=140)

<table>
<thead>
<tr>
<th></th>
<th>PAR grade &lt; 2</th>
<th>PAR grade ≥ 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>80.4 ± 7.6</td>
<td>81.7 ± 7.7</td>
<td>0.21</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.85 ± 0.19</td>
<td>1.85 ± 0.21</td>
<td>0.62</td>
</tr>
<tr>
<td>Male gender</td>
<td>30 (30)</td>
<td>24 (59)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>51 (52)</td>
<td>20 (49)</td>
<td>0.85</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>12 (12)</td>
<td>6 (15)</td>
<td>0.78</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>21 (21)</td>
<td>9 (22)</td>
<td>1</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>36 (36)</td>
<td>12 (29)</td>
<td>0.44</td>
</tr>
<tr>
<td>CABG</td>
<td>10 (10)</td>
<td>7 (17)</td>
<td>0.27</td>
</tr>
<tr>
<td>COPD</td>
<td>32 (32)</td>
<td>14 (34)</td>
<td>0.85</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>15 (15)</td>
<td>12 (29)</td>
<td>0.063</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>31 (31)</td>
<td>11 (27)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Preprocedural data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>25 (25)</td>
<td>8 (20)</td>
<td>0.52</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>144.5 ± 41.5</td>
<td>166.7 ± 46.5</td>
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<td>LVOT diameter, mm</td>
<td>21.1 ± 1.5</td>
<td>21.4 ± 1.9</td>
<td>0.33</td>
</tr>
<tr>
<td>Indexed EOA, cm²/m²</td>
<td>0.41 ± 0.11</td>
<td>0.41 ± 0.13</td>
<td>0.64</td>
</tr>
<tr>
<td>AVPG max, mmHg</td>
<td>74 ± 22</td>
<td>79 ± 24</td>
<td>0.39</td>
</tr>
<tr>
<td>AVPG mean, mmHg</td>
<td>47 ± 15</td>
<td>53 ± 18</td>
<td>0.16</td>
</tr>
<tr>
<td>AR grade ≥ 2</td>
<td>14 (14)</td>
<td>13 (32)</td>
<td>0.032</td>
</tr>
<tr>
<td>MR grade ≥ 3</td>
<td>10 (10)</td>
<td>2 (5)</td>
<td>0.51</td>
</tr>
<tr>
<td>∠ LVOT-Ao, °</td>
<td>14.9 ± 5.9</td>
<td>17.3 ± 6.1</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Preprocedural CT data</strong></td>
<td>(n=60)</td>
<td>(n=27)</td>
<td></td>
</tr>
<tr>
<td>STJ diameter, mm</td>
<td>27.3 ± 2.5</td>
<td>29.9 ± 3.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Sinus width, mm</td>
<td>30.7 ± 2.7</td>
<td>33.9 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Annulus diameter, mm</td>
<td>23.2 ± 2.2</td>
<td>24.8 ± 2.9</td>
<td>0.014</td>
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<tr>
<td>Agatston score, HU</td>
<td>1164 ± 588</td>
<td>1841 ± 1250</td>
<td>0.057</td>
</tr>
<tr>
<td>Annulus eccentricity index</td>
<td>0.26 ± 0.07</td>
<td>0.24 ± 0.08</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 mm prosthesis</td>
<td>23 (23)</td>
<td>16 (39)</td>
<td>0.065</td>
</tr>
<tr>
<td>Cover index, %</td>
<td>13.1 ± 7.4</td>
<td>8.7 ± 8.2</td>
<td>0.010</td>
</tr>
<tr>
<td>Balloon diameter, mm</td>
<td>21 ± 2</td>
<td>22 ± 3</td>
<td>0.069</td>
</tr>
<tr>
<td>Prosthesis depth, mm</td>
<td>6.6 ± 3.3</td>
<td>7.6 ± 2.9</td>
<td>0.044</td>
</tr>
<tr>
<td>Optimal prosthesis depth</td>
<td>49 (49)</td>
<td>17 (41)</td>
<td>0.46</td>
</tr>
<tr>
<td>Postdilatation</td>
<td>1 (1)</td>
<td>3 (7)</td>
<td>0.075</td>
</tr>
<tr>
<td>Procedural duration, min</td>
<td>84 ± 31</td>
<td>87 ± 28</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. PAR, paravalvular aortic regurgitation; ∠ LVOT-Ao, angle between LVOT and ascending aorta axes; STJ, sinotubular junction; HU, Hounsfield Units.
Table 3: 30-day outcome following TAVI

<table>
<thead>
<tr>
<th>Event</th>
<th>PAR grade &lt; 2 (n = 99)</th>
<th>PAR grade ≥ 2 (n = 41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>7 (7)</td>
<td>8 (20)</td>
<td>0.039</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>0 (0)</td>
<td>6 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (7)</td>
<td>3 (7)</td>
<td>1</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>19 (19)</td>
<td>12 (29)</td>
<td>0.26</td>
</tr>
<tr>
<td>VARC combined endpoint</td>
<td>13 (13)</td>
<td>10 (24)</td>
<td>0.13</td>
</tr>
<tr>
<td>Total AV Block requiring new PPM</td>
<td>17 / 88</td>
<td>5 / 35</td>
<td>0.61</td>
</tr>
<tr>
<td>New LBBB</td>
<td>36 / 75</td>
<td>19 / 29</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Values are n (%). VARC, Valve Academic Research Consortium; AV, atrioventricular; PPM, permanent pacemaker; LBBB, left bundle branch block.

Data were collected from all patients (n=125) who were alive and who had reached 1 month follow-up. In the PAR≥2 group (n=33), loop diuretic dosage was higher (2(1-2) vs. 1(0-1); p=0.019), while NT-proBNP level, pulmonary artery pressure and indexed left ventricular end-diastolic dimension were not significantly different compared with the PAR<2 group (table 4). In both the PAR<2 and the PAR≥2 group, NYHA class was improved significantly at 1 month compared with baseline (figure 2), and was not significantly different between both groups.

**Mid-term clinical follow-up**

Clinical data at mid-term compared between the PAR<2 and PAR≥2 group are shown in table 4. There were no significant differences in cumulative all-cause mortality between the PAR groups at 6 months and 1 year follow-up. Cumulative cardiac mortality was significantly different at 1 year: 7 vs. 24%, p=0.013. In the patients who had reached 6 months and 1 year follow-up respectively, no significant differences were present in NYHA class, loop diuretic dosage, pulmonary artery pressure and left ventricular end-diastolic dimensions between the PAR<2 group and PAR≥2 group. At 6 months follow-up, NT-proBNP levels were significantly higher in the PAR≥2 group (1912(879-3276) vs. 838(413-1566) ng/mL; p=0.037) compared with the PAR<2 group, but no statistically significant difference was found at 12 months. In both PAR groups, NYHA class remained stable after 1 month (figure 2).

Survival from all-cause mortality following TAVI up to 1 year follow-up is shown in figure 3, and was statistically significantly lower in the PAR≥2 group compared with the PAR<2 group (log-rank test: p=0.47, Hazard ratio (HR): 2.11, 95%CI: 1.01-4.40). Survival from cardiac death up to 1 year is shown in figure 4 and was significantly higher in the PAR<2 group compared with the PAR≥2 group (log-rank test: p=0.004, HR: 5.25, 95%CI: 1.68-16.39).
Table 4: Pre-, peri- and post-operative parameters compared between two groups based on postoperative AR grade (n=140)

<table>
<thead>
<tr>
<th></th>
<th>PAR grade &lt; 2</th>
<th>PAR grade ≥ 2</th>
<th>P-value</th>
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<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<tr>
<td>NYHA class</td>
<td>n = 99</td>
<td>n = 41</td>
<td></td>
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<tr>
<td>Loop diuretic dosage, units*</td>
<td>3 (2-3)</td>
<td>3 (2-3)</td>
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<tr>
<td>NT-proBNP, ng/mL</td>
<td>2054 (807-4753)</td>
<td>3075 (1560-5274)</td>
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</tr>
<tr>
<td>PAP, mmHg</td>
<td>43 ± 13</td>
<td>39 ± 11</td>
<td>0.24</td>
</tr>
<tr>
<td>LVEDDI, mm/m²</td>
<td>28.4 ± 4.1</td>
<td>30.0 ± 3.4</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>1 month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative mortality</td>
<td>n=92</td>
<td>n=33</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>7 (7)</td>
<td>8 (20)</td>
<td>0.039</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>0 (0)</td>
<td>6 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>7 (7)</td>
<td>2 (5)</td>
<td>0.8</td>
</tr>
<tr>
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<td>2 (2-3)</td>
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<tr>
<td>NT-proBNP, ng/mL</td>
<td>1020 (585-1721)</td>
<td>1079 (832-3922)</td>
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<tr>
<td>PAP, mmHg</td>
<td>43 ± 10</td>
<td>50 ± 14</td>
<td>0.16</td>
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<tr>
<td>LVEDDI, mm/m²</td>
<td>27.7 ± 2.7</td>
<td>27.8 ± 4.3</td>
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<tr>
<td><strong>6 months</strong></td>
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<tr>
<td>Cumulative mortality</td>
<td>n=80</td>
<td>n=30</td>
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<tr>
<td>Cardiac</td>
<td>16 (17)</td>
<td>10 (25)</td>
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<tr>
<td>Non-cardiac</td>
<td>5 (5)</td>
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<td>0.08</td>
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<tr>
<td>NYHA class</td>
<td>11 (11)</td>
<td>4 (10)</td>
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<td>Loop diuretic dosage, units*</td>
<td>2 (1-2)</td>
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<tr>
<td>NT-proBNP, ng/mL</td>
<td>838 (413-1566)</td>
<td>1912 (879-3276)</td>
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<tr>
<td>PAP, mmHg</td>
<td>39 ± 10</td>
<td>47 ± 18</td>
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<tr>
<td>LVEDDI, mm/m²</td>
<td>27.1 ± 3.0</td>
<td>26.5 ± 3.7</td>
<td>0.86</td>
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<tr>
<td><strong>1 year</strong></td>
<td></td>
<td></td>
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<tr>
<td>Cumulative mortality</td>
<td>n=67</td>
<td>n=22</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>20 (23)</td>
<td>15 (41)</td>
<td>0.053</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>6 (7)</td>
<td>9 (24)</td>
<td>0.013</td>
</tr>
<tr>
<td>NYHA class</td>
<td>14 (16)</td>
<td>6 (16)</td>
<td>0.6</td>
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<td>Loop diuretic dosage, units*</td>
<td>2 (1-2)</td>
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<td>NT-proBNP, ng/mL</td>
<td>970 (469-2056)</td>
<td>1787 (536-2665)</td>
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<tr>
<td>PAP, mmHg</td>
<td>39 ± 11</td>
<td>47 ± 15</td>
<td>0.18</td>
</tr>
<tr>
<td>LVEDDI, mm/m²</td>
<td>27.6 ± 2.5</td>
<td>27.4 ± 2.9</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Values are n (%), mean ± SD (range) or median (25,75% interquartile range). *One unit of loop diuretics is the equivalent of 40 mg furosemide or 1 mg bumetanide. PAR, paravalvular aortic regurgitation; NYHA, New York Heart Association; NT-proBNP, N-terminal pro brain natriuretic peptide; PAP, pulmonary artery pressure; LVEDDI, left ventricular end-diastolic dimension indexed for body surface area.
**Figure 2:** New York Heart Association functional status at baseline, 1 month, 6 months and 1 year following TAVI and compared between patients with and without grade 2 or more paravalvular aortic regurgitation. * P-value of difference in NYHA class at one time point between PAR groups. † P-value < 0.05 for difference in NYHA class with previous time point.

**Figure 3:** One-year survival from all-cause death after TAVI according to the occurrence of grade 2 or more paravalvular aortic regurgitation.
Discussion

The present study shows that the incidence of grade 2 or more paravalvular aortic regurgitation following transcatheter aortic valve implantation with the Medtronic-CoreValve device is 29%. The only independent predictor for significant paravalvular regurgitation was a wider sinus of Valsalva. Significant paravalvular leakage was associated with short- and mid-term all-cause mortality, predominantly determined by cardiac death due to low cardiac output syndrome. At short- and mid-term follow-up, NYHA class, diuretics need, pulmonary artery pressure and NT-proBNP levels are in essence not influenced by significant PAR. The 29% incidence of significant (at least grade 2) paravalvular aortic regurgitation after TAVI is comparable with what has been reported by other studies.\textsuperscript{6,8,11,12} The different methods applied for the grading of PAR and the two different valves used for TAVI, can account for the large variability in incidence of significant PAR reported in the different studies.\textsuperscript{2,13} The amount of PAR remains stable at follow-up in our study, with no significant changes at 1, 6 and 12 months follow-up, a finding that also has been reported in previous studies regarding TAVI with the Medtronic-CoreValve and the Edwards SAPIEN prosthesis.\textsuperscript{4,11}
Factors determining significant PAR

In transcatheter aortic valve implantation non-uniform compression of the native aortic valve against the annular wall, and ridges of calcifications in the aortic wall may hinder adequate circular stent deployment, leaving paraprosthetic spaces causing paravalvular leakage.\textsuperscript{11}

The role of mismatch between prosthesis and annulus size as cause of paravalvular regurgitation has been suggested in previous reports.\textsuperscript{8} A relatively large annulus to prosthesis size results in undersizing and incomplete coverage of the prosthetic frame against the annular wall. In our study, annular size and cover index were indeed found as a significant predictor for significant PAR in univariate analysis. However, of the different aortic valve and root diameters assessed by cardiac CT, only sinus width was identified as an independent predictor for significant PAR in multivariable analysis. A wider sinus of Valsalva probably contributes more to incomplete stent coverage of the CoreValve device and to the subsequent development of paraprosthetic spaces than a larger annular dimension.

In line with one previous report,\textsuperscript{12} we found a higher $\angle$LVOT-Ao to be associated with significant PAR following TAVI with a Medtronic-CoreValve bioprosthesis. The lower part of the ascending aorta represents the contact surface with the upper part of the prosthesis and the LVOT the landing zone of the prosthesis. A higher $\angle$LVOT-Ao will probably influence the radial force of the self-expandable prosthesis which together with a more angled insertion of the prosthesis in the landing zone can lead to incomplete sealing of the gap between the prosthesis and the annular wall.\textsuperscript{12}

Clinical impact of significant PAR

Significant paravalvular regurgitation after TAVI is often considered benign, despite the lack of solid scientific evidence and the fact that it also obviously contradicts the surgical experience.\textsuperscript{22} A recent study indeed reports a strong association between significant PAR and in-hospital mortality following TAVI.\textsuperscript{12} Our study also shows a significant effect of PAR on all-cause cumulative mortality at 30 days and 12 months after TAVI. It also shows that this higher mortality is predominantly the result of cardiac mortality, mostly caused by low cardiac output. This finding suggests that moderate or more aortic regurgitation after TAVI can lead to heart failure in this group of patients, who often have non-compliant hypertrophic left ventricles. Significant PAR after TAVI, which is known to impose a high workload on the left ventricle,\textsuperscript{23} may especially not be tolerated by patients with a reduced systolic left ventricular function.\textsuperscript{5} This is further supported by our finding that the patients with PAR$\geq$2 who died within 1 year due to low cardiac output had significantly more LVEF$\leq$40\% than the patients with PAR$\geq$2 who survived (44\% vs. 13\%, $p=0.05$).
Despite the association between significant PAR and low cardiac output syndrome, the majority of the patients with PAR≥2 survives at short- and midterm follow-up after TAVI and has an improvement in NYHA class. Furthermore, except for the loop diuretic dosage at 1 month and the NT-proBNP levels at 6 months follow-up, the patients with PAR≥2 show no significant differences in NYHA functional class, loop diuretic dosage, NT-proBNP levels and pulmonary artery pressures compared with patients with PAR<2 at short- and mid-term follow-up.

**Clinical implications**

Identification, or even better, prevention of significant paravalvular regurgitation following TAVI is of important clinical relevance, since it is shown to increase the risk of cardiac mortality. The risk of grade 2 or more PAR can be estimated prior to TAVI with the Medtronic-CoreValve prosthesis by certain parameters obtained from cardiac imaging. Multi-detector row computed tomography is a useful imaging modality for accurate measurements of annulus and sinus of Valsalva dimensions, which could help to prevent prosthesis-annulus mismatch by choosing the right balloon and prosthesis size. Different studies show that annulus sizes are probably underestimated by echocardiography as compared with cardiac CT, which could result in valve undersizing. Furthermore annular assessment by cardiac CT also show that the annulus is rather oval than round, which also makes two-dimensional assessment by echocardiography less accurate. To reduce the incidence of valve undersizing and paravalvular regurgitation, Medtronic-CoreValve have adjusted their recommendations with regard to valve sizing: for patients with annuli between 20-23 mm a small prosthesis (26 mm) is advised and for patients with annuli between 23-26 mm a large prosthesis (29 mm). Also a larger prosthesis (30 mm) is now available for annuli between 26-29 mm.

The angle between the ascending aorta and LVOT can be simply determined by contrast angiography or cardiac CT. In patients with a too large ∆LVOT-Ao, implantation of an Edwards SAPIEN prosthesis may be a better treatment option since the position of this device is not determined by the anatomy of the ascending aorta. Post-dilatation or valve-in-valve implantation remain important treatment options to be considered in order to reduce significant paravalvular aortic regurgitation following TAVI. Some of patients with PAR≥2 may benefit from a higher dosage of loop diuretics and/or an increase in heart rate by increasing the lower rate limit of a permanent pacemaker.

**Limitations**

No post-procedural cardiac computed tomography was performed to determine whether non-circular deployment of the valve prosthesis was related to the amount of paravalvular aortic regurgitation. Examining the localization and amount of
incomplete prosthesis coverage against the annular wall can further shed light on the mechanisms that result in paraprosthetic leakage. Longer follow-up and a larger patient cohort are required in order to further investigate the clinical course of patients with significant PAR in comparison with that of non-significant PAR.

Conclusion

We report an incidence of grade 2 or more paravalvular aortic regurgitation following transcatheter aortic valve implantation of 29%. A wider sinus of Valsalva measured by cardiac CT is a strong predictor significant PAR. All-cause and cardiac mortality at short- and mid-term follow-up after TAVI are higher in patients with grade 2 or more PAR compared with patients with mild or less PAR. However, compared with non-significant PAR, significant PAR is not associated with a worse outcome of other clinical parameters.
References


Chapter 4
Pressure-volume measurements in percutaneous coronary intervention
&
Other transcatheter valve therapies
Chapter 4.1

Improved long-term LV hemodynamics after primary percutaneous coronary intervention for anterior ST elevation myocardial infarction

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Jan J. Piek
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* These authors contributed equally

Submitted
ABSTRACT

Objectives    We studied long-term left ventricular (LV) hemodynamic changes after successful primary percutaneous coronary intervention (PCI) in patients with anterior ST elevation myocardial infarction (STEMI) by invasively obtained LV pressure-volume (PV) loops.

Background    STEMI causes LV remodeling, which influences LV function. Invasive assessments of these effects by means of PV-loops have not been described before.

Methods      We studied 11 consecutive patients, who presented with their first anterior STEMI within 6 hours after onset of symptoms, and in whom coronary angiography revealed an occluded left anterior descending coronary artery. Continuous PV-loops were obtained three days and four months after primary PCI by a pressure-conductance catheter.

Results     Four months after successful reperfusion, a significant increase was observed in LV end-diastolic volume index (EDVI) from 72 ± 17 to 89 ± 15 mL/m² (p = 0.001), as a result of LV remodeling after STEMI. The increase in EDVI was accompanied by improvement in diastolic LV function, as indicated by an increased end-diastolic compliance with a 3.7 ± 4.9 mm Hg (p = 0.04) downward shift of the compliance curve. End-diastolic elastance decreased from 0.13 ± 0.03 to 0.08 ± 0.03 mm Hg/mL (p = 0.007). Systolic LV function showed an improvement in stroke volume (SV) from 62 ± 20 to 86 ± 25 mL (p = 0.005).

Conclusions    Invasive assessment of LV pressure and volume performed after primary PCI in anterior STEMI patients show signs of LV remodeling, which is however accompanied by improvement in both diastolic and systolic LV function.
Introduction

Primary percutaneous coronary intervention (PCI) is currently the cornerstone treatment modality for early restoration of epicardial coronary blood flow in ST elevation myocardial infarction (STEMI). Early and successful reperfusion of myocardial tissue is crucial for reduction of infarct size which is an important determinant for post-infarction left ventricular (LV) healing and remodeling.1,2 LV remodeling and residual systolic function are important markers of outcome, which have been the focus of research for several decades.3 Several studies showed that LV remodeling, defined as at least 20% increase in LV end-diastolic volume from baseline up to one year, is still frequently observed after STEMI, despite successful coronary reperfusion.4-6 Systolic as well as diastolic LV function after STEMI have shown to be strongly related to LV remodeling and prognosis.3,7-10 However, the LV function parameters assessed in these studies have only been obtained non-invasively by means of echocardiography or cardiac magnetic resonance imaging (MRI).

Recently, we reported immediate improvements in LV function during reperfusion by invasively measured LV hemodynamics obtained directly before and after primary PCI in anterior STEMI patients.11 Invasive assessment of LV hemodynamics is a direct and accurate method to examine changes in LV function that accompany LV remodeling after STEMI.12-14 Therefore, we performed online simultaneous LV pressure and volume measurements in primary PCI patients three days and four months after their STEMI.

Methods

Patients

The study population consisted of 11 consecutive patients (8 males, mean age 58 ± 9 years), who presented with their first anterior STEMI within 6 hours after onset of symptoms. Patients were included when coronary angiography revealed an occluded left anterior descending artery prior to primary PCI (see Table 1). Exclusion criteria were cardiogenic shock, refractory ventricular arrhythmias, congestive heart failure, previous myocardial infarction, significant valvular disease, and left ventricular thrombus. The study complied with the Declaration of Helsinki and was approved by the institutional research and ethics committee. All patients gave written informed consent.

Study protocol

Patients were treated with aspirin, clopidogrel, and heparin before PCI. Heart rate and surface 12-lead ECGs were monitored and aortic pressure was measured via
the guiding catheter. Blood samples for hematology and chemistry including cardiac markers (CKMB, troponin T and NT-proBNP) were drawn. Adequate medical treatment including statins, ACE inhibitors, β-blockers, aspirin and clopidogrel was started as soon as possible after the primary PCI and continued thereafter. Three days (mean, 3 ± 1 days) and four months (mean, 140 ± 16 days) after primary PCI, LV pressure and volume loop assessments were performed in all patients by placing a 7F pigtail equipped combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands). A more extensive description of the instrumentation and LV hemodynamic measurements has been reported previously. Cardiac MRI and transthoracal echocardiography, performed four months after primary PCI, were used to assess LV volumes by non-invasive means.

LV hemodynamic measurements and analysis
LV hemodynamics were recorded continuously and were analyzed off-line. Per-beat averages of the recorded variables were calculated as the mean of all beats during a steady state of at least 12 seconds and covering two respiratory cycles. It was accounted for that selected recording were obtained during stable hemodynamic conditions, without interference of pharmaceuticals (e.g. nitroglycerin). The following indices were obtained: heart rate (HR), cardiac output (CO), ejection fraction (EF), stroke volume (SV), stroke work as the area of the pressure-volume loop (SW), end-systolic volume (ESV) index (ESVI), end-diastolic volume index (EDV, EDVI), end-systolic and end-diastolic pressure (ESP, EDP), and peak positive derivative of LV pressure (dP/dt_max). The relaxation time constant Tau, as an index for the active diastolic LV properties during isovolumetric relaxation, was defined as that time required for the cavity pressure at dP/dt_min to be reduced by half. The end-diastolic elastance (E_{ED}), as the slope on the EDPVR was estimated by EDP/EDV. The change in the passive diastolic LV properties indicated by the shift of the compliance curve, was expressed by the mean pressure value over which the overlapping portion of the PV-loop had moved (P_m), as previously described (see figure 2).

Statistical analysis
Data are expressed as mean ± SD or n (%). The 2-tailed paired t-test was used to compare LV hemodynamic data obtained at the different time points after the PCI. SPSS release 16.0.1 statistical software package for windows (SPSS Inc. 2007, Chicago, Illinois) was used for analyses. A p-value of less than 0.05 was considered statistically significant.
Results

Patient characteristics

The baseline characteristics of all 11 patients are shown in table 1. Coronary angiography revealed a right dominant system in 5 (45%) patients. In 5 (45%) patients the culprit lesion was located in the proximal LAD (segment 6) and in 6 (55%) patients in the mid part of the LAD (segment 7).

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics (n=11)</th>
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<tbody>
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<td>3-vessel disease</td>
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<td>Cardiac markers, peak</td>
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<td>CKMB, μg/L</td>
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<tr>
<td>Troponin T, μg/L</td>
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<td>NT-proBNP, ng/L</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD (range). CAD, coronary artery disease; STEMI, ST elevation myocardial infarction; LAD, left anterior descending; TIMI, Thrombolysis in Myocardial Infarction; CK, Creatine Kinase; NT-proBNP, N-terminal part of the pro-B-type natriuretic peptide.

LV hemodynamics at 4 months compared with 3 days after reperfusion

Changes in LV hemodynamics between 3 days and 4 months post-PCI are shown in table 2.

*Diastolic function.* Pronounced changes were seen in diastolic LV function. There was an increase in EDVI from 72 ± 17 to 89 ± 15 mL/m² (p = 0.001, figure
1A), with only a small but not significant change in EDP (p = 0.1). The end-diastolic elastance decreased from 0.125 ± 0.034 to 0.080 ± 0.025 mmHg/ mL (p = 0.007, figure 1B), while Tau remained unchanged. The intrinsic diastolic LV properties improved, indicated by a downward shift of the compliance curve (figure 2), and quantified by a $P_m$ of 3.7 ± 4.9 mmHg (p = 0.04).

**Systolic function.** Small but non significant increases were seen in ESVI and in EF, (both p = 0.2). Improvement in systolic LV function after 4 months was expressed by an increase in SV from 62 ± 20 to 86 ± 25 mL (p = 0.005, figure 1C) and SW from 6.02 ± 2.66 to 9.67 ± 4.15 mmHg•L (p = 0.009).

| Table 2. Changes in LV dynamics between 3 days and 4 months after primary PCI in 11 acute AMI patients |
|----------------------------------|----------------------------------|-----------------|
|                                | 3 days after reperfusion | 4 months after reperfusion | P-value |
| HR, bpm                         | 81 ± 11                      | 67 ± 15                  | 0.006   |
| Diastolic function              |                               |                            |         |
| EDV, mL                         | 143 ± 35                     | 175 ± 27                 | 0.001   |
| EDVI, mL/m²                     | 72 ± 17                      | 89 ± 15                  | 0.001   |
| EDP, mm Hg                      | 18 ± 6                       | 15 ± 6                   | 0.1     |
| $E_{ED}$, mm Hg/mL              | 0.125 ± 0.034                | 0.080 ± 0.025            | 0.007   |
| Tau, ms                         | 38 ± 5                       | 39 ± 8                   | 0.8     |
| Systolic function               |                               |                            |         |
| ESV, mL                         | 81 ± 23                      | 89 ± 25                  | 0.3     |
| ESVI, mL/m²                     | 41 ± 12                      | 46 ± 14                  | 0.2     |
| EF, %                           | 44 ± 9                       | 49 ± 12                  | 0.2     |
| $dP/dt_{max}$, mm Hg/s          | 1424 ± 320                   | 1459 ± 333               | 0.7     |
| SV, mL                          | 62 ± 20                      | 86 ± 25                  | 0.005   |
| CO, L/min                       | 5.0 ± 1.5                    | 5.7 ± 1.7                | 0.2     |
| SW, mm Hg•L                     | 6.02 ± 2.66                  | 9.67 ± 4.15              | 0.009   |

Values are mean ± SD. HR, heart rate; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EDP, end-diastolic pressure; $E_{ED}$, end-diastolic stiffness; Tau, relaxation time constant; ESV, end-systolic volume; ESVI, end-systolic volume index; EF, ejection fraction; $dP/dt_{max}$, peak positive derivative of LV pressure; SV, stroke volume; CO, cardiac output; SW, stroke work.

**Invasive LV hemodynamics at 4 months compared with non-invasive assessment**

At four months after primary PCI, echocardiography and cardiac MRI were performed in seven patients to assess left ventricular EDVI, ESVI, SV and EF and to compare these parameters with those assessed by invasive PV loops. Table 3 shows the mean values of these LV parameters.
Clinical outcomes at 4 months after reperfusion

All 11 patients had NYHA class II or less at 4 months follow-up after primary PCI. Coronary angiography at 4 months showed TIMI 3 flow of the LAD (infarct-related artery) in all patients. No cardiovascular events or revascularization procedures occurred between 3 days and 4 months post-PCI.

Figure 1. Changes in end-diastolic volume index (EDVI) (A), end-diastolic elastance (E\textsubscript{ED}) (B) and stroke volume (SV) (C) between 3 days and 4 months after successful reperfusion for ST elevation myocardial infarction (STEMI).

Figure 2. Illustration of typical PV-loops of one patient 3 days and 4 months after primary PCI for STEMI. Note the down- and rightward shift after 4 months with a marked increase in LV end-diastolic volume caused by LV remodeling after STEMI. Also, note the increase in stroke volume and downward shift of the LV compliance curve (striped lines).
Table 3. LV dynamics 4 months after primary PCI measured by invasive and non-invasive means in 7 patients

<table>
<thead>
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<th>PV loops</th>
<th>Echocardiography</th>
<th>Cardiac MRI</th>
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<tr>
<td>EDVI, mL/m²</td>
<td>90 ± 18</td>
<td>59 ± 20</td>
<td>115 ± 28</td>
</tr>
<tr>
<td>ESVI, mL/m²</td>
<td>48 ± 14</td>
<td>31 ± 16</td>
<td>69 ± 27</td>
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<tr>
<td>SV, mL</td>
<td>85 ± 28</td>
<td>57 ± 17</td>
<td>96 ± 27</td>
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<tr>
<td>EF, %</td>
<td>47 ± 11</td>
<td>50 ± 10</td>
<td>42 ± 11</td>
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</tbody>
</table>

Values are mean ± SD. LV, left ventricular; PCI, percutaneous coronary intervention; PV, pressure volume; MRI, magnetic resonance imaging; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SV, stroke volume; EF, ejection fraction.

**Discussion**

The present study is the first to describe the improvement in diastolic and systolic LV function by invasively measured LV hemodynamics between 3 days and 4 months follow-up after primary PCI in patients with anterior wall STEMI.

**Improvement in LV hemodynamics**

Recently, we have shown an immediate improvement of the intrinsic passive LV diastolic properties during primary PCI.\textsuperscript{11} The present data show a further improvement in the passive diastolic LV function on the long-term after reperfused STEMI. End-diastolic elastance decreased and the compliance curve improved during 4 months follow-up. Active myocardial relaxation however, remained prolonged. Systolic LV function also improved, as indicated by the marked increase in stroke volume and stroke work, despite the large increase in EDV due to LV remodeling.

The increase in LV end-diastolic volume is the result of post-STEMI LV remodeling, which is still frequently observed despite successful reperfusion.\textsuperscript{4-6} Our invasively measured LV volumes assessed four months after reperfused STEMI show relatively higher values when compared with those estimated by means of echocardiography, whereas they are lower when compared with those assessed by cardiac MRI. With our data, averaging the values obtained by echocardiography and cardiac MRI gives an approximation of those acquired by invasive PV loop measurements.

Conductance catheter-derived volumes have previously been shown to correlate strongly with those estimated by cardiac MRI.\textsuperscript{17} The mean relative increase in EDV
as part of LV remodeling after STEMI in this study was 24%, which is in the same range as that described in previous echocardiographic and cardiac MRI studies.\textsuperscript{4,5,9,18}

Previous reports on LV diastolic changes in LV remodeling after STEMI were based on echocardiographic parameters.\textsuperscript{5,7,8,10,18} These parameters were derived from transmitral flow velocity patterns, and therefore influenced by diastolic LV function in various ways. Parameters such as E/A ratio, mitral deceleration time and E/E’ ratio are an indirect reflection of true LV diastolic function, since they depend on left atrial (LA) pressures, pulmonary vein properties and mitral orifice area. For their optimal interpretation other parameters need to be taken into account. By obtaining LV PV-loops, active LV relaxation and passive diastolic stiffness of the myocardium can be assessed independently and in a direct and a quantitative way.

Another advantage of hemodynamic assessment by PV-loops is the possibility to directly relate LV dynamic parameters to each other. This is best described by our finding that PV-loops obtained 4 months after STEMI not only show a rightward shift with regard to those from 4 months earlier, but also a downward shift. So, not only did EDV increase as part of LV remodeling, this was accompanied by a decrease in end-diastolic elastance and an improvement in the compliance curve. Our study shows a small but no significant increase in LV ejection fraction at 4 months after primary PCI. This finding is in line with previous echocardiographic and cardiac MRI studies, showing only small increases in EF up to one year after successful PCI in STEMI patients.\textsuperscript{4,5,9,18} However, taking into account, the marked increase in EDV due to LV remodeling, ejection fraction gives an underestimation of the true systolic LV improvement, as supported by the large improvement in stroke volume and stroke work. Interestingly, cardiac output remained more or less the same, which is explained by a “compensatory” decrease of heart rate, and partially by betablocking therapy. Our description of improvement in systolic LV function as part of LV remodeling after STEMI, is another example of how different LV hemodynamic parameters can simply be related to each other by means of PV-loops. As far as we know, this is the first study that shows invasively measured LV dynamic changes accompanying LV remodeling after successful reperfusion in STEMI patients.

**Limitations**

Myocardial (un)-loading interventions to determine the EDPVR were not performed. However, we believe that interpretation of our data would have remained the same.\textsuperscript{19} No significant correlations could be found between hemodynamic or clinical parameters and the extent of LV remodeling. In order to investigate these relations a larger sample size is required.
Clinical implications

Our study is the first to show improvement in both systolic and diastolic LV function 4 months after successfully reperfused anterior wall STEMI, assessed by means of invasively measured load-independent PV-loops. The prognostic and clinical value of systolic LV function on short- and long-term after STEMI have been described extensively.\textsuperscript{3,20,21} More recent studies have shown diastolic LV function to be a strong predictor for clinical outcome after STEMI as well.\textsuperscript{7,8,10} The main finding in these studies is that diastolic LV dysfunction early after reperfused STEMI is predictive for late LV remodeling and unfavorable clinical outcome. The present study shows at long-term after reperfused STEMI that LV remodeling is accompanied by an overall improvement in diastolic LV function. The clinical importance of this finding still remains unclear and may encourage further investigations.

Conclusion

Invasive assessments of LV pressure and volume performed after primary PCI in anterior STEMI patients show evidence of LV remodeling, which however is accompanied by marked improvement in both diastolic and systolic LV function.

Acknowledgments

The authors acknowledge our nursing staff of the cardiac catheterization laboratory for their skilled assistance, especially W.J. Rohling, RN, T. Wagenaar, RN, W.R. Rozendaal, RN, and S. van Gilst, RN.
References


Chapter 4.1


Chapter 4.2

More pronounced diastolic left ventricular dysfunction in patients with accelerated idioventricular rhythm after reperfusion by primary percutaneous coronary intervention

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Jan J. Piek
Jan Baan, Jr

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ABSTRACT

Objective Reperfusion-induced accelerated idioventricular rhythm (AIVR) during primary percutaneous coronary intervention (pPCI) may be a sign of left ventricular (LV) dysfunction. We compared LV dynamic effects of reperfusion between patients with and without reperfusion-induced AIVR during pPCI for STE elevation myocardial infarction (STEMI).

Methods We studied 15 consecutive patients, who presented with their first acute anterior STEMI within 6 hours after onset of symptoms, and in whom LV pressure-volume (PV) loops were directly obtained during pPCI. Immediate effects of pPCI on LV function were compared between patients with (n = 5) and without (n = 10) occurrence of AIVR after reperfusion, as well as the direct effects of AIVR on LV function compared to sinus rhythm.

Results Patients with reperfusion-induced AIVR showed more pronounced diastolic LV dysfunction before the onset of the arrhythmia, i.e., a delayed active relaxation expressed by Tau (53 ± 15 vs. 39 ± 6 ms; p = 0.03), a worse compliance curve (p = 0.01), and a higher enddiastolic stiffness (p = 0.07). At the end of the procedure, AIVR patients showed less improvement in diastolic LV function, indicated by a downward shift of the compliance curve (-3.1 ± 2.3 vs. -7.5 ± 1.4 mmHg; p = 0.001), a decrease in end-diastolic stiffness (13 ± 18 vs. 34 ± 15%; p = 0.03) and end-diastolic pressure (12 ± 8 vs. 29 ± 19%; p = 0.07).

Conclusion STEMI patients with reperfusion-induced AIVR after pPCI showed more pronounced diastolic LV dysfunction before and after AIVR than patients without AIVR, which suggests that diastolic LV dysfunction contributes to the occurrence of AIVR and that AIVR is a sign of diastolic LV dysfunction.
Introduction

Accelerated idioventricular rhythm (AIVR) as a reperfusion arrhythmia is often observed immediately after primary percutaneous coronary intervention (pPCI) for ST-elevation myocardial infarction (STEMI). In general, AIVR is considered to be a relatively benign form of ventricular tachycardia. While some authors suggest that AIVR may be a manifestation of cellular injury, others state that the occurrence of AIVR immediately following pPCI is associated with better clinical outcome, as it is associated with reperfusion at myocardial tissue level. However, there is conflicting evidence of the clinical relevance of reperfusion-related AIVR in pPCI. Whereas, Illia et al found that the presence of AIVR was associated with ST-segment resolution, Bonnemeier et al found no difference in the incidence of AIVR among patients with optimal versus suboptimal TIMI flow grade. Furthermore, the acute effect of AIVR on left ventricular (LV) function during reperfusion by pPCI is unknown. Therefore, we assessed the acute effects of AIVR on LV dynamics, and compared systolic and diastolic LV function between patients with and without reperfusion-induced AIVR among STEMI patients treated by pPCI, in order to investigate whether AIVR implicates LV dysfunction.

Methods

Patients

The study population consisted of 15 consecutive patients who presented with their first acute anterior ST-segment elevation myocardial infarction within 6 hours after onset of symptoms, and in whom LV pressure-volume (PV) loops were directly obtained during pPCI. Recurrent episodes of reperfusion-induced AIVR were observed in 5 patients. Exclusion criteria were cardiogenic shock, refractory ventricular arrhythmias, congestive heart failure, previous myocardial infarction, significant valvular disease and left ventricular thrombus. The study complied with the Declaration of Helsinki and was approved by the institutional research and ethics committee. All patients gave written informed consent.

Study protocol

An extensive description of the instrumentation and LV dynamic measurements was previously reported. Briefly, patients were treated with aspirin, clopidogrel and heparin before PCI. Heart rate and surface 12-lead electrocardiograms were monitored and aortic pressure was measured via the guiding catheter. Blood samples for hematology and chemistry, including cardiac markers, were drawn.
Before performing pPCI, a 7 French (Fr), pigtail-equipped, combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) was placed in the LV through the contralateral femoral artery. PV-loops were continuously assessed during the procedure.

Analysis of left ventricular function

LV function effects were assessed during sinus rhythm and compared between patients with (n = 5) and without (n = 10) the occurrence of AIVR after reperfusion. AIVR was defined as a ventricular ectopic rhythm with more than 3 consecutive beats and a rate between 60 and 110 bpm. The initial baseline (pre-PCI) recordings were compared to the recordings at 30 seconds after reperfusion and/or before the onset of AIVR, and at 25 minutes after achievement of an angiographically satisfactory PCI result. Per-beat averages of the recorded variables were calculated as the mean of all beats during a steady state of at least 12 seconds and covering two respiratory cycles. It was taken into account that selected recordings were obtained during stable hemodynamic conditions, without interference of pharmaceuticals (e.g., nitroglycerin).

The active diastolic function was studied by measuring the relaxation time constant Tau, as defined by that time required for LV pressure at the peak negative derivative of LV pressure (dP/dt\textsubscript{\text{min}}) to be reduced by half. Diastolic function was further studied by measuring peak filling rate (PFR), end-diastolic volume (EDV), pressure (EDP), and stiffness (E\textsubscript{\text{ED}}) as the slope on the EDPVR was estimated by EDP/EDV. The shift of the passive diastolic LV compliance curve was expressed by the mean pressure value over which the overlapping portion of the PV-loop had moved (P\textsubscript{\text{m}}), as previously described.

Systolic function was studied by measuring stroke volume, ejection fraction, stroke work, cardiac output, end-systolic volume (ESV), pressure (ESP), and elastance as the slope on the ESPVR was estimated by ESP/ESV.

Statistical analysis

Data are expressed as mean ± standard deviations (SD) or n (%). The Fisher’s exact test was used to compare dichotomous variables. The 2-tailed paired t-test was used to compare LV dynamic data obtained before and after reperfusion. SPSS release 15.0.1 statistical software package for Windows (SPSS Inc. 2006, Chicago, Illinois) was used for analyses. A p-value < 0.05 was considered statistically significant.
Results

Patient characteristics. The patient characteristics are shown in Table 1. Markers of cardiac necrosis were higher in the patients with reperfusion-induced AIVR than in the patients without AIVR, while the clinical, hemodynamic and angiographic characteristics were not different. At baseline, just before pPCI, there were no significant differences in diastolic or systolic LV function between the patient groups.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>AIVR (n=5)</th>
<th>Non-AIVR (n=10)</th>
<th>P-value</th>
</tr>
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<tr>
<td>Age, years</td>
<td>65 ± 11</td>
<td>57 ± 12</td>
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<tr>
<td>Male</td>
<td>3 (60)</td>
<td>7 (70)</td>
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<td>Body mass index (kg/m²)</td>
<td>24 ± 2</td>
<td>28 ± 4</td>
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<td>Coronary risk factors</td>
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<td>Diabetes</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>0.5</td>
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<tr>
<td>Hypertension</td>
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<td>5 (50)</td>
<td>0.1</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>1 (20)</td>
<td>2 (20)</td>
<td>1.0</td>
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<tr>
<td>Family history of coronary artery disease</td>
<td>1 (20)</td>
<td>4 (40)</td>
<td>0.6</td>
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<tr>
<td>Current smoking</td>
<td>3 (60)</td>
<td>6 (60)</td>
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</tr>
<tr>
<td>Previous acute myocardial infarction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Clinical and angiographic features</td>
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<td></td>
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<tr>
<td>Ischemic time (minutes)</td>
<td>241 ± 171</td>
<td>271 ± 187</td>
<td>0.8</td>
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<tr>
<td>Heart rate (beats per minute)</td>
<td>71 ± 7</td>
<td>87 ± 20</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>130 ± 15</td>
<td>127 ± 24</td>
<td>0.8</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 13</td>
<td>72 ± 10</td>
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<td>LAD, culprit lesion</td>
<td>5 (100)</td>
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<td>2-vessel disease</td>
<td>2 (40)</td>
<td>2 (20)</td>
<td>0.6</td>
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<tr>
<td>3-vessel disease</td>
<td>2 (40)</td>
<td>2 (20)</td>
<td>0.6</td>
</tr>
<tr>
<td>Duke's jeopardy score (0-12 points)</td>
<td>7.2 ± 3.3</td>
<td>4.6 ± 2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>TIMI 0-1 flow before primary PCI</td>
<td>5 (100)</td>
<td>10 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>TIMI 2 flow after primary PCI</td>
<td>1 (20)</td>
<td>2 (20)</td>
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<tr>
<td>STR at 60 minutes (%)</td>
<td>50 ± 27</td>
<td>54 ± 24</td>
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<tr>
<td>Cardiac markers, peak</td>
<td></td>
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<tr>
<td>CKMB (µg/L)</td>
<td>354 ± 73</td>
<td>159 ± 118</td>
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<tr>
<td>Troponin T (µg/L)</td>
<td>14.7 ± 11.1</td>
<td>6.6 ± 4.6</td>
<td>0.06</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>2343 ± 1029</td>
<td>2765 ± 4764</td>
<td>0.9</td>
</tr>
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</table>

Values are n (%) or mean ± standard deviation. AIVR = accelerated idioventricular rhythm; LAD = left anterior descending coronary artery; Duke's jeopardy score = the angiographic extent of coronary artery disease; TIMI = thrombolysis in myocardial infarction; PCI = percutaneous coronary intervention; STR = the summed 12-lead ST-segment resolution as determined at 80 ms after the J-point; CK = creatine kinase; NT-proBNP = N-terminal part of the pro-B-type natriuretic peptide.
Chapter 4.2

Effects of PCI
Immediately after reperfusion by pPCI, the active diastolic LV function as indicated by Tau (Figure 1A), was more delayed in patients who developed AIVR (53 ± 15 ms vs. 39 ± 6 ms; p = 0.03). At the end of the procedure, at 25 minutes after reperfusion, Tau remained more delayed in the patients who had AIVR (51 ± 12 ms versus 38 ± 5 ms; p = 0.01). Compared to baseline, the AIVR patients showed a worsening in Tau, while the non-AIVR patients showed a slight improvement (8 ± 10% versus -1 ± 16%; p = NS).

Similar findings were observed in the passive diastolic LV function. Figure 1B shows that immediately after reperfusion, there was a difference in $P_m$ between patients developing AIVR versus the other patients (4.1 ± 4.2 mmHg vs. -3.7 ± 4.9 mmHg; p = 0.01). This shift in the compliance curve remained different at the end of the procedure (-3.1 ± 2.3 mmHg vs. -7.5 ± 1.4 mmHg; p = 0.001). Also, $E_{ED}$ (Figure 1C) and EDP (Figure 1D) tended to be different at these time points. Compared to baseline, the AIVR patients had shown less improvement at the end of the procedure in $E_{ED}$ (13 ± 18% versus 34 ± 15%; p = 0.03) and EDP (12 ± 8 versus 29 ± 19%; p = 0.07).

The effect of pPCI on systolic LV indices showed no difference between the patient groups, as illustrated by stroke volume and ejection fraction in Figures 1E and 1F.

AIVR versus sinus rhythm
During an episode of AIVR (Figure 2), diastolic LV function decreased as indicated by a decreased LV pressure decay, i.e., $dP/dt_{min}$ decreased by 403 ± 145 mmHg/s (p = 0.003) and Tau delayed by 5 ± 6 ms (p = NS). Furthermore, there was a decrease in PFR of 165 ± 54 mL/s (p = 0.002), in EDP of 11 ± 5 mmHg (p = 0.01), in EDV of 30 ± 18 mL (p = 0.02) and $E_{ED}$ of 0.045 ± 0.015 mmHg/mL (p = 0.002).

LV contraction decreased as indicated by a decrease in $dP/dt_{max}$ of 303 ± 125 mmHg/s (p = 0.006) and ESP of 33 ± 8 mmHg (p = 0.001). Heart rate, stroke volume, ejection fraction and cardiac output remained unchanged. The beat to beat effects at the onset of AIVR on the LV volume and pressure tracings are illustrated in Figure 3. After return of sinus rhythm, diastolic and systolic LV function showed an immediate restoration.
LV diastolic dysfunction in AIVR after pPCI for STEMI

**Figure 1.** Comparison of diastolic and systolic left ventricular (LV) function between patients with the occurrence of accelerated idioventricular rhythm (AIVR) and without the occurrence of AIVR (non-AIVR) during primary percutaneous coronary intervention (pPCI). (A) Active LV relaxation as expressed by the relaxation time constant (Tau), was worse in the AIVR patients at baseline (pre-PCI), immediately after reperfusion and/or before onset of AIVR (reperfusion + 30 seconds), and at 25 minutes after reperfusion (reperfusion + 25 minutes). (B) The shift of the diastolic LV compliance curve, as expressed by the mean pressure value (Pm), was downward and more pronounced in the non-AIVR patients. Note that immediately after reperfusion, the shift was in the opposite direction. (C) End-diastolic stiffness (EED) tended to be higher in the AIVR patients after reperfusion (p-values on top). Note that the improvement in EED was more pronounced in the non-AIVR patients (p-values at bottom). Similarly, in (D), the decrease in end-diastolic pressure (EDP) seems more pronounced in the non-AIVR patients. Stroke volume in (E) and ejection fraction in (F) show no difference between the two patient groups.
Figure 2. Illustration of a changed pressure-volume loop (PV-loop) by accelerated idioventricular rhythm (AIVR). (A) A PV-loop during sinus rhythm. (B) A PV-loop during AIVR, 6 heartbeats later. Note that AIVR substantially decreases left ventricular function as indicated by a decrease in diastolic filling and endystolic pressure, and a limited decrease in stroke volume. $P_{LV}$ = left ventricular pressure; $V_{LV}$ = left ventricular volume.

Figure 3. Illustration of the beat to beat effects at the onset of accelerated idioventricular rhythm (AIVR). Note that immediately after the onset of AIVR, there is an absence of atrial contribution to diastolic filling in the pressure and volume recordings. At the moment that the QRS complex is not being preceded by the p-top, the reflection of the atrial kick disappears, both at the start of the ascending limb of the pressure curve and by completely dissolving the peak of the volume curve. Also, maximal pressure is markedly decreased. $P_{LV}$ = left ventricular pressure; $V_{LV}$ = left ventricular volume.
Discussion

With this study, we are the first to demonstrate that STEMI patients who experienced AIVR after reperfusion by pPCI are characterized by more pronounced diastolic LV dysfunction before the occurrence of AIVR and show less diastolic LV function improvement.

Primary PCI and LV function

AIVR often occurs after reperfusion in patients with an acute myocardial infarction and is usually considered to be a beneficial sign of successful reperfusion and thus to be a benign form of ventricular arrhythmia. Our study, however, shows that in acute myocardial infarction, patients have more pronounced diastolic LV dysfunction before the occurrence of the arrhythmia. Also, the reperfusion-induced improvement in the passive diastolic LV properties compared to baseline was less in patients with AIVR. Our data therefore suggest that AIVR is not simply a beneficial sign of reperfusion, but is rather a sign of more pronounced LV dysfunction, and is thus indicative of a more strained myocardium when compared to patients without AIVR.

The more pronounced LV dysfunction may be caused by reperfusion injury, since it has been suggested that the abnormal automaticity of subendocardial tissue in AIVR patients may be a sign of additional injury due to the reperfusion process (arrhythmias, stunning, endothelial dysfunction and cell death) or a sign of poor quality of reperfusion. Our findings of a larger infarct size in AIVR patients may also partly explain the differences in LV function, although differences in infarct size were previously reported in two other studies, but not in other reports. Our findings of a more pronounced diastolic LV dysfunction in AIVR patients may be related to a difference in microvascular reperfusion, resulting in larger infarct size and less improvement in diastolic LV function by pPCI. The abnormal automaticity of subendocardial tissue in AIVR patients may be triggered by increased diastolic LV stretch on cardiac cells. It is known that diastolic LV stretch can cause ectopic excitation of myocytes, potentially triggering arrhythmias.

We recently reported improvement in the passive diastolic LV properties by pPCI in anterior STEMI patients, but there are no reports on LV function in AIVR patients immediately before and after pPCI. Studies that obtained data after reperfusion are in line with our hemodynamic findings. One study showed more severe LV dysfunction in AIVR patients compared to patients without reperfusion arrhythmias, as assessed by echocardiography within 3 days after pPCI. Remarkably, these patients also had a better prognosis, in contrast to earlier studies showing no prognostic benefit during 12-month follow up or worsening of systolic LV function within 2 months after STEMI.
In AIVR patients, we found that reperfusion-induced AIVR caused an immediate decrease in diastolic and systolic LV function as compared to sinus rhythm. There was a decrease in LV pressure decay during isovolumetric LV relaxation and a concomitant decrease in force generation by the LV as indicated by a marked decrease in \( \frac{dP}{dt_{\text{max}}} \) and ESP, as illustrated by an altered PV-loop during AIVR in Figure 2. This suggests that “elastic recoil,” i.e., the stored elastic energy during cardiac contraction, which is released in the next diastolic period,\(^{18}\) is diminished in AIVR patients. Furthermore, there was a decreased diastolic LV filling, which is caused by the absence in the contribution of the atrial contraction, as illustrated in Figure 3. Although AIVR is usually hemodynamically well tolerated and self-limiting,\(^{15,19}\) our data suggest that recurrent episodes of AIVR or sustained AIVR may worsen the hemodynamics of STEMI patients.

**Study limitations**

Myocardial (un)-loading interventions to determine the ESPVR and EDPVR were not performed, since we considered these unethical (i.e., delay of reperfusion and possible hemodynamic consequences) for the patients under these circumstances. \( E_{\text{ED}} \) estimated from steady-state PV-loops by EDP/EDV underestimates the real slope of the EDPVR at higher filling pressures, because of its nonlinearity. This study was not designed to assess mediators of reperfusion injury.\(^{11}\) Atrioventricular sequential pacing in patients having atrial fibrillation and concomitant AIVR would be the ideal setting to study the mechanism of the hemodynamic consequences of AIVR and the influence of atrial contraction. Finally, the data are limited to the acute phase of pPCI. Final infarct size was not assessed during follow up. Further studies are needed to confirm our suggested trigger for AIVR, or possibly to find other substrates for AIVR.

**Clinical implications**

AIVR is a phenomenon that is frequently seen and part of daily practice in the catheterization laboratory after reperfusion therapy by pPCI for STEMI.\(^{14}\) It is conventionally considered to be a nonspecific\(^{20}\) and benign reperfusion arrhythmia,\(^1\) and therefore of limited clinical importance. However, our study shows larger infarcts and more diastolic LV dysfunction in AIVR patients, which may result in impaired clinical outcome.\(^{21,22}\) Our acute findings of the hemodynamic consequences in patients with the occurrence of AIVR during pPCI, and the suggested mechanistic trigger for AIVR as provided by the direct LV dynamic measurements, may encourage larger studies to assess its prognostic value.
Conclusion

Online PV-loop assessment during pPCI show immediate AIVR-related systolic and diastolic LV dysfunction. STEMI patients with AIVR have more pronounced diastolic LV dysfunction before the occurrence of the AIVR and less diastolic LV function improvement than patients without AIVR, implicating that AIVR may be considered as a sign of diastolic LV dysfunction.

Acknowledgments

The authors acknowledge our nursing staff of the cardiac catheterization laboratory for their skilled assistance, especially W.J. Rohling, RN, T. Wagenaar, RN, W.R. Rozendaal, RN, and S. van Gilst, RN.
References

LV diastolic dysfunction in AIVR after pPCI for STEMI

161


Chapter 4.3

Immediate reduction of mitral regurgitation by percutaneous mitral valve repair with the MitraClip®

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Berto J. Bouma
Karel T. Koch
Jan Baan, Jr

Netherlands Heart Journal 2010 Nov;18(12):606
A 78-year-old male presented with shortness of breath due to severe mitral regurgitation. His medical history revealed terminal renal failure for which he received hemodialysis. Two months before admission he presented with an acute coronary syndrome, for which he was treated with a percutaneous coronary intervention including rotablator of the LAD and LCx. Echocardiography showed an impaired left ventricular function and a severe ischemic mitral regurgitation with a posterior jet. He was denied for surgery of the mitral valve because of his high surgical risk (logistic EuroSCORE: 21%), and accepted for percutaneous mitral valve repair using the MitraClip®. At this moment in Europe the MitraClip® is considered a useful technique for high risk and inoperable patients, in contrast with the low risk patients treated in the EVEREST trial.¹

In the catheterisation laboratory the MitraClip® device was delivered to the mitral valve through a transseptal approach. The procedure was performed under fluoroscopic and 2D-transesophageal echocardiographic (TEE) guidance. With TEE, mainly the 3 chamber- (120°), 2 chamber- (46°) and the transgastric short axis views were used to guide the clip towards its proper position, where 3D-TEE may simplify the procedure. Next, the clip was advanced into the left ventricle, after which the leaflets were grasped, where after the clip was closed and released from the delivery catheter. The clip implantation resulted in a dramatic reduction of the mitral regurgitation from severe to mild. The reduction in mitral regurgitation was especially seen after closure of the clip arms (figure 1).

![Figure 1](image_url)

**Figure 1**: Intercommissural (2 chamber) transesophageal and fluoroscopic views during closure of the MitraClip around the grasped mitral valve leaflets. Note the difference of the mitral regurgitation jet between before (A) and after (B) closure of the clip arms.

**References**

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 longterm 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.
Samenvatting

Sinds de introductie van transcatheter aortaklepimplantaties (TAVI) in het AMC in 2007, is er een snelle groei geweest van het aantal TAVI procedures in ons centrum. In de afgelopen jaren hebben we veel kennis en inzicht opgedaan met betrekking tot screening en selectie van patiënten voor TAVI, procedurele technieken, het optreden en voorkomen van TAVI-gerelateerde complicaties en het effect van TAVI op de klinische uitkomst op de korte en lange termijn. In dit proefschrift, worden de verschillende aspecten besproken van de transcatheter aortaklepimplantaties verricht in het kader van onze single-centre ervaring.

In hoofdstuk 2.1 worden de uitvoerbaarheid, veiligheid en effectiviteit beschreven van de eerste 30 transfemorale TAVI procedures met het Medtronic-CoreValve® systeem die verricht zijn in het AMC. De eindpunten werden vastgelegd in een zorgvuldig samengesteld klinisch protocol, dat is goedgekeurd door de Medisch Ethische Commissie. Deze studie laat zien dat TAVI procedures succesvol verricht zijn in ons centrum bij hoog-risico patiënten, met een procedurele succeskans van 90%, 30 dagen major adverse cardiovascular and cerebral events kans van 23% en 30 dagen mortaliteit van 20%. Na een succesvolle TAVI, was er een duidelijke hemodynamische verbetering en vermindering van klachten bij de patiënten.

Binnen enkele jaren nadat de eerste transfemorale TAVI in ons centrum was verricht, was er een snelle groei in het aantal procedures. Daarnaast, vormden de toevloeg van een ander prothesetype (Edwards SAPIEN®) en andere toegangswegen (transfemoraal, transapicaal, via de arteria subclavia and transaortaal) een verrijk van ons TAVI programma. De resultaten van ons single-centre TAVI programma, met gebruik van verschillende prothesetypes en toegangswegen staan beschreven in hoofdstuk 2.2. In deze studie onderzochten we de incidentie en voorspellers van mortaliteit op korte en lange termijn van 264 patiënten die een TAVI hadden ondergaan via de transfemorale route met de Medtronic-CoreValve prothese (n=147) of via de transapicale (n=69) of transfemorale (n=48) route met de Edwards SAPIEN prothese. Het percentage mortaliteit bij 30 dagen bedroeg 11,7 en werd voorspeld door langdurige ziekenhuisopname voorafgaande aan de procedure, linkerventrikelmassa, logistische EuroSCORE, acute nierschade (AKI), vasculaire toegangsscomplicaties, beroertes en graad 2 of meer paravalvulaire aorta-insufficiëntie (PAR). Cumulatieve mortaliteit was 23% (median follow-up duur van 14 maanden) en werd voorspeld door PAR≥2, Society of Thoracic Surgeons (STS) risico score en AKI. In deze studie werden er dus bepaalde preprocedurele risicofactoren voor vroege en late mortaliteit geïdentificeerd, wat nuttig zou kunnen zijn om bij te dragen aan een optimale selectie van patiënten voor TAVI.

Er zijn bepaalde complicaties die samenhangen met TAVI, die al dan niet gevolgen kunnen hebben voor de klinische uitkomst. In hoofdstuk 3 wordt er aandacht
besteed aan de incidentie, voorspellers en klinische consequenties van deze complicaties. **Hoofdstuk 3.1** beschrijft cardiale geleidingsproblemen als complicatie van TAVI. De incidentie en voorspellers van geleidingsproblemen werden bestudeerd in 34 patiënten die een TAVI hebben ondergaan met de CoreValve bioprothese. Na TAVI waren er 7 patiënten die een permanente pacemaker nodig hadden vanwege een totale atroventriculaire blok die optrad tijdens de procedure of binnen 3 dagen na de procedure. Een kleinere left ventricular outflow tract diameter, meer linkszijdige hartas op het ECG, meer mitraalklepannuluscalcificatie en een kleinere post-implantatie geïndexeerd aortaklepoppervlak waren geassocieerd met permanente pacemakerimplantatie. De incidentie van de novo linkerbundeltakblok was 65% en was geassocieerd met een diepere implantatie van de prothese. Een andere klinisch belangrijke complicatie van TAVI zou myocardschade kunnen zijn, waarvan bekend is dat zij vaak voorkomt tijdens hartchirurgie en percutane coronaire interventies (PCI) en dat zij geassocieerd is met postprocedureele cardiovasculaire mortaliteit en morbiditeit. In **hoofdstuk 3.2** wordt er aandacht besteed aan de incidentie, voorspellers en prognostische waarde van myocardschade tijdens TAVI met de Medtronic-CoreValve bioprothese. In 119 patiënten lieten wij zien dat de incidentie van myocardschade (postprocedurele toename van CK-MB en/of cTnT waarden van meer dan 5 maal de bovenste referentiegrens) 17% was. Onafhankelijke voorspellers van myocardschade waren de duur van de procedure, afwezigheid van het gebruik van een bètablokker, perifeer arterieel vaatlijden en prothesediepte. Myocardschade bleek een belangrijke consequentie te hebben voor de vroege uitkomst, aangezien zij een onafhankelijke voorspeller was voor 30 dagen mortaliteit.

Acute nierschade (gedefiniëerd als een afname in de geschatte glomerulaire filtratiesnelheid ten opzichte van baseline van ≥25% binnen 5 dagen na de procedure) is een belangrijke prognostische factor na hartchirurgie en in **hoofdstuk 3.3** wordt deze complicatie beschreven met betrekking tot TAVI. In deze single-centre prospectieve studie werden 195 patiënten geïncludeerd die TAVI hadden ondergaan via transfemorale route met de Medtronic-CoreValve bioprothese (n=129) of via de transapicale route met de Edwards SAPIEN bioprothese (n=66). Na TAVI was de incidentie van AKI 23%, welke onafhankelijk werden voorspeld door lisdiureticagebruik van 2 eenheden of meer, post-implantatie diastolische arteriële bloeddruk, maximale leukocytenaantal en chronisch obstructieve longziekte. Acute nierschade bleek een sterke onafhankelijke voorspeller te zijn voor zowel mortaliteit tijdens de opname en mortaliteit in 1 jaar. Op grond van deze resultaten suggereerde wij dat preventieve maatregelen voorafgaande en tijdens de procedure die gericht zijn op de voorspellende factoren voor AKI van invloed kunnen zijn op het optreden van deze complicatie en dientengevolge de uitkomst na TAVI. **Hoofdstuk 3.4** besteedt aandacht aan paravalvulaire aorta-insufficiëntie, een
veel voorkomend verschijnsel na TAVI. In deze studie werden de voorspellers en klinische consequenties op korte en lange termijn van PAR onderzocht in 140 patiënten die een TAVI hebben ondergaan met de Medtronic-CoreValve bioprothese. Na TAVI, trad graad 2 of meer PAR op in 29% van de patiënten en bleek de breedte van de sinus van Valsalva de enige onafhankelijke voorspeller hiervoor. Totale en cardiale mortaliteit op 30 dagen en op 1 jaar waren significant hoger in patiënten met PAR ≥ 2 vergeleken met PAR < 2, waaruit geconcludeerd kan worden dat significante PAR na TAVI een klinisch relevante complicatie is. Onze studies laten een instantane verbetering van klephemodynamiek na TAVI zien, welke op non-invasieve wijze is gemeten. Deze verandering in klephemodynamiek na TAVI resulteert ook in significante verbetering van linkerventrikelfunctie (LVEF) in andere studies, vooral bij patiënten met een lage uitgangsejectief fractie. Daarnaast is de verwachting dat drukontlasting van de linkerkamer na TAVI resulteert in regressie van linkerkamer hypertrofie, welke zou kunnen leiden tot verbetering in diastolische linkerkamerfunctie. Invasieve LV druk-volume (PV) metingen met behulp van de conductantiecatheter is een nauwkeurige manier om load-onafhankelijk de systolische en diastolische linkerkamerfunctie te bepalen. Deze methode zou een nuttig middel kunnen zijn voor het meten van onmiddellijke en langetermijnseffecten van TAVI op LV hemodynamiek. In ons ziekenhuis is er veel ervaring opgedaan op het gebied van LV PV-loop metingen in patiënten die een percutane coronaire interventie hebben ondergaan. In hoofdstuk 4.1 wordt een studie beschreven waarin LV hemodynamische veranderingen werden onderzocht door middel van invasief gemeten druk-volume lussen, tussen 3 dagen en 4 maanden na succesvolle primaire PCI in 11 patiënten met een ST elevatie myocardinfarct (STEMI) van de voorwand. Deze metingen lieten een toename zien van LV eind-diastolische volumes na 4 maanden als gevolg van LV remodelling na STEMI. Deze remodelling ging gepaard met verbetering van de diastolische linkerkamerfunctie op grond van een neerwaartse verschuiving van de eind-diastolische compliantiecurve en een afname van de eind-diastolische stijfheid. Verbetering van de systolische linkerkamerfunctie bleek uit een toename van het slagvolume na 4 maanden. Ook zijn er periprocedurele PV-loop metingen verricht in ons centrum tijdens PCI. In hoofdstuk 4.2 wordt de periprocedureel gemeten LV hemodynamiek vergeleken tussen patiënten met en zonder reperfusie-geïnduceerde geaccelereerde idioventriculaar ritme (AIVR) tijdens primaire PCI voor STEMI. De studie laat zien dat patiënten met reperfusie-geïnduceerde AIVR meer uitgesproken diastolische LV dysfunctie hadden vóór het begin van deze harrtritmestoornis, gebaseerd op een langere actieve relaxatieperiode, een slechtere compliantiecurve en een afname in eind-diastolische stijfheid en druk. Deze studie suggereert dat diastolische disfunctie bijdraagt aan het optreden van AIVR en dat AIVR een uiting zou kunnen zijn.
van diastolische linkerkamerdisfunctie.
Andere transcatheter hartklepinterventies worden verricht en bestudeerd in ons centrum, waaronder percutane reparatie van de mitralisklep door middel van de MitraClip® bij matig tot ernstige mitralisinsufficiëntie. **Hoofdstuk 4.3** beschrijft een succesvolle clipimplantatie bij een patiënt met symptomatische ernstige mitralisinsufficiëntie en comorbiditeit, die resulteerde in een enorme reductie van zijn kleplekkage van ernstig naar mild.

**Conclusies**

Concluderend kan er gesteld worden dat onze single-centre ervaring met transcatheter aortaklepimplantaties heeft laten zien dat het gaat om een veilige en goed uitvoerbare techniek en dat zij een goede alternatieve behandeloptie vormen voor patiënten met symptomatische aortaklepstenose, die als inoperabel worden beschouwd of een hoog chirurgisch risico hebben. De mortaliteit op dertig dagen en op 1 jaar van onze TAVI procedures zijn laag: respectievelijk circa 11,7% en 23%, welke vergelijkbaar zijn met de sterftepercentages van andere single-centre en multicentre studies en registraties. Daar komt nog bij dat TAVI resulteert in hemodynamische en symptomatische verbetering op korte termijn in de meerderheid van onze patiënten.

Echter, TAVI is geassocieerd met bepaalde complicaties, waarvan de meesten klinische consequenties hebben. Hartgeleidingsproblemen, myocardschade, acute nierschade, vasculaire toegangscomplicaties en significante paravalvulaire aorta-insufficiëntie zijn klinisch belangrijke complicaties van TAVI, die allen beschreven zijn in dit proefschrift. Preventieve maatregelen om de incidentie van deze complicaties te verminderen, zullen leiden tot een verbeterde klinische uitkomst. Daarnaast zijn er bepaalde preprocedurele risicofactoren voor vroege en late mortaliteit geïdentificeerd in onze studies. Risicostratificatie met gebruik van deze factoren zouden een handig middel kunnen zijn om patiënten voor TAVI optimaal te selecteren. Alhoewel de meerderheid van de patiënten die worden voorgesteld voor TAVI behandeld kunnen worden met een laag risico op mortaliteit, kunnen er bepaalde patiënten geïdentificeerd worden die een onacceptabel hoog risico hebben op mortaliteit tijdens en na de procedure. Voor deze patiënten dient conservatieve behandeling overwogen te worden.

Invasieve metingen van de veranderingen in LV hemodynamiek tijdens de procedure en op lange termijn blijken goed uitvoerbaar en veilig te zijn tijdens percutane coronaire interventies. Invasieve linkerkamer druk-volume metingen tijdens en na TAVI, zouden ons meer inzicht kunnen verschaffen over de exacte hemodynamische effecten van TAVI op de korte en lange termijn en over hun samenhang met klinische uitkomst.
Toekomstperspectieven

TAVI kan worden gezien als een medische doorbraak die de behandeling van aortaklepstenose enorm heeft veranderd in de afgelopen tien jaar. Studies met een langere follow-up duur zijn nodig voordat TAVI kan worden uitgebreid naar jongere patiënten en/of laagrisicopatiënten met aortaklepstenose. De grootste vraag met betrekking tot deze relatief nieuwe techniek die vooralsnog onbeantwoord blijft betreft de duurzaamheid van de transcatheter klepprothesen. Uiteindelijk zullen deze kleppen zich moeten meten met de duurzaamheid (circa 20 jaar) van chirurgische biokleppen die momenteel worden gebruikt. Testen in de preklinische fase lieten zien dat de duurzaamheid van Edwards SAPIEN en CoreValve vergelijkbaar zouden moeten zijn met de huidig beschikbare biologische klepprothesen. Tot nu toe is er geen structurele achteruitgang waargenomen bij een follow-up duur van meer dan 7 jaar bij de Cribier-Edwards klep en tot wel 5 jaar bij de CoreValve prothese.

Vermindering van bepaalde complicaties gerelateerd aan TAVI is een andere belangrijke stap om uiteindelijk laagrisicopatiënten met TAVI te behandelen. De nieuwe generatie Edwards SAPIEN en Medtronic-CoreValve systemen zouden kunnen bijdragen aan de verminderen van deze complicaties. Kleinere diameters van de klepprofielen zullen het mogelijk maken om kleinere maten catheters en sheaths te gebruiken, die zullen leiden tot een lagere kans op vaat- en bloedingscomplicaties. Toekomstige studies zullen het effect moeten evalueren van embolic protection devices in het voorkomen van cerebrale embolieën tijdens TAVI procedures. Andere ontwikkelingen op het gebied van TAVI zijn gericht op technieken om paravalvulaire aorta-insufficiëntie te verminderen, endoluminale resectie van aangedane aortaklepbladen om valvuloplastiek te vermijden en de mogelijkheid om de klepprothese terug te halen en te repositioneren, voordat deze uiteindelijk wordt ontplooid. Nieuwe transcatheter klepsystemen zijn ontwikkeld, waarmee sommige van deze eigenschappen worden nagestreefd. Vier van deze nieuwe systemen, die in klinische trials worden onderzocht voordat zij CE Mark verkrijgen, zijn: de Portico klep (St Jude Medical Inc., St. Paul, Minnesota, USA), het Sadra Lotus Valve systeem (Sadra Medical Inc., recently acquired by Boston-Scientific Inc., Natick, Massachusetts, USA), de Direct Flow Medical Aortic Valve 18F (Direct Flow Medical Inc., California, USA) and de Jena Valve (Jena Valve, Munich, Germany). Er zijn tal van andere producten in vroegere ontwikkelingsfases. Toekomstige studies en ontwikkelingen op het boeiende gebied van TAVI, zullen uiteindelijk bepalen of deze behandelingssmodaliteit een plaats zal krijgen in de standaardbehandeling van aortaklepstenose.
Appendix

Dankwoord

List of publications

Curriculum vitae

Ze Yie Yong

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Dankwoord

Het is zover: het proefschrift is eindelijk klaar en vormt een mooie afsluiting van de onderzoeksjaren die ik bij de interventiecardiologie in het AMC achter de rug heb. De totstandkoming van dit proefschrift was niet mogelijk geweest zonder de hulp en bijdrage van vele personen. In het bijzonder zou ik graag alle patiënten willen bedanken voor hun deelname aan het onderzoek dat ten grondslag ligt aan dit proefschrift. Verder zou ik in dit dankwoord van de gelegenheid gebruik willen maken individuele personen te bedanken.

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De leden van mijn promotiecommissie, Prof. dr. M.B. Vroom, Prof. dr. Y.M. Pinto, Prof. dr. R.J. de Winter, Prof. dr. J.G.P. Tijssen, Prof. dr. S.R. Redwood en Prof. dr. M.J. Schalij, dank ik hartelijk voor het kritisch beoordelen van mijn proefschrift en
voor hun bereidheid om zitting te nemen in mijn promotiecommissie. Dear professor S.R. Redwood, as an international expert on the field of transcatheter valve therapies, I feel honoured for your willingness to critically evaluate my thesis and to participate in my promotion committee.

Bij dezen wil ik de interventiecardiologen (Karel Koch, Marije Vis, José Henriques, Siyrous Hoseyni, Rob de Winter) en cardio-thoracale chirurgen (Riccardo Cocchieri, Jan van der Meulen, Antoine Driessen, Petr Symersky) bedanken voor hun belangrijke bijdrage aan dit proefschrift en voor de prettige samenwerking tijdens mijn promotietraject. Jullie vormen een hecht team samen met mijn promotores en co-promotor en bij jullie zijn de transcatheter klepinterventies in goede handen! (Caro Riccardo, anche ti voglio ringraziare per avermi aiutato a migliorare il mio italiano!)


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geleid tot een gezamenlijk stuk en een presentatie op het ESC. Ik kijk uit naar een voortzetting van onze samenwerking in de kliniek!

Kirsten Boerlage en Esther Wiegerinck, mijn paranimfen en mede-onderzoeksters bij het transcatheter kleppenproject:

Beste Kirsten, al snel toen jij begon bij de cardiologie in 2010 bleek je een waardevolle aanvulling van het ‘kleppenteam’. Na twee jaar alleen op dit project gezeten te hebben, was ik blij eindelijk een ‘partner in crime’ te hebben. De congressen in Washington D.C., Berlijn, Kopenhagen en Boedapest waren nooit zo gezellig geweest zonder jou. Ik heb je leren kennen als een heel betrokken, enthousiaste, empathische maar vooral hardwerkende collega. Daarom heb ik er het volste vertrouwen in dat het met jouw promotietraject helemaal goed gaat komen. Ik kijk nu al uit naar jouw promotie!

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Dan mijn broer, Zeling. Lieve broer, wij zijn samen opgegroeid en je bent nog steeds heel belangrijk in mijn leven. We hebben twee totaal verschillende interesses en praten inhoudelijk niet veel met elkaar over ons werk. Desondanks ben je een belangrijke (mentale) steun geweest tijdens mijn promotieonderzoek en dat ben je nog steeds nu ik in de kliniek werk. Hopelijk wordt dit ook een mooi proefschrift zonder jouw design-technische ondersteuning ;-).

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List of publications


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Curriculum Vitae

Ze Yie Yong was born in the Burgerziekenhuis in Amsterdam, the Netherlands on the 10th of January 1982. He grew up in the Indische Buurt with his 2 year older brother Zeling and still lives in this district of Amsterdam. In 1994 he started his secondary school at the Pieter Nieuwland College in Amsterdam. After graduating the VWO cum laude in 2000 he went to study Medicine at the University of Amsterdam. In January 2007 he received his doctor degree and started to work as an assistant-physician at the department of Cardiology of the Rode Kruis ziekenhuis in Beverwijk. During this period he showed a growing interest for cardiology. After several talks with the cardiologists in Beverwijk, he decided to look for a PhD project at the Cardiology department of the Academic Medical Center. In 2008 he started as a PhD student at the department of Interventional Cardiology of the AMC. Here he worked under supervision of co-promotor dr. Jan Baan and promotores prof.dr. J.J. Piek and prof.dr. B.A.J.M. de Mol. The research focused on transcatheter aortic valve implantations in high-risk or inoperable patients with aortic valve stenosis and resulted in this thesis: ‘Clinical and hemodynamic effects of transcatheter aortic valve implantation’. The author of this thesis started his residency in October 2011 at the Internal Medicine department under supervision of prof.dr. J.B.L. Hoekstra, prof.dr. J.A. Romijn and prof.dr. J.M. Prins. In October 2013 he will continue his Cardiology training under supervision of dr. Renée van den Brink.