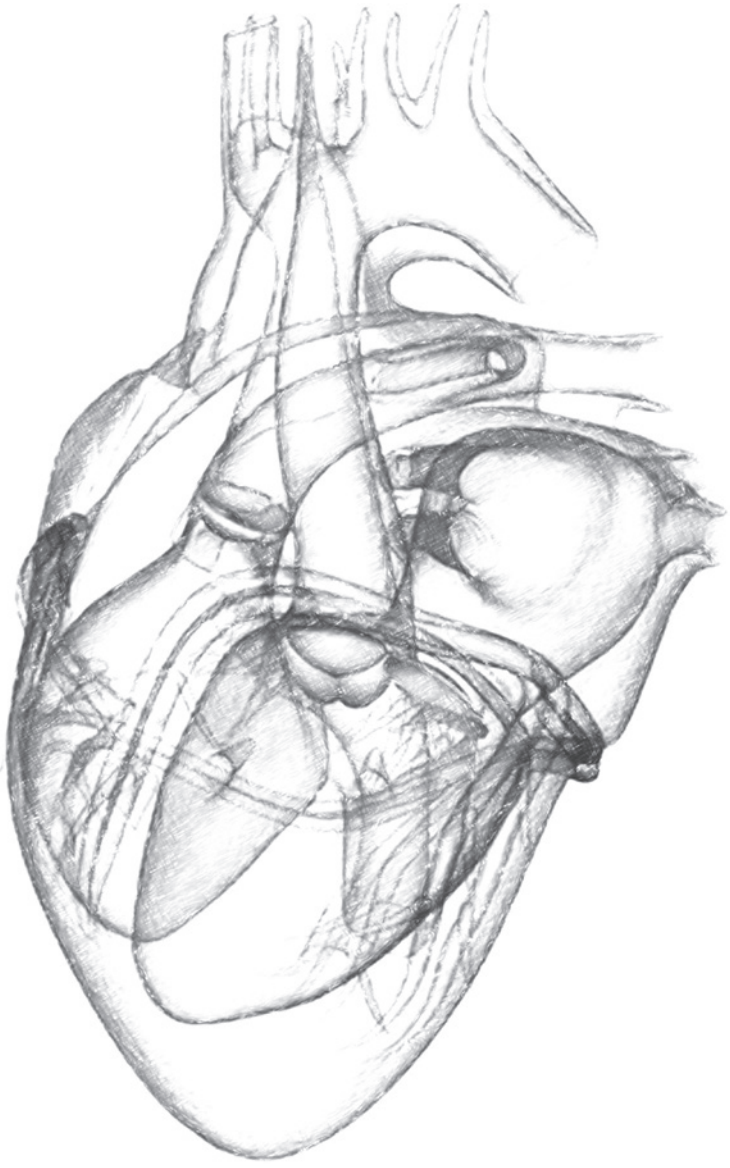
Transcatheter Aortic Valve Implantation: Insights into Clinical Complications



Robert M.A. van der Boon

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Transcatheter Aortic Valve Implantation: Insights into Clinical Complications

Percutane aortaklepimplantatie: inzichten in klinische complicaties

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Overige leden: Prof.dr. F. Zijlstra
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In liefdevolle herinnering aan mijn moeder

TABLE OF CONTENTS

CHAPTER 1

Introduction and Outline of this Thesis

INTRODUCTION AND OUTLINE OF THIS THESIS

Calcific aortic stenosis (AS) is a progressive disease that results in calcified and stiff valve leaflets increasing the left ventricular (LV) afterload. The prevalence of AS ranges from 3 to 23% and a total of 2 to 5% of all adults have significant disease with symptoms of dyspnea, angina and/or syncope[1–3]. With aging of the Western population the overall burden of AS in the general population will increase[4,5]. Once mild valve obstruction is present hemodynamic deterioration is common, leading to progressive AS and a dismal prognosis irrespective of symptoms[6–8]. The onset of symptoms or impairment in LV function heralds a predictable decline in survival with almost 50% of patients dying within 3 to 5 years[9,10]. No effective medical therapy is available ultimately requiring surgical aortic valve replacement (SAVR). In patients with symptomatic severe AS the reduction in afterload after SAVR significantly improves cardiac function, translating into improved survival[11,12]. The operative mortality associated with SAVR is dependent on both patient- and operation/surgical-related factors. The latter has decreased dramatically and 30-day mortality is currently under 3% for isolated SAVR and under 4.5% for combined SAVR, despite increasing age and comorbidities[13]. Nevertheless, a significant proportion of patients with symptomatic severe AS are at prohibitive risk to undergo SAVR due to advanced age, comorbidities and antecedents[14–16]. The concept of a less invasive technique to treat a degenerated aortic valve in order to minimize the surgical risk has been pursued since 1965 and regained interest in 1989 by Andersen et al[17,18]. Procedural and device refinement led to the first in-human implantation of a transcatheter heart valve in aortic position in 2002 by Cribier et al[19]. Since then, Transcatheter Aortic Valve Implantation (TAVI) has emerged as a viable treatment option in patients at prohibitive risk to undergo SAVR[20–23]. TAVI consists of a catheter-based procedure performed on a beating heart without sternotomy and cardio-pulmonary bypass in which a trileaflet bioprostheses is implanted in the aortic root position. In its current state, TAVI represents a transformative technology with the potential to improve symptoms and prolong life in patients who previously had no surgical options, which was underlined by the landmark Placement of Transcatheter Aortic Valves (PARTNER) randomized controlled trial[20,21]. As a result the number of procedures have increased exponentially with an estimated 150.000 valves, at the time of this writing, implanted since the initial experience in 2002. This number is expected to increase in the forthcoming years with 27.000 patients becoming eligible for TAVI annually[5]. Nevertheless, as any other surgical or interventional treatment modality, TAVI is associated with a number of adverse events such as, mortality, cerebrovascular events, bleeding- and vascular complications, conduction abnormalities and paravalvular aortic regurgitation[24]. Despite the worldwide experience there is only one randomized

trial, the aforementioned PARTNER study, comparing patients receiving TAVI to the existing standard of care[20,21]. Although randomized controlled trials form the highest level of evidence available for evaluating new therapeutic strategies, the results need to be considered in the context in which they were obtained. Often conducted under ideal circumstances and in selected patients due to the in- exclusion criteria, the external validity or generalizability of trials may be questioned. Observational single- and multicenter registry data give insight in the performance of TAVI in a "real-world" setting and the factors associated with poor outcome.

The aim of the current thesis was to evaluate the in-hospital complications and prognostic factors associated with outcome after TAVI with specific attention for the occurrence of post-procedural conduction abnormalities. **Part I** of this thesis will focus on specific patient-, procedural and device related features. This will be discussed in three different aspects. First, how specific patient variables and co-morbidities influence in-hospital and long-term outcomes after TAVI (Part IA: Chapters 2, 3, 4). **Chapter 2** will discuss the influence of reduced cardiac function, after which **Chapter 3 and 4** will give details on the effect of body mass index and chronic kidney disease on outcomes after TAVI. Secondly, how differences in (peri-) operative strategies effect post-operative complications and long-term outcomes (Part IB: Chapters 5,6,7,8). **Chapter 5** reports on the outcomes of TAVI in patients with incomplete revascularization, whereas **Chapter 6 and 7** will specifically focus on access site and valve choice. In **Chapter 6** we report on a comparison between transfemoral and transapical aortic valve implantation. **Chapter 7** consists of the first report on the differences in the outcomes between the two widely used commercial valves, the Medtronic CoreValve System and the Edwards SAPIEN Valve. **Chapter 8** assesses the frequency and role of blood transfusions in patients undergoing TAVI using a multicenter study approach (Pooled-RotterdAm-Milano-Toulouse In Collaboration or PRAGMATIC Initiative). Third, how the high frequency of post-operative infections effect long-term outcomes in the elderly population undergoing TAVI (Part IC: **Chapter 9).**

Part II aims to evaluate and discuss the occurrence of conduction abnormalities after TAVI. **Chapter 10** gives a comprehensive review of the mechanisms underlying these abnormalities and the specific anatomical-, patient- and procedural related features. **Chapters 11 and 12** address the frequency, exact timing and persistence of newly acquired conduction abnormalities, especially left bundle branch block (LBBB). The latter, known to be a risk factor for poor outcome in patients undergoing surgical aortic valve replacement. **Chapter 13** reports on the long-term follow-up in patients with TAVI-induced LBBB from a Dutch multicenter registry encompassing over 1000

patients with detailed electrocardiographic assessment. In **Chapter 14** we will discuss the changes in the occurrence of LBBB over time and with increased experience in both patients with the Medtronic CoreValve System and the Edwards SAPIEN Valve. The aggregate of information on clinical implications and treatment options of conduction abnormalities will be discussed in **Chapter 15**. TAVI with the Medtronic CoreValve System is associated with a higher frequency of post-procedural need of a permanent pacemaker. Finally, in **Chapter 16** we focus on these patients and report on the need of permanent pacing during follow-up. The most important findings of this thesis will be discussed in **Chapter 17**. In addition future perspectives on the role of TAVI will be discussed.

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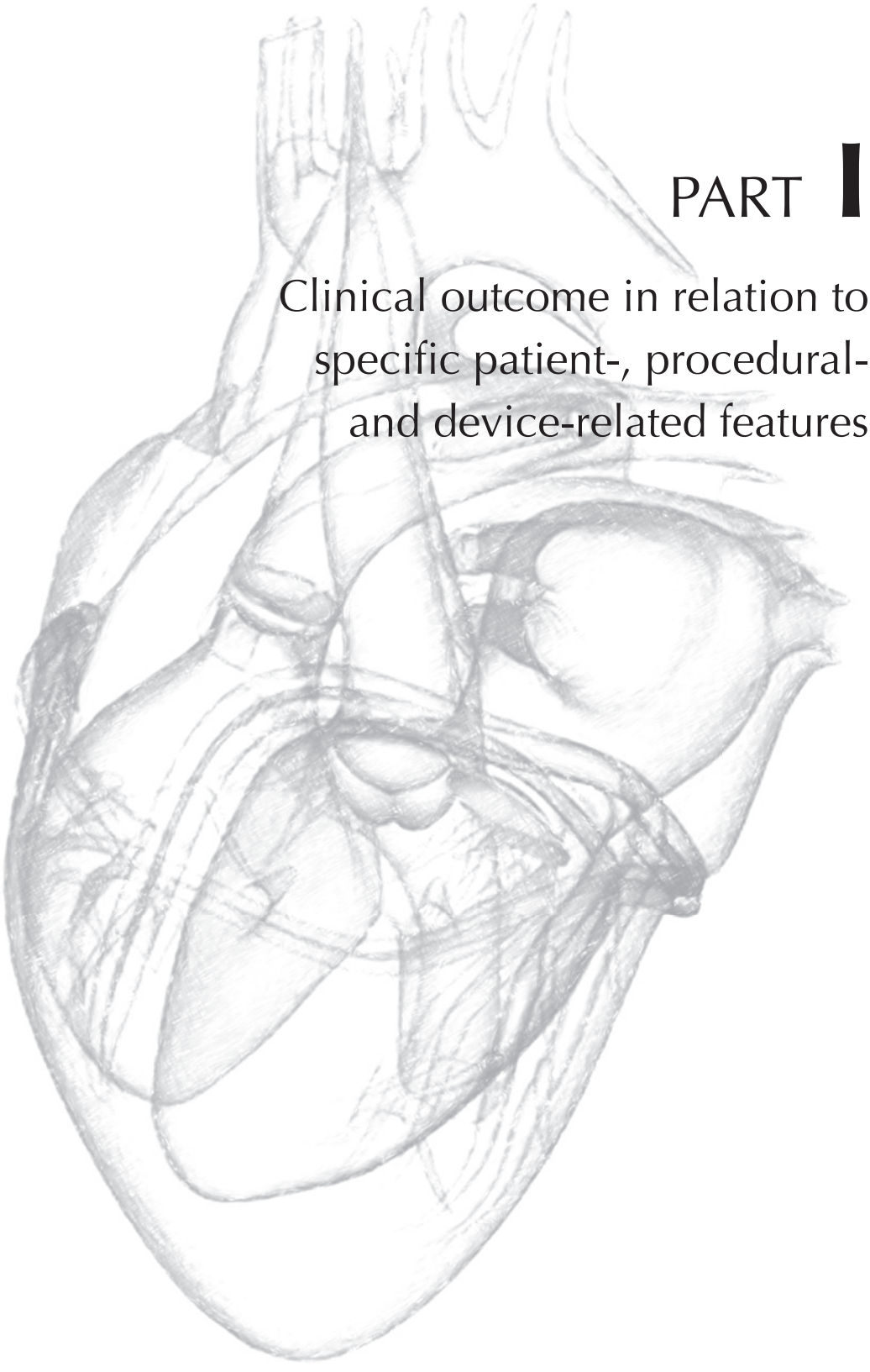
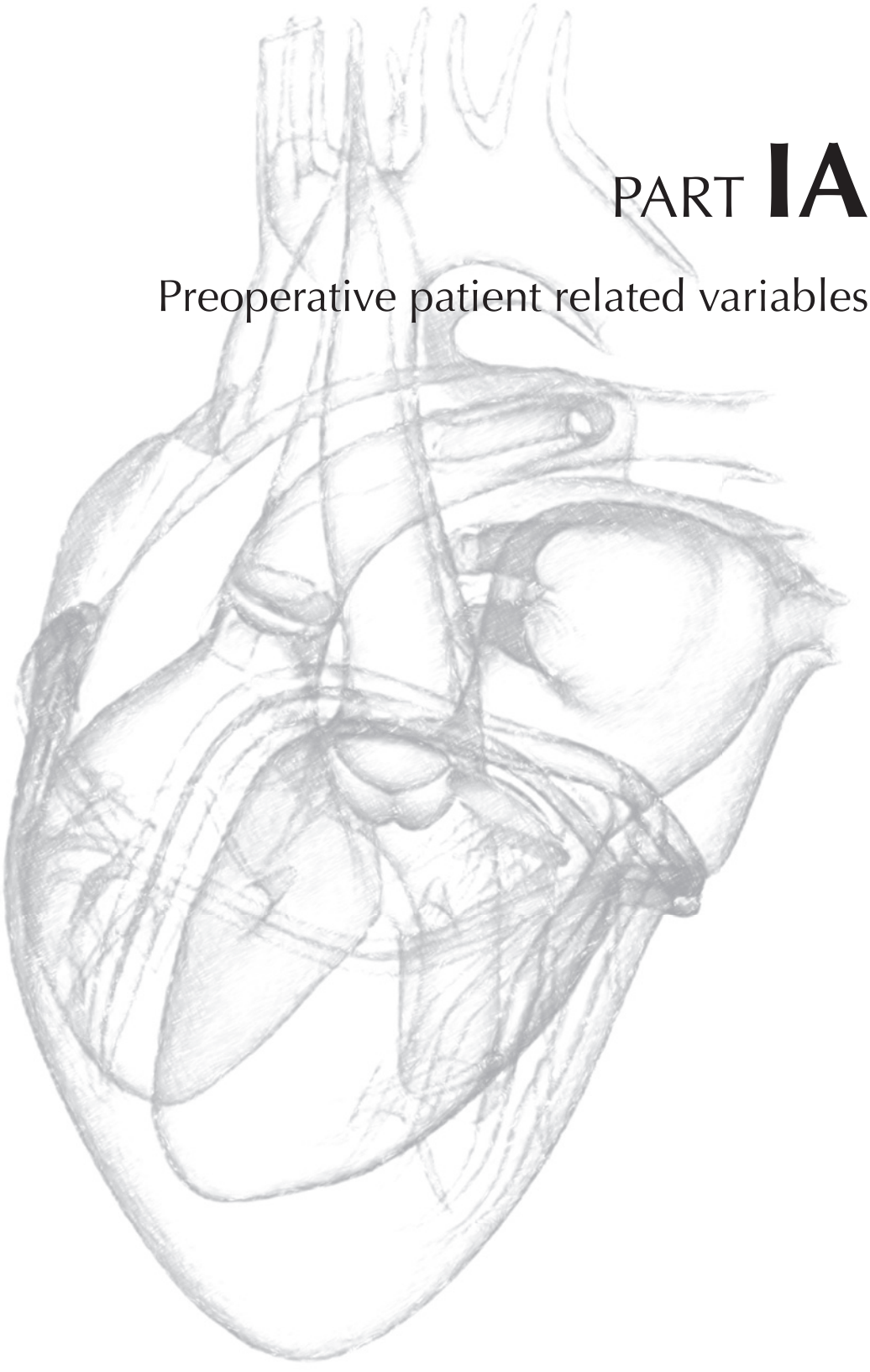


PART I

Clinical outcome in relation to specific patient-, procedural- and device-related features



PART IA

Preoperative patient related variables

CHAPTER 2

Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function

van der Boon RM, Nuis RJ, Van Mieghem NM, Benitez LM, van Geuns RJ, Galema TW, van Domburg RT, Geleijnse ML, Dager A, de Jaegere PP.

Catheter Cardiovasc Interv. 2012 Apr 1;79(5):702-10.

ABSTRACT

Objectives

To determine the prevalence of impaired left ventricular (LV) systolic function and its impact on the in-hospital and long-term outcome in patients who underwent Transcatheter Aortic Valve Implantation (TAVI).

Background

Although impaired LV function may be considered a contra-indication for aortic valve replacement, the hemodynamic characteristics of transcatheter valves may offer procedural and long-term clinical benefit in such patients.

Methods

230 consecutive patients underwent TAVI with the Medtronic-CoreValve System. Impaired LV function was defined by a Left Ventricular Ejection Fraction (LVEF) ≤ 35% (European Multicenter Study on Operative Risk Stratification and Long-term Outcome in patients with Low-Flow/Low-Gradient Aortic Stenosis). Study endpoints were selected and defined according to the Valve Academic Research Consortium recommendations.

Results

Compared to patients with a LVEF > 35% (n = 197), those with LVEF ≤ 35% (n = 33) were more often male (78.8% vs. 46.7%, p<0.001), more symptomatic (NYHA class III or IV, 97.0% vs. 77.2%, p=0.008) and had a higher prevalence of prior coronary artery disease (63.6% vs. 43.1%, p=0.029). The Logistic EuroSCORE was 14.8% and 22.8, respectively (p=0.012). No difference was observed between the 2 groups in-hospital or 30-day mortality (3.0% vs. 9.6%, p=0.21), the Combined Safety Endpoint at 30 days (24.2% and 24.4%, p=0.99) and survival free from readmission at 1 year (69.2% and 69.7%, p=0.85). After adjustment, LVEF ≤ 35% was not associated with an increased risk of 30-day mortality, in-hospital complications and survival free from readmission at follow-up.

Conclusions

The immediate and long-term outcome after TAVI did not differ between patients with an impaired and preserved LVEF. LVEF ≤ 35% did not predict adverse immediate and long-term outcome. These findings suggest that TAVI should not be withheld in selected patients with impaired LV function.

INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are considered too high a risk for surgical aortic valve replacement (AVR)[1]. In general these patients are characterized by advanced age and/or multiple co-morbid conditions, coronary artery disease in particular[2–7]. The presence of an afterload excess in addition to age and eventual coronary artery disease may impact the left ventricle (LV) systolic and diastolic function which in turn has been shown to be associated with an increased perioperative mortality during AVR[8–10]. Despite the increased operative risk in patients with an impaired LV function, those who survive the operation benefit from the valve replacement in terms of survival and symptom reduction. This has been shown in patients with and without inotropic reserve and in patients in whom inotropic reserve was or could not be not investigated[11–14]. In this respect, it is remarkable that a poor LV function is considered a contra-indication for TAVI according to some manufacturer's guidelines. Also patients with LVEF < 20% were currently excluded from recently published randomized studies[7,15]. Moreover, it contrasts with the clinical recommendation to use a valve with optimal hemodynamics especially in patients with a poor LV function as a residual gradient or small valve area are associated with poor outcome[16,17]. Optimal hemodynamics may be achieved with the currently available catheter-based aortic bioprostheses[18–20]. Furthermore, there is evidence that TAVI is associated with a better Left Ventricular Ejection Fraction (LVEF) recovery in comparison to AVR in patients with reduced LV function[21]. Since there is scant information on the outcome of patients with an impaired LVEF who underwent TAVI, we sought to determine the prevalence of impaired LV systolic function and its impact on the perioperative mortality and morbidity and long-term outcome in a series of 230 patients who underwent TAVI with the Medtronic CoreValve System (MCS).

PATIENTS AND METHODS

Patients

The study population consists of 230 consecutive patients with symptomatic aortic valve stenosis who underwent TAVI with the MCS between November 2005 and February 2011 in the Erasmus Medical Center, Rotterdam, the Netherlands (178 patients) and Angiografia de Occidente, Cali, Colombia (52 patients). Details of patient selection and planning of the procedure have previously been described[22]. In brief, all patients were first seen at a dedicated out-patient clinic. All underwent a structured interview, physical examination, laboratory assessment, 12-lead ECG and 2D transthoracic

echocardiography (TTE) including continuous wave Doppler examination of the aortic valve. If there was an indication for valve replacement, irrespective of the eventual treatment modality, patients underwent a diagnostic coronary angiography and angiography of the ileo-femoral arteries. Patients were discussed in a cardiology-cardiothoracic meeting consisting of an interventional cardiologist, cardiothoracic surgeon and general cardiologist. Patients were accepted for TAVI by consensus on the basis of the following criteria: valvular aortic stenosis (AVA < 1.0 cm^2 or ≤ 0.6 cm^2/m^2) and poor surgical candidate initially defined age ≥ 80 years or a logistic EuroScore of ≥ 20 (November 2005 – October 2006, 5 patients), followed by age ≥ 75 or a logistic EuroScore ≥15 (October 2006 – May 2007, 12 patients). During these periods, patients of ≤ 65 years were also eligible irrespective of EuroSCORE in case of severe comorbidity such as respiratory failure, pulmonary hypertension, liver cirrhosis, cachexia, previous cardiac surgery, thoracic wall deformities or a porcelain aorta. After completion of enrolment in the Cor2006-02 Registry (May 2007), treatment decision was predominantly made during heart team discussion in which risk/benefit assessment of the various treatment options played a key role in reaching consensus.

Doppler-echocardiography, LVEF

All patients underwent 2 dimensional TTE using commercially available ultrasounds systems before TAVI according to the recommendations of the American Society of Echocardiography [23]. The LVEF was calculated using the biplane modified Simpson rule [23]. In accordance with the European Multicenter Study on Operative Risk Stratification and Long-term Outcome in patients with Low-Flow/Low-Gradient Aortic Stenosis, an impaired LV function was defined by a LVEF ≤ 35%[12].

Device and Procedure

The MCS consists of a self expandable nitinol frame in which a trileaflet porcine pericardium tissue valve is mounted. The valve is currently available in sizes of 26 mm or 29 mm. TAVI was performed via femoral or subclavian artery under local or general anaesthesia. In all patients an 18F sheet was inserted into the femoral or subclavian artery to advance the 18Fr delivery catheter except 5. They consist of the first 5 patients of this cohort in whom a 21 Fr sheathless delivery catheter was used; 4 patients underwent surgical cutdown of the femoral artery and 1 patient underwent a cutdown of the subclavian artery. A temporary pacemaker wire was placed in the right ventricle during the procedure and remained in situ until 48 hours after TAVI. Valve implantation was preceded by balloon valvuloplasty of the aortic valve with a 22 mm or 23 mm balloon under rapid right ventricular pacing at 180 to 220 bpm. The MCS was then implanted under fluoroscopic and angiographic control. The aim was to implant the

ventricular end of the inflow part of the MCS 6-8 mm below the aortic annulus[24,25]. After TAVI, patients were extubated before leaving the catheterization laboratory or within 2 hours after arrival in the cardiac care unit.

Data Collection

Preprocedural demographical, clinical, laboratory and technical (electro- and echocardiography) data were prospectively collected and entered in a dedicated database.

The Valve Academic Research Consortium (VARC) recommendations were used for all separate endpoints and 30-day composite safety endpoint definitions[26]. The following 1] separate clinical endpoints were collected during or immediately after TAVI: death, myocardial infarction, cerebrovascular complications, vascular and bleeding complications, acute kidney injury (AKI), 2] therapy-specific endpoints including ventricular perforation at any time resulting in cardiac tamponade, post-implantation balloon dilatation, valve-in-valve implantation and unplanned cardiopulmonary bypass with or without conversion to open surgical AVR and 3] prosthetic valve associated complications including permanent pacemaker implantation. All cerebrovascular events were evaluated and adjudicated by a neurologist. Serum creatinine was monitored up to 72 hours after the procedure to identify patients with acute kidney injury (AKI) and data on red blood cell transfusions were recorded by the institution's blood bank laboratory. The VARC Composite Safety Endpoint at 30 days was used to define safety of TAVI and consisted of the composite of all-cause mortality, major stroke, major vascular complications, life-threatening bleeding, AKI – stage 3, periprocedural myocardial infarction, repeat procedure for valve-related dysfunction (surgical or interventional).

Follow-up information on survival and repeat hospitalisation because of cardiac reasons, as defined in the PARTNER-trial, was obtained by first contacting treating cardiologists, general practitioners and the civil registries at time intervals of 6 months[7]. A questionnaire was sent to the patient for the assessment of symptoms, cardiac events and readmission(s). Also the surviving patients were contacted by phone to confirm eventual readmission and reason. In addition all medical records were revised. If necessary the general practitioner was contacted. Follow-up was complete for all patients.

Statistical Analysis

Categorical variables are presented as frequencies and percentages and, compared with the use of the Pearson Chi Square Test or the Fisher's exact test, as appropriate.

Continuous variables are presented as means (±SD) (in case of a normal distribution) or medians (IQR) (in case of a skewed distribution) and compared with the use of Student's T-test or the Mann-Whitney U-test. Normality of the distributions was assessed using the Shapiro-Wilks test. Survival curves were constructed using Kaplan-Meier estimates and compared using the log-rank test.

Table 1. Baseline characteristics according to Left Ventricular Ejection Fraction

	Overall n = 230	**LVEF ≤ 35** n = 33	**LVEF > 35** n = 197	**p-value**
Demographics				
Age (yrs), mean ± SD	80.2 ± 7.14	78.5 ± 8.79	80.5 ± 6.81	0.13
Male, n (%)	118 (51.3)	26 (78.8)	92 (46.7)	0.001
Height (cm), mean ± SD	166.67 ± 8.50	169.45 ± 8.24	166.20 ± 8.48	0.04
Weight (kg), mean ± SD	71.52 ± 12.76	71.15 ± 12.33	71.57 ± 12.86	0.86
Body Mass Index, mean ± SD	25.71 ± 3.98	24.80 ± 4.06	25.87 ± 3.96	0.16
Body Surface Area, mean ± SD	1.82 ± 0.19	1.82 ± 0.18	1.80 ± 0.19	0.87
NYHA class III or IV, n (%)	184 (80.0)	32 (97.0)	152 (77.2)	0.008
Previous cerebrovascular accident, n (%)	38 (16.6)	2 (6.1)	36 (18.4)	0.079
Previous myocardial infarction, n (%)	47 (20.4)	10 (30.3)	37 (18.8)	0.13
Previous CABG, n (%)	55 (24.0)	11 (33.3)	44 (22.4)	0.18
Previous PCI, n (%)	54 (23.6)	13 (39.4)	41 (20.9)	0.021
Coronary artery disease, n (%)	106 (46.1)	21 (63.6)	85 (43.1)	0.029
Diabetes mellitus, n (%)	54 (23.6)	10 (30.3)	44 (22.4)	0.33
Hypertension, n (%)	144 (62.9)	21 (63.6)	123 (62.8)	0.92
Creatinine (umol/L), med (IQR)	95.48 (72.40-118.56)	116.00 (90.58-141.42)	93 (71.00-115.00)	0.001
Chronic haemodialysis, n (%)	12 (5.2)	2 (6.1)	10 (5.1)	0.81
Chronic Obstructive Pulmonary Disease, n (%)	75 (32.8)	13 (39.4)	62 (31.6)	0.38
Peripheral vascular disease, n (%)	30 (13.3)	7 (22.6)	23 (11.9)	0.10
Permanent pacemaker, n (%)	26 (11.4)	7 (21.2)	19 (9.7)	0.054
Atrial fibrillation, n (%)	48 (22.5)	6 (20.0)	42 (23.0)	0.72
Baseline echocardiogram				
Aortic valve annulus (mm), mean ± SD	22.54 ± 2.29	23.37 ± 2.13	22.40 ± 2.29	0.041
Left ventricular ejection fraction, mean ± SD	50.90 ± 14.83	25.87 ± 6.65	55.10 ± 11.25	0.0001
Peak velocity, mean ± SD	4.29 ± 0.77	3.86 ± 0.79	4.36 ± 0.74	0.001
Peak gradient (mmHg), mean ± SD	76.37 ± 27.48	61.71 ± 26.02	78.87 ± 27.00	0.001
Mean gradient (mmHg), mean ± SD	44.35 ± 17.04	34.35 ± 15.13	46.05 ± 16.80	0.0001
Aortic valve area (cm2), mean ± SD	0.66 ± 0.21	0.66 ± 0.16	0.66 ± 0.22	0.88
Aortic regurgitation grade ≥ III, n (%)	54 (23.0)	7 (21.2)	46 (23.4)	0.79
Mitral regurgitation grade ≥ III, n (%)	29 (12.6)	7 (21.2)	22 (11.2)	0.12
Logistic EuroSCORE, med (IQR)	16.40 (9.32-23.48)	22.80 (13.32-32.28)	14.75 (8.27-21.24)	0.012
STS-PROM Score, med (IQR)	4.90 (2.94 - 6.87)	5.10 (2.43 - 7.78)	4.90 (3.00 - 6.80)	0.64

Abbreviations: NYHA: New York Heart Association; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft.

For the assessment of the impact of impaired LVEF on perioperative (i.e. in-hospital or 30 day) mortality and morbidity (Combined Safety Endpoint at 30 days), a univariate logistic regression analysis was first performed comparing the baseline patient and procedural characteristics between patients with and without such a complication. Unadjusted odds ratios were then calculated for all variables with a p-value < 0.10. Thereafter, LVEF ≤ 35% was adjusted for the characteristics which were significant on univariate analysis, taking into account the restricted number of variables to be included in the multivariate logistic regression model. The same method was applied for the calculation of the un- and adjusted odds of mortality at follow-up and repeat hospitalization except that in this case Cox regression analysis was used. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analysis were performed with the use of SPSS Software 17.0 (SPSS Institute, Chicago, IL).

RESULTS

Baseline Characteristics and Procedural details

The baseline characteristics and procedural details of the total population and the two subgroups are summarized in Table. 1 and 2. A total of 33 patients (14.3%) had a LVEF ≤ 35% In comparison to patients with a LVEF > 35%, patients with a LVEF ≤ 35% were more often male (78.8% vs.46.7%, p<0.001) and more symptomatic (NYHA class III or IV, 97.0% vs. 77.2%, p=0.008). Also, there was a higher prevalence of antecedent coronary artery disease (63.6% vs. 43.1%, p=0.029) and pacemaker implantation (21.2% vs. 9.7%, p=0.054). There was no difference in the severity of aortic stenosis defined by AVA (0.66 ± 0.16 vs. 0.66 ± 0.22). The logistic EuroSCORE was significantly higher in patients with LVEF ≤35% (22.80 (13.32 – 32.28) vs. 14.75 (8.27 – 21.24), p=0.012). Circulatory support by means of Extracorporeal Membrane Oxygenation (ECMO) or percutaneous-Left Ventricular Assistance Device (p-LVAD) was more often used in patients with LVEF ≤ 35% but did not reach the level of statistical significance. Also, they underwent more often valve-in-valve implantation (12.1% vs. 3.6%, p=0.033), compared to those with a LVEF > 35%.

In-hospital or 30 day outcome is summarized in Table. 3. All-cause mortality of the total population was 8.7% (n=20). There was no difference in 30-day mortality between patients with a LVEF ≤ 35% and those with a LVEF > 35%. One patient with a LVEF ≤ 35 (no 16) died due to pneumonia. The cause of death in the 19 patients with a LVEF > 35% was cardiovascular in 15 (78.9%) and non-cardiovascular in 4 patients (21.1%). Details are summarized in Table. 4.

Table 2. Procedural details and results according to Left Ventricular Ejection Fraction			
	LVEF ≤ 35 n = 33	**LVEF > 35** n = 197	**p-value**
Vascular access, n (%)			
surgical - femoral artery	3 (9.1)	14 (7.1)	0.69
surgical - subclavian artery	2 (6.1)	5 (2.5)	0.28
percutaneous - femoral artery	28 (84.8)	178 (90.4)	0.34
Circulatory support, n (%)			
ECMO	2 (6.1)	1 (0.5)	0.009
LVAD	2 (6.1)	11 (5.6)	0.91
None	29 (87.9)	185 (93.9)	0.21
Additional interventions during TAVI, n (%)			
PTA Iliac Artery	0 (0.0)	7 (3.6)	0.27
PCI	3 (9.1)	14 (7.1)	0.69
Prosthesis size, n (%)			
26-mm*	9 (27.3)	80 (41.0)	0.13
29-mm*	24 (72.7)	115 (59.0)	0.13
Therapy-specific results, n (%)			
Post-implantation balloon dilatation	4 (12.1)	30 (15.2)	0.64
Valve-in-Valve implantation	4 (12.1)	7 (3.6)	0.033
Ventricular perforation, n (%)	0	2 (1.0)	0.56
Conversion to surgical AVR	0	0	1
Procedure time (min), mean ± SD	203.53 ± 87.38	213.58 ± 76.69	0.50
Amount of contrast (ml), mean ± SD	173.33 ± 75.50	184.00 ± 81.05	0.50

Abbreviations: ECMO : Extracorporal Membrane Oxygenation; LVAD: Left Ventricular Assistance Device; PTA: Percutaneous Transluminal Angioplasty; PCI: Percutaneous Coronary Intervention; AVR: Aortic Valve Replacement. * Two patients did not receive TAVI; one died during induction (anesthesia) and one died as a result of balloon valvuloplasty induced LVOT rupture.

No difference was observed in the individual components of the VARC Composite Safety Endpoint which was 24.2% in patients with a LVEF ≤ 35% and 24.4% in those with a LVEF > 35% (Table 3). The un-and adjusted odds ratio analysis revealed that LVEF ≤ 35% was not associated with an increased risk of procedural mortality or morbidity (VARC Composite Safety Endpoint definition) at 30 days (Table. 5). Long-term follow-up was complete for all patients and ranged from 1 to 63 months (median (IQR): 11 (1 – 21) months). The Kaplan-Meier estimates of survival and survival free of readmission because of cardiac reasons are shown in Figure 1A&B. No difference was observed between the 2 groups. Estimates of survival at 1 year were 81.5% and 77.8% (p=0.58), respectively in patients with a LVEF ≤ 35% and those with a LVEF > 35%. Survival free from readmission was 69.2% and 69.7% (p=0.85) respectively. Similar to the analysis

Table 3. In-hospital clinical outcome, prosthetic-valve associated outcome and echo-doppler findings according to Left Ventricular Ejection Fraction

	LVEF ≤ 35 n = 33	**LVEF > 35** n = 197	**p-value**
In-hospital clinical outcome			
30-day or in-hospital death, n (%)			
All-cause	1 (3.0)	19 (9.6)	0.21
Cardiovascular cause	0	15 (7.6)	0.10
Myocardial Infarction, n (%)			
Periprocedural (<72 hr)	1 (3.0)	2 (1.0)	0.35
Spontaneous (>72 hr)	0	1 (0.5)	0.68
Cerebrovascular complication, n (%)			
Major stroke	1 (3.0)	10 (5.1)	0.61
Minor stroke	0	2 (1.0)	0.56
Transient ischemic attack	1 (3.0)	4 (2.0)	0.72
Vascular complication, n (%)			
Major	3 (9.1)	19 (9.6)	0.92
Minor	1 (3.0)	18 (9.1)	0.24
Bleeding Complication, n (%)			
Life-threatening	3 (9.1)	16 (8.1)	0.85
Major	3 (9.1)	32 (16.2)	0.29
Minor	1 (3.0)	15 (7.6)	0.34
Acute kidney injury, n (%)	5 (15.2)	33 (16.8)	0.81
Stage I	3 (9.1)	27 (13.7)	0.47
Stage II	0	4 (2.0)	0.41
Stage III	2 (6.1)	2 (1.0)	0.04
Reintervention in hospital, n (%)	0	1 (0.5)	0.68
Permanent pacemaker requirement, n (%)	6 (18.2)	44 (22.3)	0.59
Combined Endpoints			
Composite Safety Endpoint, n (%)	8 (24.2)	48 (24.4)	0.99
Echocardiography results *			
Aortic valve area (cm2), mean ± SD	1.95 ± 0.64	1.97 ± 0.66	0.90
Mean aortic gradient, mean ± SD	8.29 ± 4.85	8.84 ± 4.00	0.51
Aortic regurgitation grade ≥ III, n (%)	7 (21.2)	27 (14.1)	0.30
Mitral regurgitation grade ≥ III, n (%)	5 (15.2)	19 (10.0)	0.38

* Seven Patients did not undergo post procedural echocardiography.

Table 4. Causes of 30 day or in-hospital mortality in patients undergoing TAVI

n	Number in cohort	Number of days till death	LVEF ≤ 35	Cardiovascular Death	Cause of Death
1	10	6	no	yes	Cardiac Tamponade
2	44	29	no	no	Sepsis
3	51	0	no	yes	Retroperitoneal Hemorrhage
4	54	0	no	yes	Electromechanic Dissociation
5	58	0	no	yes	During Induction
6	64	24	no	yes	Major Stroke
7	67	11	no	no	Sepsis
8	71	8	no	yes	Asystole
9	80	9	no	yes	Major Stroke
10	85	31	no	yes	Heart Failure
11	88	29	no	yes	Sudden Death
12	104	0	no	yes	Cardiac Tamponade
13	106	14	no	yes	Heart Failure
14	107	0	no	yes	Electromechanic Dissociation
15	111	0	no	yes	Retroperitoneal Hemorrhage
16	124	28	yes	no	Pneumonia
17	138	0	no	yes	Periprocedural Myocardial Infarction
18	150	32	no	no	Pneumonia
19	167	29	no	no	Pneumonia
20	217	1	no	yes	Fatal Bleeding

Table 5. Unadjusted and adjusted odds ratios of LVEF ≤ 35% for the different endpoints

	Crude OR (95% C.I.)	**Adjusted OR** (95% C.I.)
30-day mortality	0.29 (0.038 - 2.27)	0.26 (0.032 - 2.13)
Composite safety endpoint	0.99 (0.42 - 2.35)	0.73 (0.25 - 2.16)
	Crude HR (95% C.I.)	**Adjusted HR** (95% C.I.)
Mortality at follow-up*	0.83 (0.37 - 1.82)	0.63 (0.26 - 1.49)
Survival free from readmission*	1.09 (0.57 - 2.06)	1.02 (0.51 - 2.04)

*Excluding patients who died during hospital stay and within 30 days.

of the impact of LVEF ≤ 35% on 30-day outcome, LVEF ≤ 35% was not found to be associated with an increased risk of mortality or readmission during follow-up.

DISCUSSION

We found that 14% of the patients who underwent TAVI had an LVEF ≤ 35%. In comparison to patients with a preserved LV function, these patients were more often male with more symptoms and a higher prevalence of antecedent cardiac disease. Despite this difference in baseline risk, the perioperative mortality and morbidity as well as the long-term outcome did not differ between patients with an impaired and preserved LV function. LVEF ≤ 35% was not found to be associated with an increased risk of mortality or complications.

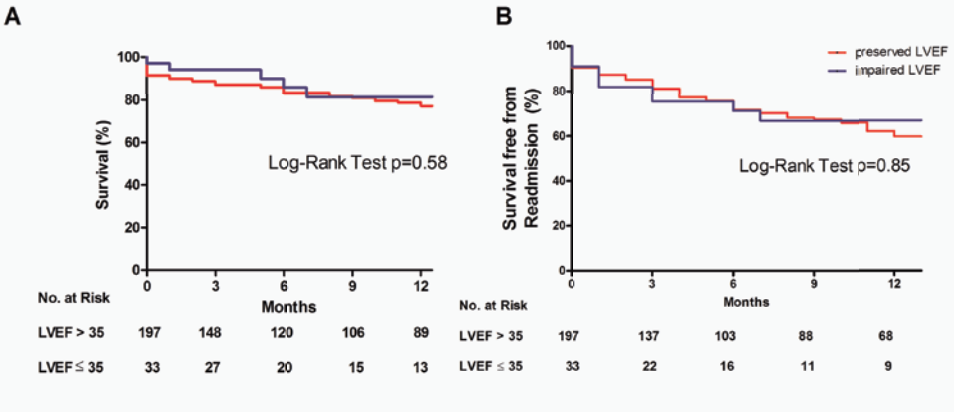


Figure 1. One-year Kaplan-Meier curves of survival (**A**) and survival free from readmission (**B**) in patients with impaired and preserved left ventricular systolic function undergoing TAVI

This summary of the main findings of the study needs to be interpreted in the context of an observational cohort study with 230 patients of whom a minority (14%) had a LVEF ≤ 35%. As a result the accuracy of the reported point estimate(s) of the outcome and its components may be questioned, since one event less or more in one group (LVEF ≤ 35% in particular), may substantially affect the direction of the findings. Yet, the adjusted odds of in-hospital or 30-day mortality and complications and, survival free from readmission revealed that LVEF ≤ 35% was not associated with an increased risk of immediate or long-term adverse events.

With respect to the findings of the immediate outcome (safety), one may question the effect of learning curve, device iterations and the use of circulatory support on the observed outcomes. The second generation MCS system was only used in 5 patients. All other patients were treated with the 3th generation MCS system via an 18 Fr sheath. We

therefore believe that this did not play a role in the present findings. Circulatory support was used more often in patients with impaired LVEF, yet this did not reach the level of statistical significance. Moreover, the use of circulatory support in this series of patients was not so much dictated by the presence of an impaired LV function but by the level of experience with TAVI and its evolution. At the initiation of the TAVI program (2005), circulatory support was part of the procedure and was used in the first 10 patients. After these patients support was stopped, except for 6 patients of whom 4 underwent TAVI in combination with complex percutaneous coronary intervention (PCI). Circulatory support because of poor LV function was only used in 2 patients. One should also acknowledge that despite the potential protective effect of circulatory support, these systems carry the intrinsic risk of major bleeding- and vascular complications which in turn may negatively affect safety.

The findings of this study indicate that TAVI is equally safe and effective in patients with an impaired and preserved LVEF. This is in accordance with findings of Ewe et al who reported on 147 patients who underwent TAVI but is in contrast with those of Tamburino et al and with the vast experience with surgical aortic valve replacement[5,11,16,27–31]. Whether the discrepancy between these findings and those of Tamburino et al is explained by differences in sample size and baseline characteristics, definition of impaired LV function and/or the distribution of data remains to be elucidated. The discrepancy with AVR in which the perioperative and long-term mortality in patients with LV dysfunction or low transvalvular gradient is consistently higher in comparison to those with a preserved LV function, may be explained by differences in the nature of TAVI and AVR on one hand, and the differences in the hemodynamic characteristics of the bioprostheses used in TAVI and AVR on the other[20,21,32–37]. At variance with AVR, TAVI is associated with a minimal surgical trauma without the need of ischemic cardiac arrest and the use of extracorporeal circulation. There is evidence that these steps are associated with apoptosis of cardiomyocytes and contractile dysfunction of the surviving cells although recovery of LVEF has been reported after AVR independent from the presence or absence of contractile reserve before the operation[14,38]. It is conceivable that TAVI does not induce myocardial injury or - at least - to a lesser degree. This is suggested by the recent findings of Rodes-Cabau et al who reported that TAVI is systematically associated with some degree of myocardial injury. Yet, in case of a greater degree of injury there was less improvement in LVEF after TAVI[39]. In addition, TAVI results in a more to almost complete relief of the outflow obstruction and a larger effective orifice area[20,36,37]. This in turn may explain the significantly better LV recovery after TAVI than AVR as shown by Clavel et al, and the fact that TAVI was an independent predictor of LV recovery[21]. The observational nature of this and the other

studies obviates firm conclusions. They, nevertheless, provide an indirect but plausible explanation of the findings from a pathophysiologic point of view.

If true and confirmed by others in eventual larger series of patients or randomized comparisons, the aggregate of information suggest that we may need to reconsider the criteria of eligibility for TAVI. According to some recommendations and randomized studies, patients with poor LV systolic function albeit LVEF ≤ 20% are excluded from TAVI. These patients may benefit from TAVI as the biggest improvement in LV recovery after aortic valve replacement has been documented in patients with the lowest baseline mean pressure gradient and LVEF[14,21].

LIMITATIONS

In addition to the ones mentioned above, echo-Doppler assessment at follow-up was not performed in all patients and precluded a comprehensive analysis of the changes in regional and global LV function. This also holds for the absence of dobutamine stress echocardiography for the assessment of contractile reserve. As a result, important mechanistic or pathophysiologic information is missing which would have allowed a better appreciation of the validity of the clinical findings and patient stratification. Conversely, we could not study the potential detrimental effects of new permanent pacemaker implantation on LV function during the follow-up period after valve implantation. With respect to generalizability, the present information only pertains to patients who underwent TAVI with the MCS system via the transfemoral approach. No conclusions can be drawn for other types of valves and access.

CONCLUSIONS

In this series of 230 patients who underwent TAVI, the prevalence impaired LV systolic function was 14%. The immediate and long-term outcome after TAVI did not differ between patients with an impaired and preserved LV function. Moreover, LVEF ≤ 35% was not found to predict adverse immediate and long-term outcome. These findings suggest that TAVI should not be withheld in selected patients with impaired LV function.

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CHAPTER 3

Effect of body mass index on short- and long-term outcomes after transcatheter aortic valve implantation

van der Boon RM, Chieffo A, Dumonteil N, Tchetche D, Van Mieghem NM, Buchanan GL, Vahdat O, Marcheix B, Serruys PW, Fajadet J, Colombo A, Carrié D, van Domburg RT, de Jaegere PP; PRAGMATIC-Plus Researchers.

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ABSTRACT

Better outcomes have been reported after percutaneous cardiac interventions in obese patients ("Obesity Paradox"). Yet, there is limited information on the impact of Body Mass Index (BMI) on outcome after Transcatheter Aortic Valve Implantation (TAVI). We, therefore, sought to determine the effect of BMI on the short- and long-term outcome in patients who underwent (TAVI). The population consisted of 940 patients of whom 25 (2.7%) were underweight, 384 had a (40.9%) normal body weight, 372 (39.6%) were overweight and 159 (16.9%) were obese. Overall, obese patients were younger (79.7 ± 6.4 years vs. 81.7 ± 7.3 kg and 80.8 ± 7.0 kg, p = 0.008) and had a higher prevalence of preserved left ventricular and renal function. By univariable analysis, obese patients had a higher incidence of minor stroke (1.3% vs. 0 and 0.3%, p =0.03), minor vascular complications (15.7% vs. 9.1 and 11.6%,p =0.028) and Acute Kidney Injury stage I (23.3% vs. 10.7% and 16.1%,p <0.001). After adjustment BMI, as a continuous variable, was found to be associated with a lower risk of mortality at 30-days (OR [95% CI]; 0.93 [0.86 – 0.98], p = 0.023) and no effect on survival after discharge (HR [95% CI]; 1.01 [0.96 – 1.07],p = 0.73). In conclusion, obesity was associated with a higher incidence of minor but no major perioperative complications after TAVI. After adjustment, obesity was found to be associated with a lower risk of 30-day mortality and had no adverse effect on mortality after discharge, underscoring the "Obesity Paradox" in patients undergoing TAVI.

INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) has become an established treatment for patients with aortic stenosis who are at high risk for surgical aortic valve replacement (SAVR)[1–4]. Given the endemic nature of obesity in developed countries, one may expect an increasing number of such patients being referred for TAVI[5,6]. Whereas obesity is associated with a higher mortality in the general population and in patients with coronary artery disease, a number of studies reveal a better outcome after percutaneous and surgical coronary intervention and after SAVR and is termed the "obesity paradox"[7–17]. Patients who currently undergo TAVI are older and have more co-morbid conditions than those who undergo percutaneous coronary intervention or cardiac surgery[18–20]. This in combination with the use of large indwelling delivery catheters may expose obese patients to a particular high risk of perioperative complications. Currently there is no information on an eventual protective or adverse effect of body weight on the procedural and long-term outcome in patients undergoing TAVI, which was the subject of the present study.

METHODS

The PRAGMATIC Plus (Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus) Initiative is a collaboration of four European institutions with established TAVI experience. Baseline patient characteristics, procedural details and clinical outcome data from a series of 944 consecutive patients were prospectively collected: 1) San Raffaele Scientific Institute, Milan (n=330); 2) Clinique Pasteur, Toulouse (n=224); 3) Thoraxcenter, Erasmus Medical Center, Rotterdam (n=206); 4) Hôpital Rangueil,Toulouse (n=184). After the Valve Academic Research Consortium (VARC) consensus document was made public, the VARC endpoint definitions were adopted and the respective local databases were modified accordingly[21]. All data were then pooled into a dedicated global multi-center database after which post-hoc analysis was performed. Patient eligibility for TAVI has been described earlier and is comparable across the four centers[20,22,23]. All patients with symptomatic severe aortic stenosis who underwent TAVI had been judged to be at high operative risk by a multi-disciplinary heart team consensus Body Mass Index (BMI) was defined as weight in kilograms divided by the square of height in metres. Weight and height of all patients were collected at hospital admission before the TAVI procedure. Categorisation of BMI was adopted from the WHO and National Institutes of Health and defined as underweight (< 18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25.0 – 30.0 kg/m^2) or obese: (> 30 kg/m^2)[24]. The primary endpoint of

this study consisted of all-cause mortality at 30 days and during follow-up. Secondary endpoints included death, myocardial infarction, cerebrovascular complications, vascular and bleeding complications and Acute Kidney Injury (AKI), in accordance to the VARC endpoint definitions[21]. After hospital discharge mortality data were collected by contacting the civil registries or the referring physician or general practitioner. Follow-up was complete in 99.5% of the patients who survived the first 30 days.

Categorical variables are presented as frequencies with percentages and compared using the Pearson Chi Square or the Fisher's exact test, as appropriate. To assess the presence of a linear-association between BMI and outcome, linear-by-linear association was used. Continuous variables are presented as means (±SD) (in case of a normal distribution) or medians (IQR) (in case of a skewed distribution) and compared with analysis of variance. Normality of the distributions was assessed using the Shapiro-Wilks test. Superiority testing was only performed between the normal weight, overweight an obese group due to the low sample size in the underweight group (n=25 patients). Univariable and multivariable logistic regression was used to assess the effect of BMI on 30 day mortality. Cox proportional hazard regression analysis was performed to determine the relation between BMI (category) and mortality during follow-up. All BMI categories, except for the underweight category, were entered into the model with normal weight patients (BMI: 18.5 – 24.9 kg/m2) as the reference group. Multivariable analysis was adjusted for all differences in baseline and procedural characteristics (age, gender, diabetes, COPD, coronary disease, learning effect (first vs. latter half of cohort), sheath size (18/19 Fr vs. >19 Fr), percutaneous vs. surgical access, peripheral vascular disease, Logistic EuroSCORE (LES), LVEF ≤ 35% and GFR≤ 60). Additionally, univariable and multivariable (logistic or Cox) regression analysis was performed with BMI as a continuous variable to determine the relation of an increase in 1 kg/m^2 and the primary end point. Survival curves for time-to-event variables were constructed in patients who survived the first 30-days after TAVI (Landmark analysis) using Kaplan-Meier estimates and compared with the log-rank test. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analysis were performed with SPSS software 17.0 (SPSS Inc., Chicago, USA).

Table 1. Baseline characteristics of the study population

Variable	Overall (n = 940)	BMI (kg/m²)				p-value
		<18.5 (n = 25)	18.5–24.9 (n = 384)	25–29.9 (n = 372)	>30 (n = 159)	
Demographics						
Age (yrs)	81.0 ± 7.03	81.4 ± 6.5	81.7 ± 7.3*	80.8 ± 7.0	79.7 ± 6.4*	0.008
Men	506/940 (54%)	8/25 (32%)	205/384 (53%)	228/372 (61%)	65/159 (41%)	<0.001
Body mass index (kg/m²)	26.26 ± 4.34	17.50 ± 0.88	22.54 ± 1.61	27.06 ± 1.34	33.38 ± 3.48	<0.001
New York Heart Association class III or IV	761/938 (81%)	18/24 (75%)	305/383 (80%)	299/372 (80%)	139/159 (87%)	0.09
Logistic European System for Cardiac Operative Risk Evaluation	20.9 (13.0–29.9)	20.5 (11.9–29.1)	21.0 (13.8–28.3)	21.6 (12.9–30.3)	18.7 (10.9–26.4)	0.002
Previous cerebrovascular accident	147/940 (16%)	2/25 (8%)	61/384 (16%)	64/372 (17%)	20/159 (13%)	0.41
Previous myocardial infarction	158/940 (17%)	3/25 (12%)	59/384 (15%)	73/372 (20%)	23/159 (15%)	0.20
Previous coronary bypass grafting	207/940 (22%)	3/25 (12%)	69/384 (18%)	100/372 (27%)	35/159 (22%)	0.013
Previous percutaneous coronary intervention	277/940 (30%)	4/25 (16%)	114/384 (30%)	121/372 (33%)	38/159 (24%)	0.14
Coronary artery disease	425/940 (45%)	6/25 (24%)	164/384 (43%)	193/372 (52%)	62/159 (39%)	0.007
Diabetes mellitus	268/940 (29%)	6/25 (24%)	86/384 (22%)	107/372 (29%)	69/159 (43%)	<0.001
Hypertension	656/940 (70%)	14/25 (56%)	265/384 (69%)	265/372 (71%)	112/159 (70%)	0.80
Serum creatinine level (µmol/L)	99.0 (72.4–125.7)	83.1 (67.2–99.0)	99.5 (74.1–124.9)	101.3 (70.0–132.6)	108.1 (87.3–128.8)	0.06
Glomerular filtration rate (ml/min/1.73 m²)†	57.6 (41.0–74.2)	71.2 (54.8–87.6)	56.9 (41.1–72.6)	57.3 (39.3–75.3)	59.9 (45.2–74.5)	0.57
Glomerular filtration rate <60 ml/min/1.73 m²	591/937 (63%)	20/25 (80%)	275/383 (72%)	221/372 (59%)	75/157 (48%)	<0.001
Chronic obstructive pulmonary disease	323/940 (34%)	8/25 (32%)	128/384 (33%)	126/372 (34%)	61/159 (38%)	0.51
Peripheral vascular disease	234/936 (25%)	8/24 (33%)	96/383 (25%)	100/370 (27%)	30/159 (19%)	0.14
Permanent pacemaker	105/940 (11%)	0/25	49/384 (13%)	46/372 (12%)	10/159 (6%)	0.08
Baseline echocardiogram						
Aortic valve annulus (mm)	23.11 ± 2.11	22.21 ± 2.30	23.02 ± 2.26	23.30 ± 1.97	23.01 ± 1.95	0.15
Left ventricular ejection fraction ≤35%	160/940 (17.0)	6/25 (24%)	79/384 (21%)	57/372 (15%)	18/159 (11%)	0.019
Aortic valve area (cm²)	0.71 ± 0.19	0.63 ± 0.18	0.68 ± 0.19	0.73 ± 0.20-	0.73 ± 0.19-	0.001

Results are reported as number(%), med(IQR) or mean ± SD.
*Statistically significant from each other using Bonferroni-correction.
† Glomerular Filtration Rate was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

Table 2. Procedural characteristics of the study population

Variable	Overall (n = 940)	BMI (kg/m²)				p-value
		<18.5 (n = 25)	18.5–24.9 (n = 384)	25–29.9 (n = 372)	>30 (n = 159)	
Prosthesis type and size						
Medtronic CoreValve 26-mm	152/940 (16%)	8/25 (32%)	59/384 (15%)	59/372 (16%)	26/159 (16%)	0.96
Medtronic CoreValve 29-mm	348/940 (43%)	5/25 (20%)	142/384 (37%)	132/372 (36%)	69/159 (43%)	0.22
Medtronic CoreValve 31-mm	5/940 (1%)	0/25	0/384	5/372 (1%)	0/159	0.025
Edwards Sapien 23-mm	155/940 (17%)	9/25 (36%)	74/384 (19%)	46/372 (12%)	26/159 (16%)	0.034
Edwards Sapien 26-mm	274/940 (29%)	3/25 (12%)	106/384 (28%)	127/372 (34%)	38/159 (24%)	0.032
Edwards Sapien 29-mm	6/940 (1%)	0/25	3/384 (1%)	3/372 (1%)	0/159	0.53
Sheath size						
18Fr Medtronic	500/940 (53%)	11/25 (44%)	200/384 (52%)	196/372 (53%)	93/159 (59%)	0.37
18–19Fr Edwards	242/940 (26%)	9/25 (36%)	106/384 (28%)	88/372 (24%)	39/159 (25%)	0.44
>19Fr	198/940 (21%)	5/25 (20%)	78/384 (20%)	88/372 (24%)	27/159 (17%)	0.20
Vascular access						
Surgical						
Femoral artery	94/940 (10%)	2/25 (8%)	41/384 (11%)	38/372 (10%)	13/159 (8%)	0.67
Subclavian artery	57/940 (6%)	0/25	27/384 (7%)	17/372 (5%)	13/159 (8%)	0.20
Transapical	89/940 (10%)	3/25 (12%)	38/384 (10%)	40/372 (11%)	5/159 (5%)	0.11
Percutaneous						
Femoral artery	696/940 (74%)	20/25 (80%)	277/384 (72%)	275/372 (74%)	124/159 (78%)	0.37
Transaortal	4/940 (0.4%)	0/25	1/384 (0.3%)	2/372 (1%)	1/159 (1%)	0.78
Therapy-specific results						
Concomitant percutaneous coronary intervention	21/940 (2%)	0/25	9/384 (2%)	7/372 (2%)	5/159 (3%)	0.73
Post-implantation balloon dilation	115/940 (12%)	3/25 (12%)	45/384 (12%)	47/372 (13%)	20/159 (13%)	0.73
Valve-in-valve implantation	31/940 (3%)	1/25 (4%)	13/384 (3%)	12/372 (3%)	5/159 (3%)	0.87
Coronary obstruction	3/940 (0.3%)	0/25	1/384 (0.3%)	1/372 (0.3%)	1/159 (1%)	0.51

Results are reported as number(%), med(IQR) or mean ± SD.

Table 3. In-hospital outcomes according to the Valve Academic Research Consortium Outcomes

Variable	Overall (n = 940)	BMI (kg/m²)				p-value
		<18.5 (n = 25)	18.5–24.9 (n = 384)	25–29.9 (n = 372)	>30 (n = 159)	
Device success	885/940 (94%)	23/25 (92%)	362/384 (94%)	350/372 (94%)	150/159 (94%)	1.00
All-cause 30-day or in-hospital death	68/940 (7%)	5/25 (20%)	33/384 (9%)	21/372 (6%)	9/159 (6%)	0.13
Cerebrovascular complication						
Major stroke	22/940 (2%)	0/25	9/384 (2%)	10/372 (3%)	3/159 (2%)	0.86
Minor stroke	3/940 (0.3%)	0/25	0	1/372 (0.3%)	2/159 (1%)	0.03
Transient ischemic attack	13/940 (1%)	0/25	5/384 (1%)	4/372 (1%)	4/159 (3%)	0.40
Myocardial infarction						
Periprocedural (<72 h)	9/940 (1%)	1/25 (4%)	3/384 (1%)	4/372 (1%)	1/159 (1%)	0.99
Spontaneous (>72 h)	6/940 (1%)	0/25	3/384 (1%)	2/372 (1%)	1/159 (1%)	0.77
Bleeding complications						
Life-threatening	129/940 (14%)	4/25 (16%)	50/384 (13%)	56/372 (15%)	19/159 (12%)	0.97
Major	198/940 (21%)	6/25 (24%)	73/384 (19%)	84/372 (23%)	159/35 (22%)	0.31
Minor	102/940 (11%)	3/25 (12%)	43/384 (11%)	37/372 (10%)	19/159 (12%)	0.96
Vascular complications						
Major	101/940 (11%)	3/25 (12%)	40/384 (10%)	41/372 (11%)	17/159 (11%)	0.87
Minor	107/940 (11%)	4/25 (16%)	35/384 (9%)	43/372 (12%)	25/159 (16%)	0.028
Acute kidney injury						
Stage I	139/940 (15%)	1/25 (4%)	41/384 (10%)	60/372 (16%)	37/159 (23%)	<0.001
Stage II	34/940 (4%)	1/25 (4%)	12/384 (3%)	12/372 (3%)	9/159 (6%)	0.21
Stage III	43/939 (5%)	2/25 (8%)	17/383 (4%)	19/372 (5%)	5/159 (3%)	0.67
Total hospital stay (days)	8.0 (5.5–10.5)	7.0 (4.0–10.0)	8.0 (5.5–10.5)	8.0 (5.5–10.5)	8.0 (5.5–10.5)	0.84
Red blood cell transfusion required	363/937 (39%)	12/25 (48%)	143/382 (37%)	144/371 (39%)	64/159 (40%)	0.53
Permanent pacemaker requirement	145/938 (16%)	3/25 (12%)	54/382 (14%)	60/372 (16%)	28/159 (18%)	0.28
Combined Safety Endpoint	248/940 (26%)	9/25 (36%)	101/384 (26%)	106/372 (29%)	32/159 (20%)	0.29

Results are reported as number(%), med(IQR) or mean ± SD.

RESULTS

940 patients with complete information on weight and height were included in this study; four patients were excluded due to missing data on either height or weight. The baseline characteristics and procedural details of the population according to the four predefined BMI categories are summarized in Table 1 and 2. Overall, 57% of the patients were either overweight or obese. The latter constituted 17% of the population. These patients were in general younger with a higher prevalence of preserved left ventricular systolic and renal function but more diabetes. The first two characteristics explain the lower LES (18.7%, IQR: 10.9% - 26.4%) in obese patients. There were no differences in procedural details between the different categories (Table 2).

In-hospital outcome (VARC definitions) is summarized in Table 3. Obese patients had a higher incidence of minor stroke (1.3% vs. 0 and 0.3% in patients with normal body weight and with overweight, respectively, p =0.03), minor vascular complications (15.7% vs. 9.1 and 11.6%, respectively, p =0.028) and AKI stage I (23.3% vs. 10.7% and 16.1%, respectively, p <0.001) Long-term follow-up was complete for 99.5% of all

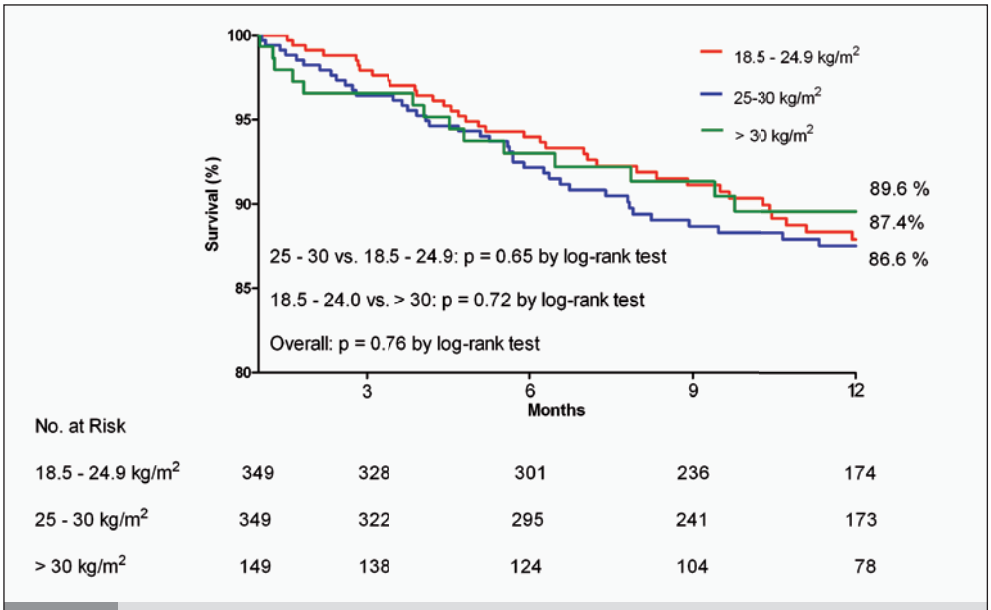

Figure 1. Impact of Body Mass Index on survival

Kaplan-Meier estimates (Landmark analysis) comparing one-year mortality for the different Body Mass Index Categories. Red depicts the normal weight group, Blue depicts the overweight group and Green depicts the obese group. Underweight was not depicted due to the low patient number.

patients and ranged from 1 to 72 months (median (IQR): 12 (6 – 18) months). Kaplan-Meier estimates of survival after hospital discharge disclose no difference in survival in the various patient categories (Log Rank; p = 0.76) (Figure 1).

Univariable and multivariable analysis of the association between BMI and short- and long-term mortality are shown in Table 4A and B. When using BMI as a categorical variable (Table 4a), no association between BMI and 30-day and 1-year mortality was found. Yet, BMI as a continuous variable was associated with a significant reduction of the risk of 30-day all-cause mortality, which remained significant after adjustment for baseline differences (OR [95% CI]; 0.93 [0.86 – 0.98], p = 0.023). BMI did not affect mortality after hospital discharge.

Table 4a. Effect of Body Mass Index (Categorical) on short- and long-term mortality

Outcome	OR (95% CI)				p-value
	BMI <18.5 kg/m^2	BMI 18.5–24.9 kg/m^2	BMI 25–29.9 kg/m^2	BMI >30 kg/m^2	
All–cause 30-day mortality					
Univariate	Excluded†	Reference	0.64 (0.36–1.12)	0.64 (0.30–1.37)	0.23
Multivariate‡	Excluded†	Reference	0.59 (0.32–1.08)	0.67 (0.29–1.55)	0.21
Mortality during follow-up*					
Univariate	Excluded†	Reference	1.11 (0.71–1.73)	0.89 (0.48–1.65)	0.81
Multivariate‡	Excluded†	Reference	1.17 (0.72–1.89)	1.34 (0.70–2.56)	0.65

* Landmark analysis included patients who did not die during hospitalization or within 30 days of index procedure. † Excluded from analysis because of low sample size. ‡ Adjusted for all differences in baseline and procedural characteristics.

DISCUSSION

The main finding of the present study is that obesity (BMI > 30) is not associated with an increased risk of major perioperative complications during TAVI and that - after correction for differences in baseline characteristics - obesity is associated with a significant decrease in all-cause 30-day mortality. BMI did not affect mortality after hospital discharge. Both underscore the "Obesity Paradox" in patients undergoing TAVI.

These conclusions stem from a multicenter observation in 940 patients of whom 16.9% were obese underscoring the "obesity paradox". Intuitively one would expect an increased operative risk in obese patients and particularly an increased risk of access site related complications. We did not find a difference in the composite VARC safety endpoint and its individual components except for minor vascular complications, minor stroke and AKI stage I. The absence of a difference in major bleeding- and

vascular complications between obese and non-obese patients cannot be explained by a different access site strategy as there was no such a difference between the four patient groups. It is acknowledged, however, that failure of closure device during TAVI has been reported to occur in 7.4% and 9.4% of the patients with a trend towards more failure in obese patients[25,26]. The latter could be a reason for the higher frequency of minor vascular complications in this cohort. The low number of patients with a stroke, minor stroke in particular, precludes any meaningful conclusion in relation to the association with obesity. With respect to AKI, it is unclear why obese patients had a higher incidence of AKI stage I after TAVI. There was no difference in baseline renal insufficiency or in use of contrast during TAVI. A relation between blood transfusion and AKI has been recently been demonstrated[27]. Yet, a different frequency of blood transfusion in the various patient groups is not likely given the similar incidence of bleeding complications in groups.

Table 4b. Effect of Body Mass Index on short- and long-term mortality

Outcome	**OR/HR** (95% C.I.)	**p-value**
All-cause 30-day mortality		
Univariate	0.92 (0.87–0.98)	0.011
Multivariate†	0.93 (0.86–0.98)	0.023
Mortality during follow-up*		
Univariate	0.98 (0.94–1.03)	0.47
Multivariate†	1.01 (0.96–1.07)	0.73

* Landmark analysis included patients who did not die during hospitalization or within 30 days of index procedure. † Adjusted for all differences in baseline and procedural characteristics.

By multivariable analysis we found a statistically significant reduction in 30-day all cause mortality and, more specifically that every increase in 1 kg/m^2 was associated with a 7% mortality reduction. Moreover, obesity did not have an adverse effect on mortality after hospital discharge. This is at variance with the findings in patients who undergo percutaneous coronary interventions (PCI) in which a lower risk of late death is reported in patients with moderate obesity[8–11,13–15,28]. This discrepancy may be explained by several factors such as definition of obesity, duration of follow-up but also by specific features related to obese patients undergoing catheter-based cardiac interventions. Similar to the findings of Sarno et al., who used the same definition of obesity in patients undergoing percutaneous coronary intervention (PCI), we found that obese patients were younger in comparison to the non-obese patients[28]. In addition, obese patients in the present study had a higher prevalence of a preserved ventricular and renal function. The combination of these characteristics may contribute and even explain the lower rate of all cause mortality at 30 days, providing a possible explanation

for the apparent paradox. The number of patients with underweight (BMI < 18.5) was too small to study the relation between underweight and outcome. As a result, the present study lacked the power to detect the previously reported U-shaped association between body weight and mortality[29,30].

LIMITATIONS

There are several limitations that should be addressed.The PRAGMATIC plus collaboration is a retrospective analysis of prospectively collected data. Despite the care of data collection and the use of VARC endpoint definitions, some degree of observation bias must be expected. Moreover, clinical endpoints were not adjudicated by an independent Clinical Event Committee. In addition, a number of variables which may confound outcome (e.g. frailty) were not available for analysis and may affect the robustness of the multivariable analysis, its interpretation and conclusions.

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CHAPTER 4

Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: a Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC-Plus) initiative substudy

Dumonteil N, van der Boon RM, Tchetche D, Chieffo A, Van Mieghem NM, Marcheix B, Buchanan GL, Vahdat O, Serruys PW, Fajadet J, Colombo A, de Jaegere PP, Carrié D. .

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ABSTRACT

Background

Only limited and conflicting data on the impact of preoperative chronic kidney disease (CKD) on outcomes after transcatheter aortic valve implantation (TAVI) are available.

Methods

We retrospectively analyzed pooled data from the prospective TAVI databases of 4 centers (942 patients). Valve Academic Research Consortium end point definitions were used. The outcomes were compared among patients with normal estimated glomerular filtration rate (≥90 mL/min), mild (60-89 mL/min), moderate (30-59 mL/min), and severe (<30 mL/min) CKD and those on chronic hemodialysis (HD). The primary end point was 1-year survival.

Results

A total of 109 patients had a normal estimated glomerular filtration rate (11.6%); 329 (34.9%) had mild, 399 (42.5%) moderate, 72 (7.5%) severe CKD, and 33 (3.5%) were on HD. Baseline and procedural characteristics were similar among all groups except for Logistic EuroSCORE. Major stroke, life-threatening bleeding, all-cause 30-day mortality (HD 15.2%, severe CKD 8.3%, moderate CKD 8.3%, mild CKD 6.7%, normal 1.8%, $P = .007$) and 1-year survival (HD 54.8%, severe CKD 67.2%, moderate CKD 80.0%, mild CKD 85.2%, normal eGFR 91.4%, HD vs severe CKD $P = .23$, severe CKD vs moderate CKD $P = .002$, moderate CKD vs mild CKD $P = .04$, moderate CKD vs normal eGFR $P = .03$, by log-rank test) differed significantly across groups. Through multivariable analysis, HD and severe CKD were independently associated with an increased risk of 1-year mortality (hazard ratios 5.07 [95% CI 1.79-14.35, $P = .002$] and 4.03 [95% CI 1.52-10.69, $P = .005$], respectively).

Conclusions

Patients with CKD who undergo TAVI have a higher-risk profile and worse 30-day and 1-year outcomes. Chronic hemodialysis and severe preprocedural CKD are independently associated with an increased risk of 1-year mortality after TAVI.

INTRODUCTION

Multiple national and international registries and the randomized Placement of AoRTic traNscathetER Valves (PARTNER) cohort A and B trials have pivoted transcatheter aortic valve implantation (TAVI) as a valid treatment option for patients with severe symptomatic aortic stenosis (AS) and a high or prohibitive operative risk[1–9]. These aging patients have a high prevalence of chronic kidney disease (CKD) that may motivate the choice of a transcatheter procedure rather than a surgical aortic valve replacement[5]. However, although the impact of renal insufficiency on short- and long-term outcomes after cardiac surgery has already been described, only limited and conflicting data on the impact of preoperative CKD on outcomes after TAVI exist, reported from observational studies including patients treated with only 1 of the commercially available prosthesis, mainly through transfemoral (TF) access[5,10–12]. Therefore, in this multicenter collaborative study, we sought to determine the impact of preexisting CKD on procedural, 30-day, and 1-year outcomes after TAVI where either a balloon or a self-expandable prosthesis was implanted using TF or alternative approaches.

METHODS

PRAGMATIC-Plus initiative

The PRAGMATIC-Plus initiative is a collaboration between 4 European institutions with high-volume TAVI activity. Baseline patient characteristics, procedural details, and clinical outcome data from a series of 944 consecutive patients who underwent TAVI were collected from the time of the introduction of the respective local TAVI programs until August 2011 (total time span was from November 2005 to August 2011): (1) San Raffaele Scientific Institute, Milan, Italy (n = 330); (2) Clinique Pasteur, Toulouse, France (n = 224); (3) Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (n = 206); and (4) Hôpital Universitaire Rangueil, Toulouse, France (n = 184). After the publication of the Valve Academic Research Consortium (VARC) consensus document, the proposed end point definitions were adopted and the local databases were modified accordingly. All data were then pooled into a global multicenter database[7,13].

Patient eligibility for the TAVI procedure in each center and technical and procedural aspects have been described earlier and were comparable across the 4 centers[14–17]. In brief, all patients with symptomatic severe AS who underwent TAVI had been judged to be of high operative risk by a multidisciplinary heart team consensus, based on calculated risk scores (Society of Thoracic Surgeons Score, Logistic EuroSCORE) and

the interpretation of other risk variables not captured by these risk models[18,19]. Both commercially available prostheses were used: the Edwards-Sapien (ES) prosthesis (Edwards Lifesciences Inc, Irvine, CA) and the third-generation Medtronic CoreValve (MCV) ReValving System (Medtronic, Minneapolis, MN). The study complied with the Declaration of Helsinki and was approved by institutional ethics committees. All patients provided written, informed consent.

Study endpoints and definitions

The primary end point was 1-year survival. Secondary end points were 30-day all-cause and cardiovascular mortality, myocardial infarction (MI), stroke, vascular and bleeding complications, acute kidney injury (AKI), device success, and 30-day combined safety end point. The VARC recommendations were used for all these end points, device success, and 30-day combined safety end point definitions[7,13]. Preoperative (<2 days) serum creatinine (SCr) values were used to calculate the baseline estimated glomerular filtration rate (eGFR) with the Modification of Diet in Renal Disease equation: eGFR (mL/min per 1.73 m^2) = 186 × $SCr^{-1.154}$ × $Age^{-0.203}$ × [1.212 if African American] × [0.742 if female][20]. Postoperative SCr was measured daily until 72 hours after the procedure, or until peak value, and at discharge. Data on red blood cell transfusions were recorded by the institutions' blood bank laboratory. The hemoglobin value was determined on first admission. We adopted the World Health Organization's definition of anemia, which defines it as a serum hemoglobin level of 13 g/dL for men and a level of 12 g/dL for women[21].

Study population

A total of 942 consecutive patients who underwent TAVI, whatever the access, with data on baseline SCr were included in the study (2 patients of the 944 included in the PRAGMATIC-Plus database were excluded because of missing preprocedural SCr). The patients were stratified according to Kidney Disease Outcome Quality Initiative staging system for CKD into the following 4 categories: eGFR ≥90 mL/min (normal eGFR), 60 to 89 mL/min (mildly decreased eGFR), 30 to 59 mL/min (moderately decreased eGFR), and <30 mL/min (severely decreased eGFR or kidney failure)[22]. Individuals who were on chronic hemodialysis (HD) were not excluded and were analyzed as a separate category.

Follow-up

After hospital discharge, mortality data were collected by contacting the civil registries or the referring physician or general practitioner and were completed in 99.5% of the patients who survived the first 30 days.

Statistical analysis

Continuous variables are presented as means (±SD; in case of a normal distribution) or medians (interquartile range [IQR]; in case of a skewed distribution). Categorical variables are presented as frequencies and percentages and are compared using the linear-by-linear association. One-way analysis of variance was used to compare means across multiple categories; a post hoc pairewise comparison was done with Bonferonni correction. In the case of a nonparametric distribution or ordinal data, the Kruskal-Wallis analysis of ranks was used; post hoc comparison was done using the Mann-Whitney test with Bonferonni correction. The normality of the distributions was assessed using the Shapiro-Wilks test. To assess the effect of renal function on short- and long-term outcomes, univariable and multivariable logistic regressions were used, where the "normal eGFR" category was used as the reference category. Multivariable analysis was adjusted for all differences in baseline and procedural characteristics (age, gender, diabetes, chronic obstructive pulmonary disease, coronary disease, peripheral vascular disease, left ventricular ejection fraction ≤35, GFR ≤60, baseline anemia category, learning effect (first vs latter half of cohort), sheath size (18/19F vs >19F), access type, and paravalvular aortic regurgitation grade ≥2. In the case of effects on long-term mortality, Cox regression analysis was used, as appropriate. The results of these analyses are reported as odds ratios or hazard ratios (HRs) with 95% CIs.

Survival curves for time-to-event variables were constructed on the basis of all available follow-up data in the overall study cohort and in patients who survived the first 30 days after TAVI (landmark analysis) with the use of Kaplan-Meier estimates and were compared with the log-rank test. A 2-sided α level of .05 was used for all superiority testing. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). 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 manuscript, and its final contents.

RESULTS

Baseline characteristics

Of the 942 patients of the cohort, 109 (11.6%) had normal eGFR, 329 (34.9%) had mild, 399 (42.5%) had moderate, and 72 (7.5%) had severe CKD, and 33 (3.5%) patients were on HD. Baseline demographics, echocardiographics, and biological characteristics of the study population are shown in Table 1. The mean age was 81.0 ± 7.0 years, and 53.8% were male. With advanced kidney failure, a New York Heart Association class III or IV, a higher Logistic EuroSCORE, and anemia were more frequent. Compared with the severe

Table 1. Baseline characteristics according to preprocedural renal function status

	Overall n = 942	Glomerular Filtration Rate (ml/min/1.73m²)					p-value
		Hemodialysis n = 33	< 30 n = 72	30 - 59 n = 399	60 - 89 n = 329	≥ 90 n = 109	
Demographics							
Age (yrs), mean ± SD	81.0 ± 7.0	76.1 ± 7.3*	81.6 ± 6.8*	82.4 ± 6.1*	80.5 ± 7.2*	78.6 ± 8.2*	< 0.001
Male, n (%)	507 / 942 (53.8)	20 / 33 (60.6)	38 / 72 (52.8)	208 / 399 (52.1)	179 / 329 (54.4)	62 / 109 (56.9)	0.82
Body Mass Index, mean ± SD	26.02 ± 4.51	24.71 ± 4.16	26.24 ± 3.53	25.95 ± 4.63	26.11 ± 4.65	26.27 ± 4.25	0.49
NYHA class III or IV, n (%)	764 / 940 (81.3)	26 / 33 (78.8)	63 / 72 (87.5)	339 / 398 (85.2)	263 / 329 (79.9)	73 / 108 (67.6)	0.001
Logistic EuroSCORE, med (IQR)	20.9 (12.9 - 28.9)	20.0 (10.8 - 29.3)	31.1 (21.5 - 40.8)	23.0 (15.8 - 30.2)	18.0 (11.0 - 25.0)	12.4 (5.2 - 19.6)	< 0.001
Previous cerebrovascular accident, n (%)	148 / 942 (15.7)	3 / 33 (9.1)	10 / 72 (13.9)	68 / 399 (17.0)	54 / 329 (16.4)	13 / 109 (11.9)	0.54
Previous myocardial infarction, n (%)	158 / 942 (16.8)	5 / 33 (15.2)	13 / 72 (18.1)	65 / 399 (16.3)	62 / 329 (18.8)	13 / 109 (11.9)	0.55
Previous CABG, n (%)	208 / 942 (22.1)	4 / 33 (12.1)	18 / 72 (25.0)	87 / 399 (21.8)	76 / 329 (23.1)	23 / 109 (21.1)	0.64
Previous PCI, n (%)	277 / 942 (29.4)	9 / 33 (27.3)	25 / 72 (34.7)	132 / 399 (33.1)	87 / 329 (26.4)	24 / 109 (22.0)	0.10
Coronary artery disease, n (%)	426 / 942 (45.2)	10 / 33 (30.3)	42 / 72 (58.3)	190 / 399 (47.6)	143 / 329 (43.5)	41 / 109 (27.6)	0.02
Diabetes mellitus, n (%)	268 / 942 (28.5)	9 / 33 (27.3)	20 / 72 (27.8)	125 / 399 (31.3)	91 / 329 (27.7)	23 / 109 (21.1)	0.33
Hypertension, n (%)	655 / 942 (69.5)	22 / 33 (66.7)	50 / 72 (69.4)	287 / 399 (71.9)	230 / 329 (69.9)	66 / 109 (60.6)	0.25
Chronic Obstructive Pulmonary Disease, n (%)	325 / 942 (34.5)	5 / 33 (15.2)	21 / 72 (29.2)	135 / 399 (33.8)	118 / 329 (35.9)	46 / 109 (42.2)	0.05
Peripheral vascular disease, n (%)	237 / 938 (25.3)	9 / 32 (28.1)	26 / 72 (36.1)	101 / 398 (25.4)	80 / 327 (24.5)	21 / 109 (19.3)	0.15
Permanent pacemaker, n (%)	106 / 942 (11.3)	2 / 33 (6.1)	12 / 72 (16.7)	55 / 399 (13.8)	29 / 329 (8.8)	8 / 109 (7.3)	0.06
Baseline echocardiogram							
Aortic valve annulus (mm), mean ± SD	0.71 ± 0.19	0.70 ± 0.19	0.74 ± 0.16	0.69 ± 0.19	0.71 ± 0.20	0.71 ± 0.19	0.37
Left ventricular ejection fraction ≤ 35%, n (%)	160 / 942 (17.0)	6 / 33 (18.2)	16 / 72 (22.2)	78 / 399 (19.5)	48 / 329 (14.6)	12 / 109 (11.0)	0.12
Aortic valve area (cm2), mean ± SD	23.11 ± 2.10	23.45 ± 2.53	23.48 ± 1.90	23.02 ± 2.11	23.14 ± 2.15	23.02 ± 1.94	0.43
Baseline laboratory results							
Creatinin (g/dl), mean ± SD	1.42 ± 1.20	6.31 ± 2.63*	2.65 ± 0.89*	1.40 ± 0.28*	0.94 ± 0.14*	0.67 ± 0.13*	< 0.001
Hemoglobin (g/dl), mean ± SD	12.13 ± 1.70	11.66 ± 1.41	11.62 ± 1.50*	12.08 ± 1.70	12.26 ± 1.74*	12.38 ± 1.67*	0.009

*Statistically significant from each other using Bonferroni-correction.Abbreviations: NYHA: New York Hearth Association; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft.

Table 2. Procedural characteristics and outcomes according to preprocedural renal function status

	Overall n = 942	Glomerular Filtration Rate (ml/min/1.73m²)					p-value
		Hemodialysis n = 33	< 30 n = 72	30 - 59 n = 399	60 - 89 n = 329	≥ 90 n = 109	
Prosthesis type and size, n (%)							
Medtronic CoreValve 26-mm	154 / 942 (16.3)	7 / 33 (21.2)	11 / 72 (15.3)	63 / 399 (15.8)	60 / 329 (18.2)	13 / 109 (11.9)	0.54
Medtronic CoreValve 29-mm	347 / 942 (36.8)	9 / 33 (27.3)	18 / 72 (25.0)	154 / 399 (38.6)	124 / 329 (37.7)	42 / 109 (38.5)	0.17
Medtronic CoreValve 31-mm	5 / 942 (0.5)	0 / 33	1 / 72 (1.4)	3 / 399 (0.8)	1 / 329 (0.3)	0 / 109	0.65
Edwards SAPIEN 23-mm	154 / 942 (16.3)	4 / 33 (12.1)	12 / 72 (16.7)	71 / 399 (17.8)	48 / 329 (14.6)	19 / 109 (17.4)	0.76
Edwards SAPIEN 26-mm	276 / 942 (29.3)	13 / 33 (29.4)	28 / 72 (38.9)	105 / 399 (26.3)	95 / 329 (28.9)	35 / 109 (32.1)	0.14
Edwards SAPIEN 29-mm	6 / 942 (0.6)	0 / 33	2 / 72 (2.8)	3 / 399 (0.8)	1 / 329 (0.3)	0 / 109	0.15
Sheath size, n (%)							
18 Fr Medtronic	501 / 942 (53.2)	16 / 33 (48.5)	29 / 72 (40.3)	219 / 399 (54.9)	182 / 329 (55.3)	55 / 109 (50.5)	0.17
18-19 Fr Edwards	244 / 942 (25.9)	9 / 33 (27.3)	13 / 72 (18.1)	100 / 399 (25.1)	88 / 329 (26.7)	34 / 109 (31.2)	0.38
> 19 Fr	197 / 942 (20.9)	8 / 33 (24.2)	30 / 72 (41.7)	80 / 399 (20.1)	59 / 329 (17.9)	20 / 109 (18.3)	< 0.001
Vascular access, n (%)							
surgical - femoral artery	94 / 942 (10.0)	7 / 33 (21.2)	7 / 72 (9.7)	38 / 399 (9.5)	31 / 329 (9.4)	11 / 109 (10.1)	0.30
surgical - subclavian artery	58 / 942 (6.2)	4 / 33 (12.1)	2 / 72 (2.8)	25 / 399 (6.3)	20 / 329 (6.1)	7 / 109 (6.4)	0.48
surgical - transapical	88 / 942 (9.3)	3 / 33 (9.1)	21 / 72 (29.2)	38 / 399 (9.5)	21 / 329 (6.4)	5 / 109 (4.6)	< 0.001
percutaneous - femoral artery	698 / 942 (74.1)	19 / 33 (57.6)	41 / 72 (56.9)	297 / 399 (74.4)	256 / 329 (77.8)	85 / 109 (78.0)	0.001
transaortal	4 / 942 (0.4)	0 / 33	1 / 72 (1.4)	1 / 399 (0.3)	1 / 329 (0.3)	1 / 109 (0.9)	0.60
Amount of contrast (ml), med (IQR)*	160.0 (115.0 - 205.0)	210.0 (165.0 - 255.0)	120 (75.0 - 165.0)	150.0 (106.3 - 193.8)	170.0 (125.0 - 215.0)	180.0 (122.5 - 237.5)	0.01
Therapy-specific results, n (%)							
Concomitant PCI	21 / 942 (2.2)	1 / 33 (3.0)	2 / 72 (2.8)	10 / 399 (2.5)	7 / 329 (2.1)	1 / 109 90.9)	0.88
Post-implantation balloon dilatation	116 / 942 (12.3)	4 / 33 (12.1)	6 / 72 (8.3)	48 / 399 (12.0)	43 / 329 (13.1)	15 / 109 913.8)	0.83
Valve-in-Valve implantation	31 / 942 (3.3)	3 / 33 (9.1)	2 / 72 (2.8)	16 / 399 (4.0)	9 / 329 (2.7)	1 / 109 (0.9)	0.17
Coronary obstruction	3 / 942 (0.3)	1 / 33 (3.0)	1 / 72 (1.4)	1 / 399 (0.3)	0 / 329	0 / 109	0.02

Abbreviations: PCI: Percutaneous Coronary Intervention.

CKD group, patients on HD were younger and with lower EuroSCORE. Other baseline data were similar in all groups. There were no significant differences in rates of diabetes mellitus (28.5% overall) or hypertension (69.5% overall), 2 potential causes of CKD.

Procedural characteristics and outcomes

Procedural data are given in Table 2. There were 506 (53.7%) and 436 (46.3%) patients who were treated with an MCV or an ES prosthesis, respectively, without any difference in size among the 4 groups. Access distribution for the overall cohort was TF in 84.0% of the cases (predominantly with a percutaneous closure strategy), transapical (TA) in 9.3%, subclavian in 6.2%, and transaortic in 0.4%. Transapical access was more frequent in cases of severe CKD. Conversely, fewer patients with severe CKD or on HD were treated through a TF approach with a percutaneous closure strategy. The amount of contrast used decreased when the CKD was severe, except for patients on HD. The mean rate of paravalvular aortic regurgitation ≥grade 2 was 17.2%, without any significant differences between groups. The overall device success rate was 94.2%, without significant variations related to renal function. Periprocedural coronary obstruction, although rare, was more frequent in the HD and severe CKD groups (3% and 1.4%, respectively, vs 0.3%, 0%, and 0%; $P = .02$). No other significant differences in therapy-specific end points were observed among the 4 groups.

Thirty-day outcomes

Thirty-day all-cause mortality was 7.2% in the overall population, with a significant and stepwise increase in mortality across groups of CKD (normal eGFR 1.8%, mild CKD 6.7%, moderate CKD 8.3%, severe CKD 8.3%, HD 15.2%, $P = .007$) (Table 3), with a similar trend for 30-day cardiovascular mortality. As shown in Table 3, a cerebrovascular complication occurred in 4% of patients, and major stroke was more frequent when the CKD was more severe (normal eGFR 1.8%, mild CKD 1.2%, moderate CKD 2.8%, severe CKD 4.2%, HD 6.1%, $P = .04$). Bleedings were seen in 45.6% of patients (life-threatening 13.8%, major 21.0%, minor 10.8%) as well as AKI stages I, II, and III at 14.8%, 3.6%, and 4.8% respectively, occurring more frequently as the renal function was impaired (except for life-threatening bleedings that were less frequent in patients on HD as compared with patients with severe CKD). Other complications such as MI (1.6%), vascular complications (major 10.6%, minor 11.5%), and permanent pacemaker implantation (15.5%) were without differences according to baseline renal function status. Finally, the combined safety end point was 48.5% in the HD group and 43.1%, 27.8%, 22.2%, and 17.4% in the severe, moderate, mild, and no-CKD groups, respectively ($P < .001$).

Looking for an association between baseline renal function and short-term outcomes,

Table 3. Thirty-day outcomes according to preprocedural renal function status

	Overall n = 942	Glomerular Filtration Rate (ml/min/1.73m²)					p-value
		Hemodialysis n = 33	< 30 n = 72	30 - 59 n = 399	60 - 89 n = 329	≥ 90 n = 109	
30-day or in-hospital death, n (%)							
All-cause	68 / 942 (7.2)	5 / 33 (15.2)	6 / 72 (8.3)	33 / 399 (8.3)	22 / 329 (6.7)	2 / 109 (1.8)	0.007
Cardiovascular	59 / 942 (6.3)	5 / 33 (15.2)	5 / 72 (6.9)	27 / 399 (6.8)	20 / 329 (6.7)	2 / 109 (1.8)	0.02
Myocardial infarction, n (%)							
Periprocedural (<72 hr)	9 / 942 (1.0)	2 / 33 (6.1)	0 / 72	5 / 399 (1.3)	1 / 329 (0.3)	1 / 109 (0.9)	0.07
Spontaneous (>72 hr)	6 / 942 (0.6)	0 / 33	0 / 72	3 / 399 (0.8)	2 / 329 (0.6)	1 / 109 (0.9)	0.53
Cerebrovascular complication, n (%)							
Major stroke	22 / 942 (2.3)	2 / 33 (6.1)	3 / 72 (4.2)	11 / 399 (2.8)	4 / 329 (1.2)	2 / 109 (1.8)	0.04
Minor stroke	3 / 942 (0.3)	0 / 33	0 / 72	1 / 399 (0.3)	1 / 329 (0.3)	1 / 109 (0.9)	0.28
Transient ischemic attack	13 / 942 (1.4)	0 / 33	1 / 72 91.4)	3 / 399 (0.8)	9 / 329 (2.7)	0 / 109	0.47
Vascular complication, n (%)							
Major	100 / 942 (10.6)	2 / 33 (6.1)	12 / 72 (16.7)	44 / 399 (11.0)	35 / 329 (10.6)	7 / 109 (6.4)	0.23
Minor	108 / 942 (11.5)	4 / 33 (12.1)	6 / 72 (8.3)	38 / 399 (9.5)	44 / 329 (13.4)	16 / 109 (14.7)	0.09
Bleeding Complication, n (%)							
Life threatening	130 / 942 (13.8)	4 / 33 (12.1)	21 / 72 (29.2)	59 / 399 (14.8)	37 / 329 (11.2)	9 / 109 (8.3)	0.001
Major	198 / 942 (21.0)	8 / 33 (24.2)	10 / 712 (13.9)	74 / 399 (18.5)	82 / 329 (24.9)	24 / 109 (22.0)	0.12
Minor	102 / 942 (10.8)	2 / 33 (6.1)	7 / 72 (9.7)	57 / 399 (14.3)	30 / 329 (9.1)	6 / 109 (5.5)	0.13
Acute kidney injury, n (%)							
Stage I	139 / 942 (14.8)	0 / 33 (0.0)	19 / 72 (26.4)	59 / 399 (14.8)	50 / 329 (15.2)	11 / 109 (10.1)	0.46
Stage II	34 / 942 (3.6)	0 / 33 (0.0)	4 / 72 (5.6)	17 / 399 (4.3)	8 / 329 (2.4)	5 / 109 (4.6)	0.89
Stage III	45 / 941 (4.8)	10 / 32 (31.2)	10 / 72 (13.9)	17 / 399 (4.3)	5 / 329 (1.5)	3 / 109 (2.8)	< 0.001
Prosthetic valve associated complications							
New permanent pacemaker requirement, n (%)	146 / 940 (15.5)	4 / 32 (12.5)	8 / 72 (11.1)	62 / 399 (15.5)	53 / 328 (16.2)	19 / 109 (17.4)	0.26
Combined Endpoints							
Combined Safety Endpoint, n (%)	250 / 942 (26.5)	16 / 33 (48.5)	31 / 72 (43.1)	111 / 399 (27.8)	73 / 329 (22.2)	19 / 109 (17.4)	< 0.001

Table 4. Effect of preprocedural renal function status on short- and long-term outcome

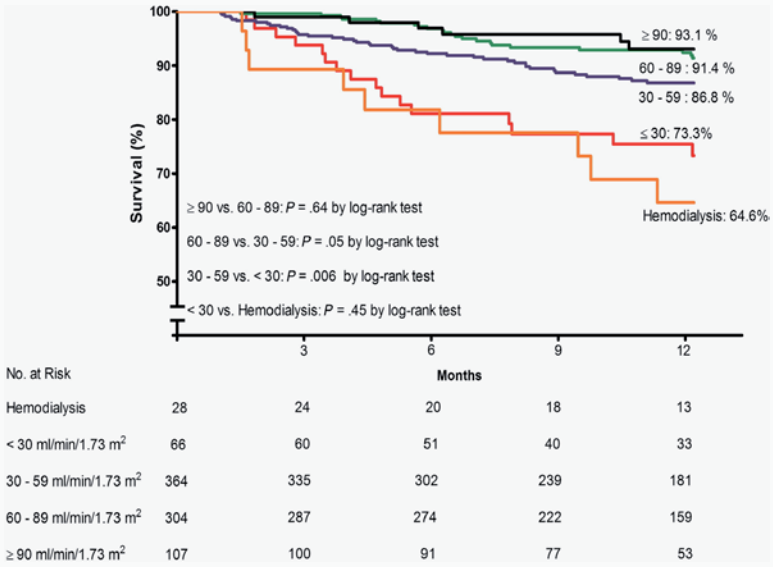
Outcome	Glomerular Filtration Rate (ml/min/1.73m²)					p-value
	Hemodialysis	< 30	30 - 59	60 - 89	≥ 90	
All - Cause 30 Day Mortality						
Univariable	9.55 (12.76 - 51.86)	4.86 (0.95 - 24.81)	4.82 (1.13 - 20.43)	3.83 (0.89 - 16.58)	ref	0.11
Multivariable†	4.72 (0.71 - 31.23)	2.00 (0.34 - 11.73)	3.71 (0.86 - 16.07)	2.50 (0.55 - 11.15)	ref	0.28
Cardiac 30 Day Mortality						
Univariable	9.55 (1.76 - 15.86)	3.99 (0.75 - 21.17)	3.88 (0.91 - 16.59)	3.46 (0.80 - 15.06)	ref	0.12
Multivariable†	4.56 (0.68 - 30.54)	1.15 (0.24 - 10.01)	3.00 (0.68 - 13.20)	2.26 (0.50 - 10.25)	ref	0.42
Combined Safety Endpoint						
Univariable	4.46 (1.92 - 10.36)	3.58 (1.81 - 7.07)	1.83 (1.06 - 3.14)	1.35 (0.77 - 2.36)	ref	< 0.001
Multivariable†	3.82 (1.57 - 9.34)	2.95 (1.42 - 6.14)	1.85 (1.05 - 3.26)	1.27 (0.72 - 2.27)	ref	0.001
Mortality during Follow-Up*						
Univariable	6.31 (2.25 - 17.73)	4.60 (1.80 - 11.76)	2.10 (0.89 - 4.93)	1.25 (0.51 - 3.09)	ref	< 0.001
Multivariable†	5.07 (1.79 - 14.35)	4.03 (1.52 - 10.69)	2.04 (0.85 - 4.86)	1.07 (0.43 - 2.68)	ref	< 0.001

* Landmark Analysis including patients who did not die during hospitalization or within 30-days of index procedure. † Adjusted for all differences in baseline characteristics and procedural characteristics.

we found that none of the CKD groups were significantly associated with an increased risk of 30-day all-cause or cardiac mortality in comparison with the patients with normal eGFR, whereas preprocedural HD and severe and moderate CKD were independently associated with an increased risk in the combined safety end point (HR 3.82 [95% CI 1.57-9.34, *P* = .003], HR 2.95 [95% CI 1.42-6.14, *P* = .004], and HR 1.85 [95% CI 1.05-3.26, *P* = .03], respectively) (Table 4).

Long-term outcomes

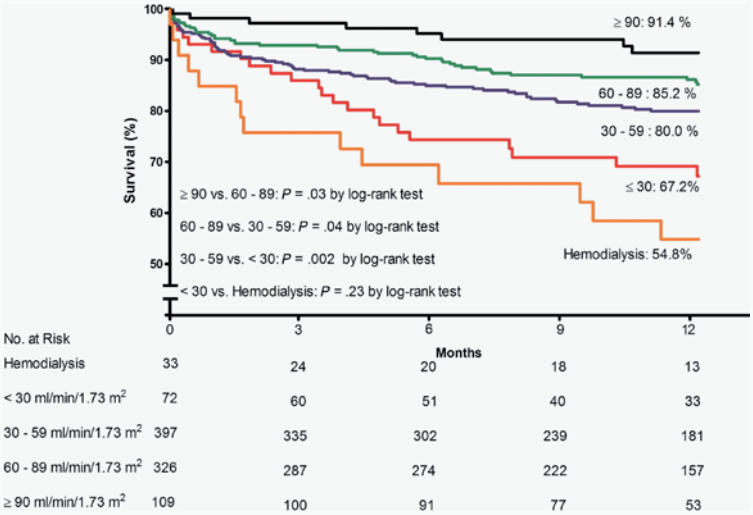
Long-term follow-up was completed for 99.5% of patients and ranged from 1 to 72 months (median [IQR] 12 [6-18] months). The 1-year survival rate was significantly impaired in patients with severe (67.2%), moderate (80.0%), and mild (85.2%) CKD, in comparison with the normal eGFR (91.4%) group (severe CKD vs moderate CKD *P* = .002, moderate CKD vs mild CKD *P* = .04, mild CKD vs normal eGFR, *P* = .03 by log-rank test). One-year survival of patients on HD (54.8%) and patients with severe CKD (67.2%) was not significantly different, despite a trend to worse outcome for patients on HD (Figure 1). Landmark analysis, excluding patients who died during hospitalization or within 30-days after the index procedure, showed very similar results, with a 1-year survival rate of 64.6% for the HD group, 73.3% for the severe CKD cohort, 86.8% for the moderate CKD group, 91.4% and 93.1%, respectively, for patients with mild and normal eGFR (HD vs severe CKD *P* = .45, severe CKD vs moderate CKD *P* = .006, moderate



No. at Risk					
Hemodialysis	28	24	20	18	13
< 30 ml/min/1.73 m^2	66	60	51	40	33
30 - 59 ml/min/1.73 m^2	364	335	302	239	181
60 - 89 ml/min/1.73 m^2	304	287	274	222	159
≥ 90 ml/min/1.73 m^2	107	100	91	77	53

Figure 1. Impact of preoperative CKD on survival: Kaplan-Meier estimates comparing 1-year survival for the different CKD categories

Orange represents the HD group; red, severe CKD group; blue, moderate CKD group; green, mild CKD group; and black, no-CKD group (reference).



No. at Risk					
Hemodialysis	33	24	20	18	13
< 30 ml/min/1.73 m^2	72	60	51	40	33
30 - 59 ml/min/1.73 m^2	397	335	302	239	181
60 - 89 ml/min/1.73 m^2	326	287	274	222	157
≥ 90 ml/min/1.73 m^2	109	100	91	77	53

Figure 2. Impact of preoperative CKD on survival: landmark analysis—Kaplan-Meier estimates comparing 1-year survival for the different CKD categories

Landmark analysis excluding patients who died during hospitalization or within 30 days of index procedure. Orange represents the HD group;red, severe CKD group; blue, moderate CKD group; green, mild CKD group; and black, no-CKD group (reference).

CKD vs mild CKD *P* = .05, mild CKD vs normal eGFR *P* = .64, by log-rank test) (Figure 2). Looking for an association between baseline renal function and 1-year mortality and after making adjustments for all differences in baseline and procedural characteristics, we found that preoperative HD and severe CKD were identified to be independently associated with an increased risk of 1-year mortality (HR 5.07 [95% CI 1.79-14.35, *P* = .002] and HR 4.03 [95% CI 1.52-10.69, *P* = .005], respectively) (Table 4).

DISCUSSION

This multicentric study is the first to specifically report outcomes after TAVI according to baseline renal function, using a large sample, treated with either ES or MCV prostheses implanted via TF or alternative approaches. The main findings are as follows: (1) CKD, classified according to the Kidney Disease Outcome Quality Initiative, is associated with an increased risk of procedural complications and 30-day all-cause mortality (however, this is not significant after adjustment for all differences in baseline and procedural characteristics), and (2) 1-year survival is significantly altered when CKD is more severe, with HD and severe CKD independently and strongly associated with 1-year mortality[22].

Procedural characteristics and differences in complications according to baseline renal function

Access strategies varied significantly across CKD groups, with more frequent TA procedures and less frequent percutaneous closure devices used in cases of severe CKD. This can probably be explained by a higher prevalence of severely calcified iliofemoral arteries in this subgroup of patients, although rates of baseline peripheral vascular disease did not differ[23]. In our study, patients under dialysis or with preprocedural severe CKD had a higher rate of major stroke (6.1% and 4.9% in comparison with 2.9% in a recent meta-analysis of 10,037 patients), assumed to probably be of embolic origin from the native aortic valve or the aortic wall[24,25]. We might interpret this higher risk of major stroke observed in these subgroups to be caused by a higher prevalence of aortic valve calcification and aortic atheroma[26–28]. Previous studies reported no association between baseline impaired renal function and the risk of AKI after TAVI, but only with non-VARC definitions of AKI[11,12]. Although there was no any significant variation of AKI stage I or II across our study groups, we found that AKI stage III occurred more frequently in patients with severe CKD, whereas the amount of contrast used was the lower in this subgroup. This could be of interest considering that severe CKD is sometimes one of the comorbidities that affects the choice of TAVI instead

of surgical aortic valve replacement for high-risk patients, precisely to avoid severe AKI, known to be associated with an increased risk of mortality after surgery, but also after TAVI[11,12,29,30]. We also noticed that patients with severe CKD were more prone to life-threatening bleedings. This association has already been described after cardiac surgery[31]. We can only hypothesize that some baseline or procedural characteristics (such as primary hemostasis abnormalities well known among patients with renal failure, a higher prevalence of baseline anemia and of TA approaches) might partly explain this difference[32]. Procedural and 30-day outcomes were dramatically impaired in patients on HD. However, the small number of subjects in this subgroup makes interpretation difficult and precludes any definite conclusion.

Effect of baseline renal function on short- and long-term mortality

The current available data on the impact of baseline impaired renal function on mortality after TAVI are limited and/or conflicting. Rodes-Cabau et al, in the description of acute and late outcomes of the multicenter Canadian experience, identified CKD (eGFR <60mL/min in this study) as an independent predictor of cumulative late mortality, whereas no association with 30-day mortality was found with renal insufficiency (defined as a preprocedural SCr >1.5 mg/dL) after a multivariate analysis in the Italian TAVI registry[4,5]. However, few studies specifically sought to compare patients with and without CKD undergoing TAVI. Sinning et al, in a monocentric study including 77 patients treated with an MCV via TF access, reported that impaired renal function at the baseline reflected by SCr ≥1.58 mg/dL was a strong predictor of 1-year mortality after TAVI[11]. Conversely, in another recently reported experience of 199 patients treated with an MCV through a TF approach, preprocedural CKD (defined as eGFR <60 mL/min) was not associated with a worse prognosis at 30 days or 1 year[12]. Unfortunately, small samples of patients with limited statistical power and the use of only 1 commercially available device make the interpretation and generalization of these data difficult. Patients on chronic HD were either few or excluded from these studies.

In our study, HD and severe CKD appeared to be independently and strongly associated with 1-year mortality after TAVI. Chronic kidney disease is an important predictor of mortality after cardiac surgery and has, consequently, been included in the major mortality risk scores in cardiac surgery[18,19]. Our results could add to the understanding of TAVI outcomes and could contribute to the elaboration of a TAVI mortality risk score. An independent, graded association has already been observed between a reduced eGFR and the risk of death and cardiovascular events in a large, community-based population, irrespective of any overt cardiac disease, but with lower ratios than those in our study focused on high-risk patients with severe AS[33]. Some of the patients currently treated by TAVI do not receive significant benefit either because of comorbidities or

because of an already limited survival. These are so-called cohort C patients who we should not offer TAVI. Because patients with severe renal insufficiency and/or end-stage renal disease requiring chronic dialysis were excluded from the PARTNER trial, results of this study cannot be extrapolated to the population with severe CKD[8,9]. Given the dramatically worse survival of such patients observed in our study, one must wonder about preoperative HD and severe CKD being one factor among others that could account for TAVI futility because of the per se worse prognosis of patients with CKD have. This uncertainty about TAVI benefit in such population could be addressed by a trial dedicated to patients on HD and with severe CKD.

LIMITATIONS

The PRAGMATIC-Plus collaboration is a retrospective analysis of prospectively collected data. Despite the care taken in collecting the data and the use of VARC end point definitions, some degree of observation bias must be expected. Clinical end points were not adjudicated by an independent Clinical Event Committee. Finally, a number of variables that may confound the outcomes such as frailty were not available for analysis and may affect the robustness of the multivariable analysis as well as its interpretation and conclusions. However, the number of patients included in this multicentric study and the implantation of both commercially available prostheses via TF as well as alternative approaches seem to reflect a "real-world" use of TAVI and, in this sense, strengthen our results.

CONCLUSIONS

Patients with CKD who undergo TAVI have a higher-risk profile and distinct procedural, 30-day, and 1-year outcomes, which become worse when CKD is more severe. Both HD and severe CKD at baseline are independently associated with an increased risk of 1-year mortality after TAVI.

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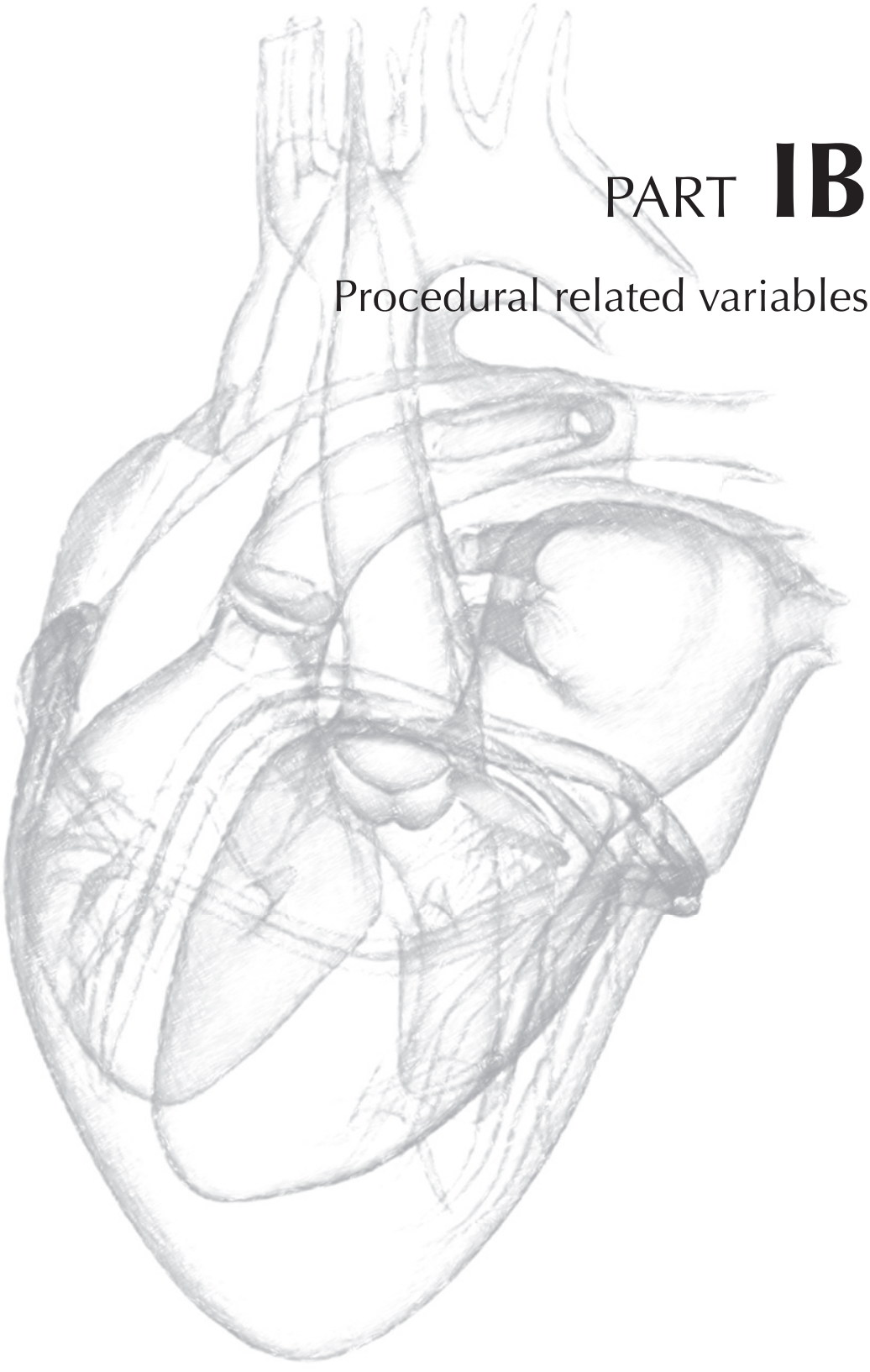

PART **IB**

Procedural related variables

CHAPTER 5

Complete Revascularization Is Not a Prerequisite for Success in Current Transcatheter Aortic Valve Implantation Practice

Van Mieghem NM, van der Boon RM, Faqiri E, Diletti R, Schultz C, van Geuns RJ, Serruys PW, Kappetein AP, van Domburg RT, de Jaegere PP.

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ABSTRACT

Objectives

This study sought to assess in patients undergoing transcatheter aortic valve implantation (TAVI), the prevalence and impact of incomplete coronary revascularization defined as >50% coronary artery or graft diameter stenosis on visual assessment of the coronary angiogram.

Background

TAVI is an established treatment option in elderly patients with aortic stenosis (AS) and a (very) high operative risk. Coronary artery disease (CAD) is often associated with AS.

Methods

A single-center cohort of consecutive patients undergoing TAVI between November 2005 and June 2012 was evaluated for the presence of significant CAD. The decision to revascularize and pursue complete revascularization was made by heart team consensus.

Results

A total of 263 consecutive patients with a mean age of 80 ± 7 years and 51% male underwent TAVI with a median follow-up duration of 16 months (interquartile range: 4.2 to 28.1 months). Significant CAD with myocardium at risk was present in 124 patients (47%), 44 of whom had had previous coronary artery bypass grafting (CABG), and the median SYNTAX score in the 81 patients without previous CABG was 9.00 (2.38 to 15.63). Staged percutaneous coronary intervention (PCI) was planned in 19 (15%) and concomitant PCI with TAVI in 20 (16%). The median post-procedural residual SYNTAX score of patients without prior CABG was 5.00 (0.13 to 9.88). Overall, 99 patients (37%) (61 with no CABG and 38 CABG patients) had incomplete revascularization after TAVI. Revascularization status did not affect clinical endpoints. Kaplan-Meier survival curves for patients with and without complete revascularization demonstrated a 1-year mortality of 79.9% versus 77.4% ($p = 0.85$), respectively.

Conclusions

In an elderly patient population undergoing TAVI for severe AS, a judicious revascularization strategy selection by a dedicated heart team can generate favorable mid-term outcome obviating the need for complete coronary revascularization.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is increasingly offered as a less invasive treatment option for elderly patients with symptomatic aortic valve stenosis (AS) at higher operative risk[1–5]. Degenerative aortic valve disease shares similar risk factors with atherosclerotic coronary artery disease (CAD), and patients with symptomatic AS often have concomitant CAD[6–9]. In surgical series, the presence of significant CAD increases the operative risk and mortality of surgical aortic valve replacement (SAVR), both when left untreated and when treated with concomitant coronary artery bypass grafting (CABG)[10–14]. According to guidelines on valvular heart disease, concomitant CAD should be treated while performing SAVR[14,15]. The impact of CAD in patients undergoing TAVI is not well established. In the randomized PARTNER (Placement of Aortic Transcatheter Valves) trial, patients with significant CAD requiring revascularization therapy were excluded from the trial[16,17]. Retrospective TAVI studies remain equivocal but tend to suggest that presence of CAD or non-revascularized myocardium is not associated with worse outcome[18–23]. The SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial introduced the SYNTAX score to assess the extent and complexity of significant CAD[24]. Incomplete revascularization was associated with worse outcome. Furthermore, in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI), a residual SYNTAX score to evaluate untreated lesions also predicts short- and longer-term prognosis[25]. The aim of this study was to assess the prevalence and impact of incomplete revascularization in patients undergoing TAVI.

METHODS

The study population consisted of all consecutive patients with symptomatic severe AS who underwent TAVI between November 2005 and June 2012 in the Erasmus Medical Center, Rotterdam, the Netherlands. All potential TAVI candidates underwent a detailed multidisciplinary and multimodality imaging assessment. Over the course of the TAVI program, a dedicated heart team was installed consisting of at least 1 interventional cardiologist, 1 cardiac surgeon, and 1 imaging specialist and was completed with an anesthesiologist, geriatrician, or neurologist upon indication. The heart team convened on a weekly basis and confirmed a patient's eligibility for TAVI based on a critical appraisal of established risk scores (STS, Logistic EuroSCORE), assessment of risk variables not included in these models, anatomical considerations, and clinical judgment. In principle, patients needed to be at high or prohibitive

operative risk. Invasive coronary angiography was mandatory in all patients and was assessed in the heart team discussion. In case of significant CAD (i.e., >50% diameter stenosis on visual assessment of the coronary angiogram), the treatment strategy and completeness of revascularization was determined based on consensus decision before the TAVI procedure, taking into consideration infarcted area, viable myocardial tissue at risk, and technical complexity. Myocardium at risk was not formally quantitated by myocardial imaging but was estimated by visual assessment of the presence of obstructive atherosclerotic disease in coronaries supplying noninfarcted myocardial territories. The revascularization options were: 1) staged PCI before the TAVI procedure; 2) PCI concomitant with the TAVI procedure; and 3) conservative approach (no PCI).

Baseline characteristics, procedural data, and outcome data were prospectively collected in a dedicated database in accordance with local institutional review board guidelines. All in-hospital clinical endpoints are defined according to the Valve Academic Research Consortium criteria[26]. Per protocol, clinical follow-up visits were scheduled at 6 weeks, 6 months, 12 months, and yearly thereafter. Survival was obtained from the Dutch Civil Registry. Clinical follow-up was derived by reviewing hospital charts and contacting referring physicians and patients' general practitioners. For the purpose of this study, all baseline diagnostic angiograms were re-assessed to capture baseline coronary status. Distinction was made between patients with and without previous CABG. In patients with previous CABG, completeness of revascularization was assessed by evaluating the native coronary circulation and the respective grafts. For patients without previous CABG, including those with prior PCI, the SYNTAX score was calculated. In patients with significant CAD after the previous CABG, or a SYNTAX score >0, treatment strategy was documented as staged intervention, concomitant intervention, or no intervention. After the TAVI procedure, the completeness of revascularization was re-assessed: a residual SYNTAX score was calculated in the no-CABG cohort. During follow-up, the need for additional coronary interventions, indication (elective or acute coronary syndrome), and success of PCI after TAVI was assessed.

TAVI procedure

TAVI procedural details have been extensively described before[27]. During the TAVI procedure, all patients were on full-dose aspirin and clopidogrel. Patients were loaded with 300 mg of aspirin and 300 mg of clopidogrel 1 day before the TAVI. Procedural anticoagulation was obtained with a heparin bolus of 70 IU/kg, aiming for an activated clotting time of 250 to 300 ms. The 2 commercially available TAVI platforms, the Medtronic CoreValve system (Medtronic, Minneapolis, Minnesota) and the Edwards

SAPIEN valve (Edwards Lifesciences, Irvine, California), were used. The transfemoral approach was the access strategy of first choice, followed by the transaxillary and transapical routes. PCI was executed according to standard practice and always before the actual valve implantation. Drug-eluting stents were the stent platform of first choice, and patients continued dual antiplatelet therapy for 1 year after PCI.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and were compared with the use of the Pearson chi square test or the Fisher exact test, as appropriate. Continuous variables are presented as mean ± SD (in case of a normal distribution) or median (interquartile range [IQR]) (in case of a skewed distribution) and compared with the use of the Student *t* test or the Mann-Whitney *U* test. Normality of the distributions was assessed using the Shapiro-Wilks test. Kaplan-Meier curves were generated to assess estimates of survival. A 2-sided alpha level of 0.05 was used for all superiority testing. All statistical analysis were performed with the use of SPSS software version 17.0 (SPSS, Chicago, Illinois).

RESULTS

A total of 263 consecutive patients underwent TAVI with a median follow-up duration of 16 months (IQR: 4.2 to 28.1 months). Baseline and procedural characteristics are displayed in Tables 1 and 2: mean age was 80 ± 7 years, and 51% were male. Mean Logistic EuroSCORE was 17.63 ± 10.41%; a transfemoral percutaneous access strategy was used in 95% of patients. The Medtronic CoreValve was the predominant device platform. Two-thirds of all patients (175 of 263 patients) had a history of past or current CAD with previous PCI or CABG in 28% and 27%, respectively, of the patients and a previous myocardial infarction in 25%. At baseline, obstructive atherosclerotic disease in coronary arteries supplying noninfarcted myocardial territories was present in 124 patients (47%), 44 of whom (35%) had had previous CABG. Nine patients initially presented with an ACS: 6 with unstable angina/non–ST-segment elevation myocardial infarction and 3 with ST-segment elevation myocardial infarction. Male sex, hypertension, chronic kidney disease, and low left ventricular ejection fraction were more prevalent in patients with incomplete revascularization at baseline.

Table 1. Baseline characteristics of the overall patient -population and dichotomized according to completeness of coronary revascularization at baseline

	Overall n = 263	Complete Revascularization n = 139	Incomplete Revascularization n = 124	p-value
Demographics				
Age (yrs), mean ± SD	80.3 ± 7.0	80.0 ± 7.6	80.5 ± 6.4	0.58
Male, n (%)	134 (51.0)	59 (42.4)	75 (60.5)	0.002
Height (cm), mean ± SD	167.31 ± 9.15	166.77 ± 9.05	167.92 ± 9.25	0.31
Weight (kg), mean ± SD	74.05 ± 12.92	73.49 ± 13.26	74.68 ± 12.55	0.46
Body Mass Index, mean ± SD	26.46 ± 4.18	26.440 ± 4.26	26.49 ± 4.10	0.92
Body Surface Area, mean ± SD	1.85 ± 0.19	1.84 ± 0.20	1.86 ± 0.19	0.35
NYHA class III or IV, n (%)	223 (84.8)	117 (84.2)	106 (85.5)	0.77
Logistic EuroSCORE, med (IQR)	12.37 (7.59 - 17.15)	11.96 (7.68 - 16.25)	13.09 (7.48 - 18.71)	0.10
Logistic EuroSCORE, mean ± SD	17.63 ± 10.41	16.13 ± 9.97	19.32 ± 10.66	0.013
Frailty, n (%)	83 (31.6)	47 (33.8)	36 (29.0)	0.41
Previous cerebrovascular accident, n (%)	62 (23.6)	25 (18.0)	37 (39.8)	0.024
Previous myocardial infarction, n (%)	66 (25.1)	24 (17.3)	42 (33.9)	0.002
Previous CABG, n (%)	70 (26.6)	26 (18.7)	42 (35.5)	0.002
Previous PCI, n (%)	73 (27.8)	23 (16.5)	50 (40.3)	< 0.001
Coronary artery disease, n (%)*	175 (66.5)	51 (36.7)	124 (100.0)	< 0.001
SYNTAX Score, med (IQR)	†	0	9.00 (2.38 - 15.63)	< 0.001
Diabetes mellitus, n (%)	70 (26.6)	35 (25.2)	35 (28.2)	0.58
Hypertension, n (%)	162 (61.6)	76 (54.7)	86 (69.4)	0.02
Glomerular Filtration Rate ≤ 60 ml/min, n (%)	137 (52.1)	62 (44.6)	75 (60.5)	0.01
Chronic haemodialysis, n (%)	10 (3.8)	5 (3.6)	5 (4.0)	0.85
Chronic Obstructive Pulmonary Disease, n (%)	70 (26.6)	38 (27.3)	32 (25.8)	0.78
Peripheral vascular disease, n (%)	39 (14.8)	11 (7.9)	28 (22.6)	0.001
Permanent pacemaker, n (%)	23 (8.7)	12 (8.6)	11 (8.9)	0.95
Atrial fibrillation, n (%)	76 (28.9)	47 (33.8)	29 (23.4)	0.06
Baseline echocardiogram				
Aortic valve area (cm2), mean ± SD	0.66 ± 0.21	0.66 ± 0.21	0.66 ± 0.21	0.93
Left ventricular ejection fraction (%), mean ± SD	50.54 ± 14.40	52.71 ± 13.97	48.18 ± 14.55	0.017
Aortic annulus diameter (mm), mean ± SD	22.57 ± 2.38	22.60 ± 2.54	22.52 ± 2.20	0.85
Peak velocity, mean ± SD	4.26 ± 0.76	4.37 ± 0.77	4.123± 0.72	0.009
Peak gradient (mmHg), mean ± SD	75.17 ± 26.39	78.97 ± 27.50	70.90 ± 24.49	0.014
Mean gradient (mmHg), mean ± SD	44.78 ± 16.74	47.12 ± 17.35	42.13 ± 15.69	0.018
Aortic regurgitation grade ≥ III, n (%)‡	44 (16.9)	26 (19.0)	18 (14.6)	0.35
Mitral regurgitation grade ≥ III, n (%)‡	27 (10.4)	19 (13.9)	8 (6.5)	0.06

*Combination of previous CABG, myocardial infarction, percutaneous coronary intervention, or current SYNTAX score >0. †The overall median SYNTAX score is not reported. Abbreviations: NYHA: New York Heart Association; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention.

Table 2. Procedural characteristics of the overall patient population and dichotomized according to completeness of coronary revascularization at baseline

	Overall n = 263	Complete Revascularization n = 139	Incomplete Revascularization n = 124	p-value
Vascular access, n (%)				
surgical - femoral artery	10 (3.8)	8 (5.8)	2 (1.6)	0.08
percutaneous - femoral artery	239 (90.9)	128 (92.1)	111 (89.5)	0.47
surgical - subclavian artery	3 (1.1)	0	3 (245)	0.07
percutaneous - subclavian artery	5 (1.9)	2 (1.4)	3 (2.4)	0.56
surgical - transapical	6 (2.3)	1 (0.7)	5 (4.0)	0.07
Circulatory support, n(%)				
ECMO	2 (0.8)	2 (1.4)	0	0.18
LVAD	15 (5.7)	6 (4.3)	9 (7.3)	0.31
IAPB	1 (0.4)	0	1 (0.8)	0.29
None	245 (93.2)	131 (94.2)	114 (91.9)	0.46
Additional interventions during TAVI, n (%)				
PTA Iliac Artery	6 (2.3)	3 (2.2)	3 (2.4)	0.89
Prosthesis type and size, n (%)				
Medtronic CoreValve 26-mm*	83 (31.6)	45 (32.4)	38 (30.6)	0.76
Medtronic CoreValve 29-mm*	153 (58.2)	79 (56.8)	74 (59.7)	0.64
Medtronic CoreValve 31mm*	9 (3.4)	4 (2.9)	5 (4.0)	0.61
Edwards SAPIEN 23mm*	5 (1.9)	3 (2.2)	2 (1.6)	0.75
Edwards SAPIEN 26mm*	10 (3.8)	5 (3.6)	5 (4.0)	0.85
Therapy-specific results, n (%)				
Post-implantation balloon dilatation	46 (17.5)	21 (15.1)	25 (20.2)	0.28
Valve-in-Valve implantation	12 (4.6)	7 (5.0)	5 (4.0)	0.70
Coronary obstruction	1 (0.4)	0	1 (0.8)	0.29
Ventricular perforation	3 (1.1)	1 (0.7)	2 (1.6)	0.50
Conversion to surgical AVR	1 (0.4)	1 (0.7)	0	0.34
Procedure time (min), mean ± SD	208.78 ± 66.71	212.24 ± 67.41	204.88 ± 66.00	0.40
Amount of contrast (ml), mean ± SD	159.73 ± 78.45	160.64 ± 81.24	158.75 ± 75.75	0.86

3 patients did not undergo final implantation; 1 died during induction (anesthesia), 1 died as a result of balloon valvuloplasty–induced left ventricular outflow tract rupture, and 1 had a major vascular complication upon access. Abbreviations: AVR: Aortic Valve Replacement; ECMO: Extra Corporeal Membrane Oxygenation; IABP: Intra-aortic Balloon Counterpulsation; LVAD: Left Ventricular Assist Device; PTA: Percutaneous Transluminal Angioplasty; TAVI: Transcatheter Aortic Valve Implantation.

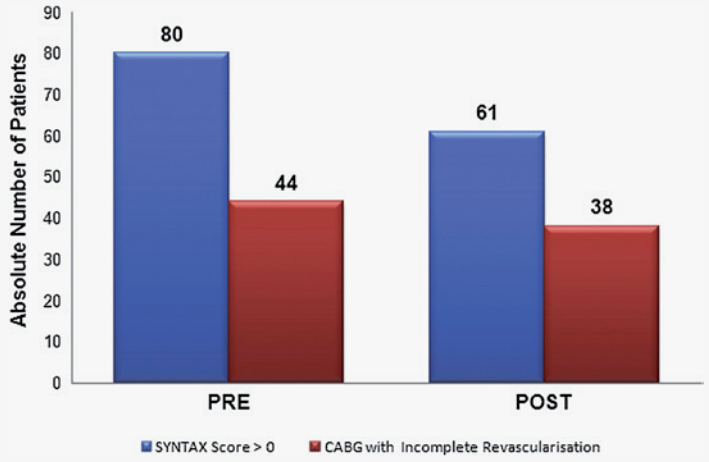

Figure 1. Revascularization status pre- and post-TAVI in patients with significant coronary artery disease at baseline

Blue: cohort with SYNTAX score >0 at baseline; red: cohort with prior CABG and incomplete revascularization at baseline. Abbreviations as previous.

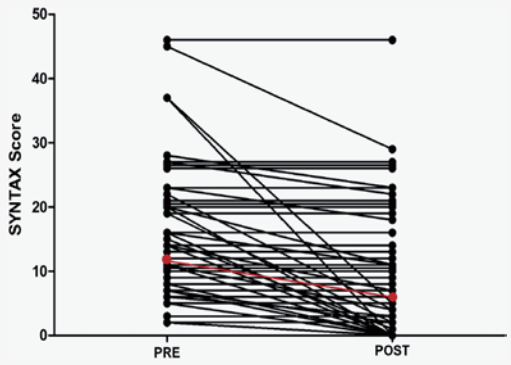

Figure 2. Reduction in SYNTAX Score in patients undergoing PCI pre-TAVI

The red line marks the change in mean score. Abbreviations as previous.

Revascularization status

All patients who initially presented with an ACS were treated with ad hoc PCI followed by TAVI at least 1 week after PCI. Of the 70 patients with prior CABG, 44 (63%) had incomplete revascularization at the time of heart team presentation because of progressive native CAD or saphenous vein graft disease. Revascularization was

planned in 6 (14%): staged PCI in 5 and concomitant with the TAVI procedure in 1. All 6 patients obtained complete revascularization (Figure. 1). A total of 80 patients with no history of prior CABG had incomplete revascularization at baseline, with a median SYNTAX score of 9.00 (2.38 to 15.63). PCI TAVI was planned in 33 patients (41% of patients with a SYNTAX score >0): staged in 14 (17%) and concomitant with TAVI in 19 (24%). The median residual SYNTAX score after TAVI was 5.00 (0.13 to 9.88). The change in SYNTAX score in the no-CABG patients who were planned for PCI and were incompletely revascularized is shown in Figure 2. Overall, 99 patients (38%) (61 with no-CABG and 38 CABG patients) were incompletely revascularized after TAVI.

Endpoints

Clinical follow-up was complete for all patients. Table 3 illustrates the clinical endpoints subcategorized according to the presence of incomplete revascularization. There were no relevant differences among the respective cohorts. Procedural time and total contrast volume were similar. There were no differences in cardiac enzyme rise between patients with or without CAD, or whether patients obtained complete revascularization or not. Remarkably, during follow-up, no evident residual angina was noted. Survival curves for patients with and without complete revascularization at baseline or after TAVI, and for patients with residual SYNTAX score <8 versus ≥8 are displayed in Figure 3. No significant differences were found in overall survival.

PCI post-TAVI

Eight patients underwent PCI a median of 140 days (IQR: 0 to 337 days) after TAVI. All except 1 were prior Medtronic CoreValve cases. Two patients had no CAD (SYNTAX score = 0) before the TAVI procedure, and 5 patients had accepted incomplete revascularization (3 after previous CABG). One patient with staged left main coronary artery PCI had a late stent thrombosis 126 days after TAVI while still on dual antiplatelet therapy. One patient had a TAVI procedure–related dissection of the left main stem and underwent intravascular ultrasound–guided PCI 1 day after TAVI[28]. One patient presented with a troponin rise, yet the coronary angiogram and intravascular ultrasound examination showed no obvious disease progression. Pragmatically, a balloon dilation was performed on the known ostial right coronary artery lesion. Two patients presented with a ST-segment elevation myocardial infarction: 1 with an acute occlusion of a saphenous vein graft, the other with a de novo thrombotic occlusion of the proximal left anterior descending coronary artery. Two PCI procedures were complicated by a neurological event (1 major stroke, and 1 transient ischemic attack).

Table 3. VARC Endpoints dichotomized according to completeness of coronary revascularization

	Overall n = 263	Complete Revascularization n = 139	Incomplete Revascularization n = 124	p-value
30-day or in-hospital death, n (%)				
All-cause	17 (6.5)	9 (6.5)	8 (6.5)	0.99
Cardiovascular	12 (4.6)	8 (5.8)	4 (3.2)	0.33
Myocardial Infarction, n (%)				
Periprocedural (<72 hr)	2 (0.8)	1 (0.7)	1 (0.8)	0.94
Spontaneous (>72 hr)	0	0	0	1.00
Cerebrovascular complication, n (%)				
Major stroke	14 (5.3)	8 (5.8)	6 (4.8)	0.74
Minor stroke	2 (0.8)	0	2 (1.6)	0.13
Transient ischemic attack	5 (1.9)	4 (2.9)	1 (0.8)	0.22
Vascular complication, n (%)				
Major	17 (6.5)	10 (7.2)	7 (5.6)	0.61
Minor	25 (9.5)	20 (14.4)	5 (4.0)	0.004
Bleeding Complication, n (%)				
Life threatening	21 (8.0)	14 (10.1)	7 (5.6)	0.19
Major	34 (12.9)	26 (18.7)	8 (6.5)	0.003
Minor	26 (9.9)	18 (12.9)	8 (6.5)	0.08
Acute kidney injury, n (%)				
Stage I	37 (14.1)	18 (12.9)	19 (15.3)	0.58
Stage II	6 (2.3)	3 (2.2)	3 (2.4)	0.89
Stage III	4 (1.5)	2 (1.4)	2 (1.6)	0.91
Reintervention in hospital, n (%)	2 (0.8)	2 (1.4)	0	0.18
Length of Stay, med (IQR)				
Total hospitalization	8.0 (4.5 - 11.5)	9.0 (5.0 - 13.0)	8.0 (4.5 - 11.5)	0.14
Prosthetic valve associated complications				
New permanent pacemaker requirement, n (%)	52 (19.8)	27 (19.4)	25 (20.3)	0.86
Combined Endpoints				
Composite Safety Endpoint, n (%)	55 (22.0)	31 (23.3)	24 (20.5)	0.59

Abbreviations: VARC: Valve Academic Research Consortium.

DISCUSSION

Our study on 263 consecutive elderly high-risk TAVI patients highlights: 1) incomplete coronary revascularization at baseline is common; 2) revascularization strategy based on heart team consensus is feasible; and 3) when revascularization strategy is based on heart team consensus, complete revascularization is not a prerequisite for good medium-term prognosis.

Prevalence of CAD in patients with AS

The prevalence of significant CAD in our study is similar to what has been reported in other TAVI registries, yet appears somewhat higher than what is reported in the surgical literature, indicating CAD in 30% to 50% of patients who undergo SAVR[20,22]. An overall older study population and the fact that patients with advanced comorbidities may also have more CAD may explain a higher prevalence of CAD in current TAVI practice. Also, patients with antecedents of complex CAD, including previous revascularization therapies, may be driven in the direction of TAVI.

Treatment strategy for AS in combination with CAD

Data on the need for combined CABG with SAVR in case of severe AS with concomitant significant CAD are relatively scarce but seem to suggest its merits[13,29]. Concomitant CABG may improve short- and long-term survival, and reduce the risk for perioperative myocardial infarction[30,31]. As such, it has been adopted in international guidelines on valvular heart disease[14,15]. Conversely, a cohort study from the Northern New England Cardiovascular Disease Study Group on 7,584 consecutive patients undergoing SAVR suggested concomitant CABG did not impact survival in octogenarians as opposed to patients <80 years of age[32]. These findings are corroborated by Maslow et al., confirming there was no difference in long-term survival between isolated SAVR and SAVR combined with CABG in octogenarians[33]. A pooled analysis of 2 TAVI feasibility registries including 201 high-risk patients suggested that a history of previous cardiovascular intervention was associated with increased short- and long-term mortality and a more than 2 times higher risk of dying at any point[21]. However, no data from invasive coronary angiograms were available, and concomitant PCI and TAVI was not allowed. In the early Vancouver experience of 136 patients, 76% had coexisting CAD. Presence of CAD or non-revascularized myocardium as determined by the Duke Myocardial Jeopardy score was not associated with an increased risk of adverse events up to 1 year[23].

The Italian CoreValve Registry enrolling 663 consecutive patients with previous PCI or CABG in 38% of cases did not find any impact of previous coronary intervention

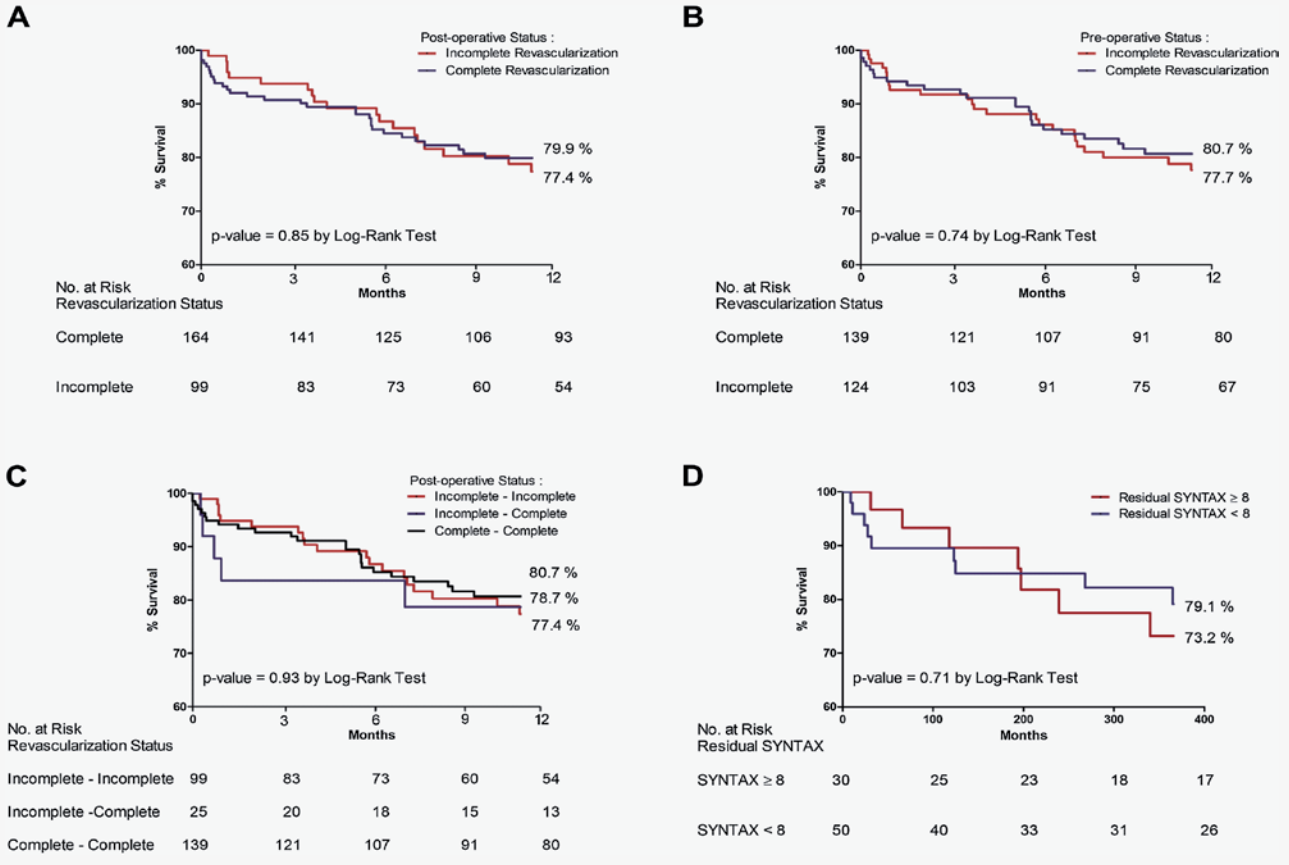

Figure 3. (**A**) Patients with complete (blue) versus incomplete (red) revascularization after TAVI. (**B**) Patients with complete (blue) versus incomplete revascularization (red) before TAVI. (**C**) Patients with incomplete revascularization before and after TAVI (red) versus patients with complete revascularization (black) versus patients with incomplete revascularization before TAVI who acquired complete revascularization after TAVI (blue). (**D**) Patients with incomplete revascularization after TAVI and residual SYNTAX score 8 (red) versus <8 (blue).

on 1-year clinical outcome[19]. The German TAVI Registry, including 1,382 patients (82% CoreValve) with CAD (defined as angiographically determined coronary stenosis ≥50%) present in 62%, did not discriminate between patients who underwent PCI in preparation for TAVI (staged PCI) or with a past history of PCI[20]. Patients with CAD had a lower ejection fraction and a greater proportion of ejection fraction <30%. Concomitant PCI was performed in only 5.5% of patients with CAD. By multivariate analysis, CAD was not associated with in-hospital mortality. A single-center experience including 125 patients adopted a strategy of PCI of all significant epicardial lesions before TAVI. Fifty-five patients required PCI, all but 3 as a staged procedure with a median time interval between PCI and TAVI of 10 days[34]. No data were provided on PCI success and actual completeness of revascularization. The need for PCI was not associated with 30-day or 6-month adverse event rates. The timing of elective PCI in patients planned for TAVI is essential in the heart team decision-making process and requires consideration of patient characteristics (age, frailty, renal function, etc.) and procedural complexity. In comparison with concomitant PCI and TAVI, a 2-step approach may result in relative reduction in procedure time and radiation and contrast exposure, yet demands arterial access twice with the inherent risk for vascular and bleeding complications and may come with additional hospitalization costs.

Our strategy on concomitant CAD with TAVI reflects what has been reported by the Bern group. In the Bern TAVI registry on 265 TAVI patients, 65% had CAD, defined as a significant stenosis >50% or previous revascularization therapy, 35% of whom underwent staged (n = 23 patients) or concomitant (n = 36) PCI[22]. PCI in addition to TAVI did not have an impact on outcome. Also, patients with significant CAD who did not undergo PCI had similar outcomes as compared with TAVI in patients without CAD. No information was provided related to completeness of revascularization in patients undergoing staged or concomitant PCI. We used the residual SYNTAX score to characterize residual stenosis after PCI. The median post-procedural residual SYNTAX score of patients without prior CABG was 5.00 (0.13 to 9.88). Complete revascularization was achieved in 20% of TAVI patients with incomplete revascularization at baseline. The residual SYNTAX score may help in risk stratifying patients for future coronary events. In moderate- to high-risk ACS patients, a residual SYNTAX score (rSS) >8 was associated with poor 30-day and 1-year survival[25]. We could not detect any impact of the residual SYNTAX score in our series. In principle, ACS and TAVI populations differ significantly because in the latter, there is no acute clinical event and patients are older. The importance of age on the impact of incomplete revascularization has been suggested in a French study on patients undergoing CABG, which found incomplete revascularization did not have an impact on survival in patients >60 years of age,

suggesting that in this particular elderly patient population at high operative risk, limited coronary revascularization may be considered when deemed necessary[35]. It may be safe to waive variable degrees of CAD without intervention, and pursuit of complete revascularization is not a prerequisite for medium-term clinical success in an elderly AS patient population, provided a rational and pragmatic approach to CAD by a dedicated heart team is guaranteed. Finally, using this selective revascularization strategy, the urge for PCI after TAVI is limited, and although it is technically feasible, may be associated with associated morbidity as suggested by 2 neurological events in our series.

LIMITATIONS

In this single-center study, extent and complexity of CAD were assessed by retrospectively calculating the SYNTAX score, yet baseline characteristics and clinical endpoints were prospectively collected. Scoring relied exclusively on visual assessment of the diagnostic angiograms. Fractional flow reserve was only used in a minority of cases but may certainly downgrade the extent of CAD. The median follow-up duration of 16 months provides insights into the impact of CAD in the mid-term, yet precludes extrapolation to longer-term follow-up. Given the relatively small sample size, our data should be interpreted with caution and demand confirmation in larger (preferably randomized) studies.

CONCLUSIONS

In an elderly patient population undergoing TAVI for severe AS, incomplete coronary revascularization is a dominant baseline feature. Judicious revascularization strategy selection by a dedicated heart team can generate favorable mid-term outcomes, obviating the need for complete coronary revascularization.

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CHAPTER 6

Transapical versus Transfemoral Aortic Valve Implantation: a multi-center collaborative study

van der Boon RMA, Marcheix B, Tchetche D, Chieffo A, van Mieghem NM, Dumonteil N, Vahdat O, Maisano F, Serruys PW, Kappetein AP, Fajadet J, Colombo A, Carrié D, van Domburg RT, de Jaegere PPT.

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ABSTRACT

Background

There are no direct comparisons between Transapical- Aortic Valve Implantation (TA-AVI) and Transfemoral-Aortic Valve Implantation (TF-AVI). Therefore, the aim of this study was to compare the short- and mid-term outcomes of TA-AVI versus TF-AVI

Methods

Data from 4 European centers were pooled and analyzed. To minimize differences between TA-AVI and TF-AVI multivariable analysis was used. Study endpoints were defined according to the Valve Academic Research Consortium-I criteria at 30 days and 1 year. Primary endpoints of this study were 30-day all-cause mortality and mortality during follow-up.

Results

A total of 882 underwent TAVI of whom 793 patients TF-AVI (89.9%) and 89 patients (10.1%) TA-AVI. Patients undergoing TA-AVI had a higher estimated risk of mortality as defined by the logistic EuroSCORE (med (IQR): 27.0 (20.2 - 33.8) vs. 20.0 (12.3 - 27.7), p<0.001) and Society of Thoracic Surgery Score (med (IQR): 10.2 (5.3 – 9.9) vs. 6.7 (3.5 – 9.9, p<0.001) and had more comorbidities. At 30 days, there was an increased risk of all-cause mortality in the TA-AVI group (OR (95% C.I.): 3.12 (1.43 – 6.82), p=0.004)). TF-AVI was associated with a higher frequency of major (OR (95% C.I.): 0.33 (0.12 – 0.90), p=0.031) and minor vascular complications (OR (95% C.I.): 0.17 (0.04 – 0.71), p=0.0015). Whereas, in-hospital stay was significantly longer in patients undergoing TA-AVI (OR (95% C.I.): 2.29 (1.28 – 4.09), p =0.05). During a median (IQR) follow-up of 365 days (174 – 557 days) TA-AVI was associated with an increased risk of all-cause mortality (HR (95% C.I.): 1.88 (1.23 – 2.87), p=0.004).

Conclusions

In institutions with a low volume of TA-AVI, TA-AVI is associated with an increased risk of all-cause mortality and longer hospital stay but less vascular complications in comparison to TF-AVI. The interaction between experience and type of treatment on outcome requires further investigation before advocating one treatment over the other.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has emerged as a viable alternative to surgical aortic valve replacement (SAVR) for patients with symptomatic aortic stenosis at high operative risk[1–4]. In case of suitable peripheral arterial anatomy transfemoral aortic valve implantation (TF-AVI) is generally considered the access site of choice. However, bleeding- and vascular complications frequently occur and are associated with increased risk of perioperative morbidity and long-term mortality[5–7]**.** Transapical aortic valve implantation (TA-AVI) entails catheter based access closer to the valve landing zone with potentially, superior control of valve positioning, potential reduction of stroke due to absence of retrograde crossing of the aortic valve in addition to lesser access site complications[8]. However, TA-AVI is considered a more invasive and complex procedure when compared to TF-AVI, which can be performed completely percutaneous under general or local anesthesia[9]. Furthermore, recovery of patients undergoing TA-AVI tends to be longer[10]. Little information is available on direct comparison of TF-AVI and TA-AVI. Therefore, the aim of this study was to compare the short- and mid-term outcomes of TA-AVI versus TF-AVI in a population from the PRAGMATIC (Pooled-RotterdAm-Milano-Toulouse In Collaboration) Registry[11].

METHODS

Patients

The PRAGMATIC initiative is a collaboration of 4 European institutions with established TAVI experience. The baseline patient characteristics, procedural details and clinical outcome data from a series of 944 consecutive patients who underwent TAVI were collected since the introduction of the respective local TAVI program until July 2011: 1) San Raffaele Scientific Institute, Milan (n=330); 2) Clinique Pasteur, Toulouse (n=224); 3) Thoraxcenter, Erasmus Medical Center, Rotterdam (n=206); 4) Hôpital Rangueil, Toulouse (n=184). After the VARC-I consensus document was made public, the proposed endpoint definitions were adopted and the respective local databases were modified accordingly[12]. All data were then pooled into a dedicated global multi-center database. Patient eligibility for TAVI at each center was described previously[13–15]. This study was approved by the Institutional Review Board/Ethic Committee of each hospital. All patient provided written informed consent for the procedure and data collection according to the policy of each hospital.

Imaging, access strategy and device choice

In all patients multi-modality imaging (transthoracic and/or transesophageal echo, angiography and/or multislice computed tomography) was performed to assess anatomical suitability for TAVI and determine the optimal access strategy. The transfemoral approach was the access route of first choice in all participating centers. When transfemoral access was deemed inappropriate, a transapical, a trans-axillary/subclavian and trans-aortic approach was considered. Final access strategy was decided upon by the treating physician or heart team decision. Both TAVI technologies with CE mark approval were used dependent on the access used. For the TF approach, the Edwards SAPIEN THV™ (ESV) and Medtronic CoreValve System (MCS) was used. With respect to the ESV, the Retroflex™ delivery catheter and a 22 or 24 French (Fr) sheath size was used until mid 2010, which was then replaced by the SAPIEN XT THV™ (SXT) and uses the Novaflex™ delivery catheter which goes through an 18 or 19Fr sheath. With respect to the MCS, a 21Fr sheath was used until 2006 which was then replaced by an 18Fr compatible system. In the TA-AVI group, the Ascendra I and II were used to deliver the ESV and the SXT since mid 2010.

Study endpoints and definitions

Primary endpoints of this study were 30-day all-cause mortality and mortality during follow-up. All endpoints were defined using the VARC-I recommendations[12]. After hospital discharge, mortality data were collected by contacting the civil registries, referring physician or general practitioner. Follow-up data was completed in 99.7% of the patients who survived the first 30-days.

Statistical Analysis

Categorical variables are presented as frequencies and percentages and, compared with the use of the Pearson Chi Square Test or the Fisher's exact test, as appropriate. Continuous variables are presented as means (±SD) (in case of a normal distribution) or medians (IQR) (in case of a skewed distribution) and compared with the use of Student's T-test or the Mann-Whitney U-test. Normality of the distributions was assessed using the Shapiro-Wilks test.

Univariable and multivariable logistic regression was used to assess the effect of access approach on short- and long-term outcome. Cox proportional hazard regression analysis was performed to determine the relation between transapical access and mortality during follow-up. Multivariable analysis was adjusted for all differences in baseline characteristics. Results of these analyses are reported as odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (C.I.), as appropriate. Survival curves for time-to-event variables were constructed on the basis of all available follow-up

Table 1. Baseline characteristics comparing TF-AVI and TA-AVI

	Overall n=882	TF-AVI n=793	TA-AVI n=89	p-value
Demographics				
Age (yrs)	81.2 ± 7.0	81.2 ± 7.0	81.2 ± 7.3	0.99
Male	470/882 (53.3)	419/793 (52.8)	51/89 (57.3)	0.42
Body Mass Index	26.01 ± 4.46	26.10 ± 4.53	25.18 ± 3.72	0.06
NYHA class III/IV	719/880 (81.7)	646/791 (81.7)	73/89 (82.0)	0.94
Logistic EuroSCORE (%)	20.8(13.0 - 28.5)	20.0(12.3 - 27.7)	27.0(20.2 - 33.8)	< 0.001
STS Score (%)	7.0(3.8 - 10.2)	6.7 (3.5 - 9.9)	10.2 (5.3 - 15.1)	< 0.001
Previous stroke	139/882 (15.8)	121/793 (15.3)	18/89 (20.2)	0.22
Previous myocardial infarction	143/882 (16.2)	129/793 (16.3)	14/89 (15.7)	0.90
Previous CABG	202/882 (22.9)	167/793 (21.1)	35/89 (39.3)	< 0.001
Previous PCI	258/882 (29.3)	229/793 (28.9)	29/89 (32.6)	0.47
Coronary artery disease	400/882 (45.4)	345/793 (43.5)	55/89 (61.8)	0.001
Diabetes mellitus	250/882 (28.3)	223/793 (28.1)	27/89 (30.3)	0.66
Hypertension	307/882 (68.8)	536/793 (67.6)	71/89 (79.8)	0.019
GFR < 60 ml/min	553/878 (63.0)	484/791 (61.2)	69/87 (79.3)	0.001
COPD	290/882 (32.9)	257/793 (32.4)	33/89 (37.1)	0.37
Peripheral vascular disease	200/878 (22.8)	140/789 (17.7)	60/89 (67.4)	< 0.001
Permanent pacemaker	99/882 (11.2)	85/793 (10.7)	14/89 (15.7)	0.16
Baseline echocardiogram				
Aortic valve area (cm2)	0.70 ± 0.20	0.70 ± 0.19	0.72 ± 0.18	0.57
LVEF ≤ 35%	152/882 (17.2)	139/793 (17.5)	13/89 (14.6)	0.49
Aortic valve annulus (mm)	23.07 ± 2.10	23.15 ± 2.13	22.44 ± 1.76	0.003

Results are reported as number(%), med(IQR) or mean ± SD. Abbreviations: CABG: Coronary Artery Bypass Graft; COPD: Chronic Obstructive Pulmonary Disease; GFR: Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association; PCI; Percutaneous Coronary Intervention.

data with the use of Kaplan-Meier estimates and were compared with the log-rank. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

During the study period 944 patients underwent TAVI of which 793 transfemoral (84.0%), 89 transapical (9.4%), 58 subclavian (6.1%) and 4 direct transaortic valve implantation. The baseline characteristics of the 882 patients undergoing either TF-AVI or TA-AVI are depicted in Table 1. Patients undergoing TA-AVI had a higher prevalence of a history of coronary artery bypass graft, coronary artery disease, hypertension and

Table 2. Procedural characteristics comparing TF-AVI and TA-AVI

	Overall n=882	TF-AVI n=793	TA-AVI n=89	p-value
Prosthesis type and size				
MCS 26-mm	135/882 (15.3)	135/793 (17.0)	0	<0.001
MCS 29-mm	313/882 (35.5)	313/793 (39.5)	0	<0.001
MCS 31-mm	5/882 (0.6)	5/793 (0.6)	0	0.45
ESV 23-mm	153/882 (17.3)	119/793 (15.0)	34/89 (38.2)	<0.001
ESV 26-mm	271/882 (30.7)	221/793 (27.9)	50/89 (56.2)	<0.001
ESV 29-mm	5/882 (0.6)	0	5/89 (5.6)	<0.001
Sheath size				
18 French MCS	449/882 (50.9)	449/793 (56.6)	0	<0.001
18-19 French ESV	232/882 (26.3)	232/793 (29.3)	0	<0.001
> 19 French	201/882 (22.8)	112/793 (14.1)	89/89 (100.0)	<0.001
Vascular access				
surgical - femoral artery	94/882 (10.7)	94/793 (11.9)	0	0.001
percutaneous - femoral artery	699/882 (79.3)	699/793 (88.1)	0	<0.001
surgical - transapical	89/882 (10.1)	0	89/89 (100.0)	<0.001

Results are reported as number(%), med(IQR) or mean ± SD. Abbreviations: ESV: Edwards SAPIEN THV; MCS: Medtronic CoreValve System.

a glomerular filtration rate < 60mL/min (79.3% vs. 61.2%, p=0.001). As expected, the frequency of peripheral vascular disease was higher in the TA-AVI population (67.4% vs. 17.7%, p<0.001). This was reflected in a significantly higher logistic EuroSCORE and Society of Thoracic Surgery (STS) Score in patients undergoing TA-AVI compared to patients undergoing TF-AVI (Logistic EuroSCORE med (IQR): 27.0 (20.2 - 33.8) vs. 20.0 (12.3 - 27.7), p<0.001 and STS Score med (IQR): 10.2 (5.3 – 15.1) vs. 6.7 (3.5 – 9.9). Procedural characteristic of both cohorts are depicted in Table 2. The MCS was implanted only in the transfemoral cohort, as it is not available for transapical access. Differences in the sheath size are explained by the intrinsic differences between TF- and TA-AVI.

Univariable and multivariable in-hospital outcome is summarized in Table 3. There was no difference in device success (OR (95% C.I.): 0.73 (0.67 – 1.99), p=0.54) between patients undergoing TF-AVI and TA-AVI. Both all-cause and cardiovascular in-hospital mortality was higher after adjustment in the TA-AVI cohort (all-cause mortality: OR (95% C.I.): 3.12 (1.43 – 6.82), p=0.004 and cardiovascular mortality: OR (95% C.I.): 2.43 (1.04 – 5.71), p=0.04). Major (OR (95% C.I.): 0.33 (0.12 – 0.90), p=0.031) and minor (OR (95% C.I.): 0.17 (0.04 – 0.71), p=0.0015) vascular complications occurred more frequently after TF-AVI. Yet, there was a significant difference in the combined

Table 3. VARC outcomes comparing TF-AVI and TA-AVI

	Overall n=882	TF-AVI n=793	TA-AVI n=89	Crude Odds Ratio (95% C.I.)	p-value	Adjusted Odds Ratio (95% C.I.)	p-value
Therapy-specific results							
Device success	834/882 (94.6)	751/793 (94.7)	83/89 (93.3)	0.77 (0.32 - 1.87)	0.57	0.73 (0.67 - 1.99)	0.54
Concomitant PCI	20/882 (2.3)	19/793 (2.4)	1/89 (1.1)	0.46 (0.06 - 3.50)	0.45	0.36 (0.04 - 3.03)	0.35
Post-implantation balloon dilatation	109/882 (12.4)	100/793 (12.6)	9/89 (10.1)	0.78 (0.38 - 1.60)	0.50	0.87 (0.39 - 1.93)	0.72
Valve-in-Valve implantation	26/882 (2.9)	22/793 (2.8)	4/89 (4.5)	1.65 (0.56 - 4.90)	0.37	1.78 (0.51 - 6.26)	0.37
Coronary obstruction	3/882 (0.3)	2/793 (0.3)	1/89 (1.1)	4.49 (0.40 - 50.07)	0.22	1.72 (0.11 - 25.97)	0.70
In hospital outcomes							
Mortality							
All-cause	65/882 (7.4)	51/793 (6.4)	14/89 (15.7)	2.72 (1.44 - 5.14)	0.002	3.12 (1.43 - 6.82)	0.004
Cardiovascular	56/882 (6.3)	45/793 (5.7)	11/89 (12.4)	2.34 (1.17 - 4.72)	0.017	2.43 (1.04 - 5.71)	0.04
Myocardial Infarction							
Periprocedural (<72 hr)	8/882 (0.9)	6/793 (0.8)	2 / 89 (2.2)	3.02 (0.60 - 15.17)	0.18	2.71 (0.42 - 17.40)	0.29
Spontaneous (>72 hr)	5/882 (0.6)	4/793 (0.5)	1/89 (1.1)	2.24 (0.25 - 20.28)	0.47	0.98 (0.09 - 11.00)	0.99
Cerebrovascular complication							
Major stroke	22/882 (2.5)	21/793 (2.6)	1/89 (1.1)	0.42 (0.06 - 3.14)	0.40	0.87 (0.11 - 7.49)	0.91
Minor stroke	3/882 (0.3)	3/793 (0.4)	0	-	0.56	-	-
Transient ischemic attack	11/882 (1.2)	10/793 (1.3)	1/89 (1.1)	0.89 (0.11 - 7.03)	0.91	1.11 (0.12 - 10.49)	0.93
Vascular complication							
Major	94/882 (10.7)	89/793 (11.2)	5/89 (5.6)	0.47 (0.19 - 1.19)	0.11	0.33 (0.12 - 0.90)	0.031
Minor	99/882 (11.2)	97/793 (12.2)	2/89 (2.2)	0.17 (0.04 - 0.68)	0.013	0.17 (0.04 - 0.71)	0.015
Bleeding Complication							
Life-threatening	122/882 (13.8)	101/793 (12.7)	21/89 (23.6)	2.12 (1.24 - 3.60)	0.006	1.29 (0.68 - 2.45)	0.43
Major	180/882 (20.4)	159/793 (20.1)	21/89 (23.6)	1.23 (0.73 - 2.07)	0.43	1.42 (0.79 - 2.58)	0.24
Minor	96/882 (10.9)	84/793 (10.6)	12/89 (13.5)	1.32 (0.69 - 2.52)	0.41	1.00 (0.48 - 2.10)	1.00
Acute kidney injury							
Stage I	136/882 (15.4)	115/793 (14.5)	21/89 (23.6)	1.82 (1.07 - 3.09)	0.03	1.74 (0.93 - 3.26)	0.08
Stage II	30/882 (3.4)	25/793 (3.2)	5/89 (5.6)	1.82 (0.68 - 4.90)	0.23	1.21 (0.35 - 4.16)	0.76
Stage III	39/881 (4.4)	31/792 (3.9)	8/89 (9.0)	2.43 (1.08 - 5.45)	0.03	1.92 (0.69 - 5.37)	0.21
Permanent pacemaker Rrquirement	133/880 (15.1)	119/791 (15.0)	14/89 (15.7)	1.05 (0.58 - 1.93)	0.86	1.40 (0.71 - 2.76)	0.33
Combined Safety Endpoint	235/882 (26.6)	200/793 (25.2)	35/89 (39.3)	1.92 (1.22 - 3.03)	0.005	1.75 (1.03 - 2.98)	0.04
Length of stay ≥ 7 days	553/887 (63.1)	484/788 (61.4)	69/89 (77.5)	2.17 (1.29 - 3.64)	0.003	2.29 (1.28 - 4.09)	0.005

Results are reported as number(%), med(IQR) or mean ± SD. Abbreviations as in Table 1.

safety endpoint at 30-days (OR (95% C.I.): 1.75 (1.03 – 2.98), p=0.04). Moreover, a hospital stay equal to or longer than 7 days was more frequent in patients undergoing TA-AVI (OR (95% C.I.): 2.29 (1.28 – 4.09), p=0.005).

Long-term follow-up was complete in 99.7% of the patients and ranged from 0 to 1337 days (median (IQR): 365 days (174 – 557 days). Kaplan-Meier estimates of survival including hospital stay and follow-up period revealed a significant difference in survival at 1-year (83.0% vs. 68.0%, Log-Rank; p=0.01). After adjusting for differences in baseline characteristics all-cause mortality remained significantly higher in the TA-AVI cohort (HR (95% C.I.): 1.88 (1.23 – 2.87), p=0.004) (Figure 1A). Kaplan-Meier estimates of survival after discharge disclosed no significant differences between TF- and TA-AVI (87.0% vs. 81.0%, Log-Rank; p=0.24).

COMMENT

We found that in institutions with predominant TF-TAVI practice and experience, TA-AVI is associated with an increased risk of 30-day mortality and all-cause mortality during follow-up. Moreover, patients undergoing TA-AVI had a longer hospital stay but less vascular complications in comparison to TF-AVI.

These findings stem from a retrospective, non-random treatment allocation in 4 institutions in which TF-AVI is the default treatment strategy while using TA-AVI in case the latter is not feasible. To address this bias favoring TF-AVI in potentially less sick patients, all outcomes were adjusted for differences in baseline characteristics. Yet,

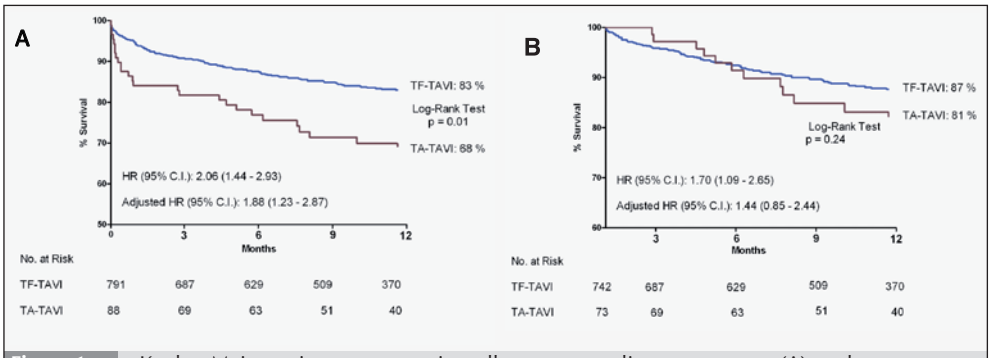

Figure 1. Kaplan-Meier estimates comparing all-cause mortality at one year **(A)** and at one year excluding patients with a follow-up period shorter than 30 days **(B)**

The blue line depicts TF-AVI and the red line depicts TA-AVI.

residual confounding may still be present due to variables that have not been collected, uniformly defined (e.g. frailty and porcelain aorta) and/or remained undetected. In addition, differences in outcome due to differences in valve used (i.e. ESV in TA-AVI while both ESV and MCS in TF-AVI) cannot be excluded. Yet, we previously found no difference in outcome at 1 year follow up between the two valves, except for a higher frequency of permanent pacemaker implantation after MCS implantation[11].

Considering the above, 30-day mortality after TA-AVI in this study is comparable to a recently reported review but contrasts with the findings of recent observational studies reporting a lower mortality at 30 days and also during follow-up[16–20]. The latter is most likely explained by the initial higher mortality in the present population as shown by the crude and adjusted hazard ratios but also the morphology of the Kaplan Meier curves. This is further supported by the landmark analysis in which no increased mortality was observed after hospital discharge. Differences in mortality may also be explained by differences in baseline risk as expressed by the Logistic EuroSCORE and STS Score. This remains speculative considering the potential variability in the use of a risk model due to - for instance - differences in interpretation and entry of variables into the model. Moreover, both the Logistic EuroSCORE and STS Score have a low predictive ability of estimating risk in patients undergoing TAVI[21]. Rather than patient-related variables, we believe that procedural and operator-related factors have played a more important role in the observed difference in outcome. As mentioned above, TF-AVI was performed in almost all patients while only 9.4% of patients underwent TA-AVI in a period of 6 years. The latter indicating a dissimilar experience and expertise with TF- and TA-AVI. The lower mortality after TA-AVI reported in recent studies stems from investigators who either pioneered TA-AVI or who are truly experienced. TAVI is known to be a complex procedure for which a multidisciplinary preparation and execution is advocated, especially in case of TA-AVI[22]. Also, a learning curve effect has been reported for both the approaches[23–25]. It is conceivable that the effect of experience on outcome is more pronounced in case of TA-AVI. The low number of cases overall and per center prohibited further analysis of this volume effect in the current population. A true difference in outcome between TA and TF-AVI may, nevertheless, be a true phenomenon given the more invasive and complex nature of TA-AVI. The interaction between independent factors affecting outcome can only be clarified by direct comparisons between TA- and TF-AVI, preferably by multicenter studies. However, continuous improvements in TAVI technology such as further reduction of the size of delivery catheters favoring TF-AVI and novel access strategies (e.g. direct aortic access) may render the design and execution of such studies difficult.

In this study, TA-AVI was associated with a lower risk of both minor and major vascular

complications in comparison to TF-AVI. This not unexpected given the frequent use of percutaneous closing techniques when performing TF-AVI in combination with the use of large-bore introducers sheaths[5,6]. We found, however, no difference in bleeding complications between both groups, which is in accordance with a recent observational study[26]. It has been shown that the frequency of vascular complications following TF-AVI decreases in function of experience and, thus, time. It is conceivable that vascular complications will further decrease following introduction of smaller delivery catheters in addition to more appropriate assessment of the femoral arteries[27,28].The reduction in catheter size also holds for TA-AVI. This has – among others – lead to the development of percutaneous closure of the apex, reducing the invasive nature of TA-AVI. Yet, the clinical recognition, management and the prognosis of access site complications following TA-AVI is likely more difficult and worry-some than after TF-AVI.

Hospitalization was longer in patients undergoing TA-AVI compared to patients undergoing TF-AVI which is consistent with the duration reported in the PARTNER-A cohort[2]. Longer stay does not only have economic implications, as was observed in studies from the United States and Europe, but may also have an effect on outcome[10,29,30]. Considering the frail patients undergoing TAVI, it cannot be excluded that a longer hospital stay is associated with an increased risk of hospital acquired infections[31].

LIMITATIONS

In addition to the ones mentioned above, the PRAGMATIC initiative is a retrospective analysis of prospectively collected data. Despite the care of data collection and the use of VARC-I endpoint definitions, some degree of observation bias cannot be ruled out. Also, heterogeneity is present across centers and clinical endpoints were not adjudicated by an independent Clinical Event Committee. To minimize biases, multivariable analysis was performed; however, hidden bias may remain due to unmeasured or undetected confounders.

CONCLUSIONS

In institutions with a low volume of TA-AVI, TA-AVI is associated with an increased risk of all-cause mortality and longer hospital stay but less vascular complications in comparison to TF-AVI. The interaction between experience and type of treatment on outcome requires further investigation before advocating one treatment over the other.

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CHAPTER 7

Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve Revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative

Chieffo A, Buchanan GL, Van Mieghem NM, Tchetche D, Dumonteil N, Latib A, van der Boon RM, Vahdat O, Marcheix B, Farah B, Serruys PW, Fajadet J, Carrié D, de Jaegere PP, Colombo A. (Pooled-RotterdAm-Milano-Toulouse In Collaboration).

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ABSTRACT

Objectives

The aim of this study was to compare outcomes after transfemoral transcatheter aortic valve implantation with the Medtronic CoreValve (MCV) versus the Edwards SAPIEN/SAPIEN XT transcatheter heart valve (ESV) for severe aortic stenosis.

Background

No large matched comparison study has been conducted so far evaluating both commercially available devices.

Methods

The data from databases of 4 experienced European centers were pooled and analyzed. Due to differences in baseline clinical characteristics, propensity score matching was performed. Study objectives were Valve Academic Research Consortium outcomes at 30 days and 1 year.

Results

In total, 793 patients were included: 453 (57.1%) treated with the MCV and 340 (42.9%) with the ESV. After propensity matching, 204 patients were identified in each group. At 30 days, there were no differences in all-cause mortality (MCV, 8.8% vs. ESV, 6.4%; hazard ratio [HR]: 1.422; 95% confidence interval [CI]: 0.677 to 2.984; p = 0.352), cardiovascular mortality (MCV, 6.9% vs. ESV, 6.4%; HR: 1.083; 95% CI: 0.496 to 2.364; p = 0.842), myocardial infarction (MCV, 0.5% vs. ESV, 1.5%; HR: 0.330; 95% CI: 0.034 to 3.200; p = 0.339), stroke (MCV, 2.9% vs. ESV, 1.0%; HR: 3.061; 95% CI: 0.610 to 15.346; p = 0.174), or device success (MCV, 95.6% vs. ESV, 96.6%; HR: 0.770; 95% CI: 0.281 to 2.108; p = 0.611). Additionally, there were no differences in major vascular complications (MCV, 9.3% vs. ESV, 12.3%; HR: 0.735; 95% CI: 0.391 to 1.382; p = 0.340) or life-threatening bleeding (MCV, 13.7% vs. ESV, 8.8%; HR: 1.644; 95% CI: 0.878 to 3.077; p = 0.120). MCV was associated with more permanent pacemakers (22.5% vs. 5.9%; HR: 4.634; 95% CI: 2.373 to 9.050; p < 0.001). At 1 year, there were no differences in all-cause (MCV, 16.2% vs. ESV, 12.3%; HR: 1.374; 95% CI: 0.785 to 2.407; p = 0.266) or cardiovascular (MCV, 8.3% vs. ESV, 7.4%; HR: 1.145; 95% CI: 0.556 to 12.361; p = 0.713) mortality.

Conclusions

No differences between the 2 commercially available transfemoral transcatheter aortic valve implantation devices were observed at the adjusted analysis in Valve Academic Research Consortium outcomes except for the need for permanent pacemakers with the MCV.

INTRODUCTION

For high-risk patients with severe symptomatic aortic stenosis, transcatheter aortic valve implantation (TAVI) has emerged as an effective alternative[1–5]. Since its introduction, 2 devices have been in widespread use throughout Europe. The first is the Medtronic CoreValve (MCV) (Medtronic Inc., Minneapolis, Minnesota), a nitinol self-expandable porcine pericardial tissue valve. The other is the balloon-expandable Edwards SAPIEN/SAPIEN XT transcatheter heart valve (ESV) (Edwards Lifesciences, Irvine, California), composed initially of stainless steel and now of a cobalt chromium frame with bovine pericardial leaflets. Currently, a substantial body of data has been published regarding outcomes following TAVI[1–8]. However, so far, no large comparison has been performed to assess differences between currently available valve types. The aim of this multicenter collaborative registry was therefore to compare 30-day and 1-year Valve Academic Research Consortium (VARC) outcomes after transfemoral (TF) TAVI with MCV versus ESV.

METHODS

Patients

The PRAGMATIC Plus (Pooled-RotterdAm-MilAno-Toulouse In Collaboration) initiative is a collaboration of 4 European institutions with established TAVI experience. The baseline characteristics and clinical outcomes from a series of 944 patients who underwent TAVI were collected since the introduction of the respective local TAVI programs until July 2011: 1) San Raffaele Scientific Institute, Milan, Italy (N = 330); 2) Clinique Pasteur, Toulouse, France (N = 224); 3) Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (N = 206); and 4) Hôpital Rangueil, Toulouse, France (N = 184). After the VARC publication, clinical outcomes were adjudicated, and all data pooled in a dedicated database. Patient eligibility for TAVI at each center was described previously[9–11].

Procedures

Patients were included in this analysis if femoral access was used. Both TAVI devices, commercially available at the onset of the study, were used: the 18-F sheath–compatible MCV (except 5 cases with the 21-F device) and the ESV, using 22-/24-F sheaths until mid 2010 when the Novaflex delivery catheter and the ESV-XT downgrading to 18-/19-F device was introduced. Sheath size was entered in the propensity matching as a dichotomous variable, thus, excluding the initial devices in the adjusted analysis. Valve choice was at operator discretion.

Study endpoints

The study endpoints were defined according to VARC[12]. Residual aortic regurgitation (AR) was evaluated by either transthoracic or transesophageal echocardiography at all centers. All patients provided written informed consent for the procedure and data collection according to the policy of each hospital.

Statistical analysis

The analysis was performed according to valve type. Continuous variables are expressed as mean ± SD and analyzed with the Student *t* test or Wilcoxon rank sum test depending on the variable distribution. Categorical variables were compared with the chi-square test with Yates correction for continuity or the Fisher exact test. Because of the nonrandomized nature of the study, to reduce treatment selection bias and potential confounding, we performed rigorous adjustment for significant differences in baseline characteristics with propensity-score matching. The score was calculated by performing a multiparsimonious multivariable logistic regression with valve type as the dependent variable. The following covariants were selected: age, sex, body mass index, logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), Society of Thoracic Surgeons score, previous MI, coronary artery bypass graft, or percutaneous coronary intervention, coronary artery disease, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, chronic kidney disease, cerebrovascular disease, ejection fraction ≤35%, aortic annulus diameter, and sheath size. The C-statistic for the propensity score model was 0.67, and the Hosmer-Lemeshow goodness-of-fit was 0.33, confirming good calibration. To identify matched pairs, we used the following algorithm: 1:1 optimal match with a ±0.01 caliper and no replacement. Clinical outcomes in the matched population were analyzed with Cox proportional hazards regression stratified on matched pairs. Multivariable Cox proportional hazards regression modeling was performed to determine the independent predictors of study objectives with purposeful selection of covariates. Variables associated at univariate analysis (all with a p value ≤0.1) and those judged to be of clinical importance were eligible for inclusion into the multivariable model-building process. The goodness-of-fit of the Cox multivariable model was assessed with the Grønnesby-Borgan-May test. Results are reported as hazard ratio (HR) with associated 95% confidence interval (CI) and p-value. Survival was recorded by Kaplan-Meier analysis with the log-rank method used for comparison. All statistical analyses were performed with STATA (version 9.0, StataCorp, College Station, Texas). A p value of <0.05 was considered statistically significant.

RESULTS

Overall, 793 patients were treated with a TF access strategy: 453 (57.1%) with an MCV and 340 (42.9%) with an ESV. Baseline characteristics of the overall population are reported in Table 1.

Table 1. Baseline characteristics of the overall population

	MCV (n = 453)	ESV (n = 340)	p-value
Demographics			
Age, yrs	80.9 ± 6.7	81.6 ± 7.3	0.125
Male	251 (55.4)	168 (49.4)	0.094
NYHA functional class III/IV	373 (82.3)	273 (80.8)	0.572
Logistic EuroSCORE	21.4 ± 12.6	23.0 ± 13.8	0.089
STS score	8.1 ± 6.2	8.9 ± 6.5	0.066
Previous stroke	75 (16.6)	46 (13.5)	0.241
Previous MI	88 (19.4)	41 (12.1)	0.005
Previous CABG	108 (23.8)	59 (17.4)	0.027
Previous PCI	128 (28.3)	101 (29.7)	0.656
Diabetes mellitus	129 (28.5)	94 (27.6)	0.797
Hypertension	292 (64.5)	244 (71.8)	0.030
GFR <60 ml/min	267 (58.9)	217 (64.2)	0.133
COPD	147 (32.5)	110 (32.4)	0.977
PVD	75 (16.6)	65 (19.3)	0.327
Baseline echocardiogram			
Annulus, mm	23.5 ± 2.3	22.7 ± 1.8	<0.001
AVA, mm^2	0.7 ± 0.2	0.7 ± 0.2	0.822
LVEF <35%	80 (17.7)	59 (17.4)	0.910

Values are n (%) or mean ± SD. Abbreviations: AVA: Aortic Valve Area; CABG: Coronary Artery Bypass Graft; COPD: Chronic Obstructive Pulmonary Disease; ESV: Edwards SAPIEN/SAPIEN XT transcatheter heart valve; EuroSCORE: European System for Cardiac Operative Risk Evaluation; GFR: Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; MCV: Medtronic CoreValve; NYHA: New York Heart Association; PCI: Percutaneous Coronary Intervention; PVD: Peripheral Vascular Disease; STS score: Society of Thoracic Surgeons predicted risk of mortality score.

Unadjusted VARC outcomes in the overall population

At 30 days, 34 patients (7.5%) died after receiving an MCV compared with 17 (5.0%) after receiving an ESV; cardiovascular death was, respectively, 28 (6.2%) and 17 (5.0%). Online supplementary Table 1 shows predictors of mortality. Major stroke occurred in 16 MCV (3.5%) and 5 (1.5%) ESV patients. Patients who had a stroke more frequently had valve embolization or required a second valve (Online Table 2).

Five patients (1.1%) with an MCV and 1 (0.3%) with an ESV had a periprocedural MI. Coronary obstruction occurred in only 1 patient in each group. Valve embolization

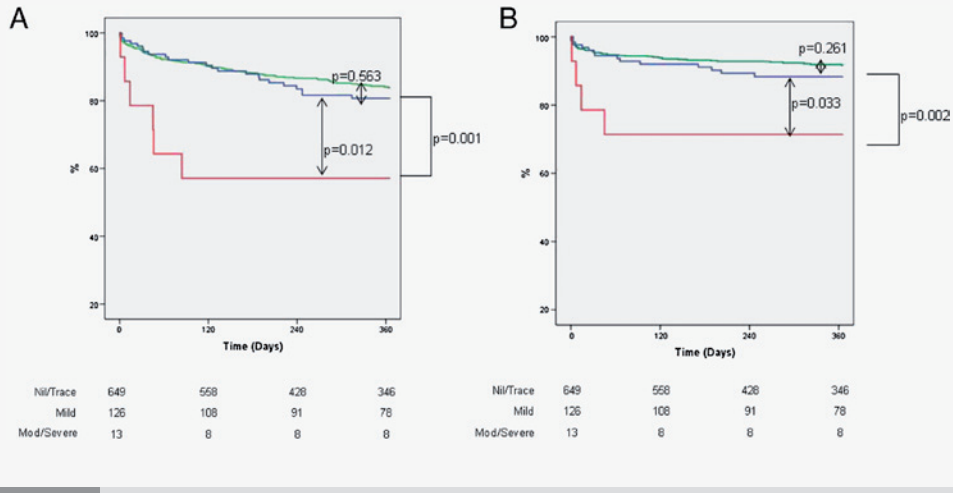

Figure 1. Freedom from all-cause (**A**) and cardiovascular (**B**) mortality at 1 year according to the grade of aortic regurgitation (AR)

The green line represents no/trace AR, the blue line mild AR and the red line moderate/severe AR.

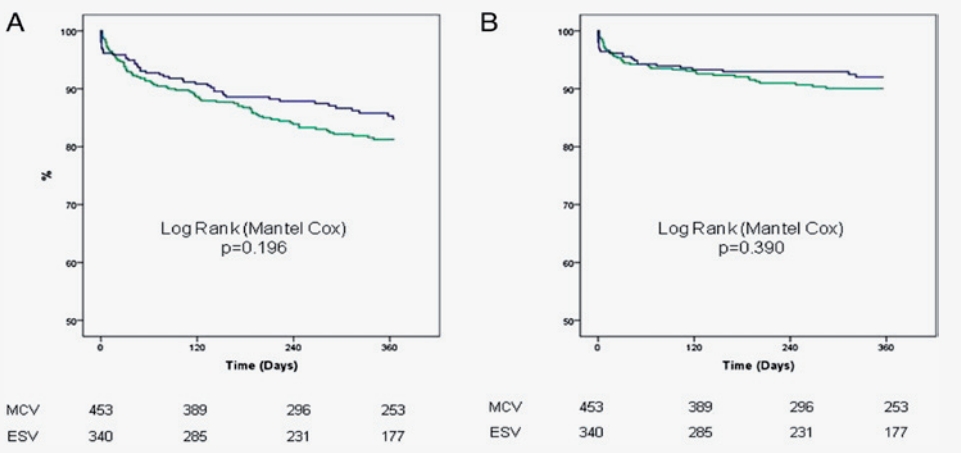

Figure 2. Freedom from all-cause (**A**) and cardiovascular mortality (**B**) at 1 year in the unadjusted analysis

The green line represents the Medtronic CoreValve (MCV) and the blue line the Edwards SAPIEN/SAPIEN XT transcatheter heart valve (ESV).

Table 2. Baseline Characteristics of the propensity-matched population

	MCV (n = 204)	ESV (n = 204)	p-value
Demographics			
Age, yrs	82.1 ± 6.0	81.8 ± 7.8	0.656
Male	92 (45.1)	100 (49.0)	0.427
NYHA functional class III/IV	169 (82.8)	163 (80.3)	0.507
Logistic EuroSCORE, %	22.1 ± 12.2	21.7 ± 13.7	0.778
STS score, %	9.3 ± 7.2	8.9 ± 7.0	0.538
Previous stroke	25 (12.3)	24 (11.8)	0.879
Previous MI	19 (9.3)	22 (10.8)	0.621
Previous CABG	27 (13.2)	31 (15.2)	0.571
Previous PCI	69 (33.8)	63 (30.9)	0.525
Diabetes mellitus	58 (28.4)	56 (27.5)	0.825
Hypertension	154 (75.5)	145 (71.1)	0.314
GFR <60 ml/min	128 (62.7)	123 (60.3)	0.611
COPD	58 (28.4)	59 (28.9)	0.913
PVD	47 (23.0)	41 (20.0)	0.470
Baseline echocardiogram			
Annulus, mm	22.7 ± 2.3	22.9 ± 1.8	0.417
AVA, mm^2	0.7 ± 0.2	0.7 ± 0.2	0.250
LVEF <35%	29 (14.2)	32 (15.7)	0.677

Values are n (%) or mean ± SD. Abbreviations as in Table 1.

occurred in 30 MCV patients (6.6%) and in no ESV patients, and there was a need for a second valve in 20 MCV (4.4%) versus ESV 2 (0.6%) patients. Residual mild AR was observed in 89 MCV patients (19.6%) versus 37 ESV patients (10.9%); moderate AR occurred in 8 MCV patients (1.8%) versus 5 ESV patients (1.5%),and severe AR in 1 MCV patient (0.2%) versus 1 ESV patient (0.3%). Figure 1 illustrates the impact of AR on unadjusted survival. The device was successful in 424 MCV patients (93.6%) and in 327 ESV patients (96.2%).

Propensity-matched analysis

After propensity-score matching was performed, there were 204 matched pairs of patients in each group. Baseline characteristics of the matched groups are shown in Table 2. In the propensity model, because sheath size was a dichotomous variable, only newer generation devices were included

VARC outcomes for the matched groups

No differences were observed between MCV and ESV patients in the occurrence of 30-day all-cause (MCV, 8.8% vs. ESV, 6.4%; HR: 1.422; 95% CI: 0.677 to 2.984; p = 0.352) or cardiovascular (MCV, 6.9% vs. ESV, 6.4%; HR: 1.083; 95% CI: 0.496

Table 3. VARC Outcomes in the Propensity-Matched Population

Outcome	No. (%) of Events		HR	95% C.I.	p-value
	MCV (n = 204)	ESV (n = 204)			
30 days					
All-cause mortality	18 (8.8)	13 (6.4)	1.422	0.677–2.984	0.352
Cardiac mortality	14 (6.9)	13 (6.4)	1.083	0.496–2.364	0.842
Spontaneous MI	1 (0.5)	3 (1.5)	0.330	0.034–3.200	0.339
Major stroke	6 (2.9)	2 (1.0)	3.061	0.610–15.346	0.174
Major vascular	19 (9.3)	25 (12.3)	0.735	0.391–1.382	0.340
Life-threatening bleeding	28 (13.7)	18 (8.8)	1.644	0.878–3.077	0.120
Major bleeding	37 (18.1)	45 (22.1)	0.783	0.481–1.273	0.324
Acute kidney injury stage 3	8 (3.9)	7 (3.4)	1.155	0.411–3.245	0.785
Device success	195 (95.6)	197 (96.6)	0.770	0.281–2.108	0.611
Combined safety	54 (26.5)	47 (23.0)	1.203	0.766–1.887	0.422
1 Year					
All-cause mortality	33 (16.2)	25 (12.3)	1.374	0.785–2.407	0.266
Cardiac mortality	17 (8.3)	15 (7.4)	1.145	0.556–2.361	0.713
NYHA functional class III/IV	23 (14.5)	15 (9.1)	1.691	0.848–3.374	0.136
Rehospitalization	22 (18.8)	23 (13.2)	1.520	0.803–2.879	0.198
Mean gradient, mm Hg	10.1 ± 5.4	10.3 ± 4.0	0.991	0.938–1.047	0.738
Moderate-severe AR	8 (5.2)	4 (2.8)	1.905	0.561–6.467	0.302
Combined efficacy	66 (32.4)	52 (25.6)	1.389	0.903–2.136	0.135

Values are n (%) or mean ± SD. Abbreviations: AR: Aortic Regurgitation; CI: Confidence Interval; VARC: Valve Academic Research Consortium; other abbreviations as in Table 1.

to 2.364; p = 0.842) mortality. In addition, there were no statistically significant differences in spontaneous MI (MCV, 0.5% vs. ESV, 1.5%; HR: 0.330; 95% CI: 0.034 to 3.200; p = 0.339) or stroke (MCV, 2.9% vs. ESV, 1.0%; HR: 3.061; 95% CI: 0.610 to 15.346; p = 0.174) (Table 3). Furthermore, there were no differences in major vascular complications (MCV, 9.3% vs. ESV, 12.3%; HR: 0.735; 95% CI: 0.391 to 1.382; p = 0.340) or life-threatening bleeding (MCV, 13.7% vs. ESV, 8.8%; HR: 1.644; 95% CI: 0.878 to 3.077; p = 0.120). Consequently, no difference was observed in 30-day VARC combined safety (MCV, 26.5% vs. ESV, 23.0%; HR: 1.203; 95% CI: 0.766 to 1.887; p = 0.422). Conversely, as expected, there was less need for a PPM after treatment with an ESV (MCV, 22.5% vs. ESV, 5.9%; HR: 4.634; 95% CI: 2.373 to 9.050; p < 0.001).

No significant differences were found in residual moderate/severe AR (MCV, 1.5% vs. ESV, 0.5%; HR: 3.015; 95% CI: 0.311 to 29.243; p = 0.341) or indeed residual mild AR (MCV, 17.3% vs. ESV, 11.7%; HR: 1.569; 95% CI: 0.887 to 2.776; p = 0.122). Supplementary Online Table 3 illustrates the degree of residual AR. Furthermore, there was no difference in the aortic valve area after the procedure (1.77 ± 0.41 mm Hg vs.

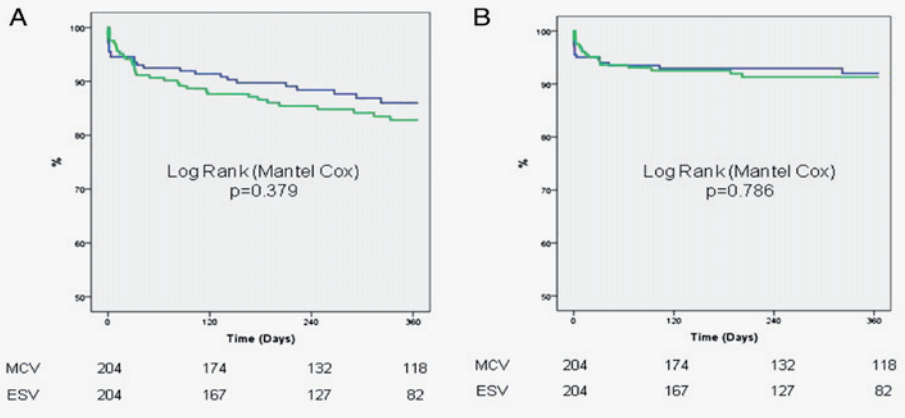

Figure 3. Freedom from all-cause (**A**) and cardiovascular (**B**) mortality in the propensity matched population at 1 year

The green line represents MCV and the blue line the ESV. Abbreviations as in Figure 2.

1.71 ± 0.32 mm Hg; HR: 1.525; 95% CI: 0.752 to 3.092; p = 0.242). Notably, there was no significant increased need for a second valve (MCV, 2.9% vs. ESV, 1.0%; HR: 3.061; 95% CI: 0.610 to 15.346; p = 0.174) with MCV despite 11 patients (5.4%) versus no patients (p = 0.001) undergoing embolization. However, this was not reflected in device success, which was similar between groups (MCV, 95.6% vs. ESV, 96.6%; HR: 0.770; 95% CI: 0.281 to 2.108; p = 0.611). At 1 year, there were no differences in all-cause (MCV, 16.2% vs. ESV, 12.3%; HR: 1.374; 95% CI: 0.785 to 2.407; p = 0.266) or cardiovascular mortality (MCV, 8.3% vs. ESV, 7.4%; HR: 1.145; 95% CI: 0.556 to 2.361; p = 0.713). No difference was also observed in the combined efficacy endpoint (MCV, 32.4% vs. ESV, 25.6%; HR: 1.389; 95% CI: 0.903 to 2.136; p = 0.135). Kaplan-Meier survival curves are shown in Figure 3.

DISCUSSION

The main findings of our study are as follows. 1) There were no differences in 30-day or 1-year mortality between MCV and ESV; 2) moreover, there were no differences in combined safety and efficacy endpoints between valves; 3) as expected, there was a greater need for PPM after MCV implantation.

TAVI is now an acceptable treatment option for those deemed at high risk of surgical aortic valve replacement. There are currently 2 commercially available devices available

for TF: MCV and ESV. A number of studies have provided a comparison, including the FRANCE 2 (French Aortic National CoreValve and Edwards) registry and the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) registry[7,8]. In addition, it is important to understand that these registries report only unadjusted analyses and do not take into account the significant differences at baseline. In our series, the adjusted all-cause mortality at 30 days (MCV, 8.8% vs. ESV, 6.4%) is similar to the unadjusted all-cause mortality reported in the FRANCE 2 (8) and the U.K. TAVI registries[7]. It is also comparable with that reported by several initial registries, varying from 0.9% to 11.0% for ESV and 6.0% to 15.2% for MCV via transfemoral approach[1,13,14]. Furthermore, at 1 year, there remained no differences in all-cause mortality between valves (MCV, 16.3% vs. ESV, 13.9%), which was favorable compared with other studies (7 and 8). No difference was also observed at 1 year in the combined efficacy endpoint. Importantly, there was no difference in major vascular complications after matching for sheath size (MCV, 9.3% vs. ESV, 12.3%). It was previously demonstrated that major vascular complications were improved with the introduction of the newer device[15]. Nevertheless, the introduction of smaller sheaths is warranted to reduce complications further. The introduction of the Edwards SAPIEN 3 will reduce the sheath size to 14/16-F, with similar improvements expected with the MCV.

In our series, the 2.6% incidence of stroke seems acceptable compared with previous experience (1.2% to 5.0%)[3,5–8,16]. Of note, patients who had a stroke more frequently had valve embolization or needed a second valve. At the center with the highest rate of stroke, the rate of embolization was 10.4%. It is possible that the process of recapturing and the subsequent retrieval of the valve and delivery system through the aorta could have played a role. As previously reported, there was a greater need for PPM with the MCV, likely related to valve structure and design[7,16]. The U.K. TAVI registry demonstrated in the comparison between valve types (unadjusted) an increased risk of moderate/severe AR with the MCV (MCV, 17.3% vs. ESV, 9.6%; $p = 0.001$)[7]. Importantly, in our study in both unadjusted and adjusted analyses, no differences were observed in the incidence of residual AR of any grade between valve types. In addition, our data confirm that moderate/severe AR is associated with increased 1-year mortality. There is growing evidence in the current literature that moderate/severe AR is correlated with higher mortality[8,17–19]. Notably, the presence of residual AR in our study significantly affected both all-cause and cardiac mortality (Figure. 1). In fact, the freedom from all-cause and cardiac mortality was significantly lower with moderate/severe AR compared with nil/trivial or mild AR. The presence of residual AR is one of the limitations of the currently available TAVI devices, and paravalvular leaks need to be decreased to improve outcomes further. In addition, facilitation of

accurate positioning, device retrieval, and reduction of the delivery catheter diameter will continue to improve outcomes. Overall, our results are encouraging, showing no difference between commercially available valve types except for a greater need for a PPM with the MCV, but clearly longer term follow-up in the setting of an adequately powered randomized clinical trial is needed.

LIMITATIONS

Due to the nonrandomized and retrospective nature of this study, the findings are subject to selection bias and confounding with regard to the pre-procedural risk of the patient. In an aim to minimize these biases, propensity-score matching was performed; however, hidden bias may remain due to the influences of unmeasured confounders. The lack of a central core laboratory and adjudication committee means potential reporting bias and is a further limitation. Finally, the clinical follow-up duration limits conclusions on valve durability.

CONCLUSIONS

No differences between the 2 commercially available TF TAVI devices were observed in the adjusted analysis in the study population in VARC outcomes at 30 days and 1 year, except for the need for a PPM with the MCV. These results need to be confirmed in a randomized trial.

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CHAPTER 8

Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: insights from the Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative

Tchetche D, Van der Boon RM, Dumonteil N, Chieffo A, Van Mieghem NM, Farah B, Buchanan GL, Saady R, Marcheix B, Serruys PW, Colombo A, Carrie D, De Jaegere PP, Fajadet J.

Am Heart J. 2012 Sep;164(3):402-9.

ABSTRACT

Background

Little is known about the impact of bleeding and red blood cells transfusion (RBC) on the outcome post transcatheter aortic valve implantation (TAVI).

Methods

Between November 2005 and August 2011, 943 consecutive patients underwent TAVI. Bleeding was assessed according to the Valve Academic Research Consortium definitions. Patients receiving RBC were compared to those not requiring transfusion.

Results

Life-threatening and major bleedings occurred respectively in 13.9% and 20.9% of the patients, significantly more frequently in the RBC cohort. Vascular complications occurred in 23.2% of the patients. Major and minor vascular complications were more frequent in the RBC group: 19.3 vs 5.2%, $P < .001$; 15.3 vs 9%, $P = .003$, respectively. Thirty-day all-cause mortality was 7.2%. Of the overall cohort, 38.9% required RBC transfusion; those receiving at least 4 U of RBC had higher 30-day all-cause mortality than those receiving 1 to 4 U of RBC and those not requiring transfusion: 14.4%, vs 6.3% vs 6.3%, respectively, $P = .008$. By multivariate analysis, transfusion of RBC was associated with an increased 30-day and 1-year mortality. Major stroke and all stages of acute kidney injury were significantly more frequent in the RBC cohort.

Conclusions

Bleeding is frequent after TAVI, mainly driven by vascular complications. RBC transfusion was associated with increased mortality at 1 year and increased risk of major stroke and acute kidney injury. Specific scores are needed to identify the patients at higher risk for TAVI-related bleeding and RBC transfusion.

INTRODUCTION

Ten years after the first-in-man case performed by Alain Cribier, transcatheter aortic valve implantation (TAVI) has become an established treatment for inoperable or high-risk patients presenting with symptomatic aortic stenosis. Independent from growing experience and technological improvements, several issues remain, including vascular complications and bleeding[1–3]. Bleeding predicts poor outcome after various cardiac interventions. In the setup of acute coronary syndromes, it is associated with a 5-fold increase in 30-day mortality[4]. Specific risk-scores, like the GRACE score, have been developed to identify the patients at higher risk of bleeding and adapt antithrombotic regimens accordingly[5,6]. Considering TAVI, there is conflicting evidence on the real incidence of bleeding as multiple definitions have been used through studies. The Valve Academic Research Consortium (VARC) initiative aimed to standardize the definitions of TAVI outcome[7]. Bleeding post-TAVI ranges from 22.8% to 77% with subsequent need for packed red blood cells (RBC) transfusion up to 40%[8,9]. We sought to evaluate the incidence, predictors and clinical impact of bleeding and RBC transfusion in a large multi-centre series of patients who underwent TAVI.

METHODS

PRAGMATIC initiative

The PRAGMATIC Plus initiative is a collaboration of four European centers with established TAVI experience. Baseline patient characteristics, procedural details, and clinical outcome data from a series of 943 consecutive patients who underwent TAVI were collected from November 2005 to August 2011: San Raffaele Scientific Institute, Milan (n = 330); Clinique Pasteur, Toulouse (n = 224); Thoraxcenter, Erasmus Medical Center, Rotterdam (n = 206); Hôpital Rangueil, Toulouse (n = 184). After the VARC consensus document was published, the proposed endpoint definitions were adopted and the respective local databases were modified accordingly. All data were then pooled into a dedicated global database.

Patient eligibility for TAVI was comparable across the 4 centers[9–11].

All patients had been judged inoperable or at high operative risk by a multidisciplinary heart team consensus[12]. The antithrombotic regimen varied slightly across centers. In Milan, Rotterdam, and Clinique Pasteur, the patients were loaded with aspirin and clopidogrel (300 mg followed by 75 mg daily) at least 1 day before TAVI. Dual antiplatelet therapy was continued post TAVI for1 to 6 months according to local

Table 1. Baseline and procedural characteristics according to transfusion and bleeding status

	Overall	RBC Transfusion	No RBC Transfusion	p-value	Bleeding	No Bleeding	p-value
	n = 943	n = 367	n = 576		n = 419	n = 524	
Demographics							
Age (yrs), mean ± SD	81.0 ± 7.0	80.6 ± 7.05	81.3 ± 7.0	0.10	80.9 ± 6.4	81.1 ± 7.5	0.74
Male, n (%)	507 / 943 (53.8)	167 / 367 (45.5)	340 / 576 (59.0)	< 0.001	210 / 419 (50.1)	297 / 524 (56.7)	0.045
Body Mass Index, mean ± SD	26.03 ± 4.51	26.03 ± 4.59	26.03 ± 4.46	1.00	25.97 ± 4.47	26.08 ± 4.54	0.72
NYHA class III or IV, n (%)	765 / 941 (81.1)	298 / 367 (81.2)	467 / 574 (81.4)	0.95	340 / 418 (81.3)	425 / 523 (81.3)	0.98
Logistic EuroSCORE, med (IQR)	20.9 (12.9 - 28.8)	21.0 (12.3 - 29.7)	20.8 (13.3 - 28.2)	0.34	21.2 (12.9 - 29.5)	20.4 (12.6 - 28.2)	0.04
Previous cerebrovascular accident, n (%)	148 / 943 (15.7)	74 / 367 (20.2)	74 / 576 (12.8)	0.003	72 / 419 (17.2)	76 / 524 (14.5)	0.26
Previous myocardial infarction, n (%)	157 / 943 (16.6)	74 / 367 (20.2)	83 / 579 (14.4)	0.021	67 / 419 (16.0)	90 / 524 (17.2)	0.63
Previous CABG, n (%)	208 / 943 (22.1)	80 / 367 (21.8)	128 / 579 (22.2)	0.88	84 / 419 (20.0)	124 / 524 (23.7)	0.18
Previous PCI, n (%)	277 / 943 (29.4)	100 / 367 (27.2)	177 / 576 (30.7)	0.25	116 / 419 (27.7)	161 / 524 (30.7)	0.31
Coronary artery disease, n (%)	425 / 943 (45.1)	163 / 367 (44.4)	262 / 57 6 (45.5)	0.75	179 / 419 (42.7)	246 / 524 (46.9)	0.20
Diabetes mellitus, n (%)	267 / 943 (28.3)	98 / 367 (26.7)	169 / 576 (29.3)	0.38	118 / 419 (28.2)	149 / 524 (28.34)	0.93
Hypertension, n (%)	656 / 943 (69.6)	243 / 367 (66.2)	413 / 576 (71.7)	0.08	288 / 419 (68.7)	368 / 524 (70.2)	0.62
Glomerular Filtration Rate < 60 ml/min, n (%)	593 / 939 (62.9)	243 / 365 (66.6)	350 / 574 (61.0)	0.08	285 / 417 (68.3)	308 / 522 (59.0)	0.003
Chronic Obstructive Pulmonary Disease, n (%)	324 / 943 (34.4)	115 / 367 (31.3)	209 / 576 (36.2)	0.12	147 / 419 (35.1)	177 / 524 (33.8)	0.68
Peripheral vascular disease, n (%)	236 / 939 (25.0)	105 / 367 (28.6)	131 / 572 (22.9)	0.05	133 / 417 (31.9)	103 / 522 (19.7)	< 0.001
Permanent pacemaker, n (%)	105 / 943 (11.1)	47 / 367 (12.8)	58 / 576 (10.1)	0.19	47 / 419 (11.2)	58 / 524 (11.1)	0.94
Baseline echocardiogram							
Aortic valve annulus (mm), mean ± SD	23.10 ± 2.10	22.97 ± 2.09	23.19 ± 2.11	0.13	23.00 ± 2.05	23.19 ± 2.15	0.20
Left ventricular ejection fraction ≤ 35%, n (%)	160 / 943 (17.0)	47 / 367 (12.8)	113 / 576 (19.6)	0.007	57 / 419 (13.6)	103 / 524 (19.7)	0.01
Aortic valve area (cm2), mean ± SD	0.71 ± 0.19	0.69 ± 0.20	0.72 ± 0.19	0.06	0.71 ± 0.20	0.71 ± 0.19	0.87
Baseline laboratory results							
Hemoglobin (g/dl), mean ± SD	12.13 ± 1.69	11.56 ± 1.62	12.48 ± 1.65	< 0.001	11.86 ± 1.72	12.33 ± 1.66	< 0.001
Anemia, n (%)	530 / 937 (56.6)	254 / 363 (70.0)	276 / 574 (48.1)	< 0.001	261 / 419 (62.3)	269 / 524 (51.3)	0.001
Mild	171 / 943 (18.1)	69 / 367 (18.8)	102 / 576 (17.7)	0.67	78 / 419 (18.6)	93 / 524 (17.7)	0.73
Moderate	181 / 943 (19.2)	78 / 367 (21.3)	103 / 576 (17.9)	0.20	80 / 419 (19.1)	101 / 524 (19.3)	0.94
Severe	178 / 943 (18.9)	107 / 367 (29.2)	71 / 576 (12.3)	< 0.001	103 / 419 (24.6)	75 / 524 (14.3)	< 0.001
Vascular access, n (%)							
surgical - femoral artery	94 / 943 (10.0)	20 / 367 (5.4)	74 / 576 (12.8)	< 0.001	35 / 419 (8.4)	59 / 524 (11.3)	0.14
surgical - subclavian artery	57 / 943 (6.0)	21 / 367 (5.7)	36 / 576 (6.3)	0.74	29 / 419 (6.9)	28 / 524 (5.3)	0.31
surgical - transapical	89 / 943 (9.4)	43 / 367 (11.7)	46 / 576 (8.0)	0.05	50 / 419 (11.9)	39 / 524 (7.4)	0.02
percutaneous - femoral artery	699 / 943 (74.1)	281 / 367 (76.6)	418 / 576 (72.6)	0.17	302 / 419 (72.1)	397 / 524 (75.8)	0.20
transaortal	4 / 943 (0.4)	2 / 367 (0.5)	2 / 576 (0.3)	0.65	3 / 419 (0.7)	1 / 524 (0.2)	0.22
Therapy-specific results, n (%)							
Concomitant PCI	21 / 943 (2.2)	14 / 367 (3.8)	7 / 576 (1.2)	0.008	4 / 419 (1.0)	17 / 524 (3.2)	0.018
Valve-in-Valve implantation	31 / 943 (3.3)	22 / 367 (6.0)	9 / 576 (1.6)	< 0.001	19 / 419 (4.5)	12 / 524 (2.3)	0.06

Abbreviations: NYHA: New York Heart Association; Med (IQR): median and interquartile range; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention.

practice. Patients from Toulouse Hôpital Rangueil were treated with aspirin alone, unless clopidogrel was needed for percutaneous coronary intervention. For all centers, unfractionated heparin was given during the procedure (70 U/kg) targeting an activated clotting time of 200 to 300.

Definitions

The VARC recommendations were used for all separate end points and a 30-day composite safety end point. Hemoglobin value was determined on first admission. Anemia was defined as a serum hemoglobin level below 13 g/dL for men and below 12 g/dL for women. Patients with anemia were divided into tertiles: mild anemia (12.99-11.81 g/dL in men, 11.99-11.31 g/dL in women), moderate anemia (11.80-10.71 g/dL in men, 11.30-10.51 g/dL in women), and severe anemia (≤10.70 g/dL in men, ≤10.50 g/dL in women)[13].

RBC categorization

Data on RBC transfusion were derived from the institution's blood bank laboratory and used to subcategorize the study population into two cohorts: patients with (n = 367) and without (n = 576) RBC transfusion. Besides this analysis, patients were subdivided according to the units of RBC transfusion to assess the effect of the number of RBC transfusion on outcome. Categories were as follows: RBC transfusion ≥4 U of packed cells (n = 111), RBC transfusion 1 to 4 U of packed cells (n = 256) and no RBC transfusion (n = 576).

Follow-up

After hospital discharge mortality data were collected by contacting the civil registries or the referring physician and was complete in 99.5% of the patients who survived the first 30 days.

Statistical analysis

Continuous variables are presented as means ± SD, in case of a normal distribution, or medians (interquartile range, IQR) in case of a skewed distribution. Categorical variables are presented as frequencies and percentages and, compared using Pearson χ^2 test or Fisher exact test, as appropriate. One-way analysis of variance was used to compare means across multiple categories; post hoc pairwise comparison was done with Bonferonni correction. In case of a nonparametric distribution or ordinal data, the Kruskal-Wallis analysis of ranks was used; post hoc comparison was done using the Mann-Whitney test with Bonferonni correction. Normality of the distributions was assessed using the Shapiro-Wilks test.

Table 2. VARC outcome according to transfusion status

	Overall	RBC Transfusion	No RBC Transfusion	p-value	≥ 4 RBC	4 - 1 RBC	p-value†
	n = 943	n = 367	n = 576		n = 111	n = 256	
In hospital clinical outcomes							
Device Success rate, n (%)	888 / 943 (94.2)	332 / 367 (90.5)	556 / 576 (96.5)	< 0.001	99 / 111 (89.2)	233 / 256 (91.0)	< 0.001
30-day or in-hospital death, n (%)							
All-cause	68 / 943 (7.2)	32 / 367 (8.7)	36 / 576 (6.3)	0.15	16 / 111 (14.4)	16 / 256 (6.3)	0.008
Cardiovascular	59 / 943 (6.3)	28 / 367 (7.6)	31 / 576 (5.4)	0.17	14 / 111 (12.6)	14 / 256 (5.5)	0.013
Myocardial infarction, n (%)							
Periprocedural (<72 hr)	9 / 943 (1.0)	4 / 367 (1.1)	5 / 576 (0.9)	0.73	2 / 111 (1.8)	2 / 256 (0.8)	0.62
Spontaneous (>72 hr)	6 / 943 (0.6)	1 / 367 (0.3)	5 / 576 (0.9)	0.26	0 / 111	1 / 256 (0.4)	0.49
Cerebrovascular complication, n (%)							
Major stroke	22 / 943 (2.3)	14 / 367 (3.8)	8 / 576 (1.4)	0.016	7 / 111 (6.3)	7 / 256 (2.7)	0.006
Minor stroke	3 / 943 (0.3)	1 / 367 (0.3)	2 / 576 (0.3)	0.84	0 / 111	1 / 256 (0.4)	0.81
Transient ischemic attack	13 / 943 (1.4)	8 / 367 (2.2)	5 / 576 (0.9)	0.09	1 / 111 (0.9)	7 / 256 (2.7)	0.09
Vascular complication, n (%)							
Major	101 / 943 (10.7)	71 / 367 (19.3)	30 / 576 (5.2)	< 0.001	46 / 111 (41.4)	25 / 256 (9.8)	< 0.001
Minor	108 / 943 (11.5)	56 / 367 (15.3)	52 / 576 (9.0)	0.003	7 / 111 (6.3)	49 / 256 (19.1)	< 0.001
Bleeding Complication, n (%)							
Life threatening	131 / 943 (13.9)	107 / 367 (29.2)	24 / 576 (4.2)	< 0.001	71 / 111 (64.0)	36 / 256 (14.1)	< 0.001
Major	197 / 943 (20.9)	104 / 367 (28.3)	93 / 576 (16.1)	< 0.001	17 / 111 (15.3)	87 / 256 (34.0)	< 0.001
Minor	102 / 943 (10.8)	80 / 367 (21.8)	22 / 576 (3.8)	< 0.001	6 / 111 (5.4)	74 / 256 (28.9)	< 0.001
Occult Bleeding	76 / 943 (8.1)	76 / 367 (20.7)	0 / 576	< 0.001	17 / 111 (15.3)	59 / 256 (23.0)	< 0.001
Acute kidney injury, n (%)							
Stage I	140 / 943 (14.8)	70 / 367 (19.1)	70 / 576 (12.2)	0.004	25 / 111 (22.5)	45 / 256 (17.6)	0.007
Stage II	34 / 943 (3.6)	21 / 367 (5.7)	13 / 576 (2.3)	0.005	9 / 111 (8.1)	12 / 256 (4.7)	0.006
Stage III	45 / 942 (4.8)	29 / 367 (7.9)	16 / 575 (2.8)	< 0.001	17 / 111 (15.3)	12 / 256 (4.7)	< 0.001
Length of Stay							
Total Hospitalization, med (IQR)	8.0 (5.5. - 10.5)	9.0 (5.0 - 13.0)	7.0 (5.5 - 8.5)	< 0.001	11.5 (5.5 - 17.5)	8.0 (5.0 - 11.0)	< 0.001
Prosthetic valve associated complications							
New permanent pacemaker requirement, n (%)	146 / 941 (15.5)	64 / 367 (17.4)	82 / 57 (14.3)	0.19	19 / 111 (17.1)	45 / 256 (17.6)	0.43
Combined Endpoints							
Combined Safety Endpoint, n (%)	251 / 943 (26.6)	155 / 367 (42.2)	96 / 576 (16.7)	< 0.001	87 / 111 (78.4)	68 / 256 (26.6)	< 0.001

† p-value for ≥4 RBC vs 1 to 4 RBC units vs no RBC transfusion.

To assess the predictors of RBC transfusion, univariable logistic regression was performed comparing patients with or without transfusion. All variables with $P \leq .05$ on univariable analysis were included in a stepwise multivariable logistic regression model to assess the strongest predictors. The same method was used to assess the predictors of the number of units of packed cells. To assess the effect of transfusion and units of packed cells on short- and long-term outcome univariable and multivariable logistic regression was used, where the no-transfusion category was used as the reference category. Multivariable analysis was adjusted for all baseline and procedural characteristics, which were available. For the impact on long-term mortality, Cox regression analysis was used. Results of these analyses are reported as ORs or HRs with 95% CIs. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data in patients who survived the first 30 days after TAVI (Landmark analysis) with the use of Kaplan-Meier estimates and were compared with the log-rank test. A 2-sided α level of .05 was used for all superiority testing. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). 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 manuscript, and its final contents.

RESULTS

Study population

The baseline characteristics of the overall study population and the subgroups dichotomized by need for RBC transfusion are listed in Table 1. Among the 943 patients analyzed, 53.8% were men. The mean logistic EuroScore was 20.9%; 28.3% of the patients were diabetics; 62.9% had renal failure; 45.1% had coronary artery disease; 34.4% had chronic obstructive pulmonary disease; and 17% had left ventricle ejection fraction ≤35%. Patients in the RBC cohort were more often females (54.5 vs 41%, $P < .001$), with a history of previous cerebrovascular accident (20.2 vs 12.8%, $P = .003$) and myocardial infarction (20.2 vs 14.4%, $P = .021$).The No-RBC cohort had more left ventricular ejection fraction (LVEF) ≤35% (19.6 vs 12.8%, $P = .007$) and surgical femoral access (12.8 vs 5.4%, $P < .001$). At baseline, anemia was highly prevalent: 56.6%. The baseline hemoglobin level averaged 12.13 ± 1.69 g/dL for the overall cohort, significantly lower in the RBC cohort. Severe anemia at baseline was also more frequent in the RBC cohort: 29.2% vs 12.3%, $P < .001$.

Table 3. Independent predictors of RBC transfusion after TAVI		
	Adjusted OR (95% C.I.)	**p-value**
Age	0.98 (0.96 - 0.99)	0.016
Female Gender	1.92 (1.42 - 2.59)	< 0.001
Previous Stroke	1.87 (1.25 - 2.79)	0.002
Surgical Access - Femoral Artery	0.26 (0.14 - 0.48)	< 0.001
Concomittant PCI	4.59 (1.71 - 12.29)	0.002
Valve-in-Valve implantation	4.40 (1.87 - 10.36)	0.001
Major Stroke	4.17 (1.46 - 11.90)	0.008
Major Vascular Complication	5.90 (3.60 - 9.67)	< 0.001
Minor Vascular Complication	2.39 (1.52 - 3.77)	< 0.001
No Anemia	ref	ref
Severe	5.50 (3.66 - 8.29)	< 0.001
Moderate	2.53 (1.68 - 3.80)	< 0.001
Mild	2.26 (1.49 - 3.41)	< 0.001

Abbreviations: PCI; Percutaneous Coronary Intervention.

Table 4. Independent predictors of RBC transfusion with ≥4 U after TAVI		
	Adjusted OR (95% C.I.)	**p-value**
Age	0.94 (0.91 - 0.96)	< 0.001
Female Gender	2.11 (1.32 - 3.37)	0.002
Previous Cerebro Vascular Accident	1.95 (1.13 - 3.38)	0.016
Peripheral Vascular Disease	1.94 (1.18 - 3.20)	0.01
No Anemia	ref	ref
Severe	3.47 (1.95 - 6.18)	< 0.001
Moderate	1.24 (0.64 - 2.40)	0.52
Mild	1.67 (0.88 - 3.21)	0.12
Major Stroke	9.85 (3.43 - 28.30)	< 0.001
Major Vascular Complication	12.40 (7.37 - 20.83)	< 0.001

Procedural outcome

The vast majority of TAVI cases (84.1%)were performed through the transfemoral route, predominantly with a percutaneous access and closure strategy. The VARC clinical endpoints are depicted in Table 2. VARC device success was achieved in 92.3% of the patients. Device success rate was lower in the RBC transfusion group (89.9% vs 93.8%; P = .03). Complex procedures like valve-in-valve implantation or TAVI with concomitant coronary angioplasty were associated with an increased need for RBC transfusion.

Thirty-day mortality and 1-year survival

Thirty-day all-cause mortality was 7.2%. By multivariate analysis, transfusion of

RBC was associated with increased 30-day mortality (Table 5). The group of patients receiving at least 4 U of RBC had higher 30-day all-cause mortality as compared to those receiving 1 to 4 U of RBC and those not requiring transfusion: 14.4%, vs 6.3% vs 6.3% respectively, *P* = .008 (Table 2 and Table 6). One year survival was significantly lower for the RBC cohort as compared to the no-RBC cohort: 75.2% vs 84.9%, *P* < .001 (Figure 1 and Figure 2). Patients who received at least 4 U of RBC had a significantly lower 1-year survival as compared to the patients with 1 to 4 U of RBC and the no-RBC cohort. After exclusion of the patients who died before 30 days, there was still an excess in overall mortality at 1 year in case of RBC transfusion (Figure 3).

Bleeding was a frequent complication of TAVI (53.6%). All the components of VARC bleeding were significantly more frequent in the RBC group. A vascular complication was observed in 23.2% of the study population, more frequently in the RBC group. Major and minor vascular complication: 19.3% vs 5.2%, *P* < .001 and 15.3% vs 9%, *P* = .003. Acute kidney injury occurred in 23.2% of the patients and was significantly more frequent in the RBC group. Major stroke occurred in 3.8% of the RBC cohort as compared to 1.4% in the no-RBC cohort, *P* = .016. Patients in the RBC cohort had a significantly longer hospital stay: 9 (5-13) vs 7 (5.5-8.5), *P* < .001.

Predictors for red blood cells transfusion

Among the risk factors for RBC transfusion post TAVI, identified by univariate and multivariate analyses, female gender (OR 2.11 (1.32-3.37), *P* = .002], previous cerebrovascular accident [1.95 (1.13-3.38), *P* = .016], peripheral vascular disease [1.94 (1.18-3.20), *P* = .01], major stroke [9.85 (3.43-28.30), *P* < .001], major vascular complication [12.40 (7.37-20.83), *P* < .001] and severe anemia [3.47 (1.95-6.18), *P* < .001] were strongly correlated to an increased risk of transfusion of at least 4 RBC (Table 3 and Table 4). Percutaneous transfemoral access and transapical route were not associated with an increased need for RBC: OR 1.24 (0.91-1.67), *P* = .18 and OR 1.53 (0.99-2.37), *P* = .057 respectively. Surgical femoral access was associated to a decreased need for RBC: OR 0.26 (0.14-0.48) *P* < .001.

DISCUSSION

The PRAGMATIC Plus Initiative is one of the largest series of patients treated with transcatheter aortic valve implantation reporting on blood transfusion and its impact on clinical outcome. VARC bleeding was frequent. More than one third of the study population experienced life-threatening or major bleeding. The most frequent cause of

Table 5. Effect of red blood cells transfusion on 30-day and 1-year mortality		
Outcome	**Odds Ratio** (95% C.I.)	**p-value**
All-Cause 30 Day Mortality		
Univariable	1.43 (0.87 - 2.35)	0.16
Multivariable†	1.79 (1.04 - 3.10)	0.036
Cardiac 30 Day Mortality		
Univariable	1.45 (0.86 - 2.46)	0.17
Multivariable†	1.76 (0.98 - 3.16)	0.06
	Hazard Ratio (95% C.I.)	**p-value**
All-Cause One - Year Mortality*		
Univariable	1.94 (1.30 - 2.92)	0.001
Multivariable†	2.03 (1.28 - 3.22)	0.003
Cardiac One-Year Mortality*		
Univariable	1.94 (0.98 - 3.84)	0.06
Multivariable†	1.67 (0.79 - 3.55)	0.18

* Landmark analysis including patients who did not die during hospitalization or within 30 days of index procedure. †Adjusted for all differences in baseline characteristics and procedural characteristics (age, gender, previous cerebrovascular accident, previous myocardial infarction, hypertension, glomerular filtration rate <60 mL/min, peripheral vascular disease, LVEF, surgical access using the femoral artery, transapical access, baseline hemoglobin level).

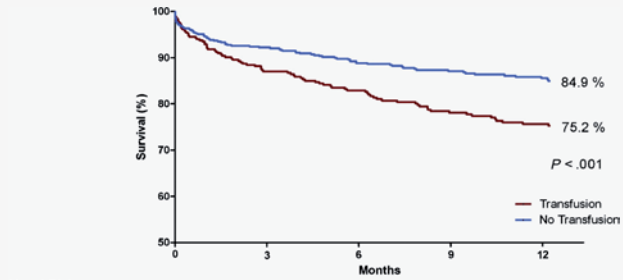
Table 6. Effect of number of packed red blood cells on 30-day mortality				
Outcome	**Odds Ratio** (95% C.I.)			**p-value**
	No Transfusion	RBC Transfusion 1 - 4 PC	RBC Transfusion ≥ 4 PC	
All - Cause 30 Day Mortality				
Univariable	ref	1.00 (0.54 - 1.84)	2.53 (1.35 - 4.73)	0.01
Multivariable†	ref	1.33 (0.69 - 2.55)	3.91 (1.93 - 7.93)	0.001
Cardiac 30 Day Mortality				
Univariable	ref	1.02 (0.53 - 1.95)	2..54 (1.30 - 4.94)	0.017
Multivariable†	ref	1.33 (0.67 - 2.68)	3.61 (1.71 - 7.63)	0.003
	Hazard Ratio (95% C.I.)			
	No Transfusion	RBC Transfusion 1 - 4 PC	RBC Transfusion ≥ 4 PC	
One - Year Mortality*				
Univariable	ref	1.35 (0.94 - 1.93)	2.56 (1.73 - 3.80)	< 0.001
Multivariable†	ref	1.59 (1.08 - 2.34)	3.07 (1.97 - 4.78)	< 0.001
Cardiac One-Year Mortality*				
Univariable	ref	1.77 (0.83 - 3.79)	2.38 (0.92 - 6.14)	0.13
Multivariable†	ref	1.66 (0.73 - 3.79)	1.69 (0.60 - 4.74)	0.41

* Landmark analysis including patients who did not die during hospitalization or within 30 days of index procedure. †Adjusted for all differences in baseline characteristics and procedural characteristics (age, gender, previous cerebrovascular accident, previous myocardial infarction, hypertension, glomerular filtration rate <60 mL/min, peripheral vascular disease, LVEF, surgical access using the femoral artery, transapical access, baseline hemoglobin level). Abbreviations: PC: Packed cells.

bleeding was vascular complication (23.2%). This vascular complication rate is higher than findings from Gurvitch et al (17.4%) or Nuis et al (16%)[14,15]. The discrepancy in reporting VARC vascular complications has been recently reported in a meta-analysis performed by Genereux et al in 3519 patients: 9.5% to 51.6%. This meta-analysis also stressed the high incidence of bleeding: 22.8% to 77% of the patients depending on the series[8]. Therefore, a close collaboration between cardiologists and surgeons remains necessary to select the appropriate access site, in a given patient, to minimize the risk of vascular and bleeding complications. It is important to notice that one fifth of the patients had minor or occult bleeding, stressing the burden of periprocedural bleeding in old and fragile patients. The adequate antithrombotic regimen remains unknown for TAVI. We could not assess the impact of clopidogrel because of insufficient data collection. There may be an interest in the use of bivalirudin, considering its efficacy in reducing bleeding complication in acute coronary syndromes[16].

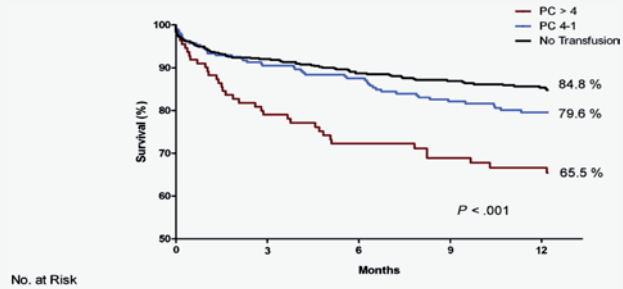
A large proportion of the patients (38.9%) required red blood cells transfusion. Due to the retrospective nature of our registry we do not have precise data on the timing of transfusion. Apart from bleeding, baseline anemia may contribute to the high transfusion rate. Anemia in general and severe anemia in particular, was significantly more frequent in patients receiving red blood cells units. Van Mieghem et al previously demonstrated that baseline anemia was frequent in patients undergoing TAVI (49%); anemic patients required more RBC transfusions with a 3-fold increase in one-year mortality (44 vs 15%, $P = .006$)[17]. In acute coronary syndromes, Bassand et al demonstrated that a low baseline hemoglobin level is an independent predictor of the risk of major bleeding as well as of the risk of death and myocardial infarction[18]. Among the identified predictors of bleeding and transfusion in PRAGMATIC Plus, baseline anemia should be tracked and possibly compensated before TAVI. Halliday et al observed, in a smaller series of 101 patients, that life-threatening bleeding and blood transfusion were associated with higher in-hospital mortality while life-threatening bleeding, a drop in hemoglobin >5 g/dl and the need for more than 2 U of red blood cells were associated with an increased 6-months mortality[19]. This is concordant with our findings. We confirmed, in a larger cohort, that blood transfusion post TAVI is associated with an adverse outcome with increased all-cause and cardiac mortality at 30-day and 1 year, but also an increased risk of major stroke and acute kidney injury. The worst outcome was observed in patients receiving more than 4 U of red blood cells.

The higher risk of bleeding and transfusion in women seems related to more frequent vascular complication as demonstrated by Buchanan et al[20]. Several risk factors for red blood cells transfusion were identified in PRAGMATIC Plus. The combination of these items in a dedicated TAVI Bleeding score could be of utmost importance in identifying



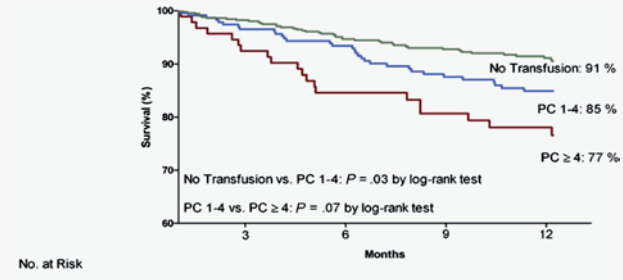
No. at Risk					
Transfusion	367	305	278	232	194
No Transfusion	571	502	461	365	242

Figure 1. One-year survival according to red blood cells transfusion status. PC, Packed cells



No. at Risk					
≥ 4 PC	111	85	75	62	51
4-1 PC	256	220	203	170	143
No Transfusion	571	502	461	365	242

Figure 2. One-year survival according to the number of red blood cells units at discharge



No. at Risk					
≥ 4 PC	95	85	75	62	51
4-1 PC	240	220	203	170	143
No Transfusion	535	502	461	365	242

Figure 3. One-year survival according to the number or red blood cells units, after exclusion of deaths within 30 days

the patients at highest risk for transfusion and subsequently poorest outcome. Larger cohorts are needed to validate a specific TAVI bleeding score.

LIMITATIONS

Our study has several limitations. It is a nonrandomized retrospective study. Patients were treated at four centers with slightly different antithrombotic treatments and transfusion policies, creating a bias in the final interpretation of the results. Intercenter and interoperator variability could not be assessed due to the high correlation with variables entered in the analysis, leading to multicolinearity. We did not have the day-by-day transfusion status, nor have the hemoglobin levels after TAVI, making it difficult to assess the patients who needed RBC transfusion due to anemia post TAVI. Also, clinical endpoints were not adjudicated by an independent Clinical Event Committee and are therefore subjected to potential reporting bias. We nevertheless believe that our study population remains a good sample of daily life patients and adequately reflects contemporary TAVI practice.

CONCLUSIONS

Bleeding is frequent after TAVI and is mainly driven by vascular complications. Red blood cells transfusion is associated with an increased mortality at 1 year and an increased risk of major stroke and acute kidney injury. Specific scores are needed to identify the patients at higher risk of TAVI-related bleeding and RBC transfusion.

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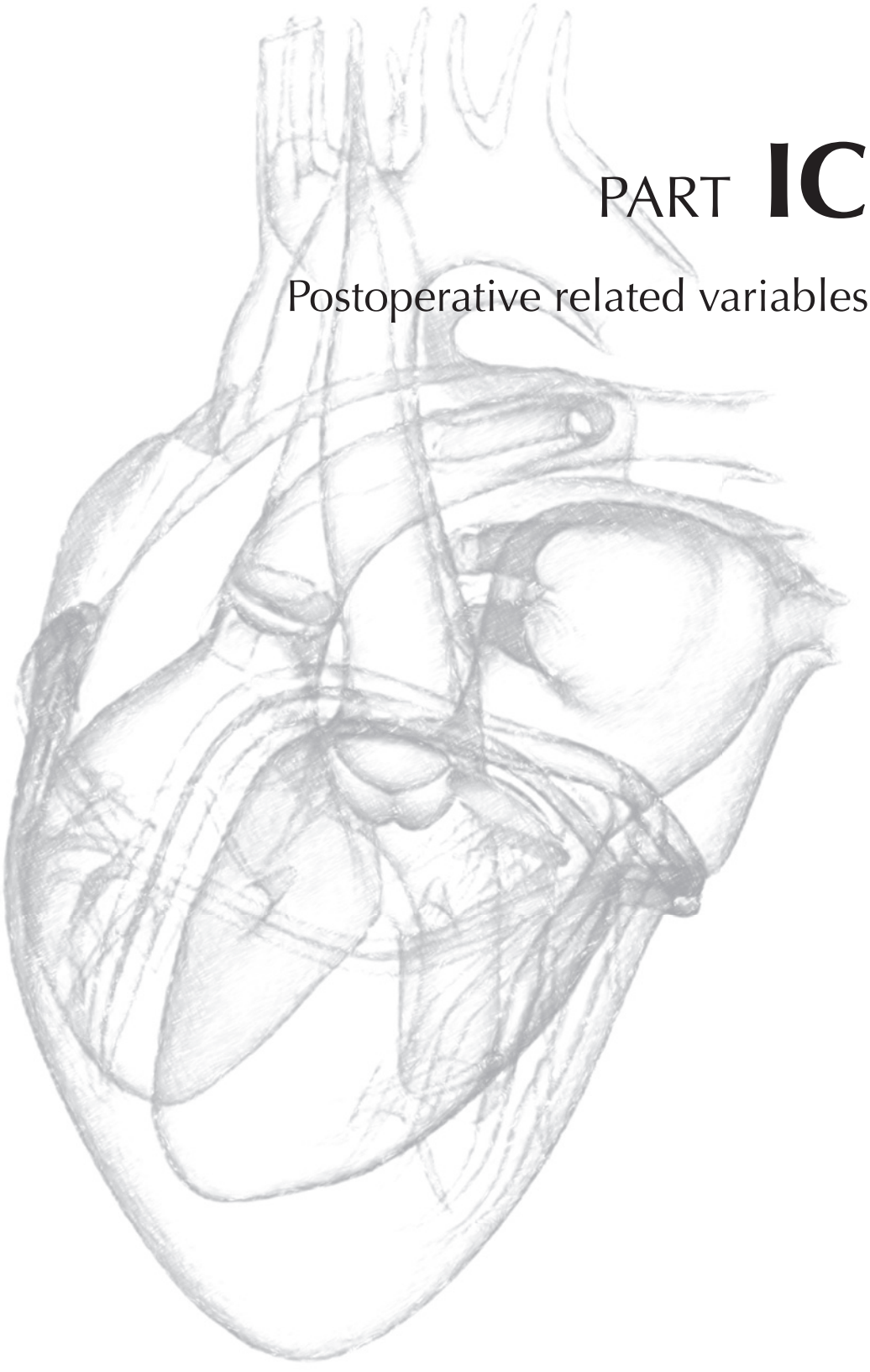

PART IC

Postoperative related variables

CHAPTER 9

Frequency, determinants and prognostic implications of infectious complications after transcatheter aortic valve implantation

van der Boon RM, Nuis RJ, Benitez LM, Van Mieghem NM, Perez S, Cruz L, van Geuns RJ, Serruys PW, van Domburg RT, Dager AE, de Jaegere PP.

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ABSTRACT

In-hospital infection (IHI) after Transcatheter Aortic Valve Implantation (TAVI) has received little attention despite the fact that it may have a significant effect on outcome and costs due to prolonged hospital stay. We, therefore, sought to determine the incidence, type, predictors and prognostic effects of IHI following TAVI. This study included 298 consecutive patients from two centers who underwent TAVI between November 2005 and November 2011. IHI during the hospital stay was defined on the basis of symptoms and signs assessed by the attending physician at the Cardiac Care Unit or Medium Care Unit in combination with all technical examinations performed to confirm infection. IHI after TAVI was observed in 58 patients (19.5%) and concerned a urinary tract infection in 25 patients (43.1%), pneumonia in 12 patients (20.7%) and access site infection in 7 patients (12.1%). In 12 patients (20.7%) the site could not be determined and 2 patients (3.4%) had multiple infection sites. Multivariable analysis revealed that, surgical access via the femoral artery was the most important determinant of infection (OR: 4.18 95% CI: 1.02 – 17.19), followed by peri-operative major stroke (OR: 3.21; 95% CI: 1.01 - 9.52) and overweight (BMI $\geq$ 25 kg/m^2, OR: 2.27; 95% CI: 1.12 - 4.59). The length of hospital stay in patients with IHI was (15.0 (8.0 – 22.0) compared to 7.0 (4.0 – 10.0) in patients without an infection ($p < 0.0001$). Kaplan-Meier estimates of survival at one year were 76.6% and 74.4% (log-rank test, $p = 0.61$), respectively. Un- and adjusted odds ratio analysis revealed that IHI did not predict mortality at 30-days (OR: 1.27; 95% CI: 0.49 – 3.30) and at one year (HR: 1.24; 95% CI: 0.68 – 2.25). In conclusion, in-hospital infection occurred in 19.5% of the patients. Patient- and more importantly procedure related variables play a role in the occurrence of infection indicating that improvements in the execution of TAVI may lead to a reduction of this complication.

INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) is increasingly used to treat patients with Aortic Stenosis (AS) and a prohibitive risk for surgical valve replacement[1–3]. Although conferring obvious benefits, TAVI is associated with a number of complications including infection[4]. The latter has received little attention despite the fact that it may have a significant effect on outcome and costs due the need of additional treatment and prolonged hospital stay[5]. The occurrence of in-hospital infection (IHI) after TAVI was anecdotally reported after the first in man experience by Cribier et al. in 2002[6]. During the subsequent period IHI including sepsis has been reported to occur between 3% -24% of all patients[7–10]. The Valve Academic Research Consortium (VARC) was established for the sake of the use of uniform endpoint criteria and definitions but did not contain criteria for infection after TAVI except for prosthetic valve endocarditis[11–15]. This is noteworthy given the fact that parallel to the increase in TAVI procedures, infectious complications will frequently be encountered in patients who underwent TAVI as these patients are at a particular risk due to age, comorbid conditions and eventually frailty[16]. We sought to explore in more detail the frequency and determinants of infectious complications after TAVI as this information may help to improve outcome. We also sought to explore the prognostic effects of infection after TAVI on mortality at 30 days and follow-up.

METHODS

The study population consists of 298 consecutive patients with symptomatic aortic valve stenosis who underwent TAVI between November 2005 and November 2011 in the Erasmus Medical Center, Rotterdam, the Netherlands (n = 230 patients) and Angiografia de Occidente, Cali, Colombia (n = 68 patients). In the 2 institutions, a similar process of patient and procedure planning was set up at the initiation of TAVI in each institution as one of the authors (PdJ) helped to initiate the program in Cali and was present during all procedures between 2008 (first implant) and 2010. This also holds for the data base and data collection during the hospital stay as previously described[17,18]

One hour prior to the procedure and upon completion of the procedure, prophylactic antiobiotic therapy was administered according to the local practice guidelines (cefazoline, 1 g at both times). If needed antibiotic therapy was continued post-procedural by the attending physician. All patients underwent transfemoral (n=287), subclavian TAVI (n=9) or transapical TAVI (n=2) under general anaesthesia (Rotterdam) or deep sedation (50% of

all patients in Cali) with the 18Fr third generation Medtronic CoreValve System® (MCS; Medtronic CV Luxembourg S.a.r.l., Luxembourg) except for the first 5 patients treated in Rotterdam in 2005 and 2006 in whom a 21Fr second generation MCS was implanted.

All data were prospectively collected and entered in a dedicated database. Source verification of the baseline data and clinical events was performed by the first (RvdB) and second author (RJN) for the patients treated in Rotterdam and Cali, respectively. Infection during the hospital stay was defined on the basis of the assessment of symptoms and signs during the daily visits of the attending physician at the Cardiac Care Unit or Medium Care Unit. The site of infection was categorized upon the presence of positive culture and/or clinical signs of inflammation into: Access Site, Urinary Tract, Pneumonia or Other Origin (undetermined origin). Causative agent was gathered using the culture report of the microbiology department. Treatment of IHI was left to the discretion of the attending physician who was in charge of the postoperative care of TAVI patients in consultation with the microbiologist.

All endpoints were selected and defined according to the Valve Academic Research Consortium (VARC)[11]. In addition, the length of hospital stay (LOS) was recorded and defined as the period between the day of the procedure until the day of discharge or in-hospital death, excluding the patients who died during the procedure. In case a patient was transferred to the referring hospital after having received TAVI, the LOS was defined as the total time spent in the treating and the referring center. All patients, except a few, were admitted in the treating center one day before TAVI. The time of hospital stay before TAVI was not included in the definition of LOS. A full blood and chemistry sample was taken before and up to 3 days after the procedure. Data on red blood cell (RBC) transfusions were recorded by the institution's blood bank laboratories. Since, packed RBC transfusions influence the post-TAVI hemoglobin level, the modified Landefeld equation was used to estimate the corrected nadir hemoglobin level and the net hemoglobin drop after the procedure[19]. The definition of anemia by the World Health Organization was adopted, which defines anemia as a serum hemoglobin level of less than 13 g/dl for men and a level of less than 12 g/dl for women[20]. Furthermore to assess the effect of the severity of anemia, patients were divided into tertiles to assess the number of patients with mild (12.99 – 11.81 g/dl in men, 11.99 – 11.31 g/dl in women), moderate (11.80 – 10.71 g/dl in men, 11.30 – 10.51 g/dl in women), and severe (≤ 10.70 g/dl in men, ≤ 10.50 g/dl in women).

Follow-up information of the patients treated at the Erasmus Medical Center was collected by first checking the vital status via the civil registries every 6 months. In case

of survival, a questionnaire was sent to the patient for the assessment of symptoms, (cardiac) events and readmission(s). Also surviving patients were contacted by telephone to confirm hospital readmission and reason after which events were verified with the treating hospital. All medical records were revised and general practitioners were contacted when necessary. Follow-up was complete for all patients. Follow-up information of the patients treated in Colombia was obtained by the regular office visit and/or telephone contact (dedicated local research nurse [LC] or doctor) with the treating physician and/or general practitioner and/or patient or family followed by verification of the event with the treating hospital. Follow-up was complete for all patients as previously described[18].

Categorical variables are presented as frequencies and percentages and, compared with the use of the Pearson Chi Square Test or the Fisher's exact test, as appropriate. Continuous variables are presented as means (±SD) (in case of a normal distribution) or medians (IQR) (in case of a skewed distribution) and compared with the use of Student's T-test or the Mann-Whitney U-test. Normality of the distributions was assessed using the Shapiro-Wilks test. Survival curves were constructed using Kaplan-Meier estimates and compared using the log-rank test. To assess the determinants of IHI, a univariable logistic regression analysis was first performed comparing the baseline patient and procedural characteristics between patients with and without IHI. Unadjusted odds ratios were then calculated for all variables with a p-value < 0.10. To study the independent predictors of 30-day mortality logistic regression was performed. All characteristics which were significant on univariable analysis and those judged to be clinically relevant were included in the multivariable logistic regression model, taking into account the restricted number of variables. The same method was applied for the calculation of the un- and adjusted odds of mortality at follow-up using Cox regression analyses. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analysis were performed with the use of SPSS software 17.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

The baseline characteristics, procedural details and outcomes of the total population and patients with and without infection after TAVI are summarized in Table 1-3. A total of 58 patients (19.5%) had an IHI. Of these infections, 43.1% were urinary tract infections, 20.7% pneumonia, 20.7% of undetermined origin, 12.1% access site infection, and 3% (n = 2) had multiple infection sites (Figure.1).

Table 1. Baseline characteristics according to occurrence of in-hospital infection

Variable	Overall	In-hospital Infection		p-value
		Yes	No	
	n = 298	(n = 58)	(n = 240)	
Demographics				
Age (years)	80.0 ± 70.0	80.4 ± 7.1	79.9 ± 7.0	0.63
Male	157 (53%)	29 (50%)	128 (53%)	0.65
Height (cm)	166.5 ± 9.3	167.3 ± 8.2	166.3 ± 9.5	0.46
Weight (kg)	72.14 ± 12.77	74.67 ± 13.34	71.53 ± 12.58	0.09
Body mass index (kg/m^2)	26.04 ± 4.21	26.71 ± 4.16	25.88 ± 4.21	0.18
Body mass index ≥ 25 kg/m^2	126 (42%)	40 (69%)	132 (55%)	0.05
Body surface area (m^2)	1.82 ± 0.19	1.86 ± 0.20	1.81 ± 0.19	0.06
NYHA class III or IV	244 (82%)	47 (81%)	197 (82%)	0.85
Logistic EuroSCORE	15.6 (9.2 - 21.9)	16.4 (10.2 - 22.6)	15.2 (8.8 - 21.5)	0.66
Previous cerebrovascular accident	56 (19%)	14 (24%)	42 (18%)	0.25
Previous myocardial infarction	77 (26%)	17 (29%)	60 (25%)	0.50
Previous CABG	76 (26%)	13 (22%)	63 (26%)	0.55
Previous PCI	81 (27%)	16 (28%)	65 (27%)	0.94
Coronary artery disease	162 (54%)	32 (55%)	130 (54%)	0.89
Diabetes mellitus	82 (28%)	18 (31%)	64 (28%)	0.50
Hypertension	193 (65%)	37 (64%)	156 (65%)	0.86
Glomerular filtration rate ≤ 60 ml/min	203 (68%)	36 (62.1)	167 (70%)	0.27
Chronic hemodialysis	12 (4%)	2 (3%)	10 (4%)	0.80
Chronic obstructive pulmonary disease	102 (34%)	19 (33%)	83 (35%)	0.79
Peripheral vascular disease	49 (16%)	9 (16%)	40 (17%)	0.83
Permanent pacemaker	33 (11%)	6 (10%)	27 (11%)	0.84
Atrial fibrillation	77 (26%)	16 (28%)	61 (25%)	0.73
Baseline echocardiogram				
Aortic valve area (cm2)	0.67 ± 0.22	0.67 ± 0.20	0.67 ± 0.22	0.95
Left ventricular ejection fraction (%)	50.5 ± 14.9	49.8 ± 15.9	50.6 ± 14.7	0.70
Aortic annulus diameter (mm)	22.39 ± 2.67	22.70 ± 2.83	22.30 ± 2.63	0.37
Peak velocity (m/sec2)	4.24 ± 0.77	4.28 ± 0.86	4.24 ± 0.75	0.72
Peak gradient (mmHg)	75.0 ± 27.4	77.2 ± 31.7	74.4 ± 26.3	0.49
Mean gradient (mmHg)	43.8 ± 17.0	45.0 ± 19.2	43.5 ± 16.5	0.59
Aortic regurgitation grade ≥ III	54 (18%)	15 (26%)	39 (16%)	0.09
Mitral regurgitation grade ≥ III	31 (10%)	7 (12%)	24 (10%)	0.64
Baseline laboratory results				
Creatinin level (umol/L)	95.0 (72.8 - 117.3)	88.0 (62.0 - 114.0)	96.8 (76.8 - 116.8)	0.30
Hemoglobin level (g/dl)	12.2 (11.2 - 13.3)	11.9 (10.8 - 13.1)	12.4 (11.3 - 13.5)	0.03
Mild anemia*	52 (17%)	11 (19%)	41 (17%)	0.74
Moderate anemia†	44 (15%)	13 (22%)	31 (13%)	0.067
Severe anemia‡	54 (18%)	9 (16%)	45 (19%)	0.57
Leukocyte level (x10^9/L)	7.1 (5.9 - 8.30)	7.1 (6.0 - 8.3)	7.0 (5.8 - 8.2)	0.76

Results are reported as number(%), med(IQR) or mean ± SD.
* Mild anemia (12.99 – 11.81 g/dl in men, 11.99 – 11.31 g/dl in women).
† Moderate anemia (11.80 – 10.71 g/dl in men, 11.30 – 10.51 g/dl in women).
‡Severe anemia: ≤ 10.70 g/dl in men, ≤ 10.50 g/dl in women).
Abbreviations: NYHA: New York Heart Association; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention.

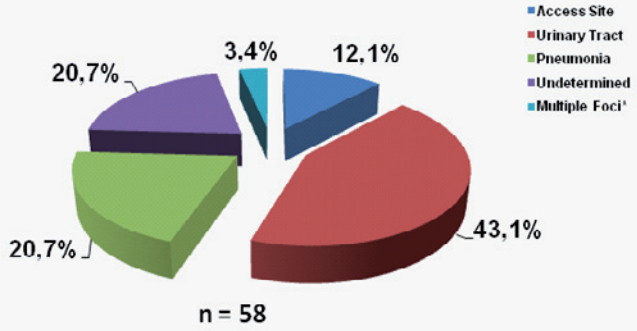

Figure 1. Frequency of the different types of In-hospital Infection

Clinically, patients with IHI were more often overweight in comparison to patients without IHI (BMI ≥ 25 kg/m^2, 69.0% vs. 55.0%, p = 0.05) and also had a lower hemoglobin level before the procedure (11.9 g/dL (10.8 – 13.1) vs. 12.4 g/dL (11.3 – 13.5), p = 0.03). There was no difference in leukocyte count at baseline between both groups (7.1 x10^9 cells per liter (6.0 – 8.3) vs. 7.0 x10^9 cells per liter (5.8 – 8.2), p = 0.76). Patients with IHI also underwent TAVI more often via surgical cutdown of the femoral artery (8.6% vs. 2.1%, p=0.013) and had a significantly longer procedure (i.e. time between entrance and departure from the catheterization laboratory); 234.7 ± 88.4 vs. 205.9 ± 76.7 (p = 0.023). Multivariable analysis revealed that in descending order of odds surgical access of the femoral artery (OR: 4.18 95% CI: 1.02 – 17.19), major stroke (OR: 3.21; 95% CI: 1.01 - 9.52) and overweight (BMI > 25 kg/m^2, OR: 2.27; 95% CI: 1.12 - 4.59), were independent determinants of IHI after TAVI (Table. 4).

A detailed summary of the infection, outcome and LOS are depicted in the Appendix. In all patients except 3, a culture was performed to determine the causative agent. Escherichia Coli was found the most frequent causative agent of IHI (15.5%, n = 9) followed by Pseudomonas Aeruginaosa and Enterobacter Cloacae. In 34.5% (n = 20) of the patients the causative agent was not found. The total hospital stay for patients with IHI was longer than for patients without IHI (15.0 (8.0 – 22.0) vs. 7.0 (4.0 – 10.0), p < 0.0001). The un- and adjusted odds ratio analysis revealed that IHI was not a predictor of mortality at 30 days (OR: 1.27; 95% CI: 0.49 – 3.30) (Table. 5a).

Long-term follow-up was complete for all patients and ranged from 1 to 72 months (median (IQR): 13.0 (3.0 – 23.0) months). The Kaplan-Meier estimates of one year survival stratified by IHI or no IHI are shown in Figure 2. There was no difference in

Table 2. Procedural details according to occurrence of in-hospital infection

Variable	In-hospital Infection		p-value
	Yes (n = 58)	**No** (n = 240)	
Vascular access			
surgical - femoral artery	5 (9%)	5 (2%)	0.013
percutaneous - femoral artery	50 (86%)	227 (95%)	0.025
surgical - subclavian artery	1 (2%)	6 (3%)	0.72
percutaneous - subclavian artery	1 (2%)	1 (0.4%)	0.27
surgical - transapical	1 (2%)	1 (0.4%)	0.27
Circulatory support			
Extracorporal membrane oxygenation	1 (2%)	2 (1%)	0.54
Left ventricular assistance device	5 (9%)	8 (3%)	0.08
Intra-Aortic balloon pump	0	8 (1%)	0.49
None	52 (90%)	227 (95%)	0.17
Additional interventions during TAVI			
PTA Iliac artery	1 (2%)	5 (2%)	0.86
Concomitant PCI	5 (9%)	15 (6%)	0.52
Prosthesis type and size			
Medtronic CoreValve 26-mm*	22 (38%)	88 (37%)	0.86
Medtronic CoreValve 29-mm*	32 (55%)	140 (58%)	0.66
Medtronic CoreValve 31mm*	2 (3%)	3 (1%)	0.24
Edwards SAPIEN 23mm*	1 (2%)	3 (1%)	0.78
Edwards SAPIEN 26mm*	1 (2%)	3 (1%)	0.78
Therapy-specific results			
Post-implantation balloon dilatation	5 (9%)	44 (18%)	0.073
Valve-in-Valve implantation	2 (3%)	12 (5%)	0.62
Ventricular perforation	1 (2%)	2 (1%)	0.54
Conversion to surgical AVR	0	0	1.00
Procedure time (min)	230 ± 84	202 ± 75	0.014
Amount of contrast (ml)	176 ± 87	167 ± 77	0.49

Results are reported as number(%), med(IQR) or mean ± SD.
*Three patients did not receive TAVI; one died during induction (anesthesia) and one died as a result of balloon valvuloplasty induced LVOT rupture.
Abbreviations: PTA: Percutaneous Transluminal Angioplasty; PCI: Percutaneous Coronary Intervention; AVR: Aortic Valve Replacement.

Table 3. In-hospital clinical outcome and prosthetic-valve associated outcome according to occurrence of In-hospital Infection

Variable	In-hospital infection		p-value
	Yes (n = 58)	No (n = 240)	
In-hospital clinical outcomes			
30-day or in-hospital death,			
All-cause	8 (14%)	20 (8%)	0.20
Cardiovascular	3 (5%)	19 (8%)	0.47
Myocardial infarction			
Periprocedural (<72 hr)	1 (2%)	2 (1%)	0.54
Spontaneous (>72 hr)	0	1 (0.4%)	0.62
Cerebrovascular complication			
Major stroke	6 (10%)	11 (5%)	0.09
Minor stroke	1 (2%)	1 (0.4%)	0.27
Transient ischemic attack	1 (2%)	3 (1%)	0.78
Vascular complication			
Major	7 (12%)	22 (9%)	0.50
Minor	5 (9%)	18 (8%)	0.77
Bleeding Complication			
Life-threatening	8 (14%)	18 (8%)	0.13
Major	5 (9%)	29 (12%)	0.46
Minor	7 (12%)	19 (8%)	0.32
Acute kidney injury			
Stage I	14 (24%)	30 (13%)	0.025
Stage II	3 (5%)	3 (1%)	0.056
Stage III	1 (2%)	3 (1%)	0.78
Reintervention in Hospital	0	2 (1%)	0.49
Length of Stay			
Total Hospitalization	15.0 (8.0 - 22.0)	7.0 (4.0 - 10.0)	< 0.001
Prosthetic valve associated complications			
New permanent pacemaker requirement	13 (22%)	53 (22%)	0.97
Combined Endpoints			
Composite Safety Endpoint	22 (38%)	49 (20%)	0.005

Results are reported as number(%), med(IQR) or mean ± SD.

Table 4. Univariable and multivariable analysis of predictors of in-hospital infection		
Variable	**Crude OR** (95% C.I.)	**Adjusted OR** (95% C.I.)
Body mass index ≥ 25 kg/m2	1.82 (0.99 - 3.35)	2.27 (1.12- 4.59)
Surgical - femoral artery	4.34 (1.24 - 15.87)	4.18 (1.02 - 17.19)
Procedure time (min)	1.004 (1.001 - 1.008)	1.00 (0.99 - 1.01)
Major stroke	2.40 (0.85 - 6.79)	3.21 (1.01 - 9.52)
No anemia	ref	ref
Anemia without transfusion	1.09 (0.58 - 2.06)	1.31 (0.65 - 2.66)
Anemia with transfusion	3.01 (1.27 - 7.14)	1.32 (0.45 - 3.87)

Table 5a. Independent predictors of 30-day mortality		
Variable	**30- Day Mortality**	
	Crude OR (95% C.I.)	**Adjusted OR** (95% C.I.)
In-hospital infection	1.76 (0.73 - 4.22)	1.27 (0.49 - 3.30)
Surgical - femoral artery	4.51 (1.10 - 18.53)	4.75 (1.05 - 21.42)
Major stroke	3.29 (1.00 - 10.90)	3.38 (0.95 - 12.05)
Life-threatening bleeding	4.67 (1.51 - 14.43)	5.00 (1.52 - 16.35)
Acute kidney injury	2.85 (1.24 - 6.60)	2.19 (0.89 - 5.38)

Table 5b. Independent predictors of mortality during follow-up		
Variable	**Mortality during Follow-Up**	
	Crude HR (95% C.I.)	**Adjusted HR** (95% C.I.)
In-hospital infection	1.16 (0.64 - 2.11)	1.24 (0.68 - 2.25)
Chronic hemodialysis	3.61 (1.65 - 7.92)	2.10 (0.91 - 4.88)
Peripheral vascular disease	2.10 (1.21 - 3.66)	1.78 (0.98 - 3.27)
Post-implantation balloon dilatation	1.97 (1.11 - 3.48)	1.64 (0.90 - 3.02)
Valve-in-Valve implantation	2.56 (1.10 - 5.92)	2.42 (0.97 - 6.03)
Life-threatening bleeding	2.84 (1.36 - 5.97)	2.45 (1.13 - 5.32)

survival between patients with (76.6%) and patients without IHI (74.4%), (log-rank test, p = 0.61). Moreover, IHI was not found to be a predictor of mortality at one year (HR: 1.24; 95% CI: 0.68 – 2.25) (Table. 5b).

DISCUSSION

We found that IHI occurred in 58 out of the 298 patients (19.5%) after TAVI and that IHI was not associated with increased short – or long-term mortality but with a longer hospital stay. We also found that procedure (i.e. surgical access of the femoral artery) and patient related (BMI > 25 kg/m2) variables were associated with an increased risk of IHI.

At present there is scant information on the frequency of IHI after TAVI. Earlier reports by Rodés-Cabau et al. and Godino et al. showed that sepsis occurred in 2.9% and 8.4% of all patients[7,8]. Recently, Onsea et al and Dehédin et al. reported a frequency of IHI of 15.1% and 24.8%, which is similar to the herein reported observation[9,10]. These current findings need to be interpreted in the context of sample size (298 patients of whom 58 with IHI) and nature of the study (observational). The relatively small sample of patients with IHI (n=58) may have precluded a more accurate and detailed analysis of determinants of IHI which is needed to propose recommendations of improvement of TAVI at the level of either patient selection, execution of TAVI and/or postoperative care. Also, it cannot be excluded that some IHI were unrelated to TAVI. For instance, despite the thorough and structured preoperative screening of patients including clinical and laboratory signs of infection and inflammation, some IHI may have been preexistent. As mentioned, we found surgical access of the femoral artery and overweight to be independently associated with IHI. Overweight and obesity cannot be used to exclude patients for TAVI since obese patients fare better in terms of long-term survival after TAVI in comparison to patients with low body mass[21]. Moreover, in this study IHI was not associated with increased mortality. It is, nevertheless, conceivable that changes in both pre- and postoperative care may prevent IHI in these patients. In addition to access site infections, most infections were of urinary tract and pulmonary origin. These findings indicate that avoidance of surgical access, preoperative pulmonary preparation (e.g. inhalation, corticosteroids), avoidance of general anesthesia and the keeping of the urinary bladder catheter as short as possible postoperatively may reduce IHI. To further elucidate this proposal, analysis of the determinants of the individual type of infections would be helpful. This study lacked the power to do so as a result of sample size (IHI and individual type of infections).

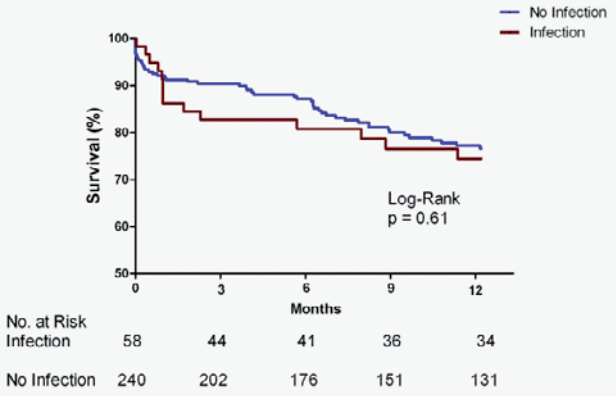

Figure 2. One-year mortality of patients with or without in-hospital Infection after TAVI

Although general anesthesia is associated with more side effects, respiratory in particular, a recent observational study revealed no difference in the incidence of sepsis, pneumonia or urinary tract infection between general and regional anesthesia[9,22]. Absence of direct comparisons or consistent findings in larger and multiple observational studies preclude any firm conclusions. At present, the appropriate anesthetic approach may be weighted upon the risk/benefit assessment on an individual patient basis using clinical variables such as general condition, antecedents (e.g. pulmonary disease, urinary tract infection) and technical variables (e.g. pulmonary function). In this series of 298 patients, 10 patients underwent TAVI via surgical access of the femoral artery; another 7 via surgical access of the subclavian artery and 2 other patients underwent TAVI via a transapical access. Despite this low absolute (n=19) and relative (6.4%) number, surgical access of the femoral artery was found to be an independent predictor of TAVI. This is not surprising given the high degree of natural contamination of the groin area, especially in elderly[23–25]. All procedures were performed in the catheterization laboratory under sterile surgical conditions. Given the present findings, it cannot be excluded that there have been errors in the execution of a strict sterile surgical access. In general, a catheterization laboratory is characterized by the presence and the coming and going of various people who are not directly involved in the procedure. This is an argument in favor of performing TAVI in a surgical environment or hybrid catheterization laboratory[10,26]. We certainly do not recommend a percutaneous access of femoral artery in order to minimize the risk of IHI when a surgical access is to be preferred since the importance of adequate hemostasis has consistently been documented in large series of patients as bleeding and vascular complications are associated with increased mortality[27–29]. We cannot explain the association between

stroke and IHI since we lack detailed information of the timing of both events. Yet, patients who suffer a stroke may be at higher risk of subsequent infection due to a longer period of immobilization, less respiratory force, longer period of urinary bladder catheter and last but not least longer hospitalization[30].

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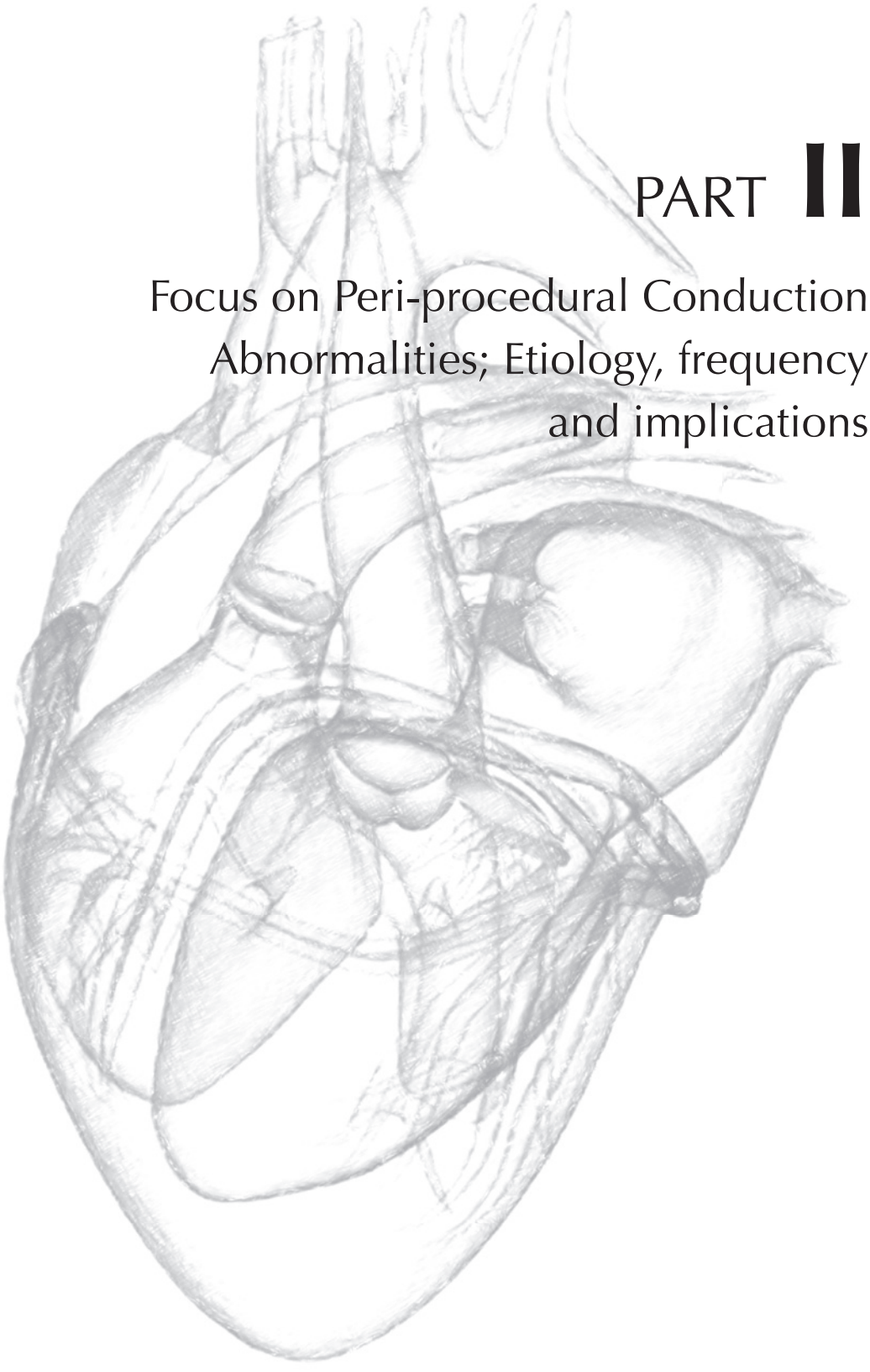

PART II

Focus on Peri-procedural Conduction Abnormalities; Etiology, frequency and implications

CHAPTER 10

New conduction abnormalities after TAVI-frequency and causes

van der Boon RM, Nuis RJ, Van Mieghem NM, Jordaens L, Rodés-Cabau J, van Domburg RT, Serruys PW, Anderson RH, de Jaegere PP.

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are considered to be too high-risk for surgical replacement of the aortic valve. Although the procedural risks are decreasing, the occurrence of new conduction abnormalities remains a vexing issue. Both left bundle branch block (LBBB) and atrioventricular dissociation can affect prognosis after TAVI. Understanding the intimate relationship between the atrioventricular conduction axis and the aortic root, in addition to elucidation of factors related specifically to the procedures, devices, and patients, might help to reduce these conduction abnormalities. The purpose of this Review is to assess and offer insights into the available information on the frequency of new conduction abnormalities associated with TAVI, their anatomical and procedural causes, and their clinical consequences.

INTRODUCTION

After the landmark experimental work of Andersen and colleagues, transcatheter aortic valve implantation (TAVI) was first performed clinically by Cribier and co-workers in 2002[1,2]. As we reach the 10-year anniversary of TAVI, it is estimated that more than 50,000 procedures have now been performed worldwide. This explosive growth in the use of an innovative treatment for patients with aortic stenosis can be explained only by a favorable ratio of risk to benefit, as reported by numerous observational, and a few randomized, studies. An additional factor is the increased familiarity of operators with the procedure that is basically surgical, but which is undertaken without direct vision of the target zone and pathology[3–13]. In the future, the prospect exists of treating younger or less-sick patients than is currently normal practice; however, a number of vexing issues remain, such as the perioperative occurrence of new left bundle branch block (LBBB)[14,15]. This conduction abnormality can affect left ventricular (LV) function and necessitate new implantation of a permanent pacemaker, both of which can affect quality of life and prognosis, although these consequences have not been assessed specifically in patients after TAVI[16–19]. At present, there are more than 20 studies, mostly observational and derived from single centers, covering this issue, with varying reported results and insights into the pathophysiology of the occurrence of new LBBB. The purpose of this Review is to assess the available information on the frequency of TAVI-associated new LBBB and its clinical consequences, in addition to offering insights to its anatomical and clinical causes.

Frequency and clinical implications

The reported frequencies of new LBBB (Figure 1), complete atrioventricular dissociation (Figure 2), and new implantation of a permanent pacemaker (Figure 3) after TAVI are summarized in Table 1. New LBBB is reported in 29%–65% of patients after the implantation of the self-expanding Medtronic CoreValve® system (Medtronic CV Luxembourg S.a.r.l., Luxembourg), and in 4%–18% of patients receiving the balloon-expandable Edwards SAPIEN® valve (Edwards Lifesciences Corporation, Irvine, CA, USA). The new implantation of a permanent pacemaker is not surprisingly, therefore, reported to be 18%–49% and 0%–12% after CoreValve® and SAPIEN® valve implantation, respectively (Table 1). After surgical replacement of the aortic valve (AVR) for aortic stenosis, regurgitation, or both (with or without combined bypass grafting, new LBBB is reported in 16%–32% of patients, while new implantation of a permanent pacemaker, mainly to treat aortic stenosis, is required in 3%–8% of surgical patients[20–30].

Table 1. Incidence and predictors of new LBBB, AV3B, or PPI after TAVI according to device type

Study	Access approach	Patients (*n*)*	Frequency of new conduction abnormalities‡			Univariable predictors for LBBB, AV3B, or PPI	Multivariable predictors for AV3B, or PPI
			LBBB (%)	AV3B (%)	PPI (%)		
Studies with the Edwards SAPIEN®§ device							
Cribier *et al.* (2006)[81]	Transfemoral	27	N/R	N/R	4	N/R	N/R
Walther *et al.* (2008)[82]	Transapical	50	N/R	4	4	N/R	N/R
Sinhal *et al.* (2008)[83]	Transfemoral	123	6	7	7	N/R	N/R
Gutiérrez *et al.* (2009)[57]	Transapical	33	18	0	0	LBBB: depth of implantation	N/R
Webb *et al.* (2009)[84]	Transfemoral Transapical	113 55	N/R	N/R	5 9	N/R	N/R
Thomas *et al.* (2010)[11]	Transfemoral Transapical	463 575	N/R	N/R	7 7	N/R	N/R
Godin *et al.* (2010)[85]	Transfemoral Transapical	54 15	13 13	2 7	4 7	N/R	N/R
d'Ancona *et al.* (2011)[86]	Transapical	322	N/R	N/R	6	PPI: age	PPI: age
Leon *et al.* (2011)[12]	Transfemoral	358	N/R	N/R	3	N/R	N/R
Smith *et al.* (2011)[13]	Transfemoral Transapical	244 104	N/R	N/R	4 4	N/R	N/R
Studies with the Edwards SAPIEN®§ and Medtronic CoreValve®‖ devices							
Erkapic *et al.* (2010)[60]	Transapical (SAPIEN®) Transfemoral (CoreValve®)	14 36	30¶	7 44	7 44	N/R	AV3B: preprocedural RBBB; CoreValve® device
Bleiziffer *et al.* (2010)[87]	Transapical (SAPIEN®) Transfemoral (CoreValve®)	36 123	N/R	6 27	6 27	AV3B: intraprocedural AV3B; CoreValve® device; valvuloplasty balloon size; balloon : annulus ratio	AV3B: intraprocedural AV3B
Koos *et al.* (2011)[61]	Transapical (SAPIEN®) Transfemoral (CoreValve®)	22 58	28¶	0 22	0 29	PPI: left ventricular ejection fraction	PPI: CoreValve® device; preprocedural RBBB
Aktug *et al.* (2011)[52]	Transapical (SAPIEN®) Transfemoral (CoreValve®)	82 72	16 38	13¶	5 28	LBBB: depth of implantation; CoreValve® device; valve : annulus ratio	LBBB: depth of implantation
Roten *et al.* (2011)[62]	Transapical (SAPIEN®) Transfemoral (CoreValve®)	26 41	12 29	12 29	12 49	AV3B: preprocedural RBBB; CoreValve® device; amiodarone use; ß-blocker use; valvuloplasty balloon size; hypertension	AV3B: preprocedural RBBB
Studies with the Medtronic CoreValve®‖ device							
Berry *et al.* (2007)[88]	Transfemoral	11	36	N/R	27	N/R	N/R
Piazza *et al.* (2008)[49]	Transfemoral	40	40		18	LBBB: depth of implantation	N/R
Calvi *et al.* (2009)[89]	Transfemoral	30	46	24	20	N/R	N/R

Jilaihawi *et al.* (2009)[90]	Transfemoral	34	N/R	30	33	PPI: left-axis deviation; LBBB with left-axis deviation; interventricular-septum thickness (>17 mm); noncoronary cusp thickness (>8 mm); heart-rate-limiting medication	PPI: LBBB with left-axis deviation; interventricular-septum thickness (>17 mm); noncoronary cusp thickness (>8 mm)
Baan *et al.* (2010)[50]	Transfemoral	34	65	22	22	LBBB: depth of implantation AV3B: left ventricular outflow tract diameter; left-axis deviation; mitral annular calcification; postimplantation effective-orifice area	N/R
Latsios *et al.* (2010)[91]	Transfemoral	81	N/R	36	47	PPI: left ventricular ejection fraction; QRU duration; Agatston score	PPI: female sex; left ventricular ejection fraction; landing-zone calcification
Piazza *et al.* (2010)[51]	Transfemoral	91	38	18	21	LBBB: male sex; previous myocardial infarction; preprocedural RBBB; postimplantation frame expansion; depth of implantation PPI: pretreatment QRS duration; interventricular-septum thickness	N/R
Ferreira *et al.* (2010)[53]	Transfemoral	32	49	30	30	AV3B: Preprocedural RBB PPI: depth of implantation	N/R
Haworth *et al.* (2010)[92]	Transfemoral	33	48	N/R	30	PPI: preprocedural RBBB, annulus diameter	N/R
Fraccaro *et al.* (2011)[54]	Transfemoral	64	44	25	39	PPI: male sex; preprocedural RBBB; depth of implantation	PPI: preprocedural RBBB; depth of implantation
Rubín *et al.* (2011)[93]	Transfemoral	18	50	17	22	N/R	N/R
Nuis *et al.* (2011)[48]	Transfemoral, subclavian	65	62	14	22	N/R	N/R
Khawaja *et al.* (2011)[94]	Transfemoral	270	48	21	33	LBBB: indication aortic stenosis; no RBBB; implantation in native valve AV3B: AV3B during implantation; baseline PR interval; left-axis deviation; valve size; QRS duration PPI: male sex; interventricular-septum diameter; left-axis diameter; preprocedural RBBB; prolonged QRS duration; peri-implantation AV3B; calcification below aortic valve	AV3B: AV3B during implantation; aortic-annulus size; entry site; baseline PR interval; interventricular septal thickness; calcification below valve PPI: peri-implantation AV3B; balloon predilatation; peri-implantation QRS duration; 29 mm prosthesis
Guetta *et al.* (2011)[55]	Transfemoral	70	30	36	40	PPI: preprocedural RBBB; pulmonary hypertension; depth of implantation	PPI: preprocedural RBBB; depth of implantation
Saia *et al.* (2011)[56]	Transfemoral, subclavian	73	N/R	25	28	PPI: Log. EuroSCORE; depth of implantation; left ventricular end-diastolic diameter; septal-wall thickness	PPI: depth of implantation; septal-wall thickness
Calvi *et al.* (2011)[63]	Transfemoral	181	50	26	32	PPI: preprocedural RBBB	PPI: preprocedural RBBB

*Total cohort studied. ‡Recalculated if needed. §Edwards Lifesciences Corporation, Irvine, CA, USA. ||Medtronic CV Luxembourg S.a.r.l., Luxembourg. ¶Combined frequency for both device types (not reported separately). Abbreviations: AV3B: third-degree atrioventricular block; LBBB: left bundle branch block; N/R: not reported; PPI: permanent pacemaker implantation; RBBB: right bundle branch block; TAVI transcatheter aortic valve implantation.

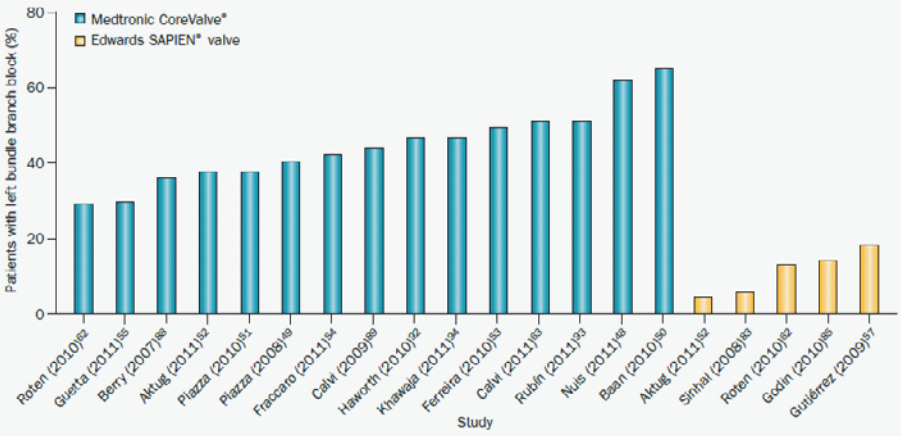

Figure 1. Incidence of left bundle branch block according to device type

Left: Medtronic CoreValve® system (Medtronic CV Luxembourg S.a.r.l., Luxembourg). Right: Edwards SAPIEN® valve (Edwards Lifesciences Corporation, Irvine, CA, USA).

The clinical consequences of new LBBB in patients undergoing TAVI remain to be elucidated. Overall, substantial improvements in quality of life have been reported in patients who undergo TAVI[31–36]. Despite a higher occurrence of new conduction abnormalities after CoreValve® implantation than with the SAPIEN® valve, improvements in quality of life have been reported with both devices. However, no distinction has been made between patients with or without new conduction abnormalities in these studies. Patients with a new conduction abnormality might benefit less from TAVI as a result of the altered ventricular activation. Interventricular and intraventricular asynchrony has been shown to affect regional and global myocardial performance owing to shortening of ventricular diastole, prolonged isovolumic contraction, impaired contractile reserve, and decreased LV ejection fraction[16–19,37–39]. In a small observational study involving 27 patients, LV ejection fraction was found to decrease from 47 ± 12% to 44 ± 10% in patients with a new LBBB after TAVI, but increased from 49 ± 12% to 54 ± 12% in patients without new LBBB[40]. Impaired prognosis might be explained by the occurrence of late arrhythmic events, their frequency being similar in patients with a new LBBB after AVR[20,41].

Conceptually, the same effects on ventricular hemodynamics and performance also occur in paced hearts, and possibly even more so in patients who receive a ventricular mode of pacing (VVI) pacing after TAVI. VVI pacing can induce atrioventricular and interventricular asynchrony, and thus create an artificial LBBB, which impairs ventricular filling, stroke volume, and cardiac output, and thereby contributes to the

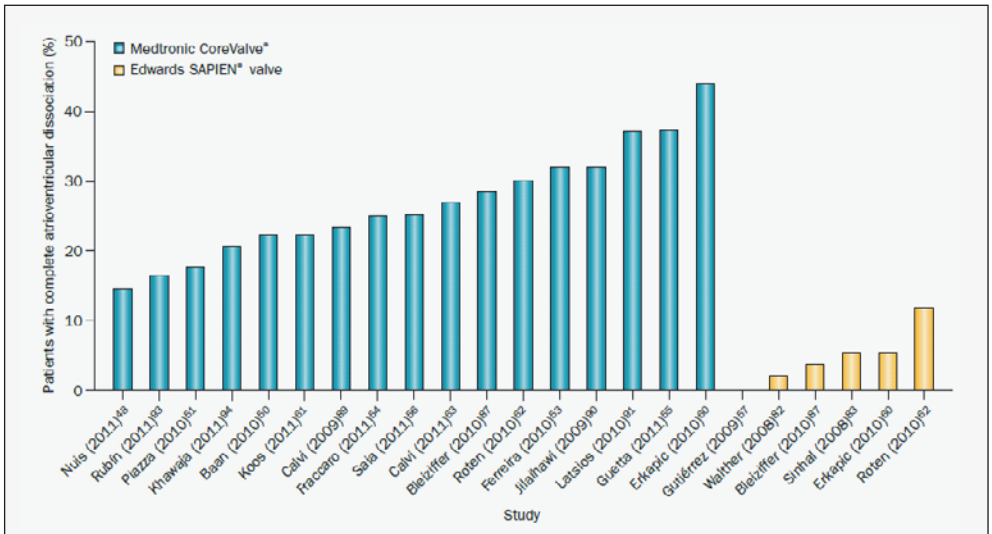

Figure 2. Incidence of complete atrioventricular dissociation according to device type

Left: Medtronic CoreValve® system (Medtronic CV Luxembourg S.a.r.l., Luxembourg). Right: Edwards SAPIEN® valve (Edwards Lifesciences Corporation, Irvine, CA, USA).

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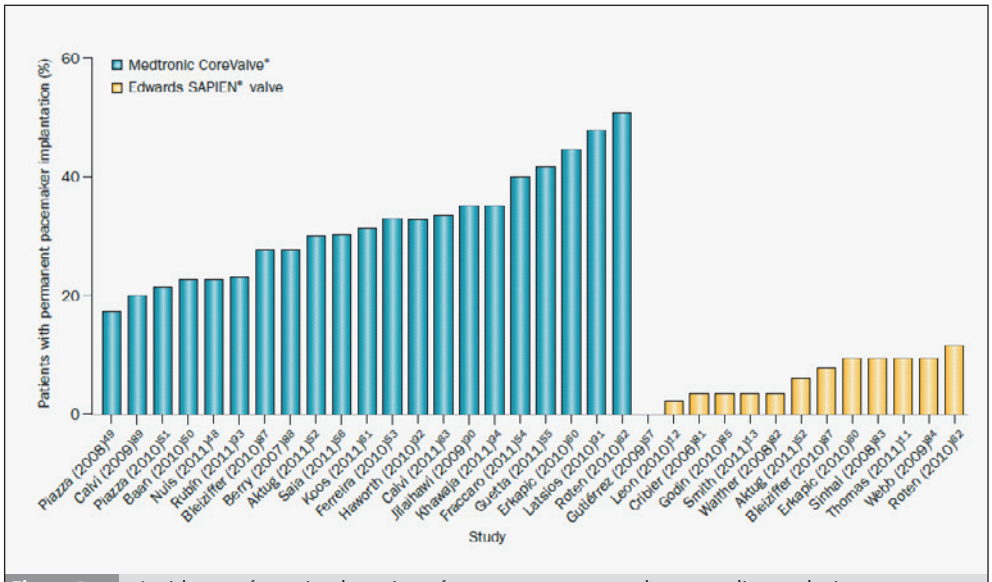

Figure 3. Incidence of new implantation of a permanent pacemaker according to device type

Left: Medtronic CoreValve® system (Medtronic CV Luxembourg S.a.r.l., Luxembourg). Right: Edwards SAPIEN® valve (Edwards Lifesciences Corporation, Irvine, CA, USA).

adverse effects on quality of life and prognosis. The potentially detrimental effects on quality of life are particularly worrisome in patients who are currently considered for TAVI, because improvement in quality of life might be more important than increased longevity in this subset of patients. TAVI is forecasted to be offered to lower-risk and also younger patients than is currently normal practice. Therefore, the effects of altered conduction on LV function and quality of life warrants close attention.

CAUSES OF NEW LBBB

Anatomical factors

As is the case after AVR, the main cause of new LBBB after TAVI is mechanical injury inflicted on the atrioventricular conduction axis, although ischemic changes cannot be dismissed. The intimate relationship and proximity of the atrioventricular conduction axis within the aortic root allows us to understand how pathologies involving the aortic valve, and therapeutic procedures such as TAVI, can cause LBBB and complete heart block. The atrioventricular node is located within the triangle of Koch, which itself is located in the right atrium. The triangle is formed apically by the convergence of the tendon of Todaro and the attachment of the septal leaflet of the tricuspid valve, with the orifice of the coronary sinus forming the base of the triangle (Figure 4a). The apex of the triangle is directly related to the central fibrous body, which separates the subaortic area of the left ventricle from the right atrium and right ventricle. The atrioventricular conduction axis penetrates this fibrous septum (Figure 4b), becoming the bundle of His once it is insulated from the atrial myocardium. Having passed through the fibrous membranous septum, it emerges directly within the aortic root, being positioned on the crest of the muscular ventricular septum (Figure 4c), where it gives rise to the fascicles of the left bundle branch. The branching bundle is intimately related to the base of the interleaflet triangle that separates the noncoronary and right-coronary leaflets of the aortic valve (Figure 4d). Having given off the branches of the left bundle, the axis then penetrates back through the muscular septum, emerging in the right ventricle as the right bundle branch, which is positioned directly beneath the medial papillary muscle of the tricuspid valve. Autopsied specimens from patients who had developed complete atrioventricular block after TAVI have shown localized hematomas within the muscular ventricular septum at the site of prosthesis expansion, and microscopic evidence of compression of the bundle of His[42].

The arterial supply of the atrioventricular node largely depends on the atrioventricular nodal artery, while the ventricular components of the axis are also nourished by the

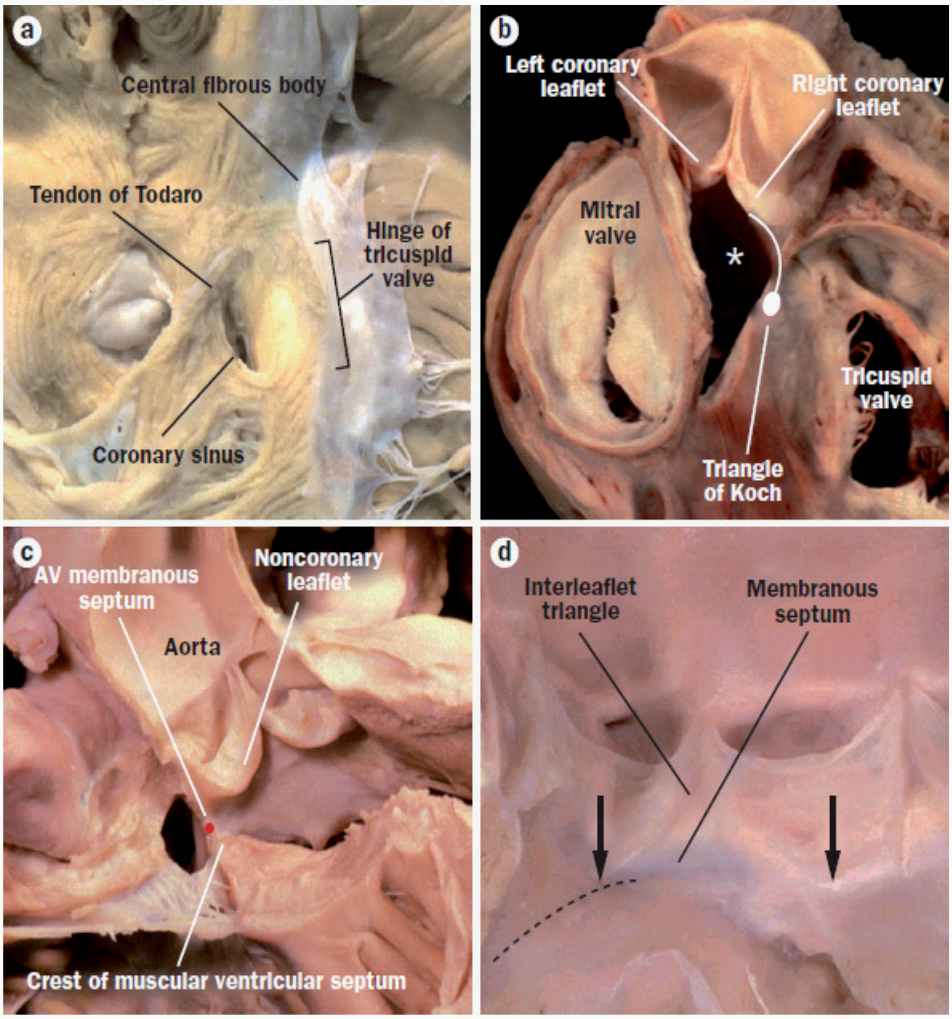

Figure 4. Anatomy and relationship between the aortic valvular complex and the atrioventricular conduction system

a | A view of the right side of the atrial and ventricular septums, illustrating the landmarks of the triangle of Koch. The atrioventricular node is located at the apex of the triangle, and the bundle of His penetrates the central fibrous body. **b** | The course of the axis as it penetrates, created by removing the noncoronary sinus of the aortic root, which reveals the deep diverticulum (star) that interposes between the mitral valve and the ventricular septum. The location of the atrioventricular node (red oval), and the course of the conduction axis (line emanating from the oval). **c** | The position of the bundle of His as it is sandwiched between the membranous and muscular parts of the ventricular septum (red circle), created by dissecting away the right ventricular outflow tract to reveal the posterior components of the aortic root. **d** | The opened aortic root viewed from the left ventricle. The basal attachments of the right and noncoronary leaflets of the aortic valve (arrows), with the location of the most-superior part of the left bundle branch as it originates from the branching component of the conduction axis (black line).

first septal perforating artery. The artery to the atrioventricular node is a branch of the inferior interventricular artery, which itself is a branch of the right coronary artery in 90% of patients (and of the dominant circumflex artery in the remaining 10% of patients). The nodal artery runs through the inferior pyramidal space to reach the atrioventricular node. The first septal perforating artery is the first branch of the anterior interventricular artery. Alternative sources of arterial supply are the descending septal artery, and anterior atrial branches, including Kugel's artery[43–47]. The latter produces a large periaortic anastomosis between the right and left coronary trunks and has several perforating branches, some of which can directly nourish the atrioventricular node[44,45″].

Procedural factors

Disruption of the atrioventricular conduction tissue can occur during the positioning and expansion of the prosthetic valve, but also during all the preparatory phases before implantation, such as the crossing of the valve with various wires and catheters, and balloon valvuloplasty. Although infrequent, injury can also occur when wires and catheters are removed from the heart at the end of the procedure. This type of injury was shown in 65 patients in whom continuous 12-lead rhythm monitoring was performed during CoreValve® implantation. In 47 patients, a total of 52 new conduction abnormalities occurred during TAVI. The conduction abnormalities first occurred after balloon valvuloplasty (40%), CoreValve® expansion (33%), CoreValve® positioning in the LV outflow tract (12%), positioning of the balloon catheter (6%), catheter removal (6%), or after wire crossing of the aortic valve (4%)[48]. Distinction should be made between temporary and permanent insults or injury because, for example, new LBBB might conceivably occur transiently after TAVI. With respect to ischemia, the heart is exposed during TAVI to episodes of extreme stress and increased mural tension, such as during balloon valvuloplasty, and to periods of hypotension, such as during rapid pacing of the right ventricle. These maneuvers can result in ischemia of the subendocardial myocardium, and of other areas of the heart such as the atrioventricular conduction axis. Elderly patients, who in general have disseminated cardiovascular atherosclerosis and impaired homeostasis, might be particularly susceptible to ischemia during such episodes of high stress.

Device-related factors

The nominal structures of the CoreValve® and SAPIEN® valve are shown in Figure 5**.** The CoreValve® consists of a self-expanding nitinol frame, to which is sewn a trifoliate porcine pericardium valve. The base of the frame is 12 mm high and covered with a skirt composed of a single layer of porcine pericardium to create a seal and prevent paravalvular aortic regurgitation after implantation. The base has a high radial force

and anchors the prosthesis within the aortic root. The middle segment is constrained to avoid obstruction of the coronary arteries after implantation, and contains the zones of coaptation of the leaflets. This segment has high hoop strength, making it resistant to deformation, and enabling the valve to maintain its size and shape, which guarantees normal geometry and function of the leaflets. The upper, or outflow, portion, which has low radial force, is implanted into the ascending aorta, and orientates the prosthesis within the aortic root in the direction of blood flow. The valve is currently available in three sizes according to the diameter of the base of the frame (Table 2). The SAPIEN® valve consists of a stainless-steel frame (or a cobalt-chromium frame in the next-generation SAPIEN XT® valve), in which a trileaflet, bovine pericardial valve is mounted. Both the stainless-steel and cobalt-chromium frames offer a high radial strength after plastic deformation by balloon inflation. The only difference between the two alloys is that the cobalt-chromium frame has fewer rows, which allows a lower crimping profile while maintaining radial strength. The height of the frame is designed for appropriate placement and minimum interference with the surrounding anatomy, and the height of the skirt varies to protect against paravalvular leakage (Table 2).

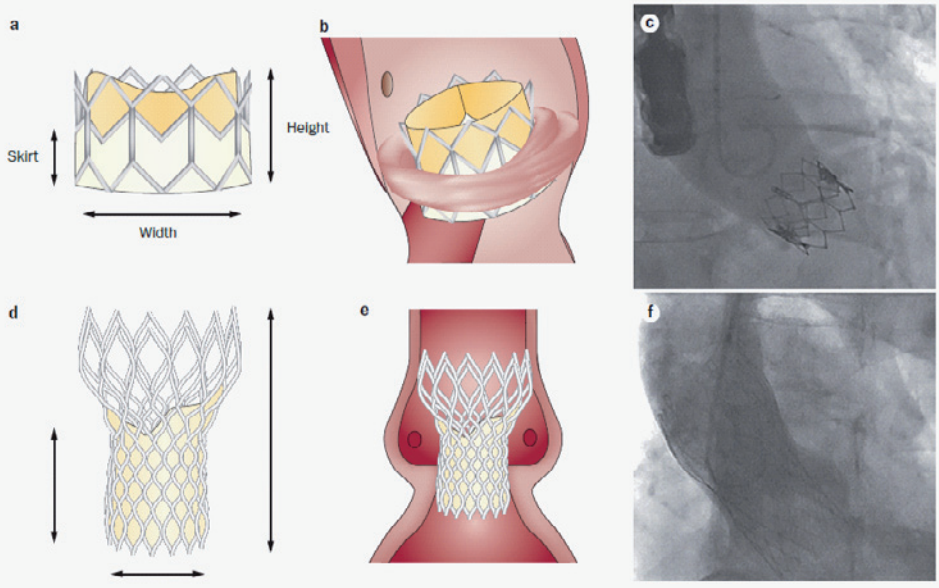

Figure 5. Description of the commercially available prosthetic aortic valves

a–**c** | Edwards SAPIEN® valve (Edwards Lifesciences Corporation, Irvine, CA, USA). **b**–**e** | Medtronic CoreValve® system (Medtronic CV Luxembourg S.a.r.l., Luxembourg). The figures depict the various dimensions of both valves summarized in Table.2. Both drawings demonstrate the approximate "placement "of the prostheses within the aortic root, and corresponding cine aortagrams.

Table 2. Dimensions of the Edwards SAPIEN* and CoreValve§ devices		
Width x height (mm)	**Annulus diameter (mm)**	**Height of skirt (mm)**
Edwards SAPIEN® valve*		
20.0 x 13.5	<19	9.4
23.0 x 14.3	18–22	9.9
26.0 x 17.2	21–25	12.3
29.0 x 19.1	25–27	14.6
Medtronic CoreValve®§		
26.0 x 55.0	20–23	12.0
29.0 x 53.0	23–27	12.0
31.0 x 52.0	26–29	12.0

* Edwards Lifesciences Corporation, Irvine, CA, USA. §Medtronic CV Luxembourg S.a.r.l., Luxembourg.

Both the CoreValve® and SAPIEN® valve are compressed on a delivery catheter and advanced towards the aortic valve. The CoreValve® is advanced into the LV outflow tract, whereupon the protective sheath is gradually withdrawn, which allows the frame to expand and anchor in the LV outflow tract, preferably at a distance of 4–8 mm below the native aortic annulus (Figure 6). The SAPIEN® valve is placed within the annulus and expanded by balloon inflation. These differences in design and technique of implantation might explain the higher frequency of new LBBB and complete atrioventricular block after CoreValve® compared with SAPIEN® valve implantation. Also, the ongoing radial force exerted by the self-expanding CoreValve® frame on the recipient anatomy might contribute to the occurrence of both new LBBB during TAVI, and the persistence of LBBB after implantation. The long-term effects of the continuous radial force on the occurrence of new conduction abnormalities during follow-up in patients with a narrow QRS complex immediately after implantation remains to be elucidated.

Although no definitive evidence exists of a causal relationship between the depth of implantation and new conduction abnormalities during TAVI, a few single-center, observational studies indicate such a relationship. Piazza and colleagues, for instance, reported that the mean distance from the proximal end of the CoreValve® frame to the lower edge of the noncoronary leaflet was significantly longer in patients with a new LBBB compared with patients without a new LBBB[49]. This finding has been confirmed in several other studies[49–56]. Moreover, Aktug *et al.* found that the depth of implantation was the only independent predictor of LBBB after TAVI with the CoreValve®[52]. In a series of 33 patients who underwent TAVI with the SAPIEN® valve, Guttierez *et al.* found that 35% of patients developed a new LBBB when the ventricular end of the prosthesis was located below the hinge point of the anterior leaflet of the mitral valve, compared with none of the patients in whom the ventricular end was implanted above the hinge point ($P = 0.03$)[57].

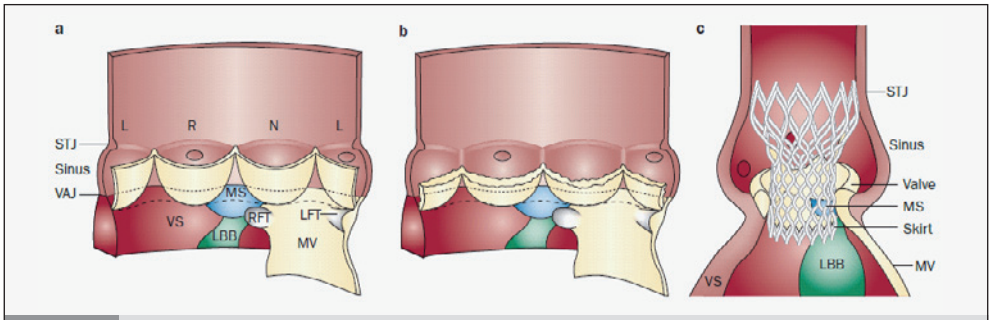

Figure 6. Relationship between the implanted prosthesis and the atrioventricular conduction system

a.The anatomy of the aortic root, valve and conduction system in the normal heart. **b.** Leaflet fusion, as seen with aortic stenosis, results in a lower (annular) attachment of the valve with reduction of the interleaflet triangle size. **c.** Position of the Medtronic CoreValve® system in the native aortic valve. Abbreviations: L, left coronary sinus; LBB, left bundle branch; LFT, left fibrous trigone; MS, membranous septum; MV, mitral valve; N, noncoronary sinus; R, right coronary sinus; RFT, right fibrous trigone; STJ, sintotubular junction; VAJ, ventriculoarterial junction; VS, ventricular septum. Permission obtained from Wolters Kluwer Health © Khawaja, M. Z. *et al.* Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). *Circulation* **123** (9), 951–960 (2011).

Patient-related factors

Some patients might be more-susceptible to new conduction abnormalities during TAVI than others (Table 1). These findings should be interpreted with caution given the nature of the studies, which were mostly single-center and retrospective, provided non-uniform definitions of the independent variables, absence of independent analysis of the findings and were on the basis of small sample sizes. Also, distinction should be made between determinants of new LBBB and complete atrioventricular dissociation. The latter can arise from new LBBB in patients with pre-existing right bundle branch block, or can be the result of injury to the atrioventricular conduction axis in patients without pre-existing atrioventricular conduction abnormalities. The former group is at higher risk of complete atrioventricular dissociation during or after TAVI than the latter group, as are patients with pre-existing right bundle branch block who undergo AVR[21,23,54,55,58–63].

CONCLUSIONS

TAVI is increasingly being used to treat patients with aortic stenosis and, although currently offered to patients who are considered to be too high-risk for AVR, clinical practice indicates a slow, but gradual, shift towards less-sick patients[64–67]. Many more patients, therefore, might benefit from this treatment, but are also exposed to the risk

of adverse effects, such as new LBBB. Insights into the causes and pathophysiology of new LBBB help to formulate changes in the technology itself, the execution of the procedure, or both. With respect to the procedure, some interventionalists advocate performing TAVI without predilatation of the aortic valve, thereby decreasing the number of manipulations in the heart[68]. Although conceptually sound, the safety of such a procedure needs to be demonstrated in large, multicenter studies, because forceful introduction of a valve might expose the patient to the risk of atherosclerotic embolization or stroke. Perhaps patients with a small amount of calcification of the aortic root might benefit from such an approach. Questions regarding the method of assessment of calcium load (preferably by non contrast multislice CT), and the definition of an appropriate threshold remain to be answered.

Another solution is to improve the accuracy of implantation by taking care to control the depth of implantation. Given the design of the frame and the technique of implantation, this issue is particularly relevant to the CoreValve®. Novel software is currently in development by Paieon Medical Systems (Paieon Inc., New York, NY, USA), which offers online tracking of the basal attachments of the aortic valvular leaflets—the so-called annulus[69,70]. This information allows the operator to make tiny adjustments while releasing the frame, thus ensuring that the inflow of the frame is as close as possible to the basal margin of the native valve. The software is still in an experimental form and, after commercial release, clinical studies will need to demonstrate its added value. This principle also holds for novel delivery systems such as the AccuTrak™ System (Medtronic CV Luxembourg S.a.r.l., Luxembourg), which is designed for improved control of positioning while the CoreValve® is released[71]. The most-challenging [innovations will come from changes in design of the frame to ensure as little contact with the surrounding tissues exists as possible, and eventually the option to retrieve the valve if it is inserted too deeply. Some clinical experience exists with prosthetic aortic valves that can be repositioned, such as the valve from Direct Flow Medical, Inc. (Santa Rosa, CA, USA) and the Lotus™ valve (Sadra Medical Inc., Los Gatos, CA, USA)[72–80]. Whether these technologies will truly reduce the occurrence of new LBBB remains to be documented. Given the current insights into the pathophysiology of new LBBB, a frame that is implanted within the length of the native aortic root, with little penetration into the LV outflow tract beyond the basal hinges of the leaflets, and minimal contact with its surrounding tissue, seems to be the ideal technology.

In summary, new LBBB frequently occurs during or after TAVI, and can affect quality of life and prognosis. Knowledge of the anatomical pathways of atrioventricular conduction, the bioprosthesis, and technique of implantation help to elucidate the

causal relationship between TAVI and new LBBB, which might, in turn, help to refine the procedure, the bioprosthesis, or both.

REVIEW CRITERIA

The MEDLINE and PubMed databases were searched for primary research articles focusing on transcatheter aortic valve implantation and conduction abnormalities published between 2000 and 2011. The search terms used were "transcatheter aortic valve implantation/replacement", "percutaneous aortic valve implantation/replacement", "transfemoral aortic valve implantation/replacement", "transapical aortic valve implantation/replacement", "conduction abnormalities", "left bundle branch block", "total atrioventricular block", and "pacemaker", both alone and in combination. All papers identified were full-text papers published in English. The reference lists of identified articles were searched for further relevant papers.

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CHAPTER 11

Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve System in patients with aortic stenosis

Nuis RJ, Van Mieghem NM, Schultz CJ, Tzikas A, Van der Boon RM, Maugenest AM, Cheng J, Piazza N, van Domburg RT, Serruys PW, de Jaegere PP.

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ABSTRACT

Aims

New-onset left bundle branch block (LBBB) and complete atrioventricular block (AV3B) frequently occur following transcatheter aortic valve implantation (TAVI). We sought to determine the timing and potential mechanisms of new conduction abnormalities (CAs) during TAVI, using the Medtronic CoreValve System (MCS).

Methods and results

Sixty-five consecutive patients underwent TAVI with continuous 12-lead ECG analysis. New CAs were defined by the occurrence of LBBB, RBBB, and/or AV3B after the following pre-defined time points: (i) crossing of valve with stiff wire, (ii) positioning of balloon catheter in the aortic annulus, (iii) balloon valvuloplasty, (iv) positioning of MCS in the left ventricular outflow tract (LVOT), (v) expansion of MCS, (vi) removal of all catheters. A new CA occurred during TAVI in 48 patients (74%) and after TAVI in 5 (8%). Of the 48 patients with procedural CAs, a single new CA occurred in 43 patients (90%) and two types of CAs in 5 (10%). A new LBBB was seen in 40 patients (83%), AV3B in 9 (19%), and RBBB in 4 (8%). The new CA first occurred—in descending order of frequency—after balloon valvuloplasty in 22 patients (46%), MCS expansion in 14 (29%), MCS positioning in 6 (12%), positioning of balloon catheter in 3 (6%), wire-crossing of aortic valve in 2 (4%), and after catheter removal in 1 patient (2%). Patients who developed a new CA during balloon valvuloplasty had a significantly higher balloon/annulus ratio than those who did not (1.10 ± 0.10 vs. 1.03 ± 0.11, P = 0.030). No such relationship was found with the valve/annulus ratio.

Conclusions

Transcatheter aortic valve implantation with the MCS was associated with new CAs in 82% of which more than half occurred before the actual valve implantation. It remains to be elucidated by dedicated studies whether new CAs can be reduced by appropriate balloon sizing—a precept that also holds for valve size given the observed directional signal of the valve size/aortic annulus ratio.

INTRODUCTION

New-onset left bundle branch block (LBBB), third-degree atrioventricular block (AV3B), and the need for new permanent pacemaker implantation (PPI) constitute an important clinical problem during transcatheter aortic valve implantation (TAVI). This is in particular true after the implantation of the self-expanding Medtronic CoreValve System (MCS). Following the latter, new LBBB, AV3B, and PPI have been reported to vary between 29 and 65%, 15 and 44%, and 9 and 49%, respectively and to vary between 6 and 18%, 0 and 27%, and 0 and 27%, respectively, after the implantation of the EDWARDS Sapien valve[1–9]. The pathophysiology of new conduction abnormalities (CAs) has not yet been elucidated. A number of studies indicate that both patient- and procedure-related factors such as septal wall thickness, non-coronary cusp thickness, pre-existing right bundle branch block (RBBB), depth of valve implantation within the left ventricular outflow tract (LVOT), post-implant prosthesis expansion, and the type of prosthesis play a role[1–4,8,10–12].

Transcatheter aortic valve implantation constitutes a complex and multi-step procedure including crossing of the aortic valve and exchange and manipulation of various guide wires and bulky catheter systems in the LVOT, which may inflict temporary or permanent injury to the conduction system. Hence, procedure-related causes of CAs during TAVI may not necessarily relate to the prosthesis itself but to many other actions inherently associated with TAVI. Therefore, we sought to examine the timing of the occurrence of new CAs in a series of 65 consecutive patients who underwent TAVI with the MCS during six pre-defined time points of the procedure while using continuous ECG analysis and sought to explore potential mechanisms of new CAs. In particular, the relationship between new CAs and the balloon and valve/annulus ratio in addition to markers of inflammation was studied. The latter stems from propositions that the implantation of a bioprosthesis may induce an inflammatory reaction due to trauma inflicted on the LVOT[2,4,8,11,13,14].

METHODS

Patients

The study population consisted of 65 consecutive patients with severe symptomatic aortic stenosis who underwent TAVI with the MCS between March 2009 and August 2010. Details of the prosthesis and procedure have been previously published[5]. Briefly, all patients were accepted for TAVI by Heart Team consensus between a cardiologist

and a cardiac surgeon who agreed that conventional open-heart surgery was associated with either too high or prohibitive risk. The prosthesis consists of a self-expanding nitinol tri-level frame to which is secured a trileaflet bioprosthetic porcine pericardial tissue valve. Currently, the prosthesis is available in sizes of 26 and 29 mm. In case a 26 mm MCS was chosen, pre-dilatation of the aortic valve was performed with a 22 mm nucleus balloon (NuMed, Hopkington, NY, USA). In case of a 29 mm MCS, a 23 mm Z-Med-II balloon was used (NuMed). The procedure was performed with the patient under general anaesthesia, with a temporary pacemaker wire positioned in the right ventricle and with default femoral arterial access through an 18F sheath. Patients were extubated before leaving the catheterization laboratory or within 2 h after arrival in the cardiac care unit. Per TAVI protocol, the temporary pacemaker was maintained for at least 48 h after the procedure or longer if indicated. This study complies with the Declaration of Helsinki.

Data collection

Patient demographics and procedural and post-procedural data were prospectively collected and entered in a dedicated database. Endpoints regarding in-hospital outcome were selected and defined according to the Valve Academic Research Consortium (VARC) recommendations, including the 30-day safety endpoint, defined as composite all-cause death, major stroke, major vascular complication, life-threatening bleeding, acute kidney injury—stage 3, peri-procedural myocardial infarction, repeat procedure for valve-related dysfunction[15].

All 12-lead surface ECGs immediately before and after the procedure and at discharge were analysed by two senior cardiologists who are not involved in the TAVI procedure and who were blinded to the results of the continuous rhythm analysis during the procedure. These surface ECGs were used to record the heart rate and rhythm, PR interval, and the presence of first-, second-, or third-degree AV block. Left and right fascicular hemiblocks and left and right bundle branch blocks were defined according to the guidelines of World Health Organization and International Society and Federation for Cardiology Task Force[16]. During TAVI, an electronic 12-lead ECG was continuously recorded and digitally collected in the catheterization laboratory database for invasive cardiac procedures. These strips were analysed by two independent researchers (postgraduate research fellows, interventional cardiology) for the assessment of new CAs after the following six pre-defined phases of TAVI. Phase 1: crossing of the stenotic valve with a straight wire and exchange for a stiff support wire; phase 2: positioning of a balloon catheter (typical size 22 or 23 mm × 4 cm) within the aortic annulus used for pre-dilatation; phase 3: full inflation of the balloon catheter under rapid ventricular

pacing at a rate of 180 or 220b.p.m.; phase 4: positioning of the MCS delivery catheter into the LVOT with the ventricular edge of the frame approximately within 6–8 mm of the lower edge of the non-coronary cusp as identified by contrast aortography; phase 5: complete expansion of the MCS prosthesis; phase 6: retrieval of all catheters and wires.

For this study, the following new CAs were collected during the procedure: LBBB, RBBB, and AV3B. For confirmation purposes, all electronic rhythm strips were printed after each individual phase. New CAs were considered (i) persistent if present during all subsequent phases of the procedure; (ii) intermittent in case of spontaneous appearance and disappearance during the procedure; and (iii) permanent if still present on the ECG at hospital discharge. To explore the mechanisms of new CAs, a univariate analysis was performed assessing the relationship between the balloon/aortic annulus ratio and new CAs during phase 3 (balloon valvuloplasty) and the valve size/aortic annulus ratio and new CAs during phase 5 (valve expansion). Also, the relationship was studied between markers of inflammation [C-reactive protein and white blood cell count (WBC) at 24 and 72 h after TAVI] and new CAs. The balloon and valve sizes were defined by the nominal size provided by the manufacturer. The aortic annulus was defined and quantified using multi-sliced computed tomography according to the protocol previously described[17]. The mean of the minimum and maximum diameter in, respectively, the sagital and coronoral view was used to define the diameter of the aortic annulus[17].

Categorical variables are presented as frequencies and percentages, and normal and skewed continuous variables are presented as means (±SD) and medians (IQR), respectively. The normality distribution for continuous data was examined with the Shapiro–Wilk test. Comparison of categorical variables was performed using the two-sided Student's *t*-test or Wilcoxon rank-sum test, and the χ^2 or Fischer's exact tests were used to compare categorical variables, with a two-sided $P < 0.05$ indicating statistical significance. All analyses were performed with the SPSS software (version 17).

RESULTS

A total of 65 consecutive patients underwent TAVI with the MCS (transfemoral 64, subclavian 1) of which the baseline characteristics and in-hospital clinical results are listed in Tables 1 and 2, respectively. The 30-day event rate was 17% both in patients with ($n = 9$) and without ($n = 2$) a new CA ($P = 1.0$). The in-hospital or 30-day mortality, however, was 11% in patients with a new CA and 0% in those without a new CA ($P =$

Table 1. Baseline patient characteristics and medication use according to patients who developed a new conduction abnormality during or after transcatheter aortic valve implantation

Characteristics	Entire cohort *(n = 65)*	New CAs *(n = 53)*	No new CAs *(n = 12)*	p-value
Demographics				
Age (years), mean ± SD	80 ± 8	80 ± 8	83 ± 5	0.22
Male, n (%)	32 (49)	24 (45)	8 (67)	0.18
Height (cm), mean ± SD	167 ± 10	166 ± 10	171 ± 9	0.11
Weight (kg), mean ± SD	73 ± 14	72 ± 14	78 ± 14	0.17
Body mass index, mean ± SD	26.1 ± 3.9	26.0 ± 4.0	26.6 ± 3.6	0.65
Body surface area, mean ± SD	1.84 ± 0.21	1.82 ± 0.21	1.92 ± 0.20	0.11
NYHA class III or IV, n (%)	44 (68)	34 (64)	10 (83)	0.31
Previous cerebrovascular event, n (%)	15 (23)	14 (26)	1 (8)	0.27
Previous myocardial infarction, n (%)	18 (28)	14 (26)	4 (33)	0.72
Previous CABG, n (%)	12 (19)	9 (17)	3 (25)	0.68
Previous PCI, n (%)	21 (32)	16 (30)	5 (42)	0.50
Diabetes mellitus, n (%)	14 (22)	11 (21)	3 (25)	1.00
Hypertension, n (%)	24 (37)	19 (36)	5 (42)	0.75
Glomerular filtration rate <60 mL/min, n (%)	32 (49)	26 (49)	6 (50)	1.00
Creatinine, mean ± SD	107 ± 73	105 67	113 ± 95	0.75
Chronic obstructive pulmonary disease, n (%)	21 (32)	17 (32)	4 (33)	1.00
Permanent pacemaker, n (%)	6 (9)	2 (4)	4 (33)	0.009
Atrial fibrillation, n (%)	16 (25)	13 (25)	3 (27)	1.00
Aortic valve area (cm^2), mean ± SD	0.65 ± 0.23	0.65 ± 0.20	0.66 ± 0.35	0.89
Aortic valve annulus (mm), mean ± SD	22.7 ± 2.20	22.4 ± 2.35	23.0 ± 1.91	0.37
Left ventricular ejection fraction ≤35%, n (%)	5 (8)	4 (8)	1 (8)	1.00
Mitral regurgitation grade ≥III, n (%)	9 (14)	7 (13)	2 (17)	1.00
Aortic regurgitation grade ≥III, n (%)	7 (11)	5 (9)	2 (17)	0.60
Logistic Euroscore, median (IQR)	11.0 (8.9–18.6)	11.1 (8.7–19.3)	11.0 (10.0–16.6)	0.67
STS score, median (IQR)	3.8 (3.3–5.6)	3.8 (3.0–5.8)	4.1 (3.3–5.1)	0.90
Baseline medication use, n (%)				
Anti-platelets	47 (72)	40 (76)	7 (58)	0.29
Diuretics	37 (57)	29 (55)	8 (67)	0.45
ACE-inhibitors	19 (29)	15 (29)	4 (33)	1.00
Angiotensin II antagonists	15 (23)	12 (23)	3 (27)	1.00
Betablockers	39 (60)	31 (58)	8 (67)	0.75
Calcium antagonists	20 (31)	19 (36)	1 (8)	0.09
Anti-arrhythmics	7 (11)	6 (11)	1 (9)	1.00
Statins	31 (48)	24 (54)	7 (58)	0.41

Abbreviations: ACE: Angiotensin-converting Enzyme; CAs: Conduction Abnormalities; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention; NYHA: New York Heart Association.

Table 2. In-hospital peri-procedural complications, therapy-specific and echocardiographic results in patients undergoing transcatheter aortic valve implantation (n = 65)

Peri-procedural complications	
Mortality (30-day or in-hospital), n (%)	
All cause	6 (9)[a]
Cardiovascular cause	4 (6)[a]
Myocardial infarction, n (%)	
Peri-procedural (<72 h)	0
Spontaneous (>72 h)	0
Cerebrovascular, n (%)	
Major stroke	3 (5)
Minor stroke	0
Transient ischaemic attack	1 (2)
Vascular, n (%)	
Major	4 (6)
Minor	6 (9)
Bleeding, n (%)	
<24 h	
Life-threatening or disabling	4 (6)
Major	11 (17)
Minor	5 (8)
>24 h	
Life-threatening or disabling	4 (6)
Major	3 (5)
Minor	0
Acute kidney injury, n (%)[b]	
Stage I	7 (12)
Stage II	2 (3)
Stage III	1 (2)
Combined safety endpoint (at 30 days), n (%)[c]	11 (17)
Therapy-specific results	
Valve-in-valve implantation, n (%)	2 (3)
Post-implantation balloon dilatation, n (%)	8 (12)
Unplanned cardiopulmonary bypass use, n (%)	0
In-hospital re-intervention, n (%)	2 (3)
Echocardiogram	
Aortic valve area (cm^2), mean ± SD	1.8 ± 0.8
Left ventricular ejection fraction ≤35%, n (%)	6 (9)
Aortic regurgitation grade ≥III, n (%)	8 (12)
Mitral regurgitation grade ≥III, n (%)	6 (9)

Mutually non-exclusive analysis (one or more events/patient possible).
[a]Including two intraprocedural deaths.
[b]Four patients with pre-procedural haemodialysis and two patients who died during TAVI were excluded from the analysis of acute kidney injury.
[c]Composite all-cause mortality, major stroke, major vascular complication, life-threatening bleeding, acute kidney injury—stage III, peri-procedural, myocardial infarction, repeat procedure for valve-related dysfunction.

Table 3. Summary of 53 patients with new conduction abnormalities during and after transcatheter aortic valve implantation

Type of CAs	During TAVI, n (%)	After TAVI, n (%)
Single type		
LBBB	36 (68)[a]	4 (8)
RBBB	2 (4)[b]	0
AV3B	5 (9)	1 (2)
Two types		
RBBB, LBBB	1 (2)	0
RBBB, AV3B	1 (2)	0
LBBB, AV3B	3 (6)	0
Total	**48 (91)**	**5 (9)**

[a]New LBBB during TAVI changed to AV3B after TAVI in two patients. [b]New RBBB during TAVI changed to LBBB after TAVI in one patient.
Abbreviations: AV3B: third-degree atrioventricular block; CAs: Conduction Abnormalities; LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block.

0.35). Two patients died during TAVI (electromechanical dissociation during phase 1 in one patient and LVOT rupture after phase 3 in another), and four deaths occurred during hospital stay [severe paravalvular aortic regurgitation (AR) at day 14 in one patient, pneumonia at day 28 in two patients, and pneumothorax following PPI at day 32 in another patient]. In these four patients, the ECG just before in-hospital death was used to determine the persistence of the CAs eventually seen during TAVI.

Details of the type and timing of new CAs are listed in Supplement A. Of the 65 patients, 12 patients (18%) had a pre-existing CA. In 3 out of these 12 patients, the pre-existing LBBB/RBBB progressed to AV3B during TAVI. In another 45 patients, a new CA was seen during TAVI. In five other patients, a new CA occurred after TAVI (as identified on ECG at discharge) but not during the procedure. In all five patients, the new CA consisted of an LBBB except in one who had a pre-existing LBBB and developed an AV3B after the procedure. Therefore, a total of 53 patients (82%) had new peri-procedural CAs: during TAVI in 48 patients (74%) and after TAVI in another 5 patients (8%). Details are summarized in Table 3. In the 48 patients with a new CA during TAVI, a single new CA was seen in 43 (90%) and two types of CAs in 5 (10%). A new LBBB was seen the most (40 patients or 83%), followed by AV3B in 9 (19%) and RBBB in 4 patients (8%). In three patients, the new CAs that occurred during TAVI changed from RBBB to LBBB at discharge in one patient (No. 5) and progressed from LBBB to AV3B in two patients (Nos 16 and 39).

In these 48 patients, the new CAs first occurred—in descending order of frequency—during phase 3 (balloon valvuloplasty) in 22 patients (46%), phase 5 (complete MCS

expansion) in 14 patients (29%), phase 4 (positioning of MCS in the LVOT) in 6 patients (12%), phase 2 (positioning of balloon catheter in the LVOT) in 3 patients (6%), phase 1 (crossing of aortic valve with wire) in 2 patients (4%), and phase 6 (removal of catheters from the body—most likely caused by the touching of the cone of the LVOT when removing the delivery catheter out of the left ventricle) in 1 patient (2%) (Figure 1). Hence, 56% of the new CAs occurred during the preparatory phases (phases 1–3) and 44% during and after valve delivery and implantation (phases 4–6). In 70% of the patients in whom the new CA first occurred before the actual valve implantation (phases 1–3), the CA was still present on the discharge ECG. It was 62% in the patients in whom the new CA first occurred during the actual valve implantation (phases 4–6). Overall, the new CAs were intermittent in 12 (25%) and persistent in 36 patients (75%) out of the total of 48 patients in whom a new CA was observed during TAVI. In 31 (65%) out of these 48 patients, the new CA was permanent (still present on the ECG at discharge). In 14 out of the 65 patients (22%), a new permanent pacemaker after TAVI was implanted because of new-onset AV3B in 10 patients, persisting bradycardia in 3, and brachy-tachy-syndrome in 1 patient (Supplement B). Among those with AV3B, the diagnosis was made during the procedure in seven patients and after the procedure in three patients (two at day 2 and one at day 5).

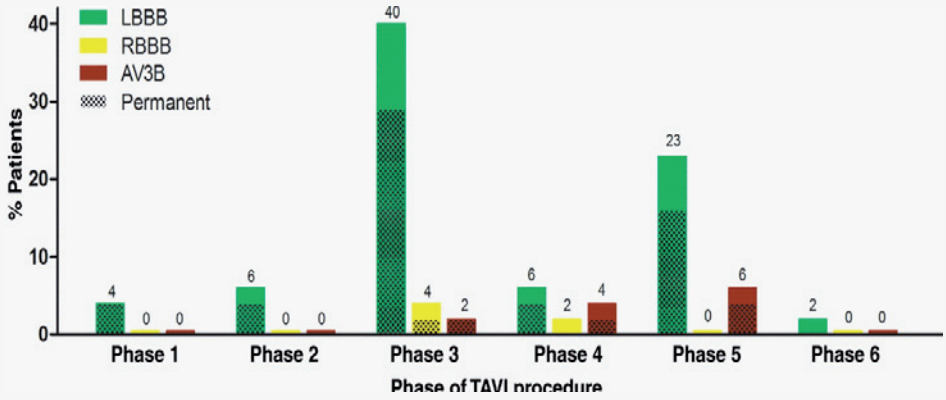

Figure 1. Distribution of first occurrence of new CAs (LBBB, RBBB, and AV3B) per phase of TAVI and associations with permanent change as identified on discharge ECG among a total of 48 patients with new CAs during TAVI

The frequencies of first appearance of new CAs (=LBBB, RBBB, and/or AV3B) on the continuous ECG analysis are presented per phase of the TAVI procedure as well as the association with a permanent change as identified on the discharge ECG among 48 patients who developed a new CA during TAVI.
Abbreviations: AV3B: third-degree atrioventricular block; CAs: Conduction Abnormalities; LBBB: Left Bundle Branch Block; RBBB, Right Bundle Branch Block; TAVI, Transcatheter Aortic Valve Implantation.

Table 4 summarizes potential determinants of new CAs during balloon valvuloplasty (phase 3) and during valve implantation (phase 5). Patients who developed a new CA during balloon valvuloplasty had a significantly higher balloon/annulus ratio than those who did not (1.10 ± 0.10 vs. 1.03 ± 0.11, $P = 0.030$). No such relationship was found with the valve size/annulus ratio. Patients who developed new CAs during valve expansion (phase 5) had a higher WBC at 24 and 72 h after TAVI than those who did not develop a new CA.

DISCUSSION

In this study in which 65 consecutive patients underwent TAVI using the MCS, we found that peri-procedural new CAs occurred in 82% of the patients. The majority of these new CAs occurred during the procedure (91%) of which 56% occurred before the actual valve implantation and most often consisted of a new LBBB (83%). A higher balloon/annulus ratio was associated with a new CA during balloon valvuloplasty. We did not find a relationship between the valve size/annulus ratio and new CAs.
The close anatomical relationship between the aortic valvar complex and the conduction tissue explains the high frequency of new CAs during TAVI with the MCS[18]. The herein reported incidence of new CAs is in accordance with the observations made by others with both the MCS and the EDWARDS valve although that the incidence of new LBBB and AV3B is higher after the self expanding MCS (29–65% and 15–44%, respectively) than after the balloon expandable EDWARDS valve (6–18% and 0–27%, respectively)[1–4,7–9]. Moreover, transapical aortic valve implantation may be associated with few CAs and new PPI most likely as a result of less manipulations and trauma to the LVOT during the procedure. The rate of AV3B and new PPI following transapical TAVI are both reported to vary between 0 and 20%[2,8,19].

Of note, we found that a new CA may occur not only during but also at some time after the procedure, which was the case in five patients in our study who were free of new CAs during the procedure. In all patients, it concerned a new LBBB except one in whom a pre-existing LBBB progressed to a complete heart block. In addition, a progression of procedural new CAs to complete heart block after TAVI was seen in three other patients. Whether the late new CAs are caused by injury or oedema of the conduction tissue by the continuous radial expansive force of the self-expanding nitinol frame of the MCS needs to be elucidated. This clinical observation underscores the importance of careful monitoring of patients who undergo TAVI by means of continuous telemonitoring similar to the surgical practice. More than half of the new CAs in our series occurred

Table 4. Technical and inflammatory associations with new conduction abnormality occurrences during phases 3 and 5 in patients undergoing transcatheter aortic valve implantation

	Phase 3 new CAs	Phase 3 no CAs	*P*-value	Phase 5 new CAs	Phase 5 no CAs	p-value
Balloon size—minimal annulus diameter ratio, mean ± SD	1.10 ± 0.10	1.03 ± 0.11	0.030	1.06 ± 0.12	1.06 ± 0.11	0.83
Balloon size—maximal annulus diameter ratio, mean ± SD	0.85 ± 0.07	0.84 ± 0.08	0.89	0.84 ± 0.07	0.85 ± 0.08	0.48
Valve size—minimal annulus diameter ratio, mean ± SD	1.36 ± 0.11	1.30 ± 0.12	0.069	1.30 ± 0.17	1.33 ± 0.10	0.35
Valve size—maximal annulus diameter ratio, mean ± SD	1.04 ± 0.07	1.06 ± 0.07	0.43	1.04 ± 0.09	1.05 ± 0.07	0.60
Depth of implantation from non-coronary cusp, mean ± SD	9.01 ± 3.64	8.01 ± 3.15	0.25	7.76 ± 3.05	8.66 ± 3.47	0.35
Depth of implantation from left coronary cusp, mean ± SD	9.68 ± 4.06	8.50 ± 3.51	0.22	8.30 ± 3.87	9.22 ± 3.73	0.39
Leucocyte count <24 h (× 109/L), mean ± SD	11.25 ± 3.48	11.43 ± 4.24	0.87	14.07 ± 5.24	10.39 ± 2.80	0.001
Leucocyte count <72 h (× 109/L), mean ± SD	12.71 ± 4.42	11.78 ± 4.18	0.41	14.97 ± 5.26	11.09 ± 3.32	0.001
C-reactive protein <24 h, mean ± SD	64 ± 90	64 ± 55	0.98	71 ± 64	62 ± 73	0.64
C-reactive protein <72 h, mean ± SD	84 ± 113	75 ± 61	0.70	85 ± 66	76 ± 92	0.74

Abbreviations: CAs: Conduction Abnormalities.

before the actual valve implantation. A minority of previous studies reported new CAs following balloon valvuloplasty prior to the valve implantation, which may be explained by the fact that in these studies no continuous ECG recordings were used to determine the occurrence of CAs during the procedure[1–4,7,8,10–12,14,20–22]. Our findings are, moreover, in accordance with the incidence of new CAs reported after isolated aortic balloon valvuloplasty[23–25].

In terms of mechanisms of new CAs, Bleiziffer et al. recently reported an association between balloon size and the occurrence of new-onset AV3B requiring PPI after TAVI[12]. In the present study, we found a significantly higher balloon/annulus ratio in patients who developed a new CA during balloon valvuloplasty in comparison with those who did not (1.10 ± 0.10 vs. 1.03 ± 0.11, $P = 0.030$). Given the preponderance of new CAs during balloon valvuloplasty and its relationship with the balloon/annulus ratio, the findings of this study suggest that new CAs (and potentially new PPI) may be reduced by using a balloon/annulus ratio close to 1.0. This is independent of the valve technology itself and the access to the aortic valve (transfemoral, transapical, subclavian, direct access via the ascending aorta) since pre-dilatation of the stenotic aortic valve is a standard step in all procedures. Yet, the observational nature of this study does not allow to draw firm conclusions. This needs to be demonstrated by appropriately designed studies in which one should also acknowledge that differences in the physical

properties of the frame between a self-expanding and a balloon expandable prosthesis (i.e. continuous radial force vs. plastic deformation without continuous radial force) and the technique of implantation in addition to shape and height of the frame may result in a difference in the incidence of new CAs during the actual valve implantation, which in turn may explain a disparity in the overall incidence of new CAs during TAVI between these two technologies.

We acknowledge that the overlap in balloon/aortic annulus between the two groups in this series is considerable. Therefore, the proposal of balloon sizing needs to be examined in larger series allowing a more precise cutoff value and needs to be validated in prospective clinical research projects. One should also bear in mind that the use of smaller balloons may result in suboptimal pre-dilatation of the native valve, leading to a higher incidence of paravalvular AR after TAVI which in turn may induce CAs due to increased wall tension and stretch of the conduction tissue[26,27]. At variance with Gutiérrez et al., who studied 33 patients who underwent transapical TAVI, we found no relationship between the valve size/aortic annulus ratio and new CAs[8]. Yet, the data of this study nevertheless indicate a higher risk of new CAs in case of a higher ratio. We most likely would have found such a relationship in case of a more disperse distribution of the data, thereby allowing a proposal of sizing. The present data indicate, however, that a ratio of approximately 1.30 (when using the minimal annulus dimension) and a ratio of approximately 1.05 (when using the maximum annulus dimension) are safe and may be recommended to avoid new CAs. Similar to the proposal of balloon size selection, proposals of valve size selection need to be confirmed by more in-depth analysis in larger cohorts of patients allowing multivariate analysis and need subsequently to be validated in prospective research projects. At present, only two sizes of valves are available. The issue will be even more pertinent when four sizes become available. We also found that the new CA occurrence during valve implantation (phase 5) was associated with increased levels of leucocyte count after TAVI (14.07 vs. 10.39 $\times$ 10^9/L, $P = 0.001$). It is unclear whether this concerns a causal relationship (e.g. more trauma and/or oedema of the conduction tissue during TAVI) or whether the increased leucocyte count is caused by post-TAVI conditions (e.g. more frequent pacing). In case of the former, all measures should be taken to limit injury and, thus, inflammation. In this respect, more direct access to the aortic valve that is achieved by transapical, subclavian, and direct access of the ascending aorta may play a role as they may be associated with less contact and injury of the LVOT[28–30]. The information currently available on PPI rates after transfemoral and transapical implantation of the EDWARDS valve, however, does not reveal a difference. It varies between 2–27% and 0–20%, respectively[8,9,19,31]. Also, better control of the positioning

and release of the valve may help to reduce injury to the tissue of the LVOT during the procedure. This may be achieved by software allowing online definition of annulus and base of frame during implantation and/or by novel delivery systems with improved ergonomics and enhanced control of catheter stability during release and the eventual retrieval of the valve[32].

LIMITATIONS

Although it concerns a prospective study in which two independent researchers continuously monitored the electrocardiographic recordings during the procedure, some electrocardiographic changes may have remained undetected, leading to an underestimation of the reported frequency of new CAs during TAVI. In addition, post-procedural onset of CAs as identified on continuous telemetry recordings was less intensively monitored and was most likely only detected in the case of more evident CAs. Also, the duration of analysis was limited to the hospital stay, and, therefore, the occurrence of late new CAs as well as late disappearance of TAVI-induced CAs remains uncertain although they are unlikely to occur.[4] Considering the observational nature of the current study, further research is needed to elucidate whether the association between balloon/annulus ratio and new CAs represents a causal relationship and if modification of the sizing will reduce the frequency of new CAs. In addition, the study lacks the power to provide a comprehensive analysis of the mechanisms or determinants of new CAs. Many potential determinants may have remained undetected.

CONCLUSIONS

Transcatheter aortic valve implantation with the MCS was associated with peri-procedural new CAs in 82% of the patients. More than half of these new CAs occurred before the actual valve implantation, and two-thirds of the new CAs were still present on the ECG at discharge. It remains to be elucidated by dedicated studies whether appropriate balloon and valve sizing will reduce new CAs.

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CHAPTER 12

Occurrence and Fate of Ventricular Conduction Abnormalities after Transcatheter Aortic Valve Implantation

Houthuizen P*, van der Boon RMA*, Urena M, van Mieghem NM, Brueren BRG, Poels TT, van Garsse LAFM, Rodés-Cabau J, Prinzen FW, de Jaegere PPT.
* Shared first-autorship

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ABSTRACT

Aims

Transcatheter aortic valve implantation (TAVI) is frequently complicated by new left bundle branch block (new LBBB). We investigated the development and persistence of LBBB during follow-up and its clinical consequence.

Methods and Results

ECGs at baseline, within 24 hours, before discharge and at 12 months after TAVI were assessed in 476 patients without pre-existing LBBB and/or pacemaker before or after TAVI. TAVI-induced new LBBB was categorized based on timing of occurrence; within 24 hours (acute), after 24 hours but before discharge (subacute), and after discharge (late) in addition to persistence (transient or persistent). A total of 175 patients (36.8%) developed new LBBB of which 85.7% occurred within 24 hours after TAVI, 12.0% before and 2.3% after hospital discharge and was persistent in 111 patients (63.4%). Implantation of the Medtronic CoreValve System (MCS) led more frequently to new LBBB than the balloon-expandable Edwards SAPIEN valve (ES) (53.8% versus 21.7%) with less recovery during follow-up (39.0% versus 9.5%). Late new LBBB was only seen in 4 patients (0.8%). During a median follow-up of 915 (578-1,234) days, persistent LBBB was associated with a significant increase in mortality as compared to no LBBB and temporary LBBB combined (hazard ratio, 1.49, 95% confidence interval, 1.10–2.03; P=0.01).

Conclusions

TAVI-induced new LBBB occurs in almost 40% of patients of which almost all before hospital discharge. It occurs 3 times more frequent after MCS than after ES valve implantation and has a twofold lower tendency to resolve during follow-up. Persistent LBBB is associated with a higher mortality.

INTRODUCTION

Since the first successful implantation in 2002,[1] transcatheter aortic valve implantation (TAVI) has become an accepted and evidence-based alternative to surgical aortic valve replacement in selected patients with aortic valve stenosis[2,3]. Despite its clinical benefits, periprocedural conduction disorders, in particular new left bundle branch block (new LBBB), frequently occur after TAVI[4–6]. New LBBB affects left ventricular function, increases the risk for postoperative permanent pacemaker implantation and has been associated with an increased mortality[4,5,7,8]. New LBBB occurs more frequently after implantation of the self-expanding Medtronic CoreValve System (MCS; reported frequency 30-60%) than after the balloon-expandable Edwards SAPIEN valve (ES; reported frequency 6-12%)[6,9–13]. There are, however, scant detailed electrocardiographic data assessing the changes of QRS duration and morphology not only shortly after TAVI but also during follow-up. Recovery of TAVI-induced new LBBB may occur but is less frequent after MCS than ES valve implantation. Also, little is known about the development of intraventricular conduction disorders after hospital discharge[5,14–16]. This was subject of the present study in which a series of 476 patients who underwent TAVI with the MCS or ES device without pre-existing LBBB, permanent pacemaker (PPM) or postprocedural PPM implantation were subjected to a detailed and prospective electrocardiographic assessment.

METHODS

Patient population

The patient population consists of 701 patients who underwent TAVI between January 2006 and July 2011 with the Medtronic CoreValve System (MCS; Medtronic Inc, Minneapolis, MN, USA) (n=339) or the balloon-expandable Edwards SAPIEN valve (ES; Edwards Lifesciences LLC, Irvine, CA, USA) (n=350) in any of following institutions: Quebec Heart & Lung Institute (n=212; ES: n=206), Erasmus Medical Center Rotterdam (n=202; MCS: n=200), Catharina Hospital Eindhoven (n=173; MCS: n=139; ES: n= 30), Maastricht University Medical Center (n=114; ES: n=114). In 12 patients the procedure was aborted without implantation of any valve. For the purpose of the study, only patients with a minimum follow-up of 1 year after TAVI were eligible. Also, patients with pre-existing LBBB and/or permanent pacemaker (PPM) before TAVI were excluded from analysis, as well as patients who did not undergo valve implantation (aborted procedure). Patients who received a new PPM within 30 days after TAVI were also excluded, since it precludes accurate assessment of eventual LBBB or other

conduction disorders. Therefore, the study population consists of 484 patients (Figure 1), of whom 6 patients (1.2%) died during or shortly after the procedure resulting in the absence of any postprocedural electrocardiogram (ECG). From another 2 patients (0.4%) there were no ECGs available after the implantation. All clinical and procedural data were prospectively collected and entered into a dedicated central database. If necessary, additional information was collected by analysis of medical records. The use of anonymous clinical, procedural and follow-up data for research were in accordance with the institutional policies.

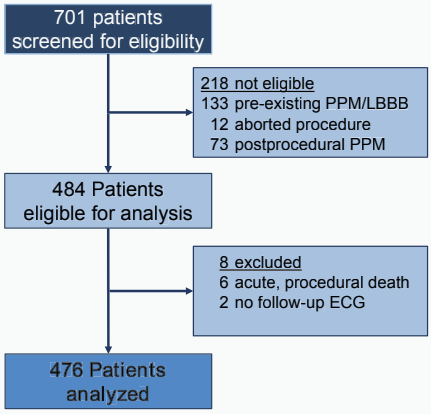

Figure 1. Study Population.

Abbreviations: PPM: permanent pacemaker; LBBB: left bundle branch block.

Objectives & data collection

The primary objective was to assess the changes in intraventricular conduction by comparing the 12-lead ECGs at baseline, within 24 hours, before discharge and 12 months after TAVI. ECG tracings were stored digitally in either the portable document (PDF) or Joint Photographic Experts Group (JPEG) format, depending on availability per patient and center. All tracings were analyzed by an experienced cardiologist (PH) to record heart rhythm, PR interval, QRS duration, QRS morphology and QRS axis in exact degrees. Digital files were zoomed to 800% to measure intervals and duration. Presence of first, second or third degree atrioventricular block, right bundle branch block (RBBB), LBBB, left anterior hemiblock (LAHB) and left posterior hemiblock (LPHB) were recorded according to the established criteria[17]. Accordingly, LBBB was defined as a V1-negative QRS-complex of ≥0.12 seconds in duration with absent Q-waves and a notched or slurred R in leads I, aVL, V5 and/or V6. A LAHB was defined as a QRS-duration ≥0.10 seconds with a frontal plane QRS-axis between –45 and –90 degrees in

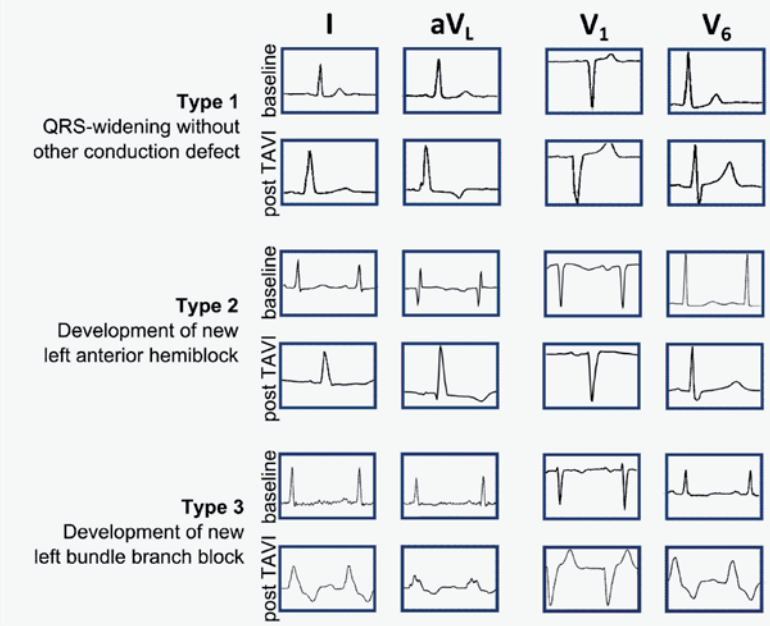

Figure 2. Examples of changes in QRS-duration and/or morphology

Illustration of different patterns of change in QRS-duration and/or morphology after TAVI. Type 1 indicates QRS-widening >120 msec without distinct conduction defect and type 2 and 3 are an example of new LAHB en new LBBB, respectively. Although there is a significant widening (>30 msec) of the QRS complex in type 1, this should not be considered a new LBBB.

the presence of a qR in leads I and aVL. In the presence of RBBB, LAHB was defined as a frontal plane QRS-axis between –45 and –90 degrees. Finally, a significant change in QRS duration was defined as an absolute change of more than 30 milliseconds (msec), based on reported interobserver variability of measured QRS duration[18]. Examples of the ECG interpretation are shown in Figure 2.

The occurrence of and recovery from LBBB was studied by comparing ECGs between the different time points. Distinction was made between a*cute LBBB* (onset within 24 hours after TAVI), *subacute LBBB* (onset after 24 hours but before discharge) and *late LBBB* (onset after discharge). In addition, *persistent LBBB* was defined by any LBBB that is present 12 months after TAVI and *transient LBBB* in case a new-LBBB resolved within 12 months. In patients who died before 1 year follow-up (n=50; 10.5%) and in those without an ECG at 1 year after TAVI (n=34; 7.1%), the last available ECG was used for classification of transient or persistent LBBB. The secondary objective was to

compare mortality between patients with temporary, persistent and no LBBB. Mortality was checked by contacting the Civil Registry in the Netherlands which continuously collects all deaths and cause of all Dutch citizens and inhabitants of the Netherlands. For the Canadian study population, mortality was checked by contacting the referring physician or general practitioner.

Statistical analysis

Categorical variables are presented as numbers and proportions. For continuous variables, normality of distribution was assessed with the Kolmogorov-Smirnov test. Normal and skewed continuous variables are presented as means with standard deviation (SD) and medians with interquartile range (IQR), respectively. Baseline variables between patients without a new LBBB, and patients with transient LBBB or persistent LBBB after TAVI were compared using repeated measures analysis of variance (ANOVA) in case of a continuous measurement. Binary logistic regression analysis was used to compare categorical variables. Where applicable, variables were compared using the unpaired t-test or Mann-Whitney U test for normal and skewed continuous variables, respectively. Categorical variables were compared using the Pearson Chi-Square test. Survival was estimated using the Kaplan-Meier method. Log-rank testing was used to compare differences in survival between patients without, with transient and with persistent LBBB. Survival was also compared between patients with persistent and patients without persistent LBBB (i.e. patients with transient or no LBBB) using both log-rank testing and Cox regression analysis. In addition, Kaplan Meier estimates of survival were also constructed for patients who received a PPM after TAVI. A two-sided p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS), version 20 (IBM SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics and procedural details of the study population of 476 patients eligible for analysis (Figure 1) and of those with a transient and persistent LBBB (Figure 3) are shown in Table 1. Overall, there was an almost even distribution of both devices (MCS in 223 patients or 46.8%; ES in 253 patients or 53.2%). The majority of patients (301 or 63.2%) underwent transfemoral TAVI and 168 (35.3%) underwent transapical TAVI. There were 175 patients (36.8%) who developed a new LBBB that occurred within 24 hours after TAVI (acute LBBB) in 150 patients (31.5%), >24 hours but before hospital discharge (subacute LBBB) in 21 (4.4%) and after discharge (late LBBB) in 4

Table 1. Clinical characteristics of the study population*

Characteristic	study population (N=476)	no LBBB (n=301)	transient LBBB (n=64)	persistent LBBB (n=111)	p-value
Demographics					
Age – yr	81 (77–85)	81 (76–85)	81 (76–86)	80 (78–85)	0.98
Male gender – no. (%)	208 (43.7)	122 (40.5)	23 (35.9)	63 (56.8)	0.06
Height† – cm	165±10	164±9	163±12	169±8	0.003
Weight† – kg	73±15	72±15	71±15	78±16	0.001
Body Mass Index† – kg/m^2	26.7±4.9	26.5±4.8	26.5±4.3	27.5±5.3	0.14
Body Surface Area† – m^2	1.8±0.2	1.8±0.2	1.8±0.2	1.9±0.2	<0.001
New York Heart Association Class ≥III – no. (%)	384 (80.7)	238 (79.1)	56 (87.6)	90 (81.1)	0.29
Logistic EuroSCORE – %	16.4 (10.1–25.4)	16.1 (10.1–25.0)	17.2 (13.0–27.0)	15.9 (9.2–24.5)	0.80
History of coronary artery disease – no. (%)	252 (52.9)	155 (51.5)	39 (60.9)	58 (52.3)	0.38
Previous myocardial infarction – no. (%)	110 (23.1)	69 (22.9)	18 (28.1)	23 (20.7)	0.53
Previous PCI – no. (%)	136 (28.6)	80 (26.6)	22 (34.4)	34 (30.6)	0.39
Previous CABG – no. (%)	148 (31.1)	90 (29.9)	28 (43.8)	30 (27.0)	0.06
History of cerebrovascular disease – no. (%)	94 (19.7)	62 (20.6)	12 (18.8)	20 (18.0)	0.82
History of peripheral artery disease – no. (%)	122 (25.6)	84 (27.9)	14 (21.9)	24 (21.6)	0.33
History of diabetes mellitus – no. (%)	128 (26.9)	74 (24.6)	16 (25.0)	38 (34.2)	0.14
History of chronic obstructive lung disease – no. (%)	131 (27.5)	73 (24.3)	21 (32.8)	37 (33.3)	0.11
Creatinine – mg/dl	1.10 (0.86–1.41)	1.09 (0.88–1.44)	1.04 (0.86–1.32)	1.19 (0.85–1.57)	0.13
Baseline electrocardiogram					
Sinus rhythm – no. (%)	388 (81.5)	254 (84.4)	51 (79.7)	83 (74.8)	0.08
PR-interval – msec	177 (160–202)	176 (156–202)	170 (159–200)	186 (166–218)	0.04
QRS-duration – msec	96 (86–108)	94 (85–107)	95 (84–106)	98 (88–110)	0.43
QRS-axis† – degrees	12±37	11±38	13±36	15±35	0.56
Baseline echocardiogram					
Left ventricular ejection fraction ≤35% – no. (%)	36 (7.6)	18 (6.0)	7 (10.9)	11 (9.9)	0.23
Aortic valve area – cm^2	0.70 (0.55–0.80)	0.70 (0.56–0.80)	0.66 (0.51–0.80)	0.70 (0.55–0.80)	0.28
Peak aortic valve gradient – mmHg	74 (60–94)	73 (59–90)	70 (61–99)	76 (62–94)	0.08
Aortic valve regurgitation ≥III – no. (%)	85 (17.9)	54 (17.9)	10 (15.6)	21 (18.9)	0.28
Procedural characteristics					
Type of access– no. (%)					<0.001
transfemoral	301 (63.2)	166 (55.1)	44 (68.8)	91 (82.0)	
Transapical	168 (35.3)	131 (43.5)	20 (31.3)	17 (15.3)	
transsubclavian	5 (1.1)	2 (0.7)	0 (0)	3 (2.7)	
Prosthesis type and size – no. (%)					<0.001
Medtronic CoreValve System	223 (46.8)	103 (34.2)	33 (51.6)	87 (78.4)	
26 mm	76 (16.0)	39 (13.0)	12 (18.8)	25 (22.5)	
29 mm	147 (30.1)	64 (21.3)	21 (32.8)	62 (55.9)	
Edwards SAPIEN	253 (53.2)	198 (65.8)	31 (48.4)	24 (21.6)	
20 mm	1 (0.2)	1 (0.3)	0 (0)	0 (0)	
23 mm	153 (32.1)	121 (40.1)	21 (32.8)	11 (9.9)	
26 mm	94 (19.5)	72 (23.9)	10 (15.6)	12 (10.8)	
29 mm	5 (1.1)	4 (1.3)	0 (0)	1 (0.9)	

Results are presented as median (interquartile range) or absolute number (percentage), unless stated otherwise. † Height, weight, body mass index, body surface area and baseline QRS axis are presented as mean±SD. Abbreviations: PCI: Percutaneous Coronary Intervention; CABG: Coronary-Artery Bypass Grafting.

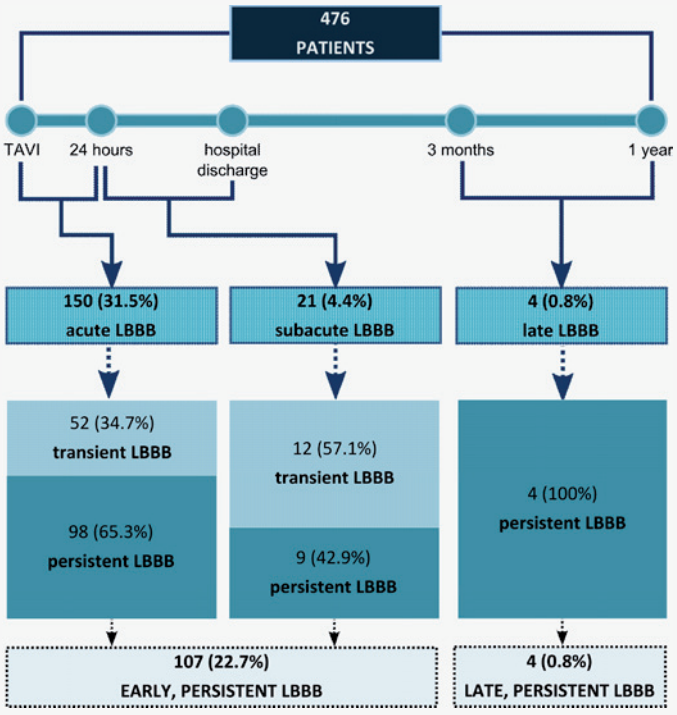

Figure 3. Frequency, timing and persistence of TAVI-induced, new LBBB

Abbreviations: LBBB ; left bundle branch block.

patients (0.8%) (Figure 2). At 12 months, TAVI-induced new LBBB was persistent in 111 out of 175 patients (63.4%) and transient in 64 (36.6%). ECG details are shown in Table 2. A new LAHB was the second most frequent ventricular conduction disorder and occurred in 17.2% (n=76) out of the 442 patients without LAHB at baseline and was persistent in 57 (75%). A new RBBB occurred in 12 patients (2.7%) without baseline RBBB (n=446). Most conduction disorders occurred before discharge. A new LBBB, LAHB and RBBB occurred during follow-up in 4, 7 and 1 patient(s), respectively.

By univariate analysis, a new LBBB occurred more frequently after MCS than after ES valve implantation and was also more often persistent (53.8% and 39.0% for MCS versus 21.7% and 9.5% for ES, respectively; $p<0.001$) (Table 1 and 3). As the transfemoral route is associated with MCS implantation, this access route was also more frequent in patients who developed new LBBB. Yet, a new LAHB was more frequent after ES valve implantation (27.5% versus 5.3%; $p<0.001$) that was also more often persistent (20.3% versus 4.4%; $P<0.001$).

Table 2. Comparison of electrocardiographic characteristics at baseline, within 24 hours after procedure, before discharge and at long-term follow-up*

Characteristic	Baseline	Post procedure	At discharge	12 months
time postprocedure – days (IQR)	–	0 (0–0)	4 (3–8)	366 (304–378)
ECG's analyzed – no.	476	468	467	392
missing ECG – no. (%)	0 (0)	8 (1.7)	9 (1.9)	84 (17.6)
no comparison ECG available – no. (%)	0 (0)	8 (1.7)	15 (3.2)	89 (18.7)
Rhythm – no. (%)				
Sinus rhythm	388 (81.5)	362 (77.4)	355 (76.0)	307 (78.3)
Atrial fibrillation/flutter	87 (18.3)	91 (19.4)	107 (22.9)	78 (19.9)
Ventricular pace	0 (0)	6 (1.3)	2 (0.4)	7 (0.1.7)
Other	1 (0.2)	9 (1.9)	3 (0.6)	0 (0)
PR-interval – msec	177 (160–202)	182 (160–210)	187 (160–220)	184 (160–210)
QRS-duration – msec	96 (86–108)	120 (100–145)	115 (100–144)	110 (95–136)
QRS-axis – degrees	12±37	–2±46	0±43	–2±45
Conduction disorders – no. (%)				
First-degree AV block	81 (17.0)	97 (20.8)	120 (25.9)	91 (23.3)
Second-degree AV block	0 (0)	1 (0.2)	1 (0.2)	0 (0)
Third-degree AV block	0 (0)	8 (1.7)	4 (0.9)	4 (1.0)
RBBB	17 (3.6)	14 (3.0)	17 (3.6)	7 (1.5)
LAHB	21 (4.4)	68 (14.5)	57 (12.2)	50 (12.8)
RBBB & LAHB	13 (2.7)	21 (4.5)	18 (3.9)	18 (4.6)
LBBB	0 (0)	150 (31.5)	134 (28.7)	89 (22.7)
Unspecified	2 (0.4)	9 (1.9)	4 (0.9)	6 (1.5)
Change in conduction disorders – no. (%)				
New RBBB	–	8 (1.7)	3 (0.6)	1 (0.2)
New LAHB	–	64 (13.4)	5 (1.1)	7 (1.5)
New LBBB	–	150 (31.5)	21 (4.4)	4 (1.0)
Recovery from RBBB	–	–	3 (0.6)	5 (1.1)
Recovery from LAHB	–	–	19 (4.0)	0 (0)
Recovery from LBBB	–	–	34 (7.1)	30 (7.7)

Abbreviations: IQR: Interquartile Range; ECG: ElectroCardioGram; AV: AtrioVentricular; RBBB: Right Bundle Branch Block; LAHB: Left Anterior Hemi Block; LBBB: Left Bundle Branch Block.

Outcome (mortality at follow-up)

Median follow-up was 898 (592–1,183), 944 (691–1,321) and 914 (268–1,333) days in patients without, with temporary and with persistent LBBB, respectively (P=0.08). Mortality at 1 year was 17.3% (n=52), 6.2% (n=4) and 27.0% (n=30) in patients

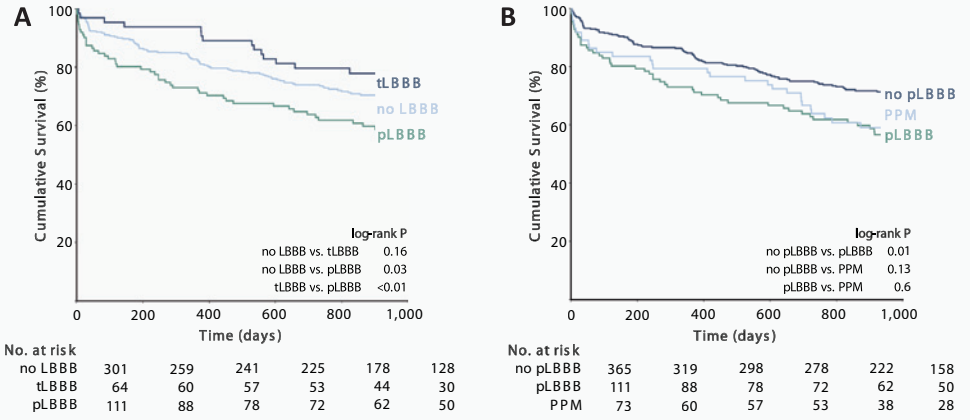

Figure 4. Kaplan-Meier survival estimate of patient without, with temporary and with persistent LBBB

Panel A compares survival between patients without, with temporary and with persistent LBBB. **Panel B** compares survival between patients with persistent and without persistent LBBB. The survival curve of patients who received a permanent pacemaker within 30 days is also shown (dashed line). Comparison was made using the log-rank test. "No LBBB" denotes patients without left bundle branch block (LBBB) induced by transcatheter aortic valve implantation (TAVI), "tLBBB" patients with temporary LBBB and "pLBBB" patients with persistent LBBB.

without LBBB, with temporary LBBB and with persistent LBBB, respectively and was 38.2% (n=115), 31.2% (n=20) and 53.2% (n=59) at total follow-up (Figure 4 – panel A). When comparing patients with persistent LBBB and patients without persistent LBBB (i.e. combining patients without LBBB and patients with temporary LBBB), mortality at total follow-up was 37.0% (n=135) and 53.2% (n=59) for patients without and with persistent LBBB, respectively (Figure 4 – panel B). By univariate regression model, the hazard of mortality was 1.49 (95% confidence interval, 1.10–2.03; P=0.01). In total 73 patients received a PPM within 30 days after TAVI in whom the mortality at total follow-up was 47.9% (n=35) (Figure 4 – panel B). The indication of PPM after TAVI was total atrioventricular block in the majority of patients (75.3%; n=55) and 19.2% (n=14) had LBBB in the postprocedural period before PPM implantation.

DISCUSSION

This study demonstrates that approximately 40% of patients develop a new LBBB after TAVI of which most persists at follow-up. A new LBBB occurs 2.5 times more often after MCS than after ES valve implantation and is also associated with less recovery. Persistent LBBB is associated with a worse prognosis (i.e. higher mortality

during follow-up). These findings contribute to better insight into the occurrence, persistence and consequence of TAVI-induced LBBB. Acknowledging the absence of direct comparisons between different valves, a consistently higher frequency of new LBBB has been reported after MCS (29-65%) than after ES valve implantation (4-18%)[11,19-21]. Given the differences in design, mode of implantation and action, the difference between both valves is plausible but does not explain the variation in LBBB frequency of each valve separately[6]. This variation may be in part due intrinsic features of observational research and variations and difficulties in the application of diagnostic criteria of LBBB as illustrated in Figure 2[22]. We also believe that –in addition to the morphologic ECG criteria– the timing of occurrence (within 24 hours, before and after hospital discharge) and recovery of new LBBB should be considered as demonstrated by Urena et al and by the present study[5]. The present study does not allow elucidating whether the prognosis in case of a persistent LBBB differs between MCS and ES implantation. A difference in mortality is conceivable, given the lesser recovery of the conduction abnormality after MCS implantation but remains to be proven. The sample size of present study, however, does not allow a valid analysis of an eventual different prognostic effect between both valves. At variance with observations in a smaller series –in which a lower frequency and degree of persistence of new LAHB was reported– we found that new LAHB occurred more often and persisted more after ES valve than after MCS valve implantation[21,23]. The difference in new LAHB between both valves may be explained by the fact that a much higher number of patients have a new (complete) LBBB after MCS valve implantation. While new LBBB is known to be associated with a decrease in left ventricular function, a higher risk of complete AV block and impaired survival, the prognostic effects of a new LAHB after TAVI remains to be established[24,25].

In concordance with a previous observation revealing a higher mortality in patients with a LBBB after TAVI at discharge, we presently found a higher mortality during follow-up in patients with a persistent new LBBB[4]. These results are supported by a recent study, showing that mortality after TAVI increases with increasing QRS-duration[26]. In conflict with these studies, however, a recent Italian multicentre registry showed no difference in mortality between patients without and with new LBBB on the ECG before hospital discharge[27]. This discrepancy between studies may be explained by differences in baseline risk of the study population, the application of diagnostic ECG criteria and differences in the degree of persistence of new LBBB. Therefore, prognostic factors other than LBBB may have played a more dominant role in the outcome of these patients. Furthermore, it is conceivable that an adverse prognostic effect is only seen in patients with a persistent LBBB. We found that up to 35% of LBBB recovers at follow-up. A difference in the degree of persistence between present and the Italian study

population may also explain the discrepancy. Registries comparing both the MCS and the ES prosthesis in large patient populations (U.K. TAVI, FRANCE 2, PRAGMATIC) did not find a difference in 1-year mortality[28–30]. Rate of postprocedural PPM implantation, however, was approximately 3 times higher for the MCS valve. These patients are protected from brady-arrhythmias thus influencing outcome.

The nature of the present study does not allow us to establish the cause of death or reason why patients with a persistent LBBB after TAVI suffer from an increased mortality. The increased risk of death in these patients may be explained by dyssynchrony-induced heart failure which may in particularly have negative effects in elderly and hypertrophic hearts. TAVI-induced LBBB has been reported to be associated with decrease in LV ejection fraction (LVEF) similar to the adverse effects of LBBB in patients or individuals with and without cardiovascular disease[5,7,8,31]. Of note, a recent study reported a substantial increase in hospitalization of patients with a moderate increase in QRS-duration indicating that decreased cardiac performance was the cause of clinical deterioration[26]. The prognostic effects of LBBB is further underscored by observations in a wide spectrum of patients with and without cardiovascular disease and the fact that after cardiac resynchronization therapy a reduction of 53% in both mortality and heart failure is seen in LBBB patients[32,33]. Another potential cause of death may be progression to complete heart block as has been demonstrated in patients with LBBB after surgical aortic valve implantation[34]. Survival of patients with new PPM is intermediary between survival of patients with and without persistent LBBB. This may be explained by the fact that these patients are protected from brady-arrhythmic death, but not from dyssynchrony-induced heart failure.

LIMITATIONS

The main limitation of the study is its observational nature and does therefore not provide full insight into the pathophysiology of the observations. For instance, depth of implantation was not included, which is known to play an important role in LBBB development[5,19,20]. This, in addition to the number of patients precluded a multivariate analysis for assessment of predictors of both transient and persistent new LBBB. Echocardiographic data were not systematically available which precluded the assessment of the influence of LBBB on left ventricular function. Although the ECG's were analysed by an experienced cardiologist (PH) using established criteria of conduction disorders, independent CoreLab analysis was not performed. Median follow-up of present study was approximately 2.5 years. The cause of mortality is

manifold. Therefore, analysis of mortality in larger populations with longer follow-up may help to increase understanding of the prognostic effects of new persistent LBBB after TAVI.

CONCLUSIONS

TAVI-induced new LBBB occurs in almost 40% of patients of which most occur before hospital discharge. It occurs 2.5 times more frequent after MCS than after ES valve implantation and has a twofold lower tendency to resolve. Late new LBBB occurs rarely. Persistent LBBB is associated with a higher mortality.

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CHAPTER 13

Left bundle-branch block induced by Transcatheter aortic valve implantation increases risk of death

Houthuizen P, Van Garsse LA, Poels TT, de Jaegere P, van der Boon RM, Swinkels BM, Ten Berg JM, van der Kley F, Schalij MJ, Baan J Jr, Cocchieri R, Brueren GR, van Straten AH, den Heijer P, Bentala M, van Ommen V, Kluin J, Stella PR, Prins MH, Maessen JG, Prinzen FW.

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ABSTRACT

Background

Transcatheter aortic valve implantation (TAVI) is a novel therapy for treatment of severe aortic stenosis. Although 30% to 50% of patients develop new left bundle branch block (LBBB), its effect on clinical outcome is unclear.

Methods and Results

Data were collected in a multicenter registry encompassing TAVI patients from 2005 until 2010. The all-cause mortality rate at follow-up was compared between patients who did and did not develop new LBBB. Of 679 patients analyzed, 387 (57.0%) underwent TAVI with the Medtronic CoreValve System and 292 (43.0%) with the Edwards SAPIEN valve. A total of 233 patients (34.3%) developed new LBBB. Median follow-up was 449.5 (interquartile range, 174–834) days in patients with and 450 (interquartile range, 253–725) days in patients without LBBB (P=0.90). All-cause mortality was 37.8% (n=88) in patients with LBBB and 24.0% (n=107) in patients without LBBB (P=0.002). By multivariate regression analysis, independent predictors of all-cause mortality were TAVI-induced LBBB (hazard ratio [HR], 1.54; confidence interval [CI], 1.12–2.10), chronic obstructive lung disease (HR, 1.56; CI, 1.15–2.10), female sex (HR, 1.39; CI, 1.04–1.85), left ventricular ejection fraction ≤50% (HR, 1.38; CI, 1.02–1.86), and baseline creatinine (HR, 1.32; CI, 1.19–1.43). LBBB was more frequent after implantation of the Medtronic CoreValve System than after Edwards SAPIEN implantation (51.1% and 12.0%, respectively; P<0.001), but device type did not influence the mortality risk of TAVI-induced LBBB.

Conclusions

All-cause mortality after TAVI is higher in patients who develop LBBB than in patients who do not. TAVI-induced LBBB is an independent predictor of mortality.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a relatively new, less invasive treatment for severe, symptomatic aortic stenosis and is advocated as an alternative to conventional surgical aortic valve replacement in patients who do not qualify for surgery. In the latter patient category, the PARTNER trial (Placement of AoRTic traNscathetER valve trial) has demonstrated that TAVI significantly reduces all-cause mortality, repeat hospitalization, and cardiac symptoms compared with standard therapy, including balloon valvuloplasty[1]. For patients at high risk for surgery, survival after TAVI was comparable to that of surgical replacement, albeit with different periprocedural risks[2]. Recent studies state that TAVI can induce cardiac conduction abnormalities, the most frequent one being left bundle branch block (LBBB). The incidence of TAVI-induced LBBB has been reported to vary between 7% and 83% and appears to depend on the device being used[3–6].

Although LBBB may appear to be a fairly harmless side effect in light of valve implantation, LBBB leads to abnormal ventricular contraction and compromised cardiac pump function[7–9]. Clinical studies have shown that LBBB is associated with increased morbidity and mortality in a broad population, which varies from healthy individuals to patients after myocardial infarction to patients with established heart failure[10]. The aim of the present study was to investigate the impact of a new LBBB after TAVI on all-cause mortality in a series of 679 patients who underwent TAVI between November 2005 and December 2010 in 8 centers in the Netherlands.

METHODS

Study Population

All patients who underwent TAVI with either the self-expandable Medtronic CoreValve System (MCS; Medtronic Inc) or the balloon-expandable Edwards SAPIEN valve (ES; Edwards Lifesciences LLC) between November 2005 and December 2010 in any of the 8 participating centers were reviewed. The study population was defined by use of prospectively collected clinical and procedural data that were entered into the dedicated TAVI database of each center. If necessary, additional information was collected retrospectively by analysis of medical records or telephone review.

Study Design

We compared patients who developed new LBBB within 7 days after TAVI with patients who did not. For this purpose, all ECGs before and within 7 days after implantation were collected and reviewed by 2 of the authors (P.H. and T.T.P.) to extract heart rhythm, PR and QRS interval, and QRS axis. Newly developed LBBB was defined as a postprocedural V_1-negative QRS complex with a duration of >120 ms and a notched or slurred R wave in at least 1 of the lateral leads (I, aVL, V_5, V_6), according to established guidelines[11]. As a surrogate for the extent of left ventricular hypertrophy, we measured the amplitude of the R wave in aVL and V_5/V_6, as well as the amplitude of the S wave in V_1, based on the Sokolow-Lyon criteria[12]. An absent Q wave in V_6 was regarded as an indicator of septal fibrosis[13,14].

Exclusion criteria for the study were an aborted procedure without valve implantation, preexisting permanent pacemaker (PPM), or preexisting LBBB. All patients who required postprocedural PPM implantation were excluded from analysis (regardless of whether or not they developed LBBB), because a pacemaker intervention protects against bradyarrhythmic cardiac death, thereby influencing mortality. Moreover, it is known that intrinsic atrioventricular conduction apparently recovers within time, because some patients who have been implanted with a permanent pacemaker do not require ventricular pacing at long-term follow-up[15]. As a result, these patients have intrinsic ventricular activation and do not exhibit the dyssynchronous activation of right ventricular pacing. Cause of death was classified into 3 categories: Cardiovascular, noncardiovascular, and sudden. Death was defined as cardiovascular if it was caused by pump failure (acute or chronic), coronary artery disease, or cerebrovascular disease. The cause of death was categorized as sudden if a patient died suddenly.

Primary Endpoint

The primary end point was all-cause mortality at follow-up and was collected by consulting the Dutch civil registry. This governmental controlled registry contains vital records of the entire population, including date of death.

Statistical Analysis

The primary hypothesis of the present study was that TAVI-induced LBBB affects all-cause mortality of TAVI patients. This idea arose from studies that showed a reduced mortality caused by cardiac resynchronization therapy (CRT) in LBBB patients. For patients with New York Heart Association class I or II, the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) demonstrated a 31% reduction in ventricular tachyarrhythmias or death caused by

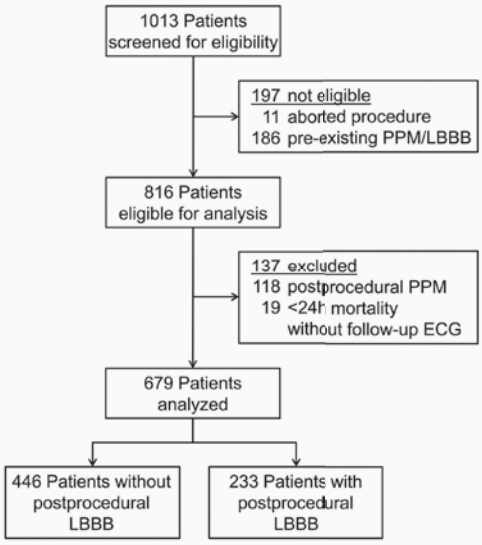

Figure 1. Study population

Categorization in either group was made on the basis of comparison of the preprocedural and ≤7 days' postprocedural ECG. Abbreviations: PPM: permanent pacemaker; LBBB: left bundle branch block.

CRT[16]. Overall 1-year mortality after TAVI in previous reports ranges from 24% to 31%[1,17]. Assuming a 30% incidence of LBBB and a 1-year mortality of 30% and 20% in patients with and without TAVI-induced LBBB, respectively, we estimated that a minimum sample size of 231 patients with new LBBB and 462 patients without would be needed (2-sided α=0.05 and a power of 0.8). Baseline variables were compared between groups. Categorical variables are presented as numbers and proportions and were compared with the Fisher exact test. For continuous variables, normality of distribution was assessed with the Kolmogorov-Smirnov test. Normal and skewed continuous variables are presented as means with SD and medians with interquartile range (IQR), respectively, and were compared accordingly with either an unpaired *t* test or the Mann-Whitney *U* test. A 2-sided probability value <0.05 was considered to be statistically significant. Survival was estimated by the Kaplan-Meier method. The log-rank test was used to compare mortality between patients with and without TAVI-induced LBBB. All variables with $P \leq 0.20$ in univariate Cox regression analysis were entered into a multivariate Cox regression analysis by the enter method to determine the effect of TAVI-induced LBBB, adjusted for other potential predictors of the primary end point. To evaluate whether TAVI-induced LBBB was subject to a learning curve,

Table 1. Baseline and procedural characteristics of patients

Characteristic	Study Population (n=679)	No LBBB (n=446)	New LBBB (n=233)	p-value
Demographics				
Age, y	81 (77–85)	82 (77–85)	81 (78–85)	0.86
Male sex	319 (47.0)	216 (48.4)	103 (44.4)	0.33
Clinical				
Coronary artery disease	319 (47.0)	207 (46.4)	112 (48.1)	0.70
Previous MI	127 (18.7)	91 (20.4)	36 (15.5)	0.12
Previous PCI	193 (28.4)	119 (26.7)	74 (31.8)	0.18
Previous CABG	164 (24.2)	114 (25.6)	50 (21.5)	0.26
Cerebrovascular disease	120 (17.7)	75 (16.8)	45 (19.3)	0.46
Peripheral vascular disease	141 (20.8)	100 (22.4)	41 (17.6)	0.16
Diabetes mellitus	160 (23.6)	94 (21.1)	66 (28.3)	0.04
COPD	178 (26.2)	118 (26.5)	60 (25.8)	0.86
Creatinine, mg/dL	1.07 (0.85–1.38)	1.07 (0.86–1.40)	1.05 (0.81–1.37)	0.60
Logistic EuroSCORE*	16.0 (10.0–25.0)	16.0 (10.0–25.0)	16.0 (10.0–24.5)	0.64
Baseline electrocardiogram				
Sinus rhythm	535 (78.8)	355 (80.0)	180 (77.3)	0.48
PR duration, ms	180 (160–202)	180 (160–202)	180 (160–202)	0.83
QRS duration, ms	98 (89–110)	100 (90–110)	96 (88–106)	0.003
QRS axis, degrees†	14.6±41.6	15.2±43.3	13.4±38.1	0.55
R wave in aVL, mm	7 (3–11)	7 (3–11)	7 (4–11)	0.55
S wave in V_1 plus R wave in V_5 or V_6, mm	27 (20–35)	27 (19–35)	29 (22–35)	0.14
Absence of Q wave in V_6, %	61.8	62.7	61.8	0.84
Baseline echocardiogram				
Maximal aortic valve gradient, mm Hg	74 (60–90)	74 (61–90)	74 (60–93)	0.86
Mean aortic valve gradient, mm Hg	45 (36–57)	44 (35–56)	45 (36–58)	0.54
Aortic valve area, cm^2	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.5–0.8)	0.35
LVEF <50%	190 (28.0)	122 (27.4)	68 (29.3)	0.65
Procedural characteristics				
Medtronic CoreValve System	387 (57.0)	189 (42.4)	198 (85.0)	<0.001
Transapical access	206 (30.3)	180 (40.4)	26 (11.2)	<0.001

Results are presented as median (interquartile range) or absolute No. (percentage), unless otherwise stated.* The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a score system ranging from 0 to 100% used to predict 30-day mortality of cardiovascular surgery. † Baseline QRS axis is presented as mean±SD. Abbreviations: LBBB: Left Bundle Branch Block; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; COPD: Chronic Obstructive Lung Disease; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: Left Ventricular Ejection Fraction.

consecutive patients at each center were ranked according to their entry time into the local TAVI program. Next, patients were grouped into strata of 20 patients according to their ranking number. The sixth and last stratum consisted of case number 100 and higher. Subsequently, data from all centers were combined. The aforementioned ranking and stratification were performed separately for both the MCS and the ES

device. For descriptive purposes, we performed analysis of subsets with and without LBBB with use of the Breslow-Day test for heterogeneity testing. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS), version 17 (IBM SPSS, Chicago, IL).

RESULTS

Study Population

Between November 15, 2005 and December 23, 2010, 1013 patients underwent TAVI in the 8 participating centers in the Netherlands. Not eligible were 197 patients because of an aborted procedure without valve implantation (n=11) and preexisting LBBB or preexisting PPM (n=186). In addition, another 118 patients were excluded because of postprocedural PPM implantation (Figure 1). There were 19 patients who died shortly after implantation, so that no follow-up ECG was available; as a consequence, it was not possible to categorize these patients. Therefore, a total of 679 patients were eligible for analysis. Baseline characteristics of the total study population and of patients with and without TAVI-induced LBBB are outlined in Table 1. Patients were septuagenarians and octogenarians with an almost even sex distribution. Baseline QRS duration was slightly but significantly shorter in patients with TAVI-induced LBBB. On the basis of ECG indices, there was no significant difference in left ventricular hypertrophy or septal fibrosis. All other baseline variables did not differ significantly between groups.

Procedural Outcomes

In 387 patients (57.0%), an MCS device was implanted (valve size 26 mm [n=192] and 29 mm [n=195]), and in 292 patients (43.0%), an ES device was implanted (valve size 23 mm [n=109] and 26 mm [n=183]). Access was transfemoral in 463 patients (68.2%), subclavian in 10 (1.5%), and transapical (ES devices only) in 206 (30.3%). Of the 8 participating centers, 2 implanted both ES and MCS devices, 3 predominantly used MCS, and 3 implanted ES devices. All procedures were performed by experienced and skilled physicians who underwent extensive training for the procedure. In all 679 patients, ECGs at baseline and before discharge were available for analysis. A new LBBB after TAVI occurred in 233 patients (34.3%). In these patients, QRS duration increased from 96 ms (IQR, 88–106 ms) before TAVI to 150 ms (IQR, 140–162 ms) after TAVI ($P<0.001$). Compared with patients without LBBB, those who developed a new LBBB also had a significantly larger increase in PR interval (18 ms [IQR, −2 to 40 ms] versus 0 ms [IQR, −16 to 16 ms], respectively; $P<0.001$).

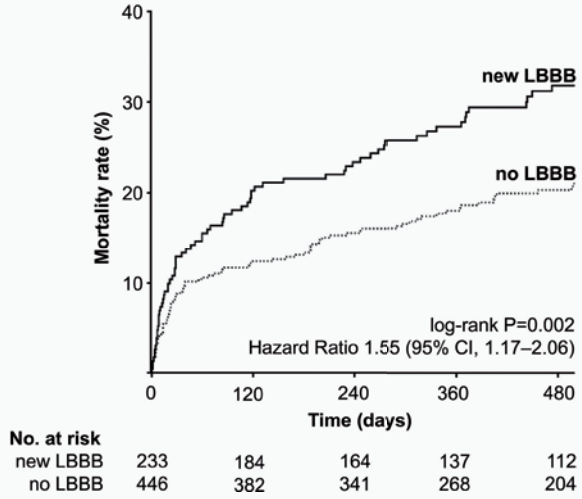

Figure 2. Kaplan-Meier survival curves for the primary end point

"New LBBB" indicates patients who developed left bundle branch block (LBBB) from the transcatheter aortic valve implantation procedure, whereas "no LBBB" indicates patients who did not. Event rates were compared by log-rank test.

Primary Endpoint

Median follow-up was 449.5 days (IQR, 174–834 days) in patients with new LBBB and 450 days (IQR, 253–725 days) in patients without new LBBB (*P*=0.90). At 30 days, the all-cause mortality rate was 12.9% (n=30) in patients who developed new LBBB compared with 8.7% (n=39) in patients who did not (log-rank *P*=0.09). At 1 year after implantation, the end point had occurred in 62 patients with new LBBB (26.6%) and 78 patients without new LBBB (17.5%; log-rank *P*=0.006), which indicates an increment in absolute and relative mortality risk for new LBBB of 9.1% and 52.0%, respectively. During total follow-up, the primary end point of all-cause mortality was reached in 37.8% (n=88) of patients with and 24.0% (n=107) of patients without new LBBB (log-rank *P*=0.002). Kaplan-Meier estimates of survival indicate a continuous worsening of outcome in patients with TAVI-induced LBBB (Figure 2). For the subset of 118 patients excluded from analysis because of PPM implantation, the mortality rate was 4.2% (n=5), 16.9% (n=20), and 28.8% (n=34) at 30 days, 1 year, and total follow-up, respectively.

Determinants of all-cause mortality at total follow-up are shown in Table 2. By univariate analysis, the following variables significantly predicted the end point, in descending order of hazard ratio (HR): Chronic obstructive lung disease (HR, 1.52;

Table 2. Univariate and multivariate Cox-regression analysis of the primary endpoint of all-cause mortality

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% C.I.	p-value	HR	95% C.I.	p-value
Age	0.99	0.97–1.01	0.20			
Female sex	1.52	1.15–2.03	0.003	1.39	1.04–1.85	0.03
Baseline creatinine	1.29	1.18–1.42	<0.001	1.32	1.19–1.43	<0.001
Previous MI	1.24	0.88–1.74	0.23			
Previous CABG	0.95	0.68–1.32	0.75			
Cerebrovascular disease	0.98	0.68–1.41	0.92			
Peripheral vascular disease	1.09	0.77–1.55	0.61			
Diabetes mellitus	1.25	0.91–1.71	0.17	1.21	0.88–1.66	0.25
COPD	1.52	1.13–2.05	0.006	1.56	1.15–2.10	0.004
LVEF ≤50%	1.46	1.09–1.96	0.01	1.38	1.02–1.86	0.03
MCS prosthesis*	1.41	1.05–1.90	0.02	1.13	0.81–1.56	0.48
Transfemoral access	1.03	0.75–1.41	0.86			
TAVI-induced LBBB	1.55	1.17–2.06	0.002	1.54	1.12–2.10	0.007

For calculation of the HR, the MCS prosthesis was compared to the Edwards SAPIEN prosthesis.
Abbreviations: HR: hazard ratio; CI: 95% confidence interval; MI: myocardial infarction; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; MCS: Medtronic CoreValve System; TAVI-induced LBBB: new left bundle branch block induced by transcatheter aortic valve implantation.

95% confidence interval [CI], 1.13–2.05), TAVI-induced LBBB (HR, 1.55; 95% CI, 1.17–2.06), female sex (HR, 1.52; 95% CI, 1.15–2.03), left ventricular ejection fraction ≤50% (HR, 1.46; 95% CI, 1.09–1.96), use of MCS prosthesis (HR, 1.41; 95% CI, 1.05–1.90), and baseline creatinine (HR, 1.29; 95% CI, 1.18–1.42). By multivariate analysis, TAVI-induced LBBB was one of the strongest independent predictors of all-cause mortality (HR, 1.54; 95% CI, 1.12–2.10), together with chronic obstructive lung disease (HR, 1.56; 95% CI, 1.15–2.10), followed by female sex (HR, 1.39; 95% CI, 1.04–1.85), left ventricular ejection fraction ≤50% (HR, 1.38; 95% CI, 1.02–1.86), and baseline creatinine (HR, 1.32; 95% CI, 1.19–1.43).

Descriptive subset analysis showed that the effect of TAVI-induced LBBB on mortality was constant throughout different subgroups, except for chronic obstructive lung disease. The mortality risk of new LBBB was similar in patients who received an MCS or ES device (Figure 3). The cause of death was cardiovascular in 42 patients without TAVI-induced LBBB (39.3%) and in 42 (47.7%) with TAVI-induced LBBB. Death was noncardiovascular in 47 (43.9%) and 31 patients (35.2%) without and with TAVI-induced LBBB, respectively, whereas the cause of death was sudden in 18 (16.8%) and 15 patients (17.0%) without and with new LBBB, respectively. In other words, the cardiovascular mortality rate was 9.4% for patients without and 18.0% for patients with TAVI-induced LBBB (log-rank $P<0.001$), whereas the noncardiac mortality rate

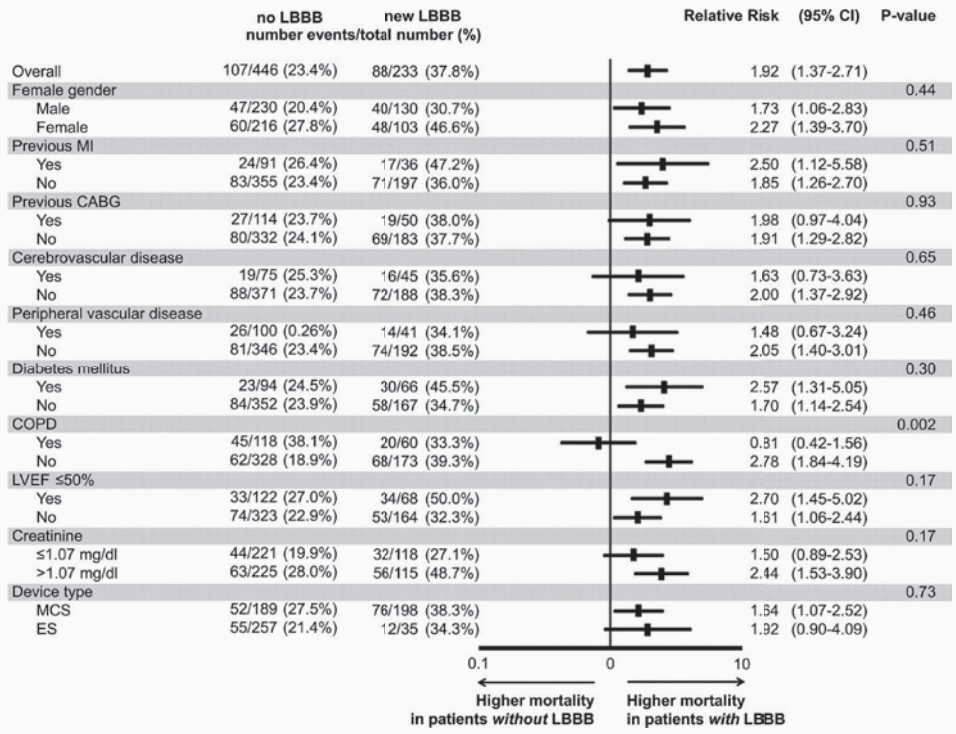

Figure 3. Subset analysis of all-cause mortality

Hazard ratio and 95% confidence interval (CI) are plotted for the primary end point of all-cause mortality at follow-up, comparing patients without (no LBBB) and with (new LBBB) transcatheter aortic valve implantation–induced left bundle branch block (LBBB).
Abbreviations: MI: myocardial infarction; CABG: coronary artery bypass grafting; COPD: chronic obstructive lung disease; LVEF: left ventricular ejection fraction; MCS: Medtronic CoreValve System; ES: Edwards SAPIEN.

was 10.5% and 13.3%, respectively (log-rank *P*=0.20). The mortality rate for sudden death was 4.0% for patients without and 6.4% for patients with TAVI-induced LBBB (log-rank *P*=0.13).

Determinants of TAVI-induced LBBB

A binary logistic regression analysis was performed to identify baseline variables associated with the development of TAVI-induced LBBB. The use of the MCS prosthesis contributed significantly to the occurrence of LBBB in univariate analysis (HR, 7.69; 95% CI, 5.13–11.54). By multivariate analysis, this interaction persisted (HR, 8.51; 95% CI, 5.53–13.11; Table 3).

Table 3. Univariate and multivariate binary logistic regression analysis of TAVI-induced left bundle branch block

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% C.I.	p-value	HR	95% C.I.	p-value
Age	0.87	0.98–1.03	0.87			
Female sex	0.84	0.61–1.16	0.30			
Baseline creatinine	0.85	0.68–1.05	0.14	0.83	0.66–1.05	0.12
Previous MI	0.71	0.47–1.09	0.12	0.78	0.49–1.24	0.29
Previous CABG	0.80	0.55–1.16	0.24			
Cerebrovascular disease	1.18	0.79–1.78	0.42			
Peripheral vascular disease	0.74	0.49–1.11	0.14	1.57	0.97–2.55	0.07
Diabetes mellitus	1.48	1.03–2.13	0.04	1.52	1.01–2.29	0.04
COPD	0.96	0.67–1.38	0.84			
LVEF ≤50%	1.10	0.77–1.56	0.60			
R(aVL) >11 mm	0.87	0.56–1.36	0.55			
$S(V_1) + R(V_{5/6})$ >35 mm	1.01	0.97–1.04	0.72			
Absent Q in V_6	1.05	0.72–1.54	0.79			

* For calculation of the HR, the MCS prosthesis was compared to the Edwards SAPIEN prosthesis.
Abbreviations: TAVI: transcatheter aortic valve implantation; HR: hazard ratio; CI: 95% confidence interval; MI: myocardial infarction; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; MCS: Medtronic CoreValve System.

Comparison of Devices

After MCS implantation, a new LBBB occurred in 198 (51.1%) of 387 patients, as opposed to 35 (12.0%) of 292 patients in whom an ES valve had been implanted (*P*<0.001). Implantation of 26- and 29-mm MCS devices resulted in new LBBB in 95 (49.5%) of 192 and 103 (52.8%) of 195 patients, respectively (*P*=0.54). For the ES device, new LBBB occurred less frequently with 23-mm valves (7 [6.4%] of 109) than with 26-mm valves (28 [15.3%] of 183; *P*=0.03). Table 4 shows the difference in mortality rate between patients with and without LBBB for the entire study population and for subpopulations who received the MCS and ES device. Mortality rate did not differ significantly between MCS and ES for patients with or without TAVI-induced LBBB (log-rank *P*=0.85 and 0.23, respectively). The frequency of LBBB development after MCS implantation decreased with increasing entry time, from ≈60% to ≈40%. Entry time did not affect frequency of LBBB development after ES implantation (Figure 4). In the 2 centers implanting both the MCS and ES devices, the frequency of new LBBB was significantly higher with MCS implantations than with ES implantations (46.7% and 15.9%, respectively; *P*<0.001). In addition, LBBB occurred in 53.7% of cases in the MCS-implanting centers compared with 10.3% of cases in the ES-implanting centers (*P*<0.001). Of the 118 patients who required postprocedural PPM implantation, 102 (86.4%) required the procedure after MCS implantation and 16 (13.6%) after ES implantation. In this patient category, the distribution of the different valve types was

Table 4. Mortality of patients without and with new left bundle branch block for the total study population and for subpopulations receiving each device type

	All	No LBBB	New LBBB
Total study population	195/679 (28.7)	107/446 (23.4)	88/233 (37.8)
Medtronic CoreValve System	128/387 (33.1)	52/189 (27.5)	76/198 (38.4)
Edwards SAPIEN	67/292 (22.9)	55/257 (21.4)	12/35 (34.3)

Values are n/N (%). Abbreviations: LBBB: left bundle branch block.

5.9% (n=7), 7.6% (n=9), 42.4% (n=50), and 44.1% (n=52) for the ES 23-mm, ES 26-mm, MCS 26-mm, and MCS 29-mm valve, respectively.

DISCUSSION

The present study shows that all-cause mortality is significantly higher in TAVI patients who develop LBBB than in TAVI patients who do not. The higher all-cause mortality is largely determined by a significantly higher rate of cardiovascular deaths among patients with LBBB. TAVI-induced LBBB is one of the strongest predictors of all-cause mortality in TAVI patients, and this effect remains after adjustment for all potential confounders. Because the PARTNER trial showed that TAVI reduced all-cause mortality at 1 year by 38% compared with standard therapy, the ≈60% increase in 1-year mortality caused by new-onset LBBB in the present study suggests that the benefit of valve replacement by TAVI is largely neutralized when LBBB develops[1]. In the broader perspective, the strong influence of abnormal conduction on clinical outcome in patients with valvular heart disease indicates that proper impulse conduction and valvular function are approximately equally important for normal cardiac function.

TAVI-induced LBBB as a Risk Factor for Mortality

Previous TAVI-related studies have cited LBBB as a complication but did not mention its possible clinical relevance, because little is known about the impact of LBBB in the setting of valvular heart disease[15,18]. However, multivariate analysis of the present data indicate that TAVI-induced LBBB is an independent and important risk factor for all-cause mortality after TAVI. Although it is not possible to completely exclude that LBBB is a surrogate for another baseline or procedural characteristic, we think that the present data strongly indicate that TAVI-induced LBBB itself is a risk factor for mortality. After all, most baseline characteristics of patients without and with TAVI-induced LBBB were comparable. Notably, in the TAVI-induced LBBB group, there was no higher incidence of left ventricular hypertrophy or septal fibrosis, both of which are known to be associated with a poorer prognosis. There was also no coincidental

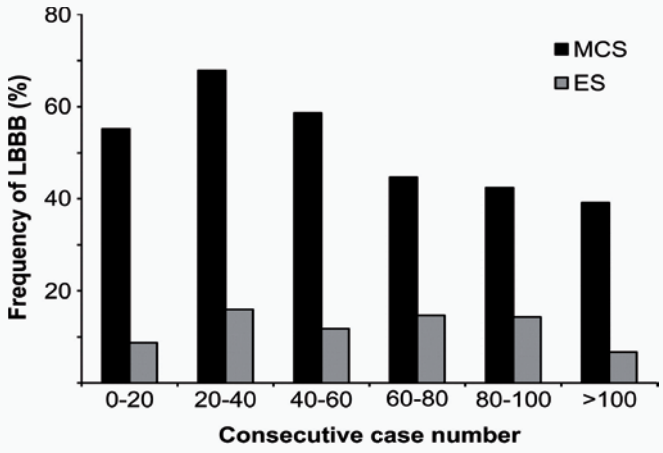

Figure 4. Incidence of transcatheter aortic valve implantation (TAVI)–induced left bundle branch block (LBBB) according to valve type

The percentages of patients who developed a TAVI-induced LBBB are shown for both the Medtronic CoreValve System (MCS) and the Edwards SAPIEN (ES) device. Patients were ranked into 6 different categories according to their entry time into the local TAVI program.

association of TAVI-induced LBBB with a noncardiovascular cause of death. In logistic binary regression analysis, the use of the MCS prosthesis was a potent predictor of new-onset LBBB; however, in multivariate Cox regression analysis for survival, the device type being used did not predict mortality. This paradox can be explained by the fact that TAVI-induced LBBB is the predominant cause of mortality.

Possible Mechanism of Increased Mortality

There are 2 possible explanations for the deleterious effect of TAVI-induced LBBB: The risk of progression to high-degree atrioventricular conduction disorders and the adverse effects of dyssynchrony induced by LBBB. With regard to the latter, this possible effect of LBBB is in concordance with literature on electrocardiology and heart failure management, in which LBBB has increasingly been recognized as an important disorder, especially since the introduction of CRT[10,16]. Moreover, the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial demonstrated that continuous right ventricular pacing (which results in a left ventricular activation pattern comparable to that of LBBB) increases the combined end point of heart failure hospitalization and death compared with backup pacing only. In that trial with 250 patients in each study arm, the HR for all-cause 1-year mortality was 1.61[19]. Both experimental LBBB and clinical right ventricular pacing lead to an early reduction in cardiac pump function followed by

worsening over time, caused at least in part by left ventricular remodeling[9,20]. Recently, a reduction in left ventricular function has also been observed in TAVI patients shortly after development of LBBB[21]. Timewise similar but directionally opposite changes are known to occur after application of CRT in heart failure patients, in which a rapid improvement in left ventricular function is seen, followed by reverse remodeling and ultimately, reduction in mortality[22–24]. Therefore, a likely cause for the higher mortality after TAVI-induced LBBB is progression of heart failure as a consequence of left ventricular remodeling induced by the abnormal contraction pattern. This hypothesis is supported by the observed larger percentage of cardiovascular deaths that occurred in patients with TAVI-induced LBBB. This is congruent with observations that in chronic right ventricular pacing, heart failure hospitalization occurs more frequently in patients with depressed cardiac function than in patients with normal cardiac function[25]. Except for pump failure, patients who develop dyssynchrony-induced left ventricular dysfunction are also susceptible to ventricular tachyarrhythmias, which could be another possible explanation for the higher mortality in the TAVI-induced LBBB group. In the present study, we were not able to differentiate between different (cardiac) causes of death. However, it is reasonable to presume that in our setting, the significantly higher rate of cardiovascular death after TAVI-induced LBBB was, in a majority of cases, caused by (dyssynchrony-induced) heart failure. Because there was no significant difference in sudden death, it seems less likely that TAVI-induced LBBB is associated with bradyarrhythmias. Future studies are needed to confirm our hypotheses on the mechanisms of increased mortality by TAVI-induced LBBB. In this way, we will be able to choose a cost-effective treatment strategy (eg, pacemaker or CRT implantation) that will improve quality of life, life expectancy, or both in this patient population composed of septuagenarians and octogenarians.

Possible Mechanism of TAVI-induced LBBB

The development of atrioventricular conduction disorders and LBBB observed with aortic valve disease and after TAVI or surgical aortic valve replacement has been explained by the proximity of the atrioventricular node and left bundle branch to the aortic valve[4,26–33]. During the TAVI procedure, pressure of the prosthesis skirt on the membranous septum and the nearby atrioventricular node and left bundle branch may cause conduction disorders[4]. Indeed, it has been demonstrated that LBBB development was predicted by deeper MCS prosthesis implantation[34]. Therefore, another possible cause of death for TAVI-induced LBBB is progression to high-degree atrioventricular block, although a postprocedural new LBBB has not been identified as a risk factor for permanent pacemaker implantation, in contrast to preprocedural LBBB[15].

Comparison of Devices

The present study corroborates data from other studies demonstrating that the incidence of TAVI-induced LBBB is higher for the MCS device than for the ES prosthesis[5,35]. A similar difference was observed for requirement of PPM implantation because of high-degree atrioventricular block, which is also in agreement with previous studies[4,5]. The higher chance of inducing conduction disorders by the MCS device has been attributed to the longer prosthesis skirt of the MCS device[28]. However, recently it has been shown that during MCS implantation procedures, LBBB develops before actual insertion of the valve device in >50% of the cases and that contact of the guidewire or compression of the left ventricular outflow orifice by the dilatory balloon may be responsible for some of the damage to the conduction system[3,6]. For the ES prosthesis, these data are not available. However, there are important differences between the delivery systems (catheters, balloon sizes and shapes) and vascular access route (ie, transapical access, in which there is no need for a curved, stiff guidewire in the left ventricle) that may explain the lower incidence of LBBB in ES implantations. The present data further indicate that the incidence of LBBB in MCS implantations decreases to some extent with increasing experience. Still, even with increasing experience, the frequency of LBBB is 40% for MCS as opposed to <10% for the ES prosthesis. Therefore, education on TAVI should not only be directed to optimal valve repair but also to prevention of LBBB. Clearly, there is a great need for better understanding of the origin of TAVI-induced LBBB to develop better tools to prevent this conduction disorder. Our observation that TAVI-induced LBBB increases the risk of mortality, combined with a >4 times higher incidence of LBBB and PPM implantation with MCS implants, should be taken into consideration when making the choice between currently available devices and when obtaining informed consent from the patient.

LIMITATIONS

The present study is based on a multicenter Dutch registry, with the inherent limitations of such a design. However, this study is composed of consecutive cases over a 5-year period from 8 of 11 TAVI-implanting centers in the Netherlands. To ensure data quality and validity, we chose a hard end point (all-cause mortality). No monitoring board or core laboratory was available for ECG analysis, but we strictly adhered to published guidelines for the diagnosis of LBBB and scored the presence of LBBB without knowledge of the actual outcome of the patient[11]. The mean 30-day all-cause mortality rate in the present study was higher and the 1-year all-cause mortality rate was lower than that of earlier reports, including the PARTNER trial, probably as a result of differences in

logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), patient characteristics, and inclusion and exclusion criteria[1,2,17].

CONCLUSIONS

In patients who develop LBBB after TAVI, all-cause mortality is significantly higher than among patients who do not develop LBBB. The excess in mortality is largely determined by a significantly higher rate of cardiovascular deaths in patients with LBBB. The frequency of LBBB is strongly dependent on prosthesis type; however, the mortality risk when LBBB occurs is equal for both devices. These data indicate that LBBB is a serious complication of TAVI that may strongly attenuate the benefit of this procedure. Further research is warranted to clarify the cause of death and the causal factors for TAVI-induced LBBB.

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CHAPTER 14

Trends in the occurrence of new Left Bundle Branch Block after Transcatheter Aortic Valve Implantation

van der Boon RMA*, Houthuizen P*, Urena M, Poels TT,
van Mieghem NM, Brueren GRG, Altintas S, van Garsse LAFM,
van Domburg RT, Nuis R, Rodés-Cabau J, de Jaegere PPT, Prinzen FW.
* Shared first-autorship

Submitted

ABSTRACT

Background

TAVI-induced new-onset left bundle branch block (TAVI-LBBB) is a frequent postoperative complication. New techniques and increased awareness are focused on the reduction of this conduction abnormality. The aim of the study was to investigate the changes in occurrence of new LBBB after TAVI with the Medtronic CoreValve System (MCS) or Edwards Sapien Valve (ESV) implantation over time.

Methods and Results

Electrocardiograms of 476 patients without pre-procedural LBBB and/or pacemaker were assessed to determine the frequency and nature of TAVI-LBBB. To study the effect of experience, patients were subdivided per center into tertiles based on the number of procedures. Univariate and multivariate logistic regression was used to study predictors of permanent LBBB after TAVI. TAVI-LBBB occurred in 175 patients (36.8%) and significantly decreased over time; from 47.2% to 28.5% (p=0.002). This effect was dependent on the valve type implanted and was only significant after Medtronic CoreValve System (MCS) implantation (MCS:68.3% vs. 53.2% vs. 35.5%,p<0.001 - ESV:24.7% vs. 16.2% vs. 24.0%,p=0.35). The same holds for the depth of implantation (MCS(mm):10.6(3.4-17.8) vs. 8.0(5.1-11.0) vs. 6.9(4.4-9.5), p<0.001 - ESV:4.1(2.4-5.9) vs. 3.3(2.0-4.6) vs. 2.2(0.1-4.3),p=0.21). Multivariate analysis stratified for valve type revealed that cohort was the only significant predictor of permanent TAVI-LBBB in patients undergoing TAVI with the MCS (OR(95% C.I.);0.12(0.02-0.58),p=0.009).

Conclusions

Over time the frequency of LBBB after TAVI decreased significantly. This effect was mainly seen in patients undergoing TAVI with the MCS in parallel to a reduction in the depth of implantation. Patients with ESV had significantly less LBBB of which its frequency showed a trend of further reduction over time.

INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are ineligible or poor candidates for surgical aortic valve replacement (SAVR). In patients who are ineligible for SAVR, TAVI has been shown to be superior to medical therapy in terms of mortality reduction and equally effective in patients who are at high risk for SAVR[1–4]. Yet, the perioperative occurrence of new conduction disorders remains a vexing issue[5]. TAVI-induced new-onset left bundle branch block (TAVI-LBBB) is reported in 29-65% of patients undergoing TAVI with the self-expanding Medtronic CoreValve System (MCS) and in 4-18% of the patients receiving the balloon-expendable Edwards SAPIEN Valve (ESV)[5]. The occurrence of TAVI-LBBB has been reported to be associated with worse long-term outcome, including higher risk of complete atrioventrioventricular block (AVB), new permanent pacemaker implantation (PPI) and mortality[6–12]. As a consequence LBBB has been included as a complication in the Valve Academic Research Consortium Guidelines (VARC-2)[13]. It is conceivable that increased awareness in addition to the insight of the relationship between depth of implantation and new LBBB in conjunction with new delivery systems incorporating more stabile deployment of the valve may have led or will lead to a decreased incidence of new LBBB[14,15]. The aim of the present study was to investigate the changes in occurrence of new LBBB after TAVI in a series of 476 patients undergoing TAVI with the MCS or ESV incorporating a detailed and prospective electrocardiographic assessment.

METHODS

Study Population

The index study population consisted of 701 patients who underwent TAVI between January 2006 and July 2011 with the Medtronic CoreValve System (Medtronic Inc, Minneapolis, MN, USA) or the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences LLC, Irvine, CA, USA) in any of following institutions: Quebec Heart & Lung Institute (n=212); Erasmus Medical Center Rotterdam (n=202), Catharina Hospital Eindhoven (n=173), Maastricht University Medical Center (n=114)[11]. Patients with pre-existing LBBB and/or permanent pacemaker (PPM) before TAVI were excluded from analysis, as well as patients who did not undergo valve implantation (aborted procedure). Patients who received a new PPM within 30 days (n=76) after TAVI were also excluded, since it precludes accurate assessment of eventual LBBB or other conduction disorders. A total of 8 patients (1.7%) died during or shortly after the

procedure resulting in the absence of postprocedural ECG. From another 2 patients (0.4%) there was no follow-up ECG available. After exclusion of these patients, the final total population consisted of 476 patients.
All clinical and procedural data were prospectively collected and entered into a dedicated central database. If necessary, additional information was collected by analysis of medical records. The use of anonymous clinical, procedural and follow-up data for research were in accordance with the institutional policies.

Measurement of Depth of Implantation
To assess the depth of implantation, quantitative angiographic analysis was performed using CAAS 5.9 (Pie Medical, Maastricht, The Netherlands) or MicroDicom 0.8.6 software (MicroDicom, Sofia, Bulgaria) in 3 of the 4 participating centers. In case of ESV calibration was achieved using the length of one vertical strut. The depth of implantation of the frame was defined as the mean of the distance from the nadir of the non-coronary and left coronary sinus to the ventricular edge of the frame. In one center only using the ESV valve (n= 137 pts), depth of implantation was assessed using post-procedural transthoracic echocardiography. Depth was defined as the distance between the hinge point of the anterior mitral leaflet and the ventricular end of the stent valve in the long axis view.

Study Endpoints
The primary endpoint was the occurrence of TAVI-LBBB at discharge ECG. To study the effect of experience, patients were subdivided per participating center into equal tertiles based on the number of procedures, which were pooled to create three "consecutive" cohorts. This method was used to correct for the difference in initiation of the TAVI-programme in each individual center. All standard 12-lead ECGs at baseline, after the procedure, before discharge and 12 months after TAVI were collected and were analyzed by an experienced cardiologist (PH) to record heart rhythm, PR interval, QRS duration, QRS morphology and QRS axis in exact degrees, as described earlier. LBBB was defined as a V1-negative QRS-complex of ≥0.12 seconds in duration with absent Q-waves and a notched or slurred R in leads I, aVL, V5 and/or V6 according to established guidelines. TAVI-LBBB was defined as the occurrence of LBBB at discharge ECG, being either temporary or persistent. Persistent LBBB was defined as LBBB which was present 12 months after TAVI, and transient LBBB as new LBBB resolved within 12 months. In patients who died before one-year follow-up (n=50; 10.5%) and in those without an ECG at one year after TAVI (n=34; 7.1%), the last available ECG was used for classification of transient or persistent LBBB [11].

Statistical Analysis

Categorical variables are presented as frequencies and percentages and, compared with the use of the Pearson Chi Square Test or the Fisher's exact test, as appropriate. Continuous variables are presented as means (±SD) (in case of a normal distribution) or medians (IQR) (in case of a skewed distribution) and compared with the use of analysis of variance. Normality of the distributions was assessed using the Shapiro-Wilks test. To study the independent predictors of permanent LBBB after TAVI logistic regression was performed. All characteristics with a p-value ≤0.10 on univariate analysis and those judged to be clinically relevant were included in the multivariate logistic regression model, taking into account the restricted number of variables. Separate models were constructed to stratify for valve type. A two-sided alpha level of 0.05 was used for all superiority testing. The statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics and procedural details

The overall and cohort-based (Cohort 1 to 3) patient demographics and procedural characteristics are summarized in Table. 1. Except for a decrease in the number of patients with severe symptoms of heart failure (New York Heart Association class III or IV; 89.8% vs. 80.9% vs. 73.9%, p = 0.001), there were no differences in the baseline clinical, electro- and echocardiographic characteristics between the three cohorts. The ESV was used in 253, (53.2%) patients and the MCS in 223 (46.8%). Transfemoral TAVI was the most frequent treatment modality (n=301, 63.2%) followed by transapical (n=168, 35.3%) and subclavian TAVI (n=5, 1.1%). Access strategy did not change over time in the three different cohorts. During the study period there was a significant decrease in median depth of implantation for the total cohort (med (IQR): 6.3 (3.0 - 9.6) vs. 5.4 (2.5 - 8.3) vs. 4.0 (1.3 - 6.7), p<0.001). When stratified for valve type this trend was only significant in patients undergoing TAVI with the MCS (10.6 (3.4 - 17.8) vs. 8.1 (5.1 - 11.0) vs. 6.9 (4.4 - 9.5), p<0.001) (Fig. 1a-c).

Post-procedural ECG

Electrocardiographic details before discharge and at long-term follow-up are depicted in Table. 2. No significant changes were found between the three cohorts on the last ECG before discharge. Follow-up ECG (med (IQR): 366 (304 – 378) days) revealed a trend towards a higher frequency of variable heart rhythms (Other: 0% vs. 0% vs. 2.4%, p = 0.04). There were no differences in PR-interval, QRS-duration or QRS-axis.

Table 1. Clinical characteristics of the study population

Characteristic	Overall n = 476	T1 n = 159	T2 n = 159	T3 n = 158	*p-value*
Demographics					
Age – yr	80.1 ± 6.9	80.7 ± 7.2	79.9 ± 6.5	79.8 ± 7.0	0.41
Male gender – no. (%)	208 (43.7)	63 (39.3)	75 (47.2)	70 (44.3)	0.39
Height† – cm	164.94 ± 9.51	164.05 ± 9.85	165.66 ± 9.09	165.09 ± 9.57	0.31
Weight† – kg	72.8 ± 15.2	71.1 ± 15.4	72.7 ± 14.5	74.7 ± 15.8	0.11
Body Mass Index† – kg/m^2	26.73 ± 4.85	26.33 ± 4.74	26.41 ± 4.60	27.44 ± 5.16	0.08
Body Surface Area† – m^2	1.82 ± 0.22	1.79 ± 0.22	1.82 ± 0.21	1.84 ± 0.22	0.11
New York Heart Association Class ≥III – no. (%)	384 (80.7)	141 (89.8)	127 (80.9)	116 (73.9)	0.001
History of coronary artery disease – no. (%)	252 (52.9)	81 (50.9)	80 (50.3)	91 (57.6)	0.36
Previous myocardial infarction – no. (%)	110 (23.1)	38 (23.9)	40 (25.2)	32 (20.3)	0.56
Previous PCI – no. (%)	136 (28.6)	49 (30.8)	46 (28.9)	41 (25.9)	0.63
Previous CABG – no. (%)	148 (31.1)	41 (25.8)	47 (29.6)	60 (38.0)	0.06
History of cerebrovascular disease – no. (%)	94 (19.7)	33 (20.8)	39 (24.5)	22 (13.9)	0.06
History of peripheral artery disease – no. (%)	122 (25.6)	43 (27.0)	40 (25.2)	39 (24.7)	0.88
History of diabetes mellitus – no. (%)	128 (26.9)	38 (23.9)	38 (23.9)	52 (32.9)	0.11
History of chronic obstructive lung disease – no. (%)	131 (27.5)	48 (30.2)	49 (30.8)	34 (21.5)	0.12
Logistic EuroSCORE – %	16.4 (10.1–25.4)	16.4 (8.5 - 24.3)	14.6 (7.6 - 21.6)	17.4 (9.4 - 25.3)	0.14
Creatinine – mg/dl	1.10 (0.86–1.41)	1.12 (0.82 - 1.41)	1.13 (0.80 - 1.47)	1.07 (0.54 - 1.30)	0.68
Baseline electrocardiogram					
Sinus rhythm – no. (%)	388 (81.5)	125 (78.6)	134 (84.3)	129 (81.6)	0.43
PR-interval – msec	177 (160–202)	176 (151 - 202)	196 (155 - 197)	180 (159 - 201)	0.57
QRS-duration – msec	96 (86–108)	98 (87 - 109)	92 (83 - 101)	94 (83 - 106)	0.10
QRS-axis† – degrees	12 ± 37	15 ± 38	12 ± 37	10 ± 35	0.43

Table 1. Continued

Characteristic	Overall	T1	T2	T3	*p-value*
	n = 476	n = 159	n = 159	n = 158	
Baseline echocardiogram					
Left ventricular ejection fraction ≤35% – no. (%)	36 (7.6)	14 (8.8)	9 (5.7)	13 (9.1)	0.46
Aortic valve area – cm^2	0.70 (0.55–0.80)	0.69 (0.56 - 0.83)	0.70 (0.58 - 0.83)	0.70 (0.58 - 0.83)	1.00
Peak aortic valve gradient – mmHg	74 (60–94)	75 (59 - 91)	76 (59 - 93)	70 (54 - 85)*	0.028
Aortic valve regurgitation ≥III – no. (%)	85 (17.9)	32 / 113 (28.3)	30 / 106 (28.3)	23 / 97 (23.7)	0.70
Type of access– no. (%)					
Transfemoral	301 (63.2)	98 (61.6)	101 (63.5)	102 (64.6)	0.86
Transapical	168 (35.3)	60 (37.7)	59 (35.2)	52 (32.9)	0.67
Transsubclavian	5 (1.1)	1 (0.6)	2 (1.3)	2 (1.3)	0.82
Prosthesis type and size – no. (%)					
Medtronic CoreValve System	223 (46.8)	82 (51.6)	79 (49.7)	62 (39.2)	0.06
26 mm	76 (16.0)	38 (23.9)	23 (14.5)	15 (9.5)	0.002
29 mm	147 (30.1)	44 (27.7)	26 (35.2)	47 (29.7)	0.32
Edwards SAPIEN	253 (53.2)	77 (48.4)	80 (50.3)	96 (60.8)	0.06
20 mm	1 (0.2)	0	0	1 (0.6)	0.37
23 mm	153 (32.1)	43 (27.0)	45 (28.3)	65 (41.1)	0.012
26 mm	94 (19.5)	34 (21.4)	34 (21.4)	26 (16.5)	0.45
29 mm	5 (1.1)	0	1 (0.6)	4 (2.5)	0.07
Depth of Implantation (mm)	6.2 (3.0 – 9.3)	6.3 (3.0 – 9.6)	5.4 (2.5 – 8.3)	4.0 (1.3 – 6.7)	< 0.001
Medtronic CoreValve System	8.7 (5.7 – 11.7)	10.6 (3.4 – 17.8)	8.1 (5.1 – 11.0)	6.9 (4.4 – 9.5)	< 0.001
Edwards SAPIEN	3.3 (1.8 – 4.8)	4.1 (2.4 – 5.9)	3.3 (2.1 – 4.6)	2.2 (0.2 – 4.3)	0.21

Results are presented as median (interquartile range) or absolute number (percentage), unless stated otherwise. † Height, weight, body mass index, body surface area and baseline QRS axis are presented as mean±SD. Abbreviations: PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft.

A total of 175 patients (36.8%) developed a new LBBB after TAVI which was persistent in 111 of 175 patients (63.4) and transient in 64 (36.6%) at a follow-up (med (IQR) of 366 (304 – 378) days. Figure 2 and 3 summarise the frequency of new LBBB at discharge and their respective nature during follow-up. The frequency of TAVI-LBBB, either transient or permanent, significantly decreased over time from 47.2% in cohort 1 to 28.5% in cohort 3 (p = 0.002). After stratification for valve type this effect was driven by patients undergoing TAVI with the MCS (68.3% vs. 53.2% vs. 35.5%, p<0.001, ESV: 24.7% vs. 16.2% vs. 24.0%, p=0.35). The same was found for permanent TAVI-LBBB in the total population (30.8% vs. 24.5% vs. 14.6%, p = 0.003) and in the MCS population (48.8% vs. 40.5% vs. 24.2%, p = 0.011) but not for ESV (11.7% vs. 8.8% vs. 8.3%, p=0.73).

Table 2. Electrocardiographic characteristics before discharge and at long-term follow-up

Characteristic	Overall	T1	T2	T3	*p-value*
Before Discharge					
ECG's analyzed – no.	467	158	156	153	
Rhythm – no. (%)					
Sinus rhythm	355 (76.0)	115 (72.8)	128 (82.1)	112 (73.2)	0.10
Atrial fibrillation/flutter	107 (22.9)	40 (25.3)	26 (16.7)	41 (26.8)	0.07
Ventricular pace	2 (0.4)	0	2 (1.3)	0	0.14
Other	3 (0.6)	3 (1.9)	0	0	0.05
PR-interval – msec	188 (158 - 218)	184 (154 - 214)	186 (161 - 211)	188 (162 - 214)	0.89
QRS-duration – msec	115 (95 - 136)	120 (99 - 141)	110 (88 - 132)	110 (90 - 130)	0.07
QRS-axis – degrees	0.04 ± 43.21	-0.31 ± 46.56	-3.39 ± 41.38	3.88 ± 41.39	186
Long-term follow-up					
ECG's analyzed – no.	392	138	131	123	
Rhythm – no. (%)					
Sinus rhythm	307 (78.3)	108 (78.3)	110 (84.0)	89 (72.4)	0.08
Atrial fibrillation/flutter	78 (19.9)	28 (20.3)	20 (15.3)	30 (24.4)	0.19
Ventricular pace	4 (1.0)	2 (1.4)	1 (0.8)	1 (0.8)	0.82
Other	3 (0.8)	0	0	3 (2.4)	0.04
PR-interval – msec	184 (159 - 209)	186 (90 - 130)	184 (164 - 204)	183 (158 - 208)	0.77
QRS-duration – msec	110 (91 - 130)	110 (90 - 130)	110 (90 - 131)	105 (86 - 125)	0.11
QRS-axis – degrees	-2.17 ± 44.97	-2.26 ± 48.68	-5.14 ± 40.44	1.10 ± 45.33	0.55

Results are presented as mean ± SD, median (interquartile range) or absolute number (percentage).

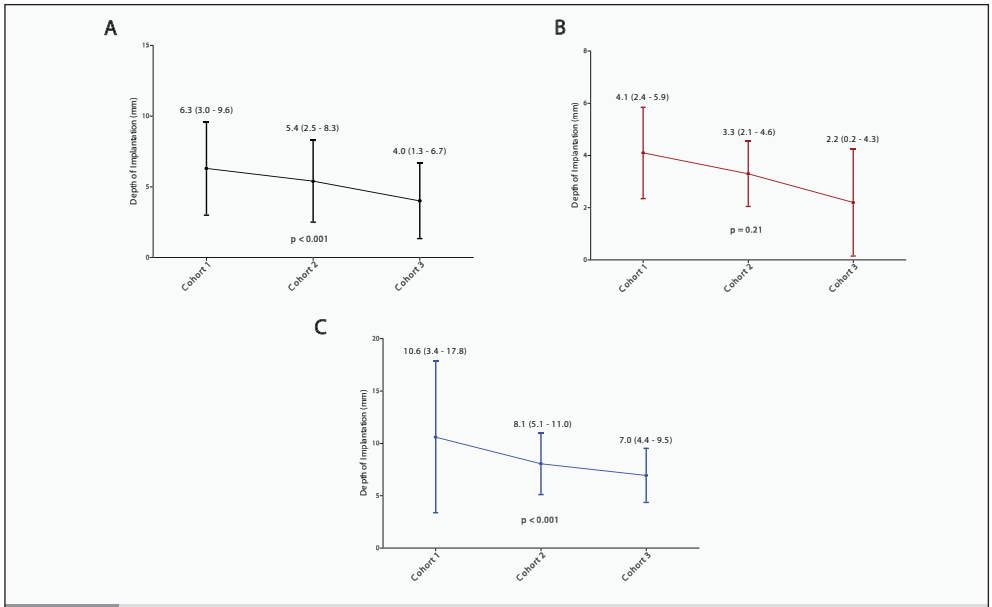

Figure 1. Depth of implantation for the tree separate cohorts in the total (**A**), Edwards SAPIEN Valve (**B**) and Medtronic CoreValve System (**C**) population

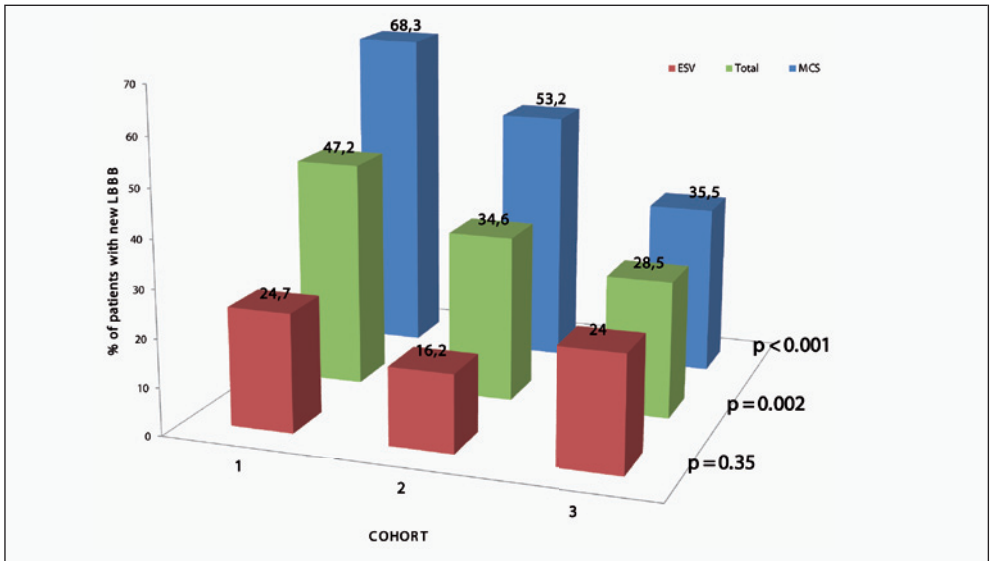

Figure 2. Frequency of new left bundle branch block after TAVI in the three separate cohorts

Green depicts the total population, Red depicts patients undergoing TAVI with the Edwards SAPIEN Valve and Blue patients with the Medtronic CoreValve System.

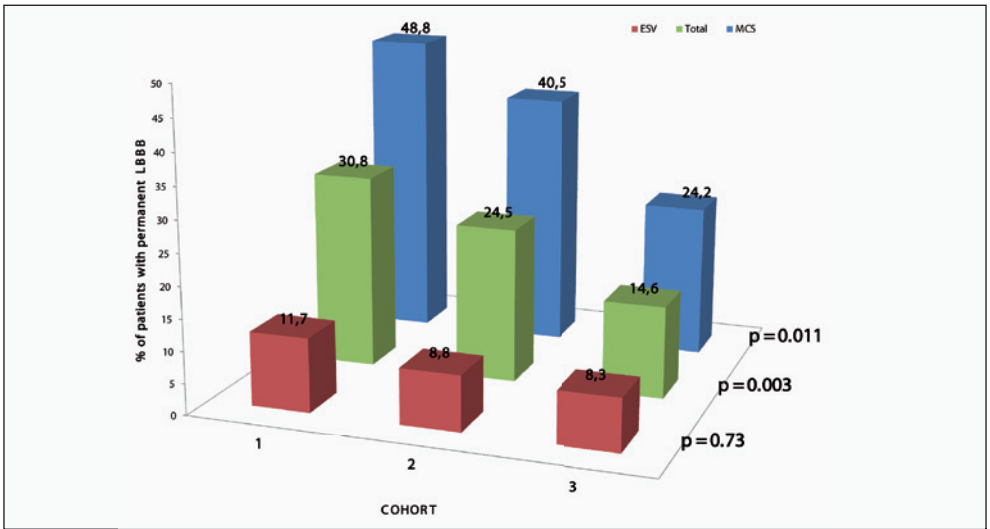

Figure 3. Frequency of permanent left bundle branch block after TAVI in the three separate cohorts

Green depicts the total population, Red depicts patients undergoing TAVI with the Edwards SAPIEN Valve and Blue patients with the Medtronic CoreValve System.

Univariate and Multivariate Analysis

Univariate analysis revealed that age, male gender, body surface area (m2), history of diabetes mellitus, baseline rhythm other than sinus rhythm, PR-interval, QRS-interval, earlier procedure and cohort were associated with an increased risk of permanent TAVI-LBBB ($p<0.10$). The crude and adjusted odds ratios stratified for valve type are shown in Table 3-4. In patients undergoing TAVI with the MCS, cohort was the only significant predictor of permanent TAVI-LBBB (Cohort 3 OR (95% C.I.); 0.12 (0.02 - 0.58), p=0.009). In patients undergoing TAVI with ESV there was no significant difference from cohort 1 to cohort 3 (Cohort 3; OR (95% C.I.): 0.51 (0.05 - 5.50), p=0.58).

DISCUSSION

The main finding of the present study is the reduction of TAVI induced new LBBB over time after both MCS and ESV valve implantation. This was predominantly seen in patients receiving the MCS valve, which is associated by a much higher frequency of new LBBB as reported here and by others [5,10]. Multivariate analysis revealed that cohort was the only independent predictor of a decrease in LBBB over time. In conjunction - but not retained by multivariate analysis - a significant decrease in the depth of implantation

Table 3. Independent predictors of permanent LBBB in MCS patients

Characteristic	Crude OR (95% C.I.)	Adjusted OR (95% C.I.)
Cohort 1	reference	reference
Cohort 2	0.72 (0.38 - 1.33)	0.40 (0.13 - 1.28)
Cohort 3	0.34 (0.16 - 0.69)	0.12 (0.02 - 0.58)
Age – yr	1.00 (0.96 - 1.04)	1.04 (0.98 - 1.10)
Male gender	1.36 (0.79 - 2.34)	1.03 (0.46 - 2.35)
Body Surface Area – m^2	2.70 (0.73 - 10.01)	2.57 (0.37 - 18.15)
History of diabetes mellitus	1.49 (0.80 - 2.77)	1.50 (0.63 - 3.58)
Sinus rhythm	0.71 (0.39 - 1.33)	-
PR-interval – msec	1.00 (0.99 - 1.02)	1.00 (0.99 - 1.01)
QRS-duration – msec	0.98 (0.97 - 1.00)	0.98 (0.95 - 1.00)
Year of Procedure	0.82 (0.64 - 1.04)	1.44 (0.83 - 2.50)

Table 4. Independent predictors of permanent LBBB in ESV patients

Characteristic	Crude OR (95% C.I.)	Adjusted OR (95% C.I.)
Cohort 1	reference	reference
Cohort 2	0.73 (0.26 - 2.05)	0.56 (0.10 - 2.88)
Cohort 3	0.69 (0.25 - 1.87)	0.51 (0.05 - 5.50)
Age – yr	0.99 (0.94 - 1.05)	1.04 (0.96 - 1.31)
Male gender	3.59 (1.47 - 8.74)	2.07 (0.65 - 6.53)
Body Surface Area – m^2	11.55 (1.70 - 78.32)	3.41 (0.22 - 53.59)
History of diabetes mellitus	3.26 (1.38 - 7.65)	4.53 (1.42 - 14.38)
Sinus rhythm	0.78 (0.25 - 2.44)	-
PR-interval – msec	1.01 (1.00 - 1.02)	1.00 (1.00 - 1.02)
QRS-duration – msec	1.01 (0.99 - 1.03)	1.00 (0.97 - 1.03)
Transfemoral access	0.83 (0.33 - 2.09)	0.64 (0.20 - 2.03)
Year of Procedure	0.92 (0.64 - 1.32)	1.13 (0.46 - 2.73)

was observed. These findings underscore that both device- and procedure-related factors play a role in the occurrence of LBBB after TAVI. This is not surprising given the nature of TAVI-LBBB and the close anatomical relationship between the aortic valve and conduction tissue [5]. This in turn may enhance our efforts to further reduce new LBBB by improved patient- and device stratification, continued training and support

and eventually advanced guidance during valve positioning and release. The efforts to reduce new LBBB is supported by the fact that LBBB is associated with interventricular dyssynchrony that in turn may affect cardiac performance, thereby, affecting quality of life and eventually prognosis[6,8,9,11,12,16–18]. With respect to treatment stratification, it reasonable to avoid the MCS valve in patients who have an increased perioperative risk of new LBBB or AV3B. For that purpose, the determinants of perioperative LBBB and the interplay between patient-, procedure-, and device- related factors need to be more clearly established. For instance, one may decide not to use the MCS valve in a patient with a pre-existing RBBB (patient related factor). Yet, the contribution of the procedure/ operator related factors (e.g. sizing, depth of implantation, experience) on top of the contribution of the device itself remains to be elucidated.

The observations of the present study in both valves and the findings of the valve specific multivariate analysis suggests that experience was the overriding factor in the reduction of TAVI induced LBBB. Yet, refinements in valve technology and delivery catheter (e.g. Accutrak system) may have played a role as well[14,15]. The reduction of the depth of implantation over time in both valves, however, is noteworthy and supports the role of experience. In previous reports, the depth of implantation has been reported to be associated with LBBB[8,14,19–24].We were not able to study this effect in a multivariate fashion due to multicolinearity (between depth of implantation and cohort), such a relation (decrease in depth of implantation - reduction in TAVI-LBBB most likely is present. Moreover, we observed that the interquartile range became smaller indicating the effect of experience, improved technology or guidance.

Clinical Implications

In subjects without and with cardiovascular disease, LBBB is associated with an increased cardiovascular morbidity and mortality[24]. In patients who underwent SAVR, postoperative LBBB is associated with syncope, sudden death and permanent pacemaker implantation during follow-up[25–27]. The effects of TAVI-LBBB on late mortality is subject of debate[6–12]. Yet, LBBB post TAVI may progress to complete atrioventricular block, syncope and PPI[7–9,12]. LBBB and PPI are associated with interventricular dyssynchrony which in turn may lead to impaired cardiac performance that has been shown to predict adverse long-term outcome and increased costs[28–31]. Also, LBBB may be associated with impaired left ventricular recovery after TAVI[8,9,32,33]. It is, therefore, plausible that LBBB post TAVI is also associated with increased morbidity and mortality during follow-up similar to the findings in patients and healthy individuals. It should be acknowledged however, that the various studies do not show consistency here: Nazif et al did not find new LBBB at discharge to be associated with increased morbity and

mortality at follow-up, while Houthuizen et al reported increased mortality in patients with persistent LBBB after TAVI (i.e. LBBB at 1 year follow-up ECG)[9,11]. Whereas, Urena et al. found TAVI-LBBB to be a predictor of sudden death and observed a trend towards higher overall mortality in TAVI-LBBB patients[12].
The gradual shift towards younger and less-sick patients highlights, nevertheless, the need to further reduce perioperative complications that may not have an immediate but a long-term effect on cardiac function and well being[34]. As mentioned above, measures such as patient-tailored valve selection, continued training, guidance of valve positioning and refinements in catheter and valve technology may serve this objective[35–37].

LIMITATIONS

This study is observational and is, thus, subject to the limitations to such a study design. Data were analyzed by an expert cardiologist (PH) using established criteria for conduction abnormalities, however, independent Corelab analysis was not performed. The same holds for depth of implantation which was evaluated separately in each center using different techniques. To study the changes over time three cohorts were pooled from each individual center creating three "consecutive" cohorts, however, residual bias in experience might still be possible. Although, this analysis included both clinical, electrocardiographical and procedural predictors of LBBB, we can not preclude the role of hidden bias due to uncollected data.

CONCLUSIONS

Over time the frequency of LBBB after TAVI decreased significantly. This effect was mainly seen in patients undergoing TAVI with the MCS in parallel to a reduction in the depth of implantation. Patients with ESV had significantly less LBBB of which its frequency showed a trend of further reduction over time.

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CHAPTER 15

Clinical Implications of Conduction Abnormalities and Arrhythmias after Transcatheter Aortic Valve Implantation

van der Boon RMA, Houthuizen P, Nuis R,
van Mieghem NM, Prinzen F,de Jaegere PPT.

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has become an established treatment option for patients with aortic stenosis at prohibitive risk to undergo surgical aortic valve replacement. Despite, conveying obvious clinical benefits and a decreasing frequency of complications, the occurrence of new conduction abnormalities and arrhythmias remains an important issue. Generally considered a minor complication, they may have a profound impact on prognosis and quality of life after TAVI. Therefore the purpose of this review is to assess and discuss the available information on clinical implications of both new conduction abnormalities and arrhythmias after TAVI.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become an established treatment option for patients with aortic stenosis who cannot undergo surgical aortic valve replacement (SAVR)[1]. In these patients, TAVI has shown to significantly decrease all-cause mortality, repeat hospitalization and cardiac symptoms when compared to the standard treatment, including medical and invasive therapy[2,3]. For patients at high surgical risk, TAVI has been shown to have a similar outcome compared to SAVR[4,5]. The prospect of treating younger and less sick patients exist in whom the effectiveness and safety of TAVI is currently studied in randomised clinical trials (SUrgical Replacement and Transcatheter Aortic Valve Implantation; SURTAVI and Placement of AoRTic traNscathetER valve-2; PARTNER-2). However, TAVI is associated with a number of vexing complications that need to be resolved. This paper in particular focuses on the frequently encountered problem of conduction abnormalities and arrhythmias after TAVI. Although generally considered benign and correctable, these complications may have profound clinical and economic effects[6–8]. This is among others reflected by the inclusion of these complications in the updated Valve Academic Research Consortium Guidelines (VARC 2) published in 2012[9]. The scope of this review article is to assess the available information on the occurrence, predictors and clinical implications of newly acquired conduction and arrhythmic disorders after TAVI.

LEFT BUNDLE BRANCH BLOCK

New left bundle branch block (LBBB) is reported in 29–65% of patients after the implantation of the self expanding Medtronic CoreValve ® system (MCV; Medtronic CV Luxembourg S.a.r.l., Luxembourg), and in 4–18% of patients receiving the balloon-expandable Edwards SAPIEN ® valve (ESV; Edwards Lifesciences Corporation, Irvine, CA, USA)[10–13]. Considering the cellular architecture of the base of the aortic root and left ventricular outflow tract where these bioprostheses are being implanted, on one hand and the differences in the geometry, physical characteristics and mode of implantations of these valves, on the other, may explain the reported frequencies. Although unproven, the main cause of LBBB after TAVI is presumed to be mechanical injury inflicted upon the atrioventricular conduction tissue. Understanding the (physiological) anatomical relationship between both valve and the surrounding tissue allows the understanding of the pathophysiological mechanism of new arrhythmias, as has been reported previously by our group[10].

The effect of LBBB on clinical outcome, however, remains subject of debate. Clinical studies have shown that LBBB is associated with increased morbidity and mortality in healthy individuals and patients with established heart failure[14]. The latter can be explained by the abnormal activation of the ventricles (i.e. intraventricular dyssynchrony) which may be associated with reduced cardiac function[15–17]. Cardiac function has been shown to be diminished in patients with new LBBB after TAVI[7,18,19]. Yet, the effects on all-cause and cardiac mortality remain equivocal. Houthuizen et al. reported on the outcome of 697 patients undergoing TAVI with both MCS and ESV[6]. Multivariate analysis revealed that new LBBB was associated with a ~55% increased risk of mortality during follow-up. Despite a significantly higher frequency of LBBB after MCS implantation, no association between mortality and valve type was found in the multivariate analysis. In contrast, two observational studies from Italy (on MCS) and Canada (on ESV) found no effect of new LBBB on mortality during follow-up[7,8]. The discrepancy between these studies may be explained by differences in the application of diagnostic criteria for LBBB and ECG assessment. The reported duration of the QRS complex in the Italian registry (lower interquatile range < 130 ms) suggests that some patients, diagnosed with a new LBBB, may in fact not have had LBBB after TAVI. The Italian registry also included patients with new permanent pacemaker > 48 hrs after TAVI and, are therefore, protected from death due to the eventual development of complete AV block or bradycardia during follow-up. Yet, it should be acknowledged that a pacemaker may protect a patient from brady-arrhythmic death, it is still associated with interventricular dyssynchrony. In addition, differences in baseline risk of the populations may have played a role. Patients in the Italian registry had a higher median EuroSCORE than in the other two studies. This means that prognostic factors other than LBBB may have played a more dominant role in the outcome of these patients.

There is little information on the persistence and eventual late development of new conduction abnormalities after TAVI. In the Canadian multi-center study encompassing 202 patients without baseline conduction abnormalities a new LBBB was found in 30.2% (n = 61) of the patients after the implantation of the ESV[7]. At discharge, recovery was observed in 23 (37.7%) of these 61 patients. After six to twelve months of follow-up LBBB had resolved in 12 (48.0%) of the remaining 25 patients with LBBB at hospital discharge. Patients with persistent LBBB at discharge had a higher incidence of syncope (16.0% vs. 0.7%, p = 0.001) and complete atrioventricular block requiring permanent pacemaker (PPM) implantation (20.0% vs. 0.7%, p < 0.001). These results show the need for more elaborate electrocardiographic follow-up of patients with or without new LBBB after TAVI and the need of differentiation between persistent and transient conduction abnormalities. Moreover, it should be studied whether this effect is also seen

after implantation with the MCS which is among other the subject of the multicenter ADVANCE II registry. This information will help to improve recommendations of pacemaker implantation after TAVI in clinical practice, which will be discussed below.

ATRIOVENTRICULAR BLOCK AND PERMANENT PACEMAKER IMPLANTATION

Similar to LBBB, a higher frequency of high degree atrioventricular block (HDAVB; second (AV2B) or third degree (AV3B) atrioventricular block) after TAVI is reported after MCS valve implantation (14 – 44%) than after ESV implantation (0 – 12%) explaining the new PPM implantation in 18 – 49% of the patients after MCS valve implantation and 0 – 12% after ESV implantation[10,20–23]. Although generally considered a minor issue, PPM implantation not only implies an additional intervention that is not free from complications by itself, it may also have physiological effects on cardiac function and, therefore, patient well being. In particular, atrioventricular and interventricular dyssynchrony may alter ventricular hemodynamics, which has been reported to be an independent predictor of adverse long-term clinical outcome in addition to increase in costs[24–31]. Yet, one study in which a new PPM was implanted in 98 out of the 305 patients (32.1%) revealed no difference in clinical outcome at 30-days and 1-year. Interpretation of the available data is not easy, given differences in populations and thresholds for PPM implantation[32]. It might well be that the implantation strategy in this cohort was too liberal which could have led to a population consisting of patient with persistent AVB and patients that recovered from AVB, thus leading to inhibition of pacemaker function[33]. Also, detrimental effects of PPM to cardiac function may only appear during longer-term follow up and therefore may become a particular issue if TAVI technology would move to younger and lower-risk patient populations who have a longer life expectancy.

Careful assessment of patients with new conduction abnormalities and/or new PPM after TAVI may help to improve outcome and patient comfort by patient tailored reduction of ventricular pacing, thereby, sustaining or restoring normal atrioventricular and intraventricular conduction. Also, prolonged right ventricular pacing may induce heart failure as shown in the DAVID trial[34]. Right ventricular pacing induced dyssynchrony is known to increase morbidity and mortality, especially if the patients are paced for > 40% of the time[35]. Noteworthy, a few studies report a reduction of pacemaker dependency after TAVI. One study including 36 out of 167 patients who received a new PPM implantation after TAVI (21.6%) revealed that during a median follow-up of

11.5 months, 20 (55.6%) of the patients were independent of their pacemaker. When specifically assessing the patients with HDAVB (n = 30), 16 (53.5%) were independent during the follow-up visit[36]. This was confirmed by Simms et al. who found that after a follow-up of 8 months only 33.3% of the patients still had a HDAVB[37]. Pereira et al. reported that 3 of the 16 (18.8%) patients who received a new PPM for HDAVB remained pacemaker dependent at follow-up[38]. It must be acknowledged that the studies summarised above concern single center observations in small number of patients with only one time point of PPM assessment after TAVI. These studies do not elucidate at what time after TAVI the patient becomes PPM independent and whether this phenomenon is transient or permanent. Secondly, the findings only pertain to the MCS. The time of PM dependence during follow-up may be explained by the nature and degree of the injury inflicted on the conduction tissue which may lead to either permanent disruption or only peri-procedural edema and inflammation as seen in post-mortem examinations[39].

It is clear that more detailed information in larger series of patients are needed before making sound proposals of criteria for new PPM implantation after TAVI. It should also be acknowledged that in clinical practice logistic problems and the risk of local infections due to the presence of a temporary pacemaker lead may render the application of a watchful waiting policy difficult. Yet, it might be safe to say that a restrictive PPM implantation policy and regular follow-up visits, with readjustments of the pacemaker settings, is recommended. With a growing body of evidence it might be possible to create more absolute indications for PPM implantation after TAVI, as proposed by Fraccaro et al[40]. However, the final decision whether to implant or not a PPM in a patients with a new conduction abnormality should be customized to the individual patient.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common arrhythmia in the general population, characterized by uncoordinated electrical activation of the atria[41]. Its prevalence increases with the age and reaches a frequency > 9.0% in patients aged 80 years or older[42]. AF has been shown to coexist in more than 50% of the patients suffering from aortic stenosis undergoing TAVI[43,44]. Similar to AV and intraventricular conduction abnormalities, AF may affect cardiac performance as a result of the loss of atrioventricular synchrony and atrial kick leading to a reduction in cardiac output and increased ventricular filling pressure[45]. Conversely, aortic stenosis results in left ventricular

hypertrophy and diastolic dysfunction, which itself may lead to the development AF, due to a change in left atrial pressures and dimensions. In addition to the effects on cardiac performance, AF is associated with an increased risk of cerebrovascular events (CVEs) and systemic embolisms (SE) as well as impaired long-term survival compared to the general population[46,47]. The presence of pre-existent AF in patients undergoing SAVR has been associated with mortality, late adverse cardiac events and CVEs[48,49]. The inflammatory response and/or increase in beta-adrenergic tone after thoracotomy and surgical repair of the heart, with concomitant myocardial injury, are responsible for the occurrence of new onset AF (NOAF)[50]. Whereas, the pathophysiological mechanism and effects of AF in the general population and in patients undergoing SAVR have been extensively studied, little is known on the impact of pre-exisiting AF and NOAF in patients undergoing TAVI, especially considering the risk of stroke in this population[51–53]. In both PARTNER studies, AF was present in 41.6% (TAVI 40.8%, SAVR 42.7%) and 40.6% (TAVI 32.9%, medical treatment 48.8%) of the patients. NOAF within 30 days from the procedure was reported 8.6% of the patients who underwent TAVI, which was significantly lower when compared to patients who underwent SAVR (16.0%, $p = 0.006$)[2,4]. The pathophysiologic mechanisms explaining this difference between TAVI and SAVR remain speculative. It may be due to the less invasive nature of TAVI and potentially a lesser inflammatory and adrenergic response to/after TAVI. This - in combination with the reduction of the afterload after TAVI - may explain the observation by Motloch in 84 patients that two-thirds of the patients with pre-procedural AF had a stable sinus rhythm during the first 72-hours after TAVI[54]. Notably, there were no cases with AF after transfemoral TAVI in this study which is somewhat remarkable and deviant from most observations in the literature. Two retrospective studies have reported on the effects of pre-exisiting AF on outcomes after TAVI, reporting a prevalence of 34.0% and 50.0% respectively[55,56]. Whereas, Salines et al. found no effect on prognosis after TAVI, Stortecky et al showed that AF was associated with a 2-fold increase in all-cause and cardiac mortality (and no effect of AF on the risk of stroke and life-threatening bleeding complications). Both studies reported an incidence of 6-7% NOAF after TAVI. Despite careful and complete assessment of patient data, the above mentioned studies did not include extensive rhythm monitoring and could therefore miss short periodes of NOAF after TAVI. Showing substantial evidence for the clinical impact of AF after TAVI, one should be careful in extrapolating data from these studies.

Recently, Amat-Santos et al. reported on 138 consecutive patients with no prior history of atrial fibrillation who underwent TAVI (ESV only) after which patients were under continuous electrocardiogram monitoring until hospital discharge[57]. In this cohort NOAF was encountered in 31% of all cases, of which 36% of the occurred during

the procedure and 27% between the procedure and day 2. A third of NOAF episodes lasted less than 1 h, emphasizing that they are likely to be ignored if not diagnosed using systematic ECG monitoring. Together with left atrial enlargement (OR 1.21, 95% C.I.: 1.09 – 3.04, $p < 0.0001$), the transapical approach (OR 4.08, 95% C.I.: 1.35 – 12.41, $p = 0.019$) was an independent predictor of the occurrence of NOAF. The latter might support the hypothesis that myocardial injury is the underlying factor. Clinically, NOAF was associated with a higher frequency of CVEs and SE after TAVI, but not with an increased risk of mortality. The results of this study will need to be confirmed in larger, prospective cohorts involving both valve systems. Dedicated research in to the mechanisms underlying NOAF might help reducing the frequency of this complication. However, a certain amount will always occur. For these patients it will be necessary to develop uniform guidelines on post-TAVI anticoagulative therapy focused on minimizing the risk of in-hospital bleeding events and CVEs. A recent statement article by Rodes-Cabau et al. may be of guidance to evolve the current concepts[58].

FUTURE PERSPECTIVES

Better understanding of the predictive factors, pathophysiologic mechanisms of the etiology and possible detrimental effects of new conduction abnormalities after TAVI help to formulate changes in valve design, patient selection, procedural planning and execution. Ensuring minimal contact between the valve frame and surrounding tissue may decrease the frequency of conduction abnormalities. This can be achieved by reduction of the height of the frame that extends into the left ventricular outflow tract and, possibly, by minimizing radial force of the frame on surrounding tissue. As mentioned above, little is known about the exact mechanisms of the development of new conduction abnormalities. For instance, it is conceivable that the moment of mechanical contact (and trauma) during implantation play a more dominant role in the onset of these abnormalties than the (continuous) radial force after full expansion of the valve. It remains to be seen whether a fully retrievable valve system, thereby, allowing a correct position with little contact of the frame with the subannular tissue, will be associated with less conduction abnormalities. Also, changes in design to address paravalvular leak may have unwanted effects on the conduction tissue. Increased data from observational studies involving new valve technologies, such as the Direct Flow Medical, Inc (Santa Rosa, CA, USA), Lotus Valve (Sadra Medical Inc., Los Gatos, CA, USA), JenaValve (JenaValve Techonolgy Inc., Delaware, USA)) and Portico System (St. Jude Medical Inc., St. Paul, Minnesota, USA) are becoming available and are showing promising results[59–62]. Moreover, currently available valve technologies are continuously

improving[63,64]. Yet, their effect on the frequency of conduction abnormalities and PPM remain to be established. The incorporation of pre-procedural multimodality imaging for proper balloon and valve sizing algorithms[13,65–67] may help to improve patient-planning and the execution of TAVI. Some advocate performing TAVI without balloon pre-dilatation[68]. This may be feasible in patients with a low calcium load. Yet, the risk of atherosclerotic embolization and stroke need to be clarified[69]. Another solution might be to improve the accuracy and precision of implantation, especially with the MCS given the mode of implantation and anchoring in the aortic root. This can be achieved using novel software, which offers the possibility of tracking the annulus during the procedure, allowing the physician to make tiny adjustments while releasing the valve[70]. Also, extra stability incorporated in novel delivery systems such as the Accutrak System, which is designed for optimal positioning of the MCS. There is some evidence from non-randomised observations that such a system is associated with less PPM implantations[71,72]. The question is to what extent operator experience has played a (confounding) role.

CONCLUSIONS

New conduction abnormalities and subsequent PPM implantation frequently occur after TAVI. Although the body of evidence regarding these complications is growing, their etiology and pathophysiologic and clinical implications remain equivocal. Carefully designed prospective studies might further elucidate the relationship between both and help to further aid in procedural refinements.

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CHAPTER 16

Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System

van der Boon RM, Van Mieghem NM, Theuns DA, Nuis RJ, Nauta ST, Serruys PW, Jordaens L, van Domburg RT, de Jaegere PP.

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ABSTRACT

Background/Objectives

To determine pacemaker (PM) dependency at follow-up visit in patients who underwent new permanent pacemaker implantation (PPI) following Transcatheter Aortic Valve Implantation (TAVI).

Methods

Single center prospective observational study including 167 patients without previous PM implantation who underwent TAVI with the self-expanding Medtronic CoreValve System (MCS) between November 2005 and February 2011. PM dependency was defined by the presence of a high degree atrioventricular block (HDAVB; second [AV2] and third degree [AV3B]), or a slow (< 30 bpm) or absent ventricular escape rhythm during follow-up PM interrogation.

Results

A total of 36 patients (21.6%) received a new PM following TAVI. The indication for PM was AV2B (n = 2, 5.6%), AV3B (n = 28, 77.8%), postoperative symptomatic bradycardia (n = 3, 8.3%), brady-tachy syndrome (n = 1, 2.8%), atrial fibrilation with slow response (n=1, 2.8%) and left bundle branch block (n = 1, 2.8%). Long term follow-up was complete for all patients and ranged from 1 to 40 months (Median (IQR): 11.5 (5.0 – 18.0 months). Of those patients with a HDAVB, 16 out of the 30 patients (53.3%) were PM independent at follow-up visit (complete or partial resolution of the AV conduction abnormality). Overall, 20 out of the 36 patients (55.6%) who received a new PM following TAVI were PM independent at follow-up.

Conclusions

Partial and even complete resolution of peri-operative AV conduction abnormalities after MCS valve implantation occurred in more than half of the patients.

INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are considered at increased risk for surgical aortic valve replacement (AVR)[1–3]. Despite the clinical benefit of TAVI, the occurrence of perioperative new conduction abnormalities and the need for a new permanent pacemaker implantation (PPI) remain a clinical problem. Multiple observational studies consistently demonstrate a higher frequency of new left bundle branch block (LBBB), total (third degree) atrioventricular block (AV3B) and PPI after the implantation of the self-expanding Medtronic CoreValve System (MCS) than after the balloon-expandable Edwards Sapien Valve (ESV)[4]. An altered electrical activation of the heart is not trivial since atrioventricular (AV) and interventricular dyssynchrony may affect left ventricular systolic function[5–11]. Also, subgroup analysis of randomized studies in heart failure patients have shown that QRS-complex duration and morphology constitute independent predictors of adverse long-term clinical outcome[12–15].

AV conduction abnormalities after TAVI may resolve over time[16–20]. Insights into the frequency of PM dependency during follow-up may help refine current decision-making related to PM indication and choice of pacing mode. Therefore, we sought to determine the prevalence of PM dependency during follow-up visit in a series of 167 patients after MCS implantation.

METHODS

Patients and Eligibility

The study population consists of 167 patients with symptomatic aortic valve stenosis and no previous PM implantation who underwent TAVI with the MCS between November 2005 and February 2011. Details of patient selection and planning of the procedure have previously been described. In brief, all patients were first seen at a dedicated out-patient clinic. All underwent a structured interview, physical examination, laboratory assessment, 12-lead electrocardiogram (ECG) and 2D transthoracic echocardiography. If there was an indication for valve replacement, irrespective of the eventual treatment modality, patients underwent a diagnostic coronary angiography and angiography of the ileo-femoral arteries and/or multi sliced computed tomography of the heart and great vessels. Patients were discussed in a dedicated heart team meeting consisting of an interventional cardiologist, imaging specialist, cardiothoracic surgeon and anesthesiologist. Patients were accepted for TAVI by consensus as previously described[21,22].

Table 1. Baseline characteristics of the overall cohort

	Overall n = 167	PPI n = 36	No PPI n = 131	p-value
Demographics				
Age (yrs), mean ± SD	81.0 ± 7.0	82.8 ± 4.8	80.4 ± 7.4	0.027
Male, n (%)	77 (46.1)	19 (53)	58 (44.3)	0.37
Height (cm), mean ± SD	167.11 ± 8.66	168.22 ± 8.21	166.81 ± 8.78	0.39
Weight (kg), mean ± SD	72.79 ± 13.63	71.5 ± 11.1	73.15 ± 14.3	0.51
Body Mass Index, mean ± SD	26.01 ± 4.17	25.24 ± 3.45	26.22 ± 4.34	0.22
Body Surface Area, mean ± SD	1.83 ± 0.20	1.82 ± 0.17	1.84 ± 0.21	0.78
NYHA class III or IV, n (%)	135 (80.8)	29 (80.6)	106 (80.9)	0.96
Logistic EuroSCORE, med (IQR)	13.40 (7.80 -19.01)	14.75 (7.13 - 22.38)	13.10 (8.60 - 17.61)	0.21
Previous cerebrovascular accident, n (%)	35 (21.0)	6 (16.7)	229 (22.1)	0.48
Previous myocardial infarction, n (%)	39 (23.4)	6 (16.7)	33 (25.2)	0.28
Previous CABG, n (%)	40 (24.0)	7 (19.4)	33 (25.2)	0.47
Previous PCI, n (%)	40 (24.0)	4 (11.1)	36 (27.5)	0.042
Coronary artery disease, n (%)	77 (46.1)	11 (30.6)	66 (50.4)	0.035
Diabetes mellitus, n (%)	36 (21.6)	7 (19.4)	29 (22.1)	0.73
Hypertension, n (%)	92 (55.1)	21 (58.3)	71 (54.2)	0.66
Glomerular Filtration Rate < 60 ml/min, n (%)	89 (53.3)	20 (55.6)	69 (52.7)	0.76
Chronic haemodialysis, n (%)	9 (5.4)	2 (5.6)	7 (5.3)	0.96
Chronic Obstructive Pulmonary Disease, n (%)	43 (25.7)	7 (19.4)	36 (27.5)	0.33
Peripheral vascular disease, n (%)	17 (10.2)	8 (22.2)	9 (6.9)	0.007
History of atrial fibrillation, n (%)	40 (24.0)	11 (30.6)	29 (22.1)	0.30
Baseline echocardiogram				
Aortic valve area (cm2), mean ± SD	0.65 ± 0.22	0.59 ± 0.19	0.66 ± 0.23	0.07
Left ventricular ejection fraction, mean ± SD	51.08 ± 14.41	50.31 ± 14.26	51.30 ± 14.50	0.72
Aortic valve annulus (mm), mean ± SD	22.47 ± 2.32	22.35 ± 2.39	22.51 ± 2.30	0.74
Peak velocity, mean ± SD	4.35 ± 0.77	4.20 ± 0.77	4.39 ± 0.76	0.20
Peak gradient (mmHg), mean ± SD	78.56 ± 27.31	73.92 ± 28.98	79.87 ± 26.79	0.25
Mean gradient (mmHg), mean ± SD	46.42 ± 17.06	45.37 ± 18.50	46.72 ± 16.68	0.68
Aortic regurgitation grade ≥ III, n (%)	38 (23.3)	11 (30.6)	27 (21.3)	0.24
Mitral regurgitation grade ≥ III, n (%)	24 (14.7)	6 (17.1)	18 (14.1)	0.65
Baseline electrocardiogram				
Rhythm, n(%)				
Sinus	126 (75.4)	24 (66.7)	102 (77.9)	0.17
Atrial Fibrillation	41 (24.6)	12 (33.3)	29 (22.1)	0.17
Junctional	0	0	0	1.00
Heart Rate (bpm), mean ± SD	71.28 ± 13.50	73.46 ± 15.66	70.70 ± 12.86	0.29
PR interval (msec), mean ± SD	187.77 ± 33.20	194.00 ± 39.11	186.29 ± 31.67	0.31
QRS width (msec), mean ± SD	108.83 ± 24.78	120.26 ± 25.98	105.75 ± 23.62	0.004
QT interval (msec), mean ± SD	416.24 ± 37.73	420.03 ± 51.78	415.22 ± 33.13	0.61
Hemiblock, n(%)				
None	146 (87.4)	30 (83.3)	116 (88.5)	0.40
Anterior	19 (11.4)	5 (13.9)	14 (10.7)	0.59
Posterior	1 (0.6)	0 (0.0)	1 (0.8)	0.60
Bundle Branch Block, n(%)				
None	131 (78.4)	22 (61.6)	109 (83.2)	0.004
Left	14 (8.4)	3 (8.3)	11 (8.4)	0.99
Right	17 (10.2)	11 (30.6)	6 (4.6)	< 0.001
Incomplete Left	5 (3.0)	0	5 (3.8)	0.23
Incomplete Right	0	0	0	1.00

Abbreviations: NYHA: New York Heart Association; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft.

Device, Procedure and Postoperative Care

The MCS valve used in the present population consisted of a 26 or 29 mm MCS of which details have been described before[22]. TAVI was performed via femoral or subclavian artery under local or general anesthesia. In all but 5 patients an 18F sheath was inserted into the femoral or subclavian artery to advance the 18Fr delivery catheter. In the first 5 patients of this cohort a 21 Fr sheathless delivery catheter was used; 4 patients underwent surgical cutdown of the femoral artery and 1 patient underwent a cutdown of the subclavian artery. Valve implantation was preceded by balloon valvuloplasty of the aortic valve using rapid right ventricular pacing at 180 to 220 bpm. The MCS was then implanted under fluoroscopic and angiographic control. After TAVI, patients were extubated before leaving the catheterization laboratory or within 2 hours after arrival in the cardiac care unit (IC/CCU). According to our TAVI protocol, all patients left the catheterization laboratory with a temporary pacemaker lead in the right ventricle for at least 48 hours after the procedure or longer if indicated[23]. All patients received continuous rhythm monitoring until hospital discharge. The decision for PPI was left at the discretion of the treating physician (IC/CCU, ward) after electrophysiology consultation.

Data Collection

Patient demographics, clinical, laboratory and technical (electro- and echocardiography) data were prospectively collected and entered in a dedicated database. Twelve-lead electrographic recordings were obtained before treatment, after treatment and at discharge. The ECGs were analyzed for rhythm, heart rate (bpm), PR, QRS, and corrected QT intervals (all in milliseconds) and the presence of AV block (AV1B, AV2B and AV3B). The guidelines of the World Health Organization and International Society and Federation for Cardiology Task Force were used to determine right- and left fascicular hemiblock and right- and left bundle branch block[24]. The ECG criteria to justify PPI were collected by reviewing the written reports of the treating physician and electrophysiologist. PM dependency at follow-up was prospectively documented in all patients who had received a new PPI during the index hospitalization by comprehensive PM interrogation at the outpatient clinic visit. In case of a paced rhythm, the PM was temporarily turned off or programmed to a VVI modus at 30 bpm to assess underlying electrical activity. Patients were considered pacemaker dependent if a HDAVB (i.e. second degree Mobitz 2 or third degree atrioventricular block) or a slow (< 30 bpm) or absent ventricular escape rhythm was observed. The degree of resolution (complete or partial) was defined by comparing the changes in the AV conduction after PPI (conduction at FU vs. conduction at PPI, table 3) with the AV conduction before TAVI. Partial resolution was defined by an improvement of the AV conduction during follow-up but not to the level of the pre-procedural conduction.

Table 2. Procedural details of the overall cohort

	Overall n = 167	PPI n = 36	No PPI n = 131	p-value
Vascular access, n (%)				
surgical - femoral artery	9 (5.4)	1 (2.8)	8 (6.1)	0.43
surgical - subclavian artery	5 (3.0)	3 (8.3)	2 (1.5)	0.034
percutaneous - femoral artery	153 (91.6)	32 (88.9)	121 (92.4)	0.51
Circulatory support, n(%)				
ECMO	2 (1.2)	0	2 (1.5)	0.46
LVAD	14 (8.4)	4 (11.1)	10 (7.6)	0.51
IABP	1 (0.6)	0	1 (0.8)	0.60
None	150 (89.8)	32 (88.9)	118 (90.1)	0.84
Additional interventions during TAVI, n (%)				
PTA Iliac Artery	4 (2.4)	2 (5.6)	2 (1.5)	0.16
PCI	17 (10.2)	6 (16.7)	11 (8.4)	0.15
Prosthesis size, n (%)				
26-mm*	56 (33.9)	10 (27.8)	46 (35.7)	0.38
29-mm*	109 (66.1)	26 (72.2)	83 (64.3)	0.38
Therapy-specific results, n (%)				
Post-implantation balloon dilatation	22 (13.2)	7 (19.4)	15 (11.5)	0.21
Valve-in-Valve implantation	8 (4.8)	2 (5.6)	6 (4.6)	0.81
Ventricular Perforation, n (%)	1 (0.6)	1 (2.8)	0	0.06
Conversion to surgical AVR	0	0	0	1.00
Depth of implantation (mm), mean ± SD	7.69 ± 3.53	8.11 ± 2.83	7.57 ± 3.71	0.36
Procedure time (min), mean ± SD†	223.54 ± 70.54	233.21 ± 80.34	220.90 ± 67.71	0.36
Amount of contrast (ml), mean ± SD	177.62 ± 83.27	166.83 ± 70.85	180.96 ± 86.77	0.38

* Two patients did not undergo final implantation † Depth of Implanation was defined as the distance from the lower edge of the non-coronary leaflet to the ventricular edge of the frame. Abbreviations: ECMO: Extracorporal Membrane Oxygenation; IABP: Intra-aortic Balloon Pump; LVAD: Left Ventricular Assistance Device; PTA: Percutaneous Transluminal Angioplasty; PCI: Percutaneous Coronary Intervention; AVR: Aortic Valve Replacement.

Statistical Analysis

Categorical variables are presented as frequencies and percentages and, compared with the use of the Pearson Chi Square Test or the Fisher's exact test, as appropriate. Continuous variables are presented as means (±SD) (in case of a normal distribution) or medians (IQR) (in case of a skewed distribution) and compared with the use of Student's T-test or the Mann-Whitney U-test. Normality of the distributions was assessed using the Shapiro-Wilks test. All statistical analyses were performed with SPSS software 17.0 (SPSS Inc; Chicago, Il).

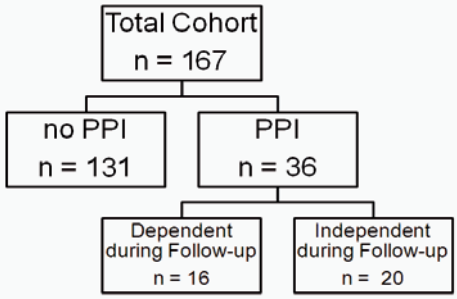

Figure 1. Flowchart of the total cohort

Abbreviations: PPI: Permanent Pacemaker Implantation.

RESULTS

Baseline Characteristics and Procedural details

The baseline characteristics and procedural details of the total population are summarized in Table 1 and 2, respectively. A total of 36 out of the 167 patients (21.6%) without a PM at baseline had PPI following TAVI (Figure. 1). The median time until PPI was 8 days (IQR: 4 – 12 days). Details of the ECG at baseline and after TAVI and, the indication and mode of PPI of these patients are shown in Table 3. In the majority of patients, a new PM was implanted because of a HDAVB (30 patients) of whom 28 because of AV3B and 2 because of AV2B. In 5 patients a new PM was implanted because of bradycardia of whom 4 with a new perioperative LBBB. One patient (patient #3, no 9 in cohort) with preexisting LBBB received an implantable cardioverter-defibrillator (ICD) because of non sustained ventricular tachycardia (VT) with LBBB morphology. The device was programmed with active bradycardia support.

All patients were seen at the out-patient clinic with at median (IQR) follow-up of 11.5 months (IQR: 5.0 – 18.0) after TAVI. Details of the ECG at follow-up and evolution of the conduction after PPI are shown in Table 3. In accordance with the definitions summarized above, 16 patients (44.4%) were still PM dependent. Of the 28 patients who had received a PM because of an AV3B, 11 patients had a complete resolution of the AV conduction abnormality and 3 patients had a partial resolution (first degree atrioventricular block (AV1B) at follow-up) while the remaining 14 patients still had an AV3B and were PM dependent. The 2 patients who had received a PM because of an AV2B had a partial resolution of the AV conduction abnormality towards an AV1B. In the 5 patients who received a PM because of postoperative bradycardia of whom 4

Table 3. Indications for permanent pacemaker implantation

n	number in cohort	ECG				Pacemaker Indication	Pacemaker Type	Follow up		
		Pre-TAVI		Post-TAVI				Dependency	Type of Rhythm	AV Conduction
		Rhythm	Conduction	Rhythm	Conduction					
1	5	SR	Normal	SR	LBBB	AV3B	BiVPM	no	SR	AV1B
2	8	SR	RBBB	SR	RBBB	AV2B	DDD	no	SR	AV1B
3	9	SR	LBBB	SR	LBBB	LBBB	BiVPM	no	SR	Normal
4	14	SR	AV1B + LAFB	AF	AV3B	AV3B	VVI	yes	SR	AV3B
5	24	SR	AV1B + LBBB	SR	AV3B	AV3B	DDD	yes	SR	AV3B
6	30	SR	AV1B + RBBB	SR	AV3B	AV3B	DDD-ICD	no	AF	Normal
7	33	SR	Normal	SR	AV3B	AV3B	DDD	no	SR	Normal
8	47	SR	RBBB + LAFB	SR	AV3B	AV3B	DDD	yes	SR	AV3B
9	54	AR*	Normal	PM	-	AV3B	VVI-ICD	no	SR	AV1B
10	66	AF	RBBB + LAFB	PM	-	AV3B	VVI	no	SR	Normal
11	70	SR	RBBB + LAFB	PM	-	AV3B	DDD	yes	SR	AV3B
12	71	SR	AV1B	SR	AV3B	AV3B	DDD	yes	SR	AV3B
13	73	SR	AV1B + RBBB	SR	AV3B	AV3B	DDD	yes	SR	AV3B
14	75	SR	AV1B	PM	-	AV3B	DDD	yes	SR	AV3B
15	81	AF	LAFB	AF	AV3B	AV3B	VVI	yes	SR	AV3B
16	91	SR	Normal	Nodal Escape / Junctional	AV3B	AV3B	DDD	yes	SR	AV3B
17	92	AF	Normal	AF	LBBB + Brady	Brady	VVI	yes	SR	AV3B
18	95	SR	Normal	Nodal Escape / Junctional	AV3B	AV3B	DDD	no	SR	Normal
19	98	SR	AV1B	SR	AV1B	AV3B	DDD	no	AF	Normal
20	103	AF	RBBB	AF	AV3B	AV3B	VVI	yes	AF	AV3B
21	105	AF	Normal	AF	Normal	Brady-Tachy Syn	VVI	no	AF	Normal
22	106	AF	Normal	AF	LBBB	AF + Slow Resp.	VVI	yes	AF	AV3B
23	118	AF	Normal	AF	AV3B	AV3B	VVI	no	SR	Normal
24	121	SR	Normal	PM	-	AV3B	DDR	yes	SR	AV3B
25	123	SR	LBBB	SR	AV3B	AV3B	DDR	no	SR	Normal
26	131	AF	Normal	AF	LBBB	Brady	VVI	no	AF	Normal
27	135	SR	Normal	SR	AV3B	AV3B	DDD-ICD	no	SR	AV1B
28	141	SR	Normal	PM	-	AV3B	DDD-ICD	no	SR	Normal
29	145	SR	Normal	PM	-	AV3B	DDD-ICD	no	SR	Normal
30	165	SR	RBBB	Nodal Escape / Junctional	AV3B	AV3B	DDD	no	SR	Normal
31	169	SR	RBBB	PM	-	AV3B	DDD	no	SR	Normal
32	170	SR	AV1B	SR	AV2B	AV2B	DDD	no	SR	AV1B
33	173	AF	RBBB	AF	AV3B	AV3B	VVI	yes	AF	AV3B
34	176	SR	Normal	PM	-	AV3B	DDD	yes	AF	AV3B
35	177	AF	Normal	AF	LBBB	Brady	VVI	no	AF	Normal
36	181	AR	RBBB	PM	-	AV3B	DDD	yes	AF	AV3B

Abbreviations: AF: Atrial Fibrillation; AR: Atrial Rhythm; AV1B: First Degree Atrioventricular Block; AV2B: Second Degree Atrioventricular Block; AV3B: Total Atrioventicular Block; Brady: Bradycardia; LAFB: Left Anterior Fascicular Block; LBBB: Left Bundle Branch Block; PM: Pacemaker; RBBB: Right Bundle Branch Block; SR: Sinus Rhythm.

with a new LBBB, the perioperative LBBB evolved towards a AV3B in 2 patients while in 2 other patients there was a complete resolution of the LBBB.

DISCUSSION

The main finding of this study is that more than half of the patients who had received a new PM after MCS valve implantation were not PM dependent when seen at a median time of 12 months (range 5-18) after the procedure. Obviously, these findings need to be interpreted in the context of a single center observational study with a restrictive use of new PPI (21.6% of the patients, predominantly because of a HDAVB) and, more importantly, the assessment of PM (in)dependency at one single time point during the follow-up period. This study, therefore, cannot elucidate at what time after TAVI exactly the patient becomes PM independent and – clinically more pertinent - whether PM independency is a transient or permanent phenomenon. The findings, nevertheless, indicate that recovery of high degree conduction abnormalities may occur after TAVI using the self-expanding MCS valve. At present there is scant information on the evolution of conduction abnormalities after TAVI in general and in patients who received a PM after TAVI. Piazza et al. reported a decrease in QRS duration at 1 month after TAVI with the MCS valve but no significant change in the QRS duration between 1-month to 6 month follow-up[16,17]. The first observation was confirmed by Gutierrez et al. and Fraccaro et al., who observed a significant decrease in QRS duration and new onset LBBB in a time period immediately post TAVI and 1-month with, respectively, the Edwards SAPIEN prosthesis and MCS valve[18,19].

In a study of 70 patients by Guetta et al, 28 patients (40%) received a new PM after MCS valve implantation of whom 25 because of a HDAVB[20]. In this study recovery of HDAVB was seen in 60% of these 25 patients at 3 months. Recovery of AV3B was also reported by Roten et al. in a series of 67 patients who underwent TAVI with both the MCS and Edwards SAPIEN Valve[25]. Complete or partial resolution of AV3B was seen in 64% of patients (7 out of the 11 who received a new PPI after TAVI) at median follow-up of 79 days. Rubin et al., however, reported that the 3 patients with an AV3B after MCS valve implantation for which a PM was implanted remained PM dependent because of the complete AV block at a median time of 16 weeks after the procedure[26]. The true frequency and nature (i.e. transient, permanent) of PM dependency after TAVI remain elusive. Also, it is unknown whether there is a difference in the recovery of conduction abnormalities and PM dependency between the currently available self-expending and balloon expandable devices. This also holds for PM dependency after

AVR and cardiac surgery in general. Merin et al. retrospectively reported on 72 patients with PPI after coronary bypass, aortic valve replacement or mitral valve surgery of whom 37% were PM independent at a mean follow-up of 72 months. They also found perioperative AV3B to be an independent predictor of PM dependency at follow-up[27]. The fact that we observed partial and even complete recovery of HDAVB in 16 out of the 30 patients who received a new PM because of AV2B or AV3B after MCS valve implantation, suggest that direct injury inflicted upon the conduction tissue by either the procedure or the self-expanding frame at least play a temporary role in the occurrence of the conduction abnormality. The function of the conduction fibers may be impaired by peri-procedural edema and inflammation as seen in post-mortem examinations [28]. These pathologic phenomena are by nature transient and may explain both the occurrence of conduction abnormalities and its spontaneous resolution. Other factors to be considered in the relationship between TAVI and new conduction abnormalities are episodes of hypotension and /or ischemia during TAVI. Hypotension may occur at various timepoints of the procedure and in particular during rapid right ventricular pacing for aortic balloon valvuloplasty and/or valve deployment when using a balloon-expandable valve. Both hypotension and balloon valvuloplasty may induce myocardial ischemia thereby inducing increased wall tension which in turn may lead to mechanical stress of the myocardium including the conduction tissue. Elderly patients, who in general have disseminated cardiovascular atherosclerosis and impaired homeostasis, may in particular be susceptible to ischemia during such episodes of high stress[29].

The clinical translation of the herein reported findings is not easy. A watchful waiting policy or a more restrictive use of new PPI after TAVI cannot be recommended on the basis of the present findings. To do so, more information is needed on the true frequency and degree of recovery of the conduction abnormalities, at what time after TAVI it occurs and whether it is permanent or transient. If recovery of conduction abnormalities occurs in a substantial proportion of the patients as seen in this study, the assessment of the clinical and procedural variables that determine recovery will help to propose a change in PM strategy and patient management (e.g. prolonged hospitalization with intense rhythm monitoring) after TAVI. The sample of the present study precluded such a detailed analysis. The drawback of patient triage on the basis of determinants of recovery or absence of recovery is that the decision to implant a permanent PM has to be taken swiftly because of the risk of infection when a temporary PM lead is in situ in addition to logistical demands. With respect to timing of recovery, this study can also not provide accurate information on time to recovery. The absence of a predefined time window between hospital discharge and PM interrogation resulted

in a substantial variation in time to follow-up, therefore, early recovery may have been missed.

From a practical point of view, readjustments of pacemaker settings on a regular basis are to be recommended so to ensure normal conduction and activation of the heart as much as possible. In the patients with conduction recovery we did not assess whether conduction remained stable during activity due to logistics and occasionally frailty of the patient. Yet, it is common practice in our institution to adjust the PM settings when recovery of AV conduction is found. Reprogramming is focused on minimizing ventricular pacing given the results of the DAVID-trial showing that right chamber pacing induces heart failure[30]. We did not assess the outcome of patients who developed a new LBBB after TAVI and who did not receive a PM. Yet, in a recent multicenter study encompassing 675 patients; it was found that all-cause mortality after TAVI was significantly higher in patients with LBBB after TAVI than in patients without LBBB (37% vs. 23%). Also TAVI-induced LBBB was the strongest independent predictor of late mortality (hazard ratio 1.61, CI; 1.17-2.21)[31].

CONCLUSIONS

Partial and even complete resolution of perioperative new conduction abnormalities after MCS valve implantation occurred in more than half of the patients at follow-up visit. PM independency was seen in 55.6% of these patients.

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CHAPTER 17

Summary and General Discussion

SUMMARY AND GENERAL DISCUSSION

Transcatheter Aortic Valve Implantation (TAVI) has emerged as a viable and safe treatment for patients with severe aortic stenosis (AS) who are considered ineligible or at prohibitive risk for Surgical Aortic Valve Replacement (SAVR)[1–4]. The aim of the present thesis was to evaluate the in-hospital complications and the determinants or factors associated with outcome after TAVI, thereby, offering insight into the pathophysiology of complications that in turn may help to propose recommendations to improve the planning, execution and follow-up of TAVI.

PART I: CLINICAL OUTCOME IN RELATION TO SPECIFIC PATIENT-, PROCEDURAL- AND DEVICE RELATED FEATURES

SAVR has been the standard of care for patients with severe aortic stenosis, improving symptoms and prolonging survival[5]. However, many patients are not referred or declined for SAVR because of the perceived risks and burden of the operation[6–8]. Since its introduction in 2002, TAVI has evolved into an evidence-based alternative to SAVR in patients who are either ineligible or at high surgical risk[9,10]. In the Placement of Transcatheter Aortic Valves (PARTNER) trial, TAVI was found to be superior to medical therapy in patients who are ineligible for SAVR and non-inferior in patients at high surgical risk. Data from this trial have shown benefits in terms of survival and quality of life[1–4,11]. Large observational registries report comparable results in the real-world experience and recent data suggest a further decline in procedural complications and mortality[12–19]. These favorable findings can be attributed to several factors such as careful selection of patients (which is enhanced by the introduction of the multidisciplinary heart-team), increased experience and a trend in selection of lower-risk patients[20–22]. In current practice treatment allocation is often based upon risk assessment using risk models such as the logistic EuroSCORE, Society of Thoracic Surgery Score and recent EuroSCORE II. These models are characterized by a low predictive value since they have neither been calibrated nor validated in patients with aortic stenosis and, in particular in those referred for TAVI[23,24]. In addition, several comorbid conditions associated with adverse surgical outcome are not included in these risk models including porcelain aorta, impaired neuro-cognitive function, chest deformities and frailty[25,26]. In Part I we addressed these patient-, procedural and post-procedural related factors determining outcome after TAVI.

PART IA: PREOPERATIVE PATIENT RELATED VARIABLES

Both left ventricular (LV) dysfunction, chronic kidney disease (CKD) and under- and overweight are known predictors of adverse outcome following SAVR[27–33]. In **Chapter 2** we found that LV dysfunction, defined as a left ventricular ejection fraction (LVEF) ≤ 35%, was present in 14% of the TAVI population. Despite differences in baseline risk between patients with or without impaired left ventricular function we observed no differences in perioperative and long-term outcome. It is conceivable that in patients who receive TAVI, which is less invasive than SAVR, preoperative LV function plays a lesser or no role in perioperative mortality. Also, the superior hemodynamic profile of transcatheter heart valves may lead to greater improvements in left ventricular function during follow-up as compared to surgical heart valves[34]. The clinical implication is that TAVI may be preferred over SAVR in patients with aortic stenosis and impaired left ventricular function. However, one may question the use of LVEF as a reliable marker of left ventricular dysfunction as a whole and also the cut-off value of 35%. As suggested by Pibarot et al, it may make more sense to assess LV performance by a more comprehensive analysis of LV geometry, global and segmental wall motion in addition to the calculation of stroke volume index not only for more appropriate assessment of the severity of disease but also for treatment stratification and analysis of treatment effects[35]. Contrary to LV dysfunction, the results of **Chapter 4** show that both baseline hemodialysis and severe CKD (estimated glomerular filtration rate < 30 mL/min) are associated with a impaired survival at one-year (67.2% and 54.8%), even after adjustment for differences in patient characteristics. This is in accordance with the surgical experience and earlier TAVI series[36,37]. This is not surprising given the prognostic effects associated with impaired kidney function itself and also given the fact that impaired kidney function is either the result or the cause of cardiovascular atherosclerosis.

Although, obesity has been associated with higher mortality in the general population, outcome in patients undergoing coronary intervention (both surgical as percutaneous) and SAVR have been reported to be better in patients with overweight[30–32]. **Chapter 3** discusses this "obesity paradox" in patients undergoing TAVI. We found that a considerable proportion of the patients were either overweight (25.0 to 30 kg/m2) or obese (> 30 kg/m2) in our population. Obesity was not associated with an increased risk of major perioperative complications after TAVI, yet, it was associated with a significant decrease in all-cause 30-day mortality. Due to a lack in power we were unable to investigate the outcome of underweight patients, a marker of frailty and a potential predictor of poor outcome. We can, nevertheless, conclude from our observations that

TAVI can be performed safely in obese patients and that, therefore, these should not be withheld from TAVI.

PART IB: PROCEDURAL RELATED VARIABLES

Significant coronary artery disease is commonly encountered in patients with severe AS referred for TAVI[38,39]. In patients undergoing SAVR, concomitant coronary artery bypass grafting has been the standard management strategy in these patients[5]. Although, Percutaneous Coronary Intervention (PCI) is technically feasible during TAVI, its effects on outcome have not been studied and were subject of investigation in **Chapter 5**. We observed that short- and long-term outcome in patients with or without complete revascularization after TAVI are comparable. These results illustrate that it may be safe to refrain from PCI in case of concomitant coronary artery disease and pursuit a pragmatic approach in patients with AS scheduled to undergo TAVI. Nevertheless, this decision should be based on the consensus of a multidisciplinary heart team taking into account the different characteristics of each individual patient. It remains to be elucidated whether this proposal will also hold for younger or less sick patients with the combination of AS and coronary artery disease.

In **Chapter 6** we compared the outcome between transfemoral and transapical TAVI, which were used in 84% and 9% of all cases. Whereas transfemoral TAVI was associated with an increased risk of vascular complications, the transapical approach was associated with a longer hospital stay and an increased risk of all-cause mortality during follow-up. Experience may have confounded this observation since experience may play a more important role in outcome in transapical than transfemoral TAVI. This interaction should be elucidated further before advocating one strategy before the other. Besides access strategy the type of device might play a role in outcome after TAVI, as they have specific properties and different methods of implantation (balloon inflated vs. self-expanding). In **Chapter 7** we investigated outcome after TAVI with the currently two most widely used valves, namely the Medtronic CoreValve System (MCS) and Edwards SAPIEN Valve (ESV). In this multicenter study, we found no difference in outcome except for a higher need of permanent pacemaker implantation (PPI) after MCS implantation. The latter has consistently being demonstrated in other observational studies and – given the differences in both the devices and technique of implantation – is caused by a higher frequency of atrioventricular conduction abnormalities after MCS implantation. The prognostic effects of the latter are subject of debate although two recent independent analyses reported that new persistent new left bundle branch block (LBBB) after TAVI is

associated with impaired survival[40,41]. This was not the case for PPI after TAVI[41].
Being less invasive in nature than SAVR, TAVI is still associated with a significant number of vascular and bleeding complications and subsequent red blood cell (RBC) transfusions[42–46]. In **Chapter 8** we found that life-threatening and major bleedings occurred respectively in 13.9% and 20.9% of all patients. Subsequently 38.9% of the patients required a RBC transfusion, which in turn was associated with an increased 30-day and 1-year mortality. These observations reveal that, although the frequency of complications is decreasing, the outcome of TAVI can be improved by reducing bleeding and vascular complications, thereby, reducing RBC transfusions.

PART IC: POSTOPERATIVE RELATED VARIABLES

The Valve Academic Research Consortium (VARC) was established to develop uniform endpoint criteria and definitions, which made it possible to compare and pool outcome in different TAVI populations[43,47,48]. Although including a wide number of complications, post-procedural infection was not included in both the first and second consensus document. **Chapter 9** gives detailed information on this complication in our combined population (Rotterdam and Cali). Despite thorough and structured preoperative screening of patients we found that infection occurred in 19.5% of our patients, which increased the hospital stay of these patients. We found surgical access of the femoral artery and overweight to be associated with an increased risk of infection. Despite the prolonged hospitalization, these patients have a good prognosis. Considered only a minor complication efforts should be made to further minimize the risk of infection and subsequent prolonged hospitalization with increased costs.

PART II: FOCUS ON PERI-PROCEDURAL CONDUCTION ABNORMALITIES: ETIOLOGY, FREQUENCY AND IMPLICATIONS

New-onset LBBB and complete atrioventricular block (AVB) occur frequently during and after TAVI and often lead to the subsequent need of a PPI[49]. Part II of this thesis specifically focuses on the mechanisms and prognostic effects of peri-procedural conduction abnormalities (CAs). Appreciation of the the intimate relationship and proximity of the atrioventricular conduction axis within the aortic root allows us to understand how pathologies involving the aortic valve can cause LBBB and complete AVB. In **Chapter 10** we describe these anatomic features in the light of TAVI and report

on the recent literature regarding this topic. Furthermore, it provides an overview of the specific patient- and procedural related determinants underlying the new CAs, establishing three major predictors of CAs after TAVI, being: pre-existent CAs, depth of implantation and valve type (more common after MCS implantation as compared to the ESV).

As TAVI constitutes a multi-step procedure using various guidewires and catheter systems in the left ventricular outflow tract (LVOT), it might well be that new CAs already occur before actual valve implantation. Using continuous 12-lead electrocardiographic monitoring during TAVI we found that over 80% of the patients developed a new CA during or after implantation with the MCS (**Chapter 11**). We also observed that more than the half of these CAs already occurred during balloon valvuloplasty, which was associated with a significantly higher balloon/annulus ratio. The latter might hold for both the MCS as the ESV, however, this was not studied. From these results together with post-mortem findings we may conclude that the occurrence of new CAs is related to the (in)direct trauma before, during and after valve implantation[50,51]. Given the nature of TAVI including various steps and intracardiac manipulations and differences in the physical properties between the MCS and ESV one might expect a difference in the transient or permanent nature of the CAs between the two valves. We observed that TAVI-induced new LBBB occurred in 36.8% of all patients and was persistent in more than 60% of these patients. LBBB occurred more frequently after implantation of the MCS as compared to the ESV (53.8% vs. 21.7%) and was also associated with less recovery during the follow-up period. Conversely, late onset LBBB was observed in only four patients (**Chapter 12**). In **Chapter 16** we revealed similar results in patient undergoing PPI after TAVI. At follow-up visit pacemaker interrogation revealed that partial or complete resolution of peri-operative CAs occurred in more than half of the patients. Unfortunately, only one pacemaker function assessment during follow-up was performed. Therefore, firm conclusions cannot be drawn and more information is needed on the degree and timing of the recovery before new policy regarding new CAs and PPI can be recommended. Nevertheless, our observations suggest that close attention to the follow-up electrocardiogram in patients with new CAs after TAVI is advocated since it is associated with poor outcome. In case of PPI, regular pacemaker interrogation and readjustments of settings to ensure normal conduction is proposed, as ventricular pacing has been shown to induce heart failure[52].

In the early experience, TAVI-induced new LBBB was considered an innocent side effect especially in the light of other complications associated with the procedure. However, LBBB leads to interventricular dyssynchrony and compromised cardiac function which

has been associated with poor outcome in different populations ranging from healthy individuals to patients with established heart failure to patients undergoing SAVR[53–55]. In **Chapter 12** and **13** we found that TAVI-induced LBBB was a strong predictor of poor outcome, independent of the type of valve implanted. Yet, this increased risk of mortality was only present in patients with persistent LBBB as compared to patients with no or transient LBBB. The adverse effects of new LBBB may either be explained by an increased the risk of progression to high degree AVB and possible sudden cardiac death and/or interventricular dyssynchrony affecting cardiac performance and eventual lack of LV recovery as shown in a number of studies[56–59,41]. The adverse effects of LBBB on prognosis is subject of debate (**Chapter 15**). While some report no adverse effects, we found an impaired survival in patients with persistent LBBB after TAVI[40,41,57,58,60,61].
As for all procedural-related complications, experience may also play a role in TAVI-induced new LBBB[22]. In **Chapter 14** we found that the frequency of TAVI- LBBB significantly decreased over time; from 47.2% in cohort 1 to 28.5% in cohort 3 and was predominantly seen in patients who were treated with the MCS. Noteworthy, the reduction in LBBB was in parallel with a reduction in the depth of implantation suggesting the effect of experience.

FUTURE PERSPECTIVES

From a transvenous antegrade transseptal procedure performed in a patient unable to undergo SAVR due to poor general and cardiac condition, TAVI has evolved to a mainstream treatment in patients with AS who are poor surgical candidates in a remarkably short period of time[9]. The rapidly increasing penetration of TAVI combined with the data from initial safety and feasibility studies in Europe led to CE approval in 2007 of both the self expanding Medtronic Core Valve and the balloon expandable Edwards valve[62]. Early data from the PARTNER trial in which its superiority to medical treatment and its non-inferiority in respectively inoperable and high risk surgical patients was demonstrated made the Food and Drug Administration decide to approve the Edwards SAPIEN Heart Valve in November 2011[1–4]. Since the first TAVI procedure in 2002, the number of TAVIs is estimated at 150.000 procedures worldwide (December 2013). This exponential use will further increase due to further innovations in technology (i.e. reduction in size of delivery catheters and the introduction of repositionable and/or retrievable systems), further increase in experience, better insights into the determinants or pathophysiology of complications, innovations in software helping the physician to obtain more accurate sizing and better valve positioning and, last but not least, awareness and demand from society for less invasive procedure[63–73]. As a result,

TAVI will move from a high risk population to younger and less sick patients[21].The latter is the scope of the currently ongoing PARTNER-2 and SURTAVI trials, comparing TAVI to SAVR in patients at intermediate risk.
Yet, TAVI remains an invasive procedure and, therefore, will remain associated with specific complications such as stroke, bleeding- and vascular complications, conduction abnormalities and paravalvular aortic regurgitation. Before moving to less sick patients, these complications need to be further reduced by a better understanding of the factors contributing or causing the complication and the relationship between these factors. Several chapters of this thesis indicate that the risk of these complications is multifactorial, which can be defined as patient-related, procedure- related (including the operator and the device implanted) and postoperative-related. This insight may in turn help to formulate proposals leading to improvements in patient- and device selection, the execution of TAVI (e.g. use of cerebral protection devices to prevent embolic stroke) and postoperative care (e.g. anticoagulant treatment in case of postoperative atrial fibrillation). However, capturing these underlying factors is troublesome and, therefore, each individual patient should be evaluated by a team of experts[74]. Also more information is needed on valve durability although the current clinical experience indicate that a similar durability may be expected from the bioprostheses used during TAVI as those during SAVR[14,75].

As a result of changes in society due to – among others – the worldwide web, the changing role and shift of accountability and responsibility of the patient and physician and health care authorities, the role of the patient in the decision making process is gradually taken a more dominant role in all domains of clinical medicine and patient care. This implies correctly informing the patient by the physician involving details of the procedure including risks and benefits to be expected from TAVI in addition to alternative treatments (including medical treatment) in order to make a balanced treatment decision. The latter should be supported by those performing TAVI as well as the person undergoing TAVI and the people supporting the patient in daily life[76]. Despite all clinical scientific innovations including complex treatment decision-making software and (sophisticated) risk models, clinical medicine remains an art that is to be performed by adequately trained physicians who are experts by actively performing such procedures in sufficient numbers while working in the right environment.

CONCLUDING REMARKS

This thesis aimed to evaluate the determinants associated with outcome after transcatheter aortic valve implantation. The different studies reveal that patients undergoing this new treatment have a good short- and mid-term survival. However, it also shows that outcome can be improved by appropriate patient selection taking into account variables not included in traditional risk algorithms and treatment allocation based on the consensus of a multidisciplinary heart team. This thesis also illustrates the role of new conduction abnormalities after TAVI, especially with the Medtronic CoreValve System, emphasizing their implications for clinical outcomes. It also offers an insight in the possible mechanisms underlying their occurrence and, therefore, a possibility to further improve outcome in this population.

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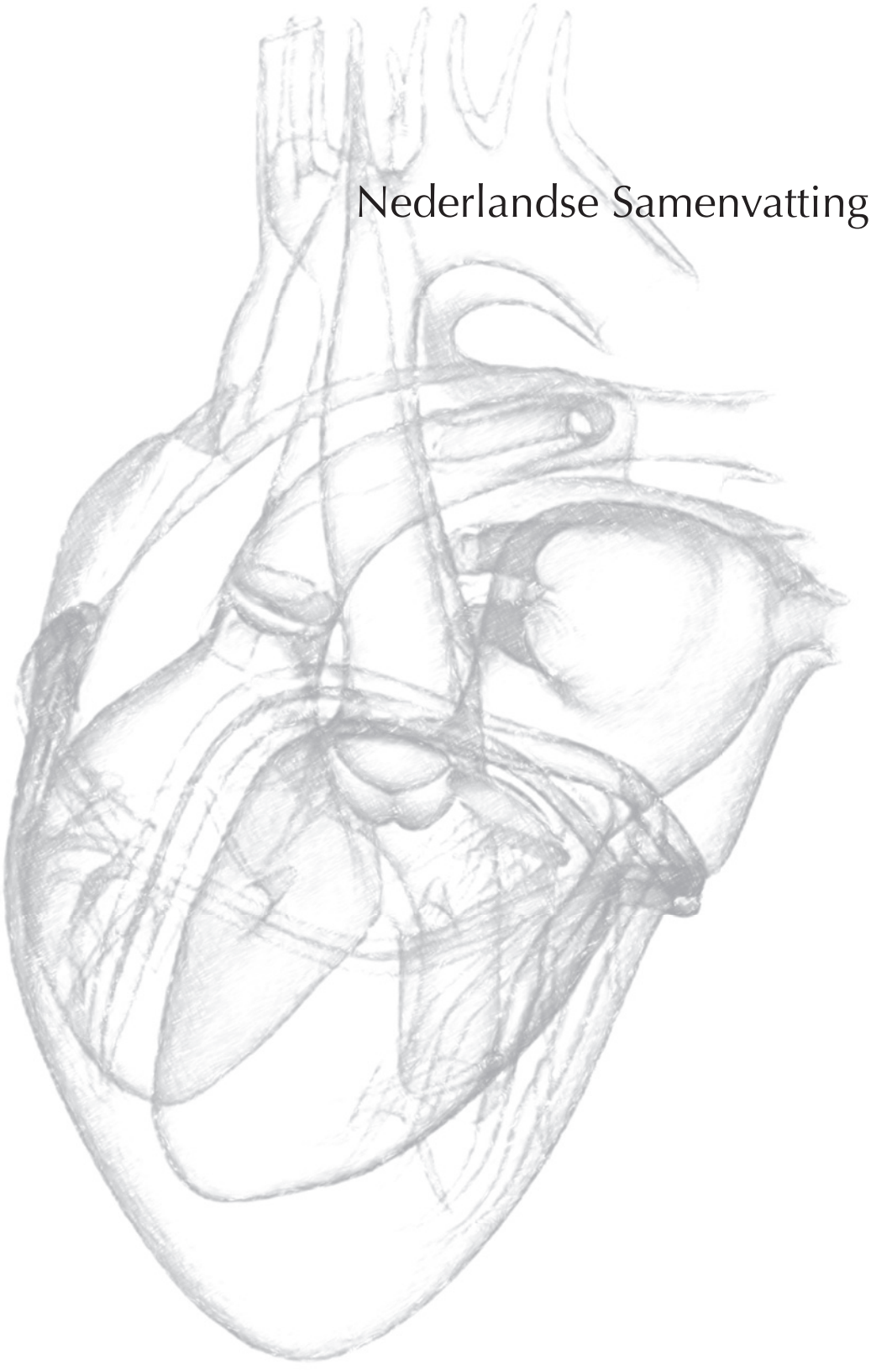
Nederlandse Samenvatting



NEDERLANDSE SAMENVATTING

Percutane Aortaklepimplantatie (TAVI) is naar voren gekomen als een uitvoerbare en veilige behandelmethode voor patiënten met ernstige aortaklepstenose (AoS) die niet behandeld kunnen worden met de chirurgische aortaklepvervanging (SAVR)[1-4]. Het doel van dit proefschrift was om een beter inzicht te krijgen in de complicaties en determinanten van de uitkomsten na TAVI en daarnaast de achterliggende pathofysiologie te achterhalen. Deze inzichten dienen te leiden tot nieuwe voorstellen om de planning, uitvoerbaarheid en lange termijn uitkomsten van TAVI te verbeteren.

DEEL I: KLINISCHE UITKOMSTEN IN RELATIE TOT PATIËNT-, PROCEDURELE- EN KLEP GERELATEERDE FACTOREN

SAVR heeft bewezen bij patiënten met ernstige AoS de symptomen te verminderen en het leven te verlengen. Het is daarmee de gouden standaard qua behandeling voor deze populatie[5]. Desalniettemin wordt een gedeelte van de patiënten niet verwezen of afgewezen voor deze behandeling vanwege het operatieve risico en het invasieve karakter van deze operatie[6-8]. Sinds de introductie van TAVI in 2002 heeft deze behandeling zich geëvolueerd tot een alternatief voor SAVR in deze populatie[9,10]. Resultaten van de Placement of Transcatheter Aortic Valves (PARTNER) studie hebben aangetoond dat TAVI superieur is aan medicamenteuze therapie bij patiënten die niet in aanmerking komen voor SAVR[1]. Daarnaast was TAVI gelijkwaardig aan SAVR bij patiënten met een hoog operatief risico[2]. Deze resultaten betreffen zowel de klinische uitkomsten als de kwaliteit van leven[1,4-11]. Nationale en internationale observationele studies hebben deze resultaten bevestigd en zelfs een verdere verbetering in procedurele complicaties en mortaliteit gerapporteerd[12-19]. Deze gunstige resultaten kunnen worden gewijd aan verschillende factoren, zoals verbeterde patiënten selectie (mede door de introductie van het multidisciplinaire hartteam), toename in de ervaring en de selectie van patiënten met een lager operatief risico[20-22]. In de klinische praktijk wordt de behandelmethode bepaald door risicostratificatie op basis van risicomodellen, zoals de Logistische EuroSCORE, Society of Thoracic Surgery Score en de recent geïntroduceerde EuroSCORE II. Van al deze modellen is aangetoond dat zij de uitkomsten na TAVI slecht voorspellen. Dit is te verklaren uit het feit dat deze modellen niet zijn ontwikkeld en gevalideerd onder patiënten met AoS en in het bijzonder de patiënten die TAVI ondergaan[23-24]. Daarnaast zijn verschillende factoren, waarvan aangetoond is dat ze een effect hebben op uitkomsten na TAVI, niet opgenomen in deze modellen. Voorbeelden hiervan zijn porseleinen aorta, neuro-

cognitieve disfunctie, afwijkingen van de thorax en frailty[25,26]. In Deel 1 bespreken we deze patiënt-, procedurele- en post-procedurele factoren die de uitkomsten na TAVI bepalen.

DEEL IA: PRE-OPERATIEVE PATIËNT GERELATEERDE FACTOREN

Van zowel linker ventrikel (LV) disfunctie, chronische nierinsufficiëntie als onder- en overgewicht is bekend dat zij voorspellers zijn van slechte uitkomsten na SAVR[27-33]. In **Hoofdstuk 2** vonden wij dat LV disfunctie, gedefinieerd als een linker ventrikel ejectiefractie (LVEF) ≤ 35%, aanwezig was bij 14% van de patiënten die TAVI ondergingen. Ondanks een hoger operatief risico voor deze patiënten zagen wij geen verschil in termen van peri-operatieve en lange termijn uitkomsten tussen patiënten met of zonder LV disfunctie. Het is denkbaar dat bij een minder invasieve procedure als TAVI, in vergelijking met SAVR, LV functie een minder belangrijke of geen rol speelt voor deze uitkomsten. Daarnaast kan het hemodynamisch karakter van een percutane hartklep leiden tot een grotere verbetering in deze functie in tegenstelling tot een chirurgische hartklep[34]. In de klinische praktijk kan dit betekenen dat TAVI wellicht een betere optie is dan SAVR bij patiënten met AoS en een verminderde LV functie. Het blijft echter de vraag of LVEF een goede maat is voor LV disfunctie en of de afkapwaarde van 35% een reële is. Het lijkt immers vanzelfsprekend om de gehele functie te bekijken middels uitgebreide analyse van de LV geometrie, globale- en segmentale wandbeweging en een berekening van de stroke volume index[35]. Dit dient niet alleen te leiden tot een betere inschatting van de ernst van de AoS maar ook tot een verbetering in de risicostratificatie. In tegenstelling tot LV disfunctie laten de resultaten van **Hoofdstuk 4** zien dat een ernstige gestoorde nierfunctie (glomerulaire filtratie snelheid < 30 mL/min) en hemodialyse voor de procedure geassocieerd zijn met slechtere uitkomsten op één jaar (67.2% en 54.8%). Dit effect bleef bestaan na te hebben gecorrigeerd voor de verschillen tussen de patiënten. Deze resultaten zijn in overeenstemming met eerdere publicaties bij zowel patiënten na TAVI als na SAVR[36,37]. Het is ook niet geheel verrassend vanwege de prognostische effecten die een gestoorde nierfunctie met zich meebrengt en het feit dat dit of het resultaat of de oorzaak is van atherosclerose.

Obesitas is een bewezen risicofactor voor mortaliteit in de algemene bevolking. Echter bij patiënten na een coronaire interventie (zowel chirurgisch als percutaan) en bij patiënten na SAVR is het aangetoond dat een hogere body mass index leidt tot betere uitkomsten[30-32]. In **Hoofdstuk 3** bespreken we deze obesitas paradox bij patiënten na TAVI. Het laat zien dat een aanzienlijk gedeelte van de populatie dan wel overgewicht

(25 tot 30 kg/m2) dan wel obesitas (> 30 kg/m2) hebben. Er was geen hoger risico op peri-procedurele complicaties, maar de sterfte op 30 dagen was significant lager bij deze patiënten. Dankzij het lage aantal patiënten met ondergewicht was het niet mogelijk om onderzoek te doen naar de effecten van deze risicofactor. Onder andere omdat dit één van de uitingsvormen van frailty lijkt te zijn. Echter kunnen we wel concluderen dat TAVI veilig uitgevoerd kan worden bij patiënten met obesitas en dat dit ook geen reden zou mogen zijn om patiënten te weigeren voor deze behandeling.

DEEL 1B: PROCEDURE GERELATEERDE FACTOREN

Significant coronairlijden komt vaak voor bij patiënten met ernstig AoS die worden verwezen voor TAVI[38,39]. Bij patiënten die behandeld worden middels SAVR heeft een combinatie met een coronary artery bypass graft (CABG) de voorkeur[5]. Hoewel het mogelijk is om een percutane coronaire interventie (PCI) uit te voeren tijdens de TAVI procedure zijn de effecten op de uitkomsten onduidelijk. Dit was dan ook het onderwerp van **Hoofdstuk 5**. De resultaten lieten zien dat de korte- en lange termijn uitkomsten bij patiënten met of zonder volledige revascularisatie vergelijkbaar waren. Dit onderstreept dat het in sommige gevallen wenselijk kan zijn om af te zien van een gelijktijdige PCI bij patiënten met zowel ernstig AoS als coronairlijden. Deze beslissing dient te allen tijde gebaseerd te zijn op de consensus van een multidisciplinair hartteam waarbij elke patiënt individueel dient te worden besproken. Het dient gezegd te worden dat verder onderzoek nodig is om te kunnen zeggen of hetzelfde geldt voor jongere of minder zieke patiënten met de combinatie van coronairlijden en AoS.

In **Hoofdstuk 6** vergeleken we de uitkomsten tussen patiënten die transfemorale (84%) of transapicale (9%) TAVI ondergingen (in 7% werd een andere toegangsroute gebruikt). Waar transfemorale TAVI geassocieerd was met een hoger risico op vasculaire complicaties bleek transapicale TAVI te leiden tot een langere hospitalisatie en een hoger risico op mortaliteit na 30 dagen. Het kan zijn dat ervaring een belangrijke rol heeft gespeeld bij deze uitkomsten aangezien transapicale TAVI meer ervaring vergt. De interactie tussen deze twee dient verder uitgezocht te worden voordat er een uitspraak gedaan kan worden over welke toegangsweg de voorkeur verdient. Naast toegangsstrategie is het ook mogelijk dat het type klep een rol speelt in de uitkomsten na TAVI, aangezien zij verschillende specificaties hebben en een verschillende manier van implanteren (zelfontvouwbaar of ballondilatatie). In **Hoofdstuk 7** hebben we dit nader onderzocht door de twee meest gebruikte kleppen, het Medtronic CoreValve Systeem (MCS) en de Edwards SAPIEN Valve (ESV), met elkaar te vergelijken. In deze

multicenter studie konden wij geen verschil aantonen tussen beiden behoudens een hoger aantal van permanente pacemaker implantaties (PPI) na gebruik van het MCS. Deze bevinding is een consequent gegeven uit verschillende observationele studies en lijkt voort te komen uit een hogere frequentie van atrioventriculaire geleidingsstoornissen na implantatie van deze klep. De klinische effecten hiervan zijn nog niet geheel duidelijk. Hoewel twee recente studies onafhankelijk van elkaar hebben gerapporteerd dat een persisterend linker bundeltak blok (LBTB) na TAVI geassocieerd is met een slechtere overleving[40,41]. Dit was niet het geval indien een pacemaker was geïmplanteerd[41].

Hoewel TAVI minder invasief van aard is in vergelijking met SAVR is de procedure nog steeds geassocieerd met vasculaire- en bloedingcomplicaties en de daaropvolgende rode bloedcel (RBC) transfusies[42-46]. Uit **Hoofdstuk 8** komt naar voren dat levensbedreigende en grote bloedingen bij 13.9% en 20.9% van de patiënten voorkomt. Een gevolg hiervan was dat 38.9% van de patiënten een transfusie nodig hadden. Dit was op zijn beurt weer geassocieerd met een slechtere overleving op 30 dagen en één jaar. Deze resultaten tonen aan dat, terwijl de incidentie van procedurele complicaties verder daalt, de uitkomsten na TAVI verder verbeterd kunnen worden door vasculaire- en bloedingcomplicaties verder te reduceren. Als gevolg hiervan zal de frequentie van bloedtransfusies ook verder dalen.

DEEL 1C: POSTOPERATIEF GERELATEERDE FACTOREN

Het Valve Academic Research Consortium (VARC) werd opgericht om uniforme eindpunten te ontwikkelen. Dit om resultaten van TAVI te kunnen samenvoegen en onderling te kunnen vergelijken[43,47,48]. Hoewel een groot aantal complicaties werden gedefinieerd stond postprocedurele infectie niet in zowel het eerste als het tweede consensus document. **Hoofdstuk 9** geeft gedetailleerde informatie over deze complicatie vanuit een gecombineerde populatie uit Rotterdam en Cali. Ondanks een uitgebreide preoperatieve screening ontstond bij 19.5% van de patiënten een infectie na de procedure. Als gevolg hiervan was de opnameduur langer voor deze patiënten. Chirurgisch vrij prepareren van de arteria femoralis en overgewicht waren geassocieerd met een hoger risico op een infectie. Ondanks de langere opnameduur is de prognose van patiënten met of zonder een postprocedurele infectie gelijkwaardig. Het feit dat dit gezien wordt als een bijkomende complicatie dient niet uit te sluiten dat verdere inspanningen nodig zijn om deze te voorkomen. Mede gezien de langere hospitalisatie en de bijkomende kosten.

DEEL II FOCUS OP PERI-PROCEDURELE GELEIDINGS-STOORNISSEN: ETIOLOGIE, FREQUENTIE EN IMPLICATIES

Een nieuw LBTB en totaal atrioventriculair blok (AVB) komen frequent voor tijdens en na TAVI en leiden in de meeste gevallen tot PPI[49]. Deel II van dit proefschrift richt zich specifiek op de onderliggende mechanismen en prognostische effecten van peri-procedurele geleidingsstoornissen. Een beter begrip van de relatie tussen en de nabijheid van de atrioventriculaire geleiding ten opzichte van de aortawortel kan het ontstaan van LBTB en AVB bij ziekten van de aortaklep verklaren. **Hoofdstuk 10** beschrijft deze anatomische kenmerken in het ogenschouw van de recente literatuur over het ontstaan van geleidingsstoornissen na TAVI. Daarnaast verschaft het een overzicht van de specifieke patiënt- en procedure gerelateerde determinanten van deze geleidingsstoornissen. Uit dit hoofdstuk komen drie belangrijke concepten naar voren: pre-existente geleidingsstoornissen, diepte van implantatie van de klep en het type klep (vaker na MCS als na ESV implantatie).

TAVI is een procedure bestaande uit meerdere stappen waarbij verschillende voerdraden en kathetersystemen in de linker ventrikeluitstroombaan (LVOT) worden gebracht. Het kan dan ook goed mogelijk zijn dat nieuwe geleidingsstoornissen al optreden voor de daadwerkelijke implantatie van de nieuwe klep. Door gebruik te maken van continue elektrocardiografische monitoring tijdens de procedure was het mogelijk om vast te stellen dat bij 80% van de patiënten een nieuwe geleidingsstoornis ontstond tijdens of na implantatie van het MCS (**Hoofdstuk 11**). We observeerden ook dat meer dan de helft van deze stoornissen al tijdens de ballondilatatie ontstonden, voornamelijk bij een hogere ratio tussen ballon en annulus. Deze observatie kan zowel voor MCS als ESV gelden. Echter hebben we dit niet kunnen onderzoeken in deze studie. Uit de combinatie van deze resultaten en de bevindingen bij post-mortem onderzoek kunnen wij concluderen dat er een relatie is tussen het ontstaan van nieuwe geleidingsstoornissen en (in)direct trauma voor, tijdens en na klepimplantatie[50,51]. De bovengenoemde intracardiale manipulaties en de verschillen in fysische eigenschappen tussen het MCS en de ESV doet verwachten dat er een verschil is in de transiente en persisterende aard van geleidingsstoornissen. In onze populatie kwam een TAVI geïnduceerd nieuw LBTB voor in 36.8% van de patiënten waarvan meer dan 60% persisterend was. LBTB kwam vaker voor na implantatie met het MCS dan na de ESV (53.% vs. 21.7%) en herstelde ook minder vaak tijdens de periode volgend op de procedure. Daarentegen zagen we maar vier patiënten met een laat LBTB na TAVI (**Hoofdstuk 12**). In **Hoofdstuk 16** zagen een zelfde tendens bij patiënten die PPI ondergingen na TAVI. Bij het uitlezen van de pacemaker was er bij meer dan de helft van de patiënten sprake van een gedeeltelijke of totale resolutie van de peri-procedureel

ontstane geleidingsstoornis. Jammer genoeg betrof dit maar één meting in de tijd en is het niet mogelijk om harde conclusies te trekken uit deze resultaten. Verder onderzoek naar de mate en de precieze timing van het herstel is nodig voordat nieuw beleid betreffende geleidingsstoornissen en PPI kan worden opgesteld. Echter onze resultaten suggereren dat nauwe monitoring van het elektrocardiogram van patiënten met nieuwe geleidingsstoornissen na TAVI van belang is. Des te meer vanwege de relatie met slechte uitkomsten. In het geval van PPI zijn regelmatige controles en aanpassingen aan de instellingen (om normale geleiding te waarborgen) aan te raden. Zeker nu aangetoond is dat ventriculaire pacing hartfalen kan induceren[52].

Tijdens de eerste ervaring werd een TAVI geïnduceerd nieuw LBTB gezien als een onschuldige complicatie, mede gezien de andere complicaties geassocieerd met de procedure. LBTB leidt echter tot interventriculaire dissynchronie en een gecompromitteerde cardiale functie. Beiden zijn geassocieerd met een slechtere uitkomst bij zowel gezonde individuen als bij patiënten met hartfalen die SAVR ondergingen[53-55]. Uit **Hoofdstuk 12** en **Hoofdstuk 13** blijkt dat TAVI geïnduceerd LBTB een belangrijke voorspeller is van slechte uitkomsten, onafhankelijk van het type klep dat werd geïmplanteerd. Dit verhoogde risico was alleen aanwezig bij patiënten met een persisterend LBTB in tegenstelling tot patiënten met een voorbijgaand LBTB of zonder LBTB. De nadelige effecten van een nieuw LBTB kunnen op verschillende manieren worden verklaard. Ten eerste bestaat er het risico dat een nieuw LBTB zicht ontwikkeld tot een totaal AVB en daaropvolgende plotselinge hartdood. Ten tweede kan een nieuw LBTB, zoals eerder aangegeven, leiden tot interventriculaire dissynchronie welke het herstel van de LV functie na TAVI kan verminderen[56-59,41]. De gevolgen van een nieuw LBTB zijn onderwerp van discussie (**Hoofdstuk 15**). Hoewel sommige studies geen slechtere uitkomsten rapporteren vonden wij in deze twee hoofdstukken dat de overleving van deze patiënten slechter was[40,41,57,58,60,61].

Ervaring speelt een belangrijke rol bij alle procedurele complicatie en zo mogelijk ook bij TAVI geïnduceerd LBTB[22]. In **Hoofdstuk 14** zagen wij dan ook dat de frequentie van een nieuw LBTB significant daalde in de tijd van 47.2% (Cohort 1) naar 28.5% (Cohort 3). Dit was het meest uitgesproken bij patiënten die TAVI ondergingen met het MCS. Het is noemenswaardig dat deze reductie van LBTB parallel liep met een afname in de diepte van implantatie. Dit lijkt des te meer de rol van ervaring te onderstrepen.

TOEKOMSTPERSPECTIEF

Van een transveneuze, antegrade en transseptale procedure welke uitgevoerd werd bij een patiënt in een te slechte conditie om SAVR te ondergaan heeft TAVI zich in een opzienbarende tijd ontwikkeld tot een mainstream behandelmethode voor patiënten met AoS en een te hoog operatief risico[9]. Het snelle intreden van TAVI in combinatie met de veelbelovende resultaten van de initiële veiligheids- en haalbaarheidsstudies zorgde voor de CE-markering van het zelfontvouwbare MCS en de ballondilateerbare ESV in 2007[62]. Na publicatie van de resultaten van de PARTNER studie werd TAVI in 2011 ook goedgekeurd in de Verenigde Staten[1-4]. Sinds de eerste procedure in 2002 hebben wereldwijd ongeveer 150.000 procedures plaatsgevonden (December 2013). Deze exponentiële groei zal verder toenemen gezien de technologische innovaties (bijvoorbeeld reductie in de grootte van het implantatie systeem en repositioneerbare of heropvouwbare systemen), toename in ervaring en verbeterde inzichten in de determinanten of pathofysiologie van complicaties, innovaties op het gebied van software waarmee de behandelend arts de klepgrootte preciezer kan inschatten en deze nauwkeuriger kan implanteren en de vraag vanuit de gemeenschap naar minder invasieve procedures[63-73]. Als gevolg hiervan zal TAVI van hoog risico verschuiven naar minder zieke en jongere patiënten[21]. Dit laatste is het onderwerp van de lopende PARTNER-2 en SURTAVI studies waarin TAVI en SAVR met elkaar worden vergeleken bij patiënten met een lager risico.

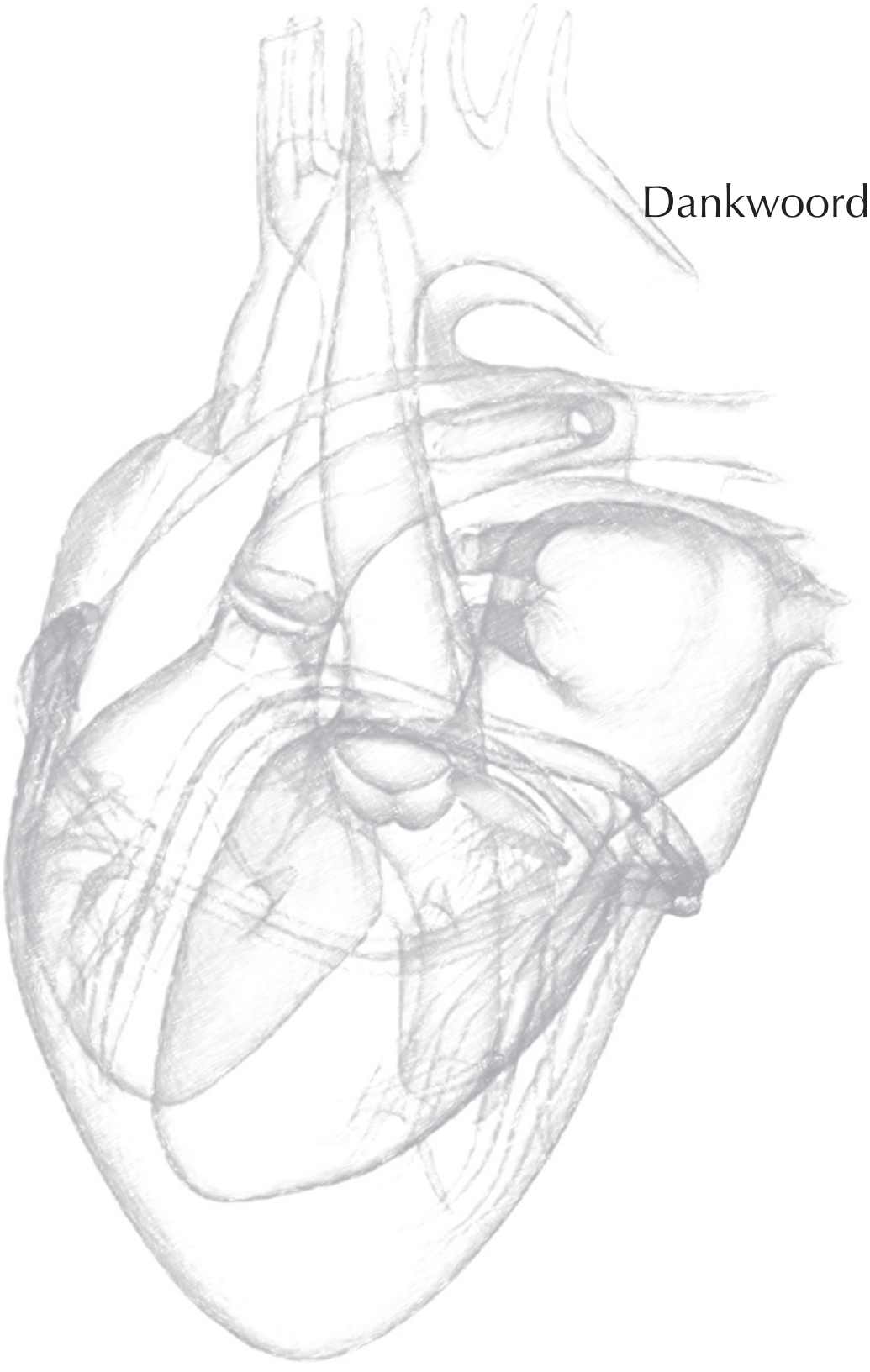
TAVI blijft echter een invasieve procedure en zal daarom altijd geassocieerd zijn met bepaalde complicaties, zoals cerebrovasculaire accidenten, vasculaire- en bloedingcomplicaties, geleidingsstoornissen en paravalvulaire lekkage. Voordat TAVI naar patiënten met een lager risico kan verschuiven is het van belang om deze complicaties reduceren. Een beter begrip van de factoren die een bijdrage leveren in het ontstaan van een complicatie en de relatie tussen deze factoren kan een bijdrage leveren in dit proces. Verschillende hoofdstukken uit dit proefschrift laten zien dat het risico op complicaties multifactorieel is, bestaande uit: patiënt gerelateerde-, procedure gerelateerde- (zowel de operateur als het type klep) en postoperatief gerelateerde factoren. Kennis van deze factoren kan helpen om voorstellen te formuleren welke kunnen bijdragen tot een verbetering in patiënt- en klepselectie, het uitvoeren van de TAVI procedure (bijvoorbeeld gebruik van cerebrale protectie systemen om embolische beroertes te voorkomen) en postoperatieve zorg (bijvoorbeeld antistollingsbeleid bij postoperatief atriumfibrilleren). Het blijft echter moeilijk om deze factoren te achterhalen en het is daarom van belang om elke individuele patiënt te evalueren in een multidisciplinair team van experts[74]. Er is ook meer onderzoek nodig naar de

duurzaamheid van de geïmplanteerde kleppen, maar op dit moment lijkt de klinische ervaring er op te wijzen dat deze te vergelijken is met de bioprotheses gebruikt bij SAVR[14,75].

Als een gevolg van de veranderingen in de maatschappij onder meer door het internet en de veranderende rol van de patiënt, de arts en gezondheidsautoriteiten, begint de rol van de patiënt in de keuze van een behandeling een steeds dominantere rol aan te nemen. Dit geldt niet alleen voor de curatieve sector, maar ook voor andere domeinen van de gezondheidszorg. Dit impliceert dat een patiënt correcte informatie voorgelegd dient te worden over de details van de procedure en de bijbehorende risico's en voordelen. Daarnaast dienen ook alternatieve behandelingen (waaronder medicamenteuze therapie) te worden besproken. Dit voordat een weloverwogen beslissing genomen kan worden in overleg met de behandelend arts en de directe omgeving van de patiënt[76]. Ondanks alle wetenschappelijke veranderingen op het gebied van software om de gewenste therapie vast te stellen en voorgestelde risicomodellen blijft geneeskunde een kunst die uitgeoefend moet worden door adequaat opgeleide artsen. Deze dienen hun expertise te hebben verkregen door de procedure uit te voeren in voldoende getale en door te werken in een stimulerende omgeving.

CONCLUSIE

Dit proefschrift had als doel om de determinanten van uitkomsten na percutane aortaklepimplantatie te achterhalen. De verschillende studies tonen aan dat patiënten die deze nieuwe behandelingsmogelijkheid ondergaan een goede overleving hebben op zowel korte- als langere termijn. Het laat echter ook zien dat de uitkomsten verbeterd kunnen worden door het selecteren van de geschikte patiënten waarbij gekeken wordt naar factoren die niet onderdeel zijn van de traditionele risicomodellen. De verdere behandelingskeuze dient gebaseerd te zijn op de consensus van een multidisciplinair hartteam. Dit proefschrift illustreert ook de rol van nieuw ontstane geleidingsstoornissen na TAVI, met name na implantatie met het MCS-, en benadrukt hun implicaties voor de klinische praktijk. Het geeft ook een beter beeld van de mogelijke pathofysiologische mechanismen en daarmee ook een mogelijkheid om uitkomsten in deze populatie verder te verbeteren.



Dankwoord

DANKWOORD

In 2009 kwam ik, in het kader van mijn master Clinical Research, voor het eerst op de afdeling Cardiologie. *"Ga maar alvast meedraaien op een afdeling die je interesse heeft"* werd er naar aanleiding van mijn sollicitatie gezegd. Het leek me fantastisch om naast mijn studie al te beginnen met het doen van onderzoek. Ik had niet kunnen vermoeden in welke achtbaan ik terecht zou komen nadat ik eenmaal was begonnen. Het was niet altijd even makkelijk om promoveren te combineren met het lopen van coschappen, maar het traject heeft mij prachtige herinneringen en talloze ervaringen opgeleverd. Ik wil van dit hoofdstuk gebruik maken om diegenen met wie ik heb samengewerkt en die mij hebben gesteund te bedanken. Enkelen wil ik graag in het bijzonder noemen.

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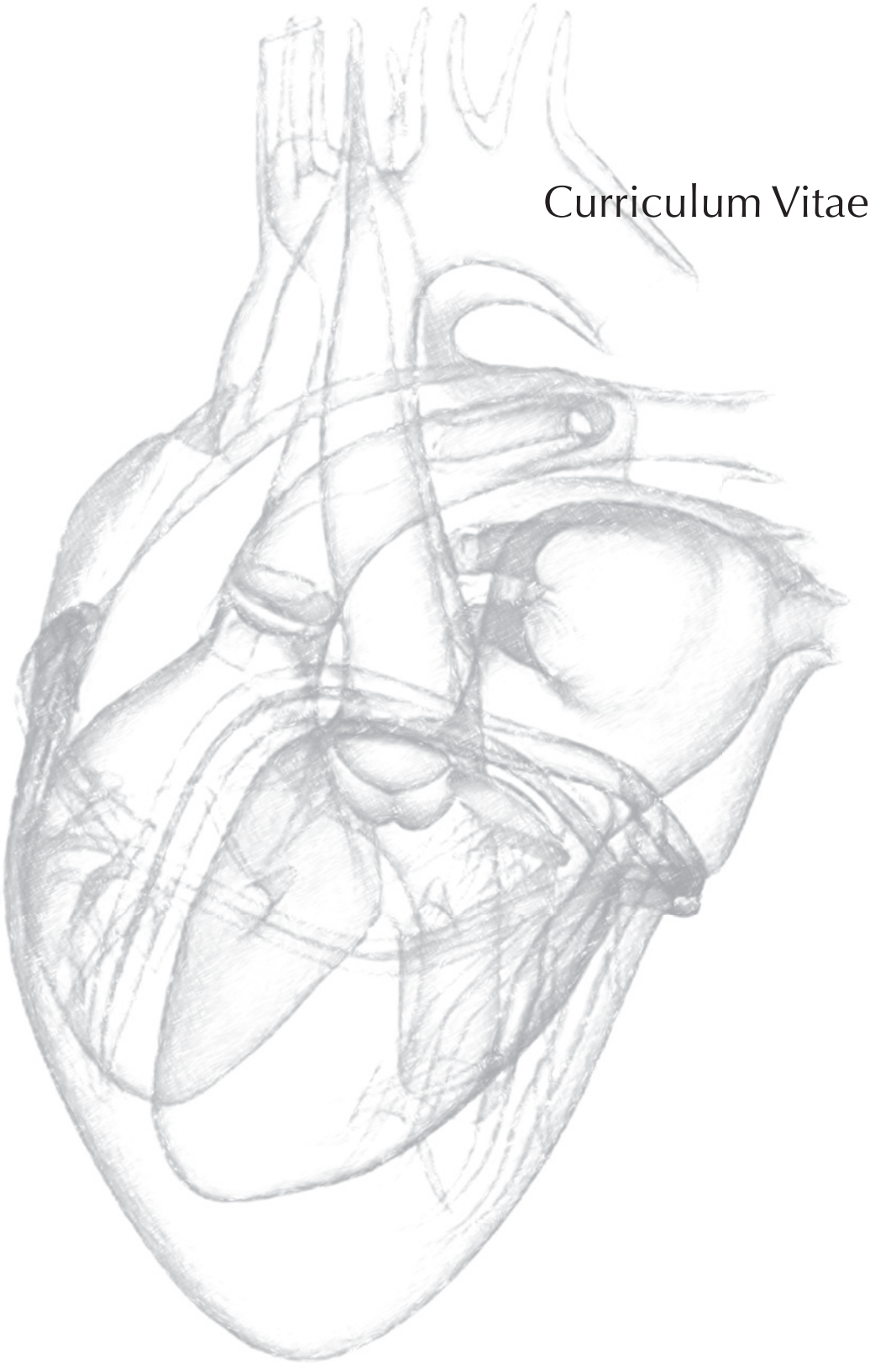
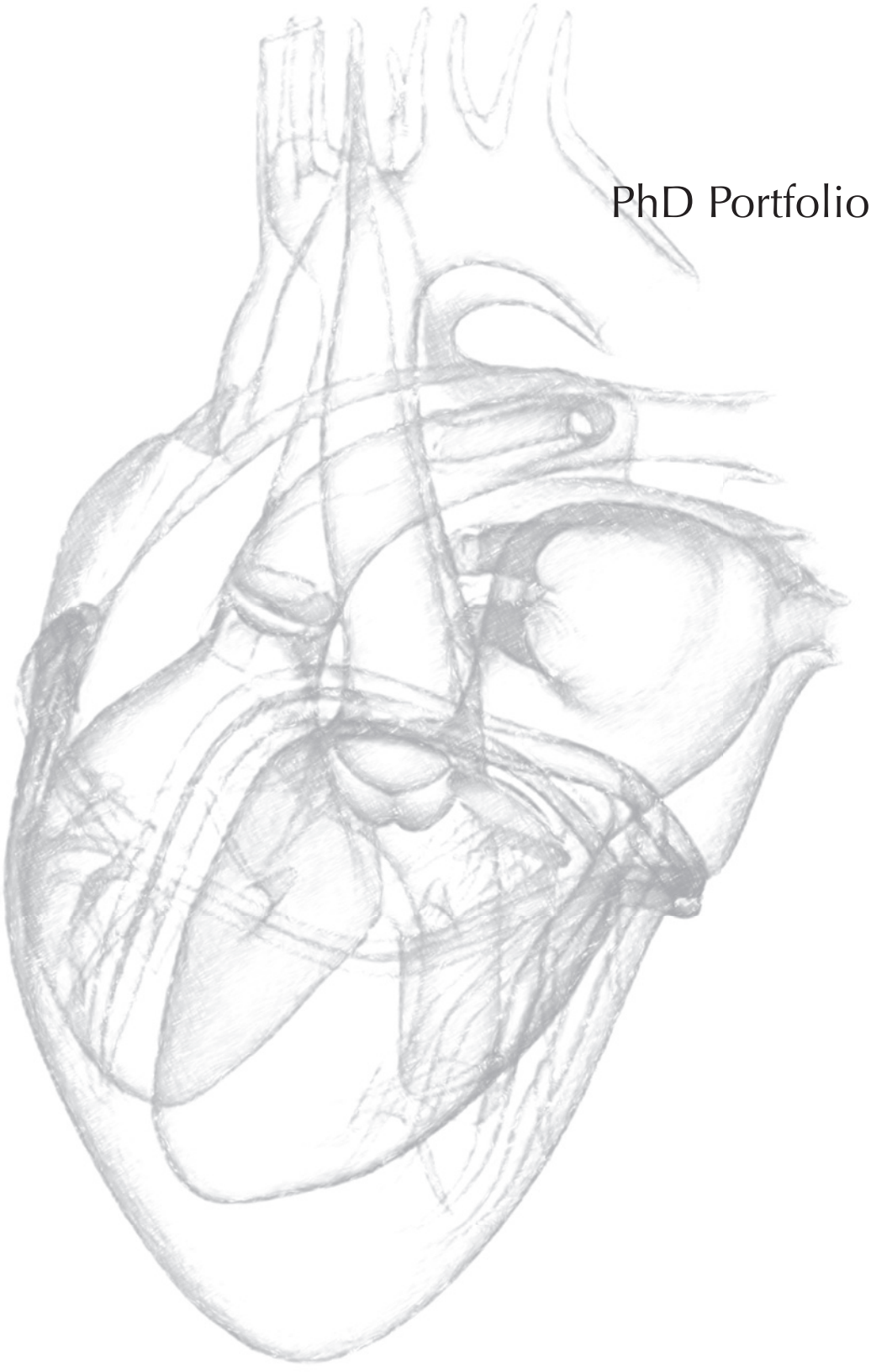
Curriculum Vitae



CURRICULUM VITAE

Robert Mathew Anthony van der Boon was born on October 21st, 1989 in Rotterdam, the Netherlands. After graduating from secondary school (Johan de Witt Gymnasium, Dordrecht) in 2007 he started his medical training that same year at the Erasmus University Rotterdam. Besides medical training he entered a Master of Science program in Clinical Research at the Netherlands Institute of Health Sciences in 2009. During this program he received training in epidemiology and data analysis, part of which was spent at Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States. Within this framework he started his research at the department of Cardiology, Erasmus Medical Center under the supervision of dr. R.T. van Domburg. Mid 2010, he became involved in the transcatheter aortic valve implantation programme under the supervision of Prof.dr. P.P.T. de Jaegere. Data collection and analysis of the Rotterdam cohort as well as (international) multicenter collaborations formed the basis of his projects. In the summer of 2012 an MSc degree in Clinical Research was obtained after a successful thesis defence. He was awarded the Gerrit-Jan Mulder Award for best research thesis for his work during this period.

In 2011 he graduated from the preclinical years of medical school after which he started his medical (clinical) internships in 2012. During this period he continued his scientific research which led to his PhD candidacy and thesis entitled: Transcatheter Aortic Valve Implantation: Insights into Clinical Complications. The author is expected to obtain the medical degree in July of 2014 after which he will pursue a residency in (interventional) cardiology.



PhD Portfolio

PHD PORTFOLIO

Name PhD Student:	Robert Mathew Anthony van der Boon
Department:	Cardiology
Research School:	Cardiovascular Research School Erasmus University Rotterdam
Title Thesis:	Transcatheter Aortic Valve Implantation: Insights into Clinical Complications
Promotor:	Prof. dr. P.P.T. de Jaegere
Date of thesis defence:	May 14, 2014

EDUCATION AND DEGREES

2011 – 2014	PhD Interventional Cardiology Erasmus Medical Center, COEUR PhD Programme, Rotterdam
2009 – 2012	MSc Clinical Research Netherlands Institute of Health Sciences, Rotterdam, The Netherlands
2007 – 2014	(expected) Medical Doctor / Artsdiploma Erasmus Medical Center, Rotterdam, The Netherlands
2007 – 2011	Doctorate in Medicine Erasmus Medical Center, Rotterdam, The Netherlands

EXTRA-CURRICULAR ACTIVITIES

2009 – 2010	Vice Chairman Student Faculty Council Erasmus Medical Center, Rotterdam, The Netherlands
2008 – 2009	Treasurer Student Faculty Council Erasmus Medical Center, Rotterdam, The Netherlands

SCIENTIFIC SYMPOSIA AND CONFERENCES

Oral Presentations

2013 Effect of body mass index on short- and long-term outcomes after transcatheter aortic valve implantation
Dutch Society of Cardiology (NVVC) Spring Congress
Noordwijkerhout, The Netherlands

2013 Transapical versus Transfemoral Aortic Valve Implantation: a multi-center collaborative study.
COEUR Annual PhD Day, Rotterdam, The Netherlands

2012 Frequency, determinants and prognostic implications of infectious complications after transcatheter aortic valve implantation.
COEUR Annual PhD Day, Rotterdam, The Netherlands

2012 Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System
COEUR Annual PhD Day, Rotterdam, The Netherlands

2012 Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System
EuroPCR Congress, Paris, France

2012 Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function
EuroPCR Congress, Paris, France

2011 Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function
Dutch Society of Cardiology (NVVC) Autumn Congress
Papendal, The Netherlands

2011 Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function
COEUR Annual PhD Day, Rotterdam, The Netherlands

Poster Presentations

2013 Effect of body mass index on short- and long-term outcomes after transcatheter aortic valve implantation
EuroPCR Congress, Paris, France

2012 Frequency, determinants and prognostic implications of infectious complications after transcatheter aortic valve implantation.
EuroPCR Congress, Paris, France

2012 Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System
Dutch Society of Cardiology (NVVC) Spring Congress
Papendal, The Netherlands

2011 Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function
Transcatheter Therapeutics, San Francisco, United States

2011 Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function
M3 MIRS, Masters in Repair Structural Heart Disease
Miami, Florida, United States

GRANTS / PRIZES

2013 Gerrit Jan Mulder Award 2012 – Best Research Thesis Erasmus Medical Center

2011 Award Best Oral Presentation Dutch Society of Cardiology (NVVC) Spring Congress - Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function

MSc CLINICAL RESEARCH

COURSE TYPE	COURSE	DATE	ECTS
Erasmus Summer Programme	Principles of Research in Medicine and Epidemiology	08-2009	0.7
	Introduction to Data-analysis	09-2010	1.0
	Regression Analysis	09-2010	1.9
	Methods of Clinical Research	08-2009	0.7
	Methods of Public Health Research	02-2011	0.7
	Clinical Trials	08-2009	0.7
	Topics in Meta-analysis	09-2010	0.7
	Pharmaco-epidemiology	08-2009	0.7
	Survival Analysis	09-2010	1.9
	Cohort Studies	08-2009	0.7
	Introduction to Decision-making in Medicine	08-2009	0.7
	Markers and Prognostic Research	08-2011	0.7
Core Courses	Study design	09-2009	4.3
Programm Specific Course	Broad orientation - medical study (BROAD)	02-2010	5.0

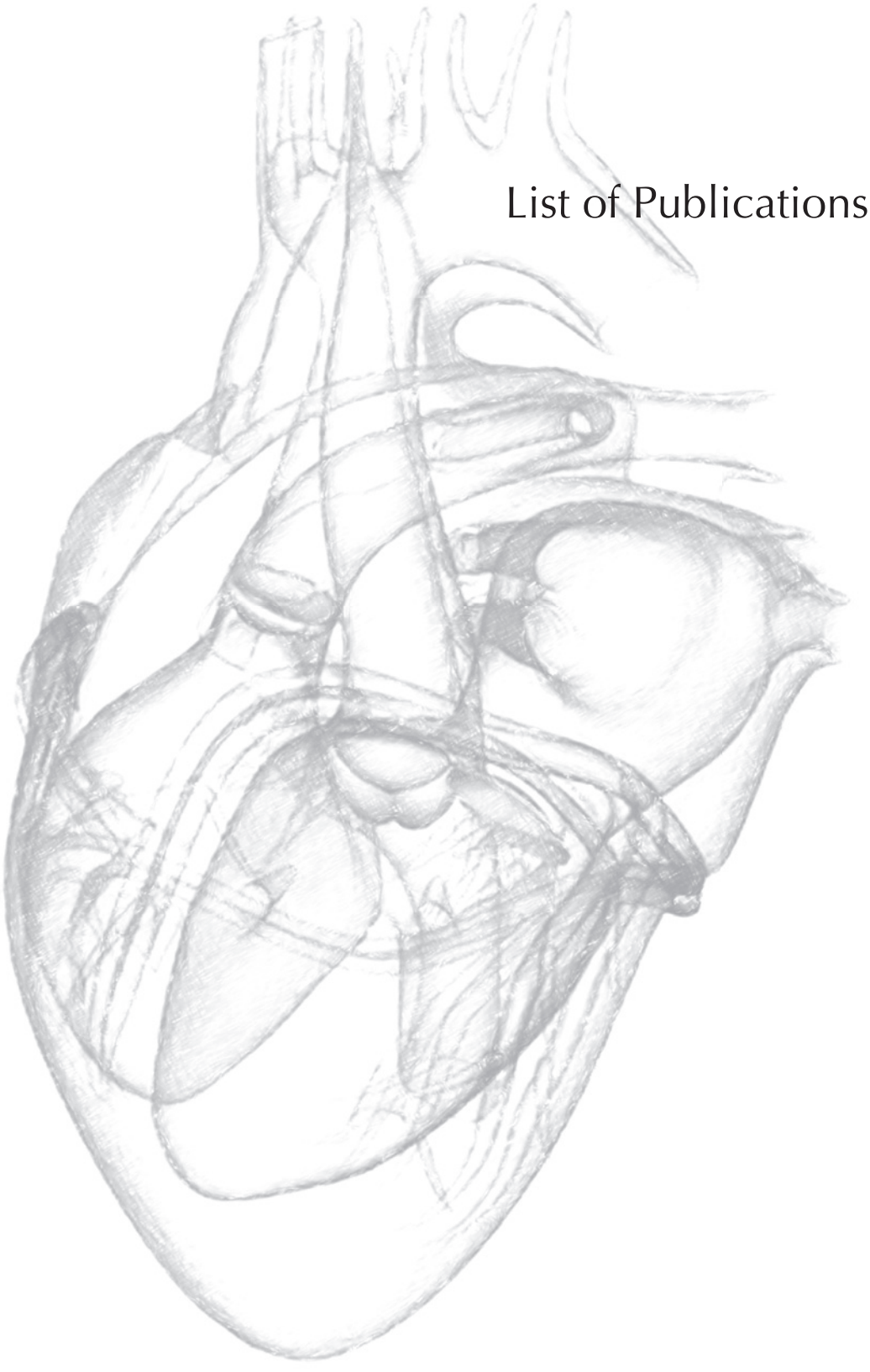
MSc CLINICAL RESEARCH continued

COURSE TYPE	COURSE	DATE	ECTS
Advanced Courses	Repeated Measurements in Clinical Studies	03-2011	1.4
	Courses for the Quantitative Researcher	12-2010	1.4
	Introduction to Clinical Research	02-2010	0.9
	Advanced Topics in Decision-making in Medicine	02-2010	1.9
	Pharmaco-epidemiology and Drug Safety	04-2012	1.9
	Intervention Research and Clinical Trials	02-2010	0.9
	Diagnostic Research	01-2010	1.1
	Advanced Topics in Clinical Trials	02-2012	1.9
	Advanced Analysis of Prognosis Studies	02-2012	0.9
	Prognosis Research	02-2010	0.2
	Principles of Epidemiologic Data-analysis	02-2012	0.7
	Research Seminars 1	07-2011	3.0
	Research Seminars 2	04-2012	3.0
	Summercourses at Johns Hopkins (USA)	07-2011	4.2
Skill Courses	Working with SPSS for Windows	01-2011	0.15
	A First Glance at SPSS for Windows	01-2011	0.15
	Scientific Writing in English for Publication	12-2011	2.0
Research	Development Research Proposal	01-2011	11.0
	Oral Research Presentation	05-2012	1.4
	Research Period	04-2012	60.3
	Research Symposium	12-2011	1.4
TOTAL			120.2

COEUR COURSES

COURSE TYPE	COURSE	DATE	ECTS
Seminar	Heart Valve Implantation: current status and future	02-2012	0.4
Lectures	New strategies for post-infarction LV Dysfunction	01-2012	0.1
	Symposium Thesis Stuart Head	10-2013	0.1

List of Publications



LIST OF PUBLICATIONS

1. **van der Boon RMA**, Nuis R-J, Van Mieghem NM, Benitez LM, van Geuns R-J, Galema TW, van Domburg RT, Geleijnse ML, Dager A, de Jaegere PP. Clinical outcome following Transcatheter Aortic Valve Implantation in patients with impaired left ventricular systolic function. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. 2012;79:702–710.
2. **van der Boon RMA**, de Jaegere PP, van Domburg RT. Multivariate analysis in a small sample size, a matter of concern. *Am J Cardiol*. 2012;109:450.
3. **van der Boon RMA**, Nuis R-J, Van Mieghem NM, Jordaens L, Rodés-Cabau J, van Domburg RT, Serruys PW, Anderson RH, de Jaegere PPT. New conduction abnormalities after TAVI--frequency and causes. *Nat Rev Cardiol*. 2012;9:454–463.
4. **van der Boon RMA**, Chieffo A, Dumonteil N, Tchetche D, Van Mieghem NM, Buchanan GL, Vahdat O, Marcheix B, Serruys PW, Fajadet J, Colombo A, Carrié D, van Domburg RT, de Jaegere PPT, PRAGMATIC-Plus Researchers. Effect of body mass index on short- and long-term outcomes after transcatheter aortic valve implantation. *Am J Cardiol*. 2013;111:231–236.
5. **van der Boon RMA**, Van Mieghem NM, Theuns DA, Nuis R-J, Nauta ST, Serruys PW, Jordaens L, van Domburg RT, de Jaegere PPT. Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System. *Int J Cardiol*. 2013;168:1269–1273.
6. **van der Boon RMA**, Nuis R-J, Benitez LM, Van Mieghem NM, Perez S, Cruz L, van Geuns R-J, Serruys PW, van Domburg RT, Dager AE, de Jaegere PPT. Frequency, determinants and prognostic implications of infectious complications after transcatheter aortic valve implantation. *Am J Cardiol*. 2013;112:104–110.
7. **van der Boon RMA**, Marcheix B, Tchetche D, Chieffo A, Van Mieghem NM, Dumonteil N, Vahdat O, Maisano F, Serruys PW, Kappetein AP, Fajadet J, Colombo A, Carrié D, van Domburg RT, de Jaegere PPT. Transapical versus transfemoral aortic valve implantation: a multicenter collaborative study. *Ann Thorac Surg*. 2014;97:22–28.
8. **van der Boon RMA**, Houthuizen P, Nuis R-J, van Mieghem NM, Prinzen F, de Jaegere PPT. Clinical implications of conduction abnormalities and arrhythmias after transcatheter aortic valve implantation. *Curr Cardiol Rep*. 2014;16:429.
9. **van der Boon RMA**, Houthuizen P, Urena M, Poels T, van Mieghem N, Brueren G, Altintas S, van Garsse L, van Domburg R, Nuis R, Rodes-Cabau J, de Jaegere P, Prinzen F. Trends in the occurrence of new Left Bundle Branch Block after Transcatheter Aortic Valve Implantation. *Submitted*.
10. Tzikas A, **van der Boon RMA**, de Jaegere PP. Contrast aortography and the aortic annulus. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. 2013;81:1254.
11. Van Mieghem NM, **van der Boon RMA**, Nuis R-J, Schultz C, van Geuns R-J, Serruys PW, Kappetein A-P, van Domburg RT, de Jaegere PP. Cause of death after

transcatheter aortic valve implantation. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. 2012;

12. Tchetche D, **Van der Boon RMA**, Dumonteil N, Chieffo A, Van Mieghem NM, Farah B, Buchanan GL, Saady R, Marcheix B, Serruys PW, Colombo A, Carrie D, De Jaegere PPT, Fajadet J. Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: insights from the Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative. *Am Heart J*. 2012;164:402–409.

13. Houthuizen P, **van der Boon RMA**, Van Garsse LAFM, Prinzen FW, de Jaegere P. Why permanent pacemaker implantation after transcatheter aortic valve implantation does not affect long-term clinical outcome. *J Am Coll Cardiol*. 2012;60:2339–2340; author reply 2340–2341.

14. Dumonteil N, **van der Boon RMA**, Tchetche D, Chieffo A, Van Mieghem NM, Marcheix B, Buchanan GL, Vahdat O, Serruys PW, Fajadet J, Colombo A, de Jaegere PPT, Carrié D. Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: a Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC-Plus) initiative substudy. *Am Heart J*. 2013;165:752–760.

15. van Mieghem NM, **van der Boon RMA**, Faqiri E, Diletti R, Schultz C, van Geuns R-J, Serruys PW, Kappetein A-P, van Domburg RT, de Jaegere PP. Complete revascularization is not a prerequisite for success in current transcatheter aortic valve implantation practice. *JACC Cardiovasc Interv*. 2013;6:867–875.

16. van Mieghem NM, **Van Der Boon RMA**. Porcelain Aorta and Severe Aortic Stenosis: Is Transcatheter Aortic Valve Implantation the New Standard? *Rev Esp Cardiol*. 2013;66:765–767.

17. Houthuizen P, **van der Boon RMA**, Urena M, van Mieghem N, Brueren GBR, Poels TT, Van Garsse LAFM, Rodés-Cabau J, Prinzen FW, de Jaegere P. Occurrence, fate and consequences of ventricular conduction abnormalities after transcatheter aortic valve implantation. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol*. 2013;

18. Nuis R-J, van Mieghem NM, **van der Boon RMA**, van Geuns R-J, Schultz CJ, Oei FB, Galema TW, Raap GB, Koudstaal PJ, Geleijnse ML, Kappetein AP, Serruys PW, de Jaegere PP. Effect of experience on results of transcatheter aortic valve implantation using a Medtronic CoreValve System. *Am J Cardiol*. 2011;107:1824–1829.

19. van Mieghem NM, Schultz CJ, **van der Boon RMA**, Nuis R-J, Tzikas A, Geleijnse ML, van Domburg RT, Serruys PW, de Jaegere PPT. Incidence, timing, and predictors of valve dislodgment during TAVI with the Medtronic Corevalve System. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. 2012;79:726–732.

20. Nuis RJ, Dager AE, **van der Boon RMA**, Jaimes MC, Caicedo B, Fonseca J, Van Mieghem NM, Benitez LM, Umana JP, O'Neill WW, de Marchena E, de Jaegere PP. Patients with aortic stenosis referred for TAVI: treatment decision, in-hospital outcome and determinants of survival. *Neth Heart J Mon J Neth Soc Cardiol Neth Heart Found*. 2012;20:16–23.

21. van Mieghem NM, Head SJ, **van der Boon RMA**, Piazza N, de Jaegere PP, Carrel T, Kappetein AP, Lange R, Walther T, Windecker S, van Es G-A, Serruys PW. The SURTAVI model: proposal for a pragmatic risk stratification for patients with severe aortic stenosis. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol*. 2012;8:258–266.

22. Nauta ST, Deckers JW, **van der Boon RMA**, Akkerhuis KM, van Domburg RT. Risk factors for coronary heart disease and survival after myocardial infarction. *Eur J Prev Cardiol*. 2012;

23. van Mieghem NM, Généreux P, **van der Boon RMA**, Kodali S, Head S, Williams M, Daneault B, Kappetein A-P, de Jaegere PP, Leon MB, Serruys PW. Transcatheter aortic valve replacement and vascular complications definitions. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol*. 2012;

24. Schultz CJ, van Mieghem NM, **van der Boon RMA**, Dharampal AS, Lauritsch G, Rossi A, Moelker A, Krestin G, van Geuns R, de Feijter P, Serruys PW, de Jaegere P. Effect of body mass index on the image quality of rotational angiography without rapid pacing for planning of transcatheter aortic valve implantation: a comparison with multislice computed tomography. *Eur Heart J Cardiovasc Imaging*. 2014;15:133–141.

25. Schultz C, Rossi A, van Mieghem N, **van der Boon RMA**, Papadopoulou S-L, van Domburg R, Moelker A, Mollet N, Krestin G, van Geuns R-J, Nieman K, de Feyter P, Serruys PW, de Jaegere P. Aortic annulus dimensions and leaflet calcification from contrast MSCT predict the need for balloon post-dilatation after TAVI with the Medtronic CoreValve prosthesis. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol*. 2011;7:564–572.

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27. Nuis R-J, Van Mieghem NM, Schultz CJ, Moelker A, **van der Boon RMA**, van Geuns RJ, van der Lugt A, Serruys PW, Rodés-Cabau J, van Domburg RT, Koudstaal PJ, de Jaegere PP. Frequency and causes of stroke during or after transcatheter aortic valve implantation. *Am J Cardiol*. 2012;109:1637–1643.

28. Houthuizen P, Van Garsse LAFM, Poels TT, de Jaegere P, **van der Boon RMA**, Swinkels BM, Ten Berg JM, van der Kley F, Schalij MJ, Baan J Jr, Cocchieri R, Brueren GRG, van Straten AHM, den Heijer P, Bentala M, van Ommen V, Kluin J, Stella PR, Prins MH, Maessen JG, Prinzen FW. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. *Circulation*. 2012;126:720–728.

29. Caliskan K, Michels M, Geleijnse ML, van Domburg RT, **van der Boon RMA**, Balk AHMM, Simoons ML. Frequency of asymptomatic disease among family members with noncompaction cardiomyopathy. *Am J Cardiol*. 2012;110:1512–1517.

30. van Mieghem NM, Chieffo A, Dumonteil N, Tchetche D, **van der Boon RMA**,

Buchanan GL, Marcheix B, Vahdat O, Serruys PW, Fajadet J, Carrié D, Colombo A, de Jaegere PPT. Trends in outcome after transfemoral transcatheter aortic valve implantation. *Am Heart J*. 2013;165:183–192.

31. van Mieghem NM, Schipper MEI, Ladich E, Faqiri E, **van der Boon RMA**, Randjgari A, Schultz C, Moelker A, van Geuns R-J, Otsuka F, Serruys PW, Virmani R, de Jaegere PP. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation*. 2013;127:2194–2201.

32. van Mieghem NM, Schipper MEI, Ladich E, Faqiri E, **van der Boon RMA**, Randjgari A, Schultz C, Moelker A, van Geuns R-J, Otsuka F, Serruys PW, Virmani R, de Jaegere PP. Response to letter regarding article, "Histopathology of embolic debris captured during transcatheter aortic valve replacement."*Circulation*. 2013;128:e478–479.

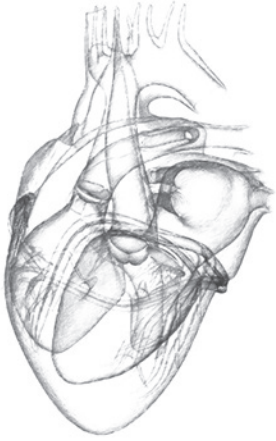
33. van Mieghem NM, Tchetche D, Chieffo A, Dumonteil N, Messika-Zeitoun D, **van der Boon RMA**, Vahdat O, Buchanan GL, Marcheix B, Himbert D, Serruys PW, Fajadet J, Colombo A, Carrié D, Vahanian A, de Jaegere PPT. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. *Am J Cardiol*. 2012;110:1361–1367.

34. Osnabrugge RLJ, Head SJ, Genders TSS, Van Mieghem NM, De Jaegere PPT, **van der Boon RMA**, Kerkvliet JM, Kalesan B, Bogers AJJC, Kappetein AP, Hunink MGM. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg*. 2012;94:1954–1960.

35. Chieffo A, Buchanan GL, Van Mieghem NM, Tchetche D, Dumonteil N, Latib A, **van der Boon RMA**, Vahdat O, Marcheix B, Farah B, Serruys PW, Fajadet J, Carrié D, de Jaegere PPT, Colombo A. Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve Revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-RotterdAm-Milano-Toulouse In Collaboration). *J Am Coll Cardiol*. 2013;61:830–836.

36. Nuis R-J, Piazza N, Van Mieghem NM, Otten AM, Tzikas A, Schultz CJ, **van der Boon RMA**, van Geuns R-J, van Domburg RT, Koudstaal PJ, Kappetein AP, Serruys PW, de Jaegere PP. In-hospital complications after transcatheter aortic valve implantation revisited according to the Valve Academic Research Consortium definitions. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. 2011;78:457–467.

37. Nombela-Franco L, Webb JG, de Jaegere PP, Toggweiler S, Nuis R-J, Dager AE, Amat-Santos IJ, Cheung A, Ye J, Binder RK, **van der Boon RMA**, Van Mieghem N, Benitez LM, Pérez S, Lopez J, San Roman JA, Doyle D, Delarochellière R, Urena M, Leipsic J, Dumont E, Rodés-Cabau J. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation*. 2012;126:3041–3053.



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